EPILEPSY IN INFANCY STUDY:

A POPULATION BASED STUDY ON EPILEPSIES WITH ONSET IN THE FIRST TWO YEARS OF LIFE

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I, Christin Martina Eltze confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London,

.....

For Ming and Charlotte, who had a lot of patience with me

Abstract

Children with the onset of epilepsy under the age of two years are a heterogeneous group with particularly poor outcome reported by studies mostly originating from specialist hospital / clinic settings.

A population based study was designed to determine the incidence of epilepsy onset under the age of two years and to ascertain a cohort for long-term follow up. This cohort observation aimed to determine usefulness of the current international classification of epilepsies in this age group, associated structural brain abnormalities, predictors of developmental function close to diagnosis; and factors that are associated with a longitudinal change of developmental scores after 12 months.

Cases were prospectively identified from residents in 15 boroughs of North London involving hospital and community based paediatricians. Information was obtained either by questionnaire anonymously or from clinical assessments of children enrolled in the observational cohort. 57 cases were enrolled giving a crude annual incidence of 54 (95% CI 41-69) /100.000 children under the age of 2 years. A two source capture recapture model determined an adjusted annual incidence of 56.3 – 88.5 (95% CI) / 100.000 <= 2 years.

Clinical assessment of children in the observational cohort at baseline and 12 months follow up included neurodevelopmental evaluation using standardised tools, central

review of EEG's and neuroimages. Data of all subjects enrolled were independently evaluated by two paediatric neurologists.

Although most cases were classified under epilepsy syndrome groups, a specific epilepsy syndrome diagnosis could not be allocated in a third of cases and there was only moderate inter-rater agreement (kappa scores: 0.48, 0.5).

Review of neuroimages of 52 children (91%) demonstrated a high yield of aetiologically relevant abnormalities in 26 (50%) with common occurrence of developmental malformations identified in 11 (43%).

Multivariate regression analysis showed that 'abnormal neurological examination' and 'presence of interictal discharges on EEG' significantly and independently predicted lower developmental function close to diagnosis. There was no significant difference between initial and developmental function on follow up after adjusting for initial infantile spasms, normal or abnormal initial EEG, seizure status at follow up, structural brain abnormalities, and antiepileptic medication taken, suggesting that the initial status determined the function after 12 months follow up.

Statement of Originality

The candidate's personal contributions are listed below:

- design of the study protocol combining population survey and cohort observation
- adaption and implementation of notification systems - telephone hotline and monthly postal survey
- design of electronic database and proformas to collect clinical, neuroimaging and EEG data
- data collection of cases that were notified
- clinical evaluation of patients enrolled in the observational cohort
- review of neuroimaging and EEG in collaboration with neuroradiologists and neurophysiologists
- collation of clinical and investigation results at baseline and follow up for classification according to the international classification of epilepsies by paediatric neurologists
- analysis of data obtained at baseline and follow up

The information that has been obtained from other sources is listed below:

- The neurodevelopmental assessments using standardised tools at baseline and follow up were conducted by a psychologist that was employed for this study. The psychologist scored the test results and entered these into an electronic data base.
- Dr Andrea Whitney, employed as fellow in complex epilepsy, collected the majority of clinical data at follow up either by meeting families and patients or by conducting a telephone interview and entered the data into the electronic data base.

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Dr Richard Chin has contributed with his research experience in the planning stage of this study. He was always available to give practical advice during the data collection phase and also helped with parts of the statistical analysis.

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I am very grateful to Dr WK Chong and Dr Tim Cox for the time they committed to this project when reviewing the neuroimaging of children enrolled in this study.

Dr Steward Boyd advised on software to review data obtained from various EEG departments and design of a proforma to analyse EEG recordings. He supervised together with Dr Stephen White EEG review and interpretation by the candidate. I am very grateful to both for their help.

I would like to thank Dr Andrea Withney for her important contribution to this work by obtaining the clinical follow up information of the children enrolled in the observational cohort approximately 12 months after the baseline evaluation.

Dr Mario Cortina provided invaluable help with the statistical analysis of the data obtained from the population survey part of this project and their presentation in this thesis.

I would like to thank Prof Brain Neville for his advise when setting up this study and also when presenting the initial data on international conferences.

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Scientific Contributions arising from this Thesis

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Newly diagnosed epilepsy in children under the age of two years in a population based setting: Incidence, aetiologies, syndrome diagnoses and developemntal status

Eltze CM, de Haan M, Whitney A, Boyd S, WK Chong, Scott RC, Cross JH
Predictors of neurodevelpmental function in children with newly diagnosed epilepsy at onset and 1 year follow up

Eltze CM, WK Chong, Cox T, Scott RC, Cross JH
The yield of magnetic resonsonance imaging in children with newly diagnosed epilepsy under the age of two years in a population based setting

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Application of the epilepsy syndrome classification (2001 prpoposal) in children under the age of two years: data form a prospective population based cohort

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List of Abbreviations

Bayley III	Bayley Scales of Infant and Toddler Development 3rd Edition
BFIS	Benign Familial Infantile Seizures
BIS	Benign Infantile Seizures
BME	Benign Myoclonic Epilepsy in Infancy
95% CI	95% Confidence Interval
CT	Computer Tomography
DCF- 0	Developmental Composite Factor at baseline - generated from Bayley III composite scores at baseline by Principal Component Analysis
DCF-1	Developmental Composite Factor at follow up - generated from Bayley III composite scores at follow up by Principal Component Analysis
DF	Developmental Raw Score Factor - generated from raw sores of Bayley III subscales by Principal Component Analysis
GAC	Bayley III: Adaptive Bahavior - General Adaptive Composite
GEFS+	Generalsied (Genetic) Epilepsy Febrile Seizures plus
ICE	International Classification of Epilepsies and Epilepsy Syndromes
ICES	Ineternational Classification of Epileptic Seizures
ILAE	International League Against Epilepsy
MCD	Malformations of Cortical Development
MRI	Magnetic Resonnace Imaging
NICE	National Institute for Clinical Excellence
NLSTPSS	North London Convulsive Status Epilepticus in Childhood Surveillance Study
SMEI	Severe Myoclonic Epilepsy in Infamcy
VABC	Vineland Adaptive Behavior Composite
VABS	Vineland Adaptive Behavior Scales Survey Form

1 CHAPTER 1: INTRODUCTION

1.1 Aims of the study

Children with epilepsy onset under the age of two years are a heterogeneous group with respect to epilepsy syndromes and underlying aetiologies, whose prognosis with few exceptions has been widely reported to be poor. Previous research originating in the majority from hospital or specialist settings has commonly focused on subgroups to delineate specific electro-clinical syndromes, determine their aetiologies (including molecular genetic defects and developmental brain abnormalities) and investigate therapeutic interventions.

The focus of this study was to collect information about the group of young children presenting with newly onset epilepsy (under the age of two years) from a population based setting. In particular data were obtained relating to frequency of epilepsy onset in this age band, types of epilepsy, associated structural brain abnormalities and developmental status. The usefulness of the international classification system of epilepsy syndromes and epilepsies (Engel, Jr., 2001), applied at the time the work was carried out, was assessed. The relationships between clinical features, neuroimaging, neurophysiology and developmental function close to diagnosis and after short term follow up (approximately 12 months) were examined in order to identify predictors of adverse outcomes.

Population based information is key for the generation of diagnostic strategies that will identify those most at risk early, improve management decisions on medical or surgical remediative interventions and help to allocate resources adequately.

1.2 Definitions

For this observational study ‘epileptic seizure’ and ‘epilepsy’ have been defined in accordance with the report of the International League Against Epilepsy (ILAE) commission on epidemiology and prognosis (ILAE Commission, 1997):

- ***Epileptic seizure***: "A clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic or psychic events perceived by the patient or an observer.” (ILAE Commission, 1997)
- ***Epilepsy***: "A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-hour period are considered a single event. Persons who have had only febrile seizures or only neonatal seizures as herein defined are excluded from this category." (ILAE Commission, 1997)

More recent definitions for the term ‘epileptic seizure’ proposed by the ILAE task force on classification and terminology are very similar to the above quoted version in the 1997 commission report. They emphasise the specific pathomechanism of abnormal neuronal activity that results in the observevable clinical manifestations, whilst the 1997 ILAE definition contains a degree of ambiguity when using the term 'presumed' in this context:

- *ILAE 2001* (Engel, Jr., 2001): “Manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurons in the brain” ;

- ILAE 2005 (Fisher et al., 2005): “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”.

A different conceptual definition of ‘epilepsy’ has been recently proposed. The requirement of ‘recurrent unprovoked seizures’ has been abandoned and instead a history of a single seizure is sufficient in the presence of an ‘enduring alteration of the brain that increases the likelihood of future seizures associated with neurobiological, cognitive, psychosocial and social disturbances’ (Fisher et al., 2005). This definition is however not practical for epidemiological research as the authors failed to specify what such an ‘enduring alteration of brain dysfunction’ constitutes and how to establish its presence especially following a first unprovoked seizure (Beghi et al., 2005). Only 40 to 50% of subjects may experience recurrence following a first unprovoked seizure as demonstrated in several observational and randomised interventional studies (FIR.S.T Group, 1993;Shinnar et al., 1996;Stroink et al., 1998;Marson et al., 2005;Berg, 2008).

An ‘***Epilepsy syndrome’*** is ‘a complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type: thus frontal lobe seizures per se, for instance, do not constitute a syndrome’ (Engel, Jr., 2001). By further describing an epilepsy syndrome as **‘symptomatic’** a reference is made to underlying identifiable pathological disturbances in cerebral structure or metabolism’. In **‘idiopathic’** epilepsy syndromes no structural or metabolic aetiology can be identified and the primary cause is assumed to be genetic (Engel, Jr., 2001;Engel, Jr., 2006). In order to accommodate syndromes that cannot be classified under either of these categories the term ‘cryptogenic’ has been applied

with various meanings. In the context of epidemiological research '*cryptogenic'* meant essentially absence of identifiable risk factors or unknown aetiology (ILAE Commission, 1997). The 1989 ILAE classification defines 'cryptogenic epilepsies' as 'presumed to be symptomatic but with unknown aetiology'. In accordance with the proposal of the task force published in 2001 in this study the term '***probably symptomatic'*** has been applied synonymously with **'**cryptogenic' as defined in the 1989 ILAE classification (Engel, Jr., 2001).

2 CHAPTER 2: BACKGROUND AND RESEARCH QUESTIONS

2.1 Classification of the epilepsies:

2.1.1 Introduction

Managing a chronic and diverse condition such as epilepsy with onset across the life span requires involvement of clinicians and professionals from multiple disciplines. Their clinical practice is informed by the increasing understanding and information provided through research. As such the need arose for a common framework that enables communication between clinicians and forms the basis for quantitative research in epilepsy. The ongoing process of developing a comprehensive classification system was started in 1985 by the 'Commission on Classification and Terminology' of the ILAE with a first proposal (ILAE, 1985). This and subsequent proposals were based on recognisable clinical patterns or epilepsy syndromes rather than on underlying conditions because of their heterogeneity and the fact that many have yet to be identified.

It is now common clinical practice in developed countries including the UK to determine seizure type and epilepsy syndrome, which can than guide further decisions on investigations and treatment (National Institute for Clinical Excellence, 2004). There is also an expectation of clinicians to be able to derive prognostic information through categorising of the epilepsy type.

In the following paragraphs, the classification systems used at the time this study was designed are briefly described. Information in the literature about their applicability or usefulness of in childhood epilepsy was reviewed.

For this purpose Medline (1966 to December 2007) was searched using the terms "epilepsy syndrome" in combination with "incidence" and "prevalence". The search

was repeated with "epilepsy classification"[1]. Studies in English were selected that applied the 1989 International Classification of Epilepsies and Epileptic Syndromes (ICE) or the diagnostic scheme published in 2001 and enrolled children (within age range 1 month up to 16 years) or children and adults (Commission on Classification and Terminology of the International League Against Epilepsy, 1989;Engel, Jr., 2001). References of identified articles were examined for additional relevant studies.

This information will set the background for the following chapter that reviews the literature with focus on children with epilepsy onset in infancy.

2.1.2 Currently used classification systems

At the time of writing two classification systems - the 1989 International Classification of Epilepsies and Epileptic Syndromes (ICE) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and diagnostic scheme published in 2001(Engel, Jr., 2001) - were recognised by the ILAE for application in clinical practice and research until a superior classification system could be agreed on that satisfied the needs of both clinicians and researchers (Engel, Jr., 2006).

The 1989 ICE (see table 2.1) supplements the 1981 International Classification of Epileptic Seizures (1981 ICES: (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Epilepsies and age specific

[1] Translation of search terms in Pubmed: epilepsy: "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields], syndrome: "syndrome"[MeSH Terms] OR "syndrome"[All Fields], classification: "classification"[Subheading] OR "classification"[All Fields] OR "classification"[MeSH Terms]; incidence: "epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms], prevalence: "epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]

electro-clinical syndromes are grouped under two major hierarchical divisions:

- Level 1 relates to seizure types (mode of seizure onset) and has 4 categories: 1. Localisation-related (focal, local, partial), 2. Generalised epilepsies and syndromes, 3. Epilepsies and Syndromes undetermined if focal or generalised, 4. Special syndromes (situation related seizures, isolated seizures or status epilepticus) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

- Level 2 refers to aetiology and has three categories: idiopathic (no underlying cause other than a possible hereditary condition), symptomatic (consequences of known or suspected disorders of the central nervous system), cryptogenic (presumed to be symptomatic, but aetiology is unknown)(Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Table 2.1: Classification of epilepsies, epileptic syndromes and related seizure disorders (ILAE 1989) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989)

1. Localization-related (focal, local, partial) epilepsies and syndromes
- 1.1. Idiopathic (with age-related onset):
  - Benign childhood epilepsy with centro-temporal spikes
  - Childhood epilepsy with occipital paroxysms
  - Primary reading epilepsy
- 1.2. Symptomatic:
  - Chronic progressive epilepsia partialis continua of childhood (Kojewnikow syndrome)
  - Seizures characterized by specific modes of precipitation
  - Other epilepsies and syndromes based on localization or aetiology
- 1.3. Cryptogenic

2. Generalised epilepsies and syndromes
- 2.1. Idiopathic (with age-related onset - listed in order of age):
  - Benign neonatal familial convulsions
  - Benign neonatal convulsions
  - Benign myoclonic epilepsy in infancy
  - Childhood absence epilepsy (pyknolepsy)
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Epilepsy with generalized tonic-clonic seizures on awakening
  - Other generalized idiopathic epilepsies not defined above
  - Epilepsies with seizures characterized by specific modes of precipitation (e.g. photosensitive epilepsy)
- 2.2. Cryptogenic and/or symptomatic (in order of age):
  - West syndrome (infantile spasms)
  - Lennox-Gastault syndrome
  - Epilepsy with myocionic-astatic seizures
  - Epilepsy with myoclonic absences
- 2.3. Symptomatic:
  - 2.3.1. Non-specific aetiology:
    - Early myoclonic encephalopathy
    - Early infantile epileptic encephalopathy with suppression-bursts
    - Other symptomatic generalized epilepsies not defined above
  - 2.3.2. Specific syndromes

3. Epilepsies and syndromes undetermined whether local or generalized
- 3.1. With both generalized and focal seizures:
  - Neonatal seizures
  - Severe myoclonic epilepsy in infancy
  - Epilepsy with continuous spike-waves during slow wave sleep
  - Acquired epileptic aphasia (Landau-Kleffner syndrome) Other undetermined epilepsies not defined above
- 3.2. Without unequivocal generalized or focal features

4. Special syndromes
- 4.1. Situation-related seizures:
  - Febrile convulsions
  - Seizures occurring only in the context of acute metabolic or toxic events
- 4.2. Isolated seizures or isolated status epilepticus

Application of the 1989 ICE in prospective population based studies enrolling both adults and children with newly diagnosed epilepsy demonstrated that although most cases could be classified up to two thirds of patients fell into less narrowly defined rather unspecific categories. Categories such as 3.2 (essentially unclassifiable cases), 1.3 (cryptogenic localisation related epilepsies) and 2.1 (other generalised idiopathic

epilepsies not defined above) provide little information to guide management and predict the clinical course (see Table 2.1: categories of 1989 ICE). A defined syndromic diagnosis could only be achieved for a minority of cases (36 - 45%) (Manford et al., 1992;Olafsson et al., 2005).

The lack of clear criteria on how to classify cases resulted in differences in interpretation and application of the 1989 ICE between studies. Cases for example with focal epileptiform EEG abnormalities, fulfilling criteria for localisation, and negative neuroimaging are classified by some authors under symptomatic by others under cryptogenic localisation related (Jallon et al., 2001).

The multiaxial 'diagnostic scheme for people with epileptic seizures and with epilepsy' was proposed by the ILAE task force on classification and terminology in *2001* and aimed to provide a more flexible individualised approach (Table 2.2) (Engel, Jr., 2001). The proposed diagnostic scheme combined description and categorisation of seizures using a glossary of descriptive terminology, epilepsy syndrome, aetiologies and impairment in a system of 5 axes (see also Table 2.2).

It was recognised that a syndrome diagnosis cannot be made for each patient. The seizure type (axis 2) was therefore 'promoted' to a diagnostic entity rather than a description of the ictal clinical and electrophysiological manifestations (as in the 1981 seizure classification) (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). A 'seizure type diagnosis' should include reference to pathomechanisms and anatomical structures involved with implications for diagnostic evaluation, treatment and prognosis. Thus it would provide an alternative for cases where a syndromic epilepsy diagnosis cannot be made (Engel, Jr., 2006). However seizures are difficult to categorize in many patients

especially young children. In addition seizure types (especially ‘generalised’ seizure types) still await delineation and the processes as well anatomical cerebral structures involved in seizure generation are not yet completely understood (Engel, Jr., 2006). Axis 3 provides the place for a syndrome diagnosis that should be selected if appropriate from an updated list in the 2001 report that also includes epilepsy syndromes “under development”.

The definitions for ‘epileptic syndrome’ in the 2001 proposal of the ILAE task force (table 2.3) and in the 1989 ICE[2] are in principal very similar. Whilst some of the epilepsy syndromes listed in the 1989 ICE are, however, predominantly defined by seizure type (e.g. temporal lobe epilepsies, frontal lobe epilepsies), the definition in the 2001 proposal requires additional clinical and electrophysiological characteristics. This appears to contradict the idea in the 2001 proposal that seizure type could be used as diagnostic entity when an electro-clinical syndrome diagnosis is not achievable (Seino, 2006).

A list of definitions of key terms specifies proposed changes in terminology (compared to 1989 ICE) and introduces new concepts (see Table 2.3). This includes abolition of the distinction between simple and complex partial seizures, change of the term 'localisation related' to 'focal' with the added explanation that the epileptogenic zone may not be restricted to a small cortical area but often can involve a wide area in one or both hemispheres diffusely (multifocal).

[2] “An epileptic syndrome is an epileptic disorder characterised by a cluster of signs and symptoms customarily occurring together; these include such items as type of seizure, aetiology, anatomy, precipitating factors […] and sometimes prognosis. However, in contradiction to a disease, a syndrome does not necessarily have a common aetiology and prognosis.” (Commission on Classification and Terminology of the International League Against Epilepsy, 1989)

One of the new concepts, ‘epileptic encephalopathy’, has particular relevance to infancy and childhood onset epilepsies. It is hypothesised that epileptiform abnormalities contribute significantly to progressive cerebral dysfunction in addition to the underlying aetiology. According to this concept epileptic activity in the immature brain interferes with brain maturation resulting in impairment of neurodevelopment and cognitive function in later life. "The epileptic encephalopathies" is one of the categories suggested in the 2001 task force report under which age dependent specific electroclinical syndromes are further organised.

Table 2.2: Proposed multiaxial diagnostic scheme for people with epileptic seizures and epilepsy, 2001 (adapted and modified from (Engel, Jr., 2001))

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that utilizes standardized terminology, and that is sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

1. Some patients cannot be given a recognized syndromic diagnosis.
2. Seizure types and syndromes change as new information is obtained.
3. Complete and detailed descriptions of ictal phenomenology are not always necessary.

Multiple classification schemes can, and should, be designed for specific purposes (e.g. communication and teaching; therapeutic trials; epidemiological investigations; selection of surgical candidates; basic research; genetic characterizations).

Axis 1	Ictal phenomenology - from the Glossary of Descriptive Ictal Terminology can be used to describe ictal events with any degree of detail needed.
Axis 2	Seizure type - from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
Axis 3	Syndrome - from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
Axis 4	Aetiology - from a Classification of Diseases Frequently Associated with Epileptic Seizures or epilepsy syndromes when possible, genetic defects, or specific pathological substrates for symptomatic focal epilepsies
Axis 5	Impairment - this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the WHO ICIDH-2.

Table 2.3: Definitions of key terms (down loaded from www.ilae-epilepsy.org, accessed in November 2007, adapted from (Engel, Jr., 2001)

Epileptic Seizure Type: An ictal event believed to represent a unique pathophysiological mechanism and anatomical substrate. This is a diagnostic entity with etiological, therapeutic, and prognostic implications. **(new concept)**

Epilepsy Syndrome: A complex of signs and symptoms that define a unique epilepsy condition with different etiologies. This must involve more than just the seizure type; thus frontal lobe seizures per se, for instance, do not constitute a syndrome. **(changed concept)**

Epilepsy Disease: A pathological condition with a single specific, well-defined etiology. Thus Progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundborg is a disease. **(new concept)**

Epileptic encephalopathy: A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. **(new concept)**

Benign epilepsy syndrome: A syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae. (clarified concept)

Reflex epilepsy syndrome: A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures, are listed as seizure types. Isolated reflex seizures can also occur in situations that do not necessarily require diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures. **(changed concept)**

Focal seizures and syndromes: Replaces the terms partial seizures and localization-related syndromes. **(changed concept)**

Simple and complex partial epileptic seizures: These terms are no longer recommended, nor will they be replaced. Ictal impairment of consciousness will be described when appropriate for the individual seizures, but will not be used to classify specific seizure types. **(new concept)**

Idiopathic epilepsy syndrome: A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms. These are presumed to be genetic and are usually age-dependent. (unchanged term)

Symptomatic epilepsy syndrome: A syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. (unchanged term)

Probably symptomatic epilepsy syndrome: Synonymous with, but preferred to, the term cryptogenic, used to define syndromes that are believed to be symptomatic, but no etiology has been identified. **(new term)**

2.1.3 Identification of epilepsy syndromes in childhood

Most population based studies in the literature describing epilepsy prevalence and incidence cohorts applied the 1989 ICE (see table 2.4) and only two studies referred to the relative recently published 2001 ILAE proposal for the classification of epilepsy syndromes (Larsson and Eeg-Olofsson, 2006;Akiyama et al., 2006). Table 2.4 lists population based studies that applied the 1989 ICE with the proportions of subjects that were categorised under specific epilepsy syndromes (electro-clinical syndromes, that are more narrowly defined) and those that were essentially unclassifiable (including category 3.2 – 'without unequivocal generalised or focal features'). The proportion of specific epilepsy syndromes listed in table 2.3 does *not* include cases that were classified under the following vague categories of the 1989 ICE: 1.3 – cryptogenic localisation-related epilepsies and syndromes, 2.1 – 'other generalised idiopathic epilepsies not defined above', and 2.3 'other symptomatic generalised epilepsies not defined above'.

In population based settings the proportion of subjects with specific epilepsy syndrome diagnoses are larger in most childhood cohorts (51 - 67%) (Eriksson and Koivikko, 1997;Callenbach et al., 1998;Beilmann and Talvik, 1999;Berg et al., 1999c;Waaler et al., 2000;Freitag et al., 2001;Kwong et al., 2001), with the exception of one Japanese study (22%) (Oka et al., 2006), compared to cohorts of adults and children (36-45%) (Manford et al., 1992;Jallon et al., 2001;Olafsson et al., 2005) [see table 2.3 for details]. This is not surprising as the majority of specific epilepsy syndromes are delineated in childhood and adolescence. In addition some paediatric studies involve child neurologists in the recruitment of cases (Berg et al., 1999c).

Whilst the majority of children can be classified using the 1989 ICE, the proportion of subjects that are essentially unclassified varies between 1 and 12% in the reviewed childhood cohorts, usually because of a lack of information (see table 2.4: (Eriksson and Koivikko, 1997;Callenbach et al., 1998;Beilmann and Talvik, 1999;Berg et al., 1999c;Waaler et al., 2000;Oka et al., 2006)). Variations in distribution of the epilepsy syndromes and the proportion of cases falling into specific epilepsy syndrome categories (51%-67% of children enrolled in North American and European studies (Eriksson and Koivikko, 1997;Callenbach et al., 1998;Beilmann and Talvik, 1999;Berg et al., 1999c;Waaler et al., 2000;Freitag et al., 2001), 22% in a Japanese prevalence cohort (Oka et al., 2006)) are compounded by differences in study design, availability of investigation results and most importantly the interpretation of the ICE criteria. Only two papers specified that cases were independently classified by several raters with subsequent consensus agreements when necessary (Berg et al., 1999c;Jallon et al., 2001). Taking methodological differences between the quoted studies into consideration, in at least a third of children a more narrowly defined epilepsy syndrome diagnosis cannot be achieved and the seizure disorder is rather vaguely described as 'localisation-related', 'generalised' or 'undetermined' epilepsy.

High inter-rater agreement can be achieved when investigators agree ‘rules’ for application of the ICE a priori as demonstrated in a community based cohort recruited through child neurology practices in the state of Connecticut (Berg et al., 1999a). Berg et al showed also that the initial syndrome diagnosis was stable over time in the majority of cases (Berg et al., 2000a). After two years the initial syndrome diagnosis was revised in only 84 of 613 of cases (~14%). Two thirds of the revised diagnoses came form the group of children who were essentially unclassified

(category 3.2 of the 1989 ICE: 'without unequivical generalised or focal features', see alo table 2.1) or partially classified (category 1.3 'cryptogenic localisation related'). In 16 cases (< 3 % of the entire cohort) more major revisions were made which included changes from non-idiopathic localisation related to idiopathic generalised. The initial diagnosis was most commonly changed when new information of subsequent EEG's or neuroimaging became available. Evolution of the initial syndrome occurred in approximately 4 % of cases (e.g. from West syndrome to Lennox-Gastaut).

The 2001 proposal of diagnostic scheme was applied by Akiyama et al, who reclassified a prevalence cohort that was originally classified according to the 1989 ICE (Akiyama et al., 2006). Specific epilepsy syndromes were identified in only 269 (12%) cases, whilst the remaining 1761 patients were described by seizure type only. Although EEG information was accessible for the majority of patients the authors did not specify the availability of other information such as neuroimaging data that would have impacted their ability to classify cases.

In summary review of the literature shows that the ILAE syndrome classification (1989 ICE) is applicable for a majority of children presenting with epilepsy. Specific syndrome diagnoses are more commonly made in childhood. However a significant proportion of children fall in unspecific categories. Few data are available to evaluate the diagnostic scheme proposed in 2001.

Table 2.4: Application of 1989 ICE in population based studies (proportion of specific epilepsy syndromes and unclassifiable cases)

Authors, Year of publication	Country	Cohort	Ascertainment	n	age [years]	Inclusion criteria	3.2 or unclassified	Specific Epilepsy Syndromes
Manford et al, 1992	UK 'The National General Practice Study of Epilepsy'	population based prospective	275 GP practices - in urban + rural areas of UK	594 (139 < 15 years)	1 months onwards	unprovoked seizures or epilepsy (recurrent unprovoked seizures)	190 (32%)	36%
Oka et al, 1995	Japan	Prevalence	survey in geographical area, medical records of hospitals	2378	< 10	children with epilepsy (single seizures + febrile convulsions)	506 (21%)	12.6%
Eriksson KJ, Koivikko MJ, 1997	Finland	Prevalence	catchment area of university hospital, hospital patient's register, PICU admissions, EEG department @ University Hospital	329	0-15	recurrent unprovoked seizures, single prolonged seizure or single SE with EEG confirming epilepsy	32 (10%)	52%
Callenbach et al, 1998	Netherlands '*Dutch Study of Epilepsy in Childhood*'	hospital based prospective	University hospitals Rotterdam, Leiden; Westeinde Hospital (The Hague), Juliana Children's Hospital,	462	1 month - 16 years	recurrent unprovoked seizures	5 (1.1%)	52%
Berg A et al, 1999	USA, Connecticut	population based prospective	through child neurologists (16/17 practices) in state	613/770 (79.6%)	1month-15	recurrent unprovoked seizures	71 (11.6%)	67%
Beilmann A, Talvik T, 1999	Estonia	Prevalence + Incidence	catchment area of university hospital, annually letters to Paediatricians/Neurologists/ EEG department @ university hospital	560	0-19	recurrent unprovoked seizures	10 (1.8%)	65%
Waaler et al, 2000	Norway	Prevalence	Catchment area, university hospital patient register, EEG department, contact to GP + other institutions	198	6-12	recurrent unprovoked seizures	22(10.6%)	64%

Authors, Year of publication	Country	Cohort	Ascertainment	n	age [years]	Inclusion criteria	3.2 or unclassified	Specific Epilepsy Syndromes
Kwong et al, 2001	Hong Kong	Prevalence (hospital based)	catchment area of hospital, attendees register	309	1month-15	recurrent unprovoked seizures	7 (2%)	51%
Freitag et al, 2001	Germany	Incidence	Mannheim, Heidelberg, hospital medical records, EEG attendees, regular contact to private paediatricians (letters, visits etc)	36	1month-15	recurrent unprovoked seizures	0	61%
Jallon et al, 2001	France 'CAROLE Study'	population based prospective	242 of 430 Child and adult neurologists throughout France and one in Geneva participated (majority hospital based)	1016 (543 < 15 years)	1 months onwards	recurrent unprovoked seizures	187 (18%)	43%
Olafsson et al, 2005	Iceland	Incidence	country wide surveillance system - of all healthcare facilities (hospitals, A&E's, EEG departments, Radiology departments etc), verification by review of synopsis by neurologist	294 (72 < 15 years)	1 months onwards	unprovoked seizure or epilepsy (recurrent unprovoked seizures)	77(26.2%)	45%
Larson, Eeg-Olafsson et al 2006*	Sweden	Prevalence	catchment area of university hospital - Uppsala + rehabilitation centre, patient's register, questionnaire to GP's	205	1 months - 16	recurrent unprovoked seizures	8 (3.9%)	49%
Oka et al, 2006	Japan	Prevalence	survey in geographical area, medical records of institutions	1337	<13	recurrent unprovoked seizures	146 (11%)	22.5%

SE = Status epilepticus; ∗ICES 1989 modified according to 2001(updated syndrome list)

2.2 Epilepsy under the age of two years

2.2.1 Introduction

Within in the childhood epilepsy group infants are often considered separately because of the high incidence of seizures and epilepsy in the first year of life, the heterogeneity of clinical presentations (with age specific seizure manifestations), the diversity of outcomes and underlying aetiologies (Arzimanoglou et al., 2004b). As discussed in the following paragraphs a number of early studies focused on outcomes of infants with seizures in the first 12 months, whilst some of the later studies included children with epilepsy onset in the first 24 months (Rantala and Ingalsuo, 1999;Altunbasak et al., 2007) . Febrile convulsions are especially common in the first year of life and only a proportion of infants may go on to develop afebrile seizures in the second year of life as part of the natural evolution of an epileptic disorder, e.g. severe myoclonic epilepsy in infancy (Verity et al., 1985;Dravet et al., 2005a;Sillanpaa et al., 2008). In order to ensure inclusion of such early epilepsy presentations the extension of the age band for an infancy epilepsy cohort from 12 to 24 for months appears justified. The candidate has taken this view when reviewing the literature and designing inclusion criteria for this work. The candidate, however, acknowledges that the choice of such age limits to form subgroups is arbitrary. Despite of the documented typical peak ages of onset in the majority of cases with delineated electroclinical syndromes, for example, the age of onset in some of the typical and atypical syndromic presentations can be wider reaching across such age bands.

The following sections review information available in the literature of *infancy epilepsy series or cohorts* (onset in the first 12 to 24 months) including distribution

of the specific epilepsy syndromes listed in the current international classification systems. Data relating to the clinical characterisation and outcome of this age group are contrasted with those obtained from *childhood epilepsy cohorts* that are composed of infants *and* older children (epilepsy onset 1 month to 16 years).

Medline (Pubmed) was searched (1966 to January 2008) with the term "infant" combined with "recurrent seizures" or "convulsive disorders" [3], repeated with "recurrent seizures" or "epilepsy" and "prognosis". The searches were limited to articles in English. Selected were studies that enrolled all infants (aged 1 month to 12 or 24 months) with recurrent seizures. Additional relevant articles were identified from references of selected papers.

Studies identified in the Medline search described in section 2.2.1 were examined for information about frequency and distribution of infancy onset epilepsy syndromes. References of a published systematic review of incidence studies were examined in order to identify all articles that provided incidence estimates of epilepsy under one or two years (Kotsopoulos et al., 2002). The Medline search in this paper (1966 to 1999) was updated (Jan 2000 to December 2006) using search terms: "recurrent seizures" or "epilepsy" and "incidence" (limits: "age 0-23 months", articles in English and human studies)[4].

[3] Translation of query: (recurrent[All Fields] AND ("seizures"[MeSH Terms] OR "seizures"[All Fields])) OR (convulsive[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "disorders"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang] AND "infant"[MeSH Terms]

[4] Translation of query: ((recurrent[All Fields] AND ("seizures"[MeSH Terms] OR "seizures"[All Fields])) OR ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields])) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) AND ("humans"[MeSH Terms] AND English[lang] AND "infant"[MeSH Terms]

2.2.2 Incidence of epilepsy in infancy

Annual incidence estimates of epilepsy onset in childhood in developed countries vary between 38 to 60/100,000 in recent publications (Camfield et al., 1996;Olafsson et al., 1996;Freitag et al., 2001;Sillanpaa, 2003;Olafsson et al., 2005;Larsson and Eeg-Olofsson, 2006). The age specific incidence curve of epilepsy in developed countries demonstrates a peak in the first year of life followed by a sharp decline in early childhood and a second increase in the elderly forming an U-shaped appearance (Hauser et al., 1993;Camfield et al., 1996;Olafsson et al., 2005;Banerjee and Hauser, 2008). The age specific incidence rates of first unprovoked seizures form a similar curve further supporting the impression that the brain is especially susceptible to seizures in very young and old age: "Epilepsy is a disease with onset at the extremes of life" (Banerjee and Hauser, 2008).

Although the onset of childhood epilepsy is most frequent in infancy the age specific incidence estimates show great variability between studies (79 – 256/100.000/year, see table 2.5). Both geographical and methodological differences including prospective or retrospective study design, ascertainment methods, and case definitions contribute to these variations. A number of studies recruit cases from the population living in the catchment area of a hospital and/or EEG department using attendance registers as the single source of ascertainment. This may result in case under-ascertainment in certain settings. Ascertainment adjustment methods such as capture-recapture methodology were not applied.

The impact of different case definitions becomes especially apparent when comparing the figures obtained from the two UK birth cohort studies (see table 2.5).

Not surprisingly, the study that ascertained all infants with one o more afebrile seizures (Verity et al., 1992) estimated a much higher incidence rate for the first year of life when compared to a cohort that included cases with recurrent unprovoked seizures ((Verity et al., 1992;Kurtz et al., 1998).

In some studies the incidence estimates for the first year of life are based on small case numbers and confidence intervals are rather wide (Blom et al., 1978;Olafsson et al., 1996;Freitag et al., 2001); see also table 2.5).

Few data are available in the literature with respect to the incidence of epilepsy in children under the age of two years because most epilepsy incidence studies provide age specific data only for the age group less than 1 year and summarize data in larger age bands (eg 1-4 years, 5-9 years etc).

Table 2.5: Studies providing incidence estimates of epilepsy in children under the age of one or two years

Author, year of publication	Ascertainment period	Country	Case definition	Case ascertainment	Age specific incidence < 1 year per 100.000	95% CI
Blom et al, 1978	1973 - 1974	Sweden	1 or more unprovoked seizures	retrospective - catchment area approach, using data/records from hospital EEG department, single EEG -service provider in area , follow up of cohort, letter + phone contact,	95.7 (n=3)	32.5 - 281
Doose et al,1983	children born 1957-1966	Germany, Kiel	> 1 unprovoked seizure	catchment area approach, information obtained retrospectively from hospital records (epilepsy centre),	201.6 (n=76)	Not available
Verity et al, 1992	Birth cohort one week 1970	United Kingdom	1 or more afebrile seizures	prospective follow up of birth cohort, screening questionnaire with subsequently obtained from GP's and hospital records	160 (n=23 first seizure)	107 - 240
Hauser et al, 1993	1935 -1984	USA, Rochester	>1 unprovoked seizure	retrospectively, information form diagnostic record system,	86 (n=36)	62 - 119
Braathen et al, 1995	1990 - 1992	Sweden	> 1 unprovoked seizure	prospective, catchment area of hospital, epilepsy team	0-2 years: 70 (n=14)	Not available
Camfield et al, 1996	1977 - 1985	Canada, Nova Scotia	>1 unprovoked seizures	retrospective, catchment area of hospital EEG department/	118 (n=112)	98 - 143
Olafsson et al, 1996	1993	Iceland	> 1unprovoked seizure	retrospective, records of healthcare centres, local hospitals, contact of Paediatricians + Neurologists	256.5 (n=4)	99.7- 657

Author, year of publication	Ascertainment period	Country	Case definition	Case ascertainment	Age specific incidence < 1 year per 100.000	95% CI
Kurtz et al, 1998	Birth cohort one week 1958	England/Scotland/ Wales	> 1 disturbances of consciousness, not associated with acute fever	prospective follow up of birth cohort, screening questionnaire with subsequently obtained from GP's and hospital records	90 (n=14)	43 -138
Freitag et al, 2001	1999	Germany, Heidelberg + Manheim	>1 unprovoked seizure	prospective, involving EEG departments, 2 University hospitals and Office Paediatricians (contacted by letters and phone calls)	146 (n=5)	47.4 - 340.1
Olafsson et al, 2005	1995 -1999	Iceland	> 1 unprovoked seizure	prospective, country wide surveillance system - of all healthcare facilities (hospitals, A&E's, EEG departments, Radiology departments etc)	79.5 (n=11)	44 -132

2.2.3 Epilepsy syndromes in the neonatal period and infancy

The number of ‘specific epilepsy syndromes’ with onset in the first two years of life that have been included in the ILAE lists of epilepsy syndromes has been increasing over the last two decades. Table 2.6 lists the syndromes according to the grouping suggested in the 2001 proposal and table 2.7 a) and b) summarise the main clinical features.

In a simplistic way neonatal / infancy onset epilepsies can be categorised under two main groups. One represents syndromes with poor prognosis for seizure control and cognitive outcome in the majority of patients (Table 2.7 b). With the exception of ‘migrating partial seizures in infancy’ these have been grouped under ‘epileptic encephalopathies’ in the 2001 proposal. A broad spectrum of underlying aetiologies is commonly represented. This includes developmental and acquired brain lesions as well as genetic and metabolic disorders. In ‘migrating partial seizures in infancy’ commonly no underlying aetiology can be recognised.

One of the electroclinical syndromes of the 'poor outcome group'- severe myoclonic epilepsy in Infancy (SMEI) or Dravet's syndrome - is here discussed in more detail because of the recent discovery of an associated ion channel mutation with implications for diagnosis and classification. In typical cases, developmentally normal infants present with atypical febrile convulsions (hemiconvulsions and/or prolonged febrile seizures) and episodes of febrile as well as afebrile status epilepticus in the first year of life. In the further evolution of this syndrome afebrile multiple seizures types including focal seizures, atypical absences, non-convulsive status epilepticus like states and myoclonus occur, frequently accompanied by

developmental plateauing or regression. Although the initial EEG may be normal a range of characteristic abnormalities evolve later including generalised spike wave discharges and photosensitivity (Dravet et al., 2005b). Atypical or SMEI borderline (SMEB) presentations share many characteristics of typical presentations but myoclonic seizures or generalised spike wave discharges may be absent and the predominant seizure type can be generalised tonic clonic convulsions (Oguni et al., 1994;Doose et al., 1998). The association between 'increase in body temperature' and seizures, a marker that has been observed in another previously identified genetic epilepsy syndrome: 'Genetic (Generalised) Epilepsy with Febrile Seizures plus +' (GEFS+) lead to the discovery of de novo sodium channel subunit mutations in patients with SMEI (SCN1A, one of the ion channel mutations previously identified in GEFS+ families) (Claes et al., 2001). Subsequently other groups confirmed SCN1A mutations with high prevalence in patients with typical and borderline SMEI presentaions ranging from 33 - 82% (Ohmori et al., 2002;Wallace et al., 2003;Nabbout et al., 2003;Fukuma et al., 2004;Harkin et al., 2007). In the largest series (SMEI: n=66, SMEB: n = 36) a higher proportion of patients with SMEI (79%) tested positive for the SCN1A mutation compared to the borderline cases (69% of SMEB) (Harkin et al., 2007). Whilst the majority of SCN1A mutations in typical and borderline SMEI arise de novo, 5 % of the reported series (mostly missense, but also truncation mutations) have familial mutations (Scheffer et al., 2009). In addition a number of families with 2 affected siblings with SMEI have been reported due to somatic or germline mosaicisms (Marini et al., 2006;Morimoto et al., 2006).

GEFS+ is a phenotypically very heterogeneous syndrome with presentations in large autosomal dominant pedigrees ranging from febrile seizures (a proportion occurring

after the age of 6 years) in isolation or in combination with mild to severe types of epilepsy (including myoclonic astatic epilepsy, SMEI and focal epilepsies) (Scheffer and Berkovic, 1997;Scheffer et al., 2007). Although five genes have been identified, encoding sodium channel subunits (SCN1A, SCN2A, SCN2B) and GABA receptor subunits (GABR2, GABRD), monogenetic inheritance is less relevant for the majority of GEFS+ cases that arise from small families or occur sporadic (Baulac et al., 2001;Wallace et al., 2002;Ito et al., 2002;Harkin et al., 2002;Scheffer et al., 2005). In one series of patients with GEFS+ eleven percent of patients with SCN1A mutations have been identified (Marini et al., 2007). The phenotypical and genetic heterogeneity within GEFS+ and familiar SMEI cases as well as the overlap between both suggests that additional genetic modifiers may play an important role in the expression of clinical features (Scheffer et al., 2009;Singh et al., 2009). GEFS+ could be understood as an accumulation of clinically delineated epilepsy syndromes that broadly share genetically determined pathomechanisms resulting in susceptibility to seizures with sensitivity to increased body temperature. SMEI lies within this spectrum at the severer end (Arzimanoglou, 2009).

Spontaneously remitting seizures or pharmacologically responsive epilepsy and normal cognitive outcome in the majority of patients is characteristic for the idiopathic syndromes in the second group. The underlying aetiology of these idiopathic forms is most likely genetic. Mutations in genes encoding ion channels have been found in some syndromes (Table 2.7 a). Benign familial (BFIS) and non familial infantile seizures (BIS) have been newly included in the 2001 proposal. Watanabe et al first described infants with focal or secondarily generalised seizures and good outcome (Watanabe et al., 1993;Watanabe and Okumura, 2000). Familial

occurrence in autosomal dominant pedigrees was subsequently recognised by Vigevano et al (Vigevano et al., 1992;Vigevano, 2005). Infants present between 3 and 20 month of age. Seizures occur often in brief clusters over one or several days. The interictal EEG outside of a seizure cluster is typically normal and there are no structural abnormalities on neuroimaging. Despite some of the common features this group of infants is phenotypically and genetically very heterogeneous. Several chromosomal loci have been identified in linkage studies of BFIS: 19p13; 2q24; 16p12- q12 (Guipponi et al., 1997;Malacarne et al., 2001;Caraballo et al., 2001). An association with other neurological conditions such as paroxysmal dyskinesias has been described in families that map to the locus on Chromosome 16 and with 'Familial Hemiplegic Migraine' in two families linked to 1q23 (Caraballo et al., 2001;Vanmolkot et al., 2003). Family members affected by 'Familial Hemiplegic Migraine' and/or BFIS carried a missense mutation in the ATP1A2 (Na^+, K^+-ATPase) gene. Sodium channel mutations (SCNA2 gene) have been identified in families whose affected members had their seizure onset in the neonatal period or in early infancy (0-6 months) (Berkovic et al., 2004;Herlenius et al., 2007). The authors suggested delineation of a new syndrome: 'Benign Infantile Neonatal Seizures' (Berkovic et al., 2004). Other phenotypical presentations of the 'BIS spectrum' are:

- 'Benign infantile focal seizures with midline spikes and waves during sleep (high voltage diphasic spikes followed by slow wave in sleep EEG): A wider age range of seizure onset has been reported in this subgroup (4-30 months) and developmental progress was normal at follow up (Capovilla and Beccaria, 2000);
- BIS in relation with gastroenteritis (especially rotavirus): Infants in this subgroup present with situation related seizures and do not

require a diagnosis of epilepsy (Specchio and Vigevano, 2006;Okumura et al., 2006).

Some patients that have been diagnosed with idiopathic infantile or familial neonatal syndromes experience a more severe course. Familial neonatal seizures with confirmed potassium channel mutation can present with epileptic encephalopathy (Dedek et al., 2003). A proportion of patients with 'Benign Myoclonic Epilepsy in Infancy' (BME) have long-term cognitive impairment: 15% in a hospital based series (Auvin et al., 2006) and 32% (25/77) of cases with information available on cognitive outcome from a literature review (Zuberi and O'Regan, 2006). The word 'benign' was therefore removed in the most recent ILAE task force report and the syndrome is now called 'Myoclonic Epilepsy in Infancy ' (Engel, Jr., 2006).

2.2.3.1 Distribution specific epilepsy syndromes with onset under two years in the general population

Population based studies enrolling patients presenting with recurrent unprovoked seizures provide limited information. Childhood prevalence studies of active epilepsy are biased towards severe types of epilepsy and may under report 'benign' syndromes in which seizures go into remission. The numbers of infants enrolled into prospective studies vary and tend to be rather small in cohorts that enrol children and adults (see also table 2.8 under 'comments '). Sixty one or 10% of the children enrolled in the Connecticut study were under 1 year at diagnosis (Berg et al., 1999c). Data specifically relating to the group of patients with epilepsy onset under the age of 2 years are not provided in the majority of publications.

West syndrome (Infantile Spasms) is most commonly represented. The proportion of infants with West syndrome varies (0.5 - 8%, see table 2.8) and tends to be higher in prevalence cohorts as well as studies that involve child neurologists in the recruitment. 'The National General Practice Study of Epilepsy' (NGPSE, conducted in the 1980's) is a community based study in which patients with a suspected new diagnosis of epilepsy older than 1 month were prospectively registered by 275 general practitioners based in surgeries around the UK over a 3 year period (Sander et al., 1990). It is surprising that amongst the 39 children enrolled in the age group 0-4 years none was identified with West syndrome (Manford et al., 1992). Whilst idiopathic syndromes' including childhood absence epilepsy (CAE, 1.6%), juvenile myoclonic epilepsy (JME, 1.1%) were recognised amongst 594 cases with a definite diagnosis of epilepsy (including 139 children age 0-14 years), other syndromes listed under the category 2.2 "cryptogenic or symptomatic generalised epilepsies" of the 1989 classification (e.g. Lennox – Gastaut syndrome, Epilepsy with myoclonic astatic seizures) were not identified (Manford et al., 1992). The authors interpret this observation with the infrequent representation of some specific epilepsy syndromes in the general population. In support of this statement a recent epidemiological study from Iceland reported an incidence of West syndrome of 0.7 per 1000 person years, whilst figures for JME and CAE were 70 and 80 per 1000 person-years respectively (Olafsson et al., 2005). Other incidence figures for infantile spasms available in the literature range from 2.9 to 4.5 per 10.000 live births (Riikonen and Donner, 1979;Sidenvall and Eeg-Olofsson, 1995;Trevathan et al., 1999). Because the study design of the NGPSE does not allow relating of case numbers to the population at risk it is difficult to compare the quoted incidence figures. Under reporting of children with more severe epilepsies including West syndrome, that are in the UK

commonly managed by hospital or community based paediatricians cannot be excluded.

Other neonatal / infantile syndromes listed in the 1989 ICE, which has been applied in the majority of studies are extremely rare (see table 2.8). Patients with milder types of epilepsy may not present to a specialist setting which explains the different proportions of BME in the 'Dutch Study of Epilepsy in Childhood' (2.4%) and the Connecticut study by Berg et al (0.2%) that recruited cases through child neurology practices (Callenbach et al., 1998;Berg et al., 1999c). Thus, the data from population based cohorts suggest that a large proportion of infants may be either unclassifiable (category 3.2) or fall into categories that are defined by aetiology (symptomatic, cryptogenic).

Two retrospective specialist hospital based studies report the distribution of epilepsy syndromes in children with seizure onset in the first year of life. In a large cohort from Argentina (n=471) the majority of patients were classified as West syndrome (47%) and symptomatic localisation related epilepsy (28%) (Caraballo et al., 1997). Seventy three children (15%) fell into non specific categories and 15 infants (3.8%) were diagnosed with benign syndromes (6 BME, 12 BFIS). Of the severe epilepsy syndromes SMEI was the second commonest (15/471, 3.2%).

