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Sleep problems in Rett syndrome

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Abstract

Rett syndrome (RTT) is a severe neurological disorder, affecting mainly females. It is generally caused by mutations in the *MECP2* gene. Sleep problems are thought to occur commonly in Rett syndrome, but there has been little research on prevalence or natural history. An Australian population-based registry of cases born since 1976 has been operating since 1993, with current ascertainment at 300. The Australian Rett Syndrome Database (ARSD) consists of information about Rett syndrome cases including their functional ability, behaviour, sleep patterns, medical conditions and genotype. The cases range in age from two to 29 years.

The aim of this study was to investigate the type and frequency of sleep problems, relationships with age and *MECP2* mutation type and to evaluate changes over time.

Parents or carers of the subjects with Rett syndrome were asked to complete a questionnaire about sleep problems on three separate occasions (2000, 2002 and 2004). Regression modelling was used to investigate the relationships between sleep problems, age and mutation type. Sleep problems were identified in over 80% of cases. The prevalence of night-time laughter decreased with age and the prevalence of reported night-time seizures and daytime napping increased with age. The prevalence of sleep problems was highest in cases with a large deletion of the *MECP2* gene and in those with the p.R294X or p.R306C mutations.

Sleep problems are common in Rett syndrome and there is some variation with age and mutation type.

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Keywords

MECP2; Rett syndrome; Sleep problems

Background

Rett syndrome is a severe neurodevelopmental disorder, mainly affecting females. The cumulative incidence in Australia is 1.09 per 10,000 females by 12 years of age [1]. Classical Rett syndrome follows a distinctive developmental course, with the achievement of apparently normal early milestones followed by developmental regression, deceleration of head growth, the onset of stereotypic hand movements and gait abnormalities.

The association between Rett syndrome and mutations in the methyl-CpG binding protein 2 (*MECP2*) gene was first identified in 1999 [2]. To date, more than 200 different pathogenic *MECP2* mutations have been identified and there appears to be considerable variation in phenotype. Some mutations (p.R270X and p.R255X) are associated with a severe clinical presentation and some (p.R294X and p.R133C) with a milder phenotype [3-8].

Children with various neurodevelopmental disabilities have been shown to have sleep problems. Females with Rett syndrome appear to have specific sleep related problems, unlike those with other neurodevelopmental disabilities [9]. Until now, there have been no large-scale data analyses describing the prevalence and predictors of sleep problems in Rett syndrome. The aim of this study was to make use of the Australian Rett Syndrome Database (ARSD) to describe the prevalence of sleep problems and its association with age and genotype.

Subjects and Methods

Data from the ARSD, a population-based registry, established in 1993, and including cases born since 1976, were used for the analysis. Questionnaires completed by the family and clinician on enrolment to the register provide information used to verify the diagnosis of Rett syndrome according to established clinical criteria [10,11]. There have now been three follow-up questionnaires completed by the parents and/or carers in the years 2000, 2002 and 2004. The questionnaires provide information about background demographic data, developmental history, medical conditions, healthcare service utilisation, functional ability, and clinical severity. Further, the *MECP2* genotype was available for most cases [12].

Data were available from 237 cases, whose parents/carers completed one, two or all three of the follow-up questionnaires. The cohort is dynamic with continual recruitment of new cases occurring simultaneously with attrition due to death or occasional loss to follow up.

Carers or parents of the child/adult with Rett Syndrome were asked if there had been any sleep problems or specific sleep disturbances. If this was a follow-up questionnaire, the carer/parent was asked if the subject had had sleep problems during the previous two years. Questions about specific problems during sleep included laughing, screaming, seizures, teeth grinding, sleep walking, sleep talking and night terrors. No definitions were provided for these items. The reporting was through a multiple response format with the six categories: “Does not occur”, “Less than once a month”, “Monthly”, “Twice a month”, “Weekly” and “Nightly”.

