Official Journal of the European Paediatric Neurology Society

Original article

Seizures in Rett syndrome: An overview from a one-year calendar study

Le Jian[a], *Lakshmi Nagarajan*[b], *Nicholas de Klerk*[a], *David Ravine*[c], *John Christodoulou*[d,e], *Helen Leonard*[a,*]

[a]*Centre for Child Health Research, The University of Western Australia, Telethon Institute for Child Health Research, PO Box 855, West Perth, WA 6872, Australia*
[b]*Department of Neurology, Princess Margaret Hospital for Children, Roberts Road, Subiaco, Perth, Western Australia, Australia*
[c]*West Australian Institute of Medical Research and Centre for Medical Research, The University of Western Australia, Perth, Western Australia, Australia*
[d]*School of Paediatrics and Child Health, University of Sydney, New South Wales, Australia*
[e]*Western Sydney Genetics Program, Children's Hospital at Westmead, Sydney, Australia*

ARTICLE INFO

Article history:
Received 18 November 2006
Received in revised form
13 February 2007
Accepted 14 February 2007

Keywords:
Rett syndrome
Seizure rate
Epilepsy
MECP2 mutations
Early development
Clinical severity
Anti-epileptic drugs

ABSTRACT

Background: Rett syndrome is a neurodevelopmental disorder mainly affecting females. It is principally caused by mutations in the *MECP2* gene. Seizures occur in about 80% of subjects but there has been little research into the factors contributing to their frequency.
Aims: To investigate seizure frequency in Rett syndrome and its relationship with other factors, including genetic characteristics and the use of anti-epileptic drugs.
Methods: Information on daily seizure occurrence and health service utilization and monthly anti-epileptic drug use was provided on 162 Rett syndrome cases for a calendar year. Age at onset of seizures, developmental history and other clinical and genetic characteristics were obtained from a contemporaneously completed questionnaire and from the Australian Rett Syndrome Database. Negative binomial regression was used to investigate factors associated with seizure rates.
Results: Seizure rates were highest in the 7–12 year age group. They were lower in those with p.R294X, p.R255X mutations and C terminal mutations. Those who had early developmental problems and poorer mobility had higher seizure rates as did those with greater clinical severity and poorer functional ability. Many different combinations of medications were being used with carbamazepine, sodium valproate and lamotrigine either singly or in combination with another being the most common.
Conclusions: Seizure frequency in Rett syndrome is age-dependent, more common in those with more severe early developmental problems and influenced by mutation type.

*Corresponding author. Tel.: +61 8 9489 7790; fax: +61 8 9489 7700.
E-mail address: hleonard@ichr.uwa.edu.au (H. Leonard).

Abbreviations: AED, anti-epileptic drug; ARSD, the Australian Rett Syndrome Database; CS2000, calendar study in 2000; FUS2000, follow-up study in 2000; NLS, the nuclear localization signal region; TRD, the transcription repression domain; SD, standard deviation; HC, head circumference; BMI, body mass index; NHMRC, Medical and Health Research Council; APSU, the Australian Paediatric Surveillance Unit

1090-3798/$ - see front matter
doi:10.1016/j.ejpn.2007.02.008

1. Introduction

Rett syndrome is a neurodevelopmental disorder mainly affecting females and caused principally by mutations in the *MECP2* gene.[1] Although the phenotype is generally severe, the clinical spectrum is variable with a number of associated comorbidities including reduced somatic growth, gastro-intestinal disease, osteopenia, autonomic dysfunction and scoliosis. Seizures, which have a considerable impact for those affected and their families occur in about 80% of subjects. The Australian Rett Syndrome Database (ARSD) has been using multiple sources to ascertain Rett syndrome cases in Australia among individuals born since 1976.[2] Information on functional, medical, educational and other aspects of the cohort have been collected every two years since 2000 through questionnaires completed by parents and carers. During 2000 families also completed a daily calendar in which they reported episodes of seizures, medical and other health appointments and hospitalizations experienced by the subjects.[3] In this report we use these contemporaneously recorded data to determine seizure rates and to investigate their relationship with demographic, clinical, genetic and other factors. We also describe the range and combinations of anti-epileptic drugs (AEDs) being used by this Rett syndrome population.