West syndrome (39%), symptomatic localisation-related epilepsies (13%) and symptomatic specific syndromes [2.3.2 (11%)] were also the commonest syndromic diagnoses in the second smaller hospital based series from Italy (n=150) (Battaglia et al., 1999). Neuroimaging data were available for all children (MRI in 49%). Only 2

cases (1.3 %) were identified as idiopathic generalised epilepsy and 23 % of the cohort were categorised in non-specific categories. Infants presenting with BIS/BFIS may have been categorized under cryptogenic partial as the authors applied the 1989 ICE.

Sarisjulis et al investigated if and when a syndromic diagnosis can be made in infants with epilepsy of unknown cause that did not have infantile spasms as the first seizure type. Their retrospective cohort was derived from a specialist hospital setting (n=140) (Sarisjulis et al., 2000). A specific syndrome diagnosis could be made in half of the patients in the first months after presentation. In 28 % of cases no syndromic diagnosis could be allocated and a further 23 % of patients fell under the non-specific category 'cryptogenic localisation related' epilepsy. The latter group included 9 (of 32) patients who later presented with infantile spasms. Only 8 patients (5.7%) with benign syndromes were identified (1.8 % of the entire retrospective cohort of patients with seizure onset in the first year of life). Forty two patients (30%) were clinically diagnosed as having SMEI (9.7% of the entire infancy onset epilepsy group), reflecting the special interest of this epilepsy centre, where this syndrome was first described. At the time this paper was published the high prevalence of SCN1A mutations in patients with typical clinical presentation of SMEI had not jet been discovered and results for this genetic investigation were unlikely to be available for this cohort at the time. The investigators had most difficulties in distinguishing between cryptogenic localisation related epilepsies and SMEI as both syndromes can present with focal seizures and normal EEG at onset. In 75% of patients with cryptogenic localisation related epilepsy the time lag between first seizure and first abnormal EEG recording was < 3 months. The initial

presentation of typical SMEI cases with febrile seizures can delay the recognition of this syndrome. In this retrospective cohort the first afebrile seizure occurred between 2 and 20 months (mean 7.6 months) and the syndrome was identified between 3 and 24 months of age (mean age 8.4 months, 88% recognised before the age of one year and 95% by 18 months of age).

Taken together there is a lack of data pertaining to the distribution of infancy onset epilepsy syndromes in the general population. Limited data available from population based studies suggest that the benign syndromes may be especially underreported. West syndrome that is characterised by a specific seizure type is most easily recognised.

Data from hospital based series are biased towards identification of the refractory types and also may reflect the special interest of the epilepsy centre in one particular syndrome. There is also a suggestion that a significant proportion of infancy onset epilepsies cannot be classified under the current classification systems. In the context of current clinical practice that applies syndromic diagnoses to guide patient management this results in uncertainty with respect to the most appropriate investigation and therapeutic strategies.

Table 2.6: Epilepsy Syndromes with onset in Neonatal period and Infancy (Engel, Jr., 2001;Engel, Jr., 2006)

Group of Syndromes	Specific Syndromes
Idiopathic Focal Epilepsies	Benign Infantile Seizures (Non-Familial) [BIS]
Familial (Autosomal Dominant) Focal Epilepsies	Benign Familial Neonatal Seizures Benign Familial Infantile Seizures [BFIS]
Symptomatic (or Probably Symptomatic) Focal Epilepsies	Limbic Epilepsies Neocortical Epilepsies: • Hemiconvulsion - Hemiplegia Syndrome • Other Types Defined by Location and Etiology • Migrating Partial Seizures of Early Infancy *
Idiopathic Generalized Epilepsies	(Benign) Myoclonic Epilepsy in Infancy [BME]
Epileptic Encephalopathies	▪ Early Myoclonic Encephalopathy [EME] ▪ Ohtahara Syndrome [EIEE] ▪ West Syndrome ▪ Dravet Syndrome [SMEI] ▪ Myoclonic Status in Non-Progressive Encephalopathies
Seizures Not Necessarily Requiring a Diagnosis of Epilepsy	▪ Benign Neonatal Seizures, ▪ Febrile Seizures ▪ *Single Seizures or Isolated Clusters of Seizures* ▪ *Rarely Repeated Seizures (Oligo-Epilepsy*)

Table 2.7 a): Epilepsy syndromes with onset in first the 2 years of life (clinical features): Syndromes with good outcome in majority of patients

	Age of onset	**Seizure types**	**Interictal EEG**	**Chromosomal loci; Genes**
Benign neonatal seizures[1] – Non familial – Familial (autosomal dominant)	1-7 days 2-3 days	Focal clonic / apnoeas Diffuse tonic probable focal	Normal or focal/multifocal abnormalities, discontinuous, 'theta pointu alternant' pattern	20q13.3; KCNQ2 8q24; KCNQ3
Benign neonatal infantile seizures* (autosomal dominant)	Mean 11 weeks +/- 9 weeks**	Focal, secondarily generalised	Normal or focal abnormalities	2q24; SCN2A[2]
Benign infantile seizures[3] – Non familial – Familial (autosomal dominant)	3-20 months (majority < 12 months) 4-8 months	Focal	Normal	16p12-q12[4], 19q[5] 1q23 (ATP1A2)[6]
(Benign) myoclonic epilepsy in infancy[7]	6 months - 3 years	Myoclonic Reflex myoclonus	Normal, Ictal EEG: generalised spike or polyspike and wave discharges	unknown

* not included in recent ILAE classification proposal (Engel, Jr., 2001); **onset from neonatal period up to 13 months (Herlenius et al., 2007); 1(Plouin and Anderson, 2005); 2(Heron et al., 2002) ; 3(Vigevano, 2005;Specchio and Vigevano, 2006;Okumura et al., 2006); 4(Caraballo et al., 2001); 5(Guipponi et al., 1997); 6(Vanmolkot et al., 2003); 7(Dravet and Bureau, 2005;Auvin et al., 2006)

Table 2.7 b): Epilepsy syndromes with onset in first the 2 years of life (clinical features): Syndromes with poor outcome

	Age of onset	**Seizure types**	**Interictal EEG**	**Other characteristics**
Early infantile epileptic encephalopathy (Ohtahara syndrome)[1]	birth – 3 months	tonic spasms, focal, rarely myoclonus	suppression – burst pattern (in waking and sleep)	Aetiology; predominantly acquired structural brain lesions or developmental brain malformations;
Severe myoclonic encephalopathy[1]	birth – 28 days	myoclonic, focal, tonic spasms (later)	suppression-burst pattern (enhanced or only in sleep)	Aetiology: unknown or metabolic disorders
Migrating partial seizures in infancy[2]	First year of life, Birth – 7 months	Focal (large variety of motor and autonomic manifestations), occur in clusters	Multifocal spikes Ictal: continuous but shifting epileptiform activity from one region to another from one hemisphere to another	No structural brain abnormalities
West syndrome[3]	birth – 2 years, majority in 1rst 12 months (peak 3 – 7 months)	spasms, focal seizures antecedent or concomitantly in 1/3	Hypsarrhythmia (absent in up to 33%)	Aetiology – wide spectrum: acquired brain lesions, developmental brain malformations, metabolic disorders, chromosomal abnormalities, genetic (e.g. ARX[4], CDKL5[5]) or unknown;
Severe myoclonic epilepsy in infancy (Dravet's syndrome)[6]	Within first year	Initially: atypical febrile convulsions (prolonged, unilateral clonic seizures) Subsequently: tonic, tonic-clonic, myoclonus, focal	Initially: normal Subsequently: generalised, focal and multifocal abnormalities	Genetic aetiology: Chromosome 5q31-q33, SCN1A[7]; ~ 80% of patients[8], Chromosome 2q24, GABR2, γ2 subunit of GABA receptor[9]

1(Aicardi and Ohtahara, 2005;Ohtahara and Yamatogi, 2006), 2(Dulac, 2005), 3 (Lux and Osborne, 2004;Dulac and Tuxhorn, 2005), 4(Kato et al., 2003), 5(Archer et al., 2006), 6 (Dravet et al., 2005b), 7(Claes et al., 2001),8(Harkin et al., 2007), 9(Harkin et al., 2002;Jansen et al., 2006)

Table 2.8: Application of 1989 ICE in population based studies: Specific Neonatal / Infancy onset Syndromes

Authors, Year of publication	Country	Cohort	n	age [years]	West syndrome	Other specific neonatal/infancy onset syndromes	Comments
Manford et al, 1992	UK	Prospective population based cohort	594	1 months onwards	0		139 < 15 years, 0-4 years: n=39
Oka et al, 1995	Japan	Prevalence	2378	< 10	40 (2.1%)	EIEE 1 (0.1%)	
Eriksson, Koivikko, 1997	Finland	Prevalence	329	0-15	25 (8%)	BNC 2(1%), BFNC 2(1%)	91 (27%) < 12 months at onset
Callenbach et al, 1998	Netherlands Dutch Study of Childhood onset Epilepsy	Prospective multi-centre hospital based cohort	462	1 months – 16 years	17 (3.7%)	BME 11 (2.4%), BFNC 1 (0.2%)	
Beilman A, Talvik T, 1999	Estonia	Prevalence + Incidence	560	0-19 years	8 (1.4%)	BME 5 (0.9%), EME 1 (0.2%)	
Berg et al, 1999	USA, Connecticut	Prospective community based cohort	613	1 month – 15 years	24 (3.9%)	BME 1 (0.2%), SMEI 1 (0.2%)	85 < 1 year at seizure onset, 61 < 1 year at diagnosis
Waaler et al, 2000	Norway	Prevalence	198	6-12 years	1 (0.5%)		infantile syndromes under-reported due to mortality + evolution of syndromes, and benign syndromes not any more active

Authors, Year of publication	Country	Cohort	n	age [years]	West syndrome	Other specific neonatal/infancy onset syndromes	Comments
Kwong et al, 2001	Hong Kong	Prevalence (hospital based)	309	1month-15 years	16 (5%)	BNFC 1, BME 1	61 (20%) onset < 12 months (15 idiopathic, 4 cryptogenic, 38 symptomatic)
Freitag et al, 2001	Germany	Incidence	36	1month-15 years	0	SMEI 1(2.8%)	5 < 12 months (14%)
Jallon et al, 2001	France	Prospective population based cohort	1016	1 months onwards	25 (2.5%)	BME 9 (0.9%)	543 < 15 years
Olafsson et al, 2005	Iceland	Incidence	294	1 months onwards	6 (1%)		72 < 15 years, 11 (3.7%) < 12 months , 10 in age group 1-4 years
Larson, Eeg-Olofson et al 2006	Sweden	Prevalence	205	1 months - 16 years	4 (2%)	BFIS 1 (0.5%), BME 1(0.5%), EME 1 (0.5%), SMEI 6 (2.9%)	44 (21%) onset < 12 months, neuroimaging in 75% (MRI : 85%, CT: 54%)
Oka et al, 2006	Japan	Prevalence	1337	<13	59 (4.3%)	EIEE 11 (0.9%)	

EIEE = Early Infantile Epileptic Encephalopathy, EME= Early Myoclonic Encephalopathy, BNC=Benign Neonatal Convulsions (Seizures), BFNC=Benign Familial Neonatal Convulsions (Seizures), BME=Benign Myoclonic Epilepsy in Infancy, BFIS=Benign Familial Infantile Seizures, SMIE=Severe Myoclonic Epilepsy in Inancy, MRI=Magnetic Resonance Imaging

2.2.4 Seizure types

Clinical manifestations of epileptic seizures in infancy can be subtle and difficult to recognise. They differ from those observed in later childhood and adult age reflecting an age dependent evolution of clinical manifestations. Typical manifestations in infancy include behavioural change with arrest of movements, hypotonia, asymmetric or symmetric clonic movements, tonic posturing (symmetric or asymmetric), version of head and eyes, as well as autonomic features such as flushing, pallor, and peri-oral cyanosis. Auras, elaborate automatisms, dystonic posturing and secondarily generalisations occur with increasing age whilst other features such as asymmetric clonus and symmetric posturing observed in infantile seizures disappear with advancing age (Nordli, Jr. et al., 2001).

Following the first description by West, who observed epileptic spasms in his infant son, these were initially recognised as major defining feature of an age dependent syndromic epilepsy presentation with poor outcome (West syndrome / Infantile spasms) rather than a seizure type (West W, 1841;Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Although the onset of spasms, typically in clusters, is frequently observed in infancy (peak presentation between 3 and 7 months) it was subsequently recognised that spasms may persist beyond 2 years of age, may occur at any age throughout childhood and are a feature of several different syndromes (Gobbi et al., 1987;Ohtsuka et al., 2001;Eisermann et al., 2006;Vigevano et al., 2007;Goldstein and Slomski, 2008). Thus epileptic spasms were included in the seizure type classification of the 2001 ILAE ICE proposal defined as "A sudden flexion, extension or mixed extension-flexion of predominantly proximal and truncal muscles which is usually more

sustained than a myoclonic movement but not as sustained as a tonic seizure i.e. about 1 second" (Engel, Jr., 2001;Blume et al., 2001). EEG as well as polygraphic features have been well described and include a generalised high amplitude slow wave (or sharp slow wave complex) coinciding with the motor manifestation (associated with a diamond shaped EMG pattern of 1-2 second duration), commonly followed by attenuation and fast activity (either preceding or following the slow wave complex)(Vigevano et al., 2001). Subcortical structures especially the brain stem have been proposed as generator for spasms because of their association with various diffuse and focal brain abnormalities as well as hydrancephaly (Neville, 1972;Dulac et al., 1999). However, neocortical epileptogenic mechanisms also contribute to generation of spasms as evident from neurophysiology, functional neuroimaging and the reported seizure free outcome following surgical cortical resections or disconnection procedures (Chugani et al., 1990;Jonas et al., 2005;Kang et al., 2006). According to one prominent hypothesis spasms are the result of a failure in the complex interplay between brainstem and neocortical structures involving two possible scenarios: a) enhanced cortical excitability (as a normal developmental stage or result of a pathological process) is insufficiently modulated (inhibited) by brain stem structures or b) increased excitability in brain stem structures is inefficiently modulated (inhibited) by descending cortical regulation (due to structural cortical abnormalities or epileptiform activity or both) (Dulac et al., 1999;Lado and Moshe, 2002).

Several investigators found that the 1981 International Classification of Epileptic Seizures could not be sensibly applied for infantile seizures (Nordli, Jr. et al., 1997;Acharya et al., 1997;Nordli, Jr. et al., 2001). The main difficulty was the determination of altered consciousness in preverbal stage of development required to

categorise partial seizures under ‘simple’ or ‘complex’. Categories describing sensory motor manifestation cannot be applied in infants for the same reason. Although the division of focal seizures in ‘simple’ and ‘complex’ has been abandoned in more recent proposals of the task force, the nature of most seizure types is based on manifestations observed in older ages. Some investigators have proposed modified seizure type classifications for infantile seizures that are based solely on clinically observable manifestations (Nordli, Jr. et al., 1997;Hamer et al., 1999;Korff and Nordli, Jr., 2006).

Analysis of video telemetry data from hospital based cohorts of infants with medically refractory seizures has shown that the repertoire of clinical manifestations in infants is relatively small. The majority of seizures were categorised as spasms, (focal) clonic, (focal) tonic, or hypomotor / behavioural arrest with version) (Hamer et al., 1999;Korff and Nordli, Jr., 2006). Automatisms when observed were simple and consisted mainly of oroalimentary manifestations (sucking, chewing). Typical tonic clonic seizures were not observed in this age group. Epileptic spasms that are categorised under generalised seizures can present both clinically and electrographically with focal features.

Clinical features that help to discriminate between focal and generalised seizures in older children and adults, such as symmetrical or asymmetrical tonic posturing, head and eye version do not reliably predict a focal or generalised ictal EEG onset in infants (Dravet et al., 1989;Nordli, Jr. et al., 1997;Acharya et al., 1997;Hamer et al., 1999). Unilateral clonic and bilateral asymmetric clonic seizures are however commonly associated with focal electrographic findings (frequently involving contra

lateral central / rolandic areas). Other seizure types with predictable ictal EEG pattern included generalised spasms, e.g. symmetrical spasms that are not associated with focal seizures, generalised clonic and atonic seizures. Thus with few exceptions clinical observation alone may not be sufficient to classify a significant proportion of infantile seizures.

Korff and Nordli observed in their cohort of infants with medication resistant seizures (n=69, 1-24 months) that 98 % (94 of 96) of seizures were commonly short, lasting less than 5 minutes (Korff and Nordli, Jr., 2006). Two seizures were significantly longer: a generalised clonic-tonic- clonic seizure lasting for 25 minutes presented in a patient diagnosed with Dravet's syndrome and a seizure with behavioural arrest, eye deviation and focal hypotonia, that ceased after 15 minutes. When spasms were excluded the median duration was 49 seconds (range 0.02 - 25 minutes). They also identified trends in the relation between age and seizure manifestations. Generalised seizures other than epileptic spasms presented at a later age (median age 12.5 months) than focal seizures (median age 9 months). Generalised clonic and atonic seizures were recorded only in infants older than 7 months. Focal clonic seizures and behavioural arrest with version were observed early but not recorded in patients older than 18 months.

There is currently no population based information in the literature about the distribution of seizure types in infants. Limited data are available from hospital and specialist clinic based series of children with seizure onset in the first year of life. In early series infantile seizures were classified based on clinical features into large categories such as infantile spasms, status epilepticus, 'others – partial' or 'others

generalised' (Chevrie and Aicardi, 1978;Cavazzuti et al., 1984). Infantile spasms were the commonest seizure type seen in 47- 68% of infants, partial or secondarily generalised seizures in 12-14% and generalised seizures in up to 25% (Chevrie and Aicardi, 1978;Cavazzuti et al., 1984;Czochanska et al., 1994). Twelve to 17% of infants presented with status epilepticus. A different distribution was reported from a large retrospective hospital based series in Japan (n = 512) (Matsumoto et al., 1983a). Generalised motor seizures were more frequent (50.5%) compared to infantile spasms (31%). Eighteen percent of infants in this series presented partial, secondarily generalised or hemiconvulsive seizures. Bias towards more severe forms of epilepsy in some series based in a specialist setting as well as the previously discussed difficulties to classify infantile seizures with the exception of infantile spasms may contribute to these variations.

2.2.5 Aetiologies

A wide and heterogeneous spectrum of aetiologies is associated with seizure onset in the first year of life. The long list of conditions includes various types of developmental cortical malformations, chromosomal abnormalities, ion channel gene mutations, metabolic disorders, as well as pre-, peri- and post-natally acquired brain lesions (Kuzniecky and Barkovich, 2001;Nabbout et al., 2003;Weaving et al., 2004;Arzimanoglou et al., 2004b;Ferrari et al., 2005;Guerrini et al., 2007). Cortical malformations, especially if diffusely involving one or both hemispheres, are frequently associated with seizure onset in the neonatal period or early infancy (Vigevano, 1999).

The notion that infancy onset epilepsies are dominated by brain pathology has been derived form early hospital / specialist clinic based series of children with seizure onset in the first year of life. The proportion of infants that have symptomatic epilepsy or significant predisposing antecedent conditions (including developmental delay) is high and varies between 52 - 80% in these studies. Less than half (17-48%) of infants fall into the cryptogenic / idiopathic group, i.e. no underlying cause is identified and patients are developmentally as well as neurologically normal at the time of seizure onset (Chevrie and Aicardi, 1977;Matsumoto et al., 1983a;Cavazzuti et al., 1984;Czochanska et al., 1994;Battaglia et al., 1999;Altunbasak et al., 2007). The considerable variations in the observed proportions of symptomatic and non-symptomatic epilepsies may be related to differences of inclusion criteria (some studies included febrile seizures and children with a single seizure: (Matsumoto et al., 1983a;Cavazzuti et al., 1984) and the degree of bias in various settings.

The most significant aetiological categories are prenatal and perinatal aetiological factors (up to 40%), that include developmental brain abnormalities as well as acquired lesions through infection and/or hypoxia (Chevrie and Aicardi, 1977;Matsumoto et al., 1983a;Matsumoto et al., 1983c;Czochanska et al., 1994). Although the availability of neuroimaging methods was limited at the time the data for most studies were obtained, 13-19% of infants with developmental brain malformations, most commonly tuberous sclerosis, were identified (Chevrie and Aicardi, 1977;Czochanska et al., 1994;Battaglia et al., 1999). More detailed documentation of the various types of malformation is not available from these series. The proportion of children with structural brain lesions may be even higher as subtle cortical abnormalities would have escaped recognition.

Population based data are available from a single study that was conducted in Finland (Rantala and Ingalsuo, 1999). Cases were ascertained through the hospital discharge diagnoses and EEG database of the University of Oulu. This institution provides the only paediatric service in its catchment area. The investigators identified all children diagnosed with epilepsy (recurrent unprovoked seizures) under the age of 2 years, excluding neonates that were born between January 1, 1976 and December 31, 1986 (n=72). Thirty four infants (47%) were classified as cryptogenic/idiopathic and 37 (51%) as symptomatic. The latter group included 16 patients with progressive encephalopathies with unknown aetiology and normal CT and/or MRI. Brain anomalies identified in 11 (15%) and chromosomal abnormalities (6 cases, 8.3%) were the most common aetiologies in this cohort. This study supports the impression that the proportion of symptomatic epilepsies in infancy is high compared to childhood epilepsy cohorts that enrol infants *and* older children (up to the age of 16 years). Eighteen to 22% of children were classified with symptomatic epilepsies in two large childhood epilepsy cohorts of which one was community based (Berg et al., 1999c) and the other conducted in a multicenter hospital setting (Arts, 2003).

2.2.6 Role of neuroimaging and EEG in infancy onset epilepsies

2.2.6.1 Neuroimaging [magnetic resonance (MR) imaging]

MRI is unsurpassed as a technique for investigating brain structure in-vivo in humans. It is widely used to investigate the spectrum of acquired and developmental brain abnormalities that has been recognised in patients with epilepsy. Developmental lesions include malformations of cortical development (MCD) with uni-hemispheric focal, multifocal or diffuse bi-hemispheric distribution. MCDs have

been classified based on MR imaging features and histological appearances (of surgical / post mortem specimens) by relating these to various stages of brain development (Barkovich et al., 2005). The number of gene defects underlying specific types of MCDs is steadily increasing and based on this information the understanding of mechanisms involved in brain development (Kato and Dobyns, 2003;Guerrini et al., 2008). Advances in MR imaging technology have also been driven in part by the search for surgical targets to treat patients with medication resistant epilepsy. MR imaging has been recommended as the mode of neuroimaging of first choice in patients with epilepsy especially if seizures are resistant to medication (Commission on Neuroimaging of the International League Against Epilepsy, 1997;Commission on Neuroimaging of the International League Against Epilepsy, 1998).

As discussed previously (paragraph 2.2.5) data from infants with new onset epilepsy in hospital and specialist settings suggest a significant proportion of underlying brain abnormalities. Therefore MR imaging is an essential tool to guide further diagnostic work up (for example targeted metabolic and genetic investigations) and also therapeutic management (consideration of epilepsy surgery) in the group of children presenting to this setting. Identification of structural brain abnormalities would also permit investigation of their relationship to developmental impairment in this early onset group.

National guidelines in the United Kingdom (UK) and more recently published ILAE guidelines for paediatric patients with epilepsy recommend MR imaging early in the course of the disorder for certain subgroups of paediatric patients (National

Institute for Clinical Excellence, 2004;Gaillard et al., 2009). Both guidelines suggest MR imaging for children with focal epilepsies, those with generalised epilepsies that cannot be categorised under the defined idiopathic electro-clinical syndromes and young children under the age of 2 years (Gaillard et al., 2009). Although a number of studies report neuroimaging findings in children following a first epileptic seizure only a proportion of subjects enrolled underwent imaging often using brain Computer Tomography as there was limited access to MR technology (see also literature review by Gaillard et al (Gaillard et al., 2009)). As in the infancy age group there is a lack neuroimaging data from community based setting. One recently published study provides data from a large community based childhood epilepsy cohort. Berg et al reported positive MRI findings relevant to epilepsy in 82 (~ 16%) of 518 children with available MRI data enrolled in the Connecticut cohort (85% of the entire cohort, children with newly diagnosed epilepsy from 1 month to 16 years of age) (Berg et al., 2009). Significantly more children with non-idiopathic epilepsy syndromes had positive MR scans compared to cases diagnosed with one of the delineated idiopathic electro-clinical syndromes (22% vs. 3%) confirming that the classification was appropriate in the majority of cases. Not surprising in this context multiple logistic regression revealed a diagnosis of a non-idiopathic epilepsy syndrome and abnormal neurological examination as significant predictors of a positive MR scan. If the classification of cases into epilepsy syndromes that was based on clinical, EEG and MRI data according to the information given by the authors, was carried out prior to the above analysis a major bias would have been introduced.

Acquisition of high quality MR images is challenging in children especially in the infancy age group. Adequate sedation including general anaesthetic is required in infants and most children under the age of 7 years with associated safety risks and costs. Thus the above mentioned guidelines raise the question if there is a justification for early MR imaging of all infants with newly diagnosed epilepsy in a community setting.

2.2.6.2 EEG

The role of the EEG (standard waking record with activation procedures and/or sleep record) in childhood epilepsy management as stated in National guidelines (for England & Wales) is essentially to support (not to exclude) a diagnosis of epilepsy and to help to determine the type epilepsy (National Institute for Clinical Excellence, 2004;Berg et al., 2009). A number of studies investigating the course after the first convulsive seizure showed an increased risk of seizure recurrence with abnormal EEG recording, but demonstrated also seizure recurrence in a proportion of cases with normal EEG findings (Shinnar et al., 1996;Pohlmann-Eden and Newton, 2008). The international epilepsy classifications, as already discussed above, are based on epilepsy syndromes that have been defined by a combination of clinical features and typical EEG appearances (Arzimanoglou et al., 2004a). Although there are EEG patterns that are quite specific for certain syndromes e.g. hypsarrhythmia in West syndrome/infantile spasms, suppression burst in EIEE/EME, normal interictal EEG in benign infantile seizures, ictal EEG appearances of malignant migrating seizures in infancy other syndromes such as Dravet's syndrome (SMEI) can be

associated with a range of EEG features in various stages of the disorder (Dulac and Tuxhorn, 2005;Dulac, 2005;Aicardi and Ohtahara, 2005;Dravet et al., 2005b).

Interictal EEG appearances in developmental cortical lesions (MCDs) are generally non-specific. However, some patterns have been recognised that may provide 'diagnostic clues' to further pursue magnetic resonance imaging. High amplitude rhythmic fast activity, for example, can be seen in recordings of infants and young children with diffuse bilateral malformations (Lissencephaly) (Dalla et al., 1996). With hemispheric lesions this pattern may be lateralised or localised (Dalla et al., 1996). Localised or focal cortical abnormalities, however, appear to be associated with more heterogeneous EEG appearances that can change over time from initially normal recordings with later evolution of abnormalities, or initially localised changes that become generalised (Guerrini et al., 1992;Raymond et al., 1995). Interictal patterns seen on scalp EEG recordings of variable proportions of children and adults with focal or lateralised cortical lesions (mostly patients undergoing pre-surgical evaluation and/or epilepsy surgery) include rhythmic (fast), repetitive or continuous epileptiform discharges and localised slow activity (Raymond et al., 1995;Gambardella et al., 1996). In infants with focal cortical dysplasia the initial EEG appearances are even more variable and include focal discharges, hypsarrhythmia and burst suppression pattern (Lortie et al., 2002). Variations of the typically described interictal and ictal EEG patterns are commonly observed in infantile spasms /West syndrome with underlying cortical abnormalities (Fusco and Vigevano, 1993;Dulac and Tuxhorn, 2005). Such EEG appearances include presence of focal discharges during clusters of spasms, fast activity seen concomitantly with spasms, or variant forms of hypsarrhythmia especially with marked asymmetry

(hemi-hypsarrhythmia) (Dulac et al., 1999;Kobayashi et al., 2004;Dalla et al., 2007). Specialised functional imaging techniques including ictal single photon computer tomography (SPECT) and [18] fluoro deoxyglucose positron emission tomography (FDG-PET) may be considered when conventional MR images fails to detect a lesion, that may be a target for epilepsy surgery (Chugani et al., 1990;Hwang et al., 1996;Mori et al., 2007;Kakisaka et al., 2009).

The role of the EEG for prediction of outcome in infancy onset epilepsy has been investigated in several hospital/specialist setting based studies. Cavazzuti et al report a significant correlation between epileptiform interictal EEG and poor seizure as well as developmental outcome in a large cohort of infants (n=482) presenting with convulsive seizures (including febrile and acute symptomatic seizures) in the first year of life (Cavazzuti et al., 1984). Similar findings have been reported by Datta and Wirrel from a smaller infancy cohort (n=40) that included unprovoked and acute symptomatic seizures with the exception of febrile convulsions (Datta and Wirrell, 2000). In a subgroup of infants presenting with focal seizures abnormalities on the initial EEG (abnormal background activities and/or epileptiform discharges) were also correlated with poor developmental and seizure outcome at 5 year follow up (Okumura et al., 2001). The three mentioned studies investigated the impact of several factors on outcome in separate analyses and none applied multivariate regression statistics. Multivariate logistic regression analysis was applied in one already quoted study investigating children diagnosed with epilepsy under the age of 2 years in a hospital setting (n=75) (Altunbasak et al., 2007). The authors examined the impact of various clinical factors including EEG in 3 separate multivariate models on a) neurological abnormality at last visit, b) developmental retardation and

c) 1 year - seizure free outcome at follow up. Epileptiform activity on EEG was a significant factor together with use of > 1 antiepileptic drug in only one model that predicted neurological abnormality at last clinic visit. Overlapping effects between the factor 'epileptic activity on EEG' and other factors as well as the number of factors included into the models with a relative small sample size are possible explanations for this result.

Several studies have looked at the relationship between the profound interictal EEG abnormalities seen in infantile spasms/West syndrome and developmental outcome. Kramer et al could not demonstrate a relationship between the various patterns of hypsarrhythmia to developmental outcome (Kramer et al., 1997). The same authors applied a hypsarrhythmia scoring system that quantified the degree of pre-treatment EEG abnormality of various characteristics such as disorganisation, amount of slow activity, amplitude and frequency of discharges. The correlation between higher hypsarrhythmia scores and worse developmental outcome was statistically significant. However, the developmental function of subjects with a particular hypsarrhythmia score showed wide variation from mild to profound developmental impairment suggesting impact of other confounding factors including aetiology, treatment lag and response to treatment. Persistence of hypsarrhythmia beyond 3 weeks, correlated in a logistic regression model with worse developmental outcome in another study (n=48, 38% cryptogenic infantile spasms) (Rener-Primec et al., 2006). As discussed by the authors persistence of hypsarrhythmia may be a marker for treatment resistance associated with worse brain pathology or the result of a longer treatment lag.

Recurrence of hypsarrhythmia between consecutive spasms within a cluster was initially reported to be associated with more favourable outcome (Fusco and Vigevano, 1993;Dulac et al., 1993). This was subsequently not confirmed by other groups (Haga et al., 1995;Gaily et al., 2001).

Information provided by the EEG is rarely diagnostically specific and interpretation requires consideration of the clinical context as well as results of other investigations. The EEG (especially video EEG) contributes to diagnosis of seizure types and epilepsy syndromes. In addition EEG appearances can also influence decisions on further diagnostic work up. Lateralised or focal ictal or interictal eletrographical features, for example, may give rise to consideration of more specialised neuroimaging techniques (such as FDG -PET scans, ictal SPECT scan) especially when 'standard' MR imaging does not demonstrate a lesion.

EEG appearances may also have a role in the prediction of outcome in infancy onset epilepsy although current data are sparse and in the majority originate from specialist settings.

2.2.7 Outcome

Several studies published in the last thirty years, report the outcome of children presenting with recurrent seizures in the first 12 and 24 months of life (Chevrie and Aicardi, 1978;Chevrie and Aicardi, 1979;Matsumoto et al., 1983c;Cavazzuti et al., 1984;Czochanska et al., 1994;Battaglia et al., 1999;Rantala and Ingalsuo, 1999;Altunbasak et al., 2007). The majority of patients have been followed up for more than 3 years in most series. Several are retrospective and most studies with the exception of one (Rantala and Ingalsuo, 1999) are hospital and specialist clinic based. There are limitations to the comparability of outcome data between studies as

inclusion criteria vary (single or recurrent seizures) and some investigators enrol also infants presenting with acute symptomatic and febrile seizures (Cavazzuti et al., 1984). Several authors state that they include all children that were diagnosed with epilepsy in the first 12 or 24 months of life without detailing the criteria that constitute such a diagnosis (Czochanska et al., 1994;Altunbasak et al., 2007). In the following paragraphs the outcome data reported in these studies are summarized under 3 different aspects: epilepsy, morbidity/mortality and neurodevelopment.

2.2.7.1 Epilepsy

The first data relating to the seizure outcome of infancy onset epilepsy were published by Chevrie and Aicardi in the late 1970's (Chevrie and Aicardi, 1979). They reported outcomes of a large hospital based retrospective cohort of children with seizure onset between 1 and 12 months of age (n=293). The median follow up period was 3 years and 6 months (range 1- 24 years). The cumulative percentage of children with persistent seizures was 70% at 2 years and 56% at 6 years following the first seizure. Persisting seizures were significantly more common in children with symptomatic aetiologies, infants presenting with status epilepticus or partial seizures compared to generalised seizures and infantile spasms. Epilepsy was less common in infants with normal developmental and neurological status at follow up. Matsumoto et al documented a slightly better seizure outcome from their retrospective hospital based infancy onset epilepsy cohort (n=251) (Matsumoto et al., 1983c). At follow up, at age 6 years and older (average age 144 months), 56% were seizure free for more than 3 years. Seizure outcome in the subgroups with symptomatic aetiology (cumulative percentage of patients > 3 years seizure free at 6 years: < 30%), infantile spasms (33% > 3 years seizure free) or secondarily generalised seizures (34% seizure free > 3 years) was worse compared to infants presenting with cryptogenic aetiology

(cumulative percentage of patients > 3 years seizure free at 6 years: > 60%), initially generalised motor seizures other than spasms (81% seizure free for > 3 years at follow up) or partial seizures (57% seizure free).

Other studies of hospital/specialist clinic based infancy cohorts showed similar proportions of children that had persisting seizures (44-47%) or were seizure free (53-56%) at follow-up. Minimum time periods without seizures necessary to classify a case as seizure free were either not further specified or relative short, defined as 6 or 12 months (Czochanska et al., 1994;Battaglia et al., 1999;Altunbasak et al., 2007).

In comparison with data from *childhood epilepsy cohorts* (composed of infants *and* older children up to the age of 16 years) the seizure outcome of infants with epilepsy presenting to hospital / specialist settings is worse. Sixty four percent of children with epilepsy onset between 1 month and 16 years enrolled in the Dutch study of childhood epilepsy (multicentre hospital based) were more than 2 years seizure free at five year follow-up (Arts et al., 2004). This proportion remains relatively stable after long term follow up over several decades according to data from a Finnish cohort with 64-67% of patients with childhood onset epilepsy (under the age of 15 years) reported to be in seizure remission (> 5 years) on or off antiepileptic medication (Sillanpaa et al., 1998;Sillanpaa and Schmidt, 2006).

Seizure outcome in population based infancy epilepsy cohorts may be better as suggested by findings of Rantala et al (Rantala and Ingalsuo, 1999). The already above mentioned retrospective population based study of infants with seizure onset in the first two years of life documented seizure remission for a mean period of 13

years (antiepileptic medication was withdrawn after 2 years being seizure free) in 60% (37/65) of children. However, the majority of the infants who became seizure free had cryptogenic epilepsy (32 of 37) apart from five with symptomatic aetiology.

2.2.7.2 Morbidity and Mortality

A significant proportion of children varying between 31 and 67% have neurological abnormalities on long-term follow-up(Chevrie and Aicardi, 1978;Matsumoto et al., 1983c;Czochanska et al., 1994;Datta and Wirrell, 2000;Altunbasak et al., 2007). This proportion was slightly lower in the series reported by Matsumoto et al (80/304, 26%) that also includes infants presenting with febrile seizures (Matsumoto et al., 1983c). Not surprisingly neurological abnormalities were more common in infants with symptomatic aetiology which is reflecting brain pathology (Chevrie and Aicardi, 1978;Matsumoto et al., 1983a;Datta and Wirrell, 2000). In the early studies presence of neurological abnormality at presentation was however used to categorize cases as symptomatic, creating a circular argument.

Seizure type at presentation and age at onset may also be relevant factors. Chevrie and Aicardi observed a higher proportion of children with gross neurological abnormalities (defined as presence of hemiplegia, bilateral pyramidal signs, pseudobulbar syndrome, major hypotonia) at follow up in the subgroups with status epilepticus (43%) and partial seizures (45%) compared with infantile spasms (27%) or generalised seizures (27%) (Chevrie and Aicardi, 1978). Nearly twice as many children that were less than 6 months old at seizure onset (38%) compared with infants older than 6 months presenting with seizures had neurological impairment at follow up (20%). This could be interpreted in two ways: a) certain brain

abnormalities associated with neurological impairment manifest with earlier seizure onset or b) early seizures especially if prolonged (status epilepticus) may result in brain injuries with subsequent neurological impairment.

Mortality of infants presenting with seizures / epilepsy in the first 12 or 24 months of life ranged from 4 -12% (Chevrie and Aicardi, 1978;Cavazzuti et al., 1984;Czochanska et al., 1994;Battaglia et al., 1999;Rantala and Ingalsuo, 1999). Causes were specified in 3 series (Matsumoto et al., 1983c;Czochanska et al., 1994;Rantala and Ingalsuo, 1999). Infection was the commonest cause. Most of the deaths in the series followed by Czochanska et al (15 of 133) occurred in children with neurological impairment (Czochanska et al., 1994). A relationship with status epilepticus was observed by Matsumoto et al in 11of 45 deaths (24%) and 1 of 6 deaths by Rantala et al (Matsumoto et al., 1983c), (Rantala and Ingalsuo, 1999). In the large retrospective cohort described by Chevrie and Aicardi mortality was higher in the subgroups of infants with symptomatic epilepsy, early seizure onset (< 6 months), status epilepticus or partial seizures (Chevrie and Aicardi, 1978).

Although the proportion of deaths in childhood epilepsy cohorts is smaller (1.9 - 3.7%) similar factors are associated with increased mortality (Callenbach et al., 2001;Camfield et al., 2002;Berg et al., 2004b). Most deaths occurred in neurologically abnormal children and were rarely attributable to seizures themselves. Conducting chi squared tests for bivariate analyses Berg et al found in their community based cohort that aetiology, epilepsy syndrome diagnosis (epileptic encephalopathy versus all other syndrome diagnoses combined), seizure control and seizure onset under 2 years were significantly associated with mortality (Berg et al.,

2004b). In a multivariable Cox proportional hazards model only symptomatic aetiology and epileptic encephalopathy syndromes were independently associated with mortality. These factors however overlap. Of the 13 deaths reported from the Connecticut childhood epilepsy cohort by Berg et al. 10 children were diagnosed with an epileptic encephalopathy syndrome (the majority with Lennox-Gastaut syndrome, one West syndrome, one Othahara syndrome and one SMEI). Nine of these cases had a symptomatic aetiology (structural brain abnormality or metabolic disorders). These findings merely confirm that death in childhood epilepsy is mostly confined to children diagnosed with severe types of epilepsy, commonly with onset in early age and with serious underlying disorders.

2.2.7.3 Neurodevelopmental status

The proportion of children with normal developmental outcome following epilepsy onset in the first year of life varied between 21 and 38 % in early hospital based retrospective studies (Chevrie and Aicardi, 1978;Matsumoto et al., 1983c). Differences in the composition of these infancy epilepsy cohorts and possible under-reporting of developmental impairments because standardised neurodevelopmental assessment tools were not applied (the developmental status was classified under gross categories, such as “normal” versus “severe retardation”) may explain this variability. Significant factors that related to poor outcome included early seizure onset (< 6 months), pre or peri-natal abnormalities, seizure type (infantile spasms, partial and secondarily generalised seizures) and symptomatic aetiology. There was a subgroup of children with better seizure and developmental outcome. These infants presented with generalised seizures, cryptogenic or unknown aetiology and had more commonly a family history of febrile or afebrile seizures suggesting aetiological

relevance of genetic factors (Chevrie and Aicardi, 1979). Later publications delineating benign familial and non familial infantile seizures focused on this subgroup in detail (Vigevano et al., 1992;Watanabe and Okumura, 2000).

Standardised assessment tools, such as Brunet-Lezine scales for infants/young children, Terman –Merill scales, Stanford Binet and Wechsler Intelligence Scales for Children were applied in more recently published specialist setting based prospective infancy epilepsy cohorts (Czochanska et al., 1994;Battaglia et al., 1999;Altunbasak et al., 2007). The primary outcome measure in these papers was full scale IQ and further details are often not provided. Thirty three to 42% of children had IQ's in normal or borderline range (IQ > 70 or 75) and a significant proportion (46 - 48%) had profound cognitive impairment on follow up (IQ's < 50). In keeping with the observations made in the initial studies symptomatic aetiology, early seizure onset (<6 months) and early abnormal development were related to poor outcome (Battaglia et al., 1999). Altunbasak et al found significant risk ratios for "developmental retardation" at the last follow up for the following factors: mental retardation at initial presentation, abnormal neurology, initial infantile spasms, use of > 1 anti-epileptic drug, history of neonatal seizures, symptomatic aetiology and perinatal anoxia. It is very likely that several of these factors are correlated. Therefore in a multivariate logistic regression analysis only two factors: 'abnormal neurology' and 'use of > 1 antiepileptic medication' were significant and independently associated with developmental impairment (Altunbasak et al., 2007).

These data originating from hospital and specialist based settings indicate that up to two thirds of children with epilepsy onset in the first 12-24 months of life have significant developmental impairment on follow up. Because of the bias associated

with the setting this observation may not be applicable to community and population based settings. Only 26.4% of children enrolled in the Connecticut community based childhood epilepsy cohort (epilepsy onset 1 month to 15 years) had some degree of global cognitive impairment, defined as IQ< 80, on follow up (Berg et al., 2008a). In this cohort, however, younger age at epilepsy onset (< 5years) was significantly and independently associated with a risk of global cognitive impairment. This would further support the notion that children with very early onset epilepsy are at high risk for developmental/cognitive impairment. It remains uncertain if seizure activity itself has a causal role or whether the impairments are a manifestation of the underlying brain disorder.

2.3 Conclusions and Research questions

- **Frequency of epilepsy with onset under the age of two years:**

  The fact that the incidence of childhood epilepsy peaks in the first year of life has been well documented and replicated in several studies as outlined in section 2.2.2.. Incidence estimates for the first year of life however show great variability. Factors that may be accountable include differences in study design (ascertainment methods), case definitions and populations in various geographical areas. Although children under the age of two are regarded as a separate vulnerable group amongst children with epilepsy there is a lack of data pertaining to the frequency of epilepsy onset in this age group.

- **Classification of epilepsy syndromes in the first 2 years of life:**

  As reviewed in section 2.1.3 the majority of children with epilepsy can be classified using the 1989 ILAE ICE. However at least a third of children

cannot be classified or fall into unspecific categories, that provide little information. Few data are available with respect to the usefulness of the 2001 diagnostic scheme. The distribution of epilepsy syndromes in the first 2 years of life in a population based setting is poorly documented in the literature as discussed in section 2.2.3. Available data give the impression that specific syndromes apart from West syndrome /infantile spasms are rare. This includes electro-clinical syndromes with good outcome. 'Benign infantile seizures', however, have only been included in the syndrome list in the 2001 ILAE proposal and may have therefore not been identified in population or community based studies using the 1989 ICE. Less severe types of epilepsy are likely to be under-represented in the discussed mostly hospital based infancy epilepsy series. There is also a suggestion that a significant proportion of children with epilepsy onset under the age of 2 years, especially when the aetiology is unknown, cannot be classified in a meaningful way using the international epilepsy syndrome classification systems that were recognised at the time this study was carried out (Sarisjulis et al., 2000). This raises the question how useful the syndromic classification suggested in the 2001 ILAE proposal is in the population of children with newly onset epilepsy under the age of 2 years at initial presentation and if diagnoses are stable after a time interval.

- **Outcome:**

  Review of the published in the majority hospital and specialist clinic based series of children with epilepsy onset in the first 12 or 24 months of life (section 2.2.7) supports the view that patients in this age group are at high

risk of poor outcome . Symptomatic aetiologies (especially structural brain abnormalities) are more common, chances of seizure remission are smaller, and mortality is higher in this age group compared to later childhood-onset epilepsies. A significant proportion of children have motor impairment and the majority have long-term neurodevelopmental and cognitive deficits. The series do however also implicate a subgroup of children that have better seizure and developmental outcome. This group may be under represented in the hospital and specialist setting. Thus the published outcome data may not truly be representative of the general population.

- **Neuroimaging and structural brain abnormalities:**

  At the time the data for some of the infancy epilepsy onset series have been obtained, available neuroimaging techniques were limited and thus subtle structural brain abnormalities especially may have been incompletely documented. Considering the wide spectrum of presentations and outcomes in this age group population based information on spectrum of structural brain abnormalities and the relation to seizure as well as neurodevelopmental outcomes is important. Information regarding the yield of neuroimaging (MR imaging) as currently applied in clinical practice in a population based setting may contribute to justification of local and national guidelines.

- **Role of EEG:**

  The EEG as reviewed in section 2.2.6.2 contributes to diagnosis and classification of epilepsy types in the infancy age group. The information on its role in prediction of developmental function at presentation and follow up

in a population based setting is very limited.

Based on the above points the following research questions were proposed for this study:

1. What is the incidence of new onset epilepsy in children aged between 4 weeks and 2 years?

2. What proportion of children with epilepsy onset under age of two years in a population based setting can be categorised using the diagnostic scheme, in particular seizure types and syndrome list, as suggested in the 2001 ILAE proposal at diagnosis (Engel, Jr., 2001) ?
   Is there consistency between raters?
   Are diagnoses reliable over time (reclassification after 12 months with additional information)
   What is the distribution of seizure types and syndromes in this population based cohort?

3. Which aetiologies and structural brain abnormalities can be identified in this cohort?

4. What are the predictors of the neurodevelopmental status close to diagnosis?

5. What are the predictors of longitudinal changes of the neurodevelopmental status at 12 months follow up?

2.4 Epilepsy in Infancy study: A population based collaborative study on epilepsies with onset under the age of 2 years in North London

In order to address research question 1, a defined population was required in which the occurrence rate of epilepsy in children under the age of 2 years could be estimated. Further descriptive information of such an incidence cohort was needed to address questions 2 to 5. Therefore a study was designed to combine population survey and cohort observation. The surveyed infancy population was defined according to the place of residence in a defined geographical area. Ascertainment and data collection methods were set up as described in the following chapter. The cases were intercepted and recruited into an observational cohort for evaluation as outlined below to address research questions 4 and 5. By combining surveillance and cohort observation cases could be recruited from a population/community setting with the aim to minimize referral bias.

3 CHAPTER 3: METHODS

3.1 Population survey

In the UK it is common and good medical practice that children presenting with seizures or new onset epilepsy to primary care physicians and accident & emergency units are referred to a paediatrician. The National Institute for Health and Clinical Excellence (NICE), an independent organisation in the UK responsible for providing national guidance on the promotion of good health, has also identified this practice as key priority for implementation: “All children with a recent-onset or suspected seizure should be seen urgently by a specialist (defined as a paediatrician with training and expertise in the epilepsies)” (National Institute for Clinical Excellence, 2004). Thus the candidate assumed that all children under the age of 2 years with new onset epilepsy would be seen by a paediatrician soon after initial diagnosis and decided to conduct a survey involving consultant paediatricians and paediatric junior doctors but not general practitioners.

The British Paediatric Surveillance Unit (BPSU, a collaboration between the Royal College of Paediatrics and Child Health, UCL-Institute of Child Health, Health Protection Agency, Health Protection Scotland and the Faculty of Paediatrics of the Royal College of Physicians of Ireland) has established a postal reporting system through consultant paediatricians in order to survey rare childhood conditions on national level. Epilepsy however is the commonest chronic neurological condition in childhood and the frequency is expected to be especially high in the first year of life. Thus, conducting the population survey for this study through the BPSU on national level would have been inappropriate.

A surveillance study in a geographically defined area of North London was set up considering the following practical aspects:

i. the area is densely populated (see section 3.1.1)
ii. the North Central London Epilepsy Network (see section 3.1.2) could be used as a forum to promote the survey
iii. a surveillance study investigating childhood status epilepticus has been previously conducted in the same geographical area of North London and the established referral network of collaborating hospitals as well as notification systems could be adapted for this study (Chin et al., 2005;Chin, 2005).

3.1.1 Geographical area in North London and target population

The target population was defined as residents in the geographical area outlined in Figure 3.1. This area consisted of 15 boroughs of North London. Residents were identified by the postal code of their home address during the period of ascertainment.

