Incidence of Hypocalcaemic Seizures Due to Vitamin D Deficiency in Children in the United Kingdom & Ireland

Emre Basatemur[1], Alastair Sutcliffe[1].

[1] Population, Policy and Practice Programme, UCL Institute of Child Health, London, United Kingdom.

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Corresponding author and person to whom reprint requests should be addressed:

Dr Emre Basatemur

Population, Policy and Practice Programme

UCL Institute of Child Health

30 Guilford Street

London, WC1N 1EH, UK

e-mail: emre.basatemur@ucl.ac.uk

Phone: +44 207 905 2324.

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Abstract

Context:

Anecdotal reports suggest that increasing numbers of children in the UK are presenting with clinical manifestations of vitamin D deficiency (VDD). However the epidemiology of symptomatic VDD is largely undetermined; existing studies are limited to local case series, and national incidence estimates of disease burden are lacking.

Objective:

To estimate the incidence of hypocalcaemic seizures secondary to VDD in children in the UK and Ireland, and describe the demographic and clinical features of cases.

Design and Setting:

Prospective, population-based active surveillance study using the established British Paediatric Surveillance Unit (BPSU) methodology.

Population:

Children aged 0-15 years, resident in the UK and Ireland, who developed a hypocalcaemic seizure due to VDD between September 2011 and September 2013.

Main Outcome Measure:

Overall incidence of hypocalcaemic seizures due to VDD in children age 0-15, and incidence stratified by age, sex, and ethnicity.

Results:

91 confirmed or probable cases were reported, equating to an overall annual incidence of 3.49 per million children age 0-15 years (95% CI: 2.81-4.26). Incidence was significantly greater in males compared to

females, in infants compared to older children, and in children of South Asian or Black ethnicity compared to children from white ethnic backgrounds.

Conclusions:

Current implementation of public health policy in the UK is not successful in preventing children from developing one of the severe manifestations of VDD. Further studies are required to evaluate the epidemiology of symptomatic VDD more broadly, in order to guide future public health policy decisions.

Introduction

Vitamin D deficiency (VDD) can cause various clinical problems in children including rickets, hypocalcaemia, and myopathy (1). Despite national recommendations in the United Kingdom for vitamin D supplementation in early childhood, anecdotal reports suggest that increasing numbers of children are presenting with clinical manifestations of VDD (2). However, the epidemiology of symptomatic VDD is largely undetermined; most existing studies are local case series, without denominator data for calculation of incidence (2−4).

We report a 2-year prospective national surveillance study of hypocalcaemic seizures secondary to VDD in children in the UK and Republic of Ireland (ROI), using the British Paediatric Surveillance Unit (BPSU) reporting system. Hypocalcaemic seizures are an acute clinical presentation of VDD, likely to be managed almost exclusively by paediatricians. We report national incidence estimates, and the demographic and clinical features of cases.

Methods

BPSU Methodology

The BPSU is an established active surveillance system for rare childhood disorders. Participating consultant paediatricians (94% of UK and Irish paediatricians in 2009) receive monthly reporting cards (5). Response rates are high (93.3% in 2012) (6). Surveillance of hypocalcaemic seizures secondary to VDD ran from September 2011 to September 2013. Paediatricians who reported cases were sent a data-collection form requesting case details.

Case Definition

Paediatricians were asked to report children aged 0-15 years with a suspected seizure in the presence of both:

1. Serum corrected calcium <2.0 mmol/L
2. Serum 25-hydroxyvitamin D (25-OH-D) <50 nmol/L

Children with a previous hypocalcaemic seizure due to VDD were excluded. The 25-OH-D cut-off of <50 nmol/L defines insufficiency in UK and international guidance (1,7).

Case details were assessed for the following exclusion criteria:

1. An alternative cause of seizures.
2. Pathology that can cause secondary VDD (e.g. chronic renal or liver disease, gastrointestinal disease with malabsorption, inherited disorders of vitamin D metabolism).

Cases meeting the above criteria were defined as 'confirmed' cases.

In some reports pre-treatment blood samples were insufficient for 25-OH-D measurement, although the working diagnosis was a hypocalcaemic seizure secondary to VDD. These were defined as 'probable' cases if they otherwise met the case definition, and ≥1 additional feature suggestive of rickets was present:

1. High serum alkaline phosphatase (ALP) or parathyroid hormone (PTH), according to local reference range.
2. Radiological signs of rickets (reported by clinician).

