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Valproate and risk of fracture in Rett syndrome

H Leonard,1 J Downs,1 L Jian,1 A Bebbington,1 P Jacoby,1 L Nagarajan,2 D Ravine,3 H Woodhead4

ABSTRACT

Objectives Some associations between antiepileptic drugs (AEDs) and fracture risk have been reported in the general population. This study investigated the relationships between fracture risk and commonly used AEDs in Rett syndrome, a genetic disorder associated with intellectual and physical disability.

Study design Cases (n=233) were sourced from the population-based Australian Rett Syndrome Database and longitudinal data were used. The Cox proportional hazard model was used to analyse relationships between fracture and prescribed AEDs, mobility, epilepsy diagnosis and genotype.

Results After controlling for mobility, epilepsy diagnosis and genotype, use of valproate increased the risk of fracture threefold after at least 1 year (HR 3.56; 95% CI 1.85 to 6.82) and after 2 or more years (HR 3.02; 95% CI 1.90 to 4.80). There was a lesser increased risk (HR 1.99; 95% CI 0.99 to 4.02) with lamotrigine in the first year of use but not for subsequent years of use. Carbamazepine slightly decreased the risk (HR 0.60; 95% CI 0.35 to 1.02) after 2 or more years of use.

Conclusions The effect of valproate on bone health should be considered when managing epilepsy in Rett syndrome. Multiple mechanisms could be contributing to this effect.

INTRODUCTION

Rett syndrome (RTT) is a neurodevelopmental condition associated with physical and intellectual disability. Reduced bone mineral density (BMD) and a fracture rate nearly four times that of the general population have been reported in this condition with the most commonly fractured bone being the femur. The principal genetic cause of RTT is a spectrum of loss-of-function mutations within the X linked MECP2 gene. There is evidence that severity of phenotype and fracture risk are influenced by the nature of the underlying mutation.

We previously reported that seizures were occurring in approximately 80% of girls and women with RTT prompting widespread long-term use of antiepileptic drugs (AEDs) among those affected. We also found that a diagnosis of epilepsy increases fracture risk, even after adjusting for genotype. In the present study, we have investigated the association between fracture risk and commonly used AEDs in the same population base, taking into account duration of use, mobility and MECP2 mutation type.

METHODS

The study was approved by the Princess Margaret Hospital Ethics Committee. Cases were sourced from the population-based Australian Rett Syndrome Database (ARSD), which was established in 1993 and includes Australian RTT subjects born since 1976. Data were collected from biennial questionnaires completed by the family or care givers between 1996 and 2004 (excluding 1998) and from a year long calendar study carried out in 2000. Information on fracture history, AEDs, mobility, age at epilepsy diagnosis and genotype was used for this analysis.

Data management

Details recorded from the questionnaires about fractures included age at occurrence and location of all fractures experienced over the lifespan of the subject with RTT. A single fracture event was a report of an episode when bone fracture occurred, even if the event resulted in two or more fractures. Age at fracture was calculated from age at 31 December for the year of fracture.

Information on AEDs, including generic name of each drug, start date and duration that each AED was prescribed was extrapolated from follow-up questionnaires and the calendar study. Assumptions for any missing data were as follows:

- If no data were recorded in a previous questionnaire, but were present in a later follow-up year (and no start time was indicated), the start time for AED use was assumed to be midway between the two periods.
- If there were missing data for one questionnaire, but the AED regimen remained the
same in previous and later follow-up questionnaires, we assumed the regimen had continued unchanged over that period.

If a discrepancy occurred between two sources of information, we used the data closest to the year of the AED use.

It was possible to construct the medication history in all but one case using these assumptions. Only medications taken by 20 or more subjects (during their life time), excluding the short-term ‘rescue’ medications (diazepam and midazolam), were considered in the analysis.

Current mobility was recorded at the time of each questionnaire on a 9-point (0–8) Likert scale, with 0 representing wheelchair-bound subject and 8 unaided mobility as previously described.20 Scores for years between surveys were linearly interpolated.


Data analysis

The effect of AED exposure, mobility and genotype on fracture risk was assessed using the Cox proportional hazard model (after ensuring adequacy of all assumptions), with a counting process style of input and robust standard errors to account for recurrent fractures. The data set was analysed on a year-of-event basis, with one record per person per year of age. Age censoring was at 31 December for each year of follow-up. In those who had experienced more than one fracture episode in a calendar year, additional records censored at date of fracture were added. Following a preliminary analysis which showed no increase/decrease in fracture risk after 2 years of use and to avoid assumptions of linear increase in fracture risk over time, it was elected to treat AED exposures as time-varying categorical predictors, calculated as either 0, 1 or 2+ full years of continuous use. In each analysis cases were censored after the AED of interest had been stopped. An epilepsy diagnosis variable was created to act as an indicator of possible use of AEDs other than the AED being investigated and was set to 0 in the years before epilepsy diagnosis and 1 thereafter. The relationships between use of commonly prescribed AEDs and genotype were assessed with Pearson’s χ² tests. Statistical analysis was performed using STATA V.9.