2. Material and methods

2.1. Data sources

Families and caregivers of 162 verified female cases ascertained from the ARSD (www.ichr.uwa.edu.au/rett/aussierett/),[4] participated in a year long calendar study in 2000 (CS2000).[3] These cases represented 81.4% of the cases who were in the ARSD at that time. Over three quarters (78.4%) were classical according to the recently revised criteria[5] compared with 67% in a more recent cohort.[4] Families were asked to record, in a calendar format, and return on a monthly basis information, detailing daily events in seven categories: medical, health and therapy appointments; hospital stays; nursing care; seizure activity; and other health events. The reasons for each appointment and the type of doctor or health professional involved were recorded. Details of all prescribed and non-prescribed medications were also recorded on a monthly basis. As well as completing the calendar, families also participated in a follow-up study in 2000 (FUS2000) the methodology for which has been previously described.[2] Information provided by families and caregivers, for example regarding mobility and the presence of health problems such as abnormal breathing and sleep disturbance as well as weight, height and head circumference (HC) measurements, was available for this analysis. Epilepsy diagnosis was based on the age at seizure onset as previously[6] or if AEDs were being used for seizure control ($n = 4$).

2.2. Severity scores

Several severity scores derived from the FUS2000 data[2] were also included in the current analysis. The modified WeeFIM is a composite score that increases to a maximum of 126 with increasing independent functioning.[7] The Kerr score was developed from the system suggested as a guideline for reporting clinical severity in Rett syndrome,[8] the Pineda score from the scaling system originally developed by Monros et al.[9] and the Percy score from the score modified by Schanen and Percy[10] from Amir and Zoghbi.[11] In contrast to the WeeFIM, these numerical scores increase with increasing severity.

2.3. Mutation testing

MECP2 gene mutation testing has been completed in the majority of cases (154/162, 95.1%), with pathogenic mutations identified in 118 (72.6%). Details of the methods employed for *MECP2* mutation testing have been previously described.[6] X inactivation was categorized as skewed when one X-chromosome was active in 25% or less of all analyzed cells.[12]

2.4. Data management

To examine the relationship between parent-reported seizure activity and genetic findings, the cases were categorized into the following mutation types: p.R168X, p.T158M, p.R294X, p.R270X, p.R255X, p.R133C, p.R306C, p.R106W, large deletions involving exon 3 and 4, C-terminal deletions in exon 4, early truncating (truncations up to and including the nuclear localization signal (NLS) region within the transcription repression domain (TRD), except for p.R270X, p.R255X and p.R168X), and a final group that included all other pathogenic mutations. Separate categories were included for those in whom a *MECP2* mutation was sought but not identified and those who were not tested.

The z-score for HC in 2000 was calculated based on the following formula: (HC of child – reference mean HC)/reference standard deviation (SD) of HC. The reference mean and SD were obtained from a Dutch study which provided population norms.[13] Z-scores for body mass index (BMI, kg/m^2) were calculated using the formula and reference median values for females aged 2–20 years provided by the Centre for Disease Control.[14] The reference value for age 20 years was also applied to any individual over this age. HC z-score in 2000 and BMI z-score in 2000 were divided into three categories based on the distribution of the cases in this study: a reference group with z-scores ranging from 25th percentile (P_{25}) to 75th percentile (P_{75}), with the other two groups below P_{25} and above P_{75}.

Information on the use of AEDs was collected from CS2000. Cases were classified as users of an AED if they used it for one or more months in the year. Combination(s) of AEDs used the same "no/yes" model. The AEDs were categorized as "old" drugs if they belonged to the first line AEDs according to the specifications of the Australian Pharmaceutical Benefits Scheme (PBS).[15] The rest (lamotrigine, topiramate, clobazam, vigabatrin, gabapentin and tigabine) were categorized as "new" drugs. Cases using any new medication were coded as being on new medication irrespective of the continuation of the additional use of old medications. To investigate the relationship between parent-reported seizure episodes and the pattern of AED use, those on AEDs in 2000 were also divided into two groups according to whether they had