Data Collection Form

Minimal patient identifiers (NHS number, hospital number, date of birth, sex, district level postcode) were collected to identify duplicate reports. Ethnicity was recorded using UK Census 2001 categories (8). Details regarding clinical presentation, co-morbidities, investigations, and clinical management were requested.

Denominator Data

Mid-2012 population estimates from the UK Office for National Statistics and Irish Central Statistics Office were used for incidence calculation (9,10). Population data stratified by ethnicity was only available for children age 0-14 years in England, Wales, and ROI, using 2011 estimates (9,10).

Statistical Analysis

Data are summarised using means and standard deviations if approximately normally distributed, or medians and interquartile ranges if non-normal. Confidence intervals around incidence estimates were calculated using the exact Poisson method. Differences in biochemistry by age were examined using independent t-tests for normally distributed data and Wilcoxon rank-sum tests for non-normal data. Analyses were performed using StataSE 13.1.

Ethical Approval

Ethnical approval was obtained from the London Central Research Ethics Committee (Ref:11/LO/0838). Approval for collection of patient identifiers without consent was obtained from the National Information Governance Board (ECC/BPSU/6-02(FT7)/2011).

Results

Of 137 notifications in total, there were 81 confirmed and 10 probable cases. 18 were duplicate notifications, and 18 didn't meet the case criteria (Supplementary Figure 1). Case status could not be ascertained for 10 notifications (7%), because clinicians couldn't recall patient details (n=5) or didn't respond despite several reminders (n=5). The 91 confirmed and probable cases were included for analysis.

The majority of cases were male (82%), and from high-risk ethnic groups (Table 1). Cases fell into two age groups; 95% were young children aged 0-2 years, and 5% were adolescents aged 11-15 years. There was a seasonal pattern in presentation (Supplementary Figure 2).

The estimated annual incidence of hypocalcaemic seizures secondary to VDD was 3.49 per million children age 0-15 years (95% CI: 2.81−4.26). Incidence was significantly greater in males compared to females, in infants compared to older children, and in children from South Asian or Black compared to White ethnic backgrounds (Table 2).

61% had multiple seizures. In most cases seizure duration was <5 minutes (69%), with seizures lasting ≥10 minutes in 19%. 80% of children did not have other clinical features of VDD, whilst 15% exhibited features of rickets. Serum biochemistry is shown in Table 1, and the relationship between biochemistry and age in Supplementary Figure 3 and Supplementary Table 1. Where available, 25-OH-D levels were <25 nmol/l in 86% of children and 71% of mothers. Radiographs were performed in 30 cases, with 23 exhibiting features of rickets (77%). Electrocardiograms were performed in 40 cases, with a prolonged QT interval reported in 16 (40%).

98% of cases were admitted to hospital, for a median duration of 3 days (IQR: 2−5). 51% were given acute treatment to terminate a seizure or prevent recurrence (Table 1). 78 children (87%) received colecalciferol or ergocalciferol, of whom 9 were given single high-dose stoss therapy (intramuscular in 7 cases and oral in 2). 12 children (13%) received alfacalcidol, whilst 3 (3%) received vitamin D replacement only in the form of Abidec or Dalivit multivitamin preparations. No children died, and one had sequelae at discharge (a burn from extravasation of i.v. calcium gluconate).

Discussion

This is the first study in the UK to report national incidence estimates for any clinical manifestation of VDD. Most previous studies of symptomatic VDD are single or multi-centre case series (2−4). The exception is a regional prospective study in children aged up to 5 years, conducted in the West Midlands between 2000-2001, which identified 24 cases of symptomatic VDD equating to an incidence of 7.5 per 100,000 (11). 6 cases presented with hypocalcaemic convulsions. However, the results are not generalizable to the UK as a whole due to regional differences in ethnic demography; the West Midlands has a higher South Asian population, particularly Pakistani, than the UK average (9). National incidence estimates for symptomatic VDD are available for Denmark (2.9 per 100,000 children age 0-14 years) and Canada (2.9 per 100,000 children age 0-18 years) (12,13).

