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Temporal trends in incidence of Rolandic epilepsy, prevalence of comorbidities and prescribing trends: birth cohort study

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ABSTRACT
Objective To examine temporal trends in incidence of Rolandic epilepsy (RE), prevalence of comorbidities and antiepileptic drug (AED) prescribing patterns.
Design Retrospective cohort study.
Setting The UK.
Patients Children aged 0–16 years born 1994–2012 were followed from birth until September 2017, transfer to another general practitioner practice or death or practice withdrawal from The Health Improvement Network (THIN), whichever occurred first.
Main outcome measures Incidence of RE, prevalence of morbidity and AED prescribing patterns. Read codes for comorbidities and AEDs were adapted from other UK population-based epilepsy studies.
Results There were 379 children with first RE event recorded between 2000 and 2014 from active THIN practices with available mid-year population counts. Crude annual incidence across all years was 5.31/100 000 (95% CI 4.81 to 5.88). There was no significant time trend in adjusted incidence rate ratios (aIRR) (0.99/ year, 95% CI 0.96 to 1.02). Males had higher aIRR (1.48, 95% CI 1.20 to 1.82) as did children aged 6–8 and 9–11 years compared with 4–5 years (aIRR 2.43, 95% CI 1.73 to 3.40; aIRR 2.77, 95% CI 1.97 to 3.90, respectively). There was recorded comorbidity in 12% with 6% with a recorded diagnosis of pervasive developmental disorder. Half of children with RE had a record of being prescribed AEDs.
Conclusions UK incidence of RE has remained stable with crude incidence of 5/100 000/year. Carers and clinicians need to be aware that comorbidities may exist, particularly pervasive developmental disorders. Carbamazepine is consistently the most commonly prescribed AED for RE in the UK.

INTRODUCTION
Information on frequency, cause and natural history of Rolandic epilepsy (RE) is necessary to develop optimal treatment strategies. There are few published studies on the incidence of RE.1–4 Several factors influence incidence of epilepsy including socioeconomic status, gender, ethnicity, adaptation of regional or international guidelines in classification and management of epilepsy, availability of experts in epilepsy.5–7 As the presence and distribution of such factors can vary between countries, country-specific data on incidence of RE are most appropriate for resource allocation. Furthermore, country-specific incidence would best inform feasibility of recruitment targets for research studies. There are no contemporary UK studies on incidence of RE.
A retrospective, chart review, hospital-based study of 196 children with RE found high prevalence of comorbid cognitive and behavioural problems. Attention deficit hyperactivity disorder (ADHD) was found in 31%, 22% had specific cognitive problems and 11.7% had behavioural problems including anxiety, depression and pervasive developmental disorder (PDD).8 Other hospital-based studies have reported a higher prevalence of cognitive problems in RE compared with control data.9 10 A case-control study of 89 children with RE found they had higher anxiety and depression scores to controls.11 Hospital-based studies compared with population-based studies are more likely to produce biased results. There are no population-based studies on comorbidities in RE.
There has been a long-standing view RE does not need treatment with antiepileptic drugs (AEDs). However, recent data suggesting positive treatment effects on cognitive and/or behavioural comorbidities may influence whether to treat RE with AEDs. The potential negative cognitive and/or behavioural effects of AEDs are well recognised, with newer AEDs theoretically having fewer effects. In the UK, for children who are given treatment, carbamazepine and lamotrigine are the recommended first-line AEDs. In Germany, Austria and Israel, it is sulthiame and in France it is valproate. The scientific evidence for these recommended AEDs is poor. Although there has been a UK survey on current treatment approaches, it is unclear whether prescribing patterns of AEDs in RE has changed over time. Given lack of evidence of optimum treatment of RE, well-designed trials, with realistic recruitment targets based on contemporary country-specific incidence estimates, are needed.

The aims of this study were to investigate temporal trends in incidence of RE, prevalence of comorbidities and AED prescribing patterns in the UK.