The items were examined separately in binary format and then combined into a single rating scale measuring severity of sleep problems using the Rating Scale Rasch model [13,14]. The item ‘night seizures’ was not included in the sleep severity scale, because it measured epilepsy, rather than specific sleep problems. The remaining six items were then tested using a generalised item analysis, which provided item thresholds, weighted mean square fits and

parameter estimates. The item 'sleep walking' fitted less well and was removed from further analysis because there were few positive (only six) responses to this question. The remaining five items were combined into the single scale using Maximum Likelihood Estimation: night laughing, night screaming, teeth grinding, sleep talking and night terrors.

Two additional items from the Rett Syndrome Behaviour Questionnaire (RSBQ) [15], "spells of screaming for no apparent reason during the night" and "frequent naps during the day", were also used. These items had the response format of *not true*, *sometimes true* and *often true* and were combined into a binary format (absent or present).

Using a previously developed scale, parents/carers were asked to indicate the child's sleeping pattern by ticking one of nine boxes, which measured night-time wakefulness and included information about daytime napping [16]. These responses were then recoded into four categories: normal, mild, moderate and severe for night-time awakening.

The ages of each subject at the time of completion of the questionnaires (all three), were grouped into four categories: 0 to 7 years, 8 to 12 years, 13 to 17 years and 18 years and over. The genotypes of each case, with a previously identified *MECP2* mutation (164/216 of those tested), were categorised as follows: p.R168X, p.T158M, p.R294X, p.R270X, p.R255X, p.R133C, p.R306C, p.R106W, large Exon 3 and 4 deletions, C-terminal deletions, early truncating mutations (up to and including the nuclear localisation signal region within the transcription repression domain, except for p.R270X, p.R255X and p.R168X), and a final group which included all 'other' pathogenic mutations in the *MECP2* gene.

Logistic regression models were fitted giving rise to odds ratios for the explanatory variables age group and mutation type. A Generalised Estimating Equations (GEE) approach was used to account for lack of independence due to repeated measures within cases. Robust standard errors were used to estimate the 95% confidence intervals. Fitted probabilities of sleep problems were then calculated for each age group and mutation type.

Regression modelling was also conducted using the continuous severity of sleep problems scale. The scale was then fitted with the explanatory variables age group and mutation type. The GEE model accounted for the repeated measurements on the subjects over each of the three years of data collection. The regression coefficient for each age group was referenced to the 0-7 year old age group and plotted for the continuous scale.

The statistical analyses were conducted using the computer software programs ConQuest [14], STATA version 9 [17] and SPSS for Windows version 13 [18].

Results

There were 163, 196 and 202 questionnaires returned for each of the years 2000, 2002 and 2004 respectively. Of the 237 cases, 131 (55%) had questionnaires completed for all three years, 56 (24%) had two questionnaires completed and 50 (21%) had only one questionnaire completed. In 537/561 (95.7%) of these questionnaires, there was a response to the principal question about sleep problems. The prevalence of *any sleep problem* in the different age groups varied across questionnaires (Table 1). However, the fitted probability, adjusted using GEE, was highest in the youngest age group.

The most commonly reported specific sleep problems in 2004 were laughing and teeth grinding (prevalences 58.9% and 55.0% respectively), followed by screaming and seizures (prevalences 35.6% and 26.2%, respectively) (Table 2). In 2004, frequent daytime napping was reported in over 77% of cases and long spells of night screaming in 36% of cases (Table 3).

Awakenings at night appeared to be moderate to severe amongst the younger children (with 54% reporting frequent night awakenings for the 0-7 year old age group). Awakenings at night were less common in the older cases but still reported frequently in 40% of the over 18 year old age group.

The frequency of some sleep problems showed specific modulation with age, with daytime napping and night-time seizures tending to increase with age and laughing, screaming and teeth grinding tending to decrease with age. Using a regression model, statistically significant variations between age groups were only detected for night laughing, night-time seizures and daytime napping (Figure 1). While the prevalence of daytime napping increased progressively by age group, the occurrence of night seizures, peaked in the 13-17 year old age group (Figure 1).

The continuous scale, representing severity of sleep problems, showed a decrease with age to 17 years. There then appeared to be a little increase in severity from 18 years onwards.

