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Incidence, Aetiology and Morbidity

of Status Epilepticus

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Abstract

Status epilepticus (SE) is a common neuro-medical emergency for which medical institutions should be well prepared as well as at community level. This review considers available epidemiological studies of SE in the last decade (1996-2006) in order to: (a) determine the incidence of status epilepticus as recorded in population and hospital based studies; (b) determine the causes of SE as defined in these studies; and (c) to ascertain the rates of morbidity, in terms of neurological deficit and continuing epilepsy, of SE._PUBMED search was carried out a total of eleven population based studies and 20 hospital based studies were included. In addition, 10 studies provided sufficient data to be included for the purposes of determining morbidity.

Incidences of SE among the studies included are quite different. The incidence rate range between highest 41/100.000/y to lowest 9.9/100.000/y among population based studies. Among hospital based studies incidence of SE varies between highest of 13.1/100.000/y to lowest incidence of 4.9/100.000/y. This difference in the incidence rates among these studies depend on the different case identification methods used. In all epidemiologic studies under ascertainment is the major problem. In addition, an actual change in the frequency of SE over time may exist with the improvement in diagnosis and management of epilepsy.

Remarkably, there is considerable consistency across the studies regarding several important features in SE epidemiology. Most of these studies agreed about the bimodal distribution of SE between children less than five years and elderly more than 65years. Another consistency among the different studies is that SE shows slight predominance between male genders (except in two studies which shows slight female predominance).

The main cause of SE among children was febrile status epilepticus up to 50%. In comparison the main cause of SE among adults was symptomatic epilepsy up to 40%. Not all SE are attributed to epilepsy, de novo SE is an important category of SE, contributing to almost half of SE cases.

Morbidity from SE varies from 35% acute neurologic sequalae to no neurologic deficit recorded at all. Morbidity was associated with age of the patients, symptomatic epilepsy and seizure duration.

The incidence of SE is not well established and varies between different studies. SE is an under recognized neurologic emergency that needs more investigation. Consistency between different studies regarding bimodal distribution of SE between elderly and children less than five years. The main aetiology of SE between children was febrile status epilepticus and between adults is symptomatic SE. Morbidity and outcome of SE is a matter of debate, since it may represent the causal of SE rather than the sequalae of it. Further studies are, however, needed to determine accurately the incidence, aetiology and morbidity rates of SE, and if there is any changes in these rates over time.

INTRODUCTION

What is status epilepticus (SE)? ... no really satisfactory definition of SE is available. The WHO dictionary definition is: a condition characterized by epileptic seizures that are sufficiently prolonged or repeated at sufficient brief intervals so as to produce an unvarying and enduring epileptic condition. The question arises as to how long the condition must persist to consider it as SE. Another widely used definition of status is: a condition in which epileptic activity persists for 30 minutes or more causing a wide spectrum of clinical symptoms and with a highly variable pathologic physiological, anatomical and aetiological basis (Shorvon 1994). This definition provides a minimum time limit for status epilepticus of 30 minutes which is justified by physiological considerations. In the classical animal models of status, a seizure lasting for over 30 minutes leads to definite neuronal damage (Shorvon 1994). What have been termed 'operational definitions' are also in current use, these define status as a continuous or recurrent seizure lasting for more than 5 or more than 10 minutes? These have been introduced to ensure that treatment is started early to prevent longer seizures with their consequent risk of cerebral damage, and are justified by the view that tonic-clonic seizures lasting 5 or 10 minutes or more are seldom self limiting.

None of these definitions of SE differentiate between continuous seizure and intermittent seizures. For all definitions, in clinical practice there remains the problem of how accurate such a time measure can be? It is sometimes not easy to decide when a seizure starts or when it stops. Furthermore, it is a common clinical experience that EEG changes can occur before any clinical change and also continue post ictally.

There are many types of status epilepticus. Gastaut maintained that any type of epileptic seizure can develop into SE. However, a classification of status epilepticus should be based on more than simply seizure type. Other considerations include the pathophysiological mechanism of seizure, clinical feature of the status itself as well as EEG findings. Subdivisions depending solely on clinical features of the status are difficult to rely upon since some non convulsive seizures have subtle signs or are even not manifest clinically at all. EEG classification is not recommended since EEG is relatively non-specific, classification criteria tend to be loose and the scalp EEG can be only a very indirect measure of underlying electrical and chemical activity of the brain. New classification systems have been proposed which incorporate many aspects of status epilepticus and these have more validity. Any classification system must be flexible and dynamic.

SE probably starts in the same way as any other isolated seizure attack. The reason for the seizure becoming prolonged or failing to stop is not clear. It is difficult to differentiate the causes and consequences of SE pathologically, as it is well known that SE can cause cerebral damage.

Tonic-clonic SE is a true medical emergency where prompt and appropriate treatment is essential to prevent brain damage and possible death. Clinically without any previous history, it is difficult to know if one observed seizure is going to be self-limiting or to initiate SE. Furthermore, postictally it is difficult to predict that the patient has recovered completely, or will have further seizures. Diagnosis also is not without problems, and patients with intermittent decorticate or decerebrate posturing can be mistakenly treated as SE, and the syndrome of non-epileptic SE (pseudo SE) is more common in tertiary practice than true SE. It should be suspected whenever there is an unusual presentation of seizure type, or if the response to anti epileptic drugs (AEDs) does not follow the expected pattern.

The principles of treatment of status are very different from those of chronic epilepsy. The priorities are to stop seizure activity as rapidly as possible, prevent injury, maintain cardio-respiratory function and avoid secondary medical complications. In the great

majority of cases drug treatment control seizure activity and the status will resolve. If drug treatment failed to control seizure complicating factors as inadequate drug regimens, additional medical factor or misdiagnosis e.g. Pseudo SE, should be considered.

SE has a high mortality and morbidity and these rates are influenced by underlying causes; being low in idiopathic epilepsy and high in symptomatic status. Morbidity and mortality are also highly depending on the duration of status, and to a lesser extent on the patient's age. The risk of morbidity is greater in children than adults. SE morbidity can take the form of (a) neurological deficits (usually cognitive or motor); (b) ongoing epilepsy. There is also an increased risk of after status epilepticus attack, as well as status follows epilepsy. There is high morbidity risk especially in children with neurological abnormalities or patients with symptomatic epilepsy.

A study of the epidemiology of SE can contribute to understanding the natural history of the disease. SE study is a problematic condition since SE occurs not only in epileptic patients but also de novo status in non epileptics exists. Changes definitely occur over years in the incidence and outcomes of SE. Technologic advances in EEG and imaging make it more specific to diagnose epilepsy. New drugs for the treatment of epilepsy, which are more potent and with less side effects are now available improving the chance for seizure control. Health education about epilepsy and its complications play a major role in the control of epilepsy. However we still have non epileptic who are prone to develop this condition. Accurate and up to date information about this emergency situation is very important for monitoring of all these issues.

<u>AIMS</u>

The objectives of this review are, using the literature of the previous decade:

1. To ascertain the incidence of status epilepticus as recorded in population and hospital based studies.

2. To ascertain the causes of SE as defined in hospital and community based epidemiological studies.

3. To ascertain the morbidity of SE.

METHODS

Articles pertaining to status epilepticus incidence and prognosis were identified by screening the electronic database PubMed between 1996 to 2006.The following search terms were used:

- Status epilepticus / incidence
- Status epilepticus / cause
- Status epilepticus / epidemiology
- Status epilepticus / morbidity
- Status epilepticus / outcome

The reference lists of all articles identified were also examined to identify additional relevant studies. All hospital based and population based studies on SE, where the outcome was incidence or aetiology of SE, were included. Reference lists from each of the articles were manually searched for papers not identified from the databases. Recent book chapters were also scanned for any relevant materials.

Inclusion Criteria:

1. All population based studies with end point incidence of status epilepticus published in PubMed between 1996 - 2006.

2. All hospital based studies with end point of incidence of status epilepticus published in PubMed between 1996 -2006.

3. All studies with morbidity of status epilepticus end point published in PubMed between 1996 -2006.

4. Studies published in English.

Exclusion Criteria:

1. Studies which were restricted to specific aetiological groups of status epilepticus (e.g. status epilepticus amongst stroke or tumour patients).

2. Studies for which the primary purpose was the study of the mortality of status epilepticus.

RESULTS

The PUBMED review revealed 590 studies. Of these only 11 population-based studies and 20 hospital-based studies provided sufficient original data to be included in this study. In the others, the reasons for rejection were as follows:

- Most of these studies looked after SE in specific aetiologic conditions like SE and stroke, neoplasm, malaria....etc.
- Large numbers of these studies investigate on the effect of certain drugs and management of SE.
- Another study group on the mechanism, pathology and molecular neuropathology of SE.
- Studies where the mortality was the end point were also rejected.