RESULTS

A total of 288 cases were known to the ARSD when the 2004 follow-up questionnaire was administered. The families of 240 cases had provided at least one follow-up questionnaire since 1996, with 233 families providing information relating to the occurrence of fractures. At the time of censoring the median age of all girls/women was 14.7 years (range 2–29 years), 191 (82.0%) had a diagnosis of epilepsy and 84 (36.1%) had experienced at least one episode of fracture. Fifty-two (22.3%) had had one fracture episode, 18 (7.7%) two fracture episodes, seven (3.0%) three and six (2.6%) four or more. The median level of mobility on the 9-point Likert scale for subjects at 5 years of age was 5 (range 0–8), representing walking with assistance and for subjects at 20 years of age was 3 (range 0–8), suggesting increased difficulty in walking with age. Genetic testing had been performed in 215/233 (92.3%) cases, with a pathogenic mutation identified in 164/215 (76.3%) of those tested.

Valproate, carbamazepine, lamotrigine and benzodiazepines were the most frequently used AEDs (table 1). The number and proportion of other AEDs used by the cohort, in decreasing order of use, included phenytoin (19, 8.2%), keppra (12, 5.2%), phenobarbitone (9, 3.9%), primidone (8, 3.1%), acetazolamide (5, 1.3%), sulthione (2, 0.7%) and tiagabine (1, 0.4%). Vigabatrin was used by 20 subjects, but for less than 1 complete year in every case and additional analysis for this AED was not conducted. The common pairs of AEDs used are shown in table 2. There were no statistically significant relationships between the mutation type and use of valproate (p=0.53), carbamazepine (p=0.82), lamotrigine (p=0.92), benzodiazepine medications (p=0.22) or topiramate (p=0.56).

The fracture risks associated with potential confounders are shown in table 3. Univariable analyses showed that use of valproate for more than 12 months was associated with a threefold increase in fracture risk (HR 3.22; 95% CI 1.75 to 5.92, p<0.001, HR 3.44; 95% CI 1.71 to 6.94, p<0.001 (when restricted to mutation positive cases)) when compared to the risk associated with no or any other prescribed AED and that the elevated risk (HR 2.78; 95% CI 1.88 to 4.13, p<0.001, HR 3.16; 95% CI 1.99 to 5.07, p<0.001 (when restricted to mutation positive cases)) persisted in subsequent years. Lamotrigine may also increase the risk of fracture (HR 1.95; 95% CI 0.98 to 3.87, p=0.06, HR 2.21; 95% CI 1.06 to 4.63, p=0.04 (when restricted to mutation positive cases)) in the first year of use. The risk of fracture occurrence was not significantly altered by carbamazepine, topiramate or benzodiazepines (clobazam, clonazepam and nitrazepam) (table 4).

Taking genotype, diagnosis of epilepsy (as a proxy for use of AEDs other than valproate in cases not currently using valproate) and level of mobility into account, use of valproate on its own, or in combination with any other AED, remained associated with a threefold increased risk of fracture after 1 year (HR 3.56; 95% CI 1.85 to 6.82, p<0.001, HR 3.58; 95% CI 1.71 to 7.49, p<0.001 (when restricted to mutation positive cases)) and after 2 or more years (HR 3.02; 95% CI 1.90 to 4.80, p<0.001, HR 3.43; 95% CI 2.05 to 5.73, p=0.001 (when restricted to mutation positive cases)). Carbamazepine was associated with a slight decrease in the risk of fracture after 2 or more years (HR 0.60; 95% CI 0.35 to 1.02, p=0.06, HR 0.54; 95% CI 0.29 to 0.99, p=0.05 (when restricted to mutation positive cases)). The other commonly used AEDs were not associated with an increased or decreased risk of fracture (table 4).