Authoritative data about the residential population are based on the Census that is conducted every 10 years in the UK. The last Census took place in April 2001. Information on accommodation, relationship, demographic characteristics (e.g. sex, age, and marital status), cultural characteristics, health and provision of care, qualifications and employment were obtained from every household. These data are updated by the Office for National Statistics (ONS) annually in order to produce "mid-year population estimates" for the years in between the Censuses. Mid-year estimates are made with reference to the residents on the 30th June with

the population on 30th June of the previous year as starting point. The cohort component method is used whereby the previous mid-year population is aged-on by one year and the population change is estimated by accounting for the births and deaths in the previous 12 months as well as migration to and from the area. Further adjustments are made for mobile groups that are not captured by the migration estimates. Plausibility checks of these estimates are carried out including calculation of demographic rates and ratios (National Statistics, 2004;Jefferies and Fulton, 2005).

According to the mid - 2006 estimates 3,218,810 residents live in the defined geographical area of North London. Of these 609,287 (19%) are children (under the age of 16 years) and 98,090 (3 %) are under the age of 2 years (Office for National Statistics, 2008). Compared to the 2001 census data the population has increased (see appendix 1: Resident population of surveyed geographical area in North London). This can be in part be explained by increased immigration numbers over recent years. Figures published by the National Office for Statistics based on several sources (International Passenger Survey, Labour Force Survey) demonstrated that London has the highest immigration figures compared to other destinations within the UK. Twenty nine percent of immigrants state their intend to be resident in London (The National Office for Statistics, 2008).
Table 3.1 lists the population density by borough in the target geographical area. The highest childhood population density is in Hackney and the lowest in the City of London.

As a large metropolitan population the composition of ethic groups is different in North London compared to England and Wales (see also appendix 2 for distribution of ethnic groups in childhood population 0-15 years in North London and England and Wales).

Figure 3.1: Surveyed geographical area in North London

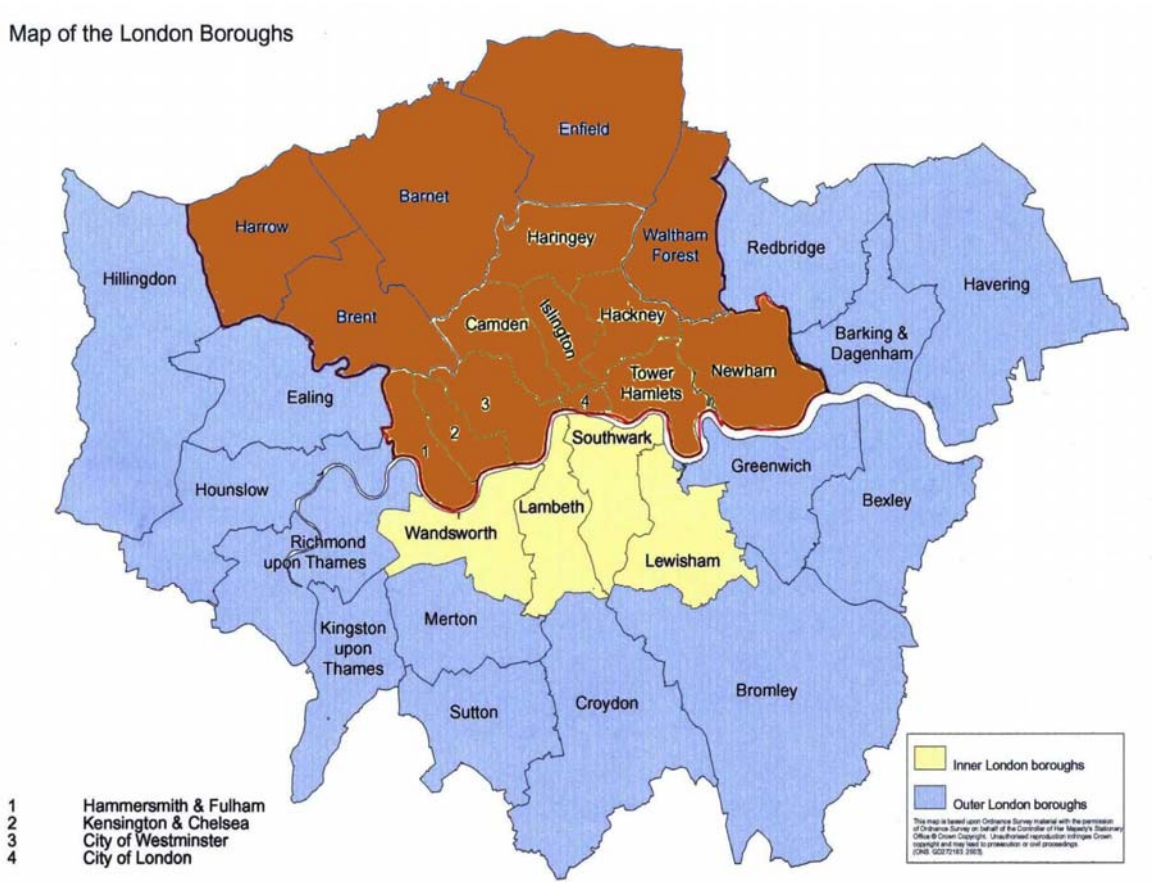


Table 3.1: Population density in the surveyed geographical are of North London (based on Mid -2006 population estimates, Population Estimates Unit, Office For National Statistics)

BOROUGHS	Childhood Population <= 2 years	Land Area (km)	Population density children <=2 years per sq km	Density children aged < 16 years per sq km
CITY OF LONDON	104	3	36	254
BARNET	9,357	87	108	812
BRENT	8,514	43	197	1,245
CAMDEN	5,668	22	260	1,716
ENFIELD	8,748	81	109	782
HACKNEY	8,171	19	429	2,555
HAMMERSMITH & FULHAM	4,822	16	294	1,763
HARINGEY	7,460	30	252	1,564
HARROW	5,758	50	114	891
ISLINGTON	4,937	15	332	2,151
KENSINGTON & CHELSEA	4,149	12	342	2,368
NEWHAM	10,050	36	277	1,717
TOWER HAMLETS	7,427	20	376	2,355
WALTHAM FOREST	7,755	39	200	1,273
WESTMINSTER	5,141	21	239	1,469

3.1.2 The North Central London Epilepsy Network

The North Central London Epilepsy Network, established in 2003, represents a partnership of paediatricians, paediatric neurologists and other health professionals involved in the management of children with epilepsy that work together across organisational boundaries. The aim is to create better integrated services for children with epilepsy in North London, this includes sharing of resources (information for patients, families, teachers etc.), training, regional guidelines, audit and research. Although the network has been primarily established with health professionals caring

for the population in North Central London (Enfield, Barnet, Islington, Haringey, Camden) the network meetings, held 3 monthly are also attended by consultant paediatricians from other hospital / primary care trusts in North East and North West London (that do not have their own epilepsy networks). Members of the network were approached to support and collaborate with the survey. The study was promoted on network meetings and the members were provided with updates about the progress.

3.1.3 Ascertainment

3.1.3.1 Notification systems

Identifying cases through a single source may result in under-ascertainment or bias. Thus, a multi-tiered notification system that was successfully applied in a prospective paediatric study on convulsive status epilepticus conducted in the same geographical area of North London (North London Status Epilepticus in Childhood Surveillance Study, NLSTEPSS) was adopted (Chin et al., 2005). This combined passive method (24 hour telephone line) and active notification methods (regional BPSU like regional postal survey). As outlined by Chin re-call bias may occur, because responders are asked at the end of each month to report cases in the preceding month; under-ascertainment and delayed notification of cases are additional weaknesses of the postal survey (Chin, 2005). Chin also discusses strategies that have been identified to increase the response to postal surveys which include design of a short questionnaire, first class outward mailing and postal follow up (reminder) that includes a questionnaire (Chin, 2005).

The regional BPSU like postal survey and the telephone system used in NLSTEPSS have been adapted for this study in such a way that cases could be either notified

anonymously and anonymised information was obtained subsequently or registered with name as well as contact details after consent of the patient's parents / carers was obtained to be contacted by the researcher. The latter was necessary in order to intercept cases and enrol these in the observational cohort:

Telephone hotline:

A telephone line was set up to notify cases at the time these were seen. This notification method was similar to that used in NLSTEPSS and was primarily directed to paediatric junior medical staff and nursing staff involved in the care of patients with epilepsy. Messages could be left 24 hours by using an automated system that requested the following information: contact details of the caller, patient's initials, date of birth, postal code or name, address or patient's name as well as contact details when consent of the parents/carers to be contacted subsequently by the research team was obtained. The system was checked for messages daily during the working week. The telephone number was displayed on posters and in hospital wards, outpatients and admission units of collaborating hospitals. In addition "study promotion cards" in business-card format displaying telephone number and "Epilepsy in Infancy Study" website address were distributed to paediatric junior and consultant staff.

Monthly postal survey:

A regional postal survey was directed to hospital and community based consultant paediatricians that provide services to the residents in the surveyed geographical area. Case notification forms and self addressed envelopes were sent out by first class mail at the end of each month during the ascertainment period. The forms were

designed in a way to achieve optimal response on a single A4 page, orange coloured paper (see appendix 3). Simply by ticking a box the recipient could indicate 'No cases seen' in the previous month. Cases were notified on the form either by giving identifiers (patient's initials, date of birth, postal code) or name, contact number and address with consent of the parents/carers that were informed about the study by the paediatrician. Reminder letters were sent out if a response was not received within 4-6 weeks.

A list of all consultant paediatricians regardless of subspecialty was generated by contacting all hospital paediatric departments and community services in the surveyed area. The information obtained was compared to the list of paediatricians published annually in the handbook of the Royal College of Paediatrics and Child Health. From Great Ormond Hospital for Children (GOSH) only Paediatric Neurologists were included in the mailing list. It is practice at GOSH that provides highly specialised tertiary and quaternary paediatric services to refer all patients with newly diagnosed epilepsy to the paediatric neurology team. In addition the care for the patients admitted to GOSH is usually shared with a consultant paediatrician based in the local hospital. The latter would have been included in the postal survey. Similar to the BPSU system a list of positive responders was generated. Posting of monthly questionnaires was omitted for consultant paediatricians with subspecialisation in a field, in which they were unlikely to be involved in the primary management of infants with newly presenting epilepsy (such as paediatric endocrinologists, paediatric haematologists) either on their own request or if they failed to return questionnaires for more than 3 months, despite of reminders. These subspecialty paediatricians were informed in a letter that they were excluded from

the monthly mailing list and unless they inform the researcher otherwise the researcher assumed their agreement to notify any cases meeting including criteria for the study.

Consultant paediatric neonatologists of one hospital department (Homerton Hospital) requested to be excluded from the postal survey stating that all eligible patients would be referred to consultant paediatricians in their department or paediatric neurologists. During the 13 months ascertainment period the mailing list was updated according to information sent to the researcher with return of notification forms and also when in contact with paediatric departments in the surveyed area whilst promoting the study or collecting data.

Other sources:

A number of cases were directly notified to the candidate, who was based at UCL-Institute of Child Health /Great Ormond Street Hospital by paediatric neurology team members, through telephone calls (not using the study phone number) or by electronic-mail. This was especially the case for infants that were referred by the general paediatricians directly to the 'Rapid Neurology Assessment Unit' based at Great Ormond Street Hospital. Medical and nursing staff notified the researcher directly (verbally or by e-mail) about such cases. As in the methodology described by Chin these cases were considered as passive notifications and categorised as being identified by “Telephone” (Chin, 2005).

3.1.4 Case definition and ascertainment period

Inclusion criteria:

Infants and young children who met the following criteria were eligible for enrolment:

- Age between 4 weeks and 24 months
- newly diagnosed epilepsy, history of 2 or more unprovoked seizures
- seizure onset in the first 4 weeks of life but continuing beyond this age

Exclusion criteria:

Patients with seizures provoked by acute conditions such as fever, infections, trauma, electrolyte disturbances, transient metabolic or endocrine disorders as well as neonates with seizures that did not recur after 28 days of age were excluded.

Cases were ascertained over 13 months (1st September 2005 until 1st October 2006).

3.1.5 Promotion of the study

Information about the plan to conduct the survey was posted 3 months prior to the start of the ascertainment period to all hospital and community based paediatricians providing services to the target population. This information letter contained a reply section for the recipient to request further information about the planned study (a telephone call or visit from the researcher to the paediatric department). In each participating hospital a consultant paediatrician agreed to be the local collaborator for this study. The collaborators took local Research & Development responsibility, helped to promote the study in their departments and also served as a link to the

research team.

The researcher presented the study at departmental meetings in participating hospitals that were attended by consultant and junior staff. Information sheets for paediatricians and parents were distributed on these occasions. In addition the study was also presented on regional RCPCH study days and the regional monthly neurodisability training meetings. The latter were attended by community paediatricians.

The study was also promoted through posters that were displayed in the paediatric wards, A&E units and outpatient departments of collaborating hospitals.

A website (www.epilepsyininfancy.ich.ucl.ac.uk) provided information about the study, and also had links to download information leaflets for parents and medical staff. The website address and study telephone number were displayed on promotion cards in business card format that were distributed to consultant and junior medical staff.

Newsletters providing updates and information about progress of the study were posted approximately 6 monthly during the 13 months ascertainment period to consultant paediatricians in order to maintain awareness (see Appendix 4: Newsletters).

3.1.6 Data collection

Data were collected using a standard epilepsy history proforma, which was generated with input of the local collaborators in the participating hospitals (see Appendix 5: Standard History Proforma). Epilepsy history proformas that where in clinical use at

the time (Great Ormond Street Hospital, Nottingham University Hospital) served as model for the initial draft. The following information was requested: seizure history (age at onset, description of manifestations of first, subsequent and current seizures, frequency), details of antiepileptic medication, birth and neonatal complications, other medical or genetic diagnoses, family history, information about previous and current developmental progress, ethnic background, investigations results.

The proforma was designed for prospective completion at the time a patient with suspected epilepsy was seen (e.g. in outpatients or admission units) and could be filed as part of the hospital notes. Tick boxes were included wherever possible in order to make completion easier. The section requesting information about the developmental progress for example included milestones based on the Denver screening questionnaire, with answers to be circled as appropriate ("yes", "no", "don't know").

The epilepsy history proforma was distributed in all participating hospitals and could also be downloaded from the "Epilepsy in Infancy Study" website. Anonymised copies of the epilepsy history proforma (identifiers: patient's initial's, date of birth, first part of postal code of home address) were requested with the notification of a case by the researcher. When the proforma was not available anonymised clinical documents including clinic letters, discharge summaries and investigation reports were obtained.

3.1.7 Case verification

The clinical information obtained was reviewed by two paediatric neurologists independently. Cases were enrolled if both assessors agreed that inclusion criteria

were met. Where disagreement occurred cases were discussed and consensus obtained.

3.1.8 Two Source capture-recapture method

The capture-recapture methodology has been originally developed in wildlife research for the estimation of the size of animal populations. Animals are captured, tagged, released and recaptured again. The population size is estimated from information provided by multiple overlapping samples (e.g. the proportion of recaptured animals identified by their tags) (International Working Group for Disease Monitoring and Forecasting, 1995b).

In human epidemiology and disease monitoring samples are represented by information from multiple *incomplete* sources (lists / registries of cases). Typically cases are 'recaptured' by matching unique identifiers of cases on several lists. Capture-recapture methods have been increasingly applied in disease surveillance over the past 60 years. Because information from incomplete registries is combined, such methods can be more cost effective. More importantly they provide a means to assess completeness of ascertainment. However application of capture-recapture methods requires some caution as assumptions are being made for estimates to be valid (International Working Group for Disease Monitoring and Forecasting, 1995a;Chao et al., 2001). This is especially the case for the simplest model using only two sources of information:

a) There should be no change of the population through migration or loss of cases during the study period ('closed' population). An assumption that is difficult to meet in practice for human as well as some wildlife studies.

b) Unique identifiers are required to match individuals on each list. The accuracy, with which cases are correctly diagnosed and enrolled, should be the same for each list.

c) Each individual should have the same chance to be 'caught' on each list (homogeneity). Severity of the condition, age or geographical location (for example case resident at boundaries of the surveyed area) may influence whether cases are registered.

d) Both sources are independent, e.g. enrolment in list A should not make it more likely to be included in list B. For example if cases are notified by the same specialised clinician to a register, who also requests specific investigations (if surveillance of laboratories, EEG or radiology departments are used as second source).

Case homogeneity (c) and independence (d) are difficult to achieve completely in human studies. Stratification of the analysis by variables which may be related to enrolment such as 'case severity' is one of the methods to adjust for case heterogeneity. If 3 or more sources are available log linear models can be applied to assess source dependency as well as case heterogeneity and incorporate these aspects into the final model (Chao et al., 2001). The process of fitting log-linear models can be complex and requires the scientist to decide on the optimal model or set of models.

A two source capture recapture model was applied in this study to calculate an ascertainment adjusted estimate (source 1: cases enrolled through 'postal survey', source 2: all cases notified by 'telephone' and other sources of passive notification as

described in section 3.1.3.1.). A disadvantage of this approach was that correction for list dependency and case heterogeneity was not possible. The candidate explored the option to use EEG departments providing services to residents in the surveyed geographical area as 3rd source in the initial phases of the study. Several departments were visited and searched for EEG request forms and EEG reports of children in the age range of interest. The clinical information on the request forms, EEG reports or on documents completed by EEG technicians, when patients attended for recordings, was however very variable and frequently insufficient to decide whether cases would meet inclusion criteria. Considering also the time required for regular visits and searches of electronical data bases or through request forms in several EEG departments a decision was made no longer to pursue this 3rd source of ascertainment.

Although use of at least three sources / registers has been recommended if capture-recapture techniques are applied, in practice (as also experienced in this study) limitations on time, resources and availability of sources meeting criteria of similar diagnostic accuracy are reasons to consider the advantages of a two source model against a traditional case registration approach. Capture – recapture techniques tend to underestimate the true number of cases (overestimation of completeness of ascertainment) if there is positive dependency between two lists (caused by list dependency or/and case heterogeneity, which make case enrolled in list A more likely to be included in list B). In the case of negative dependence (enrolment on list A makes is less likely to be included on list B) the reverse is the case; capture-recapture techniques overestimate the number of true cases (Brenner, 1995). Brenner demonstrates that in the case of positive dependence the two source capture recapture

technique can help to reduce the underestimation of the true case number by traditional case registration, especially if the sources have low rates of completeness (Brenner, 1995). In the case of negative case dependency application of the capture-recapture method has no benefits or can be even disadvantageous compared to the traditional case registration method. The direction of the source dependence cannot be inferred from the data of a two source surveillance model, instead the specific circumstances of case registration need to be taken into consideration.

In this study positive dependence between the two sources of case ascertainment ('postal survey' and 'telephone') was expected. Consultant paediatricians could use the 'telephone hotline' to notify eligible children or instruct the junior doctors in their team to call at the time cases are seen. The same consultants could also return the monthly posted notification form notifying the case at a later time point. Based on the above argument the two source capture recapture method was applied in this study to reduce the underestimation of the traditional case registration approach.

3.2 Cohort observation

3.2.1 Recruitment of subjects

The parents / carers of eligible patients were initially informed by their paediatricians about the study. With their consent the paediatrician forwarded contact details to the researcher using the above described notification systems (telephone hot line, monthly postal survey). The families were approached by the researcher either directly if patients attended appointments at GOSH or by phone and a meeting was

arranged subsequently. At the first meeting written consent from parents/carers was obtained and the children were enrolled in the observational cohort.

3.2.2 Evaluation

3.2.2.1 Clinical assessment at baseline

All patients in the observational cohort underwent clinical assessment at the time of enrolment (baseline assessment). A detailed patient history was obtained from the parents /carers during an interview and documented on an evaluation proforma (see Appendix 6: Evaluation proforma). The following information was recorded:

- age of seizure onset,
- seizure history (description of manifestations during first, subsequent and current seizures; duration; frequency, seizure free periods, status epilepticus, history of febrile seizures)
- antiepileptic medication, including side effects and response
- birth history and complications in the neonatal period
- other medical and genetic diagnoses and their treatments,
- family history (febrile seizures, epilepsy, neurological conditions, genetic diagnoses)
- developmental progress prior and following onset of seizures,
- concerns about visual and hearing impairment
- investigations
- ethnic background

Patients were examined by the researcher and the findings were also documented on the evaluation proforma. Copies of previous investigation results (blood/urine/cerebrospinal fluid) were requested from the paediatrician who notified the patient.

3.2.2.2 Assessment of Neurodevelopmental Status (Baseline):

The neurodevelopmental assessment using the standardised methods described below was conducted by a psychology assistant, who was supervised by a psychologist. The psychology assistant was not aware of the clinical details of the infants and conducted the tests either during the same session when subjects and parents/carers were seen by the candidate or during a separate appointment (home visits, or if children were seen at Great Ormond Street Hospital combined with other clinical attendances).

In order to determine the developmental status close to diagnosis of epilepsy and 12 months later the *Bayley Scales of Infant and Toddler Development 3rd edition [Bayley III]* were administered (Bayley N, 2006a;Bayley N, 2006b).

The Bayley Scales of Infant and Toddler Development are a standardised, widely applied and comprehensive assessment battery for infants and young children between 1 and 42 months of age (Bayley and N, 1993). The scales have recently been revised to include the following scales:

- Cognitive Scale: These items assess sensory-motor development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing. For this revised version of the Bayley II (1993) items were rewritten to decrease the impact of motor ability.

- Language Scale: Items are separated in two subscales measuring *receptive* and *expressive communication*. The subscales also include items to assess preverbal behaviours, vocabulary development and social referencing.
- Motor Scale: This includes two subscales:

  Fine Motor: items measure skills related to visual tracking, reaching, object manipulation and response to tactile information.

  Gross Motor: - measures static positioning (e.g. sitting, standing); dynamic movement, including locomotion and coordination as well as motor planning.

The Bayley III provides norm referenced scores including: scale and composite scores (Cognition, Language, Motor).

'Social-Emotional' and 'Adaptive Behaviour' domains are also assessed by the Bayley III using a questionnaire for completion by the primary care givers:

- Social-Emotional Scale:

  skills and functions assessed include self-regulation and interest in the world, communication needs, engaging others and establishing relationships, use of emotions in interactive, purposeful manner, use of emotional signals or gestures to solve problems.
- Adaptive behaviour scale: skills assessed include the following areas: Communication, Community Use, Health and Safety (showing caution keeping out of danger, Leisure (playing, following rules), Self-Care (eating, toileting, bathing), Self-Direction (self-control, following directions), Functional Pre-academics (letter recognition, counting, drawing of simple

shapes) Home –Living (helping adults with household tasks etc), Social and Motor. The scores form the General Adaptive Composite.

Following the assessment the questionnaire was given to the parents for completion together with a self addressed stamped envelope.

The developmental state prior to seizure onset was determined by using the *Vineland Adaptive Behavior Scales Survey Form (VABS*) (Sparrow S.S. et al., 1984). The Survey Form questionnaire is administered to the primary caregiver by an interviewer and measures personal as well as social sufficiency of an individual form birth to 18 years 11 months old. The following domains are assessed: communication, daily living skills, socialisation and motor skills. The composite of these scales forms the Adaptive Behavior Composite.

Prior to administration of the Survey Form by the psychology assistant (following the Bayley III assessment) or by the candidate the purpose of the interview was explained to parents / carers. They were asked to describe activities that their child usually performed *just prior* to onset of the first seizure. Also during the interview they were reminded to consider only behaviours demonstrated *prior* to seizure onset. Because of the small number of items in the VABS that apply to the neonatal age and limitations of carers to give accurate information about skills in this age retrospectively the Survey Form was only administered when epilepsy onset occurred after the neonatal period.

3.2.2.3 12 months review assessment

Twelve months after the initial evaluation the carers were contacted to arrange follow up assessments. When carers and patients were unable to attend appointments at UCL-Wolfson Centre / Great Ormond Street Hospital for Children the psychology assistant visited the families at home to administer the Bayley III. A member of the research team conducted interviews with the family either over the phone or when patients for attended developmental assessments. A standard follow up proforma was used to record the following information:

- seizure status since last evaluation, seizure manifestations, frequency, duration
- anti epileptic medication (changes, current, reasons for withdrawal)
- investigations performed since baseline evaluation
- general health and other medical / genetic diagnoses made since baseline evaluation
- developmental progress since baseline evaluation
- general and neurological examination results (if this could be performed)

3.2.2.4 Review of neuroimaging and EEGs

Neuroimages, which were requested by the physicians responsible for the care of the patients as part of the initial investigations, were obtained. Two collaborating consultant neuroradiologists, who were unaware of the clinical details of cases apart from inclusion criteria, reviewed the images independently. A proforma was completed to document imaging sequences and planes (e.g. axial T2 weighted), signal abnormalities according to anatomical area and interpretation of findings. On

the proforma the neuroradiologists were also asked to make a subjective judgement about the quality of the images (graded “good”, “acceptable” and “insufficient”). This referred to their ability to extract sufficient information to come to a diagnostic conclusion with a certain level of confidence. In addition they commented if further repeat MR imaging should be performed (see Appendix 7: Proformas for review of Neuroimaging and EEG). Disagreements were resolved by discussing the individual cases.

Digitised recordings of the EEGs requested by the physician responsible for the care of the patients were obtained. The recordings were reviewed by the candidate together with consultant neurophysiologists using a universal software program (Persyst). Information relating to the following points was documented on a proforma: type of recording, state of patient, background activities, interictal and ictal epileptiform activities, description and type of seizures if indicated (see Appendix 7).

3.2.2.5 Feed back to parents and physicians

The results of the Bayley III assessment were summarised in a short report and send to the notifying physician with an extra copy to be forwarded to the parents. If the review of neuroimaging and /or EEG recordings revealed different findings form the reports issued at the local hospital this information was shared with the notifying physician.

3.2.3 Classification of seizures and epilepsy syndromes

In order to test if seizures and epilepsy syndromes in children with epilepsy onset under the age of two years can be determined according to 2001 ILAE task force proposal (research question two, chapter 2) two paediatric neurologists independently evaluated the clinical information including description of seizure manifestations, investigation results (EEG and neuroimaging data, other investigations) and results of the Bayley III assessments. Both paediatric neurologists, who managed predominantly patients with epilepsy in their clinical practice, applied the 2001 proposal with the definitions of key terms according to their own clinical judgement without prior agreement on 'rules'. Cases were firstly categorised under one of the epilepsy syndrome groups that were suggested in the 2001 commission report (table 5 in (Engel, Jr., 2001) and than allocated a specific epilepsy syndrome diagnosis if possible.

In order to classify an infant under the 'idiopathic focal or generalised epilepsy syndrome group' for example, in accordance with the definition given in the 2001 proposal absence of structural brain abnormalities, other neurological signs / symptoms and any other underlying aetiology was required. In addition in keeping with the descriptions of the specific syndromes with onset in infancy in the idiopathic group the developmental status prior and after epilepsy onset was age appropriate and seizures usually responded to first line medication.

Seizure types (axis 2) and epilepsy syndromes (axis 3) were classified at two time points: following the initial (baseline) assessment and after the 12 months review. The reclassification following the 12 months review was conducted in two steps: in

step one the raters were asked to consider only information that was available following the baseline evaluation (intra-rater reliability); in step 2 the raters were also provided with additional data available after the 12 months-review (e.g. manifestations of continuing seizures, results of further investigations). The purpose of the latter was to assess change or evolution of the initial syndromic diagnosis. Seizures were classified according to the list of seizure types provided in the 2001 proposal that was also published on the ILAE website at the time the study was conducted (see table 3 in (Engel, Jr., 2001). The 2001 task force proposal suggested organizing epilepsy syndromes under syndrome groups (see table 5 in (Engel, Jr., 2001). Thus the raters were asked to determine the epilepsy syndrome group (level 1: e.g. idiopathic generalised, idiopathic focal, symptomatic or probable symptomatic focal, epileptic encephalopathies) and specific epilepsy syndrome (level 2: e.g. West syndrome, benign myoclonic epilepsy in infancy).

3.2.4 Handling of data

Clinical information of patients that were notified but not enrolled in the in the observational cohort was obtained and anonymised using identifiers (Initials, DoB) as described above. Non- anonymised data of patients enrolled in the observational cohort were collected in individual files that were stored safely at the institution this project was based (UCL-Institute of Child health, Neurosciences Unit).

Two electronic password protected databases were created in Microsoft Access 2003. One database contained names and addresses of all consultant paediatricians involved in the survey, information about returns of the monthly posted notification forms and number of cases notified. The second database held information about

cases that were notified to the study, patients enrolled in the observational cohort including clinical, EEG, neuroimaging and psychometric data.

3.2.5 Statistical Analysis

Statistical analysis of the data was performed using the following statistical programmes: SPSS version 15, R version 2.6.1, Stata Version 9.

3.2.5.1 Incidence estimates

As denominator for the calculation of the incidence of epilepsy in children to the age of 2 years per year the mid-year population estimates 2006 (obtained from Office for National Statistics) for each of the 15 boroughs in the surveyed geographical area was used. The method applied to generate mid-year population estimates has been described in section 3.1.1.1. The 95% confidence intervals were calculated by applying the exact method for a single proportion. Poisson regression analysis was applied to investigate influence of sex and age bands (age band 0: < 12 months, age band 1: 12-24 months). A poisson regression model using case numbers and population risk for the appropriate age bands (0 and 1) from other studies identified in the literature as well as data from this project was fitted in order to determine the risk of epilepsy in the first compared to the second year of life. Poisson regression analysis was also applied to estimate the relative risk of ethnic group. The white ethnic group was used as reference group and odds ratios as well as 95% confidence intervals were requested.

The ascertainment adjusted incidence estimate was calculated using a two source capture-recapture method.

3.2.5.2 Inter-rater agreement

Inter-rater agreement between the two paediatric neurologists that classified seizures and epilepsy syndromes was assessed by calculating Kappa (κ). Kappa is a measure for inter-rater agreement that is corrected for agreement occurring by chance ('chance corrected proportional agreement'). If there is complete perfect agreement the value of kappa obtains +1 and it becomes 0 when there is no agreement beyond chance. Commonly suggested categories for the interpretation of Kappa are:
< 0.20 - poor, 0.21- 0.40 fair, 0.41 - 0.6 moderate, 0.61 - 0.8 good, 0.81-1 very good (Landis and Koch, 1977). The choice of such benchmarks however may be to a degree arbitrary and interpretation should take clinical circumstances into consideration. For a circumstance in which highest possible agreement is desired the difference between kappa and 1 indicates the unachieved agreement beyond chance. In the case of agreement on a clinical diagnosis for example a view could be taken that a value of kappa significantly below 0.5 indicates poor agreement (Altman D, 1991). The magnitude of kappa is affected by the prevalence in the categories (e.g. common conditions versus rarer conditions) and also by the number of available categories. Comparison of kappa values between different studies is therefore limited.

3.2.5.3 Predictors of neurodevelopmental status close to diagnosis:

A principal component analysis was applied to generate a 'Developmental raw-score Factor (DF)' from language, cognitive and motor raw scores at baseline evaluation. Raw scores were used to generate the DF as the distribution of composite and scale scores was not normal. Exploratory analyses were conducted using Analysis of Covariance (ANCOVA) entering the DF with ‘age at testing as covariate’ in order to

determine relevant factors. Stepwise multivariable linear regression was subsequently carried out to determine significant independent predictors of the developmental function close to diagnosis.

3.2.5.4 Longitudinal change of neurodevelopmental status and predictors:

By entering Bayley III composite factors (cognitive, language and motor) in a principal component analyses a 'Developmental Composite Factor' was generated and further analysis carried out using repeated measures ANOVA.

3.2.6 Approval of the study

The study was approved by the UCL-Institute of Child Health / Great Ormond Street Hospital for Children joint Ethics Committee as non local investigator study. The project was then registered with the ‘Research & Development’ departments of all acute Hospital and relevant PCTs in the surveyed geographical area.

4 CHAPTER 4: RESULTS AND DISCUSSION

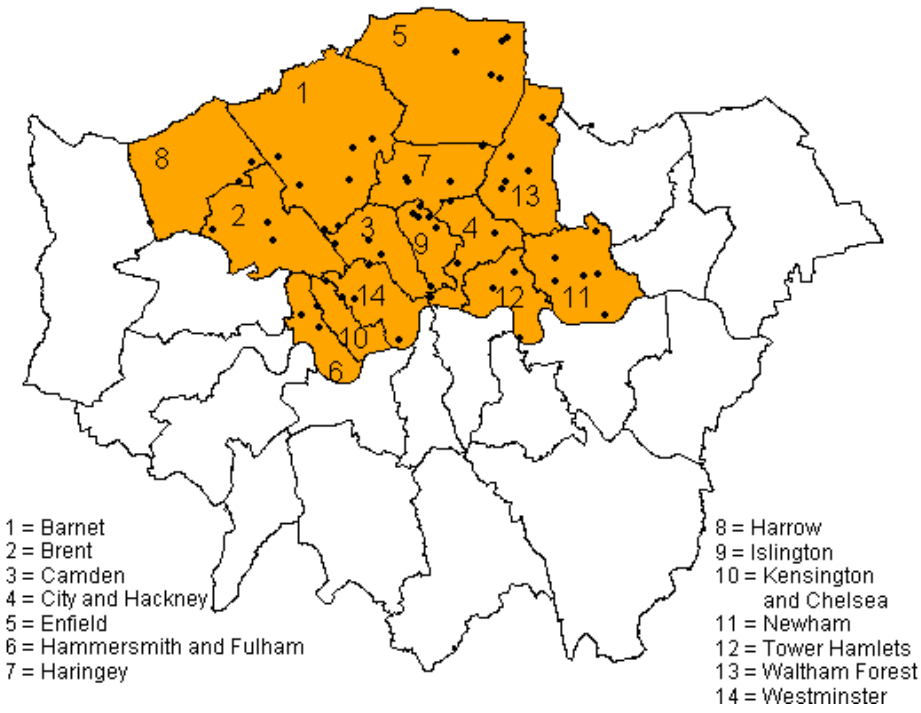
This chapter is organised in sections according to the research questions. Following each section the findings are discussed in the context of existing literature.

4.1 Population Survey and incidence estimate of newly diagnosed epilepsy under the age of two years

4.1.1 Cases ascertained and notification systems:

Fifty seven cases met inclusion criteria and were enrolled. Thirty five cases were notified through the postal survey (returning of notification form), 41 by 'phone', and 19 by both systems. Figure 4.1 shows the distribution of the cases according to residence in the geographical target area (the legend lists only 14 sections as 'City' and 'Hackney' on the map are combined in one). Cases from all 15 boroughs have been ascertained. The mean monthly responder rate (responders / notification forms sent out) of the postal survey was 77%.

Figure 4.1: Distribution of cases ascertained in the geographical target area



4.1.2 Incidence of epilepsy in children under the age of 2 years

The crude incidence of epilepsy under the age of 2 years in North London was 53.6 (95% CI 41.4 - 69.5) / 100.000 children < = 2 years/year (see also table 4.1).

4.1.3 Age-specific incidence of epilepsy (first and second year of life) and sex

The incidence of newly diagnosed epilepsy in the first year of life with 82.1 / 100.000 / year was higher compared to the second year of life (23.4 / 100.000 / year, see also table 4.1). The incidence figures for males and females were similar in both age bands (see also table 4.2 & figure 4.2.). Poisson regression models were fitted using R version 2.6.1 with log (Population at risk) as an offset term, allowing the calculation of incidence rates directly from the model. Main effect terms for sex and age group ("< 12 months", "12 – 24 months") and their interaction terms were fitted.

Likelihood ratio tests confirmed that only the main effect for age group was significant; the difference in risk for epilepsy between the "< 12 months" and "12-24 months" group was 3.52 (95% Confidence interval: 1.86 – 6.65; $p < 0.0001$).

Table 4.3 shows the incidence figures from the North London study in comparison to the incidence estimates from other studies, which provide cases and population at risk for the first and second year of life (Camfield et al., 1996;Kurtz et al., 1998). Poisson regression models with log (population at risk) as offset term with main effects on "age group" and "study", and their interaction term were fitted. Including the interaction term did not significantly improve the goodness of fit of the model (likelihood ratio test $p = 0.77$). This means that age dependence of the risk for epilepsy in the first two years of life is similar in the three studies. Thus the final model comprised main effects of age and studies only. The estimate for the risk ratio of epilepsy between the first and second year of life adjusted by study is 2.88 (95% CI 2.15-3.9; $p < 0.0001$). Looking at the age-adjusted incidence of epilepsy in the first two years the risk was significantly lower in the London study than in the Nova Scotia study (Risk ratio = 0.71, $p = 0.026$) . There was no difference in the age-adjusted incidences of the North London and the 1958 national child development study cohort (Risk ratio = 0.93, $p = 0.7949$).

Table 4.1: Incidence of epilepsy in the first and second year of life

Age	Population at risk*	N	Incidence per 100.000/yr	95% CI
< 12 months	54,810	45	82.1	61.4 – 109.8
12 - 24 months	51,423	12	23.4	13.3 - 40.8
All (<= 2 years)	106,233	57	53.6	41.4 – 69.5

* over 13 months , CI = Confidence Interval

Table 4.2: Incidence and sex (Epilepsy onset under the age of 2 years)

Age groups	**Male**			**Female**		
	N	I	Population at Risk*	N	I	Population at Risk*
< 12months	24	85.7	28,006	21	78.3	26,804
12-24 months	7	26.6	26,335	5	20	25,088
All (<=2 years)	31	57.05	54,341	26	51.05	51,892

N = number of cases, I = incidence per 1000,000, * over 13 months

Figure 4.2: Age specific incidence rates of epilepsy by sex (bars illustrate 95% CI)

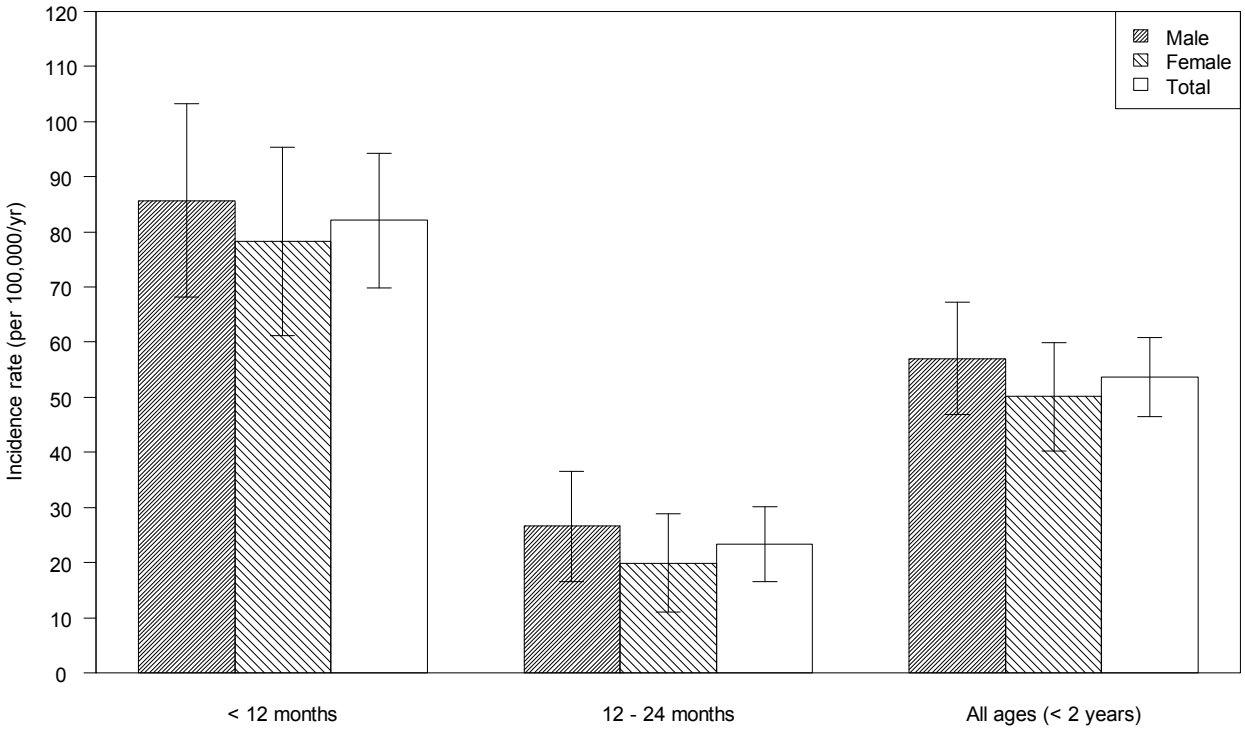


Table 4.3: Comparison of incidence estimates of North London Epilepsy in Infancy Study with other studies

Study	Age group [months]	Cases	Population at Risk	Incidence[1]	95% CI
North London	< 12 m	45	54,810[2]	82	61-110
	12-24 m	12	51,423[2]	23	13 - 41
Nova Scotia ♣	< 12 m	112	94,800	118	98 -143
	12-24 m	42	96400	42	30-57
1958 NCD cohort♣♣	< 12 m	14	15,496	90	43 -138
	12-24 m	5	15,482	31	14 -76

CI = Confidence Interval,
[1] Incidence per 100.000/year,
[2]over 13 months
♣ Nova Scotia (1977-1985)(Camfield et al., 1996)
♣♣1958 National child development study cohort (Kurtz et al., 1998)

4.1.4 Ascertainment adjusted incidence estimate

The adjusted ('true') number of cases according to a two source capture recapture model (see also table 4.4 for details of the estimates) was 75 over the 13 months period. Thus under-ascertainment was 24%. Completeness of ascertainment according to sources was: 46.7% for the postal survey and 54.7% for the passive notification system 'telephone'. The ascertainment adjusted estimate for the incidence of newly diagnosed epilepsy under the age of 2 years is 56.3 – 88.5 (95% CI) / 100.000 <= 2 years/ year.

Table 4.4: Capture-recapture estimates

	Postal Survey		
Telephone	Registered	Not registered	Total
Registered	19	22	41
Not registered	16	18*	34
Total	35	40	75**

*calculated: $d = n - 19 - 22 - 16$
**$n = 35 \times 41/19$; 95%CI n +/- $1.96 \sqrt{(35 \times 41 \times 16 \times 22/19^3)} = 58\text{-}92$

4.1.5 Ethnic composition of the incidence cohort

Information on ethnicity was grouped in the following categories: 'White' (British, Irish, other White), 'Asian' (Indian, Pakistani, Bangladeshi, other Asian), 'Black' (African, Caribbean, other black), 'Other' (Chinese or other ethnic group), ' Mixed' (White and black Caribbean, White and black African, White and Asian, White and other non-white, other non-white).

Figures 4.3 and 4.4 illustrate the distribution of ethnic groups in the incidence cohort of children with epilepsy onset under the age of 2 years and the resident population under the age of 2 yeas in the surveyed area of North London. Sixty percent of cases in the incidence cohort belonged to the non-white groups and of these the Asian group was the largest with 38% of the total cohort. Poisson regression analysis showed that the risk of presenting with epilepsy under the age of 2 years was higher for infants belonging to one of the non-white groups compared to the white group: risk ratio 2.5, 95% CI 1.4 - 4.3, $p = 0.0001$.

A second poisson regression analysis with white ethnic group as reference demonstrated a significant higher risk only for the Asian group: risk ratio 3, 95%CI 1.6 – 5.4, $p < 0.001$ (‘Black’ group: 1.9, 95%CI 0.9 – 4, $p = 0.09$; ‘Other’ group 1.9, 95%CI 0.5 – 8.3, $p=0.4$).

Figure 4.3: Ethnic composition of the North London infancy epilepsy cohort

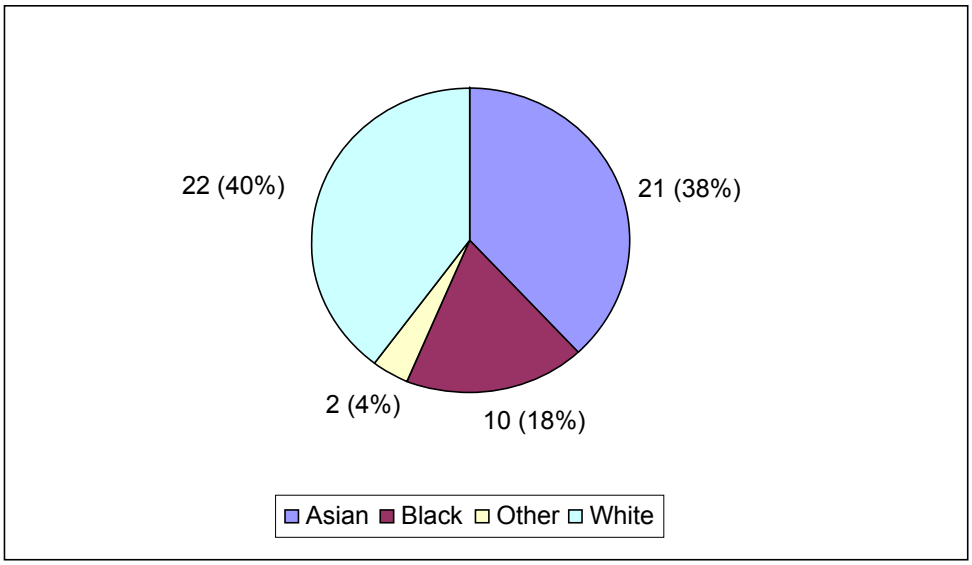
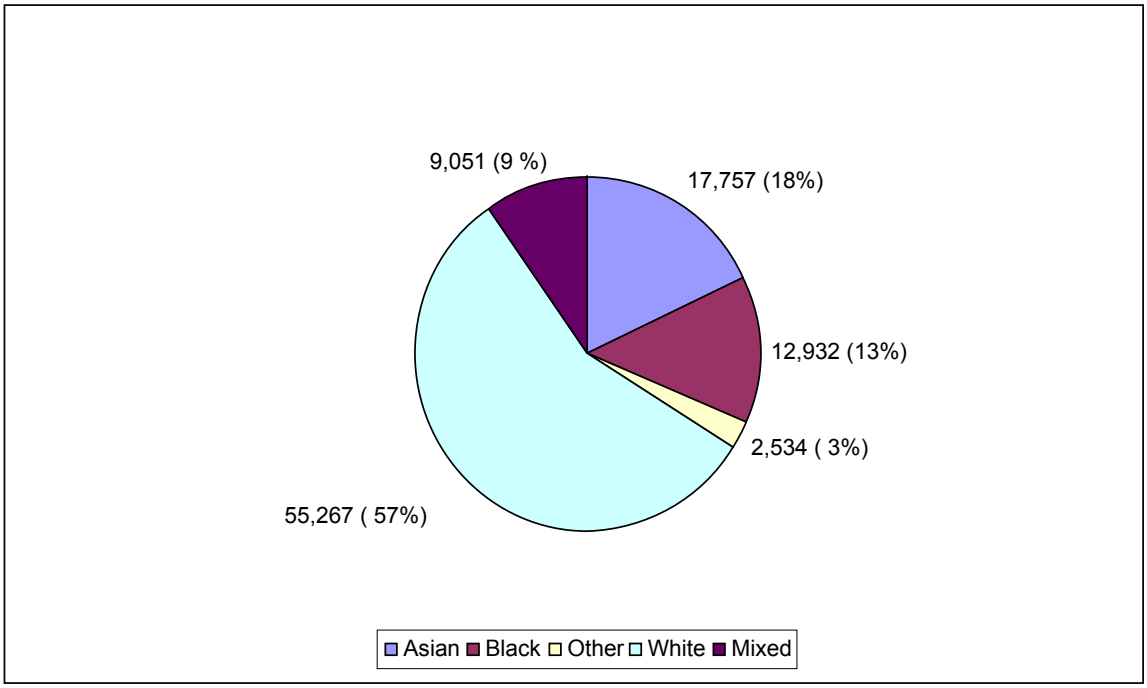


Figure 4.4: Ethnic composition of resident population under two years of age in surveyed geographical area of North London (mid-year 2006, Population Estimates by Ethnic Group; National Office for Statistics, 2008)



4.1.6 Discussion of incidence estimate in the context of other studies

The paucity of age specific incidence estimates for epilepsy with onset under the age of two years in the literature has been already highlighted in section 2.2.2. However, incidence estimates for comparison can be calculated from two studies that provide case numbers and population at risk in the appropriate age bands:

- a population based study in Nova Scotia, Canada: 81 (95% CI 67-93)/ 100.000 person years (children < 2 years) (Camfield et al., 1996).
- the UK 1958 National Child Development Study Cohort: 61 (95% CI 39-95) /100.000 children < 2 years /year (Kurtz et al., 1998).