In Table 1, the population studies are summarised.(page 41).

In Table 2, the hospital based studies are summarised. (page 47).

In Table 3, the aetiology of SE in population-based studies is summarised. (page 53).

In Table 4, the aetiology of SE in hospital-based studies is summarised. (page 54).

In Table 5, the morbidity studies are summarised. (page 56).

DISCUSSION

1. Population Based Studies:

I. Study design and inclusion/exclusion criteria:

A total of eleven population based studies between 1996-2006 were included in this review. This is a relatively small number given the serious nature of SE and its high mortality and morbidity.

Eight out of eleven are prospective studies (1, 3, 4, 5, 6, 8, 9, and 10) *see appendix table 1*, which generally speaking give more accurate information about the incidence and morbidity of SE. Three out of eleven are retrospective studies (2, 7, and 11) which are prone to various types of selection bias *see appendix table 1*.

The definition used for SE in all studies was that suggested by Shorvon (1994) – defined by a minimum duration of 30 minutes. No study utilised the operational definitions (duration of 5 to 10 minutes) which are often used clinically.

Inclusion criteria in the different studies varied. Study by **(Delorenzo et al, 1996)**, excluded patients with paroxysmal lateralising epileptiform discharges (PLEDs) and in study by **(Coeytaux et al, 2000)** patients with PLEDs and post-anoxic myoclonic and post-surgical patients was excluded. There is controversy about whether some patients with post-anoxic cerebral damage and PLEDS are exhibiting a form of non convulsive SE and their exclusion will have a significant impact on incidence figures. A similar situation (coma with EEG evidence of PLEDS) can arise from partially treated GTCS.

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Study conducted by (**Cascino et al, 1998**) includes non febrile SE only. The definition of febrile seizure was not clearly mentioned in any of these studies, and it is not clear if febrile seizure were defined as only those occurring in children between the ages of 6 months and 6 years, or symptomatic febrile seizures at any age were also excluded. Again, the inclusion of febrile SE will have a significant impact on incidence figures.

Chin et al, 2006 includes only convulsive seizures in the paediatric population. Incidence of convulsive SE was estimated as 18-20 per 100.000 per year in the north London paediatrics population in comparison with 4-6/100.000/ year in adults and 21-38/100.000/year in childhood population including non convulsive SE.

Cases identification techniques are quite different between the studies. Hospital medical records are used in all the studies. Neurology Department, Emergency Department and ICU records are used in study by (**Knake et al, 2001**) and uncertain cases are excluded. No EEG data were used in this study and by which under ascertainment of the diagnosis of SE may occur. Some of the cases may be missed as in minor SE or non convulsive SE. In addition over estimation may occur by including patients with pseudo status epilepticus, which may not be easy clinically, especially in the absence of previous medical history. EEG during the episode will definitely provide an answer for the doubtable clinical presentation.

Family interviews were used in studies by (**DeLorenzo A et al, 2004**) and (**Berg et al, 2004**) which are quite unreliable. We know that epilepsy carries a lot of social stigmata almost all over the world and most of the patients and their relatives may be unwilling to admit the disease occurrence, in addition to avoidance as much as possible to prevent losing their insurance benefits or opposite way around, gaining social benefits.

Neurologic data, EEG, and emergency records data are used in study by (**Vignatelli et al, 2005**). Emergency, neurology, paediatric, EEG, psychiatric and geriatric records are used in study no. (4) (**Coeytaux et al, 2000**). EEG data collection is important when trying to include non-convulsive forms of SE particularly.

The type of hospital used for the collection of data can have an impact on frequency measures. Two of the studies were done in University hospitals (study nos. 5, 6) and five were conducted in public hospitals (study nos. 1, 2, 4, 8, 9) *see appendix table 1*. SE patients are more likely to present to the local public hospitals as emergency cases. Cases which present to the university hospitals or tertiary centres are more likely to be refractory SE or symptomatic SE, which may lead to a significant bias in data analysis and results.

DeLorenzo et al, 2004, published a population based Virginia twin sample study, using a completely different case ascertainment method. Cases were taken from the Virginia Twin register. The frequency of SE in this very specific population was found to be 8.52 per 100.000 twins which are quite high in comparison to the incidence in the general population. History of seizure and SE was validated from medical records in addition to personal self reporting or parent interviews, which are not reliable enough and will give a bias in the rating of SE. We know that family members and patients are very sensitive regarding seizure documentations and lack of the knowledge of SE definition, in addition to that the occurrence of SE without hospitalization is less likely. In this study they depend on questionnaire or telephone interviews of parents for the paediatric age group. For adult twins group, tracing through Department of Motor Vehicle records will exclude those who were not driving and by this excluding intractable seizure twins who are prohibited from getting driving licence, in addition to those who have brain damage or neurological deficit who are more likely to have SE. Out of 19,453 contacted twin, 11,207 pairs answered the questionnaire. This will affect the number of adult twin included, which could be because they are unaware of their seizure or avoiding social stigmata of being epileptic. However this was the only study which looked after a defined population (twins) and the pattern of SE in the MZ and DZ shows evidence of genetic factors contribution.

Waterhouse et al, 1999 study is a population based study comparing intermittent and continuous convulsive SE. In this study continuous SE found to carry a higher mortality rate than intermittent SE in adults, not in children. In this study the number of

adult population was actually double that for children (433 adults and 212 for children) and this may give great bias to their results, in addition to the difficulties in identification of intermittent or continuous convulsive seizure clinically and only 60% of the cases had EEG monitoring.

II. Classification of SE:

There are different forms of SE and there is no universally agreed classification system. Different studies used different schemes which render comparison across studies difficult. Many schemes rely on both clinical and electrographic findings, and yet in many epidemiological studies, the electroencephalogram is not available.

III. No. of Patients:

The number of patients with SE included in the study was: 204-199-645-172-150-150-332-27-226-58-184 patients (in study no. 1-2-3-4-5-6-7-8-9-10-11) respectively, *see appendix table no.*1. The average no. of patients included by each study was 213 patients.

The maximum no. of patients was 645pts in **Waterhouse et al, 1999 study**. In this study, both the adult and paediatric population were included.

The minimum no. of patients was 27 in study by (**Vignatelli et al, 2005**) which was a prospective study carried out over a 2 years period and in a well-defined urban area.

IV. Gender:

Most of the studies show slight male predominance in patients with SE, which may indicate that there is a slight female protection from SE. It is well established that some females have more seizure attacks around the time of menstruation (cataminic epilepsy) which is associated with hormonal changes. The question of oestrogen hormone effect on the threshold of epilepsy is not yet clearly answered. Also, some of the common certain aetiologies are more

common in male population more than females, e.g. cerebrovascular diseases. However, one study shows slight female predominance (Knake **et al 2001**) where M:F ratio was 46:54.

V. Age:

Six studies include adult and paediatrics population study no. (1, 2, 3, 4, 7, 11) *see appendix table 1:2.*

Two studies included adult population only (**Knake et al, 2001**) and (**Vignatelli et al, 2005**).

Three studies include paediatrics populations study no (6, 9, and 10) *see appendix table 1.*

VI. De novo SE:

De novo SE accounted for 58%, 54%, 57%, in the adult and paediatric population (study no. 1, 2, 4) respectively *see appendix table 1.*De novo SE occurred in paediatrics population with frequency of 73% in study by (**Sillanpaa et al, 2002**) and 176/226 (77.8%) in study by (**Chin et al, 2006**). Among adults, de novo SE occur at a rate of 50% as in study by (**Knake et al, 2001**) and 59.4% in study by (**Vignatelli et al, 2005**). De novo SE account for more than half of the adult patients with SE and up to three quarter of de novo SE in children. Among children de novo SE is more likely because of the time limit duration and first attack of seizure may present as SE. Minor seizures in children may be missed by the parents and with recurrence and without treatment may lead to SE. In elderly acute brain insult can present as SE. In addition, metabolic diseases can present as de novo SE.

In two studies (**Coprey et al, 2004**) and (**Berg et al, 2007**) all the patients included had existing epilepsy.

VII. Incidence:

The incidence of SE in these population based studies ranges between 41- 9.9/100.000/year. There is great variation in the figures given by each study and this no doubt relates to the difference in methodology noted above. However, all studies agree about the bimodal distribution of SE between children less than one year and elderly more than 65 years. The most common cause of SE among children in most of the studies is febrile SE and in elderly is symptomatic epilepsy acute or remote.