The estimated probability of any sleep problem for most genetic mutations was over 80% and was little different (78.8%) for those without a mutation. The highest probabilities were for those with large deletions (100%), p.R294X (95%) and p.R306C (95%) (Figure 2). The estimated probability of daytime napping was highest for subjects with the p.R270X, p.T158M, p.R106W and p.R255X mutations (Figure 4). Some mutation types had a higher probability of other specific sleep problems, such as night laughing (Figure 4; large deletions) and night time seizures (Figure 3; p.R255X) and other mutation types had a higher probability of night screaming (Figure 3; large deletions). However, none of these differences were statistically significant.

The regression coefficients for the continuous sleep severity scale were highest for mutations p.R106W, p.R168X, p.R306C and large deletions (Figure 5). Those with early truncating mutations appeared to have the least and those with p.R306C mutations the greatest severity.

Discussion

We have demonstrated the high prevalence of sleep problems in Rett syndrome (80-94% in different age groups in 2004). Sleep problems were identified most frequently in the younger age group. Daytime napping, night-time laughter, teeth grinding, night screaming and seizures were the problems most frequently reported. Some specific sleep problems did appear to vary with age with night laughing decreasing with age and daytime napping increasing with age.

Our study suggested there was some variation in sleep problems according to mutation type. In addition to large deletions, the two common mutations, where any sleep problem was most often reported, were p.R294X and p.R306C. On the other hand, sleep problems were least likely to be reported in those with C terminal deletions. Night-time laughing was commonest in those with a large deletion while daytime napping was commonly reported in cases with p.R270X, p.R255X and p.T158M mutations. For some sleep problems, such as night screaming and night seizures, there were no statistically significant relationships with mutation type.

This study used information from the ARSD, a population based, comprehensive register of children and adults with Rett syndrome. The size and representativeness of the ARSD has provided a reliable and comprehensive source of data for studying sleep problems in Rett syndrome. The longitudinal nature of the database (with ongoing ascertainment) means that new cases continue to be recruited while existing cases may die or be lost to follow up. Despite every effort to maintain retention, there has been some attrition, with ongoing contact not always possible for all families.

For the development of the 2002 and 2004 questionnaires, some questions regarding sleep problems were modified from the previously used open style questions to a closed response format, which provided a more consistent and reliable measurement. For the data analysis, we recoded some of the questions used in 2000 to make them compatible with the questionnaires used in 2002 and 2004. We selected this as a better option to excluding the use of the 2000 data.

We found that some sleep problems increased and some decreased with age. Therefore, when looking at the composite variable created for this study, statistically significant age trends were not found. This lack of consistency in the variation by age group and mutation type of the individual suggested that there may be different mechanisms operating and that perhaps sleep items should be treated individually, rather than as a composite variable. Further, while it is important and aetiologically relevant to examine the features of Rett syndrome by individual mutations, the numbers in each group were small and thus limited the power of our statistical analysis.

In the general population of children, the total number of hours slept in a 24 hour period decreases with age and daytime sleep decreases to near zero after four years of age [19]. The prevalence of sleep problems in the normal population is estimated to be between 18 and 37% in different studies [20,21]. Much of this variability in findings may be due to the varied perceptions of what a sleep problem is. Nevertheless, our study showed that individuals with Rett syndrome appear to experience more sleep problems than their age related peers.

A previous study reporting on Rett syndrome, showed that hours of daytime sleep increased and hours of night-time sleep decreased with age [9]. In other research, hours of daytime sleep remained stable with age, although significantly higher than in children/adults from the general population. This finding is, however, similar to ours where we demonstrated a statistically significant increase in daytime napping with age.

A study involving 83 Australian individuals with Rett syndrome, (mainly ascertained from the ARSD in 1998), used a sleep diary for seven consecutive days and nights and compared the data obtained with normative sleep data [16]. This was a first attempt to assess sleep patterns in Rett syndrome and the study showed that in contrast to the normal children, total sleep time, including daytime sleep, did not drop off with age. In the present study, we did not use a sleep diary as it would have placed an additional burden upon families completing comprehensive follow-up questionnaires.