A third childhood incidence study ascertained form a hospital catchment area in Sweden states a mean annual incidence of epilepsy in children under the age of 2 years of 70/100.000 based on 14 cases (total number of cases under the age of 16 years with newly diagnosed epilepsy ascertained over 2 years: *n* =79) (Braathen and Theorell, 1995). The authors do not provide information about the age specific population at risk. Hence the confidence interval cannot be calculated. The case definitions are similar in the three studies (see also table 2.5 in section 2.2.2).
The ascertainment adjusted incidence determined in the North London Epilepsy in Infancy Study (56.3 – 88.5 (95% CI) / 100.000 <=2 years/ year) overlaps with the confidence intervals estimates of the incidence estimates calculated from the data of the Novo Scotian study and the 1958 national child development study cohort. However the confidence interval of the incidence estimate from the data of the UK 1958 national child development study based on only 14 cases is wide compared to the study by Camfield et al. (Camfield et al., 1996). The latter authors ascertained 152 cases under the age of 2 years over an 8 year period. For the Nova Scotian study

the denominator for each age group was estimated by averaging data from the Canadian Tax Office available for year 4 and 6 of the ascertainment period assuming that there was little change in the population of this Canadian province during the period of ascertainment. Different methods of case ascertainment were used in the three quoted studies. Two of the studies ascertained cases from the resident population in a catchment area using either a single source (records of the only EEG department in the province (Camfield et al., 1996)) or several sources (hospital attendances, district general paediatricians (Braathen and Theorell, 1995)) whilst the in the third a birth cohort was surveyed using a screening questionnaire at several time points (Kurtz et al., 1998). Because a traditional case registration approach was applied in the three studies, information with respect to completeness of ascertainment cannot be derived. This information is important to assess the quality of registers (notification systems) used and helps to interpret data correctly.

According to the two source capture-recapture model applied in this study completeness of ascertainment was relatively high at 76%. This is however likely to be an overestimate as positive dependence between the two sources can be assumed. As already discussed in the method section (3.1.8) the lack of a third source in the 'Epilepsy in Infancy Study' meant that a log linear model could not be applied to correct for this. Underascertainment could have occurred due to lack of cooperation of some paediatricians to notify eligible cases despite of all efforts to promote the study in the collaborating paediatric departments regularly and availability of several notification methods. Other reasons for a failure to notify cases could be a delay in recognition of paroxysmal events as seizures, which can be especially difficult in infants and young children, by paediatricians, general practioners or parents. The

discrepancy in numbers between infants with seizure onset under 12 months compared to those with onset between 12-24 months enrolled in the 'Epilepsy in Infancy Study' may suggest that underascertainment of children in the second year of life was higher. Stratification of the 2 source capture-recapture model according to age, by calculating the model for each age band separately (age < 12 months, and age 12-24 months) could have been considered. The small case number in the 12-24 months age band would have resulted in a larger confidence interval of the estimated number of true cases with greater impact of classification errors on the model considering the small numbers in each cell. Most of all, however, the finding of several other epidemiological studies, as discussed in more detail in the next section (4.1.6.1), demonstrating a similar pattern with sharp decrease of the age specific incidence after the first year of life could explain the discrepancy in case numbers between the age band < 12 months and 12-24 months in the 'Epilepsy in Infancy Study' and would count against the notion of higher underascertainment in the second year of life.

One hundert percent complete ascertainment is difficult to achieve in epedimeiological studies. Chin et al report overall completeness of ascertainment in NLSTEPSS (North London Convulsive Status Epilepticus in Childhood Surveillance Study) of 74-81% (95%CI 62-84%), which is similar to the figure estimated in the 'Epilepsy in Infancy Study' using a two source capture-recapture model (Chin, 2005;Chin et al., 2006). As mentioned in the methods chapter (sections 3.1.1 & 3.1.3.1) in NLSTEPSS the same geographical area in North London was surveyed and very similar notification systems were applied (BPSU like postal survey, telephone hotline). Because a third source based on information of ICD 10 codes

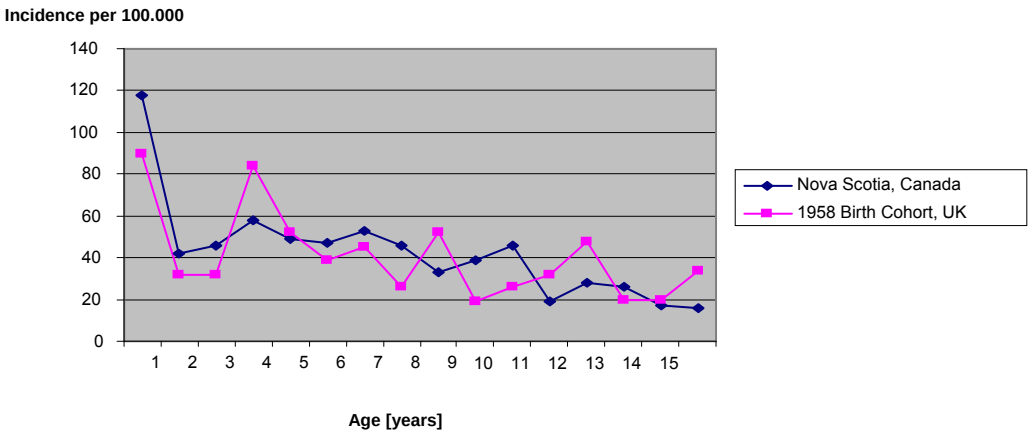
obtained in 6 hospitals was available a log-linear model could be applied to adjust for source dependence. The ascertainment in NLSTEPSS between the two sources ('postal survey' and 'phone') was more heterogeneous compared to the 'Epilepsy in Infancy Study'. Case ascertainment in NLSTEPSS by postal survey was slightly lower (39-43%), whilst the proportion of cases ascertained by the passive system 'phone' was higher (62-68%). Completeness of ascertainment by the BPSU like regional postal survey used in NLSTEPSS and in this study was in the range reported by other researchers using the BPSU scheme to ascertain cases nationally (45-56%) (Rahi and Dezateux, 1999;Heath et al., 2004).

4.1.6.1 Age specific risk of epilepsy in the first two years of life

Data from the 'Epilepsy in Infancy study' show the same pattern of age specific incidences of epilepsy in early childhood previously documented by other authors: the incidence is highest in the first year of life followed by a sharp drop in the second year (Hauser et al., 1993;Camfield et al., 1996;Kurtz et al., 1998). This is illustrated by Figure 4.3 which is based on data from the 1958 UK birth cohort and the Novo Scotian childhood epilepsy cohort (Camfield et al., 1996;Kurtz et al., 1998). The age specific incidence rates remain stable during the first decade and fall again in adolescence. A poisson regression model based on data of these two studies for the first two years of life and the North London 'Epilepsy in Infancy study' demonstrates that there is no difference in the age dependent risk of epilepsy between males and females (see section 4.1.3). This model shows also that the risk of epilepsy onset in the first year is almost three times as high compared to the second year of life.
Age dependent seizure susceptibility has also been demonstrated in various animal models (Holopainen, 2008). Status epilepticus and recurrent seizure rodent models

show that the immature brain has propensity for seizures but is more resistant to seizure induced damage (Haut et al., 2004). The mechanisms for this phenomenon are poorly understood. Shift of GABA receptor function from initially excitatory to inhibitory is one concept that may explain seizure susceptibility in the early neonatal period (Dzhala et al., 2005;Ben-Ari and Holmes, 2006). There is also emerging evidence that seizure activity in the immature brain triggers numerous sequential and overlapping plastic and regenerative processes including changes of neurotransmitter receptors and formation of synaptic connections. Such alterations of neuronal circuits facilitate further seizure generation and have negative impact on long-term cognitive function (Holmes, 2005). It is difficult to separate the effect of seizures from the consequences of brain pathologies such as developmental malformations, molecular genetic defects and inborn errors of metabolism that are diagnosed in a significant proportion of infants (as shown in the following paragraphs). However because of the propensity of the immature brain for seizures brain pathologies may be more likely manifest with epilepsy in this young age.

Figure 4.5: Age specific incidence rates of childhood epilepsy
Based on data from (Camfield et al., 1996;Kurtz et al., 1998)



4.1.6.2 Multi-ethnic composition of North London epilepsy in infancy incidence cohort

The Epilepsy in infancy study ascertained cases from an urban multi-ethnic population. This offered also the opportunity to investigate differences in the occurrence of epilepsy under the age of two years in different ethnic groups. With the white group taken as reference, children belonging to the non-white groups were over 2 times more likely to present with epilepsy under the age of 2 years. Separate analysis demonstrated that only Asian children had a 3 times higher risk presenting with epilepsy, whilst the risk was not significantly higher in the 'black' and 'other' ethnic groups (The latter includes Chinese and other ethnic groups). Information about socioeconomic background that may be a relevant factor has however, has not been considered in this analysis.

Little information is available in the literature with respect to the interaction of ethnicity and incidence of epilepsy. Most epilepsy incidence studies were conducted

in white European populations or populations with European ancestry whilst studies based in Asia and Africa were looking at relatively homogeneous groups. Some US based studies suggest higher epilepsy prevalence and incidence in the black compared to the white population (Shamansky and Glaser, 1979;Haerer et al., 1986). There is also a suggestion of an age specific relationship between unprovoked seizures and ethnicity. Annegers at al determined the incidence of epilepsy and unprovoked seizures in members of a multiethnic Heath Maintenance Organizations (Annegers et al., 1999). Because information about ethnicity was not included in the membership records they evaluated the impact of ethnicity as part of a nested case-control study. The authors calculated odds ratios for an initial unprovoked seizure using the non-Hispanic white population as reference. Whilst the overall odds ratios for African-American and Hispanic ethnicity were very similar, in young children under 5 years the ratios were 1.69 (0.73-3.94) for African-Americans and 1.81 (0.76-4.32) for Hispanics. Interpretation of these data is difficult because of the relatively small case number in the age band < 5 years (n=38) and wide confidence intervals. Chin et al demonstrated in NLSTEPSS an independent association of ethnicity and socioeconomic status to the risk of status epilepticus (SE) (Chin et al., 2009). The incidence of SE was higher in Asian children compared to white and other ethnic groups. Further analysis with respect to association to epilepsy and aetiologies of SE showed that the risk of SE caused by prolonged febrile convulsions was almost 3 times higher in Asian children compared to other ethnic groups. The association to epilepsy and ethnicity was less apparent because of the small number of incidence cases related to an underlying diagnosis of epilepsy (21 of176, 12%, of these two thirds (n=13) had a previous diagnosis of epilepsy) enrolled in NLSTEPSS (Chin et al., 2006;Chin et al., 2009). The NLSTEPSS data cannot be extrapolated to

demonstrate a relationship between epilepsy and ethnicity; they do however support the concept of population genetic factors influencing susceptibility for seizures.

4.2 Cohort observation: North London infancy epilepsy cohort (children with newly diagnosed epilepsy under 2 years)

4.2.1 Description of cohort

4.2.1.1 Data obtained

Of the 57 cases that met inclusion criteria 50 patients underwent clinical baseline assessment conducted by the researcher. Children were clinically evaluated (n=50) after a median time interval of 7 weeks (interquartile range 4 - 11 weeks) following the diagnosis of epilepsy. Anonymised clinical information was obtained for 7 cases that were not enrolled in the observational cohort.

4.2.1.2 Clinical features

Clinical details of the cohort are summarised in table 4.5. Abnormalities on neurological examination at enrolment (observed in 46% including 19% with pyramidal signs, hemiplegia or hemidystonia) and developmental impairment preceding seizure onset (39%) were common in this infancy epilepsy cohort. The time interval from first to second seizure was short; 79% of infants experienced the second seizure within 1 week and 97 % within 1 month. Seizure onset was in the neonatal period in 8 cases (14% of the total cohort). Thirty seven percent of the North London infancy epilepsy cohort reported daily seizures whilst the majority (57%) experienced seizure free periods of more than one week at the time of enrolment. Forty nine percent were on their first anti-epileptic drug at enrolment.

Table 4.5: Clinical features of North London infancy epilepsy cohort (n=57)

		Range	sd
Sex M/F	31/26		
Mean age of epilepsy onset [months]	6.9	0.1 - 22	5.8
	N (%)		
Time interval: first to second seizure <= 1 week >1- 4 weeks > 4 weeks	 45 (79) 10 (17.5) 2 (3.5)		
Neonatal seizures:	14 (25)		
Febrile convulsions:	12 (21)		
Status epilepticus (SE), one or more episodes: SE preceding diagnosis SE at diagnosis (second seizures) Recurrent episodes	 7 (12) 3 1 3		
Neurology at time of enrolment: Normal Unspecific abnormalities: Hypotonia / Posturing Focal signs	 31 (54) 14 (25) 11(19)		
Abnormal development prior to epilepsy onset (when onset after neonatal period, N=48)	19 (39)		
Consanguinity:	9 (16)		
Severity of seizures at baseline: Daily Weekly Monthly (< 12 weeks seizure free) Seizure free for > 12 weeks	 21 (37) 2 (3.5) 29 (57) 3 (5)		
Number of antiepileptic drugs trialled: 0 1 2 3 >3	 3 (5) 28 (49) 12 (21) 7 (12) 7 (12)		

4.2.2 Axis 2: Seizure types at initial assessment

Initial seizure types [first seizure(s)] were most commonly focal (53%, 95% CI 40 - 65%) followed by nearly equal proportions of spasms (23%, 95% CI 14 - 35%) and other generalised seizures (21%, 95% CI 12 - 33%; see also figure 4.6). Details of classification of the initial seizures are provided in Table 4.6. Evolution to different seizure types in subsequent seizures was reported in 20 cases (35%, see table 4.8). This included the emergence of spasms with initially focal or undetermined seizures (n=5), secondarily generalised seizures with initially focal seizures (n=6) as well as multiple seizure types (n=3). Most common subsequent seizure types were focal seizures (47%, 95% CI 35 - 60%) and spasms (32%, 95% CI 21 - 44%) see also figure 4.7 and table 4.7 with details of the classification.

Kappa (κ) as a measure of inter-rater agreement was calculated based on gross categories 'generalised', 'focal' (included secondarily generalised seizures), 'focal and generalised', 'spasms' and 'not able to classify'. For the classification of the initial seizure types and subsequent seizure types Kappa was 0.64 (95%CI 0.48 – 0.8) and 0.62 (95% 0.46-0.78) respectively indicating good agreement between the two paediatric neurologists (Altman D, 1991).

Figure 4.6:

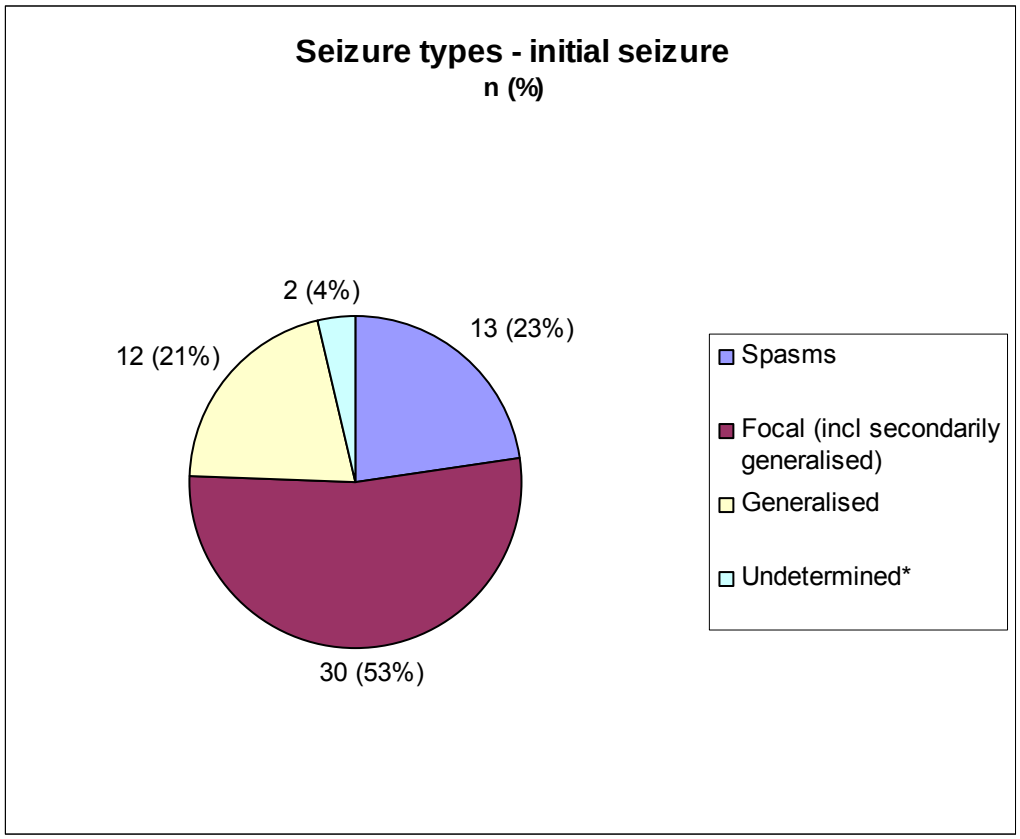


Figure 4.7:

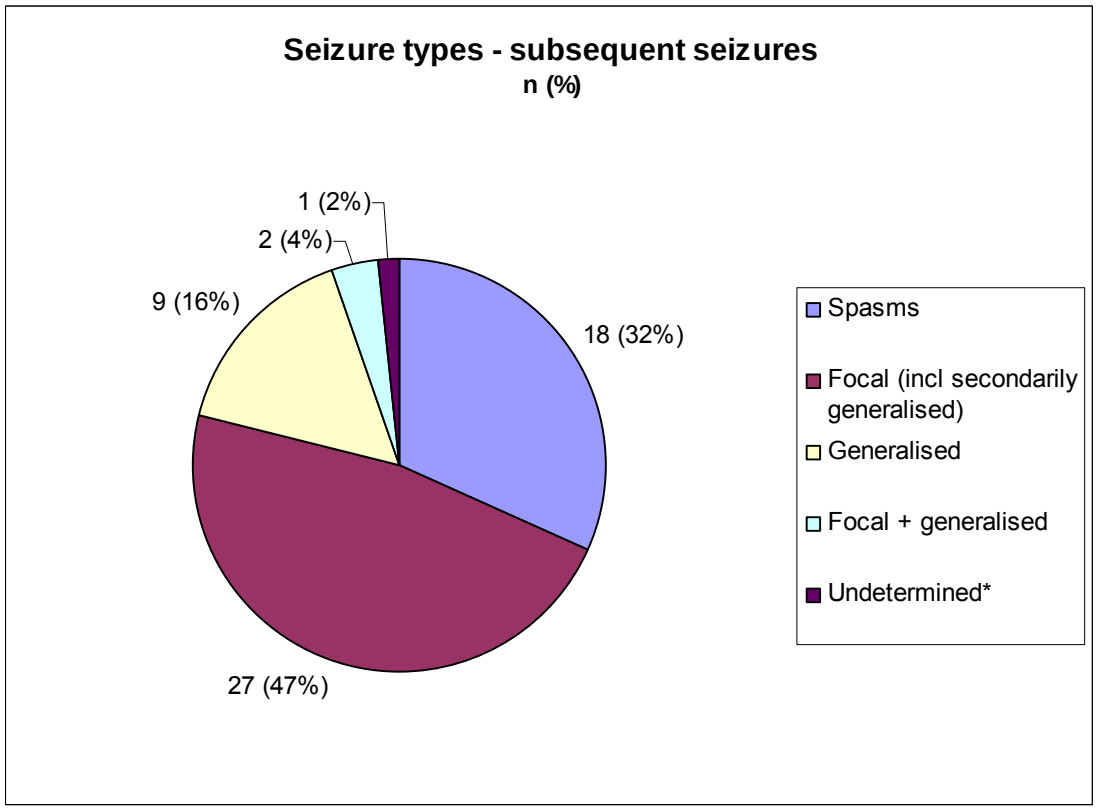


Table 4.6: Initial seizure (s)

Seizure types:	N (%)
Generalised (not further classified)	2 (3.5)
Tonic-clonic	5 (8.8)
Tonic	2 (3.5)
Myoclonic	3 (5.3)
Spasms	13 (22.8)
Focal (not further classified)	13 (22.8)
Focal motor	12 (21)
Focal motor with automatisms	1(1.8)
Focal motor + secondarily generalised	1(1.8)
Secondarily generalised	3 (5.3)
Undetermined*	2 (3.6)
Total cases	57

* unable to classify (1), no agreement between raters (1)

Table 4.7: Subsequent seizures:

Seizure types:	N (%)
Generalised (not further classified)	3 (5.3)
Tonic-clonic	1 (1.8)
Tonic	2 (3.5)
Tonic + atonic	1(1.8)
Myoclonic	2 (3.5)
Spasms	18 (31.6)
Focal (not further classified)	11(19.3)
Focal motor	5 (8.8)
Focal motor with automatisms	1(1.8)
Focal + secondarily generalised	1(1.8)
Secondarily generalised	9 (15.9)
Focal + generalised (multiple types)	2 (3.6)
Undetermined*	1 (1.8)
Total cases	57

*no agreement between raters

Table 4.8: Evolution of initial seizure types (n=20)

Initial seizure(s)	**Subsequent seizures**	**N**
Secondarily generalised	Focal	1
Secondarily generalised	Generalised	1
Focal (1 focal motor)	Secondarily generalised	6
Undetermined*	Spasms	1
Focal (2 focal motor)	Spasms	4
Focal motor	Multiple types	1
Tonic	Focal + generalised	1
Myoclonic	Focal	1
Tonic-clonic	Focal	1
Tonic-clonic	Tonic	1
Undetermined**	Tonic + atonic	1
Tonic-clonic	Undetermined*	1

*no agreement between raters, ** unable to classify

4.2.3 Axis 3: Epilepsy syndromes

Following consensus discussion all but 3 cases could be categorised in one of the epilepsy syndrome groups. Specific syndrome diagnosis, however, could not be allocated in a third of children (19, 33%; see also table 4.9: Epilepsy syndrome groups and table 4.10: Specific epilepsy syndromes).

The majority of cases in this cohort were categorised under 2 syndrome groups: epileptic encephalopathy (39%, 95% CI 27 - 52%), symptomatic focal (28%, 95% CI 18 - 41%) or probably symptomatic focal epilepsy (10%, 95% CI 5-21%; see also table 4.10). Amongst the epileptic encephalopathies, West syndrome was the commonest specific epilepsy syndrome diagnosis [16 of 22 cases, others: 2 Ohtahara syndrome (2), Severe Myoclonic Epilepsy in Infancy (3), Undetermined (1)]. Only 16% (95% CI 8.5 - 27%) of cases were classified as idiopathic. The majority of these were idiopathic focal epilepsies.

The values for Kappa were 0.48 and 0.5 for the classification of the epilepsy syndrome group and specific epilepsy syndromes respectively indicating moderate to poor agreement between the two paediatric neurologists refering (see table 4.11 and 4.12 for 95% Confidence intervals of κ).

Differences between the two raters in categorising a number of cases are illustrated by two examples:

- Infants with infantile spasms and cortical abnormalities on magnetic resonance imaging were classified under epileptic encephalopathy by rater B but as symptomatic focal epilepsy by rater A
- Rater B classified cases as idiopathic focal that were classified by rater A as probably symptomatic focal.

Reasons why cases could not be classified under specific epilepsy syndromes included lack of information (e.g. no data on neuroimaging, or EEG data) or the clinical presentation (especially history of seizure manifestations) was felt not to be in keeping with any of the in the ILAE classification listed syndromes in this age group.

Table 4.9: Epilepsy syndrome groups:

	N	%
Epileptic encephalopathies	22	38.6
Symptomatic focal	16	28.1
Probably symptomatic focal	6	10.5
Symptomatic generalised	1	1.8
Idiopathic focal	8	14
Idiopathic generalised	1	1.8
Undetermined*	3	5.3
Total	57	100

*Unable to classify

Table 4.10: Specific epilepsy syndromes:

	N	%
West syndrome (8 symptomatic)	16	28
Ohtahara syndrome	2	3.5
Dravet syndrome (Severe myoclonic epilepsy in infancy)	3	5.3
Neocortical epilepsies*	13	22.8
Mesial temporal lobe epilepsy with hippocampal sclerosis	1	1.8
Benign infantile seizures (non familial)	2	3.5
Benign myoclonic epilepsy in infancy	1	1.8
Undetermined**	19	33
Total	57	100

*"other types defined by location and aetiology"

** Unable to classify (16); No agreement between raters (3)

Table 4.11: Classification of epilepsy syndrome groups after baseline assessment

	Rater B					
Rater A	Epileptic encephalopathy	symptomatic or probably symptomatic focal	Idiopathic focal	Not able to classify	Idiopathic generalised	Total
Epileptic encephalopathy	13	2	1	0	0	16
Symptomatic or probably symptomatic focal	5	18	3	3	0	29
Idiopathic focal	0	0	4	1	0	5
Not able to classify	1	2	1	1	2	7
Idiopathic generalised	0	0	0	0	0	0
Total	19	22	9	5	2*	57
Kappa (n=55)*	0.48 (95% CI 0.3 – 0.66)					

* 2 cases classified by rater B as idiopathic generalised epilepsy were excluded to calculate Kappa

Table 4.12: Classification of specific epilepsy syndromes after baseline assessment

	Rater B								
Rater A	BIS (non familial)	BME♦	SMEI	MTS	NAC	Neocortical epilepsies*	Ohtahara syndrome	West syndrome	Total
BIS (non familial)	1	0	0	0	3	0	0	0	4
BME	0	0	0	0	0	0	0	0	0
SMEI	0	0	0	0	2	0	0	0	2♦
MTS	0	0	0	1	0	0	0	0	1
NAC	0	1	0	0	11	1	1	0	14
Neocortical epilepsies*	0	0	0	0	9	8	0	5	22
Ohtahara syndrome	0	0	0	0	1	0	0	0	1
West syndrome	0	0	0	0	0	0	0	13	13
Total	1	1♦	0	1	26	9	1	18	57
Inerrater agreement	Kappa♦ = 0.5 (95% CI 0.34 - 0.66)								

BIS = Benign Infantile seizures, BME = Benign myoclonic epilepsy, SMEI = Severe myoclonic epilepsy in infancy, MTS = Mesial temporal lobe epilepsy with hippocampal sclerosis, NAC= Not able to classify; * 'Other types defined by location and aetiology'; ♦ cases excluded for calculation of kappa

4.2.4 Reclassification of Epilepsy syndromes

Thirty two cases, that underwent follow up evaluation approximately 12 months after the initial evaluation were reclassified. As outlined in the methods Chapter (section 3.2.3) this involved two steps in order to investigate consistency of classification and also to evaluate possible changes of the diagnosis overtime with new information becoming available.

4.2.4.1 Step 1: Consistency of classification

Each rater's reclassification based on information available after baseline assessment was compared to the first classification following consensus discussion. The tables 4.13 a) and b) show classification results of epilepsy syndrome groups. The majority of cases were classified in the same syndrome groups and κ values (Rater A: κ= 0.87; Rater B: κ = 0.84) indicated very good agreement. In particular there was no change of more narrowly defined syndrome diagnoses such as epileptic 'encephalopathy' and 'symptomatic focal' epilepsy when cases were rated a second time. Differences involved cases initially classified under 'idiopathic focal', 'not able to classify' or 'probably symptomatic focal': Rater A – changed from 'not able to classify' to 'idiopathic focal' (1 case) and 'probably symptomatic focal' to 'idiopathic focal' (1 case); Rater B – change from 'idiopathic focal' to 'idiopathic generalised' (3 cases).

Although first and second classification of specific epilepsy syndromes showed good concordance there was more variability (see table 4.14 a) and b). Rater A allocated specific syndromes to a number of cases that were in the first classification

categorised as ‘not able to classify’. These included diagnoses such as benign infantile seizures (3), Generalised (Genetic) Epilepsy Febrile Seizures + (1) and Neocortical epilepsies ‘other types defined by location and aetiology ‘(4). Rater B appeared to be more consistent in allocation of specific syndromes as reflected in the higher kappa value (Rater A: $\kappa = 0.69$, rater B = 0.83, see also table 4.15 b). Similar to the reclassification of syndrome groups there was little variability when cases with more narrowly defined specific syndromes such as West syndrome were reclassified.

Table 4.13 a): Reclassification of epilepsy syndrome groups – Rater A

First Classification (after consensus)	**Reclassification based on information available after initial assessment**						
	Epileptic encephalopathy	Symptomatic focal	Probably symptomatic focal	Idiopathic focal	Idiopathic generalised	NAC	Total
Epileptic encephalopathy	11	1	0	0	0	0	12
Symptomatic focal	0	11	0	0	0	0	11
Probably symptomatic focal	0	0	2	0	1	0	3
Idiopathic focal	0	0	0	3	0	0	3
Idiopathic generalised	0	0	0	0	1	0	1
NAC	0	0	0	1	0	1	2
Total	11	12	2	4	2	1	32
Kappa	0.87 (95% CI 0.7-1)						

NAC = Not able to classify

Table 4.13 b): Reclassification of epilepsy syndrome groups – Rater B

First Classification (after consensus)	**Reclassification based on information available after initial assessment**						
	Epileptic encephalopathy	Symptomatic focal	Probably symptomatic focal	Idiopathic focal	Idiopathic generalised	NAC	Total
Epileptic encephalopathy	12	0	0	0	0	0	12
Symptomatic focal	1	10	0	0	0	0	11
Probably symptomatic focal	0	1	2	0	0	0	3
Idiopathic focal*	0	0	0	0	3	0	3*
Idiopathic generalised	0	0	0	0	1	0	1
NAC	0	0	0	0	1	1	2
Total	13	11	2	0	5	1	32
Kappa	0.84 (95% CI 0.68 -1)						

*Cases excluded for calculation of Kappa
NAC = Not able to classify

Table 4.14 a): Reclassification of specific epilepsy syndromes – Rater A

	Reclassification based on information available after initial assessment									
First Classification (after consensus)	West syndrome	Ohtahara syndrome	Neocortical epilepsies*	NAC	MTS	GEFS+♣	SMEI	BME	BIS (non familial)	Total
West syndrome	10	0	0	0	0	0	0	0	0	10
Ohtahara syndrome♣	0	0	1	0	0	0	0	0	0	1♣
Neocortical epilepsies*	0	0	7	0	0	0	0	0	0	7
NAC	0	0	4	1	0	1	0	0	3	9
MTS	0	0	0	0	1	0	0	0	0	1
GEFS+	0	0	0	0	0	0	0	0	0	0
SMEI	0	0	0	0	0	0	1	0	0	1
BME	0	0	0	0	0	0	0	1	0	1
BIS (non familial)	0	0	0	0	0	0	0	0	1	1
Total	10	0	12	1	1	1♣	1	1	4	31
Kappa♣	0.69 (95% CI 0.5-0.87)									

MTS = Mesial temporal lobe epilepsy with hippocampal sclerosis, SMEI = Severe myoclonic epilepsy in infancy, GEFS+ = Generalised epilepsies with febrile seizures plus, BME = Benign myoclonic epilepsy in infancy, BIS = Benign infantile seizures, NAC = Not able to classify,*other types defined by location and aetiology ;♣ Cases excluded for calculation of Kappa

Table 4.14 b): Reclassification of specific epilepsy syndromes – Rater B

First Classification (after consensus)	**Reclassification based on information available after initial assessment**								
	West syndrome	Ohtahara syndrome	Neocortical epilepsies*	MTS	SMEI	BME	BIS (non familial)	NAC	Total
West syndrome	10	0	0	0	0	0	0	0	10
Ohtahara syndrome	0	1	0	0	0	0	0	0	1
Neocortical epilepsies*	1	0	7	0	0	0	0	0	8
MTS	0	0	0	1	0	0	0	0	1
SMEI	0	0	0	0	1	0	0	0	1
BME	0	0	0	0	0	1	0	0	1
BIS (non familial)♣	0	0	0	0	0	0	0	1	1♣
NAC	0	0	3	0	0	0	0	6	9
Total	11	1	10	1	1	1	0	7	32
Kappa	0.83 (95%CI 0.67- 0.98)								

MTS = Mesial temporal lobe epilepsy with hippocampal sclerosis, SMEI = Severe myoclonic epilepsy in infancy, BME = Benign myoclonic epilepsy in infancy, BIS = Benign infantile seizures, NAC = Not able to classify

* other types defined by location and aetiology; ♣ Case excluded for calculation of Kappa

4.2.4.2 Step 2: Classification of syndromes after 12 months review

Clinical data and investigation results obtained at the 12 months reassessment were considered by the raters, who were also instructed to indicate whether the new information lead to revision of the initial epilepsy syndrome diagnosis. The syndrome diagnosis was changed in only a small number of cases: Rater A revised the initial diagnosis in 3 and Rater B in 4 cases (9% and 12 % of the follow up cohort respectively, see table 4.15 for details). Additional information resulted in allocation of syndrome diagnoses in 3 cases that were initially not classifiable or indicated evolution of the epilepsy syndrome (West syndrome to focal symptomatic epilepsy). For example rater A categorised two cases that were 'not classifiable' after baseline assessment under 'Seizures not necessarily requiring a diagnosis of epilepsy': one child remained seizure free without antiepileptic treatment throughout the follow up period; the other child had several febrile seizures whilst on anti epileptic medication. Case 11 demonstrated clinical evolution from West syndrome to focal symptomatic epilepsy (following remission of spasms and seizure free period focal seizures recurred). With the exception of one case (ID 11) there was no concordance between the raters with respect to the cases in which the diagnoses were revised.

Table 4.15: Change of epilepsy syndrome diagnosis after 12 months review

Rater A				
ID	**Initial syndrome group**	**Initial specific syndrome**	**Syndrome group after 12 months review**	**Specific Syndrome after 12 months review**
11	Epileptic encephalopathy	West syndrome	Symptomatic focal	Neocortical epilepsies
55	NAC	NAC	Seizures not necessarily requiring a diagnosis of epilepsy	Febrile seizures
87	NAC	NAC	Seizures not necessarily requiring a diagnosis of epilepsy	Isolated cluster of seizures

Rater B				
ID	**Initial syndrome group**	**Initial specific syndrome**	**Syndrome group after 12 months review**	**Specific Syndrome after 12 months review**
2	NAC	NAC	Idiopathic generalised	Idiopathic generalised epilepsies with variable phenotypes (?)
11	Epileptic encephalopathy	West syndrome	Symptomatic focal	Neocortical epilepsies
35	Epileptic encephalopathy	West syndrome	Symptomatic focal	Neocortical epilepsies
73	Epileptic encephalopathy	West syndrome	Symptomatic focal	Neocortical epilepsies

The tables 4.16 a) and b) give details of the epilepsy syndrome diagnoses allocated by rater A and B after the 1 year review. Discrepancies between the raters are especially obvious with respect to the specific epilepsy syndrome diagnoses. Rater B was unable to allocate a specific syndrome diagnosis in 9 cases (28% of the review cohort), whilst rater A classified all cases. Most differences were observed with the classification of the less severe epilepsies (idiopathic types or children with infrequent seizures).

Table 4.16 a): Reclassification of epilepsy syndrome groups after 12 months review

Rater A	Rater B					Total
	Epileptic encephalopathy	**Symptomatic or probably symptomatic focal**	**Idiopathic generalised**	**Idiopathic focal**	**Seizures not necessarily requiring diagnosis of epilepsy**	
Epileptic encephalopathy	8 (24%)	1(3%)	0	0	0	9 (27%)
Symptomatic or probably symptomatic focal	2 (6%)	14 (42%)	0	0	0	16 (48%)
Idiopathic generalised	0	1 (3%)	1(3%)	0	0	2 (6.1%)
Idiopathic focal	0	0	4 (12%)	0	0	4 (12%)
Seizures not necessarily requiring diagnosis of epilepsy	0	0	2 (6%)	0	0	2 (6%)
Total	10 (30%)	16 (48%)	7 (21%)	0	0	33 (100.0%)

Table 4.16 b): Reclassification of specific epilepsy syndromes after 12 months review

Rater A	**Rater B**											
	WS	SMEI	OS	Neocortical epilepsies*	MTS	GEFS+	IGE variable phenotypes	BME	BIS	Isolated seizures/ febrile seizures	NAC	Total
WS	8 (25%)	0	0	1(3%)	0	0	0	0	0	0	0	9 (28%)
SMEI	0	1(3%)	0	0	0	0	0	0	0	0	0	1(3%)
Neocortical epilepsies*	0	0	1(3%)	9(28%)	0	0	0	0	0	0	3(9.4%)	13 (40.6%)
MTS	0	0	0	0	1 (3%)	0	0	0	0	0	0	1(3%)
GEFS+	0	0	0	0	0	0	0	0	0	0	1(3%)	1(3%)
IGE variable phenotypes	0	0	0	0	0	0	0	0	0	0	0	0
BME	0	0	0	0	0	0	0	1 (3%)	0	0	0	1(3%)
BIS	0	0	0	0	0	0	1(3%)	0	0	0	3 (9.4%)	4(12.5%)
Isolated seizures / febrile seizures	0	0	0	0	0	0	0	0.	0	0	2 (6%)	2(6%)
NAC	0	0	0	0	0	0	0	0	0	0	0	0
Total	8(25%)	1(3%)	1(3%)	10 (31.3%)	1(3%)	0	1(3%)	1(3%)	0	0	9 (28%)	32 (100.0%)

WS=West syndrome, OS=Ohtahara syndrome, SMEI=Severe myoclonic epilepsy in infancy (Darvet syndrome); MTS =Mesial temporal lobe epilepsy with hippocampal sclerosis; BME=Benign myoclonic epilepsy in infancy; GEFS+= Generalised (Genetic) epilepsies with febrile seizures plus; BIS=Benign infantile seizures (non familial); IGE= Idiopathic generalised epilepsy; NAC=Not able to classify

4.2.5 Underlying aetiologies (Axis 4)

Underlying aetiologies could be determined in 29 children (51% of the cohort). Details are provided in table 4.17. Infants presenting with recurrent unprovoked seizures owing to CNS insults, such as infection or perinataly acquired injuries including hypoxic ischaemic brain injuries, resulting in a static encephalopathy were categorised under acquired - remote symptomatic aetiologies (ILAE Commission, 1997).

Developmental brain malformations were the largest aetiological category (n=12, 21%), see also figure 4.8. Cortical malformations were extensive involving both hemispheres in 5 infants and 2 additional infants had multilobar unilateral lesions (focal cortical dysplasia). Eight infants in the subgroup with developmental brain abnormalities (68%) presented with seizures in the first six months of life including 4 (33%) with epilepsy onset in the neonatal period. Eight children in this subgroup (68%) experienced daily seizures at the time of evaluation. Acquired - remote symptomatic aetiologies (details see table 4.17) were the second largest aetiological group in this cohort (16%). Only one of 9 (11%) infants presented with seizure onset in the neonatal period. Epilepsy onset in the neonatal period was also observed in 3 of 4 (75%) children with confirmed or strongly suspected metabolic disorders. Of the two children with probable mitochondrial disorder one child had low complex IV on assays performed on muscle tissue and skin fibroblasts. The other child had low concentration of all four respiratory chain enzymes in muscle tissue. Ongoing molecular genetic tests have so far not yet determined a specific genetic diagnosis in both cases.

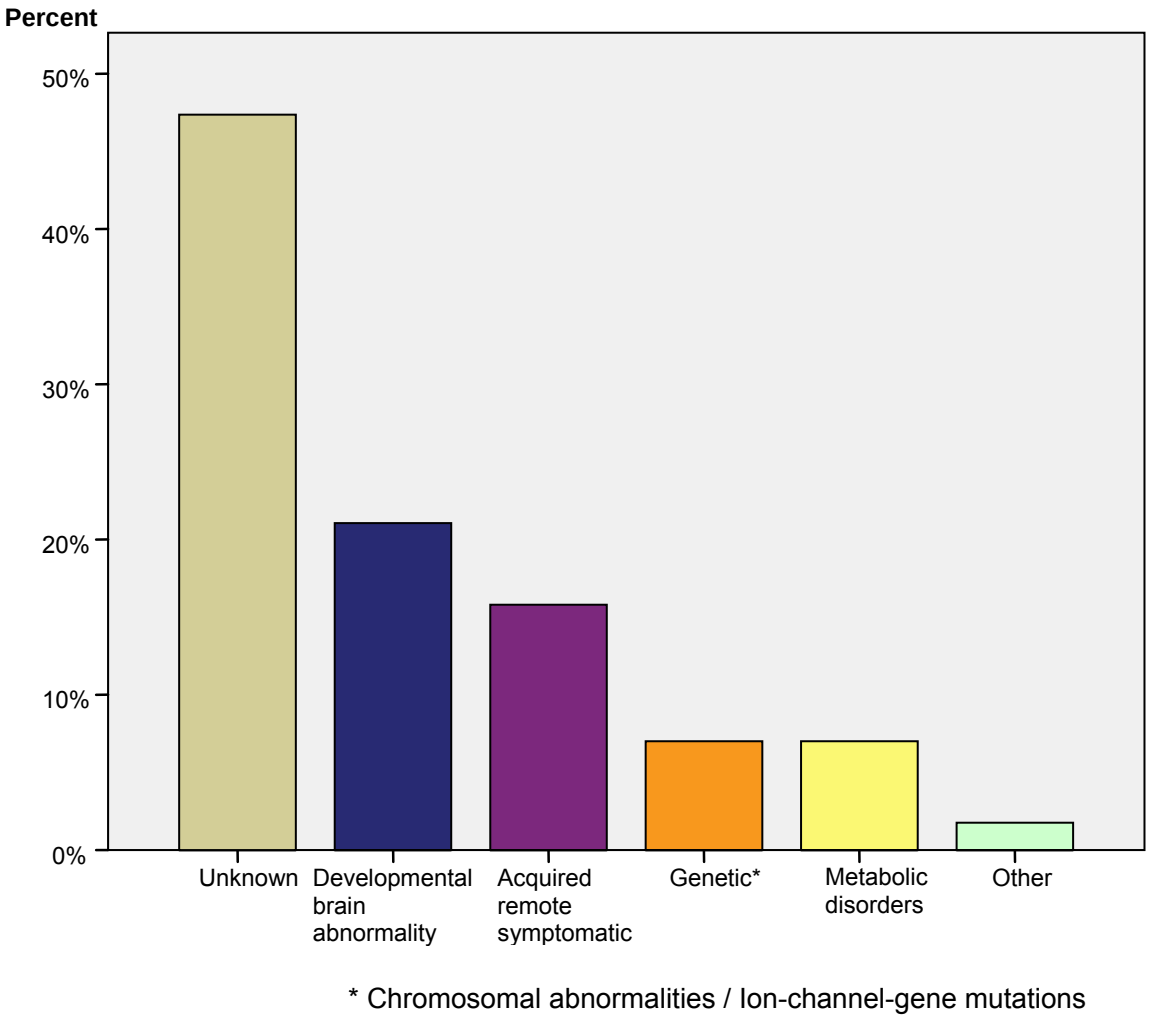
One infant with a chromosomal abnormality associated with an increased risk for epilepsy, Trisomy 21, presented with recurrent unprovoked seizures following pneumococcal meningitis and was therefore categorised under acquired remote symptomatic epilepsies.

Table 4.17: Aetiologies identified in the North London infancy epilepsy cohort

Categories	**N (%)**	**Details (number of cases)**
Developmental brain abnormality	12 (21)	Unilateral multilobar focal cortical dysplasia (2) Polymicrogyria (4): ▪ Bilateral polymicrogyria (mesial frontal, parietal, occipital lobes) ▪ Bilateral polymicrogyria + right periventricular heterotropia ▪ Bilateral polymicrogyria + hemimegalencephaly ▪ Bilateral polymicrogyria + cerebellar hypoplasia, small brain stem Tuberous sclerosis (3) Lissencephaly Microcephaly + absent corpus callosum Occipital arterial venous malformation
Other	1 (2)	Probable Mesial Temporal Sclerosis
Aquired remote symptomatic:	9 (16%)	
Infection	5 (9)	Viral encephalitis (2) Pneumococcal meningitis Neonatal meningitis/sepsis (2)
Perinataly acquired	4 (7)	Hypoxic ischaemic brain injury (3) Extreme prematurity with intraventricular haemorrhage
Metabolic disorder	4 (7)	Molybdenum Cofactor Deficiency Biotinidase deficiency Probable mitochondrial disorder (2)*
Chromosomal abnormalities / Ion channel gene mutations	4 (7)	Chromosomal abnormalities (2) ▪ monosomy 1p36 ▪ isodicentric Chr 15 SCN1A mutation (2)**
Unknown	28 (49)	

* Low respiratory chain enzymes in 2 patients: 1 low complex IV in muscle tissue and skin fibroblasts, 1 with low complex I, II, III and IV on muscle biopsy.
** missens mutation c.1088C>G, p.Thr363Arg, whole SCNA1 gene deletion .

Figure 4.8: Aetiologies identified in the North London infancy epilepsy cohort (n = 57)



4.2.6 Neuroimaging and associated structural brain abnormalities

4.2.6.1 Imaging practice and protocols

Neuroimaging was performed in 55 children (96% of the total cohort) of which 54 underwent magnetic resonance (MR) imaging and one child computed tomography (CT). Eight infants had both (CT and MR scans). Images of 52 children (94%) were obtained and independently reviewed by two experienced neuroradiologists as described in the methods chapter (section 3.1.2.2.4). This included 65 MR images of 51 children. Repeat scans were performed for 12 (23%) children including 2 infants who had 3 MR scans.

According to information provided by copies of imaging request forms, imaging reports or clinical correspondence (clinic letters, discharge summaries) the indications for requesting magnetic resonance imaging was established. The majority of the MR images (51, 78.5%) were requested to investigate epilepsy / afebrile seizures. Other indications that may have preceded diagnosis of epilepsy included suspected brain abnormality not associated with epilepsy (4, 6%), CNS infection (5, 8%), peri-natal hypoxic ischaemic brain injury (3, 4.6%), status epilepticus (1) and for one infant with epilepsy controlled on antiepileptic drugs – “investigation of global developmental delay" in the context of a preceding abnormal CT scan.

MR images were performed in several institutions, using systems with magnetic field strengths from 0.5 to 1.5 tesla and different imaging protocols. The protocols applied for the acquisition of 36 MR scans (55% of the reviewed images) complied with the generic principle of combining T2 weighted images in two planes supported by T1 weighted images in two planes as recently suggested by Saunders (Saunders et al.,

2007). T1 weighted images in two planes were available for 50 (77%) and T2 weighted images in two planes in 47 (72%) MR scans. Seventeen scans (26 %) did not include coronal T2 weighted sequences (T2 weighted techniques including fluid-attenuated inversion recovery [FLAIR] images). Sequences recommended to investigate epilepsy (especially focal epilepsy) such as 3-D volume T1-weighted acquisition were obtained for 19 (29%) MR scans and coronal T2 weighted images tilted to lie perpendicular to the hippocampi for 14 (22%).

The image quality was judged by the neuroradiologists to be ‘good’ (48, 71%) or ‘acceptable’ (12, 18.5%) for the majority of scans. Images of 7 MR scans (11%) were insufficient, including 4 scans that were obtained using fast acquisition techniques and one that acquired only a single plane sequence (axial T2 weighted image, see also appendix 9 for examples of 'insufficient' quality images). Of the 7 MR scans with images of insufficient quality five were repeated. Three of the repeat MR scans provided positive diagnostic information.

The neuroradiologists stated that repeat MR imaging was indicated after 13 scans (20%) because of insufficient image quality (7), in order to evaluate the evolution of signal changes over time (4) or to achieve better definition of a brain malformation (3). Repeat imaging after 23 scans (25%) was felt to be only appropriate if seizures persisted and / or epilepsy surgery was considered.

Of the 14 MR scans, that were repeat images, 7 provided new diagnostic information, 2 showed evolution of previously seen abnormalities and 5 did not demonstrate any positive findings.

'Local' reports were compared with the findings of the two neuroradiologists. Eleven of 57 (24%) available local reports differed from the report provided by the two reviewers. Two of the 11 'local' reports came from the same institution in which the two collaborating neuroradiologists were based. Diagnoses that differed significantly from the local reports, which stated images were essentially normal, included 'tuberous sclerosis' and 'bilateral polymicrogyria'.

4.2.6.2 Neuroimaging - Findings

The findings of the neuroimaging review were categorised under 'aetiologically relevant', 'not aetiologically relevant or uncertain' and 'normal - no positive findings' (see table 4.18). The details of the imaging findings for each subject are listed in appendix 9, which also contains examples of MR images demonstrating developmental and acquired brain lesions. 'Aetiologically relevant' were structural abnormalities that are commonly reported in children with epilepsy, whilst neuroimaging appearances of 'uncertain aetiological relevance' are commonly observed in children presenting with a broader range of neurological and neurodevelopmental problems.

Aetiologically relevant abnormalities were seen on the images of 27 (52%) children. Of these the imaging appearances were in keeping with acquired lesions in 55% and with developmental brain malformations in 41%. Neuroimaging findings of 9 (17%) children were of uncertain aetiological relevance. These included delayed myelination, lack of white matter bulk, thin corpus callosum or arachnoid cysts. Details of the neuroimaging findings for each subject are listed in appendix 9.

Table 4.18: Neuroimaging findings in the North London infancy epilepsy cohort, N=52
The details of the imaging findings for each subject are listed in the appendix 9.