The study with the highest incidence rate was **Delorenzo et al, 1996)**. This study found an incidence rate of 41.100.000/y with a bimodal distribution in children less than one year old 150.00.000/y and elderly 86/100.000/y. This was a prospective population based study of patients living in Richmond Virginia. It gives a good representation of the incidence and aetiology of SE. SE cases were identified in main university hospitals and all the community hospital in area, in addition to reporting by ER personnel of cases presenting to emergency rooms, ICUs and the neurology morning report service. More accurate and detailed clinical history was obtained by the investigators, in addition to EEG and lab data collection. This comprehensive case ascertainment method led to what is probably the best estimate of incidence in the studies under review. Other points in favour of this study are the large number of cases and its prospective design. The study used the 30 minutes time period for the definition of SE and if a shorter time period had been used, no doubt more cases would have been found.

In comparison, **(Hesdorffer et al, 1998)** study gives an age adjusted incidence rate of SE of 18.3/100,000/y. This rate is much lower than the other study partly of the exclusion of febrile seizures in young children and the retrospective study design. In this study there was a clear time trend increase in the incidence rate of SE over time (13.9-22.4/100.000/ybetween 1965-1974 and 1975-1984 respectively) which could be a false trend explained by better hospital records (in a retrospective study, this is of course extremely important) or a genuine result due to the increased life expectancy

period and the therefore higher incidence of SE due to symptomatic causes such as CVA, anoxia and CNS tumours.

The lowest figure was found in (**Coeytaux et al, 2000**) study. Here are the incidence of SE was found to be 9.9/100.000/y with the same bimodal distribution of SE as shown in the previous two studies. In order to reach a perfect ascertainment of case identification for all the patients included EEG was performed where EEG is available 24 hours a day in this area. In this study, post anoxic encephalopathy was excluded which may partly explain the lower figure than found in study by (**Delorenzo et al, 1996**), although this would be expected to account for only about 10% of the cases and does not explain the other differences.

Knake et al, 2001 gives a similar approximate incidence of SE among adults of 15.8/100/1000/y. The study was conducted prospectively around specific service area (zip code area) with also an additional case ascertainment by retrospective computer based review of the discharge letters. Also resident patients within that specific area who develop SE outside their area and admitted with SE to other hospitals are excluded.

In study by (**Sillanpaa and Shinnar, 2002**) the incidence of SE among epileptic children was found to be 27% during period of follow up 1964-1997 with cumulative risk of 0.22 at onset, 0.25 at one to two years after onset and 0.03 later. These figures demonstrate that with follow up most of the risk of SE is in the first few years of the epileptic disorder. In this study 39% of the patients who developed SE had symptomatic epilepsy. However, this is following review of their National Health Service records with all the problems of case under ascertainment. **Berg et al, 2004** also evaluated the incidence of SE in epileptic children over a period of eight years. The incidence of SE among their patients was 10% during their follow up period. It was associated with previous history of SE in 32% and was more common among symptomatic and younger children.

Vignatelli et al, 2005 give SE incidence which was found to be lower than previous studies, of 16.5/100.000/y and the main aetiology for SE was acute symptomatic epilepsy 30%. This study was retrospective and prospective evaluating certain medical codes and it was done in a rural area in Italy over two years of follow up. The number of patients included was small with 27 patients only over their two years of follow up. They used the strict EEG criteria in their definition of cases which may be more dangerous for a rural treating hospital. By that time 30 minutes patients may be transferred to a main hospital or tertiary centre. In this study a higher incidence of SE in female with ratio of 20:7 female:male ratio was shown. This could be of unexplainable reason but the small number of patients included may give a higher chance of bias, as well as lack of knowledge regarding ratio of female and male in their population and the commonest neurologic diseases affecting both gender in that area.

The incidence of SE among children is higher than that for adults 17-23/100.000/y and more in acute febrile symptomatic epilepsy according to (**Chin et al, 2006**). It is a prospective study in which SE children notification was done through a clinical network of 18 hospitals in London in addition to telephone calls to the Children Acute Transport Service centre for cases identification. They exclude non convulsive SE because of unavailability of EEG all over the hospitals. The most important message from this study is with SE in children, primary consideration should be to rule out an acute symptomatic cause.

Under ascertainment is be a problem in population based studies mainly for patients who did not present to the hospital, may have suffered death at home before hospital admission and passed unnoticed. Other patients likely to be missed are the non convulsive SE form of SE. A third group could be missed is the one with milder form of SE. Among population based studies the effect of ethnicity and genetic factors in the incidence of SE and different level of susceptibility to SE is not yet known. Advances in EEG technology may contributed to the diagnosis, new neuroimaging techniques, better outpatient treatment of repetitive seizures among epileptic

patients in addition to pre-hospital treatment of SE may all contribute to apparent decline or variability in SE incidence figures.

VII. Aetiology:

The most common cause for SE in children was febrile illness 52% and in elderly was acute symptomatic epilepsy 22% and LAED 34%. *See appendix table no. 3 and table no. 4* There are difficulties in deciding if acute brain insult is due to de novo SE or the opposite way. Since half of their patients were not known to have seizure (58%) and 70% of elderly were not known epileptics, the figure of 34% of adult aetiology due to low anti-epileptic drug levels (LAED) is overestimated because of the small number of known elderly epileptic patients .Also there is no clear explanation for defining LAEDs terms .

Different types of classification were used *see appendix table no. 3 and 4*, some depending on the aetiology of the SE and others depend on type of the seizure, whether partial or generalized myoclonic...Motor activity in generalized tonic clonic seizure evolves over several phases. The tonic phase becomes prolong over time, clonic jerks become less frequent and finally become completely absent. At presentation focal facial twitching could be a result of prolong GTCS. Coma presentation could be a presentation for non convulsive status as well as late stage of GTCS. Most of the time seizure detailed presentation in emergency admission data will not be available and may be inaccurate. Semiologic classification is the most probable way to classify an emergency situation by mainly describing what you are seeing. EEG is needed to classify SE according to the last ILAE classification system (1998). The new proposed classification may solve the problem since it is systematic and more flexible.

Incidence of low antiepileptic drug (LAED) among status patients is not assessed in all the studies, varies between 20-30%. The implication in these studies is of poor compliance, but of course this is not the only cause of a low level. The time of AED level measurements were not mentioned, and for some drugs with short

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half lives, this is important (e.g. valproate). With some epileptics their seizures can be controlled with suboptimal AED levels and so the level itself, without clinical information, is a rather meaningless statistic. Some of the AEDs are not monitored by certain drug level and the only way to monitor is patient admittance. Therefore, in most cases it is difficult to determine about it as a cause for SE unless the patient or relatives admit non compliance to AEDs.

Febrile status is a form of convulsive SE common in children most likely represents up to 50% of SE in children in comparison to 14% among all age groups. No clear definition for febrile SE is available in comparison to febrile seizure, which is well defined by ILAE.

Hospital Based Studies

I. Study Format:

A total of 20 hospital based studies were included in this review, which were published between 1996-2006 in English. In general terms, hospital based studies have a greater propensity for selection bias and thus may not be representative of the overall medical community. This is true particularly for less severe forms of SE, for SE treated in the community (as much is nowadays with benzodiazepines) and for non convulsive forms. However, almost all cases of established convulsive SE will require admission. The advantage of hospital based studies is that the documentation is generally better. Many studies were excluded from consideration here because they were restricted to SE in certain aetiologies of status only. For example, study by (**Knake et al, 2006),(Rumbach et al, 2000), (Velioglu et al, 2001), (Afsar et al, 2003)** looked at SE and stroke, study by **(Waterhouse et al 2000)** on NCSE in comatose patients, study **(Delanty et al, 2001)** de novo SE among hospitalized patients, study by **(Dennis et al, 2002)** NCSE after subarachnoid haemorrhage, study **(Rose et al, 2003)** SE during inpatient video monitoring , study by(**Sankar et al, 2005**) post temporal lobectomy and study no **(Hu et al, 2005 c)** post anoxic myoclonic epilepsy.

All are retrospective studies except two which are prospective studies no. (6, 18) *see appendix table* no. 2. All retrospective record reviews are likely to have missed cases with milder form of SE or those diagnosed with their primary aetiological diagnosis. Another point is that data available in the clinical notes most likely does not include seizure duration and may be passed as simple isolated seizure not status. I thought that conduction of prospective hospital based studies is much easier than population based studies being in hospital setting and facilities available in hospital.