Previous reports suggest that hypocalcaemic seizures represent 12-25% of cases of symptomatic VDD presenting to secondary care, depending on the age of children included (2,4,11,13). We chose to limit our study to hypocalcaemic seizures, rather than investigate symptomatic VDD more broadly, for two reasons. Firstly, we anticipated that musculoskeletal manifestations of VDD might present to healthcare professionals other than paediatricians, such as general practitioners and orthopaedic surgeons. Secondly, we anticipated that the incidence of rickets as a whole could exceed the then recommended capacity for BPSU studies (300 cases per year).

Our results are consistent with previous reports that South Asian and Black ethnic groups are at highest risk of symptomatic VDD (2−4,11), and that hypocalcaemic symptoms present in two distinct periods; early childhood (the majority of cases) and adolescence (2,4), possibly because of higher metabolic demand for calcium during these periods of rapid bone growth (1,4). 11 children were from white backgrounds; two adolescents with autistic spectrum disorders and restricted diets, one 2-year-old with multiple allergies and a restricted diet, and 8 aged between 0-2 years without co-morbidities.

We observed an unexpected male predominance, which has been reported in two previous case series; a Turkish study of 93 infants aged 1-24 months with hypocalcaemic seizures due to suspected rickets (14), and an American study of 78 term neonates (age <31 days) with transient hypocalcaemia (15). In our study, the

male predominance was present in both neonates (79%) and children aged ≥1 month (85%). Males aged 0-36 months are reported to have higher bone mineral content than females (16), and we hypothesise whether gender-specific differences in metabolic calcium demand during periods of rapid growth may predispose males to hypocalcaemia in the presence of VDD.

Phosphate levels were not depressed as expected in VDD rickets, a finding previously reported in children with hypocalcaemic presentations of VDD (4). Authors have suggested that this could be due to presentation in the early stage of VDD, before a secondary hyperparathyroid response has developed, or due to PTH resistance in later stages of deficiency (1,4). We observed a difference in the pattern of serum biochemistry by age, with neonates exhibiting lower ALP, PTH, and higher phosphate levels compared to older children. Previous studies of neonatal hypocalcaemia have reported low vitamin D levels in combination with low/normal PTH levels and hyperphosphataemia (15). Authors have proposed that various factors may play a synergistic role in the development of hypocalcaemia in neonates, including late maturation of the parathyroid axis, hypomagnesaemia, and VDD (15).

The main strength of the study is the use of an established active surveillance system, with national coverage and consistently high response rates. However, there are several limitations. We were unable to ascertain case status for a minority of reports (7%), similar to previous BPSU studies (5-10%) (17,18). A degree of under-reporting is likely with any voluntary surveillance system. As there was no alternative source available for case ascertainment we cannot estimate the potential extent of under-reporting, however with monthly reminders we expect it to be relatively low. In some cases pathology other than VDD may have contributed to the development of hypocalcaemia, such as immaturity of the parathyroid axis and hypomagnesaemia in neonates. Three children (4.2%) had low PTH levels suggesting co-existing hypoparathyroidism; two moderately premature neonates (32−36 weeks gestation) aged <1 week (one Pakistani, one Caucasian), and a 5-month-old Pakistani with radiological signs of rickets and a raised ALP. All were vitamin D deficient (10−15.9 nmol/l).

The current implementation of public health policy in the UK is not preventing children from developing severe manifestations of VDD. The Department of Health advises that all pregnant women, and all children aged 6 months to 5 years consuming <500 ml/day of infant formula milk, take a daily vitamin D supplement of between 300-400 units. However, supplements are only available free of charge to low-income families through the Healthy Start Scheme, and uptake is low (19). The Chief Medical Officer has instructed the National Institute for Health and Care Excellence to examine the cost-effectiveness of universal supplement provision (20). Robust data regarding the epidemiology and health burden of VDD is necessary to guide public health decisions. Given that 27% of cases were <1 month of age, our results support recommendations to promote supplementation during pregnancy and in infants from soon after birth, at least in at-risk ethnic groups (7). 19% of cases were exclusively formula-fed, questioning whether current guidance that formula-fed infants do not require additional supplementation is appropriate. Further studies are required to evaluate the epidemiology of symptomatic VDD more broadly in the UK.