Table 1 Frequencies and duration of use for the commonly used anti-epileptic drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number (%) of cases ever used</th>
<th>Median duration of use (years)</th>
<th>Median age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>134 (57.5)</td>
<td>5.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>114 (48.9)</td>
<td>4.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>100 (42.9)</td>
<td>3.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Topiramate</td>
<td>37 (15.9)</td>
<td>3.2</td>
<td>16.6</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>27 (11.6)</td>
<td>3.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Clobazam</td>
<td>26 (11.2)</td>
<td>3.0</td>
<td>15.4</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>20 (8.6)</td>
<td>3.0</td>
<td>18.9</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>7 (3.0)</td>
<td>5.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Combined</td>
<td>52 (22.3)</td>
<td>4.5</td>
<td>15.9</td>
</tr>
<tr>
<td>benzodiazepines</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Original article

Use of valproate as a monotherapy (compared to cases using no other medication) was associated with more than three times the risk of fracture in both the univariate and multivariable models (table 4). However, use of carbamazepine as a monotherapy (compared to cases using no other medication) showed no significant effect on fracture risk after 1 year, or 2 or more years of use, in the univariate or multivariable model (table 4). All analyses were repeated including only cases with pathogenic MECP2 mutations (n=183) with similar results to the analyses including all clinically diagnosed RTT cases (already shown in table 4).

DISCUSSION

A high proportion (~80%) of RTT subjects in this study had epilepsy. The most frequently prescribed AEDs were valproate, carbamazepine and lamotrigine, with valproate commonly used in combination with carbamazepine or lamotrigine. After controlling for mutation type and mobility, use of valproate for more than 1 year was associated with a threefold increase in risk of fracture.

Fracture is the main clinical end point of interest when considering bone health. To our knowledge, this is the first reported longitudinal study examining the potential relationship between specific AEDs and fracture risk in a chronic neurological condition with the associated co-morbidities of severe intellectual disability and constrained mobility. Data were collected over 8 years from a long-standing RTT population-based register9 and thus the potential for missing information due to recall errors was reduced. Furthermore, mutation data were available on the majority of subjects, making this study the first to include the role of genotype as a moderator variable in the analysis of relationships between fracture and AED use in a specific neurological disorder.

Nevertheless, we did not have access to radiological information to confirm reports of fracture. The mechanism of fracture was not always reported and we were unable to identify the proportion of fractures prompted by the seizures themselves. As information was provided by parents and care givers, changes in care giver could have resulted in difficulties recalling changes in medication regimens. Theoretically, the use of progesterone-only medications or gonadotropin-releasing hormone analogues for menstrual suppression could increase fracture risk in older subjects. However, since in our study population these medications were used by only a few subjects and for a limited time period we were unable to investigate these theoretical risks in this study.

We observed that the risk of fracture was elevated for valproate, prescribed on its own or in combination with other AEDs after 1 or more years. This is practical information of relevance to the management of childhood epilepsy in a complex neurological condition and consistent with two earlier population studies studying mostly adults with idiopathic epilepsy.11 12 Souverein et al found a one-and-a-half times risk of fracture in patients taking valproate alone, compared to taking no or any other AED medication. After adjustment for prior fracture, use of corticosteroids, co-morbidity, social variables and a diagnosis of epilepsy Vestergaard et al found a small increase in the risk of fracture if valproate was ever used. A retrospective study13 found a relationship between valproate use and fracture in 50 children and adults with a severe physical and intellectual disability and epilepsy. However, only 14 subjects sustained a fracture, the number prescribed valproate being 26, compared to 9 taking no or any other AED medication. After adjustment for prior fracture, use of progesterone-only medications or gonadotropin-releasing hormone analogues for menstrual suppression could increase fracture risk in older subjects. However, since in our study population these medications were used by only a few subjects and for a limited time period we were unable to investigate these theoretical risks in this study.

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Valproate was estimated to contribute 5% of the variance of fracture. Although consistent with these earlier findings, the magnitude of the increased fracture risk associated with valproate was greater in our study.

The risk of fracture in our RTT population was not additionally increased for medications such as vigabatrin, topiramate or benzodiazeptines, or longer-term use of lamotrigine. Use of carbamazepine may be slightly protective of fracture, when used for longer than 2 years. The limited findings in the literature relating to these other AEDs are mixed, with carbamazepine associated with increased or no increased risk13 14 of fracture. Valproate was greater in our study.