Nine of these studies were done in University Hospitals, referral hospitals or tertiary hospitals study no. (1, 6, 8, 9, 10, 11, 14,

15, 17, 20) *see appendix table 2*. The figures coming from these studies may reflect a higher incidence of intractable SE or symptomatic SE, which are most likely being referred from local public hospitals. Status epilepticus is an emergency situation most likely to present to the local hospitals, rather than to tertiary centres where sometimes no emergency service is available. I expected to get much lower incidence rates of SE from these tertiary hospitals than from public hospitals, which most likely present the population around. In contrast, the mortality and morbidity figures given will be much higher because of the higher numbers of symptomatic epilepsy in their patients and co morbidity present between their patients.

Eleven of these studies were conducted in public general hospitals, community or emergency admissions no.(2 ,3, 4, 5, 7, 12, 13, 16, 18, 19) *see appendix table 2* which may give true or better reflections for the population in that area . The incidence figures from these studies more reliable than the tertiary centre figures and closer to the figures from the population based studies. Also the morbidity rates can give us more information about the natural history of the disease itself, as well as how much these hospitals are prepared to fight against this disease.

Nine studies looked after SE in paediatric populations study no (1, 4, 8, 9, 11, 13, 15, 19, and 20) *see appendix table 2*, because SE in children has special concern since it is more common than other populations and has a higher incidence of morbidity and mortality. Patient age and level of cerebral development is critical in the classification of epilepsy. Patients with mental handicap are at particular risk of developing SE.

Kroczka et al, 2005 looked at SE in paediatric hospitalized epileptic patients. Children with established epilepsy have higher chance of developing SE than others without. In this study most of the epileptic children included had symptomatic epilepsy (85.7%) and symptomatic epilepsy patients are more likely to develop SE. This study is retrospective study with data mainly collected from neurology department admissions. By excluding the emergency department data they have lost a major sector of patients with simple SE and not complicated admissions and it was difficult to conclude that the low frequency of SE neither related to continuous access to

neurologist nor experienced nurse team. Additionally in the study the number of SE patients included was very small 22 out of 1505 epileptic patients during eight years of their review (1996-2004).

Patients of all ages were included in four studies study no, (2, 3, 6, and 18) *see appendix table 2.* Patients of adult age were included in six studies study no (5, 7, 10, 12, 14, and 17) *see appendix table no. 2.*

One study included only elderly patients, **(Hui et al 2005 b),** and this is an age group which should receive more attention since SE has two peaks, one in children and one in the elderly. Also, SE in the elderly has different causes, and the aging of the population would suggest that there will be an increasing incidence of SE over years. In this study the most common cause of SE was found to be acute symptomatic disturbance cerebral infarction (35%) and cerebral haemorrhage (17.5%). Control of the vascular risk factors could be one of the preventive measures of SE in elderly.

Four studies looked at incidence of SE only in previously epileptic patients study no. (13, 18, 19, 20) *see appendix table no. 2.* In study by **(Szczepanik et al, 2003)** the incidence of SE between their epileptic patients in the first five years of follow up was 6.1%. In comparison study by **(Mah and Mah, 1999)** where the incidence was quite high 27.8 during period of follow up of five years. **Szczepanik et al** in 2003 reviewed 600 recently diagnosed epileptic patients over 5 years treatment and follow up prospectively 39 patients (6.1%) develop SE identifying the 5 years risk to develop SE. It was a prospective study and follow up recently diagnosed patient on treatment for five years. In comparison, **(Mah and Mah, 1999)** was a retrospective study in which the incidence of SE among all seizure episode admissions was evaluated over five years. The evaluation of duration of SE is difficult and it is not clear how this was considered in this study. In this study, 59 out of 212 seizure admissions were due to SE. This study is more specific giving a figure of 27.8% rate of SE between epileptic patient's admissions. I think most seizure admissions are of complicated cases or symptomatic epilepsy, and so this high estimate may reflect the refractory nature of the admissions. In study by **(Gulati et al, 2005)** which was a study of emergency admissions to a neurological unit

found that 30 out of 451 were SE. The incidence of SE among the paediatric ICU admissions over seven years retrospectively was found 6.6%, similar to the estimation given in by (**Szczepanik et al, 2003**). Although epilepsy is a common sequelae of SE it is difficult to decide if SE is due to epilepsy alone. Epilepsy is a multi factorial disease and I suspect SE is multifactorial also. Since SE physiologically initiated similar to isolated seizure the mechanism by which seizure is spread and maintained and the sudden cessation of it is not yet clear.

(**Szczepanik et al, 2003**) looked at the usefulness of the international league against epilepsy (ILAE) classification (2001). It was the only study in my review which looked after classification. Classifying SE is confusing and difficult. Different types of SE present as different types of seizure. Classification could be based on aetiology but at the same time, not all seizure aetiologies are known that is why the idiopathic and cryptogenic words were invested. Idiopathic presumed as genetic epilepsy and cryptogenic presumed to have underlying pathologic explanation that eludes current diagnostic techniques. SE could be classified based on clinical presentation as convulsive, non convulsive, myoclonic and so on. But some types of SE are not presented as overt clinical seizure and some can present as coma state, so it is difficult to categorize based on clinical data available. Classifying SE depending on EEG alone is not recommended because of overestimation as well as unavailability at the acute stage. Epilepsy and SE classification is not currently satisfactory and a revision of the classification is underway.

In all these studies there were difficulties to classify the type of seizures since each study used different type of classification. Aetiological classification was used in most of them study no (1,2 ,4 ,5 ,6 ,9 ,13,16) *see appendix table* no.2 but it was not in a systematic way like acute –chronic then the sub divisions of acute infection, CVA or metabolic. The aetiological classification used was randomly made by selecting different specific aetiology and then look for it. By this method it is easy to miss certain aetiological factors.

II. Incidence:

The incidence of SE among these hospital based studies ranged between 13.1/100.000/y highest and lowest 4.9/100.000/y in comparison to population based studies incidence rates between 41/100.000/y to 9.9/100.000/y. All the studies agreed about the bimodal distribution of SE between elderly more than 65 years and children less than 5 years. As population ages, and there are more individuals living into their 70s and 80s it is expected to find more individuals developing SE, as well as many common causes of SE are diagnosed primarily in the elderly including stroke, brain tumour and anoxia. High incidence of SE among paediatrics population could be due to the high incidence of symptomatic febrile status among this group, SE could be the first presentation of epilepsy and improvements in survival for factors that can cause epilepsy such as in cerebral palsy and very low birth weight infants.

Incidence from hospital based studies have some limitation, coding system may give under diagnosis figures since SE may not be a primary diagnosis and the types of hospitals included, public hospitals give an estimation of SE near to that from population based studies in comparison to tertiary hospitals which may reflect figures of symptomatic SE and co morbid SE patients.

The incidence of SE in study by **Wu et al** in 2002 is 4.9/100,000/y noticeably lower than the incidence in study by Tabarki et al in 2001 but has the same bimodal distribution. In this study, (**Wu et al, 2002**) cases reported from federal hospitals were excluded (23 hospitals) as well as patients with SE whose zip code did not indicate residence in that state. Furthermore, only first admissions with SE were included, and this will reduce the numbers ascertained significantly as that SE carries higher risk for recurrence. As in other studies, the use of 30 minutes definition most likely led to omission of minor cases of SE. An important finding from this study was the fall of incidence of SE over time. The annual incidence decreased by 42% from 8.5 to 4.9 between1991 to 1998. This decrease in incidence over time may reflect improved control and early diagnosis of epilepsy. One can speculate that the main reason for this is the recent tendency to treat prolonged seizures in

the community before arriving at hospital. Other improvements in epilepsy care over this period include the introduction of more than six new mainline anti epileptic medications since 1991, the significant effort is going on to educate the community about epilepsy causing the community to become more aware about the disease, and the improved diagnosis due to neuroimaging and early treatment of symptomatic epilepsy- this latter point is important for SE as most cases of SE in this study were symptomatic epilepsy patients.

Kang et al, 2005 estimate the incidence of GTSE among their 189 patients was 73.5% in comparison to NCSE which was 26.5%. It was a retrospective study depending on medical record data with all the bias of missing data and incomplete information. Electrophysiological data reviewed in this study but there was no mention regarding how frequently EEG was done to SE patients. As EEG is essential in the diagnosis and categorization of NCSE, this is important. In many studies, the true incidence of NCSE is greatly underestimated for this reason.

In study by **(Garzon et al, 2003)** the risk of developing SE was higher between epileptic patients 59.4% in comparison with non epileptic patients. Among epileptic patients the most common cause of SE was non compliance to AEDs. This study was conducted in emergency department representing community medical population.