METHODS
We carried out a retrospective cohort study using The Health Improvement Network (THIN), a large UK-wide clinical database that prospectively captures Vision software electronic health record (EHR) data on prescriptions, diagnoses and symptoms in patients presenting to their general practitioner (GP). THIN has been used to carry out a number of population-based epilepsy studies and are provided as online supplemental material (online supplemental tables 2 and 3).

We summarised over time number of practices contributing mid-year population counts and returning data satisfying THIN quality criteria. Mid-year population counts were summarised across practices.

For denominators, we examined number of children in every THIN practice irrespective of whether they identified cases of RE (ie, the base population) at the midpoint of each study year, broken down by: (i) age group in years 4–5; 6–8; 9–11; 12–14, 15–16 years; (ii) gender; (iii) GP practice, (iv) quintiles of Townsend scores of socioeconomic deprivation. Townsend scores were not updated since 2011, and 7% of contributing practices did not contribute Townsend data. Also, data provided at the practice level were a mean of individual participants’ quintile Townsend score which lacks interpretability and is much less sensitive to differences between practices. Therefore, we were unable to adjust for socioeconomic status.

Gender and age at onset of RE were summarised descriptively, as was presence of comorbidities. The proportion and 95% CIs of children with a record of any AED prescription after RE diagnosis were summarised over time.

Among the full cohort of children with RE who had at least 10 years of follow-up from birth, the cumulative distribution of time to diagnosis of RE was estimated using Kaplan-Meier (KM) curves. We defined time to diagnosis as time from birth until first occurrence of RE diagnosis in GP records. Cumulative incidence of RE diagnosis by age 5 years and age 8 years and 95% CIs were calculated. KM curves were plotted for four birth groups: 1994–1996, 1997–1999, 2000–2002 and 2003–2006. To investigate changes over time in age of diagnosis, HR for each birth group (against the 2003–2006 reference group) and its 95% CIs were estimated from a Cox proportional hazards model. Significance of temporal changes was assessed by log-rank test for trend.

Crude incidence rates per 100000 were summarised by year and age group. The number of children with a RE Read code was analysed using mixed effects Poisson regression including an offset for mid-year population. The model included potential confounders such as year, gender and age group as fixed effects and practice as a random effect. Year was modelled as categorical (3-year groups) or continuous variable: the continuous version was centred on year 2000 and scaled if necessary. A linear year effect, cubic B-spline and categorical representation were compared using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to determine which best modelled the relationship between year and incidence. Adjusted incidence rate and 95% CIs were calculated for each year adjusting for age, gender, year and GP practice. Adjusted incidence rate ratios (aIRR) and 95% CIs for model variables were calculated. As a sensitivity analysis, requirement to extend the model to a negative binomial or zero-inflated Poisson regression was investigated by comparing values of AIC and BIC.
Figure 1 Kaplan-Meier plot of time to first Rolandic epilepsy (RE) diagnosis by year of birth for children with a diagnosis of RE and at least 10 years of follow-up from birth.

Table 1 summarises age at diagnosis and gender, overall and by nation of residence for the incidence sample of 379, and for the full cohort of 516 children. Age of RE diagnosis was similar across UK regions (mean age of 9 years).

Figure 1 illustrates time to RE diagnosis by year of birth, with no significant evolution in time to diagnosis (p=0.51). The proportion of children with RE diagnosed by 5 years was 14.2% (95% CI 10.2% to 18.5%) and by 8 years was 55% (95% CI 49.5% to 60.4%).