			N (%)
Aetiologically relevant findings		Details (n)	27 (52)
	Developmental malformations:	Unilateral multilobar focal cortical dysplasia (2) Polymicrogyria (4): ▪ Bilateral polymicrogyria (mesial frontal, parietal, occipital lobes) ▪ Bilateral polymicrogyria + left periventricular heterotropia ▪ Bilateral polymicrogyria + Hemimegalencephaly + left closed lip schizencephaly ▪ Bilateral polymicrogyria + cerebellar hypoplasia, small brain stem Tuberous sclerosis (2) Lissencephaly Microcephaly + absent corpus callosum Occipital arterial venous malformation	11
	Acquired brain lesions	Secondary to CNS infections, hypoxic ischaemic injury, metabolic disorders or seizure activity	15
	Other	Probable mesial temporal sclerosis	1
Not aetiologically relevant or uncertain		Details (n)	11 (21)
	Incidental / immaturity	Arachnoid cyst (2) Delayed myelination, lack of white matter bulk, small chiasm and/or thin corpus callosum (7)	9
	Uncertain	– Suspicious localised area of signal abnormality on T2 weighted image, (insufficient image quality) – Asymmetry of white matter signal in temporal lobes, one hippocampus slightly smaller	2
No positive findings (normal)			14 (27)

4.2.7 EEG data

Eighty nine EEG recordings of 48 children were reviewed (1 recording for 19 [40%] subjects, 2 for 18 [37%], 3 for 10 [21%] and 4 for 1 child).
At least one recording that included sleep was available for 35 (73%) children.
Photic stimulation was performed in recordings of 32 (66%) subjects. Overall photic stimulation was performed in 42 (47%) of the reviewed EEG recordings.

Fourteen (16%) of the reviewed recordings were normal. Interictal discharges were seen in 56 (63%) recordings and were focal or lateralized in 26 (see table 4.19 for details). Background activities with excess of slow activity were observed in a third of the recordings (unspecific background abnormalities, see table 4.19) and gross abnormalities with absence of age appropriate activities in 38 (43%). Six (7%) recordings demonstrated typical appearances of hypsarrhythmia. The term 'modified hypsarrhythmia' was not applied, instead the features of the EEG were described (e.g. grossly abnormal background activities and distribution of interictal discharges).

Twenty eight (31%) EEGs included ictal recordings. Details of the ictal onset are given in table 4.19. The onset of almost two thirds of the recorded seizures was focal or lateralized. Three of the 5 seizures with undetermined onset and all ictal events with generalized onset were infantile spasms.

Table 4.19: Findings of EEG review (89 records of 48 subjects)

	N (%)
Background activities:	
Normal	22 (25)
Unspecific abnormalities*	27 (30)
Grossly abnormal**	38 (43)
Burst-suppression pattern	7
Unable to comment	2 (2)
Interictal discharges:	**56 (63)**
Focal	18 (32)
Unilateral	8 (14)
Bilateral	18 (32)
Multifocal	13 (23)
Hypsarrhythmia	6 (7)
Ictal recordings:	**28 (31)**
Seizure onset: - focal	12 (43)
- bilateral	3 (11)
- unilateral	4 (14)
- generalised	4 (14)
- undetermined	5 (18)
Normal recordings	**14 (16)**

***** excess of slow activities with some age appropriate activities present

** no age appropriate background activities present

4.2.8 Developmental function

4.2.8.1 Developmental function close to diagnosis (Bayley III)

Forty nine children were assessed after a median time interval of 9 weeks (interquartile range 5 - 15) following the diagnosis of epilepsy. Clinical data of this cohort are summarized in table 4.20. At the time of evaluation over a third

experienced daily seizures and all but five children were taking at least one antiepileptic drug.

Table 4.20: Clinical details of cohort that was assessed with the Bayley III

F/ M	22/27
Median age of seizure onset [months] (interquartile range)	5 (2.2 - 8.7)
Median age when assessed [months] (interquartile range)	9.5 (5.6 - 17.4)
History of neonatal seizures	12
Frequency of seizures n (%) Daily Weekly Monthly Seizure free: < 1 month 1-3 months > 3 months	 18 (37) 4 (8) 3 (6) 6 (12) 14 (29) 4 (8)
Number of anti epileptic drugs taken at evaluation n (%): None 1 2 3	 5 (10) 24 (49) 15 (31) 5 (10)

The means of the composite and scale scores fall in the borderline or extremely low range (see table 4.21). The scores are widely distributed as illustrated in figure 4.9 a) and the majority of the values are more than 1 standard deviation (sd) below the mean of the standardisation sample. The distribution of scores is skewed towards the lower values and fairly similar across the three major domains: cognition, motor and language. Values in the bottom quartile cluster around the lowest obtainable scores for cognition, receptive language -, fine motor- and gross motor subscales. The distribution of 'cognition' and 'fine motor' scale scores and is very similar with the median falling more than 2 sd below the mean of the standardisation group (see figure 4.9 b).

Table 4.21: Bayley III scores at baseline assessment, n = 49

Scores	Mean	sd	Range
Cognition	72.1	20.7	55 - 115
Language Composite	68.7	17.9	47 - 106
Motor Composite	67.7	22.6	46 - 127
Expressive language (scale score)	4.7	3	1 - 11
Receptive language (scale score)	4.7	3.4	1 - 11
Fine Motor (scale score)	4.6	4.2	1 - 15
Gross Motor (scale score)	4.6	3.5	1 -14

Figure 4.9 a): Distribution of Bayley III composite scores at baseline assessment

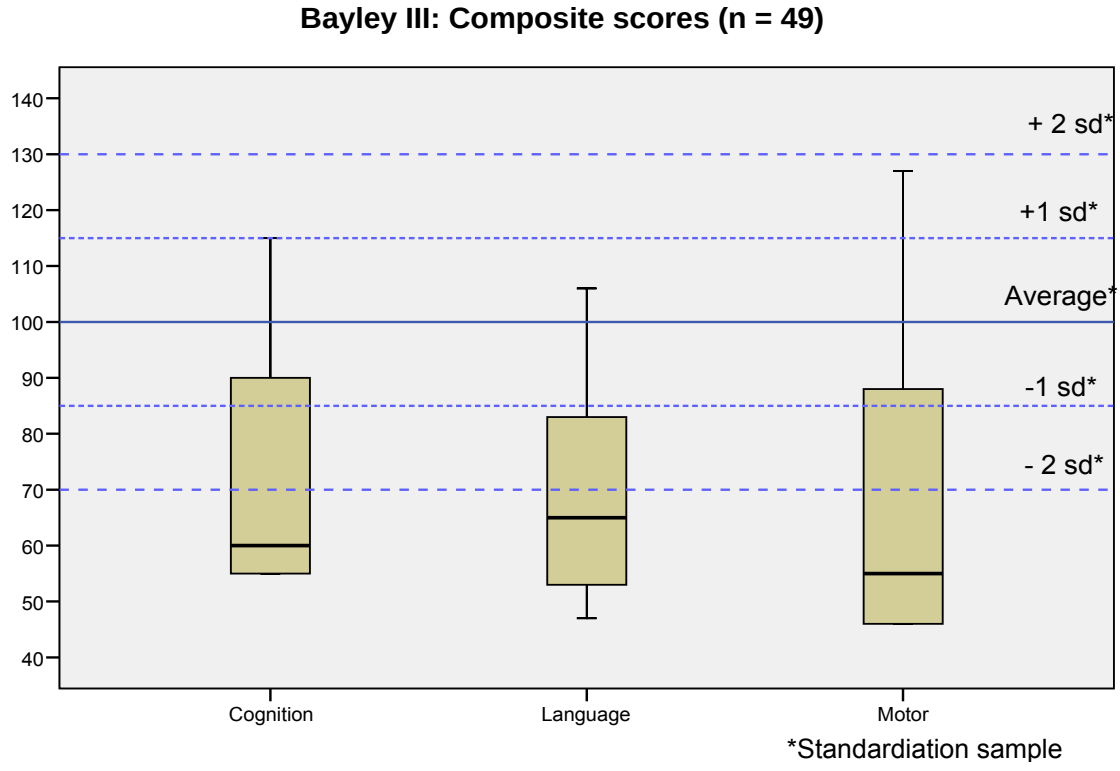
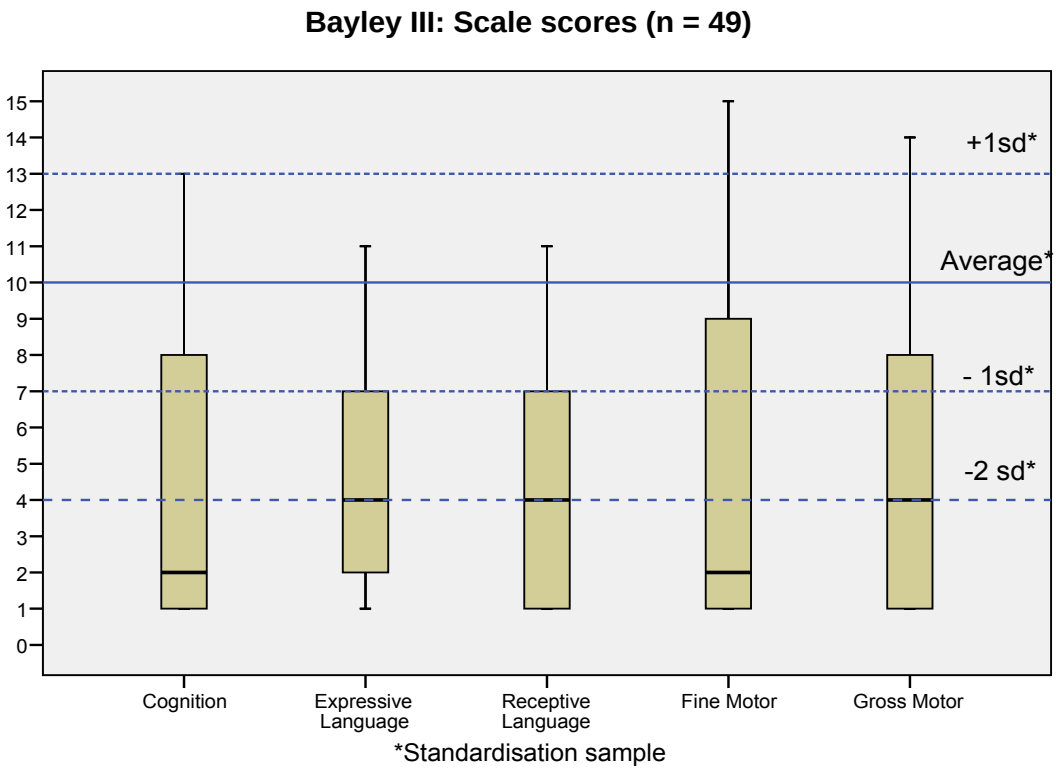


Figure 4.9 b): Distribution of Bayley III scale scores at baseline assessment



The Bayley III adaptive behavior questionnaire was completed by carers of 32 children (65% of subjects assessed with the Bayley III). Descriptive statistics of the composite scores are detailed in table 4.22.

Figure 4.10 (a and b) illustrates the distribution of the scores for the adaptive behavior domains (Social, Conceptual, Practical), general adaptive composite (GAC) and the Bayley III composite scores of this subgroup. Although the clustering of scores at the bottom of the scale is not observed in the adaptive behavior composite scores the distribution of the GAC scores in relation to the standardisation sample is similar to cognitive, language and motor composite scores. The majority of scores are 1 sd and the median is more than 2 sd below the mean of the standardisation sample. Thus the carers perception of developmental function in the home

environment (Bayley Adaptive Behavior Scale scores) was in keeping with the Bayley III assessment.

Table 4.22: Bayley III: Adaptive Behavior Scale Composite Scores at baseline assessment (n = 32)

Composite scores	**Mean**	**sd**	**Range**
Social Domain	79.6	19.4	48 - 130
Conceptual Domain	78.5	20.8	49 - 132
Practical Domain	84.1	20.7	52 - 136
General Adaptive Composite	77.4	23.5	40 - 140

Figure 4.10 a): Distribution of Bayley III: Adaptive Behavior Scale Composite Scores

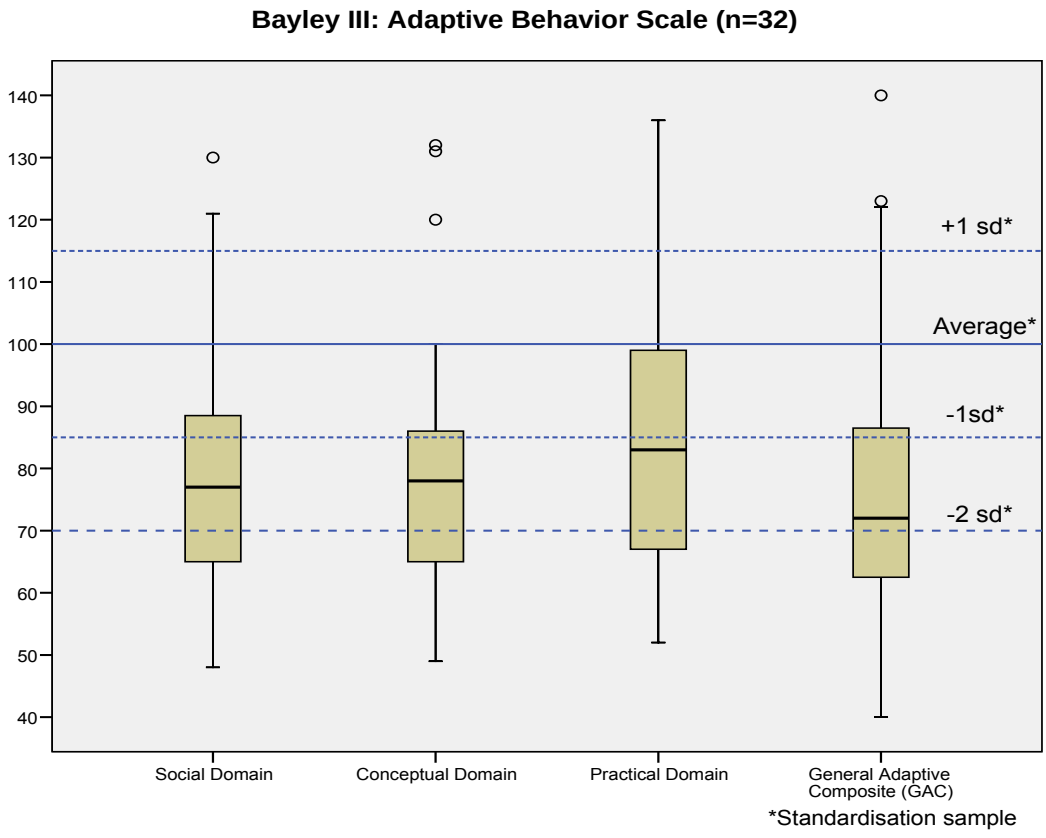
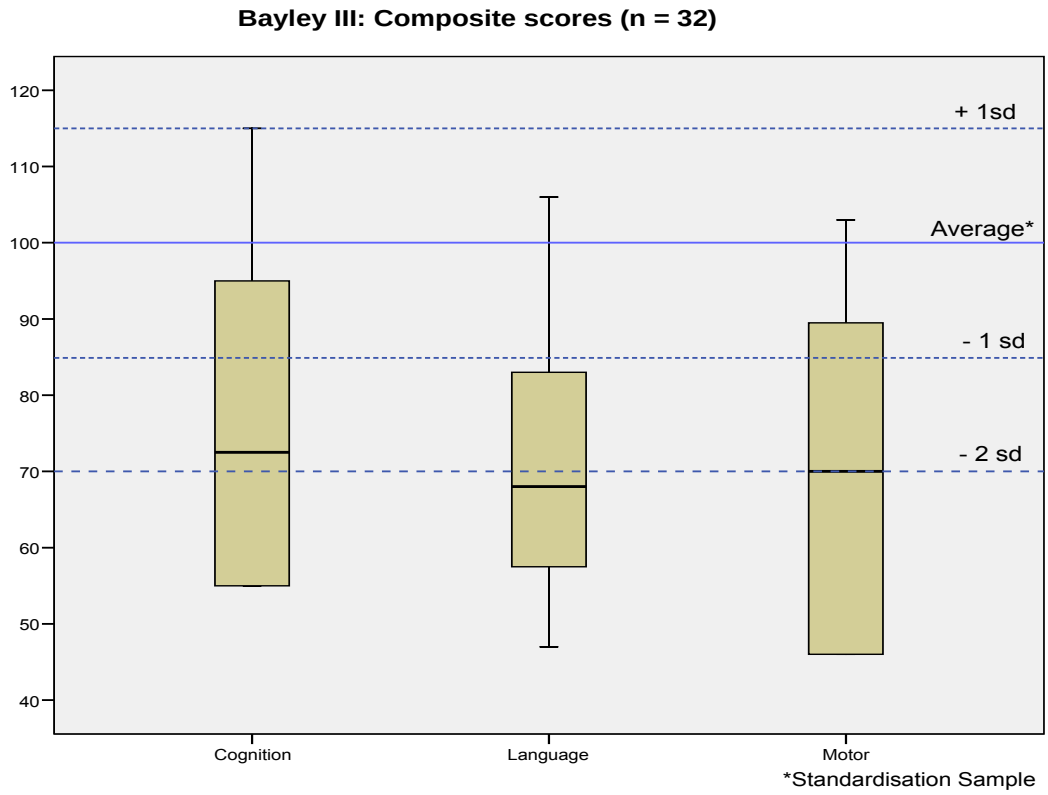


Figure 4.10 b): Distribution of Bayley III composite scores (subgroup with available Bayley III: adaptive Behavior Scale Scores)



4.2.8.2 Parental perception of developmental function prior to seizure onset

The Vineland Adaptive Behavior Scales Survey Form (VABS) was completed for 39 subjects, 79.6 % of the 49 children that were also assessed with the Bayley III scales. As explained in the methods chapter (section 3.2.2.2) the VABS data were not obtained for 8 children with seizure onset in the neonatal period and data for 2 subjects were missing.

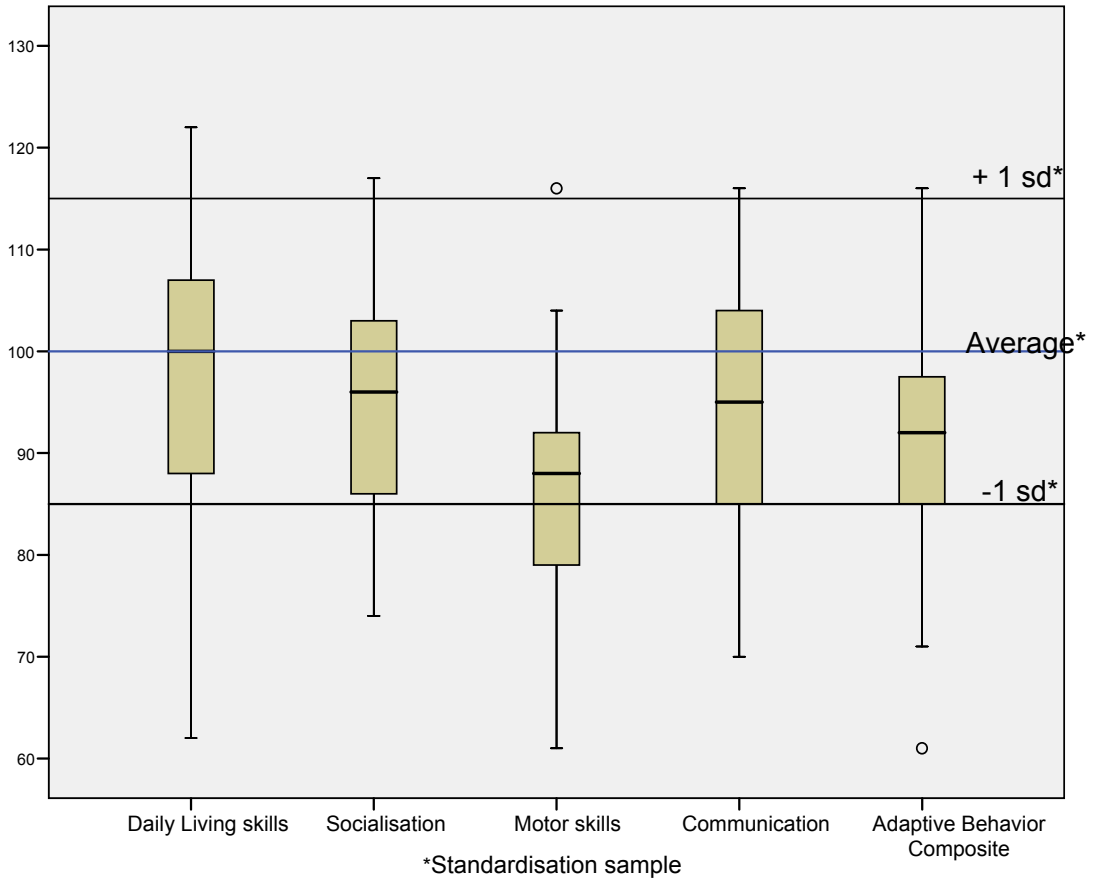
Descriptive statistics of the 4 domains and the Vineland Adaptive Behavior Composite (VABC) are detailed in table 4.23 and figure 4.11 illustrates their distribution in relation the standardisation sample. The range of scores is wide reflecting the heterogeneity of the cohort. Motor skill scores (derived from behaviours observed prior to seizure onset) were lower compared to the other

domains. Fifty percent of the VABC sores in this cohort were ranked at or lower than the 31st percentile of the age matched standardisation sample. Twenty-five percent of children had VABC scores that ranked between 2 to 1 sd below the age matched standardisation group.

Table 4.23: Results of Vineland Adaptive Behavior Scales - Survey Form (n=39)

Domains	**Mean**	**Sd**	**Range**
Daily Living Skills	98.5	14.2	62 - 122
Socialization	94.4	12.2	74 - 117
Communication	94	11.7	70 - 116
Motor Skills	86.5	10.7	61 - 116
Adaptive Behavior Composite	91.2	12.2	61 - 116

Figure 4.11: Distribution of Vineland Adaptive Behavior Scale domains (n = 39)



4.2.8.3 Predictors of the developmental status close to diagnoses (at baseline assessment)

In order to explore the relationship between developmental status close to diagnosis and clinical factors, neurophysiology and neuroimaging the Bayley III subscale data (obtained at enrolment) were reduced for further analysis. As described in the method chapter a single factor (Developmental Raw Score Factor [DF]) was generated using principal component analysis of the raw subscale scores. The proportion of the total variance explained by the DF was 93.7% (see appendix 10 for further details: component matrix with proportions of variance for each subscale raw score that can be explained by the factor).

Explorative univariate analyses of covariance with DF as dependent factor and age at testing as covariate revealed significant relationships between lower developmental function and the following factors: 'more than 20 seizures or cluster of seizures prior to the Bayley III assessment', 'abnormal neurological examination', 'aetiologically relevant neuroimaging findings', 'presence of interictal discharges on EEG 'and 'grossly abnormal EEG background abnormalities' (see table 4.24 for details). The developmental function as reported by the carers prior to seizure onset (VABC score) was significantly related to the results of the Bayley III assessment (DF) following diagnosis of epilepsy. There was no significant relationship with the age of seizure onset, number of anti epileptic drugs taken at the time of assessment and predominant seizure type.

Table 4.24: Results of explorative analysis – predictors of developmental function: Univariate Analyses of Covariance (dependent factor: DF*, covariate: age at testing)

Independent Factor	n	DF* mean (sd)	F - ratio	p-value
Epilepsy onset			F (1,46) = 0.89	0.35
< 6 months	27	-0.37 (.78)		
> 6 months	22	0.46 (1.1)		
Number of AEDs at the time of evaluation			F(3,44) = 2.84	0.49
0	5	1.31 (1.1)		
1	24	0.13 (0.89)		
2	15	-0.39 (0.82)		
3	5	-0.76 (0.65)		
Number of seizures /seizure clusters prior to developmental assessment:	15	0.68 (0.79)	F (1,45) = 17.69	**<0.001**
<= 20	33	-0.37 (0.84)		
> 20				
Seizure types:			F(2,44) = 0.56	0.58
Spasms	15	-0.48 (0.40)		
Generalised	6	1.3 (0.71)		
Focal and secondarily generalised	28	-.016 (1.06)		
Development prior to seizure onset :	39		F (1,36) = 5.06	**<0.001**
VABC score**				
Neurological examination:			F(1,46) = 56.21	**<0.001**
Normal	25	0.73 (0.85)		
Abnormal	24	-0.76 (0.38)		
Neuroimaging Findings:			F(2,43) = 6.23♣	**0.004**
Aetiologically relevant	23	-0.460 (0.92)		
Aetiologically uncertain or not relevant	10	0.20 (0.78)		
Normal	13	0.45 (0.90)		
EEG:			F(1,44) = 13.57	**0.001**
Normal	8	1.04 (0.86)		
Abnormal	39	-0.28 (0.62)		
EEG - Interictal epileptiform discharges:			F(1,44) = 8.51	**0.006**
Absent	17	0.51 (1.1)		
Present	30	-0.37 (0.73)		
EEG – Background activities:			F (2,42) = 4.18♣♣	**0.022**
Grossly Abnormal	18	-0.79 (0.37)		
Unspecific abnormalities	15	0.31 (0.10)		
Normal	13	0.53 (0.91)		

*DF = Developmental –Raw-Score Factor: generated from raw sores of Bayley III subscales by Principal Component Analysis

**VABC = Vineland Adaptive Behaviour Composite score entered as covariate in addition to 'age at testing'

♣Contrasts 'Neuroimaging Findings': higher DF values with 'normal' compared to 'aetiologically relevant' findings [t(43) = -3.51, p=0.001, r=0.5], DF values not significantly different with normal compared to 'aetiologically uncertain or not relevant' findings [t(43) = -1.512, p 0.138, r=0.2]

♣♣Contrasts 'EEG – background activities': higher DF values with normal compared to grossly abnormal [t(42) = -2.89, p = 0.006, r = 0.4], DF values not significantly different with normal compared to unspecific background abnormalities (t (42) = -1.332, p= 0.19, r = 0.2).

The factors that were significantly related to the DF ('abnormal neurological examination', 'presence of interictal discharges on EEG', 'grossly abnormal EEG background activities, unspecific EEG background abnormalities', 'aetiologically relevant neuroimaging findings', aetiologically uncertain or not relevant neuroimaging findings',> 20 seizures/seizure clusters prior to developmental assessment' and 'VABC score') and 'age at testing' were entered into a stepwise linear regression model (backwards method). The independent significant predictors in the final model were 'abnormal neurological examination' and 'presence of interictal discharges on the EEG' as well as development prior to seizure onset (VABC score), that had a weaker effect compared to the other factors (see table 4.25 for coefficients and p values).

There was a significant relationship between neurological examination and neuroimaging findings (χ^2 (1) = 15.2, p < 0.001) as well as neurological examination and background EEG activities (χ^2 (1) = 17.63, p < 0.001, see also tables 4.26 a) and 4.26 b)).

Table 4.25: Multivariable linear Regression (model1) - Coefficients (Dependent factor DF♦)

	B	95% Confidence Interval	β	p
Constant	-1.719	(-3.1) – (-0.34)		
Age at testing	0.09	0.07-0.11	0.68	< 0.01
Interictal epileptiform discharges	-0.4	(-0.71) – (-0.14)	-0.21	< 0.01
Abnormal neurology	-0.64	(-0.9) – (-0.34)	-0.35	< 0.01
VABC♦♦ score	0.012	0 – 0.02	0.17	0.051

Note R^2=0.87

♦ Dependent factor: Developmental –Raw-Score Factor: generated from raw sores of Bayley III subscales by Principal Component Analysis

♦♦ VABC = Vineland Adaptive Behavior Composite

4.26 a): Relationship between neuroimaging findings and neurological examination

		Neurological examination		Total
		Normal	Abnormal	
Neuroimaging:	Normal or not aetiologically relevant findings	20	5	25
	Aetiologically relevant abnormalities	7	20	27
Total		27	25	52
χ^2 (1) = 15.2, p < 0.001				

4.26 b): Relationship between EEG background activities and Neurological examination

		Neurological examination		Total
		Normal	Abnormal	
EEG Background activities	Normal or abnormal not otherwise specified	23	6	29
	Grossly abnormal	3	15	18
Total		26	21	47
χ^2 (1) = 17.63, p < 0.001				

Because both epileptic activity and structural brain abnormalities may manifest in abnormal neurology the relationship of neuroimaging, EEG and prior seizure activity to the developmental function were explored in a separate model. The following factors were entered in a backward linear regression analysis: ‘abnormal EEG’, ‘aetiologically relevant neuroimaging findings’, ‘aetiologically uncertain or not relevant neuroimaging findings' and ‘number of seizures / seizure clusters prior (> =20 versus < 20)’. The final model revealed significant independent relationships of both abnormal EEG and aetiologically relevant neuroimaging findings to developmental function. Frequent seizures prior to assessment (> =20) had also although non significant effect (see table 4.27).

Table 4.27: Multivariable linear Regression (model 2) - Coefficients
(Dependent factor DF♦)

	B	95% Confidence Interval	β	p
Constant	-0.25	-0.69 – (-0.19)		
Age at testing	0.08	0.06 - 0.10	0.62	< 0.01
Aetiologically relevant Neuroimaging findings	-0.3	(-0.59) – (-0.02)	0.17	0.035
Abnormal EEG	-0.55	(-0.94) – (-0.16)	-0.24	< 0.01
Seizures prior testing♦♦	-0.29	-0.63 – 0.04	-0.15	0.085

Note R^2=0.81

♦ Dependent factor: Developmental –Raw-Score Factor: generated from raw sores of Bayley III subscales by Principal Component Analysis

♦♦ Number of seizures/ seizure clusters prior Bayley III assessment (> =20 versus < 20)

4.2.8.4 Clinical features of the children at 1 year follow up

Of the 49 children that underwent initial assessment with the Bayley III 32 (65% of the initial cohort) were retested after a mean interval of 12.5 months (range 10-18 months). Seventeen children were lost to follow up: 12 children moved out of the area or the carers declined further participation and 5 children died during the follow up period (case fatality: 9% (95% CI 4 - 19)). Three of the later group had developmental brain malformations with neurological impairment; one was diagnosed with Ohtahara syndrome and one with SMEI (SCN1A missense mutation). Known causes of death included aspiration pneumonia in two cases and status epilepticus in the infant with SMEI (findings on post mortem examination performed in this child were in keeping with clinical history of status epilepticus). The post mortem examination of the child diagnosed with Ohtahara syndrome did not reveal any cause for the sudden death.

Table 4.28 illustrates the initial clinical features and epilepsy syndrome diagnoses of the 'follow up cohort' compared to the group that was lost to follow up. Children with epileptic encephalopathies and idiopathic epilepsies appear to be stronger represented in the group that was lost to follow up. The mean age of epilepsy onset was earlier in the subgroup lost to follow up.

Table 4.28: Clinical features and epilepsy syndrome diagnosis ***at baseline*** of patients followed up and those lost to follow up

	Follow up assessment carried out n = 32[1]		**Lost to follow up n = 17**	
Age at epilepsy onset [months] mean (sd)	7.9 (6.2)		3.8 (4.6)	
		N (%)		N (%)
Male		20 (62.5)	Male	8 (47)
Seizure status	Daily Weekly Monthly Seizure free < 3 months Seizure free > 3 months	11 (34) 2 (6) 2 (6) 13 (40) 4 (12)	Daily Weekly Monthly Seizure free < 2 months	7 (41) 1(6) 1 (6) 8 (47)
Epilepsy syndrome group	Epileptic encephalopathy Symptomatic focal (11) or Probably symptomatic focal (3) Idiopathic focal (3) or generalised (1) NAC	11 (34) 14 (43) 4 (12.5) 3 (9)	Epileptic encephalopathy Symptomatic focal (3) or probably Symptomatic focal (1) Symptomatic generalised Idiopathic focal	8 (47) 4 (23) 1 (6) 4 (23.5)
Specific Epilepsy Syndrome	West syndrome Ohtahara syndrome Neocortical epilepsies* Mesial temporal lobe epilepsy with hippocampal sclerosis BIS (non familial) BME NAC	10 (31) 1 (3) 8 (25) 1 (3) 1 (3) 1 (3) 10 (31)	West syndrome Ohtahara syndrome Dravet syndrome Neocortical epilepsies* BIS (non familial) NAC	4 (23) 1(6) 2 (12) 3 (18) 1 (6) 6 (35)

NAC = not classified, , * defined by location and aetiology, BME = Benign myoclonic epilepsy in infancy, BIS = Benign Infantile seizures; [1] Three children were not included in repeated measures ANOVA as data sets were incomplete: Idiopathic focal epilepsy – Benign infantile seizures (1), symptomatic focal epilepsy – Neocortical epilepsy (2)

Information about severity of epilepsy and number of antiepileptic drugs the children were treated with at the time of the follow up assessment is provided in table 4.29.

Table 4.29: Clinical features of subjets that were re-assessed with the Bayley III

	N=32
Age at follow up assessment [months]: mean (sd):	26.7 (8.6)
Retest interval [Months]: mean (sd)	12.5 (1.5)
Seizure severity: Daily Weekly Monthly Seizure free < 6 months (21 weeks) Seizure free >= 6 months	 8 (25%) 2 (6.3%) 2 (6.3%) 1 (3%) 19 (59%)
Number of antiepileptic drugs on: 0 1 2	 7 (22%) 18 (56%) 7 (22%)

4.2.8.5 Longitudinal changes of Bayley III scores and associated factors

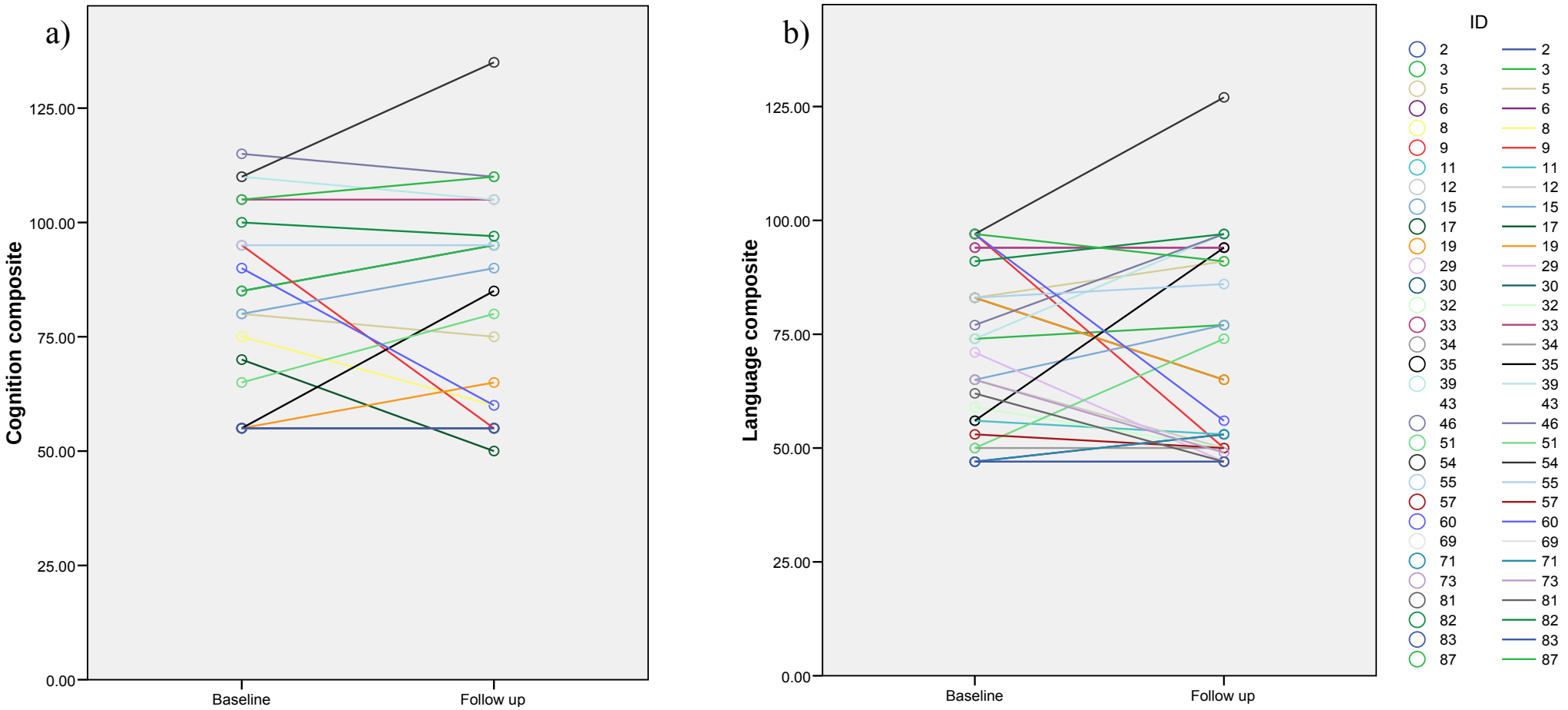
Figure 4.12 illustrates the longitudinal progress of Bayley III composite scores (cognition, language and motor) for each subject. The progress between baseline and follow up assessment is variable showing improvement, deterioration or no change. A Wilcoxon signed-rank test revealed no significant differences between cognitive and language composite scores at baseline and follow up assessment. The motor composite scores were slightly higher at follow up (mean 70.7, range sd 25.4) than at baseline testing (mean 67.7, sd 22.6), $z = -2.07$, $p=0.035$, $r = 0.3$. The difference between gross motor scale scores and fine motor scale scores at baseline and follow up, did not reach significance on statistical analysis:

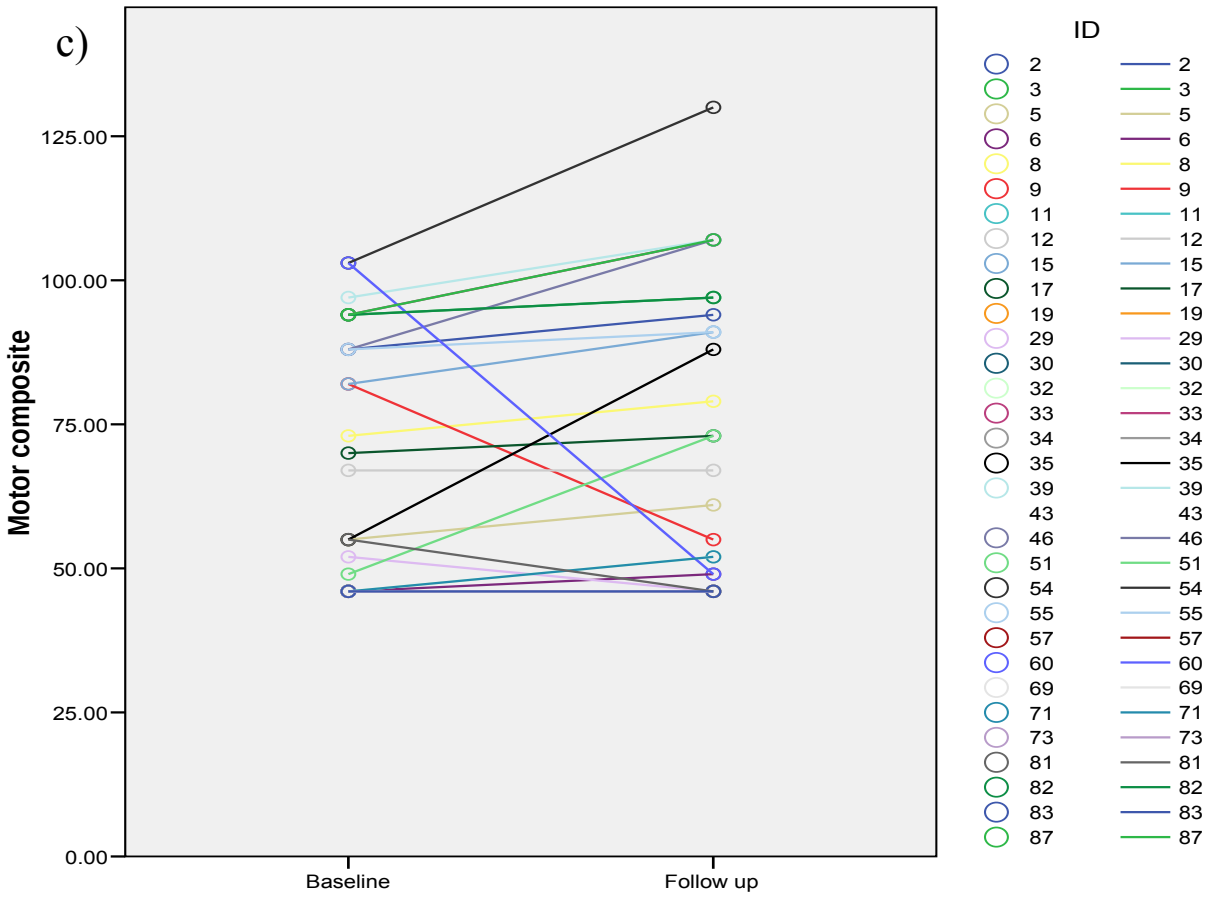
gross motor (baseline: mean 4.6, sd 3.5; follow up mean 5.1, sd 3.9) $z = -1.7$, $p=0.91$; fine motor (baseline: 4.6, sd 4.2; follow up 4.9, sd 4.5) $z = -1.6$, $p = 0.105$.

In order to explore the effect of clinical factors, neuroimaging and EEG findings to the longitudinal change of individual developmental function further analysis was conducted in two steps. The data were reduced using separate principal component analyses for the Bayley III composite scores at baseline and follow up. Each generated a single factor: Developmental composite factor at baseline [DCF-0] and follow up [DCF-1] (See appendix 10 for details of total variances explained and component matrices]. A repeated measure ANOVA revealed no significant difference between DCF-0 (baseline) and DCF-1 (at follow up). There was also no difference after adjustment for the following factors: 'neurological examination', 'seizure free for 6 months', 'presence of aetiologically relevant neuroimaging findings', 'EEG at enrolment' and 'number of AEDs at follow up assessment' (between-group variables).

Independent of the longitudinal effects (within subject analysis) 'EEG' [$F(1, 21) = 13.22$, $p = 0.002$] and 'neurological examination' [$F(1,21) = 13.3$, $p = 0.002$] at enrolment influenced significantly the DCF value (between subject analysis). Subjects with normal baseline EEG or normal neurological examination at enrolment had higher mean DCF values (average of DCF-0 and DCF-1) compared to those with abnormal initial EEG and abnormal initial neurological examination.

Figure 4.12: Change of Bayley III composite scores within subjects over follow up period:
Cognition (a), Language (b), Motor (c); (n = 32)




c)
Motor composite
125.00
100.00
75.00
50.00
25.00
0.00
Baseline
Follow up
ID
2
3
5
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4.2.9 Discussion: Findings of the observational cohort study (North London infancy epilepsy cohort)

4.2.9.1 Clinical features of the cohort

In this section the clinical features of the North London infancy epilepsy cohort (see table 4.5 in section 4.2.1.2) are discussed in the context of published data from other population or community based childhood epilepsy cohorts (composed of infants *and* older children).

The time interval between first and second seizure appears to be shorter in the North London infancy epilepsy cohort compared to other childhood epilepsy cohorts. Nearly all of the seizures / cluster of spasms (96%) in the 'Epilepsy in Infancy' cohort recurred within 4 weeks and the majority within one week (79%). After exclusion of seizure types that rarely occur as single events (such as spasms and myoclonic seizures), this pattern remained unchanged (recurrence aftert first seizure within 1 week in 72% and within 4 weeks in 95%). A smaller poportion of children between 1 month and 16 years registered in the childhood epilepsy cohort form Nova Scotia cohort[5] experienced their second seizure within the first month (70%) and the mean time interval between first and second generalized tonic clonic or partial seizure was 4.9 months (mean age at first seizure: 6.7 years, approximately 12% were under the age of 12 months)(Camfield et al., 1993;Camfield and Camfield, 2003). In the 'first seizure cohort'of children and adolescents from 1 month to 19

[5] Children, resident in Novo Scotia (Canada) presenting with recurrent unprovoked seizures between 1977 and 1985, were identified retrospectively through an EEG department of the single tertiary pediatric centre for the province (Camfield et al., 1996).

years of age ascertained by Shinnar et al from an inner city population[6] the mean time interval of recurrence was 9.6 months with a median of 6 months (mean age at first seizure 6.7 years) (Shinnar et al., 1990). Cases with absence seizures, myoclonic seizures and infantile spasms were excluded in the latter.

The relatively shorter time interval of seizure recurrence in infants would in keeping with the notion of increased propensity of the immature brain for seizures.

In the North London infancy epilepsy cohort the proportion of patients with preceding neonatal seizures was higher compared to childhood epilepsy cohorts. A history of neonatal seizures was observed in a quarter of cases, including 14% of children with seizure onset in the neonatal period. A similar proportion of cases with neonatal seizures has been recently reported from a hospital based cohort children with epilepsy onset under 2 years (23%) (Altunbasak et al., 2007). Only 2.6% (16 of 613) of children with newly diagnosed epilepsy in the Connecticut childhood epilepsy cohort (epilepsy onset at age 1 month to 15 years) had neonatal seizures (Berg et al., 1999c). Results of a large retrospective population based cohort study from Novo Scotia that investigated the relation of pregnancy and neonatal factors to subsequent development of childhood epilepsy were recently published (Whitehead et al., 2006). Neonatal seizures regardless of cause and pre-eclampsia were factors that were associated with the highest risk for the development of childhood epilepsy. The authors calculated the population attributable fractions for the risk factors. "The population attributable fraction is most commonly defined as proportional reduction in average disease risk over a specified time interval that would be achieved by

[6] Children and adolescents with a first unprovoked seizure seen at Montefioe Medical Centre, Bronx Municipal Hopita Centre, North Central Bronx Hopsital or private practices of authors were propectively enrolled (between October 1983 and September 1987) and followed (n=283, mean follow-up period: 30 months, 63% > 2 years) (Shinnar et al., 1990).

eliminating the exposure(s) of interest from the population while distribution of other risk factors in the population remains unchanged." (Rockhill et al., 1998). In case there are no other confounding exposer(s) of interest this can be calculated as follows: (Cumulative proportion of total population developing disease over specified time [IP_t] - cumulative proportion of unexposed persons who develop disease over interval [IP_0]) / Cumulative proportion of total population developing disease over specified time [IP_t] (Rockhill et al., 1998).

The population attributable risk of 'neonatal seizures' was relatively small with 5.3%. This means according to the quoted definition that, the average risk for childhood epilepsy could be reduced by 5.3 % if exposure to neonatal seizures were to be eliminated or only 5.3% of childhood epilepsy cases could be prevented following elimination of exposure to neonatal seizures, assuming these were causal. There was no significant association of childhood epilepsy with labour and delivery events. The population attributable fractions of other prenatal and neonatal factors ranged in this study from 2% to 8% (e.g. prenatal CNS anomalies: 2.8%, small for gestational age 7.4 %, neonatal metabolic disorders 5.7%). Although prenatal and neonatal factors (including neonatal seizures) contribute to the risk of developing epilepsy later in childhood they occur relative infrequent in the childhood epilepsy cohort and other factors (e.g genetic factors or later aquired brain injuries) that were not investigated here may have a larger weight. In the infancy epilepsy cohort, however, neonatal seizures may be more relevant for the risk to develop epilepsy. To confirm this hypothesis a poplation based case control study design would be required.

Febrile convulsions have an age dependent distribution with the majority occuring in the first 2 years of life (Verity et al., 1985;Sillanpaa et al., 2008). Therefore it is not

suprising that the proportion of subjects with a history of febrile convulsions in the North London infancy epilepsy cohort (21%) is higher compared to childhood epilepsy cohorts (10.3 – 16 %), that include infants *and* older children (Berg et al., 1999c;Camfield and Camfield, 2003;Arts et al., 2004;Larsson and Eeg-Olofsson, 2006).

One or more episodes of status epilepticus (SE) were reported in 7 (12%) of subjects enrolled in the North London infancy epilepsy cohort at baseline assessment, close to diagnosis. Similar or higher figures (12-17%) have been documents in hospital /specialist setting based infancy epilepsy cohorts (seizure onset under 1 year) (Chevrie and Aicardi, 1978;Cavazzuti et al., 1984). These proportions are higher when compared to data from childhood epilepsy cohorts around the time of diagnosis / enrolment (8.1% - 9.1%) (Berg et al., 1999b;Stroink et al., 2007). The notion that young children may be of particular risk is further supported by the observation that the incidence of convulsive SE (CSE) in childhood is highest in the youngest age group (< 1 year) (Chin et al., 2006) and by the follow up data of the Connecticut childhood epilepsy cohort showing a significant independent relationship of the risk for CSE with young age at epilepsy onset, previous CSE and symptomatic aetiology (Berg et al., 2004a). Four of the 7 cases with history of SE in the North London infancy epilepsy cohort had symptomatic focal epilepsies and 3 epileptic encephalopathy syndromes (2 testing positive for SCN1A mutations and 1 Ohthahara syndrome). Both the community based Connecticut and the hospital based Dutch childhood epilepsy cohorts demonstrated that the majority of cases of CSE occur *at or prior to the diagnosis* of epilepsy (and that an episode of CSE increases the risk for future episodes (Berg et al., 2004a;Stroink et al., 2007).

The proportion of children with developmental impairment preceding seizure onset in the North London infancy epilepsy cohort was relative high (39%) reaching values that have been previously reported from hospital or specialist clinic based settings (38-53%) (Chevrie and Aicardi, 1977;Matsumoto et al., 1983c;Battaglia et al., 1999). In addition neurological abnormalities at enrolment were observed in a significant proportion of children, giving further the impression that preexisting brain pathology was common in this population based infancy cohort.