The crude incidence rate was 13.1/100.1000/year in their adult population in study by **(Vignatelli et al, 2003)**. The main aetiological category for SE in this group of patients was symptomatic epilepsy 34%. Higher risk of SE was found to be in elderly and women (but statistically this was not significant for women). The incidence in this group of patients is higher in comparison with other studies **(Coeytaux et al, 2000)** and **(Wu et al, 2002)** 9.9 and 4.9/100.000/year respectively. Case identification was both prospective as well as retrospective to minimize the number of patients lost. Post anoxic encephalopathy patient were included, which may lead to higher incidence figures. However, the number of patient included is small, with a total of 44 and 24 patients developing SE while being hospitalized as inpatient. This may reflect the high percentage of symptomatic epilepsy in their

group, being hospitalized means a systemic illness is going on lead to SE. The highest percentage of SE in women than in men may be a simple effect of chance since the number of bias is higher in smaller samples.

III. Aetiology:

Since most if not all SE patients need hospitalization, hospital based studies deal within this review as a separate section. In addition to that, SE inpatients are most likely to be well investigated and better detailed information about its aetiology was expected.

In most of the studies the aetiologic causes of SE were divided into acute symptomatic and remote symptomatic as in (**Tabaraki et al, 2001**) (**Coeytaux et al, 2000**), (**Kang et al, 2005**) (**Vignatelli et al, 2003**). The definition of acute symptomatic SE is not clearly mentioned in all of these studies since acute symptomatic SE could include: anoxia, CVA, fever, metabolic, LAED, acute trauma and first presentation of tumour. Another type of studies includes symptomatic epilepsy without mentioning acute or chronic in detail as in study by (**Asadi-Pooya and Poordast, 2005**) (**Eriksson and Koivikko, 1997**) (**Visudtibhan et al, 2006**).

Remote symptomatic epilepsy as a cause of SE was evaluated in different studies giving quite different figures, as in study in studies by (**Tabaraki et al, 2001**) (**Coeytaux et al, 2000**) (**Kang et al,2005**) 6.4%, 28.4%, 16,4% respectively. This indicates that patients with history of symptomatic epilepsy constitute a group at risk of developing SE approximately up to 30%. At the same time SE occur in up to 70% of patients with no previous history of epilepsy.

The most common cause of SE in elderly was symptomatic SE and in particular CVA with a percentage of up to 42.1% as evaluated in (**Vignatelli et al, 2003**). Febrile SE is the most common cause in children up to 66% of patients as in study by (**Garzon et al, 2003**).

LAED as a cause of SE is not mentioned in many studies, (**Tabaraki et al, 2001**), (**Coeytaux et al, 2000**), (**Kang et al, 2005**), (**Vignatelli et al, 2003**) and (**Visudtibhan et al, 2006**) and was evaluated up to 48% in two studies (**Garzon et al, 2003**) and (**Sagduyu et al, 1998**). LAED is not clearly defined in these studies in addition to the difficulties in analysing the drug levels in relation to seizure control.

Metabolic causes as aetiologic cause of SE is found to be higher among elderly 22.2% in comparison to young adults of 8.9% as evaluated in by (**Garzon et al, 2003**). No comment was there about if these metabolic disturbances act as a precipitant factor or as a direct cause of SE.

Idiopathic and cryptogenic epilepsy is another cause of SE especially among paediatric population with a figure of up to 40% as evaluated by (**Kang et al, 2005**).

Looking at table no. 3 and 4 in the appendix a lot of aetiological data is missing between the different studies. Although, there was concordant data between hospital and population based studies, regarding the aetiology of SE. Data in the aetiology of SE agreed with that that: febrile symptomatic SE is the main cause SE among children while in elderly symptomatic epilepsy, mainly CVA and metabolic causes are the main causes of SE in this group. The variation in percentage between different aetiologic factors among different studies most likely due to defining certain terms like LAED and symptomatic acute versus chronic.

Morbidity

SE is associated with significant morbidity and mortality. However there is controversy to the extent these adverse effects are caused by with SE rather than the underlying cause of the SE, and it is often impossible in individual cases to make this differentiation. Data available on outcome is important for both clinician and patients in giving prognostic information and natural history of the disease.

This search was done on PubMed between 1996-2006, the terms of status epilepticus combined with the terms of outcome and morbidity was used, references of identified articles were examined for additional relevant studies. A total of more than 200 studies were identified, of which 10 studies met the criteria for entry into the review which was morbidity as the primary outcome and all the studies included were in English. Most of the excluded studies excluded had mortality as the end point, and as mortality data is well established this was not considered further in this MSc thesis.

Seven studies were retrospective study no. (1, 2, 3, 4, 7, 8, and 10), three studies were prospective studies study no (5, 6, and 9) *see appendix table 5.*

One population based study focused entirely on morbidity of SE (**Cascino et al**, 1998), and has the potential to give important information about the natural history of SE and outcomes.
This study excluded febrile seizures. The morbidity related to 184 cases of non-febrile SE in the first 30 days was found to be 3.4%. Only those patients with symptomatic epilepsy (acute or remote) sustained any neurological morbidity (the percentage of patients with symptomatic epilepsy included in this study was 54.3%). This emphasizes the difficulty in disentangling the effects of SE from the

effects of the underlying cause, particularly in those with an acute cerebral insult.

Four studies were of SE in children study no. (2, 3, 5, 6) *see appendix table 5*. The morbidity rates were (15%, 33%, 26%, none) respectively *see appendix table* respectively. **Eriksson** and **Koivisto** in 1997 reported the lowest morbidity rates which was 15% only. This study was conducted in a university hospital and an aim of the study was to assess the effects of a treatment protocol. The conclusion that the presence of a clear treatment protocol is associated with less morbidity is important.

Chin et al in 2006 reported a well conducted population based study of childhood SE, and notes a recurrence rate of convulsive SE in paediatric patients of 16% over one year.

In study by **Shinner et al** in 2001, no formal cognitive test was conducted but the authors concluded that no neurological complication was found in any of their paediatric SE patients. In this study a comparison between febrile SE and simple febrile seizure was made. Children with febrile SE were more likely to be neurologically abnormal 20%, have a history of neonatal seizure 3% and a family history of epilepsy 11%. Those with family history of febrile seizure are less likely to have febrile SE. In this study, children with CNS infection or electrolyte imbalance were excluded from inclusion in the febrile SE group.

Morbidity in the adult population was found in 23% of patients in study by **Classen et** al, 2002, 26% in study by **Hui et al** in 2003 and 39% in study by **Shneker** and **Fountain** in 2003. In all studies morbidity was associated with symptomatic epilepsy and length of hospitalization and older age.

Shneker and **Fountain**, 2003 give morbidity estimation of 39% without a significant relationship between morbidity and EEG type in this group of patients They included NCSE patients from medical records in addition to EEG recording data. This group of patients included SE of diverse pathophysiology. The outcome of non convulsive status depends on the aetiology – with high rates of morbidity and mortality in patients with acute symptomatic NCSE

(usually due to anoxic brain damage) and low rates from most other causes.

Morbidity in some studies was evaluated using standardized scale like GOS as in study no (4, 7, and 9) *see appendix table 5* which could give more accurate evaluation about the neurological status. In the study by (**Shneker** and **Fountain, 2003**) the author mention mental status assessment without specifying which scale was used if any.

In some of the studies morbidity was assessed at follow up without assessing the neurological status prior to the SE (e.g. Hui et al, 2003) which may give rise to an overestimation of the morbidity rates. In this Chinese study, the commonest cause of SE was acute or remote cerebrovascular disease and it was not possible to differentiate the effects of the vascular insult from the effect of the consequential SE.

Adachi et al published in 2000 a prospective study were neuropsychiatry evaluations carried out one or more year after SE. A formal Wechsler IQ test was performed before and after SE. No intellectual decline post SE of significant statistical value was found. The number of patients identified was small 15/1685 (0.89%) epileptic patients and this does not reflect the real incidence of SE perhaps because the hospital setting was a tertiary centre.

Ala Kokko et al, 2006 retrospectively looked at the incidence of infection among SE admitted to ICU specifically as part of morbidity. 42% of SE patients admitted to their ICU acquired hospital infection and that was related to longer ICU admissions.

One study only used the operational definition of SE (**Classen et al**, 2002), in which SE was defined as seizure for equal or more than 10 minutes or intermittent seizure without return of consciousness for or more than 30 minutes.

Periods of follow up in these studies were variable and often short term and long term outcomes were not well defined. In study no (3), the follow up period was not clearly defined. 30 days follow up was used in study no. (1, 6) *see appendix table 5*. In study no. (4,

7, 8, 10) *see appendix table 5*, follow up was conducted only during hospitalization and the period was not specified. The longest period of follow up in the studies was a mean of 3.6 years in study by Eriksson in 1997. A few studies looked at long term complications (study no. (1, 2, 3, 5) *see appendix table 5*. They mainly looked at SE recurrence over certain period time. Other very important long term outcomes, such as the occurrence of subsequent epilepsy and hippocampal injury MTS were not studied in detail.