Although not reported consistently, valproate has generally been found to be associated with reduced BMD. Evidence that valproate stimulates osteoclast activity suggests that increased bone resorption may be the mechanism responsible for the valproate-associated reduction of BMD. Another important question is whether the increased rate of fractures associated with valproate is specifically higher in RTT. Valproate is an inhibitor of class I histone deacetylases (HDACs) (HDACs 1–3) and the class II HDACs 4, 5 and 7. HDACs play an important role in modulating chromatin structure and gene transcription, with deacetylated chromatin tending to be more compact with an associated reduction in gene expression. The MECP2 gene, which is disrupted by inactivation mutations in RTT cases, offers binding sites for HDACs 1, 2 and 8. The potential functional overlap of consequences of MECP2 deficiency and valproate activity may aggravate the risk of valproate toxicity in RTT. Support for an inherent effect of MECP2 mutations on bone mineralisation could be speculated in the light of the findings of Haas et al, who showed that females with RTT have lower bone density compared to a similar group with cerebral palsy. We have previously shown that those with the p.R270X or p.R168X mutations are more likely to fracture. It would therefore seem that there are complex links between mutation, bone health and AEDs in RTT and additional investigations of these potential interactions are warranted.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Years of use</th>
<th>Univariable risk</th>
<th>Multivariable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (p value)</td>
<td>CI</td>
</tr>
<tr>
<td>In combination with another AED or as monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate 0</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>3.22 (&lt;0.001)</td>
<td>1.75 to 5.92</td>
<td>3.56 (&lt;0.001)</td>
</tr>
<tr>
<td>2 or more</td>
<td>2.78 (&lt;0.001)</td>
<td>1.88 to 4.13</td>
<td>3.02 (&lt;0.001)</td>
</tr>
<tr>
<td>Carbamazepine 0</td>
<td>1.00</td>
<td>–</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
<td>0.74 (0.61)</td>
<td>0.23 to 2.35</td>
<td>0.63 (0.44)</td>
</tr>
<tr>
<td>2 or more</td>
<td>0.70 (0.16)</td>
<td>0.42 to 1.16</td>
<td>0.60 (0.06)</td>
</tr>
<tr>
<td>Lamotrigine 0</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1.95 (0.06)</td>
<td>0.98 to 3.87</td>
<td>1.99 (0.09)</td>
</tr>
<tr>
<td>2 or more</td>
<td>0.94 (0.83)</td>
<td>0.56 to 1.60</td>
<td>0.94 (0.66)</td>
</tr>
<tr>
<td>Topiramate 0</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1.89 (0.28)</td>
<td>0.60 to 5.99</td>
<td>1.98 (0.25)</td>
</tr>
<tr>
<td>2 or more</td>
<td>1.07 (0.89)</td>
<td>0.43 to 2.64</td>
<td>1.24 (0.65)</td>
</tr>
<tr>
<td>Benzodiazepines 0</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1.05 (0.95)</td>
<td>0.26 to 4.26</td>
<td>1.13 (0.98)</td>
</tr>
<tr>
<td>2 or more</td>
<td>1.24 (0.52)</td>
<td>0.64 to 2.38</td>
<td>1.15 (0.79)</td>
</tr>
<tr>
<td>As monotherapy only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate 0</td>
<td>1.00</td>
<td>–</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>3.21 (0.005)</td>
<td>1.41 to 7.29</td>
<td>3.24 (0.01)</td>
</tr>
<tr>
<td>2 or more</td>
<td>3.67 (&lt;0.001)</td>
<td>2.16 to 27</td>
<td>3.57 (0.001)</td>
</tr>
<tr>
<td>Carbamazepine 0</td>
<td>1.00</td>
<td>–</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
<td>1.46 (0.55)</td>
<td>0.44 to 4.83</td>
<td>1.10 (0.89)</td>
</tr>
<tr>
<td>2 or more</td>
<td>0.83 (0.70)</td>
<td>0.33 to 2.07</td>
<td>0.64 (0.40)</td>
</tr>
</tbody>
</table>

*Risks of fracture after controlling for mobility, genotype and diagnosis of epilepsy.
that involved the administration of four questionnaires over 8 years, the German study administered only one question-naire, allowing the possibility of recall bias as the time between initiation of therapy and questionnaire completion increased. No information was provided on response and it is conceivable that there could also have been a bias towards retention of milder cases with a less complicated and easier to recall medication history. However, given carbamazepine’s known adverse effects in unclassified and some generalised epilepsies and its possible contributions to seizure exacerbation and cognitive regression,23 one needs to be cautious about blanket recommendations regarding its use. Despite its effectiveness, valproate also has potential drawbacks including side effects such as tremor and weight gain; idiosyncratic reactions such as impaired liver function, thrombocytopenia and pancreatitis; and in early pregnancy, an increased risk of congenital abnormalities.24 We would recommend that AEDs other than valproate also be considered when planning epilepsy management in RTT, both to avoid current episodes of fracture and as part of a larger plan to optimise bone health for the later years. However, where valproate remains the preferred drug it is particularly important to have other strategies in place to maximise bone health. What we still do not know is whether the effect we have seen with valproate in RTT is of equal magnitude in children with other causes of epilepsy.

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