The observed proportion of consanguineous marriages in the North London infancy epilepsy cohort (16%) may well be a reflection of the particular ethnic composition with different traditions of the surveyed inner city population. Consanguineous marriages are common in certain countries (North and sub-Saharan Africa, the Middle East, West, Central and South Asia) with 20 to > 50% compared to < 1% in most parts of Europe and North America of marriages between couples related as second cousins or closer (Bittles, 2008). The composition of the surveyed inner-city target population with relative high proportion of residents belonging to the non white ethnic groups (36%) as well as ethnic composition of the infancy cohort has been discussed previously (see sections 4.1.5; 4.1.6.2). Consanguinity is a potential risk factor for infancy onset epilepsy because autosomal recessive traits / disorders are more likey to be expressed. Ideally an age matched normal control group ascertained from the same population would be required to establish whether the relative high proportion of consanguineous marriages in the North London infancy epilepsy cohort is related to an increased risk for infancy onset epilepsy. Masri et al applied a case control design to investigate risk factors of for infancy onset epilepsy

(Masri et al., 2008). They acsertained an age matched 'normal' control group (n=111) from attenders of the general paediatric clinic of their institution (Jordan University Hospital) for comparison with their retrospective specialist clinic based cohort of children with epilepsy onset in the first year of life (n=55, attenders of the neurology clinic). Consanguinity was one of the significant risk factors (60% parental consanguinty in the patient group versus 30% in the control group). The authors have not provided further information about the patient population that attends the clinics at their institution. Thus, there are limitaions to which their findings can be applied to the general population as ascertainment bias cannot be assessed.

The case fatality of 9% observed in the North London infancy epilepsy cohort during the here described study period (see section 4.2.8.4) is similar to the figures reported previously from hospital and community based infancy epilepsy cohorts (7-10%) (Chevrie and Aicardi, 1978;Matsumoto et al., 1983c;Battaglia et al., 1999;Rantala and Ingalsuo, 1999;Datta and Wirrell, 2000). In comparison to the infancy epilepsy cohorts the documented proportions of deaths in childhood epilepsy cohorts range from 1.9-3.7% (Callenbach et al., 2001;Camfield et al., 2002;Berg et al., 2004b). Similar to the observations in the childhood epielpsy cohorts the deaths in the North London infancy epilepsy cohort occurred in children with neurological impairments and a diagnosis of a severe epilepsy syndrome. This included also one case that met criteria for definite sudden unexpected death in epilepsy (SUDEP)(Tomson et al., 2008).

4.2.9.2 Distribution of seizure types at enrolment, classification (Axis 2) and interrater agreement

Contrary to the reports from early hospital/specialist clinic based infancy epilepsy cohorts focal and secondarily generalised seizures were the commonest seizure types in the North London infancy epilepsy cohort documented at enrolment (Chevrie and Aicardi, 1978;Matsumoto et al., 1983a;Czochanska et al., 1994). Spasms were less frequent compared to some of these earlier studies occurring in around a third of infants. A similar proportion of infantile spasms were reported from a retrospective population based Finnish infancy epilepsy cohort (seizure onset between 28 days and 24 months (Rantala and Ingalsuo, 1999) and one hospital based series (Matsumoto et al., 1983a). As mentioned in the introduction, Korff and Nordli analysed video-telemetry data from infants (aged 1 -12 months) investigated in a specialist setting (epilepsy centre) (Korff and Nordli, Jr., 2006). The majority of seizures (101 events in 69 children) were classified as focal seizure types (76%) including spasms with features suggesting focal onset (28 of 76). Only 23 events were classified as generalised and 13 of these were spasms. Although bias of this series of infants investigated by Korff and Nordli towards more severe and lesional epilepsy cannot be excluded, these observations support the impression that the majority of seizures in children under two years are focal.

Explanations for the differences in proportions of seizure types between the various discussed infancy epilepsy cohorts include selection bias associated within various settings and that classification was based in most cases on description or clinical observation. There are limitations to which the electrographical correlate can be predicted accurately based on observation (Nordli, Jr. et al., 1997;Korff and Nordli,

Jr., 2006), descriptions of seizure manifestations may vary in content and quality, and application of the international seizure classifications (ILAE, 1981, 2001) to seizures occurring in infancy without modification is difficult. These limitations became apparent in the North London epilepsy in infancy study because in a significant proportion of cases the raters were not able to classify seizure types as listed in the 2001 ILAE proposal beyond gross categories such as 'focal' or 'generalised' (see tables 4.6 and 4.7 in section 4.2.2). Using large categories there was good inter-rater agreement between the two paediatric neurologists, who both had a special interest in epilepsy.

Data in the literature show that inter-rater agreement with respect to seizure types was mostly moderate. In one study ratings of a paediatric neurologist with 3 junior doctors in training were compared when applying the 1981 ILAE classification to seizure description in records of children newly diagnosed with epilepsy (Ottman et al., 1993). There was only poor or fair agreement and kappa scores improved when cases with insufficient information were removed. Six paediatric neurologists classified first seizures of children enrolled in the Dutch Study of Epilepsy in Childhood into 5 seizure categories, eg simple partial, complex partial, generalised etc, based on information from a questionnaire completed by a paediatric neurologist at enrolment (Stroink et al., 2004). There was moderate agreement when they used their own judgement (average kappa score 0.46) with some improvement of kappa scores when additionally specific criteria were used (average kappa 0.57).
Inter – rater agreement remains only moderate even when the bias introduced by seizure descriptions is removed and seizures are rated based on video recordings. In a recently published study 3 epileptologists independently classified 138 seizures by

analysing video tapes (obtained during video-telemetry sessions) of 60 patients (aged between 2 and 59 years, median age 26 years) whilst comparing the ILAE 1981 classification with a semiologic seizure classification (Parra et al., 2001). Average kappa scores for the ILAE 1981 seizure classification were 0.41(agreement in 39% of cases) and for the semiologic seizure classification were 0.56 (agreement in 63%).

The reviewed data from the literature as well as observations from the North London Epilepsy in Infancy Study show that seizure classification, especially in infants, based on clinical description is only limited possible and frequently unreliable with the exception of certain types such as epileptic spasms that have more narrowly defined motor manifestaions and frequency patterns. Video EEG can achieve more accurate classification, however, in everyday clinical practice there are limitaions to the availability of this resource and seizures may occur too infrequently. Thus the suggestions of the ILAE task force in the 2001 ICE proposal to apply seizure types as diagnostic entities, whith therapeutic and prognostice implications where a diagnosis of a specific electro-clinical syndrome cannot be obtained, is at least in the infancy group not practical (Engel, Jr., 2001). A classification of the type of epilepsy with relevance for patient management and prognosis requires especially in this early onset group a descriptive approach that incoporates information about aetiology, neurological as well as developmental status prior and after seizure onset, seizure severity and response to antepileptic treatment.

4.2.9.3 Distribution of epilepsy syndromes (Axis 3) at enrolment

Although for a third of infants in this cohort following baseline assessment a specific epilepsy syndrome could not be allocated the vast majority could at least be

categorised in one of the epilepsy syndrome groups that were suggested in the 2001 ILAE proposal. Specific epilepsy syndromes could not be determined because of insufficient information or mismatch of clinical data with the descriptions of the syndromes. For the classification of cases enrolled in the North London Epilepsy in Infancy Study we accepted two 'levels' of epilepsy syndrome diagnoses (first level: epilepsy syndrome group – second level: specific epilepsy syndrome if possible) and thus we were able to allocate an axis 3 description to the majority of infants.
Akiyama et al applied the 2001 proposal in a different way when they reclassified their large prevalence childhood epilepsy cohort (Akiyama et al., 2006). They were only able to identify an axis 3 diagnosis in 12% using solely the list of specific epilepsy syndromes without considering epilepsy syndrome groups. The majority of their cohort was described by seizure type (axis 2) as suggested in the 2001 proposal.

Contrary to our expectations only a relatively small proportion of cases in the North London infancy epilepsy cohort were identified with idiopathic epilepsy syndromes (9, 16%), mostly focal idiopathic epilepsy. Allocation of specific epilepsy syndromes in this 'idiopathic group' was difficult and only achieved in 3 of 9 cases (benign non-familial infantile seizures (2), BME (1)). Compared to later childhood, in the idiopathic epilepsy group specific syndromes with onset in infancy (outside the neonatal period) are less well delineated. Only two syndromes are currently included in the ILAE syndrome list (Benign myoclonic epilepsy in infancy and benign infantile seizures [BIS]- familial and non familial forms). (This issue will bediscussed further in the following section 4.2.9.4.)
More than two thirds of infants enrolled in the in the North London infancy epilepsy cohort presented with epilepsy syndromes associated with guarded long term seizure

outcome and developmental impairment. There are no population based data in the literature to compare these results as already discussed in the introduction. Comparison with hospital / specialist setting based cohorts of children with epilepsy onset under the age of 2 years is difficult because of the application of different syndrome classification systems, 1989 ICE in most studies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989;Caraballo et al., 1997).

Despite the collaborative population based design of this study to avoid referral bias under-ascertainment of clinically less severe epilepsy presentations cannot be completely ruled out. Reasons may include failure of notification but also possible failure of mild clinical presentations to meet inclusion criteria. 'Benign infantile seizures' [BIS], for example, have been described as a spectrum of conditions with variable severity of seizure presentations, some of which may be regarded as ‘seizures not necessarily requiring a diagnosis of epilepsy ‘, a category listed in the 2001 ILAE proposal (Engel, Jr., 2001;Specchio and Vigevano, 2006;Okumura et al., 2006). In pedigrees from families with SCN2A mutations for example some infants presented with a single seizure or single seizure cluster (Berkovic et al., 2004). Such cases may not meet inclusion criteria (recurrent seizures), when a single cluster of seizures within 24 hours is regarded as one event. In addition the age of onset of one recently described familial form overlaps with the neonatal period (benign neonatal infantile seizures, (Herlenius et al., 2007). Such cases may not be enrolled if these present with neonatal seizures only. BIS associated with gastroenteritis would not meet inclusion criteria because seizures are situation related rather than unprovoked.

In appendix 11 details of 4 cases are given that were initially enrolled in the North London infancy cohort but subsequently excluded because inclusion criteria were not met.

4.2.9.4 Classification of epilepsy syndromes: inter-rater agreement, intra-rater consistency, and stability of diagnoses after1 year follow up

The inter-rater agreement for epilepsy syndrome groups and specific epilepsy syndromes was only moderate or even poor referring to the issues discussed in the methods chapter (section 3.2.5.2). This is a striking result considering that both raters were paediatric neurologists with an interest in epilepsy and highlights the diagnostic difficulties when applying the syndrome group or specific syndrome diagnosis list of the 2001 proposal in the infancy epilepsy group.

Berg et al reported a high level of agreement (application of weighted kappa) between three child neurologists, who independently classified cases enrolled in the Connecticut childhood epilepsy cohort using the 1989 ICE (Commission on Classification and Terminology of the International League Against Epilepsy, 1989;Berg et al., 1999a). This was achieved because the raters agreed *a priori* rules on the application of the ICE. In the North London epilepsy in infancy study both paediatric neurologists applied the ILAE 2001 proposal according to their own judgement, a situation which more closely reflects the 'reality' of clinical practice. Berg et al observed slightly lower, although not statistically significant, Kappa values in the < 2 year old group (0.78-0.82) compared to children 2 years and older (0.83-0.85). In the < 2 year old group, similar to the observations in the North London epilepsy in infancy study, common discrepancies related also to the classification of cases as symptomatic focal epilepsies or infantile spasms (if these occurred as manifestation of a secondarily generalised syndrome). Epileptic spasms can be

generated by a focal lesion and as such be understood as secondarily generalised manifestation of symptomatic focal epilepsy. This aetiological approach may be justified as catastrophic onset focal symptomatic epilepsy (without epileptic spasms) may well present with developmental regression or arrest similar to that observed in West syndrome/infantile spasms. The electroclinical delineation of this aetiologically and clinically heterogeneous syndrome (West syndrome/infantile spasms) is not without controversies (Lux and Osborne, 2006). A recent consensus proposal suggests defining two main groups: a) West syndrome as essential combination of specific EEG feature (hypsarrythmia) and seizure type (clusters of epileptic spasms) with variable presence of developmental impairment before or after onset, and b) 'Infantile Spasms without hypsarrythmia' (Lux and Osborne, 2004). In order to justify such grouping further research needs to determine which other characteristics including clinical presentation; underlying aetiology and outcomes differentiate these two groups of patients with infancy onset epileptic spasms.

The second area of discrepancy in the North London Epilepsy in Infancy Study arose between 'idiopathic focal' and 'probable symptomatic focal' epilepsy. Both 'syndrome groups' are less narrowly defined with overlapping features and negative neuroimaging. Information about the further clinical progress is often required.

Intra-rater consistency for syndrome groups was high when cases were reclassified after a time interval. However there was more intra-rater variability with respect to specific epilepsy syndromes. Change of 'not able to classify' (NAC) to 'neocortical epilepsy' in several cases within the focal symptomatic epilepsy group by both raters may indicate increased familiarity with the 'formal' classification process compared

to the initial rating. Other changes particularly related to NAC cases within the idiopathic group. This involved alteration of the initial classification from focal and generalised idiopathic (rater B), and NAC to specific 'idiopathic' syndrome' diagnoses (including BIS and GEFS+, rater A). The diagnostic uncertainty that involves especially infants presenting with milder clinical presentations and normal interictal EEG becomes apparent. The initial diagnoses in this group are variable between experts and less consistent.

After a relatively short follow up interval (12 months) additional information did result in a change of syndrome diagnosis in only a small portion of cases (9-10%), that were followed (n=32). Berg et al reported changes in syndrome diagnosis 2 years following enrolment in the Connecticut childhood epilepsy cohort in a slightly higher proportion of cases (~14%). This may be due to the longer follow up period compared to this study. Similar to the observations by Berg et al reasons for change of syndrome diagnoses in this infancy epilepsy cohort was either evolution of the syndrome (West syndrome to focal symptomatic epilepsy) or further information lead to allocation of syndrome in cases that could not be diagnosed before. Variability of diagnoses over time affected especially infants with mild epilepsy presentations in the idiopathic group. As previously observed most discrepancies between raters occurred on the level of specific epilepsy syndrome diagnoses in this group. Two cases were classified under 'seizures not necessarily are requiring a diagnosis of epilepsy' by one rater for example whilst the other rater determined idiopathic generalised epilepsy not further classifiable.

This again demonstrates the overlap of syndrome categories in the ICE. Children meeting criteria for BIS and presenting with rare seizures or a single seizure cluster may not require a diagnosis of epilepsy. The latter judgment is impossible to make at the onset. Although some authors report that early diagnosis for example of BIS may be possible in a significant proportion ultimately a follow up period is required to confirm this (Okumura et al., 2000).

At onset an epilepsy syndrome diagnosis is possible in most infants. Infants with milder seizure presentations (rare seizures or seizure cluster often triggered by illnesses), with normal neuroimaging and interictal EEG, however, are difficult to pigeonhole in the current syndrome list of the ICE. An epilepsy syndrome lead approach to guide management and derive prognosis can not be applied in this group. Thus, a descriptive approach using the multi axial system of the 2001 ILAE task force proposal and omitting axis 3 (specific electroclinical syndrome) may be more appropriate.

4.2.9.5 Application of International Classification of Epilepsies and Epilepsy Syndromes in Infancy

The 1989 ICE grouped epilepsies and electro-clinical syndromes according to mode of onset of seizures and aetiological category. This resulted in a situation as discussed in the introduction that some entities were narrowly defined (e.g. infantile spasms/West syndrome or benign myoclonic epilepsy in infancy) whilst others were rather unspecific providing little information (cryptogenic focal epilepsy). The diagnostic scheme proposed in 2001 provided more flexibility. Epilepsy syndromes, however, were grouped in a similar dichotomous fashion as in the 1989 ICE with

introduction of additional groups including 'epileptic encephalopathies'. Although by applying 'epilepsy syndrome groups' and 'specific epilepsy syndrome' diagnosis most infants enrolled in the North London infancy epilepsy cohort could be classified, certain less narrowly defined categories such as 'idiopathic focal / idiopathic generalised' and 'probable symptomatic focal' provided little information and there was more inter-rater disagreement with variability over time. Determination of the mode of seizure onset based on clinical description in this age group is difficult as are assumptions with respect to outcome at outset when the aetiology is unknown (cases categorised under idiopathic or probable symptomatic). It is questionable whether such diagnoses are useful beyond the description of certain key clinical characteristics (e.g. seizure type, neuroimaging findings, developmental status, and response to medication).

There was also overlap between syndrome groups defined by aetiological category plus mode of seizure onset such as symptomatic focal and the epileptic encephalopathy group as observed in cases with infantile spasms / West syndrome in the presence of structural brain abnormalities. Presence of encephalopathy associated with frequent seizures or near continuous epileptiform activity on EEG is not confined to the specific electroclinical syndromes grouped under epileptic encephalopathies but can also occur with 'focal symptomatic epilepsies'. On the other hand encephalopathy may not be part of the clinical presentation of some infants meeting criteria for one of the syndromes grouped under epileptic encephalopathies (e.g. infantile spasms/West syndrome).

The identification of genetic aetiologies in a number of epileptic encephalopathy syndromes including Dravet syndrome (SCN1A), infantile spasms (CDKL5, ARX) and Othahara syndrome (STXBP1, Saitsu et al, 2008) resulted in further overlap of the epileptic encephalopathy syndromes with idiopathic syndrome group. Genetic aetiology is part of the definition of the latter syndrome group according to the 2001 proposal. The 'idiopathic' syndrome group in infancy onset epilepsies becomes thus rather heterogenous with regards to outcomes and its further justification is questionable. The term 'idiopathic' that infers a 'benign' prognosis because the majority of patients diagnosed with syndromes associated with onset in later childhood and adolescence respond to anti-epileptic medication, becomes misleading.

In the latest update the commission on classification and terminology of the ILAE has addressed some of these issues (see draft document available on www.ilae-epilepsy.org/visitors/centre/ctf/ctfoverview.cfm; commission report July 2009,(Berg et al., 2010)). The use of 'syndrome' should be restricted to a list of entities that are defined by a 'reliably identifiable cluster of electro-clinical characteristics', essentially the list of specific epilepsy syndromes organised according to peak age of onset (neonatal period, infancy, childhood, adolescence-adult). Description of epilepsies solely according to mode of seizure onset and aetiological category (idiopathic, symptomatic, cryptogenic) in the fashion of the 1989 ICE is discouraged. Instead epilepsies that do not meet criteria of the specific epilepsy syndromes should be organised in the first instance according to underlying cause or according to key characteristics if cause is unknown (seizure type, age at onset, interictal focus). Proposed groupings are:

electro-clinical syndromes, constellations (electroclinical-features in combination with specific lesions or causes, e.g. Rasmussen's encephalitis, mesial temporal lobe epilepsy with hippocampal sclerosis, gelastic seizures with hypothalamic harmatoma); epilepsies secondary to specific structural or metabolic lesions or conditions, epilepsies of unknown cause.

The commission proposes further changes to the terminology of the aetiological categories listed in the 1989 ICE: 'structural/metabolic' instead of 'symptomatic', 'genetic' or 'presumed genetic' instead of 'idiopathic', 'epilepsy of unknown cause' instead of 'cryptogenic'.

The commission retained the 'epileptic encephalopathy' concept with the notion " that certain forms of epileptic activity lead to severe cognitive and behavioural impairment above and beyond what might be expected from underlying pathology alone". Part of this concept is the idea that cognitive impairment associated with such forms of epileptic activity is potentially reversible with effective treatment. Further more suppression of epileptic activity early in the course could prevent negative and irreversible interference with maturation processes in the immature brain and thus improve neurodevelopmental and cognitive outcomes. The term 'epileptic encephalopathy' is according to this proposal no longer restricted to specific syndromes, but can now also be applied to individuals that present with encephalopathic features or worsening of these after the onset of epilepsy. The proposal also acknowledges that not all cases diagnosed with an epileptic encephalopathy syndrome (group of syndromes with a high risk for individuals to

develop cognitive or behavioural deterioration associated with epileptic activity) manifest cognitive or behavioural impairments.

To prove the epileptic encephalopathy concept in the context of infancy onset epilepsies is difficult because of the complex most likely reciprocal relationships between epileptic activity and underlying brain abnormalities.

As discussed in the introduction (section 2.1.1) historically the development of an epilepsy classification system based on electro-clinical characteristics was sensible because of the heterogeneity of the underlying conditions, which were frequently unknown. Over time the diagnostic tools including neuroimaging have become increasingly sophisticated and more widely available. In conjunction with the contributions of neurogenetics new aetiological entities have also been discovered. The syndromic approach has proved useful for clinicians to guide their choice of investigations and anti-epileptic medication as well as prediction of prognosis in the context of more narrowly defined electro-clinical syndromes. Review of the literature and results from the North London epilepsy in infancy study, however, shows that with the exception of West syndrome/infantile spasms other specific electro-clinical syndromes in this age group occur relative infrequently. A significant proportion of patients was classified according to gross aetiological categories and seizure onset (symptomatic focal, probably symptomatic focal or idiopathic focal etc) an approach that contributes little to management and prediction of outcome in a proportion of patients as discussed. Because epilepsy surgery procedures can now be offered to a proportion of patients, epilepsy management in recent years is driven more by an aetiological approach especially with the notion that intervention at an earlier stage may result in better outcomes. It is therefore very appropriate that the most recent

evolution of the epilepsy classification adopts more 'specific' aetiological categories (i.e. 'structural/metabolic', 'genetic', 'unknown cause') with less emphasis on the mode of seizure onset for patients that do not meet criteria for a specific electro-clinical syndrome. The new aetiological categories, however, overlap in individual cases and thus application may be challenging (e.g. specific genetic defects are associated with developmental brain abnormalities such as mutations in ARX, lis1 or DCX genes in patients with lissencephaly). Both should be stated - the electroclinical syndrome- if this can be determined *and* the aetiological category or if known the specific underlying cause to describe an epilepsy presentation appropriately.

A flexible organisation of epilepsies according to dimensions that are relevant for the specific purpose as suggested by the ILAE commission rather than a fixed classification system would offer a realistic option to meet the needs of research and clinical practice. Such a flexible approach would allow one to group non-lesional epilepsies according to clusters of electro-clinical features in order to conduct research into genetic aetiologies, or lesional versus non-lesional epilepsies to guide therapeutic interventions. A stronger emphasis on specific underlying causes would also allow research into predictors of natural progress within the specific electro-clinical syndromes.

4.2.9.6 Structural brain abnormalities and underlying aetiologies (Axis 4)

In keeping with the recently published guidelines on management of epilepsy in primary and secondary care (National Institute for Clinical Excellence, 2004) brain MR imaging was performed with exception of only 3 in all children enrolled in this study. Availability of neuroimaging (particularly MR imaging) data has contributed to the relatively high proportion of identified aetiologies in half of the cases in the

North London infancy epilepsy cohort. The identified disorders reflect the wide spectrum of aetiologies associated with epilepsy in this age group. Limited availability of magnetic resonance imaging and discovery of 'genetic' epileptic encephalopathies, with infancy onset more recently may be factors that explain the lower proportion of identified aetiologies in the retrospective Finnish population based infancy epilepsy cohort (22 of 72, 31%), that was mentioned in the introduction (Rantala and Ingalsuo, 1999). Similar to the findings in the North London infancy epilepsy cohort, with 41% of known aetiologies (~ 21% of the entire cohort), developmental brain lesions/malformations were the largest aetiological category in the Finnish infancy cohort , identified in 11 (50%). Although developmental brain lesions/malformations are also common aetiologies in childhood epilepsy cohorts as documented in a recent Swedish population based study with 43% of known aetiologies (28 of 65 children, 13.6% of the total cohort: n=205) the proportion in relation to the whole cohort is smaller compared to the infancy age group (Larsson and Eeg-Olofsson, 2006). Review of brain MR imaging data available from 518 (85%) children enrolled in the Connecticut childhood epilepsy cohort identified developmental lesions and malformations of cortical development in 51% of abnormalities potentially relevant to epilepsy (41 of 81 cases with aetiologically relevant lesions, 8% of cases with available MRI data) (Berg et al., 2009).

Nearly two thirds of children with developmental cortical malformations in the North London study had extensive unilateral or bihemispheric abnormalities. Seizure onset in this group was commonly early in the first six months of life, in a third of cases in the neonatal period. Although the age of seizure onset is variable amongst the

various forms of malformations of cortical development early onset in the first year appears to be a common feature especially in children with bilateral and diffuse abnormalities presenting to hospital / specialist based settings (Dalla et al., 1996;Vigevano et al., 1996;Kloss et al., 2002). In the North London infancy epilepsy cohort seizure onset in the neonatal period appeared also to be more frequent in the group of children with confirmed or strongly suspected metabolic conditions. The number of children with known aetiologies in this study, however, was too small for subgroup analysis to determine the relationship between aetiological categories and clinical features.

In most population / community based childhood epilepsy cohorts the proportion of cases with identified aetiologies is considerably smaller: between 18 % and 36% (Eriksson and Koivikko, 1997;Arts et al., 1999;Berg et al., 1999c;Larsson and Eeg-Olofsson, 2006). The higher proportion of remote symptomatic epilepsy in one retrospective Finish childhood epilepsy cohort (50%, children diagnosed in the 1960's) can be partially explained by the way cases were categorised, in accordance with the 1993 ILAE commission guidelines for epidemiologic studies(ILAE, 1993;Sillanpaa et al., 1999). Classification under remote symptomatic was based mainly on clinical evaluation and included cases with abnormal neurological examination (cerebral palsy) and / or learning difficulties.

Despite possible under recognition of symptomatic aetiologies in the childhood epilepsy cohorts because of the limited application of modern magnetic resonance imaging methods and genetic investigations, the impression that brain pathologies, especially structural abnormalities, are an important aetiological factor associated with epilepsy onset in infancy is upheld by our observations in a population based setting.

4.2.9.7 Quality of MR imaging and yield of neuroimaging in children with epilepsy onset under the age of 2 years

Despite the variability of MR imaging protocols, with a relative small proportion of sequences recommended to investigate 'epilepsy', and different magnetic field strength systems, the diagnostic yield was high in the North London infancy epilepsy cohort. Aetiologically relevant findings were documented in half and uncertain or not aetiologically relevant findings in a further 20 % of children imaged, giving a total of 70% positive findings. This yield of aetiologically relevant findings is significantly higher when compared with the to observations from Berg et al in the Connecticut childhood epilepsy cohort who initially reported lesions related to epilepsy in 12.7% of those imaged; 80% of the total cohort underwent neuroimaging: 63% MRI, 32% CT, 16% MRI and CT) (Berg et al., 2000b). In a more recent study Berg et al reviewed MRI data available of 518 (85%) of children enrolled in the Connecticut childhood epilepsy cohort (Berg et al., 2009). This included research MR images of 299 children (57%) who were able to undergo MR scanning without sedation, clinical scans with various protocols available for 103 (20%) and written reports for 113 (21%) cases. Available MR scans were reviewed independently by two neuroradiologists. Eighty two (16%) children had positive MRI scans with aetiologically relevant lesions for epilepsy. Although the yield of MRI was higher in the age group under 2 years in this cohort (approximately 25%) 'age under 2 years' was not a significant predictor for positive MR findings in a multivariate regression model. Abnormal neurological examination was the strongest significant predictive factor for positive findings on MR in this cohort. The heterogeneity of MRI data with probably different sensitivities for the diagnosis of lesions may partially explain the

lower yield of positive findings in the age group under 2 years in the Connecticut cohort compared to the North London infancy epilepsy cohort.

A small proportion of images reviewed in the North London 'Epilepsy in Infancy Study 'were judged to be of insufficient quality. When these were repeated, just over half these MR scans revealed new diagnostic information (3 of 5 repeat scans). In a quarter of MR images reviewed, dedicated epilepsy protocol sequences were recommended in order to identify a focal lesion should seizures persist or surgical treatment be considered. Overall 20% of the MR images reviewed in this study were repeat images and half these obtained new diagnostic information. The recommendation by 'NICE' to perform MR imaging in all children with new onset epilepsy under the age of two years seems justified considering the high yield of positive relevant findings in then North London infancy epilepsy cohort (National Institute for Clinical Excellence, 2004;Berg et al., 2009). This high yield was, however, achieved with a proportion of MR images needing to be repeated with increased risk from sedation and additional costs. In order to achieve optimal MR images appropriate sedation protocols (with consideration of general anaesthetic in individual cases) as well as adequate/specialised sequences are required (Saunders et al., 2007). These were not uniformly available across institutions as demonstrated in the North London 'Epilepsy in Infancy Study'. In order to minimise false negative MR imaging results due to inappropriate MR protocols with poor sensitivity and the need for repeat scans the NICE guidelines should thus also provide recommendations, at least basic generic principles, regarding adequate protocols for this particular patient group. Choice of sequences of a standard protocol could follow the generic principle of combining T2 - weighted images in two planes

supported by T1-weighted images in 2 planes, which has been found to be useful in practice (Saunders et al., 2007). Coronal images (obtained to lie perpendicular to the hippocampus) for optimal visualisation of mesial temporal lobe structures combined with axial images in T2 weighted sequences and 3-D T1- weighted volume acquisition reconstructed in 3 planes (sagittal, axial, coronal) have been recommended in international guidelines for neuroimaging of children with recent onset epilepsy (Gaillard et al., 2009). The stage of physiological brain maturation with increased brain water in children less than 2 years requires consideration and special sequences to achieve optimal contrast resolution in this age group are necessary. Dual-echo short tau inversion recovery (STIR) sequence may therefore be considered in preference to the conventional T2 weighted fast (or turbo) spin-echo sequence in children under 2 years (Saunders et al., 2007). There are, however, other ways to address this problem of increased brain water content in young children using conventional T2 weighted sequences (i.e. fast spin-echo) and it is therefore difficult to include such details in national guidelines beyond a general statement that this needs to be resolved in discussion with local neuroimaging services.

The guidelines should also state the need for specialised MR technologies in individual cases with medication resistant seizures, when MR imaging is negative and focal epilepsy is still suspected. Standard MR imaging does not appear to be sensitive enough to identify focal lesions as shown in a series of 123 consecutive adult patients with refractory epilepsy undergoing pre-surgical work up by von Oertzen et al (Von et al., 2002). In the setting of a specialist epilepsy centre, external standard MR scans reviewed by expert neuroradiologists failed to identify 55% of focal lesions recognised with dedicated epilepsy protocol scans. More recently such observations have also been reported from paediatric epilepsy surgery programs.

Salamon et al compared external and internal MRI reports of a selected series of 42 paediatric patients that underwent epilepsy surgery with a histopathologically confirmed diagnosis of focal cortical dysplasia at their institution (University of Calfifornia, Los Angeles) (Salamon et al., 2008). Reports of external scans identified abnormalities in 38% (15 of 42 patients), whilst reports of internal MR images (scans performed at their institution) identified an extra 40% of lesions (11 subtle and 6 obvious abnormalities).

Application of specialised MR techniques with high sensitivity to diagnose focal lesions across the whole group of children with recurrent afebrile seizures may not be cost effective. Some of these issues have been addressed in recently published recommendations by a task force of the ILAE (Gaillard et al., 2009).Von Oertzen et al also highlighted the importance of expertise in reporting of MR images. The sensitivity of MR reports for focal lesions of radiologists, who were not experienced in reporting of images of epilepsy patients, was lower (39%) compared to those from expert 'epilepsy' neuroradiologists (50%) (Von et al., 2002). To some extent a similar observation has also been made in the North London Epilepsy in Infancy Study, when significant brain pathologies were not mentioned in local reports in at least 2 cases, namely 'Tuberous sclerosis' and 'bilateral polymicrogyria'. NICE guidelines should thus also emphasise that MR images should be interpreted by radiologists with sufficient experience in paediatric neuroradiology.

4.2.9.8 Developmental status close to diagnosis and its predictors

This is the first study that has used standardised validated methods to evaluate the developmental status in a population based infancy epilepsy cohort close to diagnosis. The majority of children demonstrated developmental impairment with

63-71% of composite scores falling below the average for the standardisation sample (composite scores < 80: motor 63.3 %, language 71.4 %, cognition 63.3%). Over half of this cohort had severe developmental impairment with Bayley scores in the extremely low range (>2 sd below the average of the standardisation sample) and similar distribution in all subscales (expressive and receptive language, fine and gross motor, cognition). In keeping with the observations from hospital and specialist clinic based cohorts after longer follow up periods only approximately a third of infants demonstrated developmental status in average range (Czochanska et al., 1994;Battaglia et al., 1999;Altunbasak et al., 2007). This study shows that developmental/cognitive impairments are already present in approximately two thirds of infants close to diagnosis. The significant relationship between the DF and the VABC identified in our study suggests that in many of the children with developmental impairments the abnormalities were present prior to presentation with seizures.

The proportion of individuals with subnormal global cognitive function is much higher in the infancy epilepsy cohorts compared to childhood epilepsy cohort. Berg et al found subnormal global cognitive function in just over a quarter of children nine years after enrolment in the Connecticut cohort (Berg et al., 2008a).

'Symptomatic aetiology' has been an important predictor of adverse developmental /cognitive outcome of infants with seizure onset in the first 12 o r 24 months of life (Chevrie and Aicardi, 1978;Matsumoto et al., 1983c;Cavazzuti et al., 1984;Czochanska et al., 1994;Battaglia et al., 1999). In the early studies categorisation of cases as symptomatic or remote symptomatic was based on history

(including preceding developmental status), neurological examination or, neuroimaging if available grouping subjects with *known* or *assumed* static (mostly structural) brain pathologies together (Chevrie and Aicardi, 1977;Czochanska et al., 1994). As most infants in the UK with new onset epilepsy undergo neuroimaging in accordance with current national management guidelines data could be obtained in this observational study to examine the relationship of 'structural brain abnormalities' and other factors to developmental status separately. In univariate analyses similar factors as implicated in the hospital based infancy epilepsy cohorts were significantly associated with lower developmental function: developmental status prior to seizure onset (Vineland Adaptive Behaviour Composite, VABC), seizure severity prior to the developmental assessment, abnormal neurological examination, aetiologically relevant findings on neuroimaging and EEG abnormalities (interictal discharges, grossly abnormal background activities)(Matsumoto et al., 1985;Battaglia et al., 1999;Altunbasak et al., 2007).

Contrary to the observations in some of the hospital based series no significant relationships to younger age at seizure onset (< 6 months) and seizure type was demonstrated (Chevrie and Aicardi, 1978;Matsumoto et al., 1983b;Cavazzuti et al., 1984;Battaglia et al., 1999). In those series not only infantile spasms but also partial and secondarily generalised seizures were associated with worse outcomes compared to children with generalised seizures (other than infantile spasms). The difficulties to classify seizures in this age group with considerable inter-rater variability have been already discussed. Variations in seizure classification may be partially responsible for the observed lack of relationship between seizure type and developmental

function in the North London infancy epilepsy cohort. Only a small proportion of children was classified as having predominantly generalised seizures.

Multivariable regression analysis revealed abnormal neurological examination and presence of interictal discharges on EEG as factors that independently predicted and significantly poor developmental function close to diagnosis. In addition preceding developmental status (VABC) had an effect, which however did not reach significance. It is not surprising that aetiological relevant findings on neuroimaging were not retained as predictor for developmental status in the model. Patients with abnormal neuroimaging were also likely to have abnormalities on neurological examination. 'Abnormal neurology ' was significantly associated with 'aetiological relevant findings on neuroimaging' and 'grossly abnormal EEG background activities' therefore only one factor was retained after correction for the other. When the relationship of neurophysiology, neuroimaging findings and seizure severity to the developmental status was investigated in a separate multivariate linear regression model both 'abnormal EEG' and 'aetiological relevant neuroimaging findings' had significant independent effects. Incidental or uncertain neuroimaging findings were not significantly related to the neurodevelopmental status.

These findings support the view that developmental impairment in children with infancy onset epilepsy is already present in a large proportion at onset and that epileptiform activity and structural brain abnormalities are important predictive factors. This would further indicate that at or close to diagnosis the cerebral processes that determine developmental impairment may have already taken effect beyond reversibility before therapeutic interventions can be practically considered.

Thus the degree to which these impairments can be reversed or alleviated by *early* therapeutic interventions may be largely determined by the underlying aetiology which manifests itself with abnormal developmental status *and* epileptiform activity.

4.2.9.9 Longitudinal change of developmental function and associated factors

The developmental trajectories of children enrolled in the North London infancy epilepsy cohort observed over a short period of approximately 12 months following the diagnosis of epilepsy were variable. Some infants continued on the same level, others improved and some deteriorated. This may be a reflection of the heterogeneity of this group with respect to clinical presentation and underlying aetiologies. Across the whole group there was no significant common trend for either worsening or improvement in cognition and language composite scores. Although there was a significant trend of motor composite scores to increase over the follow up period the difference was small (only 3 points). This may indicate that motor skills (especially gross motor skills) show some recovery over the follow up period, whilst this is not the case for cognition and language. However, the slight increase of gross motor and fine mptor scale scores observed over the follow up period did not reach statistical significance; most likely explained by the small sample size.

There was no significant difference of the developmental composite factors (derived from the Bayley III composite scores by principal component analysis) between baseline (DCF-0) and follow up (DCF-1). Following correction for confounding factors such as ‘Aetiologically significant structural brain abnormalities on neuroimaging’, ‘6 months seizure free status’, ‘initial abnormal EEG’, ‘initial abnormal neurological examination’ and ‘number of anti-epileptic medications taken

at follow up assessment' in the statistical model no significant difference of developmental function at baseline and follow up. Independent from longitudinal changes children with normal EEG and neurological examination at enrolment demonstrated better developmental function compared to those with abnormal neurology and EEG. Thus, the initial developmental status (in the first 3 months after diagnosis) determined the developmental function after short term follow up. However, small longitudinal changes in developmental function over the relative short observation period may not have become significant due to sample size effects. Small changes in developmental function are likely to be cumulative over time and therefore longer observation periods may be required for longitudinal differences to become significant.

Data to compare these findings are available in the literature. Berg et al observed adaptive behaviour function of children with early onset epilepsy enrolled in the Connecticut childhood epilepsy cohort over 3 years (Berg et al., 2004c). The Vineland Adaptive Behavior Survey (VABS) was completed with carers of children with newly onset epilepsy under the age of 3 years at enrolment and annually (n = 172, 67 % under 2 years at onset, complete data sets available for 70% of subjects). Remote symptomatic aetiology, diagnosis with an epileptic encephalopathy syndrome, and intractable epilepsy at 3 years follow up were all significantly associated with lower adaptive behaviour function at baseline. Following adjustment for aetiology a diagnosis of an epileptic encephalopathy syndrome had only modest and marginally significant effects. After adjustment for aetiology and epileptic encephalopathy syndrome intractable seizures (assessed at 3 year follow up) did not have an effect on baseline Vineland scores. Longitudinal analysis demonstrated that

most children who had average (normal) adaptive behaviour function at enrolment continued on the same level without decline. These were individuals with non-symptomatic epilepsy who were not diagnosed with an epileptic encephalopathy syndrome. Children with risk factors (symptomatic epilepsy, epileptic encephalopathy syndrome, intractable seizures at 3 year follow up) had lower function already at enrolment and demonstrated further decline during the follow up period (probably indicating a failure to acquire skills at an adequate rate).

'Epilepsy syndrome diagnosis' is a description of a cluster of several factors including EEG characteristics, seizure type, and other clinical features, which infers prognostic expectations especially in the case of epileptic encephalopathy syndromes. Thus, strong correlations between remote symptomatic aetiology, epileptic encephalopathy syndrome and intractable epilepsy as reported in the study by Berg et al are not surprising (Berg et al., 2004c). The subgroup of children diagnosed with epileptic encephalopathy syndromes is by definition likely to be biased towards developmental impairment and therefore the argument becomes circular. Taking this issue into account as well as the fact that adaptive behaviour based on perception of carers and a formal neuropsychological assessment are not equivalent but related measures, the study from Berg at al is in keeping with the observation made in the North London Epilepsy in Infancy Study that developmental function at diagnosis determines largely the status at follow up. Although the cognitive outcome of children diagnosed with idiopathic or cryptogenic epilepsies is generally more favourable, specific more subtle intellectual deficits such as slower processing speed have been identified on long term follow up in individuals with average intellectual function (Berg et al., 2008b).

Data from a population based setting confirm the observations from specialist settings that epilepsy onset in the first 2 years of life is associated with a higher risk for developmental/cognitive impairment compared to epilepsy onset in later childhood and that this is strongly related to the underlying, in the majority structural, brain pathologies manifesting with seizures in this age group. The observations of Berg et al, who documented subnormal cognitive function on long-term follow up in a quarter children enrolled in the Connecticut childhood epilepsy cohort (epilepsy onset 1 month to 15 years) have been mentioned in the introduction and previous section (Berg et al., 2008a). In the Connecticut childhood epilepsy cohort multivariable logistic regression analysis demonstrated that developmental and acquired brain pathology (remote symptomatic aetiology) was the factor associated with the highest risk for global cognitive impairment, followed by young age at onset (< 5 years), ongoing antiepileptic treatment and lastly epileptic encephalopathy syndrome diagnosis. The latter combines some of the effects of the other factors. Even within the subgroups defined by aetiology (symptomatic versus idiopathic/cryptogenic epilepsy) or syndrome diagnosis (focal symptomatic and idiopathic generalised epilepsy) children with early epilepsy onset (<5 years) were more likely to be cognitively impaired compared to subjects with later onset (> 5 years). Despite of the overlapping effects of the factors, the data from the Connecticut childhood epilepsy cohort support the idea of an additional independent adverse effect of seizure activity in young age on cognitive outcome. In a separate study, age at epilepsy onset was the best predictor of intellectual dysfunction in a cohort of children with temporal lobe epilepsy undergoing pre-surgical evaluation. Children with epilepsy onset in the first year of life had a particular high rate of

intellectual impairment (82% versus 32% in the rest of the study population) (Cormack et al., 2007). From this observation in a hospital based cohort of children with focal brain lesions it can however not be excluded that early age of seizure onset and degree of cognitive impairment are also determined by the underlying brain abnormality itself.

Tuberous sclerosis (TS) has been used as model to investigate the relationships of underlying brain pathology, epileptic activity, cognitive function and autistic spectrum disorder. Tuber load, location of tubers, early seizure onset and presentation with epilepsy were all found to be relevant risk factors for autistic spectrum disorder (Bolton, 2004;O'Callaghan et al., 2004). Bolton et al reported that location of tubers in the temporal lobe appeared necessary but was not sufficient to explain outcome with autism in a mixed TS cohort of patients attending a specialist clinic and referrals form an epidemiological study. Data were obtained from a retrospective case note review. The following significant and independent neuro-epileptic predictors were additionally determined: 'age of seizure onset in the first 3 years of life' and 'presence of temporal lobe discharges'. Although the authors found a significant relationship between history of infantile spasms and autism, this factor became not significant in a multivariate regression analysis when the other two neuro-epilptic predictors were entered. Most likely because of the overlap of these factors (early seizure onset and history of infantile spasms). In a different study O'Callaghan et al investigated the relationship between tuber load, history of infantile spasms and IQ in a population based cohort of patients with tuberous sclerosis (O'Callaghan et al., 2004). Patients without a history of infantile spasms had significantly higher median IQ values compared to those with a history of infantile

spasms. In a multivariable regression model both factors tuber load and infantile spasms had significant and independent effects on IQ (whereby in the model tuber load explained 33% and infantile spasms 15% of the variance of the IQ values). This result would add more support of the notion that epileptic activity in very early age has an additional negative impact on cognitive outcome beyond the underlying brain pathology.

Early interventions to achieve seizure control could thus have most impact on developmental and cognitive outcome in the subgroup of infants with unknown aetiology and signs of developmental impairment with onset of the seizure disorder. The impact of a lag of treatment on developmental outcome has been investigated in a number of studies in children with infantile spasms of unknown aetiology (cryptogenic, normal development prior to onset) and Down's syndrome with controversial results. Several studies suggest that longer time period to start of treatment or cessation of spasms is associated with poorer developmental outcome (Eisermann et al., 2003;Kivity et al., 2004;Hamano et al., 2007;O'Callaghan et al., 2011). The numbers of children included are relative small and the design is often retrospective with the exception of 2 studies (Eisermann et al., 2003;O'Callaghan et al., 2011). Two other studies (one prospective intervention study, the other retrospective case note review) could not find a relationship between treatment lag and developmental outcome in the subgroup with cryptogenic infantile spasms (Glaze et al., 1988;Partikian and Mitchell, 2010).

The impact of time to start of antiepileptic treatment and developmental status at enrolment and 12 months follow up has not been investigated in the North London infancy epilepsy cohort and this could be subject of further data analysis.

Both closely interrelated factors 'underlying brain pathology' and 'epileptic /seizure activity' have adverse effects on developmental/cognitive outcome in this early age group. The magnitude of their independent effects is difficult to disentangle in human observational studies and experimental animal studies are required to shed more light on these complex relationship (Holmes, 2005). The negative impact of brief recurrent seizures on the normal immature brain has been documented in animal rodent models. Exposure to seizures at an very early age was associated with cognitive dysfunction especially spatial memory at later age (Sayin et al., 2004;Karnam et al., 2009). Following exposure to hypoxia, trauma, status epilepticus or febrile seizures at very young age a cascade of events on a molecular and a cellular level is triggered with the result that rodents present later with spontaneous seizures. Such processes involve interference with the normal age dependent expression of receptor subunits with impact on balance of excitatory glutamatergic and inhibitory GABAergic neurotransmission, induction of abnormal dendtritic sprouting and alteration of synaptic pruning as well as neurogenesis (Rakhade and Jensen, 2009). The result is not only epilepsy but also cognitive dysfunction as shown in rodent pubs exposed to febrile seizures (Dube et al., 2009).

5 CHAPTER 5: LIMITATIONS AND CONCLUSIONS

This study aimed to obtain population based data on children under the age of 2 years with newly onset epilepsy. In particular the purpose was to determine frequency of epilepsy onset in this age group, associated structural brain abnormalities, types of epilepsy and whether these can be classified according to the international classification system of epilepsies and epileptic syndromes (2001 proposal). In addition the neurodevelopmental status of children enrolled in this observational

incidence cohort was examined using standardised evaluation tools with the aim to determine predictors of neurodevelopmental function close to diagnosis and factors related to longitudinal change.

The literature review in section 2.2 concluded that data available in the literature pertaining clinical presentation and outcome of infants with newly onset epilepsy may not be representative of the general population. Much of the information has been obtained retrospectively and if prospectively collected, data origin from hospital or specialist settings may be biased to more severe types of epilepsy. In addition application of modern neuroimaging techniques (MRI) was limited at the time most infancy epilepsy series were published with possible under documentation of associated structural brain abnormalities as a consequence.

In the population survey part of this study active and passive notification systems, providing two sources of ascertainment, were successfully applied to determine an ascertainment adjusted incidence of new onset epilepsy in children under the age of 2 years of 56.3 – 88.5 (95% CI) / 100.000 children under 2 years/ year. These figures overlap with confidence intervals of incidence estimates calculated from data of other comparable studies (Camfield et al., 1996;Kurtz et al., 1998). The case numbers enrolled in the North London Epilepsy in Infancy Study were small and therefore the confidence interval is relatively wide. A two source capture recapture method was applied taking into account that this approach would not permit adjustment for case heterogeneity and list dependence in the statistical model. Because positive dependency between the two sources in this study could be assumed and in accordance with the argument made by Brenner, the two source

capture recapture method was used rather than a traditional case registration approach in order to reduce the degree of case underestimation associated with the latter (discussed in paragraph 4.1.1.4)(Brenner, 1995). The completeness of case ascertainment as determined in this study (76 %) is likely to be an overestimate. This figure, however, is comparable with completeness of ascertainment estimated by Chin in NLSTEPSS, who applied similar notification systems in the same geographical area using 3 sources and log-linear capture-recapture modelling (Chin, 2005;Chin et al., 2006).

In keeping with the findings of previous studies the incidence of new onset epilepsy falls steeply in the second year of life (Hauser et al., 1993;Camfield et al., 1996;Kurtz et al., 1998). The risk of new onset epilepsy in the first year of life is almost 3 times higher compared to the second year when data of two other comparable studies and the 'North London Infancy in Epilepsy in Infancy Study' are fitted with poisson regression models (2.88; 95% CI 2.15-3.9; $p < 0.0001$) (Camfield et al., 1996;Kurtz et al., 1998). These observations in human populations would be compatible with the findings in animal rodent studies of susceptibility of the immature brain for seizures.

The survey in the North London Infancy in Epilepsy Study was conducted in a densely populated inner city area of North London with marked ethnic diversity. Population genetic factors associated with different ethnic back grounds are likely to be a relevant compounding factor for infancy onset epilepsy. Results of this study are supportive of this hypothesis. Without taking information regarding socioeconomic background into account Asian children under the age of 2 years were 3 times more

likely to present with epilepsy compared to white children. Further evidence has emerged from childhood epilepsy cohorts (Shamansky and Glaser, 1979;Annegers et al., 1999) and hospital based series of infantile onset epilepsy with high prevalence of consanguinity (Masri et al., 2008). Chin and other authors documented ethnicity as a significant independent risk factor for convulsive status epilepticus in childhood (Chin, 2005;Chin et al., 2006;Raspall-Chaure et al., 2007).