The major problem in all these studies is the fact that the effects of SE can not usually easily be differentiated from the effects of the precipitating cause. Whilst few authorities doubt that SE can induce cerebral damage, the extent of this damage is still controversial and these studies on the whole do not provide satisfactory data. The rate of acute neurologic complications after SE differed markedly between studies. Study no. (1, 2, 3 4, 5) give rate of acute neurologic complication of 3.4%, 15%, 33%, 26% and none respectively *see appendix table 5*. Most of these studies agreed that the morbidity rates are higher in the young or elderly patients, in those with symptomatic causes, and after delay in the treatment study no (1, 3, 4,) *see appendix table 5*.

Very few studies looked at the long term effect of SE in patients like subsequent epilepsy, recurrence of SE and death study no (1, 2) *see appendix table 5*. Most of the studies available concentrate on the short term outcomes during hospitalization or 30 days follow up. Out come data available is not satisfactory depend mainly on the study methodology used and absent of enough data on long term follow up of SE.

Recommendations

1. More epidemiological studies in SE are recommended.

Epidemiologic studies give important information regarding the natural history of the disease and its risk factors. Hospital and community based data are needed, and these could help more in planning resources and preventive measures.

2. Assessment of methodological quality in addition to long durational follow up which may make long term outcomes well known.

Methodological quality must be improved, and this should focus on definition, classification, documentation, better case ascertainment and appropriate statistics. The terms used in the study should be clearly defined.

3. Standardized definition of the terms used in each study.

It would be very helpful to use standard definitions and classification schemes, and standard case inclusion criteria. Also, diagnostic and investigatory criteria should be better defined. The ILAE should formulate guidelines for SE studies in the way it has formulated guidelines for other forms of epilepsy.

4. Hospital data based systems and research clinics departments upgrading.

Failure of clear documentation in hospital records about the type of seizure upon arrival and the duration of the seizure is a cause of bias in most of the hospital based studies. Emergency departments are the first line receiving SE patients and most of the time the priority is for management before documentation. Specific forms to be filled for certain emergency situation under investigation may solve this problem.

SUMMARY AND CONCLUSION

In this thesis, I have reviewed all the recent literature relating to the incidence, aetiology and morbidity of SE. For reasons which are shown above, the literature is flawed in a number of important ways. As a result, there are no findings which can be considered definitive. This is a deficiency which requires attention and further studies are needed.

The main problems relate to methodology and interpretation, and can be summarized as follows:

i. The definition of SE is not agreed, and different studies have used different definitions.

ii. The classification of SE – particularly NCSE is even more controversial and no standard exists.

iii. Case ascertainment of cases is sub-optimal in many studies for a number of reasons. This is especially true of minor cases and NCSE, the latter to the extent that it is fair to say that no adequate incidence figures exist. The situation is better for TCSE. Poor ascertainment could be due to the difficulties in diagnosis of SE depending on clinical features alone.

iv. There is a lack of standardization of data collection or presentation in hospital records. Miscoding of the discharge diagnoses and poor hospital records information among hospital based studies may lead to poor information. Lack of detailed information on seizure types underlying aetiology and precipitating factors of SE give misleading and under estimating figures.

v. There is bias in case selection, particularly from tertiary or University hospital settings, which have been often used in these studies, and which will emphasize severe and refractory

cases. The inclusion/exclusion of febrile SE cases or NCSE for instance will greatly affect numbers.

vi. Given the age-related changes in frequency, incidence rates should be standardized by age to provide meaningful results. Other statistical problems in the epidemiological studies include: (a) often very small numbers; (b) the lack of clearly defined population frames (an issue for instance when patients are ascertained through A&E departments outside areas of residence); (c) lack of clarity of diagnostic criteria.

vii. The proportion of cases in which aetiology can be ascertained will clearly depend on the level of investigation – and this too is often not documented – and this makes accurate comparison across studies difficult to achieve.

viii. An overwhelming problem for morbidity studies is the difficulty of differentiating the effects of SE from those of the underlying causal aetiology (particularly in patients with no prior history of epilepsy, and SE caused by an acute neurological injury). Because of this, in general terms, the literature reviewed above can make no clear statement about the morbidity of SE.

ix. Morbidity studies too should have the duration of follow up clearly defined or standardised. This was seldom achieved. In addition to that morbidity is usually poorly defined as mild, moderate or severe.

x. The recent tendency for more intensive pre-hospital treatment with buccal or rectal benzodiazepine drugs is likely to have reduced the numbers of cases presenting to hospital A&E departments with SE and hospital-based studies will therefore under-estimate the true numbers of SE. This has not been fully accounted for.

xi. The effect of improvement of diagnosis and management over time in the actual incidence of SE is not well looked after. It is not know if there is an actual change in the incidence of SE

over time with the major advances in neuroimaging and availability of new AEDS.

The following general conclusions can however be drawn from the studies:

Incidence:

- The incidence of SE is generally found to be between 41/100.000/y and 4.9/100.000/y.
- The incidence is higher in children and in the elderly.
- The incidence may be falling because of more intense immediate and pre-hospital treatment of prolonged seizures.
- Over 60% of cases occur de novo in patients without a previous history of epilepsy and are due to acute brain injury.
- There is not enough data to make any statement about the incidence of NCSE.

Aetiology:

- The most common cause of SE among children was febrile SE contributing to more than 50% of SE among children.

. The most common cause of SE among adults was symptomatic epilepsy contributing to more than 40% among adults.

- In patients with epilepsy, the finding of low AED concentrations can not be taken to mean that compliance is poor.

Morbidity:

- This is not possible to ascertain from these studies, due to the confounding effect of the underlying aetiology.

Abbreviations:

- SE: Status epilepticus.

- NCSE: Non convulsive status epilepticus.

- GTCS: Generalized tonic clonic seizure.

- ILAE: International league against epilepsy.

- AEDs: Anti epileptic drugs.

- LAED: Low anti- epileptic drug .

- PLEDS: Paroxysmal lateralizing epileptiform discharges.

- CVA: Cerebrovascular accident.

Appendix

Table (1) Population Based Studies:

Study No.	Study Format	No. of Pts.	Gender	Age	De novo SE	Aetiology	Findings
1	Prospective Virginia 1989-1991 30mins defn EEG PLEDs excluded Population M:F58-42% Black:white 55:45%	204	M:F 55:45	>31days All ages	58%all 70% elderly	Paeds: Fever52% Remote39% LAED21% Others10% Adults: LAED34% Remote24% CVA22% GTCS74% Partial26%	-Incidence 41/100.000/y -Frequency 50/100.000/y -Elderly Incidence86/100.000/y Paeds Incidence: 50/100.000/y White incidence; 20/100.000.y Nonwhite: 57/100.000/y
2	Retrospective 1965-1984 30mins defns EEG	199	M:F 94:72	All ages	54%	General 28% 2ry general 17% Partial 41% Febrile 8% Acute sym 50% Infect 17% CVA 17% Unprovoked 42% Idio/crypt 20% Remote symptom 47%	Incidence (1965-1974) : 13.9/100.000/y Incidence (1975-1984) : 22.4/100.000/y (1975-1984) age adjusted incidence 18,3/100.000/y Incidence ^paeds<1y Elderly and males Cumulative incidence 1/100/yr of age 2/1000/yr by 60 years of age

Study No.	Study Format	No. of Pts.	Gender	Age	De novo SE	Aetiology	Findings
3	Prospective Virgina SE intermittent Continuous Mortality	645 212pae 433adu	??	All	??	??	Incidence not evaluated
4	Prospective 1997-1998 Switzerland French 60 Hospitals University & Community Hospitals 30 mins definition PLEDs excluded Post anoxic Excluded Presurgical Excluded Emergency, neuro, paeds EEG, psych geriatric	172	*M:F* 14.5:9.7	*All ages*	57%	Acute sym 62.7% CVA 30.5% Fever 4.9% LAEDs 18.9% Remote sym 28.4% Unknown 8.7% Partial sz 44.8% GTCS 33.1%	Incidence not evaluated

Study No.	Study Format	No. of Pts.	Gender	Age	De novo SE	Aetiology	Findings
5	Prospective 1997-1999 University hospitals Atypical low age 30mins defns Neuro, emergency ICU Uncertain Incomplete excluded	150	M:F 46:54	Adults >18yrs	67%	-Acute symptom 4.6% -Remote symptom 4% -Unknown 0.6%	-Crude incidence 15.8/100.000 -Age adjusted incidence 17.1/100.000/y >60yrs -Incidence Of 60yrs 54.5/100.000 -Young incidence 4.2/100/000/y
6	Prospective Epileptics 1994-1997 Observation Hospital Records SE 30 mins definition	150		Paeds <16yrs	All are epileptics	-Convulsive 98% -Tonic clonic78% -Partial 8cases -Remote symptom 39% -Idiopathic 14% -Crypt21%	27% one or more SE Cumulative risk 0.22 at onset 0.25 at1-2yr Later 0.03 Recurrence SE 56%