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Table 1. Demographic & clinical characteristics, investigations and management.

Sex (n=91)	**n (%)**
Male	75 (82%)
Female	16 (18%)
Ethnicity (n=91)	**n (%)**
Any white background	11 (12%)
Pakistani	35 (38%)
Indian	11 (12%)
Other South Asian*	8 (9%)
Black (African / Caribbean / other)	22 (24%)
Mixed & other ethnicity†	4 (4%)
Age at presentation (n=91)	**n (%)**
<1 month	24 (27%)
1 – 11 months	55 (60%)
1 – 2 years	7 (8%)
3 – 10 years	0 (0%)
11 – 15 years	5 (5%)
Feeding, for infants age < 1 year (n=77)	**n (%)**
Exclusively breast fed	42 (55%)
Exclusively formula milk	15 (19%)
Mixed breast & formula milk	7 (9%)
Weaned onto solids	13 (17%)
Serum biochemistry‡	**Median (IQR)**
25-OH-D, in nmol/l (n=81)	11.2 (8 to 19.2)
Alkaline phosphatase (ALP), in iu/l (n=89)	667 (452 to 1003)
Parathyroid hormone (PTH), in pmol/l (n=72)	21.8 (9.0 to 37.1)
	Mean (SD)
Corrected calcium, in mmol/l (n=91)	1.42 (0.21)
Phosphate, in mmol/l (n=86)	2.13 (0.76)
Maternal 25-OH-D (nmol/l) (n=42)	**Median (IQR)**
	18.8 (12 to 27.9)
Acute treatment to terminate or prevent seizures (n=89)	**n (%)**
None	44 (49%)
Intravenous calcium gluconate	39 (44%)
Anticonvulsant: Any	23 (26%)
Benzodiazepine	12 (13%)
Phenobarbitone	10 (11%)
Phenytoin	4 (4%)

* 2 Bangladeshi, 2 Afghan, 1 Iranian, 3 unspecified South Asian background.
† 2 children with mixed ethnicity, 1 Libyan, and 1 Iraqi.
‡ Reference ranges vary by laboratory. Indicative reference values from University College London Hospital are: 25-OH-D: <25 = deficient, 25-50 = insufficient; ALP: upper limit of normal varies with age between 250–460; PTH: 1.6-6; Calcium: 2.15-2.55; Phosphate: age 10d to 2yr = 1.45-2.16, age 2yr-13yr = 1.45-1.78.
Abbreviations: 25-OH-D, 25-hydroxyvitamin D; IQR, interquartile range; SD, standard deviation

Table 2. Annual incidence estimates: overall and stratified by sex, age, and ethnicity.

	Number of cases[*]	Population estimate	Annual incidence per million (95% CI)
All children age <16 years	91	13,037,071[†]	3.49 (2.81 – 4.26)
Stratified by sex			
Male	75	6,673,852[†]	5.62 (4.42 – 7.04)
Female	16	6,363,219[†]	1.26 (0.72 – 2.04)
Stratified by age			
< 1 year	79	890,510[†]	44.36 (35.12 – 55.28)
1 – 2 years	7	1,745,821[†]	2.00 (0.81 – 4.13)
3 – 10 years	0	6,430,876[†]	-
11 – 15 years	5	3,969,864[†]	0.63 (0.20 – 1.47)
Stratified by ethnicity[‡]			
White	8	8,674,415[§]	0.46 (0.20 – 0.91)
South Asian (all)	52	998,463[§]	26.04 (19.45 – 34.15)
Black (all)	21	507,205[§]	20.70 (12.81 – 31.64)
Mixed & other	4	662,816[§]	3.02 (0.82 – 7.73)

[*] Number of confirmed and probable cases over the 2 year study period
[†] Mid-2012 population estimates for children age 0-15 years in England, Wales, Scotland, Northern Ireland, & Republic of Ireland.
[‡] Analysis stratified by ethnicity is for children age 0-14 years in England, Wales & Republic of Ireland only. As denominator data by ethnicity is not available for children in Scotland and Northern Ireland, or for children aged 15 years, the number of children in this analysis is less than the total number of confirmed and probable cases.
[§] Mid-2011 population estimates for children age 0-14 years in England, Wales, & Republic of Ireland.