Clinical features of the population based infancy epilepsy cohort that differed from childhood epilepsy cohorts included shorter recurrence interval after the first seizure (even after exclusion of cases with infantile spasms and myoclonic seizures), higher proportion of cases with a history of neonatal seizures (25% vs. 2.6%) and status epilepticus (12% vs. 9.1%). The case fatality in The North London 'Epilepsy in Infancy Study' was 9%. Most infants that died during the observation period in the North London 'Epilepsy in Infancy Study' had neurological impairment (associated with symptomatic epilepsy) and severe types of epilepsy in keeping with observations from community based childhood epilepsy cohorts (Berg et al., 2004b).

Data from the North London infancy epilepsy cohort demonstrate a high rate of identified underlying aetiologies (51%) compared to most childhood epilepsy cohorts (18-36%). Developmental as well as acquired structural brain abnormalities are the most common causes for epilepsy in this early age group in a population based setting. This is in keeping with the observation that over a third of infants enrolled in this study presented with a history of developmental impairment preceding the onset of their seizures and almost half had some abnormalities on neurological examination at baseline evaluation. The diagnostic yield of magnetic resonance imaging was high

in this infancy epilepsy cohort despite of the variability of image quality and different imaging protocols obtained from various centres. A proportion of MR scans were repeated. This observation supports recommendations of current national and international guidelines but also reveals a need for standardised magnetic resonance imaging protocols to minimise risks associated with sedation and repeat imaging as well as costs (National Institute for Clinical Excellence, 2004;Gaillard et al., 2009). The sensitivity of neuroimaging reports by expert neuroradiologists versus non -expert radiologists for abnormalities has to be considered in this context.

Findings of the North London 'Epilepsy in Infancy Study' suggest that over two thirds of infants with new onset epilepsy in a population based setting present with epilepsy types / syndromes associated with poor or guarded prognosis (epileptic encephalopathies 39%, focal symptomatic epilepsy 28%) and only approximately a third have syndromes compatible with milder or uncertain course (idiopathic focal and generalised 16%, probable symptomatic focal 10%). Under ascertainment of milder presentations with single seizures or single seizure cluster (spectrum of benign infantile seizures) may have occurred because either cases failed to meet inclusion criteria or may not have been identified as infants with (probable) new onset epilepsy. Although such cases do not necessarily require a diagnosis of epilepsy (Engel, Jr., 2001), this may have to be determined in retrospect when infants remain seizure free or subsequent seizures occur only in relation to febrile illnesses as also demonstrated in this study.

Infants enrolled in this study were classified according to the list of epilepsy syndrome groups and specific epilepsy syndromes (electro-clinical syndromes) as

suggested in the 2001 ILAE proposal (Engel, Jr., 2001). Most cases could be categorised into epilepsy syndrome groups. A specific epilepsy syndrome diagnosis however, could not be allocated in over a third of children at enrolment similar to findings in a large community based childhood epilepsy cohort (Berg, 2003). Inter-rater agreement between two paediatric neurologists, who classified cases independently was only moderate and lower compared to a study in which a priory rules on application of the ICE had been agreed (Berg et al., 1999a). Disagreement occurred between West syndrome/infantile spasms and focal symptomatic epilepsy (with infantile spasms as secondarily generalised seizures) demonstrating the overlap between epileptic encephalopathy syndromes and syndrome groups defined by aetiology with mode of onset. Other areas of disagreement related especially to cases without known aetiology in less narrowly defined syndrome groups (defined according to aetiology and mode of seizure onset) such as 'idiopathic focal / generalised' or 'probable symptomatic focal'. Such diagnoses were less consistent within raters and also more variable over time. Classification according to mode of seizure onset is especially difficult in infants when this is based on clinical description of events. Such syndrome group diagnoses in cases without known aetiology that do not meet criteria for a specific electro-clinical syndromes, provide little additional information (Berg, 2003). For these cases a descriptive approach by using the other axes of the diagnostic scheme (seizure types, aetiology and impairments) would be more appropriate. The list of seizure types in the 2001 proposal is however difficult to apply in infants. A descriptive approach for cases that do not fit into the defined electro clinical syndromes rather than using syndrome groups defined by aetiological category and mode of seizure onset has also been

suggested in the most recent ILAE task force proposals (draft document: www.ilae-epilepsy.org/visitors/centre/ctf/ctfoverview.cfm; version July 2009).

The North London 'Epilepsy in Infancy Study' is the first study that obtained prospectively data relating to the neurodevelopmental status of infants with new onset epilepsy in a population based setting using standardised assessment tools (Bayley III Scales of Infants and Toddler Development). Over two thirds of infants demonstrated developmental impairments that were already present close to diagnosis (in the majority within 3 months). Cognition, language and motor function as evaluated by the Bayley III were affected in similar way without much difference between these domains. Independent negative predictors of the developmental function at enrolment were abnormal neurological examination and presence of interictal discharges on the EEG. When investigating relationships of investigation results (neuroimaging, neurophysiology) and seizure severity prior to assessment with developmental function at enrolment in a separate linear regression model both aetiologically relevant neuroimaging findings and abnormal EEG were strong independent negative predictors of developmental function close to diagnosis.

Overall in the group of children followed up there was no significant longitudinal change of acquisition of developmental skills over the period of approximately 12 months. After correction for confounding factors developmental function at initial assessment did not differ from follow up evaluation. The developmental function at follow up was determined by the function at epilepsy onset.

Limitations of this part of the study have been discussed above and include small numbers of subjects that underwent evaluations at the two time points, findings only applicable to the relative short reassessment interval and possible bias due to patients being lost to follow up at the mild as well as severe end of the 'epilepsy syndrome spectrum'.

In this observational study investigations including neuroimaging and neurophysiology have not been conducted according to a standardised protocol as this would be the case in an experimental or interventional trial design. Subtle structural brain abnormalities, rare genetic or metabolic conditions may have not been recognised in this cohort. However a major strength of this study is the reflection of current practice in investigation and management of infants presenting with new onset epilepsy in North London.

6 CHAPTER 6: FUTURE DIRECTIONS

In order to adequately document course and outcome of children presenting with recurrent seizures in the first two years of life in a community setting a prospective study with longer follow up period is required. This would allow the investigation of the complex relationships between aetiology, natural history of the epileptic disorder, impact on education, cognitive and psychosocial outcome.

Diagnostic difficulties at the onset concern particularly infants at the clinically milder end of the spectrum, who present few seizures or a single seizure cluster. Factors predicting long-term outcome would be especially helpful in this group in order to tailor the diagnostic work up at onset more cost effectively and provide adequate information to families.

Psychiatric disorders are more commonly associated with childhood epilepsy (37%) compared to other chronic conditions in the general population as shown in a recent epidemiological study (Davies et al., 2003). Associated hyperactive as well as pervasive developmental (autistic) disorders were particularly increased in epilepsies complicated by learning difficulties and neurological problems (Davies et al., 2003). The infancy onset epilepsy group is therefore likely to be especially at risk because of the high prevalence of cognitive and neurological impairments that were also documented in the North London 'Epilepsy in infancy Study'. A significant proportion of infants with West syndrome/infantile spasms were diagnosed with autistic spectrum disorders on follow up in several observational studies (Riikonen and Amnell, 1981;Jambaque et al., 2000;Askalan et al., 2003;Saemundsen et al.,

2008). Other types of infancy onset epilepsies are also associated with a higher risk for autistic spectrum disorder as suggested by the data from a recent retrospective population based study carried out in Iceland (7% autistic spectrum disorders in children with unprovoked seizures in the first year of life excluding infantile spasms versus 0.5 -1% in the general population) (Baird et al., 2006;Saemundsen et al., 2007).

Long-term follow up of children enrolled in the North London infancy epilepsy cohort will provide an opportunity to obtain data about frequency and risk factors of mental health problems including behavioural impairments and autistic disorders associated with epilepsy onset in the first 2 years of life. In the currently ongoing follow up phase of the North London 'Epilepsy in Infancy Study' subjects are assessed 3 years after enrolment. Data are collected on the clinical course of the epilepsy, neurological status, and standardised tools are used to assess social communication, behavioural and attention difficulties, general cognitive function, as well as memory. Assessment of children enrolled in this cohort is challenging because of the heterogeneity of neurodevelopmental function and association with motor as well as sensory impairments. Therefore in addition to the standardised neuropsychological tests novel neurophysiological methods involving event related potentials (ERP's), that do not require motor or verbal responses, are also applied to measure memory and social-communication processing. ERP methods have been increasingly applied in studies investigating the normal development of social processing in young children and abnormal course in children with autism /autistic spectrum disorders (Dawson et al., 2005;Grossmann and Johnson, 2007;Wong et al., 2008).

Future data collection in the North London infancy epilepsy cohort should also focus on health related quality of life. Adequate instruments (parental reports versus patient questionnaires) need to be considered in this group with high cognitive and neurological impairments (Ronen et al., 2003;Soria et al., 2007;Waters et al., 2009). Such information is however paramount to decide on the best therapeutic management strategies and provide appropriate support to patients and their families.

Design of larger epidemiological studies enrolling children with recurrent unprovoked seizures under two years of age would add to the case numbers required to determine incidence and risk factors (for active epilepsy, medication resistance, mortality, cognitive, behavioural and neurological impairments) more precisely with smaller confidence intervals. The North London 'Epilepsy in Infancy Study' could be a model for such studies that survey larger populations. A computer based on-line registry could facilitate case notification and data collection. This could be part of a larger epilepsy patient register, a project that may be included in the portfolio of the clinical research network established in the UK, especially the recently launched UK Epilepsy Research Network (UKERN, February 2010). Issues relating to data confidentiality especially if the aim is to obtain longitudinal data would have to be adequately addressed.

A larger infancy epilepsy cohort ascertained with national or international collaboration using electronic registries would also allow to determine frequency of genetic syndromes in this age group (Wallace et al., 2003;Herlenius et al., 2007;Guerrini et al., 2007;Kato et al., 2007;Rosas-Vargas et al., 2008;Saitsu et al., 2008;Depienne et al., 2009a). Clinical data detailing the course of the seizure

disorder and developmental trajectories from larger case numbers are often lacking to correlate genotypes and phenotypes (Depienne et al., 2009b). The SMEI / GEFS+ syndrome spectrum would be an example for which genetic studies in a population based infancy epilepsy incidence cohort could provide data that are less biased and give insight into factors that determine milder phenotypic manifestations.

The North London 'Epilepsy in Infancy Study' obtained prospectively population based data that contributed to a better understanding of the early clinical course of children with epilepsy onset under the age of two years. The ongoing longitudinal data collection in this project will provide additional information to address important questions relating to cognitive, behavioural and educational outcomes. This information may not resolve the question about the causal relationships between developmental disorders, underlying brain pathology and epileptic activity but can be the basis for the formulation of research hypothesis and design of studies to determine the impact of early interventions. Ultimately this approach will help to promote the development of better therapeutic and remediative strategies that may reduce the impact of associated morbidities on children and their families.

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8 APPENDICES

8.1 Appendix 1: Resident population in North London

Resident Population in surveyed geographical area* of North London - Census 2001 (Office for National Statistics)

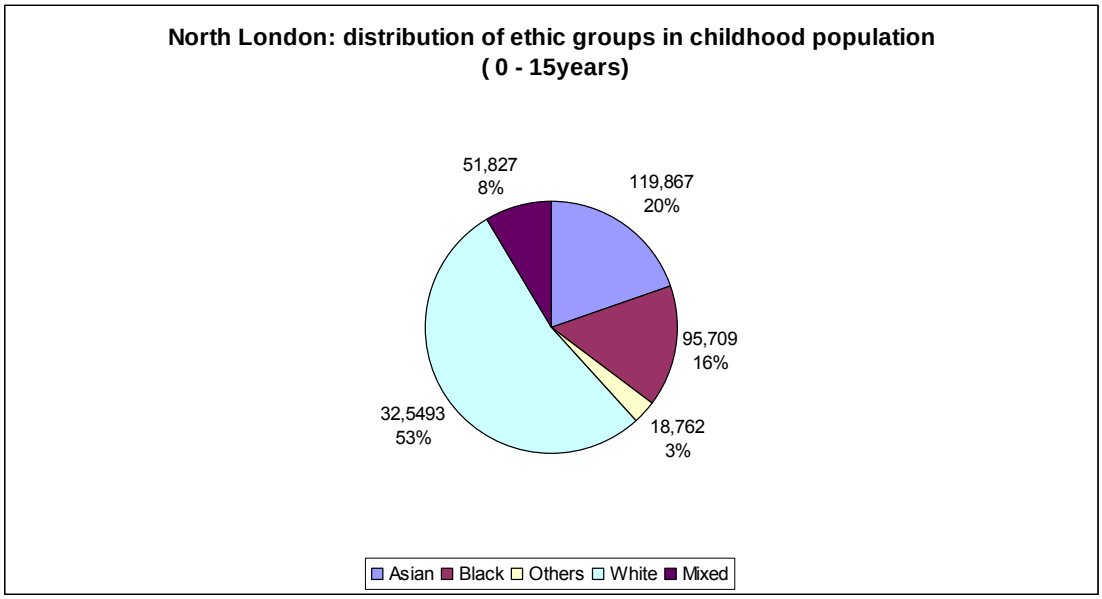
	Males	Females	Total
All ages	1,477,952	1,586,652	3,064,604
0-1 (<= 2 years)	42,795	40,859	83,654
0 -15 (< 16 years)	305,473	295,451	600,924
*15 Boroughs: Barnet, Brent, Camden, City of London, Enfield, Hackney, Hammersmith and Fulham, Haringey, Harrow, Islington, Kensington and Chelsea, Newham, Tower Hamlets, Wandsworth, Westminster			

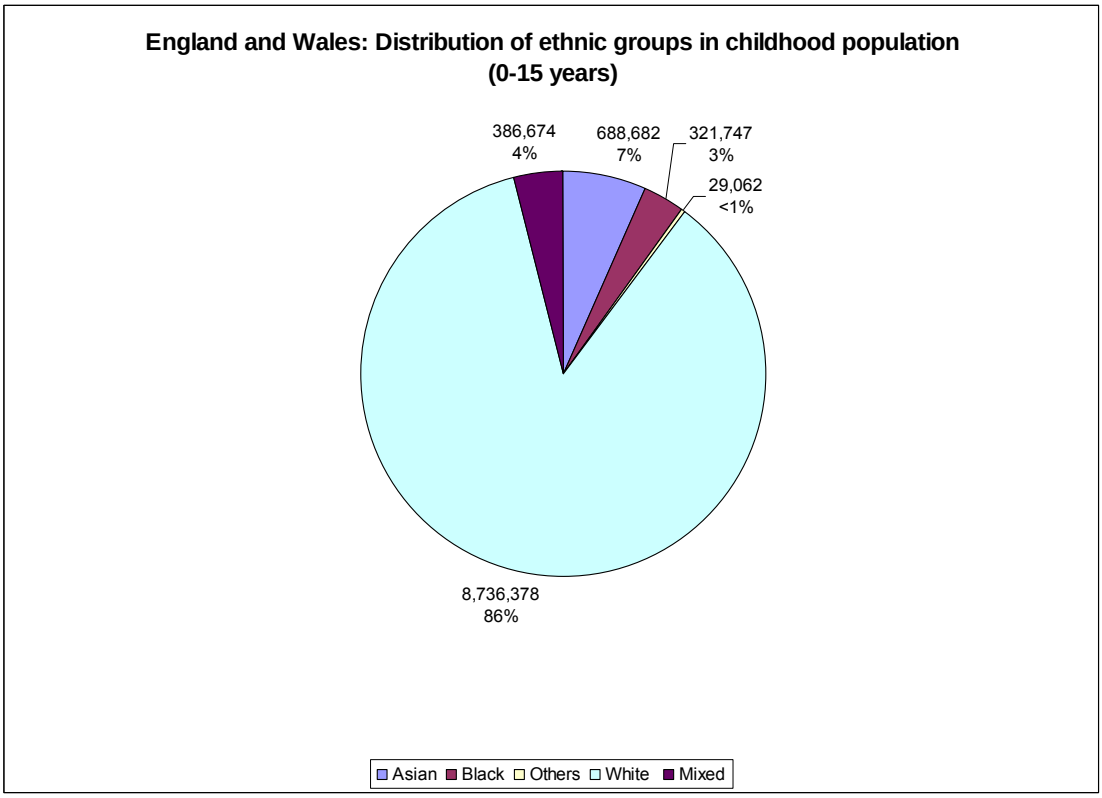
Resident Population in surveyed geographical area* of North London Mid 2006 population estimates (Office for National Statistics)

	Males	Females	Total
All ages	1,598,285	1,620,525	3,218,810
0-1 (<=2 years)	50,161	47,929	98,090
0 -15 (< 16 years)	310,933	298,354	609,287
*15 Boroughs: Barnet, Brent, Camden, City of London, Enfield, Hackney, Hammersmith and Fulham, Haringey, Harrow, Islington, Kensington and Chelsea, Newham, Tower Hamlets, Wandsworth, Westminster			

8.2 Appendix 2: Ethnic composition of childhood population in North London and England and Wales

(Mid 2006 estimates, Office for National Statistics 2009; 2010)





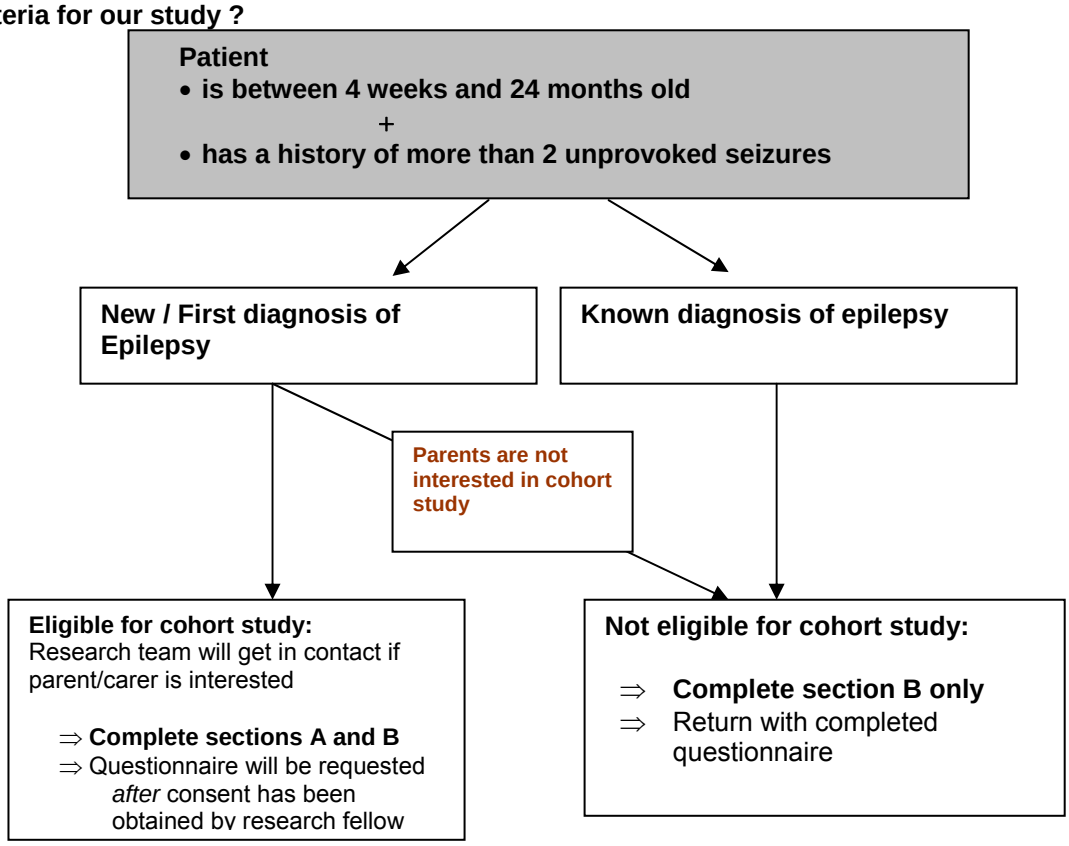
8.3 Appendix 3: Notification Forms

Epilepsy in infancy study

Notification form [Month] – [Year]

Dear Dr [Name of Consultant Pediatrician]

Have you seen in this month of [month] patients, who meet the following inclusion criteria for our study ?



Please return in addressed envelope.

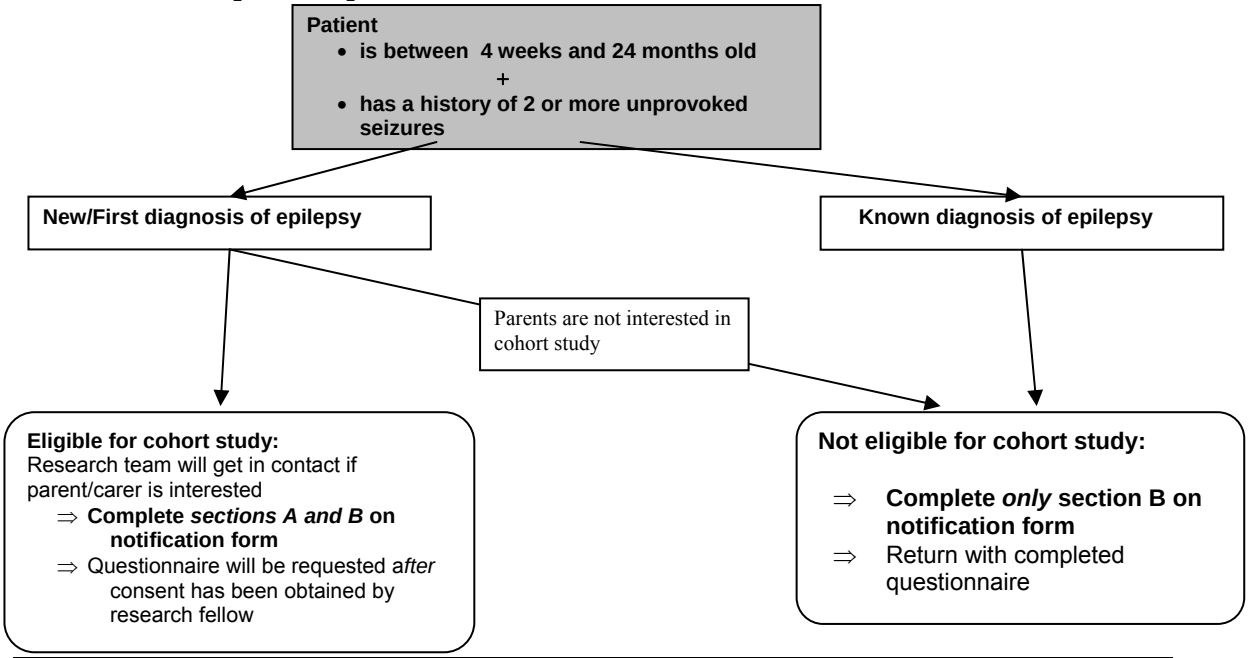
No Cases ☐	Cases of epilepsy ☐

A			B			
Name	Address	Telephone number	Patient's Initials	Sex M/F	Date of Birth	Partial Postal Code (eg SW17)

Epilepsy in Infancy Study: Institute of Child Health, **Neurosciences Unit, The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP, Phone 020 7837 7618**
Investigators: JH Cross, CM Eltze, R Scott, BGR Neville

Notification form (Reminder):
(ID) [Months] [Year]
Dear Dr [Name of Consultant Paediatrician]

Thank you for assisting with our study. Unfortunately we did not receive a reply for [Months].
Please indicate below, in the appropriate box, the number of cases, who meet the following inclusion criteria for our study that you have seen or been informed of in [Months] or tick the box 'No cases seen'.



Please tick:	No cases seen ☐	Cases of epilepsy ☐

A			B			
Name	Address	Telephone number	Patient's Initials	Sex M/F	Date of Birth	Partial Postal Code (eg SW17)

Please complete this form and return in self addressed envelope or fax: 020 7833 9469
Epilepsy in Infancy Study: **Institute of Child Health**, **Neurosciences Unit, The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP, Phone 020 7837 7618**
Investigators: CM Eltze, JH Cross, BGR Neville, RC Scott,

8.4 Appendix 4: Newsletters

Newsletter May 2006

Epilepsy in Infancy Study

Collaborative Study of Early Onset Epilepsies in North London

- **Age: 4 weeks to 24 months**
- **History of 2 or more unprovoked seizures**

www.epilepsyininfancy.ich.ucl.uk
Call **01342 831260** to notify

Investigating:

- **incidence of epilepsy onset in the first 2 years of life**
- **spectrum of aetiologies and syndromic presentations in a population based setting**
- **short term outcome**

Period of case ascertainment: 1st September 2005 until 31st August 2007

Dear Colleagues,

We would like to thank you for your help with our important study and provide an update of our progress. Since the start of case ascertainment 51 children with a possible first diagnosis of epilepsy have been notified to us. Thirty five of these were suitable for enrolment in our prospective cohort study. Clinical evaluation and formal neurodevelopmental assessment (conducted by a Psychologist) has been carried out in 25 children so far. We have also started reviewing EEG recordings and MRI scans. A feed back report will be formulated after each assessment. These will be forwarded to the responsible Consultant Paediatrician with a copy to the parents, so that information can be related in the context of local care. Review of the patients enrolled in the prospective cohort is planned 6 and 12 months following baseline assessment.

The period of case ascertainment has been extended to 24 months from 1st September 2005 until 31st August 2007. We require several sources of case ascertainment in order to apply capture recapture methodologies for the calculation of incidence estimates. We would therefore be grateful if you could notify patients with a known and first diagnosis of epilepsy, who are between 4 weeks and 24 months old:

- by ***phoning our telephone hotline 01342 831260*** (24 hour automated service) at the time eligible patients are seen
- ***and returning*** the ***notification form,*** which is send to you at the end of each month.

Information sheets for parents and consultants are available on our website.

Yours sincerely,

Dr J H Cross (Principal Investigator)
Reader & Honorary Consultant Paediatric Neurologist
h.cross@ich.ucl.ac.uk

Dr C M Eltze
Clinical Research Fellow in Paediatric Neurosciences
c.eltze@ich.ucl.ac.uk

Newsletter November 2006

Epilepsy in Infancy Study - One year on

Collaborative Study of Early Onset Epilepsies in North London

- **Age: 4 weeks to 24 months**
- **History of 2 or more unprovoked seizures**

Investigating:

- **incidence of epilepsy onset in the first 2 years of life**
- **spectrum of aetiologies and syndromic presentations in a population based setting**
- **longterm outcome**

www.epilepsyininfancy.ich.ucl.uk
Call **01342 831260** to notify cases!

Case ascertainment: 1st September 2005 until 31st August 2007

Dear Colleagues,

Thank you very much for your help with this important study. In the first year of our study we were notified about 79 children with an existing or possible first diagnosis of epilepsy. So far we have assessed 46 children of the 51 patients suitable for enrolment in our cohort study of newly diagnosed patients. We are in the process of reviewing EEG's, MRI scans and other investigating results. Analysis of the initial data will commence soon.

Twelve months following the base line assessment we will invite patients for a follow up review which will include clinical and neurodevelopment evaluation. Anna Merrett(Clinical Psychology Assistant) who has joined our team since March 2006, will also be involved in liaising with families. As for the baseline assessment, a feedback report will be forwarded to the responsible Consultant Paediatrician with a copy to the parents.

We will continue case ascertainment until the end of August 2007. We would be grateful if you could encourage junior doctors, nursing staff and colleagues in your department to notify us of patients with a known or first diagnosis of epilepsy, who are between 4 weeks and 2 years old, by ***phoning our telephone hotline 01342 831260*** (24 hour automated service) at the time patients are seen. In addition, please return the notification form, which is sent to you at the end of each month.
An information leaflet to introduce our study to parents and more information about inclusion /exclusion criteria can be downloaded from our website (www.epilepsyininfancy.ich.ucl.ac.uk). We will phone parents, who have given permission to be contacted by our team, in order to answer questions and arrange dates for assessments.

Yours sincerely,

Dr J H Cross (Principal Investigator)
Reader & Honorary Consultant Paediatric Neurologist
h.cross@ich.ucl.ac.uk

Dr C M Eltze
Clinical Research Fellow in Paediatric Neurosciences
c.eltze@ich.ucl.ac.uk

8.5 Appendix 5: Standard History Proforma

Epilepsy in Infancy Study

History Proforma for Patients with Epilepsy:

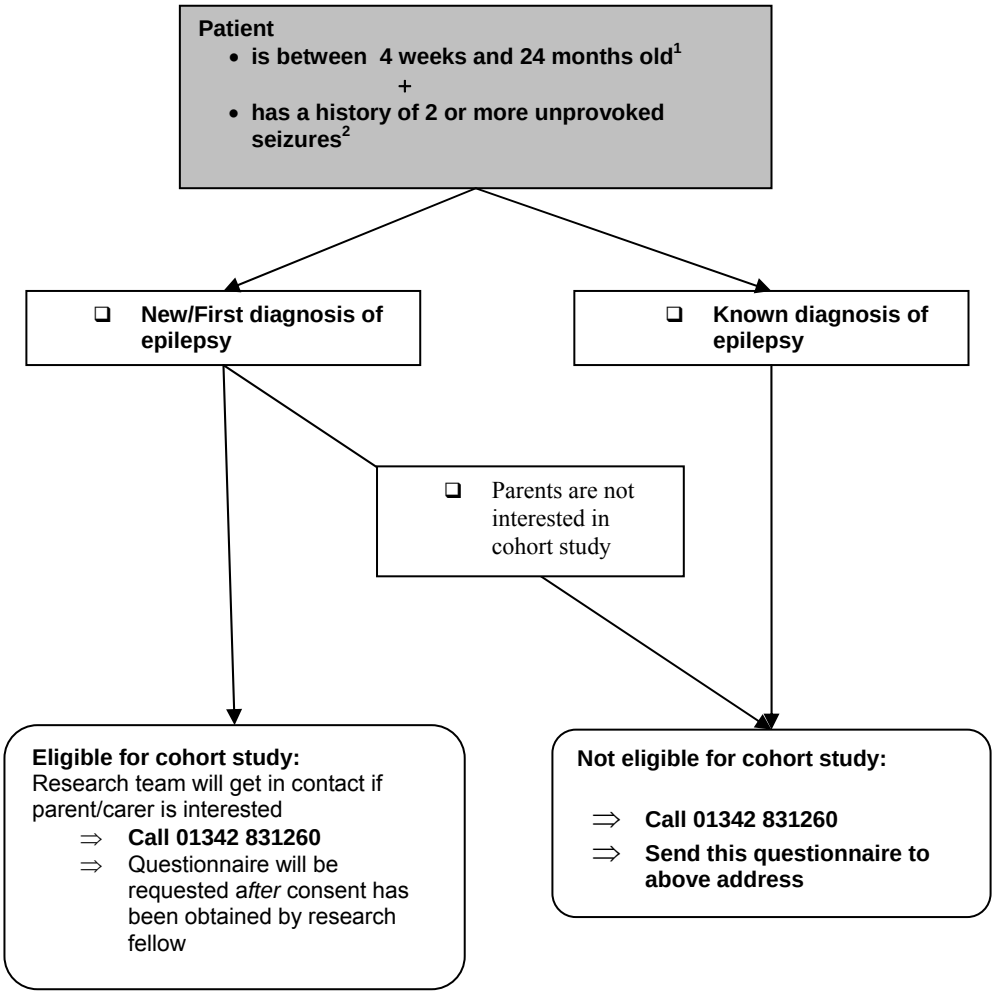
Date:

Person completing:

Position:

Patient's initials:	
Date of Birth	
Sex:	
Partial postal code (eg SW17):	

Please, tick as appropriate:



[1] **This includes patients, whose seizure onset is in the first 4 weeks of life – but who continue to have seizures beyond 4 weeks**

[2] **Seizures without any acute underlying cause such as fever, infection, trauma, stroke, electrolyte imbalances, intoxication.**

Problem List:

Background information:		
		Comments/Details
Birth history: Complications:	□ No	□ term (≥ 37 weeks) □ premature (< 37 weeks):……. □ Yes:……
Neonatal History	□ normal	□ abnormal:……
Relevant past medical history	□ No	□ Yes:…… ……
Febrile convulsions:	□ No	□ Yes: (Age, duration, focal or generalised)…… ……. …….
Genetic diagnosis/ Chromosomal abnormality	□ No	□ Yes:…… ……..
Family History: Seizures (Learning difficulties, genetic conditions): Consanguinity:	□ No □ No	□ Yes:…… …….. □ Yes:…… ……
General Examination:	□ normal	□ abnormal:…… ……

Headcircumference: ……..cm centile:…….. Weight: …….kg centile:…….		
Neurological Examination	□ normal	□ abnormal:…… …… …….
Seizure History		
Age at first afebrile seizure:		
Seizure Types:		Please describe clinical manifestations - ictal and postictal, triggers, duration and frequency (number of seizures per day)
First afebrile seizure Timing: □ awake □asleep Duration:…….		

Subsequent seizure types: 1. Age: Timing: □ awake □asleep Duration:…….. Frequency:…… 2. Age: Timing: □ awake □asleep Duration:…….. Frequency:…… 3. Age: Timing: □ awake □asleep Duration:…….. Frequency:…… …	
Current Seizure Types: 1. Timing: □ awake □ asleep Duration:…….…… … Frequency:…… 2. Timing: □ awake □ asleep Duration:…….…… … Frequency:…… . Timing: □ awake □ asleep Duration:…….…… … Frequency:…… …	

Status epilepticus:	□ No	□ Yes at first presentation: □ Yes □ No □ Unsure Please specify age, duration, number of episodes:
Longest seizure free period		

Antiepileptic Medication		
Drug (+ maximum dose [mg]):	Duration	Comments (side effects, reason for withdrawal):
Initial/previous:		
Current:		

Response to current regime:	□ Seizure free How long ? ……days/weeks/months (quantify and circle as appropriate) □ Improved but not seizure free □ Little improvement or unchanged
Developmental progress prior to seizure onset:	
Domain:	Comments (concerns, loss of skills)
Motor: □ normal	□ delayed □ regression:…….. …….
Social communication – play □ normal	□ delayed □ regression:…….. …….
Language: □ normal	□ delayed □ regression:…….. …….

Current Development								
Chronological age:								
Domain:	Please circle (Y = Yes, N = No, DK = don't know) if appropriate and/or comment (other achieved milestones, concerns or loss of skills)							
Gross Motor: □ normal □ delayed □ regression	Y	N	DK	Lifts head in prone position for several seconds (face makes approximate angle of 45° with surface)	Y	N	DK	Stands alone (> 10 seconds)
	Y	N	DK	Head control in sitting position (holds head steady)	Y	N	DK	Walks well (good balance, falls rarely)
	Y	N	DK	Pull to sit – no head lag	Y	N	DK	Runs
	Y	N	DK	Sits - no support	Y	N	DK	Walks up steps (holding onto rail or wall for support, not to person)
	Y	N	DK	Stands holding on	Y	N	DK	Jumps up (gets both feet of the floor at same time)
	Y	N	DK	Pulls to stand from sitting position				
Gross Motor - Comments:								
Fine Motor and vision: □ normal □ delayed □ regression	Y	N	DK	In supine - follows object from one side past the midline	Y	N	DK	Picks up 2 cubes one in each hand
	Y	N	DK	In supine - brings hands together in midline (over chest or at mouth)	Y	N	DK	thumb finger grasp (brings together thumb and one or several fingers to pick up small objects)
	Y	N	DK	In supine - follows 180°	Y	N	DK	scribbles
	Y	N	DK	Reaches for objects (in sitting position)	Y	N	DK	Looks at pictures in book
	Y	N	DK	transfers objects from one hand to other (without help of mouth, body or table)	Y	N	DK	Turns pages in book
Comments:								

Personal – Social- Play □ normal □ delayed □ regression	Y N DK	regards face	Y N DK	Waves bye-bye
	Y N DK	smiles responsively (when talked to)	Y N DK	Points to share interest (not for wants/needs)
	Y N DK	Regards own hand	Y N DK	Imitates (household) activities (eg talking on phone, wiping up)
	Y N DK	feeds self (finger food)	Y N DK	Use Spoon/Fork
	Y N DK	turns to name	Y N DK	Feeds doll (Symbolic play)
	Y N DK	Indicates wants (by pointing, reaching + making sounds, pulling, saying words, putting arms up to be picked up)	Y N DK	Puts on clothing (can put on any clothing eg socks, shoes, jacket)
Comments:				
Language: □ normal □ delayed □ regression	Y N DK	vocalizes	Y N DK	one word
	Y N DK	laughs	Y N DK	6 words or more
	Y N DK	turns to voice	Y N DK	combines words
	Y N DK	single syllables	Y N DK	Follows one part command
	Y N DK	DADA/MAMA (non specific)	Y N DK	Follows two part command
	Y N DK	DADA/MAMA (specific)		
Comments:				

Sensory Impairments		
Vision	□ normal	□ concerns:……
Hearing	□ normal	□ concerns:……

Which ethnic group does the patient belong to ?	
Mixed: □ White and Black Caribbean □ White and Black African □ White and Asian □ Other (please state)…… White: □ British □ Irish □ Other (please state):…….. Chinese or other Ethnic Group: □ Chinese □ Other (please state):……..…	Black/Black British: □ Caribbean □ African □ Other (please state):…… Asian/Asian British: □ Indian □ Pakistani □ Bangladeshi □ Other (please state):……..

Investigations		
		Details (you may consider enclosing anonymised copy of report)
EEG □ Yes □ No	□ normal □ abnormal □ results awaited	
MRI □ Yes □ No	□ normal □ abnormal □ results awaited	
CT □ Yes □ No	□ normal □ abnormal □ results awaited	

Other Investigations:		Details if abnormal:
	□ normal □ results awaited	

	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	

8.6 Appendix 6: Clinical evaluation proformas (baseline and 12 months)

Epilepsy in Infancy Study:

Evaluation Proforma **(Baseline)**:

Patient details:

Name:		Local Hospital / Community Clinic:	
Date of Birth:		Local Consultant:	
Address:		Contact number/ e-mail:	
Contact Number:		GP:	

Date seen:
Attended with:
Consent signed by:

Evaluation:
Baseline (detailed history)
Review……..
Neuropsychology (Tests):……..
……
……
Blood sample taken
Spare sample from local hospital requested

Local EEG:
Done (Department……..)
Awaiting Appointment
Have Appointment – date:……; Department:…….
Digital recording requested for review

Local MRI:
Done (Department……..)
Awaiting Appointment
Have Appointment – date:……; Department:…….
Images requested fro review:

Background information:		
		Comments/Details
Pregnancy – complication: **Birth:** **Complications:**	□ No □ No	□ Yes: □ term (≥ 37 weeks) □ premature (< 37 weeks):…… …… Mode of delivery: Birth weight: □ Yes:…… ……
Neonatal History	□ normal	□ abnormal:…… ……
Relevant past medical history	□ No □ DK	□ Yes:…… …… …… ……
Febrile convulsions:	□ No □ DK	□ Yes: (Age, duration, focal or generalised)…… …… …… …… ……
Genetic diagnosis/ Chromosomal abnormality	□ No □ DK	□ Yes:…… …… …… ……

Family History: Seizures (Learning difficulties, genetic conditions): □ No	**Family tree:**

Seizure History

Age of first afebrile seizure:	
Seizure Types:	**Clinical manifestations - ictal and postictal, triggers, duration and frequency (number of seizures per day)**

First afebrile seizure:

Timing:
□ awake □ asleep Duration:……

Subsequent seizure types: Please document: Age, if occurs when awake or when asleep, duration, frequency for each type		
Current Seizure types: Please document: If occurs when awake or when asleep, duration, frequency for each type		
Status epilepticus:	□ No	□ Yes at first presentation: □ Yes □ No □ Unsure Please specify age, duration, number of episodes:

Longest seizure free period		
Antiepileptic Medication		
Drug	**Maximum Dose [mg]):**	**Duration + Comments (side effects, reason for withdrawal):**
Initial/previous:		
Current:		
Response to current regime:	□ Seizure free How long ? ……days/weeks/months (quantify and circle as appropriate) □ Improved but not seizure free □ Little improvement or unchanged	

Developmental progress **prior** to seizure onset: (Milestones)	
Motor:	
Social communication – play	
Language:	

Current Development							
Chronological age:							
Domain:	Please circle (**Y = Yes, N = No, DK = don't know)** if appropriate and/or comment (other achieved milestones, concerns or loss of skills)						
Gross Motor: □ normal □ delayed □ regression	Y	N	DK	Lifts head in prone position for several seconds (face makes approximate angle of 45° with surface)	Y	N	DK	Stands alone (> 10 seconds)
	Y	N	DK	Head control in sitting position (holds head steady)	Y	N	DK	Walks well (good balance, falls rarely)
	Y	N	DK	Pull to sit – no head lag	Y	N	DK	Runs
	Y	N	DK	Sits - no support	Y	N	DK	Walks up steps (holding onto rail or wall for support, not to person)
	Y	N	DK	Stands holding on	Y	N	DK	Jumps up (gets both feet of the floor at same time)
	Y	N	DK	Pulls to stand from sitting position				
Comments:								

Fine Motor and vision: □ normal □ delayed □ regression	Y	N	DK	In supine - follows object from one side past the midline	Y	N	DK	Picks up 2 cubes one in each hand
	Y	N	DK	In supine - brings hands together in midline (over chest or at mouth)	Y	N	DK	thumb finger grasp (brings together thumb and one or several fingers to pick up small objects)
	Y	N	DK	In supine - follows 180°	Y	N	DK	scribbles
	Y	N	DK	Reaches for objects (in sitting position)	Y	N	DK	Looks at pictures in book
	Y	N	DK	transfers objects from one hand to other (without help of mouth, body or table)	Y	N	DK	Turns pages in book
Comments:								
Personal – Social- Play □ normal □ delayed □ regression	Y	N	DK	regards face	Y	N	DK	Waves bye-bye
	Y	N	DK	smiles responsively (when talked to)	Y	N	DK	Points to share interest (not for wants/needs)
	Y	N	DK	Regards own hand	Y	N	DK	Imitates (household) activities (eg talking on phone, wiping up)
	Y	N	DK	feeds self (finger food)	Y	N	DK	Use Spoon/Fork
	Y	N	DK	turns to name	Y	N	DK	Feeds doll (Symbolic play)
	Y	N	DK	Indicates wants (by pointing, reaching + making sounds, pulling, saying words, putting arms up to be picked up)	Y	N	DK	Puts on clothing (can put on any clothing eg socks, shoes, jacket)
Comments:								
Language: □ normal □ delayed □ regression	Y	N	DK	vocalizes	Y	N	DK	one word
	Y	N	DK	laughs	Y	N	DK	6 words or more
	Y	N	DK	turns to voice	Y	N	DK	combines words
	Y	N	DK	single syllables	Y	N	DK	Follows one part command
	Y	N	DK	DADA/MAMA (non specific)	Y	N	DK	Follows two part command
	Y	N	DK	DADA/MAMA (specific)				

Comments:	

Sensory Impairments		
Vision	□ normal	□ concerns:…… ……
Hearing	□ normal	□ concerns:…… ……

Which ethnic group does the patient belong to ?

Mixed:
□ White and Black Caribbean
□ White and Black African
□ White and Asian
□ Other (please state)……

White:
□ British
□ Irish
□ Other (please state):……..

Chinese or other Ethnic Group:
□ Chinese
□ Other (please state):……..…

Black/Black British:
□ Caribbean
□ African
□ Other (please state):……

Asian/Asian British:
□ Indian
□ Pakistani
□ Bangladeshi
□ Other (please state):……..

Examination:

Headcircumference:
Weight:
Height/Length:

Dysmorphic features:

Neurocutaneus stigmata:

Neurological examination:

General Examination:

Investigations:		Details if abnormal:
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	

Epilepsy in Infancy Study
Follow up Assessment

ID:

Patient details:

Name:		Local Hospital / Community Clinic:	
Date of Birth:		Local Consultant:	
Address:		Contact number/ e-mail:	
Contact Number:		GP:	

Date seen: Age (months):
Time since base line assessment (months):
Attended with:

Evaluation:
Neuropsychology (Tests):……..
……
……
Blood for DNA stored

Investigations reviewed so far:

EEGs (Department……..)
MRI (Department……..)

Comments:

Seizure History		
Seizure types since baseline assessment: Age, if occurs when awake or when asleep, duration, frequency for each type		
Status epilepticus:	□ No	□ Yes at first presentation: □ Yes □ No □ Unsure Please specify age, duration, number of episodes:

Longest seizure free period		
Antiepileptic Medication		
Drug	Maximum Dose [mg]):	Duration + Comments (side effects, reason for withdrawal):
Initial/previous:		
Current:		
Response to current regime:	Seizure free How long ? ……days/weeks/months (quantify and circle as appropriate) Improved but not seizure free Little improvement or unchanged	

General Health:
Any new diagnostic information (genetic syndrome/ diagnosis, metabolic disease ect, results of ophthalmology or audiology examinations:
Family Tree (if not documented at baseline assessment), FH of febrile convulsions, Epilepsy, disabilities, learning difficulties:

Developmental progress since baseline assessment: (Milestones, any concerns)		
Motor		
Social communication – play		
Language		
Sensory Impairments		
Vision	□ normal	□ concerns:…… ……

Hearing	□ normal	□ concerns:…… ……

Examination:

Headcircumference / centile:
Weight / centile:
Height/Length:

Dysmorphic features:

Neurocutaneus stigmata:

Neurological examination:

General Examination:

Investigations:		Details if abnormal:
	□ normal □ results awaited	
	□ normal □ results awaited	
	□ normal □ results awaited	

8.7 Appendix 8: Proformas for review of Neuroimaging and EEG

Reporting Proforma – Neuroimaging (Early onset Epilepsy < 2 years):

Reported by:
Date:

Study ID:
Name:
DOB:

Date:
Type: □ MRI □ CT
Where performed:

System:

MRI Sequences:

- T1 weighted:……
  Planes: □ axial □ sagital □ coronal .....

- T2 weighted:…….
  Planes: □ axial □ coronal
  □ sagital
  □ coronal 90° to long axis of hippocampus
  whole head: Yes No:……

- 3D T1-weighted Gradient echo dataset (MPRAGE)

- FLAIR
  Planes: □ axial □ coronal □ sagital

- Other:…….
  ……..
  …….

Quality of images: □ good □ acceptable □ insufficient

Comments:……
……

Cortex: Normal: □ yes □ no:
Abnormalities (Extend, Localisation):

□ Bilateral: …….

□ Unilateral:…….

Description (signal characteristics):
T1:
T2:

Comments:

White Matter: Normal □ yes □ no:
Myelination: □ age appropriate □ delayed
Comments:……
…….

Abnormalities (Extend, Localisation):

□ Bilateral …….

□ Unilateral:…….

Description (signal characteristics):
T1:
T2:

Comments:

Ventricles: □ Normal □ Abnormalities:……

Corpus Callosum: □ Normal □ Abnormalities:……
……

Basal Ganglia: Normal: yes no;
Abnormalities:
 Bilateral:…….
……
……
……
 Unilateral:……..……
….
……
……
……

Description (signal characteristics):
T1:
T2:
Comments:

Hippocampus: Normal: yes no:
Abnormalities:
 Bilateral Unilateral:……
Description (signal characteristics, size):
T1:
T2:
Comments:

Brain stem: Normal Abnormalities:……
……
……
……

Cerebellum: Normal Abnormalities:……

Other anatomical structures: Normal Abnormalities:…….

Conclusion/Diagnosis:

Further images required :
□ No □ Yes
(Sequences):……..
…….
…….

EEG-Reporting Proforma:

Study-ID:
Name:
DOB:

Recording details:
Date:
EEG department:
EEG number:

Antiepileptic Medication: □ no □ yes:

Sleep: □ yes □ no
Photic stimulation perfomed □ yes □ no
State of patient during recording:

Age and state appropriate background activities:

Awake:

- □ present
- □ only abnormal activities
- □ some activities present but to slow for age
- □ not able to assess

Drowsiness (stage 1 sleep – disappearance of α , presence of Vertex – waves):

- □ present
- □ only abnormal activities
- □ some activities present but to slow for age
- □ not able to assess

Sleep (presence of sleep spindles and K-complexes):

- □ present
- □ only abnormal activities
- □ some activities present but abnormal for age
- □ not able to assess

Photoparoxysmal response: □ yes □ no

Abnormal slow activity: □ No □ Yes:

- Unilateral / Focal::……
- Bilateral:……..
- Diffuse:…….

Epileptiform activity:

- □ Focal
- □ Unilateral (hemispheric)
- □ Multifocal
- □ Bilateral

Localisation:

Seizures recorded: □ yes □ no

Seizure type:

Ictal onset:

- □ Focal:……
- □ Unilateral:……..
- □ Generalisedl:…….
- □ Undetermined…….

Conclusion:

□ Normal (age and stage appropriate activities) □ Abnormal

Compatible with …….....