Study No.	Study Format	No. of Pts.	Gender	Age	De novo SE	Aetiology	Findings
7	Retrospective Twin study Medical records Pts –Family Interview 381 epileptic twins Virgina Twin hx of sz on One or both Zygosity Molecular test	332	??	2-75 yrs	All pts are Epileptic Twins 48%adults 60% school	-Localized 27% -Generalized 9% -Situation related 46% -Localized symptom 19%	Frequency SE in adults: 493/100.000 Frequency SE in school age: 493/100.000
8	Prospective 1999-2001 Italy Rural area 30mins defn Medical records Public Hospitals Neuro, EEG Emergency	27	M:F 7:20	Adults >20yr	59.4%	-Acute symptom 30% -CVA 60% -Remote symptom 25.9% -Partial 37% -Generalized 7.4%	Crude incidence 16.5/100.000 Age adjusted Incidence 11.6/100.000/y
9	Prospective Paeds 2002-2004 30mins definition 18 hospitals North London	226	M:F 95:81	Paeds 29days - 15yrs	77.8%	-Acute symptom 17% -Remote symptom 16% Cryptogenic Idiopathic 12% LAED 0.4%	-Ascertainment adjusted incidence : 17-23/100.000/y -Crude incidence : 14.5/100.000 -Incidence in <1yr: 51/100.000/y

Study No.	Study Format	No. of Pts.	Gender	Age	De novo SE	Aetiology	Findings
10	Prospective London Epileptic 613 pts Parents Medical record 8yrs time follow up Risk of SE	58pts SE 9.5%	M:F 347:346	Paeds 1month - 15yrs	All epileptic	??	SE occur 10% of epileptic paeds SE associated with : -Young age -Symptomatic -Hx.Epilepsy -Hx SE 32.1%
11	Retrospective Minnesota Non Febrile sz 1965-1984	184	??	All	??	??	Morbidity issues

Population Based Studies key:

Study No.	References
1	Delorenzo et al (1996).
2	Hesdorffer et al (1998).
3	Waterhouse et al (1999).
4	Coeytaux et al (2000).
5	Knake et al (2001).
6	Sillanpaa and Shinnar (2002).
7	Corey et al (2004).
8	Vignatelli et al (2005).
9	Chin et al (2006).
10	.Berg et al (2004).
11	Cascino et al (1998).

Table (2) Hospital Based Studies:

Study Format	Age	Number of Patients	Aetiology & Incidence	Study Format
1-	Retrospective University Hospital 1990-1997 Tunisia	Infants Mean age 11 month	-Acute symp 56 -Febrile 57 -Remote symp 9 -Progressive10 -Idiopathic 7 -GTCS 74%	139 F:M 74:65
2-	Retrospective All six hospitals in Switzerland Emergency, ICU, EEG, Neurologeist Paeds departments. 1997-1998	All cases	-Acute symp62.7% -Remote symptom 28.4%. -Unknown 8.7%. -Crude incidence 9.9/100,000 -Annual incidence 10.3/100,000	172
3-	Retrospective Hospital data base with discharged diagnosis of SE1991-1998	All cases	Incidence of GCSE 4.9/100,000 Highest in -Paeds <5years 7.5/100.000 -Elderly 22.3/10.000	19.491
4-	Retrospective Medical records SE 1994-2003 Follow up for 17 months.	Paeds Mean age 37months	-Idiopathic 40.7% -Epilepsy29.1% -Remote symptom 16.4% -Acute symptom 13.3 Febrile 35.4% -Incidence of GTSE 73.5% -Incidence of NCSE 26.5%	189 M:F 59:41

Study Format	Age	Number of Patients	Aetiology & Incidence	Study Format
5-	Retrospective Urban Hospitals. Chinese 1996-2001 Medical, ICU, emergency	Adults	SE associated with : -CVA -Metabolic -AED withdrawal -Alcohol related	107
6-	Prospective University hospital Brazil Clinical and labrotary data and EEG	All ages 3 months - 98yrs	Incidence highest in first year of life Hx. epilepsy59.4% De novo 40.6% SE associated with : -Non compliance -CNS infection -stroke -metabolic	111
7-	Retro and prosp All public general hospitals. Bologna in Italy. Neurology units and all epilepsy discharges 1999-2000. Discharge code. Post anoxic encephalopathy included. 30 days case fatality evaluated.	>20 years	-Crude incidence 13.1/100.000 -Standardized incidence 10.7/100.000 Higher in elderly -Acute symptom 34% CVA 41% post anoxic24% -Remote symp34% -Progressive11% -Idioand crypt7% -Hx of sz 39%	44 20 SE outside Hospital. 24 SE inside Hospital.

Study Format	Age	Number of Patients	Aetiology & Incidence	Study Format
8-	Retro 1999-2004 Main paeds Hospitals. Iran	1 month - 15 yrs	-Fever the most common cause of SE -No different in age and gender	135 76 boys 59 girls
9-	Retrospective University	Paeds	Symptom40% Fever 37%	65%
10-	Retrospective University hospitals Neurology ICU 1988-1997	Adults	-Hx of sz 72% SE associated with: -AED withdrawal -Drug toxicity -CNS infection -CVA -Tumors	66
11-	Retrospective Referral hospital. Thailand 1981-2000 Medical records	Paeds 1 month - 15 yrs	-Hx of epilepsy12 pts -Acute CNS insult7pts	32 15boys-17 girls
12-	Retrospective Acute management and outcomes. Emergency room 2000-2004	Adults >18 yrs Mean age 45 yr	Hx of epilepsy 80% Sub drug level 60%	45 18 males 27 females

Study Format	Age	Number of Patients	Aetiology & Incidence	Study Format
13-	Retrospective Polish hospitalized Epileptic pts. 1996-2004 paeds ,neuro admissions (1505 children with epilepsy)	Paeds 1 month -18 yrs	-Symptomatic 85.7% LAED is not a reason of SE. SE common in 1st yr	Incidence of SE 21children out of 1505(1.4%). 9 girls 12 boys
14-	Retrospective 1997-2004 Two university Hospitals. Boston ,USA Adults with EEG confirmed SE Excluding cerebral anoxia Aetiology and outcome	Adults with EEG- SE	Aetiology?? look	96pts
15-	Retrospective University hospital. Turkey1994-2001 medical record SE admissions to paeds unit.	Paeds	High risk SE: Polypharmacy LAED Neuromotor retard EEG abnormality	83 SE among 166 epileptic pts.
16-	Retrospective Two urban hospitals. 1996-2002 Aetiology 6 months follow up.	Elderly 60-93 yrs Mean age 74.2 yrs	Acute symptomatic: Cerebral infarct 35% Cerebral haemorage 17.5%	80
17-	Retrospective 1992-1998 University hospital.	Adult	Male 63.2% De novo SE 49.2%	57

Study Format	Age	Number of Patients	Aetiology & Incidence	Study Format
18-	Prospective 600epilepsy pts Recent diagnosis and long term treatment (mean 5 yrs) Incidence in paeds and adolescents. Usefulness of new classification	All Paeds and adolescent	SE correlated to: -Onst age <5yrs -Epileptic syndromes / Incidence among follow up 6.1%	Out of 600 epileptic patients followed 39 pts develop SE (6.1%).
19-	Retrospective Case records Admission to PICU Neuro& emergency Tertiary centre 1993-2000 Immediate outcome	Paeds 1-120 months Mean 56.6	SE associated with: Hx of sz Prior AED Acute aetiology Prolong sz time before admission	59 Out of 212 sz Admissions 27.8%
20-	Retrospective Case record Admission to PICU neuro emergency Tertiary centre 1993-2000	Paeds 1-120 months	Se is associated with : <60 month 17 pts De novo SE 53.3%	30 (Out of 451 neuro. emergency pts. 6.6%

LAED = Low anti epileptic drug levels   PICU = paediatric ICU   Paeds = paediatrics   ?? = not mentioned   Sz = seizure

Hospital based studies Key:

Study No.	References
1	Tabarki et al, 2001.
2	Coeytaux et al, 2000.
3	Wu et al, 2002.
4	Kang et al, 2005.
5	Hui et al, 2003a.
6	Garzon et al, 2003.
7	Vignatelli et al, 2003.
8	Asadi-Pooya and Poordast, 2005.
9	Eriksson and Koivikko, 1997.
10	Sagduyu et al, 1998.
11	Visudtibhan et al, 2006.
12	Muaygil et al, 2007.
13	Kroczka et al, 2005.
14	Rossetti et al, 2006.
15	Karasal et al, 2003.
16	Hui et al, 2005 b.
17	Minambres et al, 2001.
18	Sczepanik et al, 2003.
19	Mah and Mah , 1999.
20	Gulati et al, 2005.