Crude incidence rate over the study period was 5.31/100,000/year (95% CI 4.81 to 5.88). Crude incidence rate by age group and year are provided in Table 2A. In the Poisson regression model, a linear representation of year was clearly most appropriate, with lowest BIC (linear 4515; spline 4523; categorical 4540). Age-adjusted and gender-adjusted incidence in 2014 was 3.20/100,000/year (95% CI 2.53 to 4.05). Table 2B summarises aIRRs. Males showed significantly greater incidence (aIRR 1.48, 95% CI 1.20 to 1.82) as did children aged 6–8 and 9–11 years compared with aged 4–5 years reference group (6–8: aIRR 2.43 (95% CI 1.73 to 3.40); 9–11: aIRR 2.77 (95% CI 1.97 to 3.90)). There was no significant time trend in aIRR (p=0.38); Figure 2 illustrates point estimate and 95% CI for adjusted incidence rate by year. Sensitivity analysis confirmed suitability of the Poisson regression model (AIC 4451; BIC 4515) compared with negative binomial (AIC 4450; BIC 4523) and zero-inflated Poisson (AIC 4454; BIC 4583).

Table 3 provides data on comorbidities. Among the 379 incidence RE children, 12% had a record of any co-existing disorder and 6% had a pervasive developmental disorder. Half of children with RE were recorded as being prescribed AEDs; there was a higher proportion among those aged 6–11 years with prescriptions in more recent years (online supplemental figure 1). The most frequent AEDs were carbamazepine (34%), sodium valproate (16%), lamotrigine (7%) and levetiracetam (5%). Over the study period, carbamazepine and valproate remained most frequently prescribed.

DISCUSSION

The main findings of this population-based study are: incidence of RE in the UK remained virtually unchanged over the study period.
period with a crude rate in 2014 of 5/100,000/year (similar to the 1990s Icelandic studies) and a higher incidence among males and greatest incidence in children aged 6–11 years; confirmation of the presence of comorbidities in RE, with a higher proportion of pervasive developmental disorders than reported in the general population; 'older' type medications, in particular carbamazepine, are consistently preferred prescribed AEDs.

While there are studies that have examined temporal trend of childhood epilepsy as a whole (and show a decreasing incidence), we are not aware of any other studies that have examined temporal trends of other specific benign childhood epilepsy syndromes. Our contemporary incidence rate of RE in the UK and factors that influence rate are similar to those reported in an Icelandic population-based study in 1998 that identified 38 children but lower than the 21/100,000/year in a hospital-based Swedish study in 1975. All three have similar sociodemographic composition and ready access to paediatricians with expertise in epilepsy so difference in country-specific rates are likely to related to study design. With a crude incidence rate of 5.31/100,000/year, applied to the 10,217,388 UK population of children aged 4–16 years (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandestimates/datasets/populationestimatesforukandwinslowscoalandnorthernireland), we estimate 542 new RE cases annually in the UK. This is higher than the 340 new RE cases estimated in 2012 by the UK-wide Epilepsy Audit, but lower than the 751 estimated by a 2014 cross-sectional survey of UK paediatricians with clinical responsibility for epilepsy. Discrepancy between our estimate and these two other UK studies may be related to differences in the study designs, low rate of syndromic diagnoses by reporting clinicians in Epilepsy Audit, but lower than the 751 estimated by a 2014 cross-sectional survey of UK paediatricians with clinical responsibility for epilepsy. There is no financial incentive for UK GP practices to be more exacting in coding for epilepsy syndrome/type and it is possible that we missed RE cases recorded under another non-specific epilepsy code. However, equally there is no reason to believe that GPs would systematically not be more specific in coding.