By studying the sleep-wake-rhythm in a small case series ($n=11$), Nomura and colleagues found that total daytime sleep in Rett syndrome was longer, when compared with the normal population [22]. They suggested that the symptoms in Rett syndrome occur in an orderly sequence and speculated that an early abnormality in the brain stem, in particular nuclei and neurotransmitters, sequentially influences development and growth of particular segments and functions of the higher centres in the central nervous system. Perhaps the sleep problems are related to those early abnormalities in the aminergic systems of the brain stem and their influence on other neuronal circuits, modified by secondary changes in receptor sensitivity and environmental influences. This may explain why the circadian sleep rhythm does not mature, sleep morphology and sleep patterns in Rett syndrome are different, and why some sleep problems increase and some decrease with age [22-25].

Laughter and humour are emotions that have endured and are thought to be sophisticated traits in human beings involving complex neurological networks. Laughter is often thought to have beneficial health effects. However, laughter may be pathological and may occur with brain dysfunction. It may be seen after traumatic brain injury and in disorders of the brain and brain stem (e.g., Multiple Sclerosis, Motor Neurone Disease, brain tumours and vascular lesions). It

may also be seen with epileptic seizures arising from the frontal lobe, the hypothalamus, the temporal lobe, the cingulate cortex and these seizures are often referred to as gelastic seizures [26-28].

In our cohort, night-time laughter was reported in 58.9% of cases. This is similar to the report by Coleman and colleagues [29] where night-time laughter was found in 83%. Not much is written regarding night laughter in Rett syndrome. This is surprising, considering the high prevalence. Disordered hand function and early epileptiform activity in the perirolandic region suggest dysfunction in the sensorimotor cortex in Rett syndrome. Perhaps pathological laughter, with these areas involved in its genesis, is caused by impairment in the same regions. We do not feel that pathological laughter in Rett syndrome is epileptiform in nature. More thought needs to be given and work done to fully understand this commonly reported feature in Rett syndrome.

This is the first study to examine the relationship between sleep problems and the *MECP2* genotype. We found that cases with the common mutations, p.R270X, p.R255X and p.T158M, were more likely to have frequent daytime napping. The p.R270X and p.R255X are nonsense mutations located in the nuclear localisation signal of the transcription repression domain and appear to have a relatively severe phenotype [4,7]. In a different study, the p.T158M mutation was associated with increased severity [30]. Therefore, it appears that increased daytime napping is a phenomenon associated with more severe mutations. We found that p.R294X and p.R306C, mutations associated with milder phenotypes [4,31], had high probability of sleep problems. However, these apparently milder mutations also appear to be more likely to have other behavioural problems [32]. C terminal mutations are usually mild in severity [33]; they also had a low prevalence of sleep problems. We found that cases with a large *MECP2* deletion were the most likely to have a sleep problem and night-time laughter was reported in all cases. Until recently, very little has been known about the phenotype of cases with large deletions [34].

This has been the first attempt to study the prevalence of sleep problems in a population cohort of subjects with Rett syndrome. The results of this study show that sleep problems are common; they may not necessarily diminish with age; and some mutation types appear to be more associated with sleep problems than others. The presence of sleep problems can impact significantly, not only on the individual with Rett syndrome, but also on their families or carers. Where sleep problems are significant, carers and families need additional support, especially as the child with Rett syndrome becomes an adult. An assessment of the sleep pattern of a female with Rett syndrome should be considered as part of the overall multidisciplinary management. An important area for future research is the extent to which the sleep dysfunction is amenable to pharmacological or behavioural intervention.

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Figure 1.
Fitted probability of sleep problems by age group.

Figure 2.
Fitted probability by mutation type: any sleep problems and night laughing.

Figure 3.
Fitted probability by mutation type: night seizures and night screaming.

Figure 4. Fitted probability by mutation type: sleep patterns (night awakenings) and frequent daytime napping.