Table (3) Aetiology of SE Among Population Based Studies

Study No.	Anoxia and Hypoxia	CVA	Tumour	Fever	Metabolic	LAED	Trauma	Hx Brain Insult	Idiopathic Cryptogenic
1-adults	Adults 20%	22%	5%	5%	15%	35%	2%	??	1%
1-paed	paeds 5%	10%	8%	55%	10%	20%	1%	??	5%
2-	20%	17%	??	??	??	??	50%	47%	20%
3-	21%	#31% Acute CNS	#	#	12%	33%	? Acute CNS	15% remote	15% remote
4-	62.7% Acute symptom	30.5%	# Acute symptom	14.9%	??	18.9%	# Acute symptom	28.4% Remote	8.7% unknown
5-	??	30.7%	12%	??	8.7%	8.7%	7.3%	62.7% remote	8.7% unknown
6-	??	??	??	??	??	??	??	39% remote	15%idiopathic 22%cryptogenic
7-	??	??	??	31%	??	??	??	??	28%
8-	29.% Acute symptom	60% acute symptom	16%	??	28% Of acute symptom	??	??	11.1%	7.4% cryptogenic
9-	17% Acute symptom	??	??	33.3%	??	??	??	16% Remote symptom	21%
10-	#	#	#	#	#	#	#	#	34,3%idio 47.8%crypt
11-	54.3% Acute symptom	#	#	#	#	??	#	??	45.6% unprovoked

LAED = Low anti – epileptic drug level   Hx. = history   Paeds = paediatrics   CNS = central nervous system   CVA = cerebrovascular accident

?? = not mentioned   # = not mentioned in specific mentioned as part of acute or remote symptomatic

Table (4) Aetiology of Status Epilepticus Among Hospital Based Studies

Study No.	Anoxia and Hypoxia	CVA	Tumour	Fever	Metabolic	LAED	Trauma	Hx Brain Insult	Idiopathic Cryptogenic
1-	Acute 40.2%	Acute 40.2%	Acute 40.2%	41%	Acute 40.2%	??	Acute 40.2%	6.4% remote	5%
2-	Acute 62.7%	Acute 62.7%	Acute 62.7%	??	Acute 62.7%	??	Acute 62.7%	28.4% Remote	8.7% unknown
3-	8.0%	1.6%	1.8%	5.3%	8.7%	3.9%	0.4%	13.2%	15.3%
4-	Acute 13.3%	Acute 13.3%	Acute 13.3%	35.4%	Acute 13.3%	??	Acute 13.3%	16.4 remote	40.7%
5-									
6-	9.65%	21.1%	??	16.6%	21.03%	12.4%	??	??	10.6%
7-	Acute 48%	Acute 41%	??	??	Acute 48%	??	??	??	11.1%
8-	# symptom 11.9%	#symptom 11.9%	#symptom 11.9%	51.1%	2.9%	21.5%	1.5%	#Symptom 11.9%	37%
9-	#symtom 40%	??	??	37%	??	??	??	??	??
10-		10.6%	13.6%	6.06 CNS	9.09%	48.4%	13.6%		50%
11-	21.8%	21.8%	21.8%	high	??	??	??	Symptom idiopathic 37.5%	Symptom idiopathic 37.5%
12-						60%			
13-	symptom 85.7%	Symptom 85.7%	Symptom 85.7%	??	??	0	Sympto 85.7%	Symptom 85.7%	14.8%
14-	Acute 58.3%	Acute 58.3%	Progress 19.7%	??	??	??	??	Remote 19.7%	3.1%
15-	Acute 15.6%	Acute 15.6%	Progress 2.4%	9.6%	3.6%	??	??	Remote 50.6%	31.3%

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Study No.	Anoxia and Hypoxia	CVA	Tumour	Fever	Metabolic	LAED	Trauma	Hx Brain Insult	Idiopathic Cryptogenic
11-	21.8%	21.8%	21.8%	high	??	??	??	Symptom idiopathic 37.5%	Symptom idiopathic 37.5%
12-						60%			
13-	symptom 85.7%	Symptom 85.7%	Symptom 85.7%	??	??	0	Symptom 85.7%	Symptom 85.7%	14.8%
14-	Acute 58.3%	Acute 58.3%	Progress 19.7%	??	??	??	??	Remote 19.7%	3.1%
15-	Acute 15.6%	Acute 15.6%	Progress 2.4%	9.6%	3.6%	??	??	Remote 50.6%	31.3%
16-	??	52.5%	??	??	??	??	??	??	??
17-	Acute 49.2%	Acute 49.2%	??	??	??	38.6%	??	??	??
18-	Known epileptic Look								
19-									
20-	??	??	??	??	??	??	??	??	??

LAED = Low anti – epileptic drug level   Paeds= paediatrics   CVA = cerebrovascular accident   CNS=central nervous system

Hx. = History.   ?? = not mentioned   # = not mentioned in specific mentioned as part of acute or remote symptomatic

Table (5). Morbidity

Study No.	Study Format	Age	No. of Pts.	Morbidity	Aetiology	Time of Follow- up
1-	-Population study. -Retrospective -Non febrile SE. -??30mins definition. -No scale used.	??all ages	184	-Neurologic complications 3.4%. -SE recurrence18.5%	-Acute symptom 54.3%. -Unprovoked 45.6%	30 days
2-	-Retrospective -University H. -Treatment protocol assessment. -??30mins -No scale used.	Paeds	65	-Neurologic complications 15%. -Subsequent epilepsy 23%.	-Symptom 40% -Fever induced 37%	Mean 3.6 years
3-	-Retrospective -University H. -30mins definition. -No scale used.	Paeds	189	-Neurologic complications 33%. More in GTCS -Recurrence of SE 16%. More in remote symptom and GTCS.	-Acute symptom 13.3%. -Remote symptom 16.4%. -Idiopathic 40.7%. -Epileptic 29%.	??
4-	-Retrospective Government Hospitals. -30mins definition. -GOS used.	Adults	107	-Neurologic complications 26%. Older age Delay treat CVA CNS infection - Recur SE 0.93%	-CVA 27% -Metabolic 18% -Idiopathic 18% -AED withdrawal 14%	-Time to discharge -Mean 16.4days
5-	-Prospective -population study. -Convulsive	Paeds	226	-Neurologic complications?? -SE recurrence 16%	-Febrile 56%. -CNS infection 12%	One year

Study No.	Study Format	Age	No. of Pts.	Morbidity	Aetiology	Time of Follow-up
6-	-Prospective -Febrile SE -30mins definition -No scale used.	Paeds	180	-Neurologic complications Non.	-Hx. of neonatal sz 3%. -Neuro abnormal 20%. -F/H of SE 11%.	30 days
7-	-Retrospective -Medical centre -GOS -10mins SE definition.	Adults	130	-Neurologic complications 23%. Acute symptom Length of hospitalization.	Acute symptom 54%.	Discharge Time
8-	-Retrospective -ICU SE -Specific incidence of infection among SE Medical record ICU??	?adults	161	-Community acquired infections 20.4%. -Hospital acquired 42%. -Longer ICU admission.	Specific Incidence of infection.	Discharge time.
9-	-Prospective. -Neuropsych test before and>1yr after SE. -Wechsler adult intelligence scale IQ. -30mins definition.	Adults	15/ 1685	No post SE intellectual decline	Specific Neuropsychic test.	One year
10-	-Retrospective -NCSE -EEG -30mins definition. Mental status assessment??	all	100	-Acute neurologic complications 5%. -Systemic complication 39%.	Acute medical 52%. Epileptic 31%. -cryptogenic 17%.	

Pts = patients   paeds = paediatrics   AED = anti epileptic drug   F/H = family history GOS = Glasco outcome score   ?? = not mentioned   sz. = seizure

Morbidity studies Key :

Study No.	References
1	Cascino et al, 1998.
2	Eriksson , 1997.
3	Du et al, 2005.
4	Hui et al, 2003.
5	Chin et al, 2006.
6	Shinner et al, 2001.
7	.Classen et al, 2002.
8	Ala- kokko et al, 2006.
9	Adachi et al, 2005.
10	Shneker and Fountain, 2003.

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