Table 2

<table>
<thead>
<tr>
<th>Year</th>
<th>4–5</th>
<th>6–8</th>
<th>9–11</th>
<th>12–14</th>
<th>15–16</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000–2002</td>
<td>2.5 (1.1 to 6.1)</td>
<td>4.9 (2.6 to 9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003–2005</td>
<td>4.6 (2.6 to 8.1)</td>
<td>7.6 (5.3 to 10.8)</td>
<td>9.9 (6.8 to 14.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2008</td>
<td>3.1 (1.6 to 6.0)</td>
<td>6.9 (4.8 to 9.8)</td>
<td>8.4 (6.1 to 11.4)</td>
<td>3.2 (1.7 to 5.9)</td>
<td></td>
</tr>
<tr>
<td>2009–2011</td>
<td>3.1 (1.7 to 5.7)</td>
<td>9.8 (7.3 to 13.0)</td>
<td>8.3 (6.1 to 11.3)</td>
<td>3.3 (2.1 to 5.4)</td>
<td>1.5 (0.6 to 3.9)</td>
</tr>
<tr>
<td>2012–2014</td>
<td>1.9 (0.9 to 3.9)</td>
<td>6.1 (4.3 to 8.6)</td>
<td>6.9 (4.9 to 9.8)</td>
<td>2.7 (1.6 to 4.7)</td>
<td>0.6 (0.2 to 2.4)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Co-existing Disorder</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any co-existing disorder</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Behavioural/emotional/social functioning/mental health</td>
<td>&lt;10*</td>
</tr>
<tr>
<td>Developmental (unspecified)</td>
<td>31 (8%)</td>
</tr>
<tr>
<td>Motor function/hyperkinetic/tic</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Pervasive developmental</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>School problems</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Speech and language</td>
<td>&lt;10 (-)%</td>
</tr>
</tbody>
</table>

*N presented due to disclosure of small numbers.
having received confirmation of a specific epilepsy syndrome from hospital specialists. Given identification of copy number variants at Xp22.31 as a risk factor for RE, we hypothesise higher incidence in males may be related to an X linked recessive genetic pre-disposition.4

RE was often previously referred to as benign RE as the seizures were often age-limited and were easily controlled. Our results provide further evidence that RE is more than seizures.14 25–27 Consideration should be given to monitoring carefully for co-existing cognitive and/or behavioural problems particularly pervasive development disorders. Concerns that such comorbidities may not be well recorded in practices would suggest that our results are underestimates and true additional burden is more substantial.

Our finding that half of children with RE were prescribed AEDs by GPs is similar to the 60% of paediatricians who reported substantial.

CONCLUSIONS

The contemporary UK incidence of RE is 5/100 000/year and has remained virtually unchanged between 1997 and 2014; males and children aged 6–11 years have highest incidence. Carers and clinicians need to be aware that comorbidities may exist, particularly pervasive developmental disorders. Carbamazepine is consistently the most commonly prescribed AED for RE in the UK. Designing potential UK clinical trials for RE should take these study findings into consideration. Finally, prospective studies with comprehensive enrolment of all epilepsy cases and detailed review by epileptologists could be useful to confirm our study findings.

LIMITATIONS

THIN is representative of the UK population but care outside the GP setting is not fully captured. Studies using routine administrative datasets like THIN provide an opportunity to provide population-based data on research topics, obtain insight on real-life patient management and address clinically relevant questions more quickly and at lower cost than other study types. However, there may be data that are systematically missing and this limitation needs to be borne in mind.

The risk of misdiagnosis of epilepsy is well known.30 We were unable to achieve the ideal of carrying out a direct validation of RE and comorbidities diagnoses and our results need to be considered in this context. However, medical diagnoses in THIN have high validity.31–33 and high validity of epilepsy diagnoses, as whole rather than specific subtypes, in THIN has been previously reported. The high validity of diagnosis codes in THIN is likely related to the close relationship between THIN GP practices and hospital services. Although diagnosis of RE (as well as comorbidities) were extracted from GP records, the coded diagnoses are very likely to reflect clinical assessments by GPs as well as hospital specialists. RE has been a well-known epilepsy syndrome for decades with a well-established specific GP Read code. These factors, plus our finding of a stable incidence rate over time which is similar to that previously reported in another Western European country, plus not dissimilar estimated annual new RE cases compared with a national UK epilepsy audit and a UK cross-sectional study of RE23 24 give confidence that RE diagnoses were true cases. THIN coding for other childhood epilepsy syndromes may not be the same as for RE. We postulate representatbility of THIN as a source of scientific research of specific childhood epilepsy syndromes will be related to how familiar
Original research


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