Figure 5.
Predictions of severity of sleep problems by mutation type.

Table 1

Prevalence of any sleep problems by age group and year of questionnaire.

Age Groups	Year of Questionnaire [n (%)]		
	2000	2002	2004
0-7 years	32 (86.5)	28 (71.8)	33 (94.3)
8-12 years	38 (82.6)	38 (71.7)	37 (78.7)
13-17 years	40 (95.2)	43 (91.5)	36 (76.6)
18+ years	29 (76.3)	45 (78.9)	56 (76.7)
Total Positive Responses	139 (85.3)	154 (78.6)	162 (80.2)
Total Cases	163	196	202

Note 1: Total responses to sleeping question = 561 (includes unique and repeated cases).

Note 2: Denominator is all questionnaires for that age group and year.

Table 2
Prevalence and frequency of specific sleep problems (Year = 2004).

Response	Night Laughing	Night Screaming	Night Seizures	Night Teeth Grinding	Sleep Walking	Sleep Talking	Night Terrors
Does not occur	83	130	149	91	132	166	166
Less than once a month	47	29	14	29	1	11	20
Monthly	19	7	10	6	4	6	6
Twice a month	17	9	6	10	1	6	2
Weekly	30	18	17	27	0	8	7
Nightly	6	9	6	39	0	5	1
Total (responses)	202	202	202	202	138 ¹	202	202
Prevalence (%) ²	58.9	35.6	26.2	55.0	4.3	17.8	17.8

¹ Sleep walking can only occur if the female is ambulatory (can walk). Many cases with Rett syndrome cannot walk so there was a low response to this question.

² Prevalence was calculated for any behavioural response from *Less than once a month* to *Nightly*.

Table 3
Prevalence of specific sleep items by age group (Year = 2004).

Sleep Item	Age Group [%]				Total
	0-7 Years	8-12 Years	13-17 Years	18+ Years	
Night Laughing	68.57	61.70	59.57	52.05	58.91
Night Screaming	54.29	36.17	29.79	30.14	35.64
Night Seizures	20.00	21.28	31.91	28.77	26.24
Night Teeth Grinding	74.29	46.81	44.68	57.53	54.95
Night Sleep Walking	4.00	6.25	6.67	1.96	4.35
Night Sleep Talking	34.29	10.64	14.89	16.44	17.82
Night Terrors	40.00	19.15	12.77	9.59	17.82
Frequent Daytime Naps	77.14	69.57	73.33	84.29	77.04
Spells of Night Screaming	45.71	40.00	35.56	29.58	36.22

Table 4

Prevalence of any sleep problem by mutation type for each questionnaire year.

Mutation Classification	Sleeping Problems Prevalence n (%) 2000	Sleeping Problems Prevalence n (%) 2002	Sleeping Problems Prevalence n (%) 2004
No Mutation	31 (91.2)	31 (68.9)	32 (76.2)
p.T158M	13 (92.9)	14 (93.3)	11 (78.6)
p.R168X	14 (93.3)	14 (87.5)	16 (88.9)
p.R294X	9 (100.0)	12 (100.0)	13 (86.7)
p.R270X	11 (91.7)	11 (78.6)	11 (84.6)
p.R255X	8 (100.0)	5 (71.4)	9 (90.0)
p.R133C	4 (66.7)	8 (88.9)	9 (90.0)
p.R306C	7 (100.0)	8 (88.9)	9 (100.0)
p.R106W	3 (100.0)	1 (50.0)	3 (75.0)
Other	9 (81.8)	12 (92.3)	10 (76.9)
Early Truncating	7 (87.5)	9 (81.8)	8 (80.0)
Large Deletion	5 (100.0)	8 (100.0)	8 (100.0)
C Term	11 (78.6)	12 (80.0)	13 (76.5)
Total with Sleeping Problem	132 (90.4)	145 (82.4)	152 (83.1)

Note: Denominator is cases tested for mutations for each year: Year 2000 = 146; Year 2002 = 176; Year 2004 = 183