Comments:

8.8 Appendix 9: Details of neuroimaging findings and examples of MR images

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
Abnormal – aetiologically relevant	4	M P	MRI	non specific signal changes on T2-weighted images: increased deep white matter signal bilaterally in parietal occipital areas, differential diagnosis: oedema - due to hypoxic ischaemic brain injury, metabolic disorder or seizure related	Acquired non specific
	8	JS	MRI	decreased grey to white matter differentiation in right anterior temporal lobe, increased signal on T2 weighted images in right hippocampus, probable mesial temporal sclerosis	Other
	9	VK	MRI	asymmetrical atrophy of cortex left more than right (left temporal lobe atrophy) appearances compatible with infection or seizure related (coronal T2 weighted images through temporal lobe only)	CNS infection
	11	JR	MRI	asymmetric Peri-ventricular leucomalacia with white matter loss affecting more the right hemisphere, cortical atrophy right more than left , right Ventricular-peritoneal -shunt in situ	Perinatally acquired /HIE
	14	ZH	MRI	extensive area of cortical dysplasia in right hemisphere (mesial, middle, inferior frontal lobe, frontal operculum, perisylvian, superior parietal lobe), thickened septum pellucidum (feature suggesting hemimegalencephaly)	Developmental lesion
	15	NE	MRI	bilateral tubers (largest left frontal), subependymal nodules, diagnostic for Tuberous Sclerosis	Developmental lesion

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
	17	A K-H	MRI	maturation of changes seen in initial scan - asymmetrical atrophy of affected cortical and subcortical areas, involvement of left lentiform nucleus and thalamus, mild atrophy of left hippocampus, consistent with encephalitis	CNS infection
	19	M D-S	MRI	bilateral symmetrical signal abnormalities on T2 weighted images in globus pallidum and dorsal pons, in addition increased white matter signal on T2-weighted images in left temporal - occipital area with decreased signal on T1-weighted images in same area giving appearance of thickened cortex, This could be seizure related.	Metabolic/ neurodegenerative
	29	IT	MRI	grossly abnormal with cystic encephalomlacia, thin cortex with paucity of gyration (preserved in occipital lobe), small brain stem and cerebellum, basal ganglia involved	Acquired non specific
	30	SD	MRI	bilateral polymicrogyria (mesial frontal/parieto-occipital), microcephaly	Developmental lesion
	34	TG	MRI	bilateral asymmetric polymicrogyria (left: frontal, temporal, parietal right: frontal perisylvian,insular) + left periventricular heterotropia	Developmental lesion
	35	ML	MRI	blurring of grey/white matter junction and abnormal white matter signal in left temporal lobe (also coarse gyral pattern) extending in occipital area and insular cortex, consistent with area of focal cortical dysplasia	Developmental lesion

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
Abnormal – aetiologically relevant	40	DG	MRI	multiple developmental abnormalities:1. extensive bilateral hemispheric polymicrogyria, left frontal cortex appears thinner (which may suggest an Insult) 2. right hemisphere is larger with thickened septum pellucidum - features of hemime-galencephaly 3. left closed lip schizencephaly	Developmental lesion
	42	A-R M	MRI	cerebellar hypoplasia/dysplasia with abnormally bright signal in the hemispheres, small brain stem; in addition bilateral polymicrogyria in frontal operculum and insular cortex	Developmental lesion
	43	MK	CT	maturation of changes seen initially, asymmetric atrophy, left more than right, also involving deep gray matter, hypodense changes left periventricular white matter, enlarged ventricles (left more tha right), consistent with infection with hypoxic insult (infarction), but lesion does not adhere to vascular territory	CNS Infection
	56	AM	MRI	symmetrical increased signal on T2-weighted images in dorsal pons, single lesion in right thalamus with increased signal on T2-weighted images, lesion in left caudate with increased signal on T2-weighted images, suggestive of metabolic disorder (e.g. mitochondrial cytopathy)	Metabolic/ neurodegenerative
	57	RAI	MRI	generalised cortical swelling, periventricular cystic encephalomalacia and areas of periventricular haemorrhage, pathological enhancement of periventricular lining, abnormal signal in the thalamus bilaterally. The differential diagnosis includes infection with hypoxic ischaemic injury and metabolic disorder.	Acquired non specific

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
	58	AP	MRI	asymmetrical cortex and white matter signal changes (oedema and haemorrhage especially right deep white matter) affecting more the right hemisphere, basal ganglia bilaterally are also involved, appearances consistent with global vascular injury (affecting more the right hemisphere) hypoxic ischaemic injury	Ischaemic/vascular
	60	DR	MRI	bilateral multiple tubers, largest in the left frontal lobe (calcified) and multiple subependymal nodules, diagnostic for Tuberous sclerosis	Developmental lesion
	64	SH	MRI	global atrophy, delayed myelination, consistent with metabolic disorder or progressive neurodegenerative disorder	Metabolic/ neurodegenerative
	65	IY	MRI	anterior pachygyria, posteriorly smooth cortex, consistent with Lissencephaly	Developmental lesion
	70	HY	MRI	abnormal white matter signal on T2 weighted images (especially internal capsule and cerebellum), more consistent with leucodystrophy than hypomyelination	Metabolic/ neurodegenerative
	73	SC	MRI	bilateral cortical atrophy with increased signal in peri-rolandic cortex, lack of white matter bulk , thin corpus callosum, delay of myelination, bilateral signal abnormalities in basal ganglia on IR and T2 weighted sequences, small pos and vermis atrophy consistent with profound hypoxic ischaemic injury at term	Perinatally acquired /HIE

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
Abnormal – aetiologically relevant	76	ZA	MRI	lack of white matter bulk (volume loss),could be consistent with periventricular malacia, slightly delayed myelination, increased subcortical white matter signal on T2 weighted images in right occipital areal non specific – differential includes hypoglycaemia, hypoxic ischaemic injury and malformation	Unable to categorise
	81	JS	MRI	Microcephalus vera (asymmetric) cerebellar diaschisis, coarse gyral pattern	Developmental lesion
	82	HK	MRI	right temporal occipital aterial venous malformation supplied by posterior cerebellar artery	Developmental lesion
	83	AP	MRI	acute changes diffuse swelling and oedema of cortex and white matter, deep grey matter also involved, (subtentorial subdural haemorrhage), consistent with bilateral hemispheric infarction - global hypoxic ischaemic injury	Ischaemic/vascular
Total N (%)	**26 (50%)**				
Incidental / immaturity/ uncertain	5	EP	MRI	arachnoid cyst right lateral ventricle (trigonum)	
	6	LM	MRI	delayed myelination, lack of white matter bulk, white matter immaturity and increased perivascular spaces	
	12	GH	MRI	mild lack of white matter bulk, thin corpus callosum	
	13	MA-H	MRI	mild delay of myelination	
	16	NR	MRI	asymmetry of wm signal in temporal lobes (right more advanced / or left delayed) right hippocampus slightly smaller - weak lateralising sign	
	33	HD	MRI	subarachnoid cyst over left sylvian system, no localising or lateralising features	

Neuroimaging – Findings	ID	Initials	Imaging Type	Review - Conclusion	Aetiological Category
	39	AK	MRI	delayed myelination	
	48	00	MRI	delayed myelination	
	69	MA	MRI	delayed myelination. Lack of white matter bulk and thin corpus callosum, small chiasm, no localising abnormalities	
	85	MD	MRI	delayed myelination	
	88	A K-O	MRI	suspicious area of abnormal signal (decreased on T2 weighted images) right posterior frontal, fronto-parietal, insufficient imaging quality to determine for certain	
Total N (%)	**10 (17.5%)**				
No abnormalities seen	3	TW	MRI	normal	
	7	RK	MRI	normal	
	32	HV	MRI	normal	
	36	AM	MRI	normal	
	38	PMJ	MRI	normal	
	41	MD	MRI	normal	
	46	JF	MRI	normal	
	51	ZM	MRI	normal	
	52	OG	MRI	normal	
	54	RH	MRI	fast speed imaging, limited quality scans, not sufficient for epilepsy pathology - no gross structural abnormalities	
	55	JT	MRI	normal	
	71	DM	MRI	normal	
	84	RA	MRI	normal	
	87	PD	MRI	normal	
Total N (%)	**14 (25%)**				

CT = Computer Tomogram, MRI = Magnetic Resonance Image

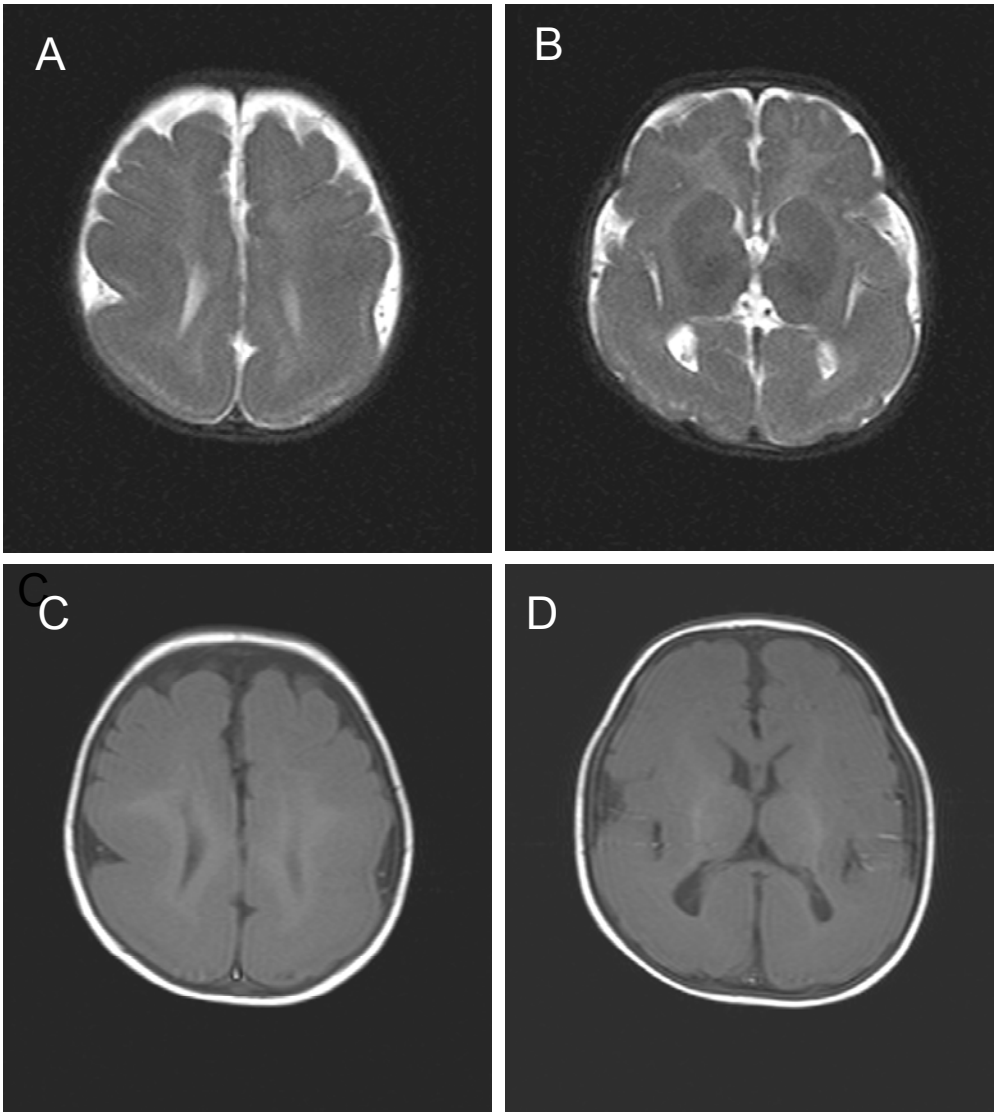
Examples of MR imaging findings

Abrevations for sequences:
TSE: Turbo Spin Echo
FSE: Fast Spin Echo
IR: Inversion Recovery
DESTIR: Double Echo Short Tau Inversion Recovery

<u>Developmental lesions / malformations</u>:

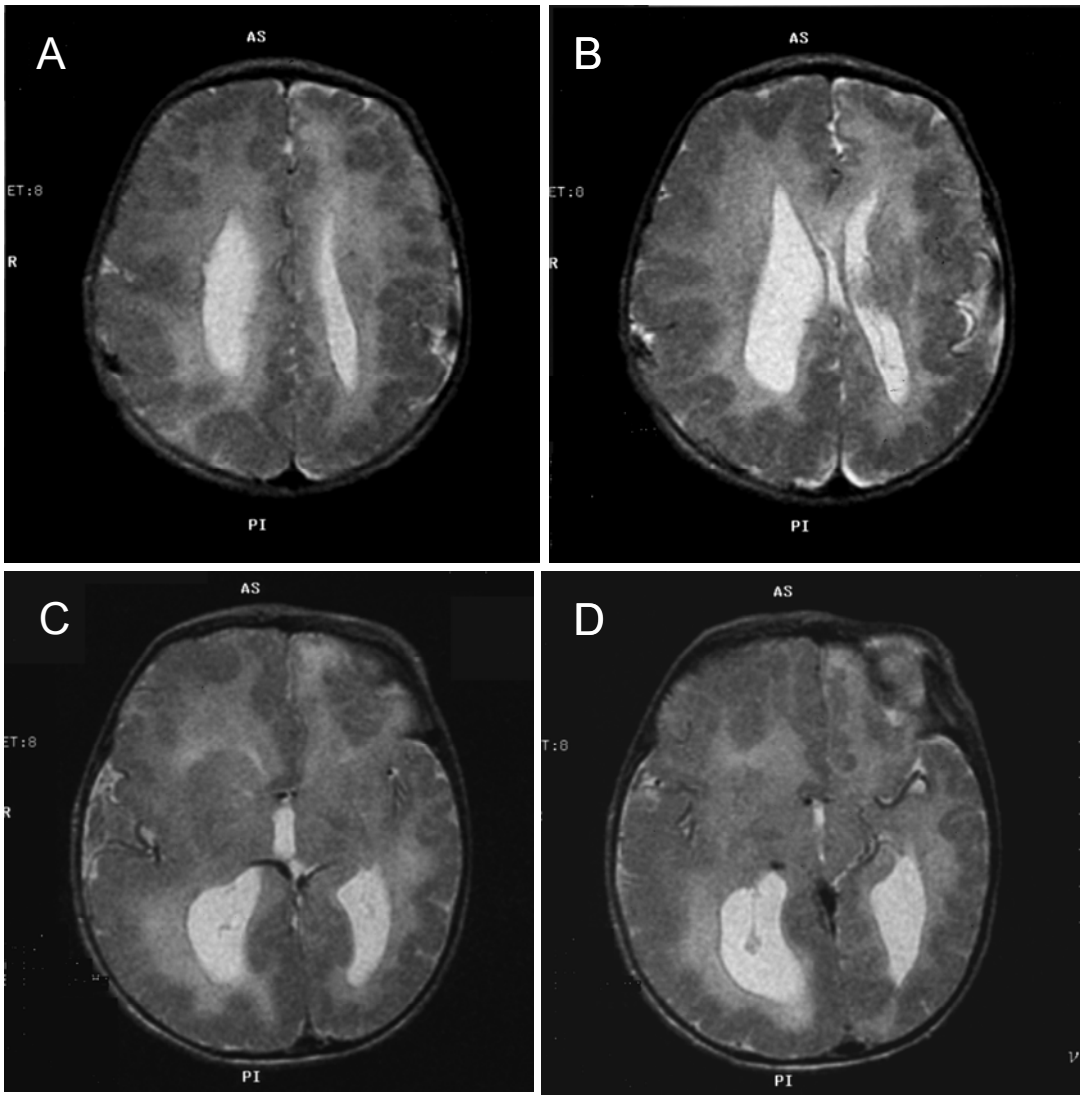
Diffuse bilateral hemispheric involvement:

Figure 8.1



Axial T2 (TSE) weighted (A , B) and T1 weighted (C and D) images showing anterior pachygyria and posteriorly smooth cortex consistent with Lissencephaly, ID 65, male infant, 6 months of age at the time of imaging

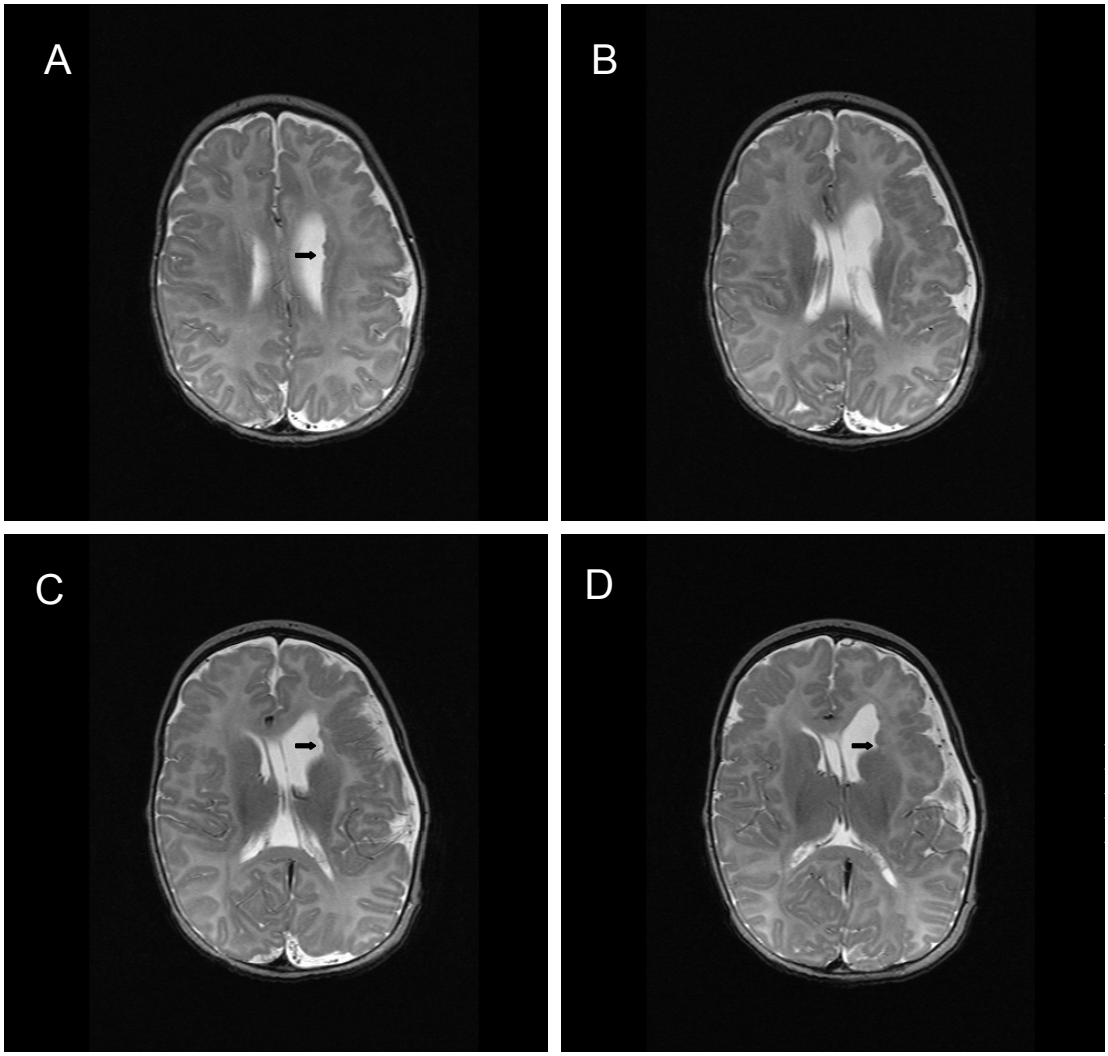
Figure 8.2:



A-D: axial T2 (FSE) weighted images showing several abnormalities: 1. extensive bilateral hemispheric polymicrogyria, 2. the left frontal cortex appears thinner, which may suggest an insult, 3. the right hemisphere is larger with thickened septum pellucidum, which is a feature of hemimegalencephaly, ID 40, male infant, 2 weeks at the time of imaging

Bilateral multi-lobar hemispheric involvement

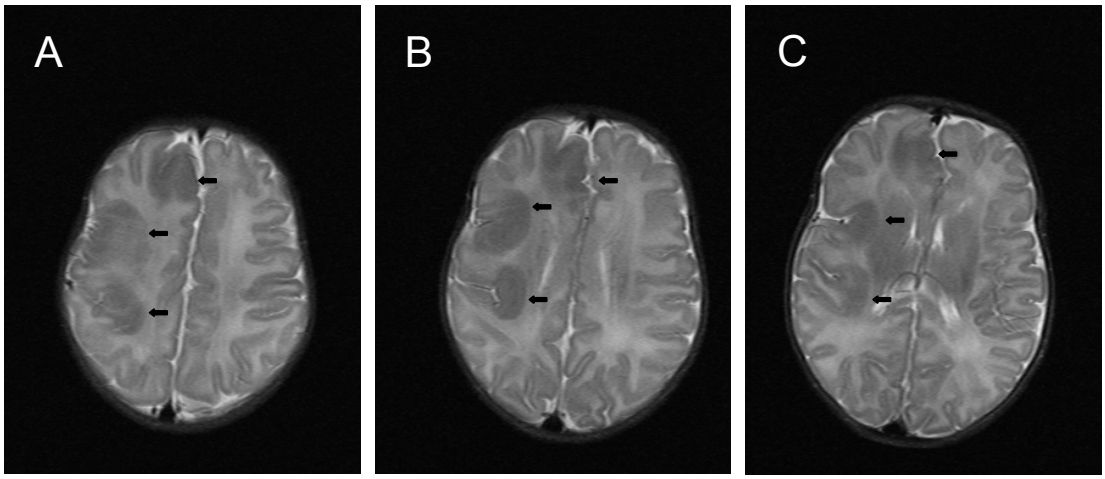
Figure 8.3:



A-D: T2 weighted (TSE) images showing bilateral asymmetric polymicrogyria involving frontal, temporal and parietal lobes in the left hemisphere, on the right frontal lobe, perisylvian and insular areas. In addition there is left periventricular heterotropia (demonstrated by black arrows). ID 34, male infant 3.2 months at the time of imaging

Unilateral multi-lobar hemispheric involvement:

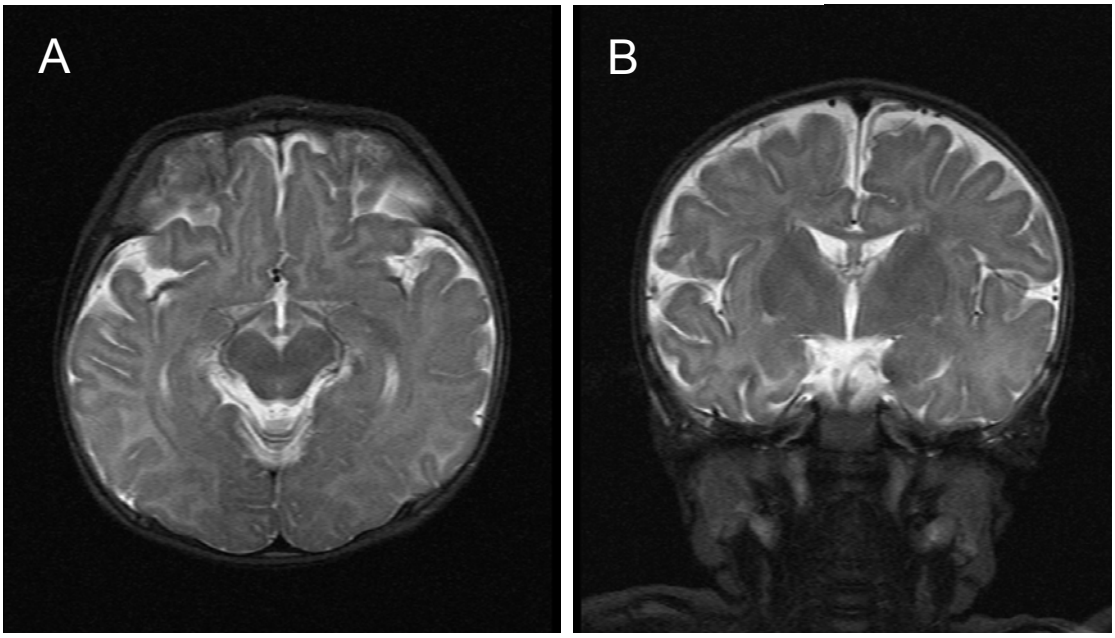
Figure 8.4:



A- C: axial T2 (DESTIR) images showing extensive area of cortical dysplasia in right hemisphere involving mesial, middle, inferior and frontal lobe, frontal operculum, perisylvian area as well as superior parietal lobe (black arrows). ID 14, female infant, 3 weeks of age at the time of imaging

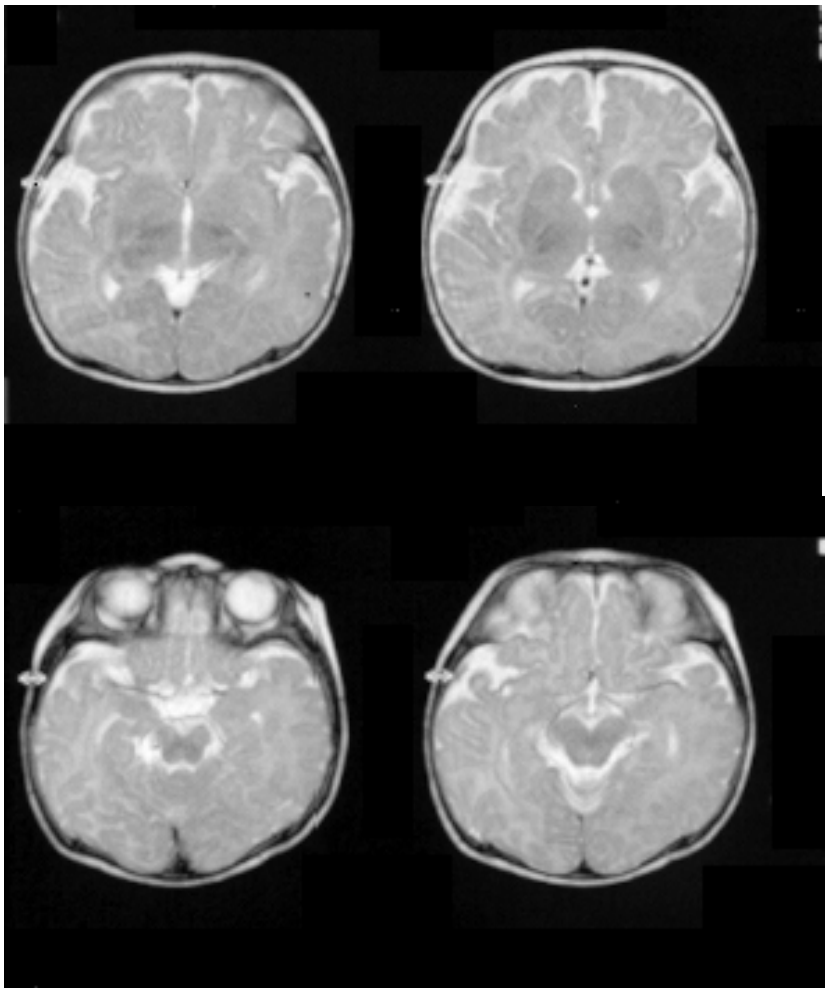
Unilateral uni-lobar involvement:

Figure 8.5



Axial (A) and coronal (B) T2 weighted (DESTIR) images demonstrating coarse gyral pattern and blurring of grey/white matter junction and in left temporal lobe extending in occipital area consistent with area of focal cortical dysplasia. ID 35, male infant, repeat MR images performed at 4 months of age; first MR images at 2.7 months of age see Figure 8.6.

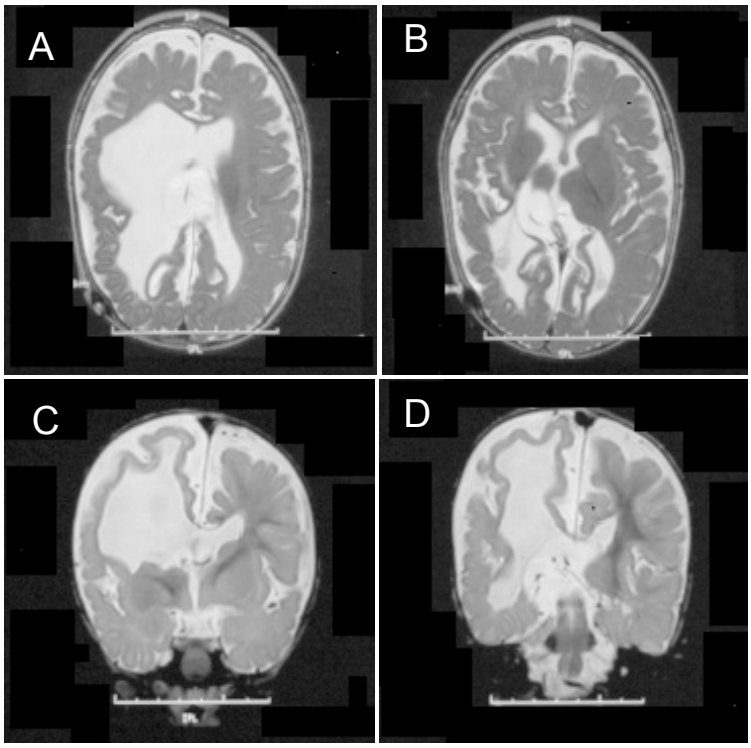
Figure 8.6:



Initial MR images of case 35 performed at 2.7 months of age - axial T2 (TSE) weighted. No structural abnormalities were identified. The images wer of acceptable quality as judged by collaborating neuroradiologists. A repeat MR scan at 3 months of age demonstrated subtle abnormality in left temporal lobe extending to occipital and insular cortex (see Figure 8.5)

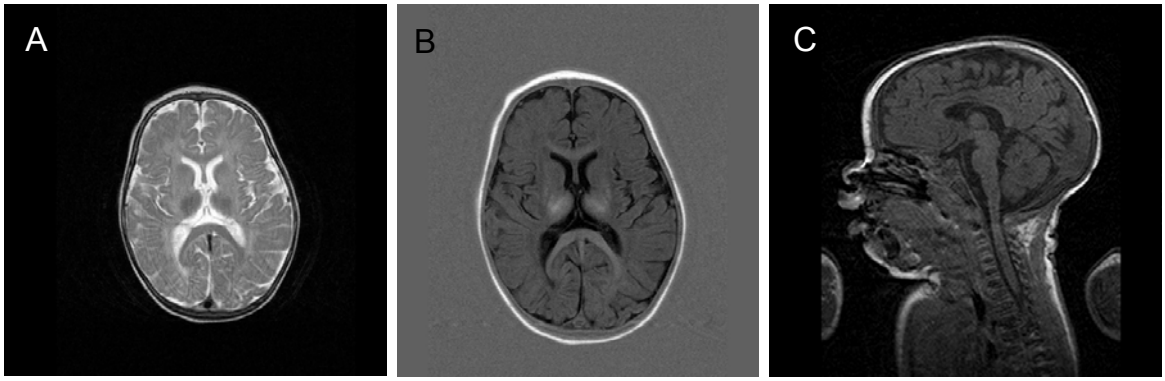
Acquired brain lesions:

Figure 8.7



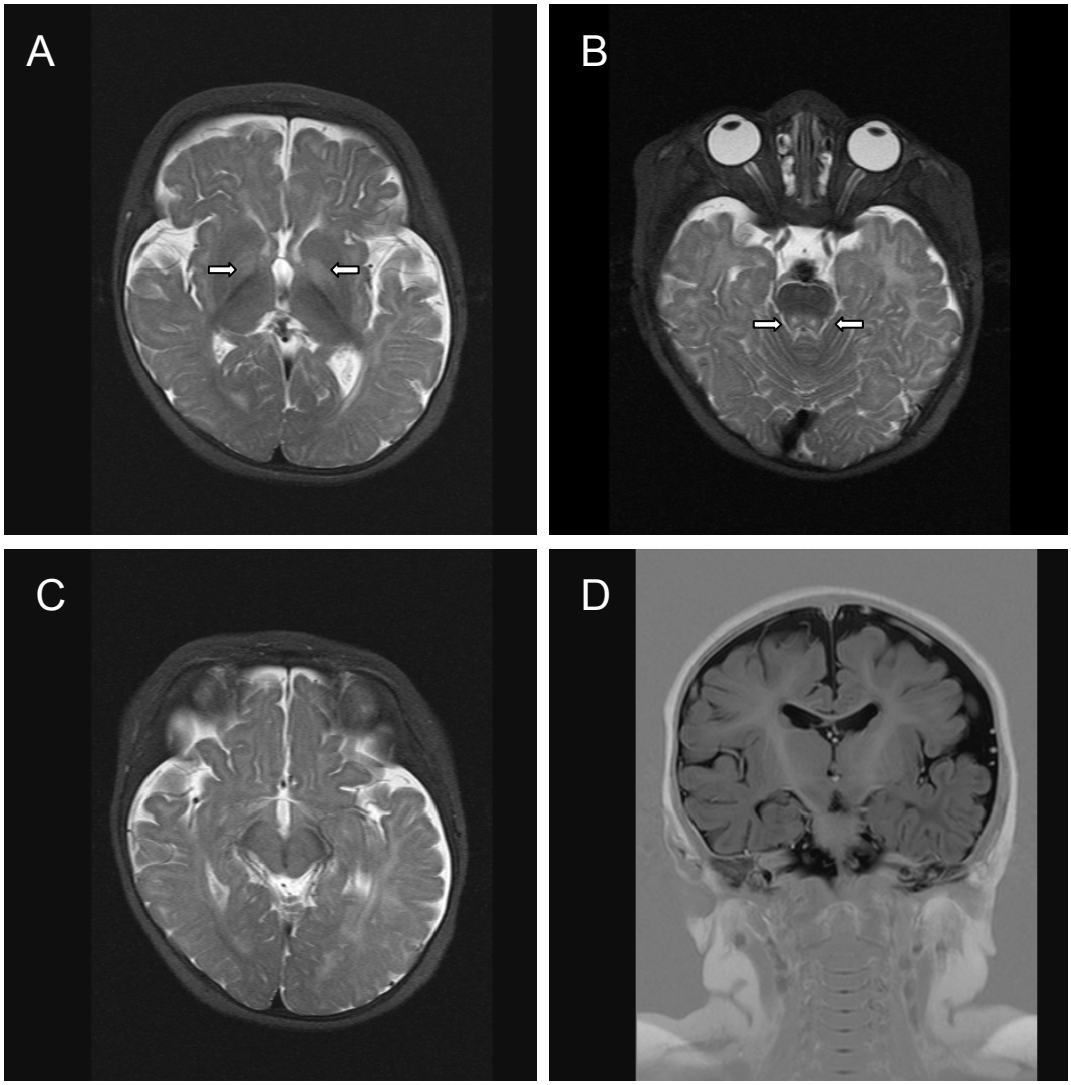
Axial (A and B) and coronal (C and D) T2 (FSE) weighted images demonstrating asymmetric peri-ventricular leucomalacia with white matter loss affecting more the right than the left hemisphere as well as cortical atrophy that is more severe on the right. ID 11, male infant, 9 months corrected gestaional age at the time of imaging, premature at birth (25 weeks of gestation), sustained grade 4 asymmetric intraventricular haemorrhages in first days of life with subsequent evolution to post haemorrhagic hydro-cephalus.

Figure 8.8:



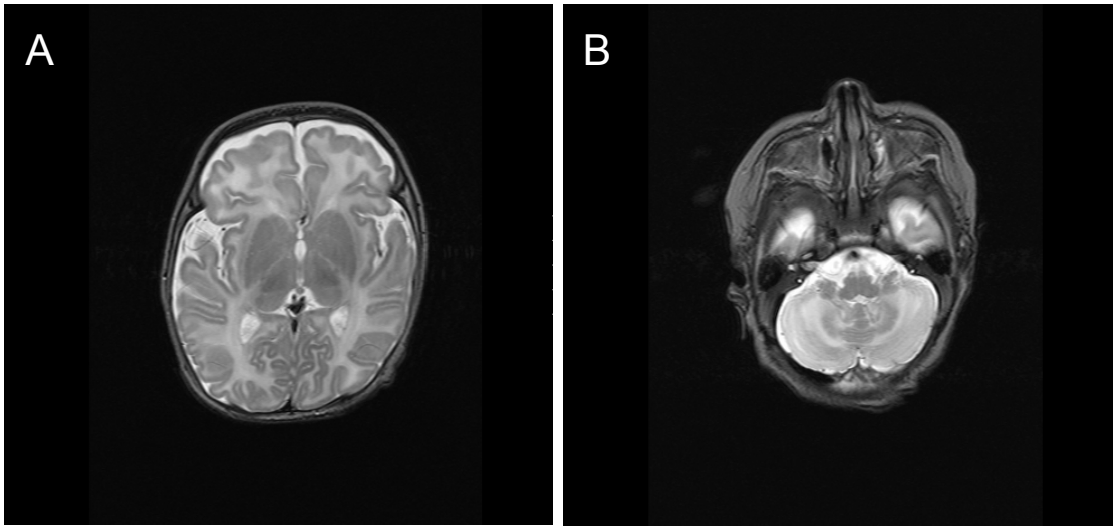
Axial T2 (DESTIR) weighted (A) and axial T1 (IR) weighted (B) images showing bilateral cortical atrophy with lack of white matter bulk, delay of myelination and bilateral signal abnormalities in basal ganglia, thalami and posterior limb of the internal capsule. Sagital T1 weighted (C) image demonstrating thin corpus callosum small pons and vermis atrophy. Appearances are consistent with profound hypoxic ischaemic injury at term. ID 73, male infant , 6 months at the time of imaging, required cardio pulmonary resuscitation after birth at term and ventilation on the neonatal intensive care unit.

Figure 8.9:



Axial T2 weighted (DESTIR) images (A and B) demonstrating bilateral symmetrical signal abnormalities in globus pallidum and dorsal pons (white arrows) suggestive of metabolic disorder such as mitochondrial cytopathy. Increased white matter signal on axial T2-weighted (DESTIR) image (C) in left temporal - occipital area and T1 weighted (IR) (D) image showing decreased signal in same area giving appearance of thickened cortex, which could be seizure related. ID 19, female infant, 9 months at the time of imaging.

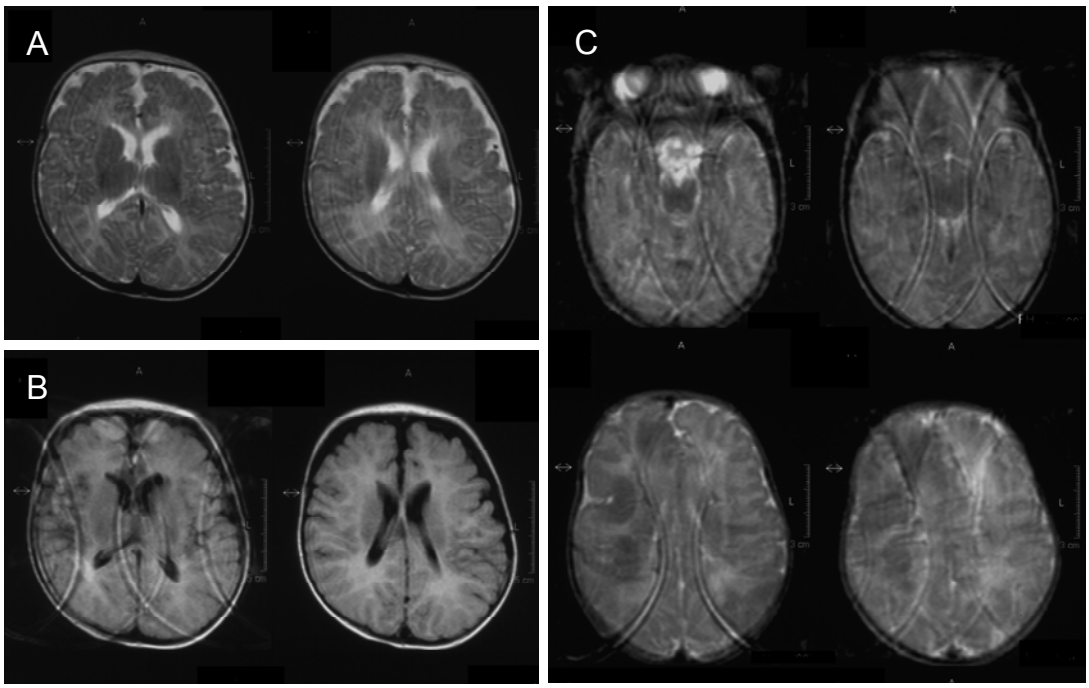
Figure 8.9:



A and B: Axial T2 weighted (DESTIR) images showing abnormal white matter signal on T2 weighted images, especially internal capsule and cerebellum, in keeping with leucodystrophy. ID 70, female infant, 2 months of age at imaging, significantly low plasma biotinidase in keeping with diagnosis of biotinidase deficiency.

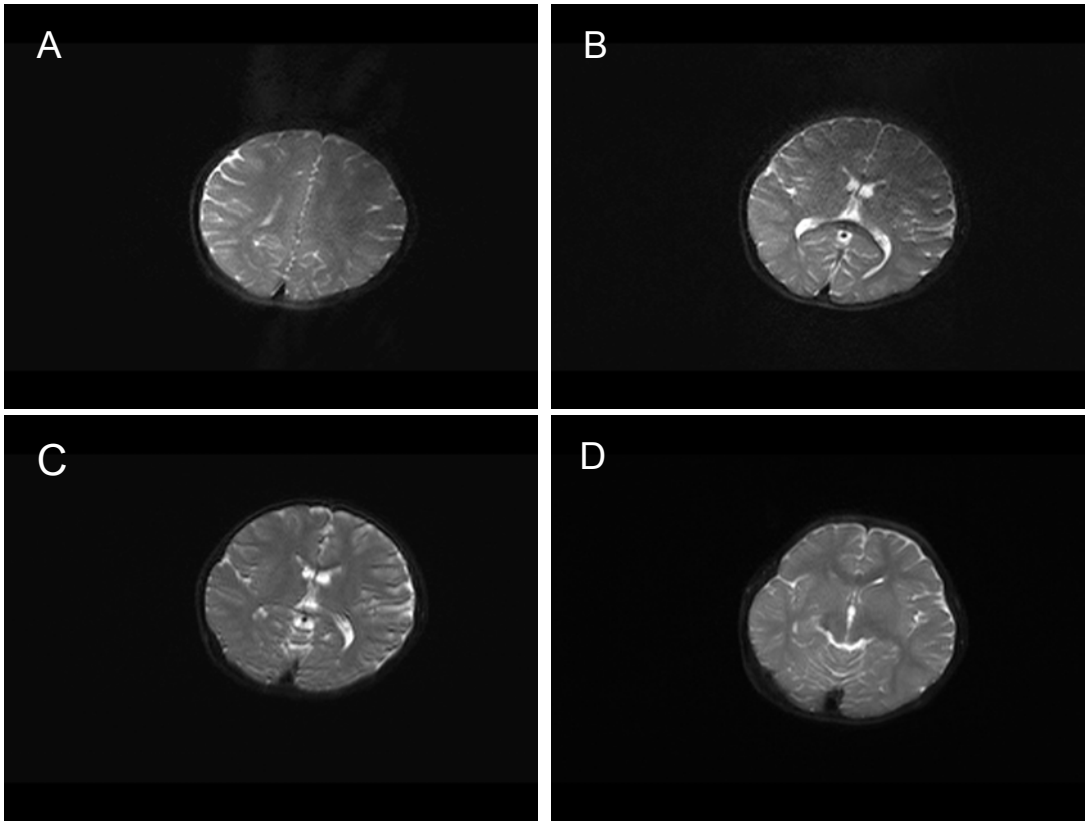
Examples of MR images of insufficient quality

Figure 8.10:



Panel A and B: axial T2 weighted (Fast Spin Echo) images (A), axial T1 weighted (Inversion Recovery sequence) images (B), with movement artefacts of female patient (ID 19) at 3 months of age, abnormalities on repeat MR images at 8 months of age are illustrated in figure
Panel C: axial T2 weighted images with movement artefacts of female patient (ID 14) at 2 weeks of age, for abnormalities on repeat MR imaging at 3 weeks of age see figure 8.3

Figure 8.11:



Panels A-C: example of ultra fast axial T2 weighted sequence images with reduced contrast to noise as obtained in 4 cases (IDs 41, 54, 56 and 84), 3 MR scans were repeated with positive findings in one (ID 56)

8.9 Appendix 10: Principal Component Analysis (Bayley III subscale raw scores)

Total Variance Explained

Component (raw subscale scores)	Initial Eigenvalues			Extraction of Sums of Squared loadings		
	Total	% of Variance	Cumulative%	Total	% of Variance	Cumulative %
Cognition	4.687	93.746	93.746	4.687	93.746	93.746
Expressive language	0.211	4.222	97.967			
Receptive language	0.054	1.090	99.057			
Fine Motor	0.033	0.656	99.713			
Gross Motor	0.014	0.287	100.000			

Extraction Method: Principal Component Analysis.

Table of Communalities

Raw subscale scores	Initial	Extraction
Cognition	1	0.973
Expressive language	1	0.910
Receptive language	1	0.911
Fine Motor	1	0.944
Gross Motor	1	0.950

Extraction Method: Principal Component Analysis.

Component Matrix[a]

	Component
Raw subscale scores	1
Cognition	0.98
Expressive Language	0.95
Receptive language	0.95
Fine Motor	0.97
Gross Motor	0.97

Extraction Method: Principal Component Analysis.
[a] 1 components extracted.

8.10 Appendix 11: Principal component analysis:
Bayley III composite scores at baseline / follow up

Total Variance Explained

Component (composite scores baseline)	**Initial Eigenvalues**			**Extraction of Sums of Squared loadings**		
	Total	**% of Variance**	**Cumulative%**	**Total**	**% of Variance**	**Cumulative %**
Cognition	2.654	88.452	88.452	2.654	88.452	88452
Language	0.252	8.403	96.855			
Motor	0.094	3.145	100.000			

Extraction Method: Principal Component Analysis.

Component Matrix[(a)]

	Component
Bayley III composite scores (baseline)	1
Cognition	0.95
Language	0.91
Motor	0.96

Extraction Method: Principal Component Analysis.
[a] 1 component extracted: Developmental composite factor 0 (DCF-0)

Total Variance Explained

Component (composite scores follow up)	**Initial Eigenvalues**			**Extraction of Sums of Squared loadings**		
	Total	**% of Variance**	**Cumulative%**	**Total**	**% of Variance**	**Cumulative %**
Cognition	2.863	95.421	95.421	2.863	95.421	95.421
Language	0.106	3.550	98.970			
Motor	0.031	1.030	100.000			

Extraction Method: Principal Component Analysis

Component Matrix[(a)]

	Component
Bayley III composite scores (follow up)	1
Cognition	0.983
Language	0.971
Motor	0.970

Extraction Method: Principal Component Analysis.

[a] 1 component extracted: Developmental composite factor 1 (DCF-1)

8.11 **Appendix 12:** Cases that were excluded form the North London infancy epipesy cohort after initial enrolement

ID	Age at onset [months]	Details:	Reason for exclusion
21	**6**	Female infant who experienced 4 episodes within 24 hours with the following manifestations: behavioural arrest, staring blankly, palor, lip cyanosis lasting up to 3 minutes. She was commences on phenytoin and did not experience any further events after withdrawal of the antiepileptic medication 6 months later. Her interictal EEG was normal. She had a developmentally normal stepsister who experienced 2 afebrile seizures within 1 one week at the age of 4 months and had remained seizure free ever since.	Not meeting inclusion criteria - because all events belonging to a single episode
22	**1.9**	Male infant with preceding history of 2 days diarrhoea and vomiting, experienced cluster of several afebrile seizures occurring in one day: eyes rolled back, lips blue, generally rigid, unresponsive for 1-2 minutes afterwards sleepy. Similar events (4-5) were observed after admission to hospital. He was terated with iv phenytoin. On admission low blood glucose (BM - 2.9) and metabolic acidosis (Base exess -19, bicarbonte 11.9 mmol/L) were documented. Brain Computer tomography scans were reported to show marked brain and cerebellar swelling with bilateral posteriorly hypodense changes consistent with encephalitis or metabolic disorder. He recovered completely and remained seizure free for 6 months. Phenytoin was discontinued.	Acute symptomatic seizures
37	**3**	A male infant who experienced two focal of seizures lasting up to 3 minutes approximately 5 minutes apart. MR brain imaging and interictal EEG were normal. He has not been started on anti-epileptic medication and remained seizure free for 6 weeks at the time the parents were interviewed by the researcher.	not meeting inclusion criteria - because events belonging to a single episode
66	**2.5**	Male infant (notified at age 8.5 months). Was admitted following normal vaginal delivery to neonatal intensive care unit with respiratory distress. Required 9 days of assisted ventilation (continuous positive air pressure. Subsequently presented global developmental delay and 4 cerebral palsy. His mother noticed from 2.5 months of age onwards abnormal episodic movements: punching himself with arms, shaking with legs, foaming, occurring in clusters every 2 days. Brain MR scan reported by local team to show periventricular leucomalacia, EEG was grossly abnormal. anonymised information provided by the paeditrician, who notified the case.	lack of information to categorise paroxysmal events as epileptic seizures in this particular clinical context