Epilepsy in Rett syndrome: Association between phenotype and genotype, and implications for practice

Basil Cardoza a,*, Angus Clarke b, Jodie Wilcox a, Frances Gibbon c, Phil E.M. Smith d, Hayley Archer b, Anna Hryniewiecka-Jaworska b, Mike Kerr e

a Learning Disability Directorate, ABM University Health Board, Tresider Way, Cardiff, Wales, CF5 5WF, UK
b Institute of Medical Genetics, University Hospital Wales, Cardiff, CF14 4XW, Wales, UK
c Department of Child Health, University Hospital Wales, Cardiff, CF14 4XW, Wales, UK
d Department of Neurology, University Hospital Wales, Cardiff, CF14 4XW, Wales, UK
e UK School of Medicine, Cardiff University, Cardiff, CF14 4XW, Wales, UK

A R T I C L E   I N F O

Article history:
Received 27 January 2011
Received in revised form 13 April 2011
Accepted 17 June 2011

Keywords:
Rett syndrome
Epilepsy
Epileptic seizure
MECP2 (methyl-CpG-binding protein 2) gene mutation
Non-epileptic vacant spells

A B S T R A C T

Purpose: To investigate the association between genotype (methyl-CpG-binding protein 2 (MECP2 gene mutation)) and epileptic seizure phenotype in Rett syndrome.

Methods: We used the British Isles Rett syndrome survey to identify 137 subjects with one of the nine most frequent MECP2 gene mutations and invited their parents or carers to participate in a postal questionnaire and telephone interview. The questionnaire recorded information about epileptic seizure types, non-epileptic vacant spells and treatments. Two investigators conducted telephone interviews and three epileptologists classified their epileptic seizures.

Results: 89 subjects (65%) responded. The epilepsy prevalence was 67%, and 74% had non-epileptic vacant spells. The epilepsy prevalence within specific genotypes ranged from 47% (mutation C-terminal deletion, downstream of the Transcription Repression Domain) to 100% (mutation p.R270X, c.808C>T). The prevalence of non-epileptic vacant spells within genotypes ranged from 50% (mutation p.R306C, c.916C>T) to 100% (mutation p.R106W, c.316C>T). The epileptologists differed considerably in their classification of events, particularly of non-epileptic vacant spells.

Conclusions: The large majority of people with Rett syndrome have epilepsy. Most have multiple epileptic seizure types, although generalised tonic–clonic seizures are the most common. There were no significant clinical differences between genotypes. The clinical differentiation of non-epileptic vacant spells is difficult. Discordance in epileptic seizure classification between clinicians suggests that caution is needed, since the clinical history alone cannot adequately classify the epileptic seizure type in Rett syndrome.

© 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Rett syndrome is a neurodevelopmental disorder seen almost exclusively in females, and usually associated with mutation in the methyl-CpG-binding protein 2 (MECP2) gene at Xq28.1 The prevalence of the classic syndrome ranges from 1:10 000 to 1:15 000.2,3 The phenotype is often severe, with several characteristic features including a period of loss of hand and verbal skills, severe psychomotor retardation, stereotyped hand movements, truncal and gait dyspraxia: there are also several potential comorbidities including scoliosis, autonomic dysfunction and epilepsy.4,5

Epilepsy occurs in between 70%-8 and 90%= of individuals with Rett syndrome. Epileptic seizures are commonly of multiple types, including complex partial, atypical absence and generalised tonic–clonic.10 They usually start between early infancy and late childhood; although often remitting with progressing age, they remain severe and treatment resistant in a minority.11,12 After the teenage years, the epilepsy severity tends to decrease, with lower epileptic seizure frequency and relatively more partial-onset seizures.9

Epileptic seizure rates are highest in the 7–12 years age group and lower in those with p.R294X, p.R255X mutations and C-terminal mutations.13 Other studies have shown that MECP2 mutations most frequently associated with epilepsy were T158M (74%) and R106W (78%), and less frequently R255X and R306C (both 49%).14 Epileptic seizures frequently appear during the regression stage, with an early onset predicting a more severe course.15 The same study showed that brain-derived neurotrophic factor (BDNF) Val/Met polymorphism was correlated with earlier onset of epileptic seizures, whereas MECP2 type and location did not influence epilepsy.15 Early onset of epileptic seizures has also
been linked to the combined MECP2 and BDNF genotypes. The BDNF Met66 allele may protect against epileptic seizures, whereas missense mutations in the MBD of MECP2 are more frequently associated with early epileptic seizures.\(^6\) There is no significant relationship between the underlying mutation and the likelihood of either drug-resistant epilepsy or abnormal electroencephalography (EEG).\(^1\) Cases without a detectable MECP2 mutation had a higher risk of epileptic seizure onset up to 4 years of age, but a lower risk after 4 years.\(^17\) Epilepsy differs among the various phenotypes and genotypes with respect to age at onset, drug responsiveness, and epileptic seizure semiology.\(^18\) Infantile spasms, early-onset intractable epilepsy, and a Rett syndrome like phenotype have also been associated with mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene in Xp22.13,19,20

Ambulation, hand use and language dysfunction also vary with the underlying mutation; such abnormalities are fewer in those with the R133C mutation, and greater in those with the R168X mutation. In contrast, those with carboxy-terminal truncations are more likely to walk and use words.\(^2\) Individuals with epileptic seizures had greater overall clinical severity, and greater impairment of ambulation, hand use, and communication.\(^14\) Significant differences by mutation are seen for individual phenotypic characteristics such as hand use, ambulation, and language.\(^14\) During the EEG recording, the intermittent EEG abnormality and behavioural changes indicate abnormal fluctuating arousal, possibly of midbrain or brainstem origin.\(^5,6\)

Epileptic seizures have a negative impact on the lives of many children and their families. This is especially so in patients with generalized, prolonged, cyanotic and drug-resistant epileptic seizures.\(^26\) Non-epileptic “Rett episodes” (or non-epileptic vacant spells) can be mistaken by observers, parents or professionals for epileptic seizures and some “genuine” epileptic seizures may not be noticed. These non-epileptic vacant spells can include motor activity, such as twitching, jerking, head turning, falling forward, and trembling, as well as staring, laughing, pupil dilatation, breath holding and hyperventilation.\(^27\) Breath holding may include expiratory apnoea after hyperventilation, reflex expiratory apnoea, inspiratory apnoea, apnoea or hypventilation not otherwise specified.

Abnormal brainstem activity might cause behaviours that could be confused with epileptic seizures, such as eye blinking, facial twitching, vacant spells without EEG epileptiform activity, and cyanosis.\(^28\) Irregular breathing is also characteristic and Rett syndrome is regarded a cause of congenital dysautonomia. Abnormal awake breathing is common and over 70% have either hyperventilation or breath holding. Up to thirteen types of abnormal breathing have been described, sometimes with several being displayed sequentially in the same person.\(^29\) Ventilatory and autonomic monitoring has demonstrated reduced resting vagal tone with episodes of central autonomic instability.\(^30\)

This study aimed to determine the type and frequency of epileptic seizures and non-epileptic vacant spells in Rett syndrome, and any association of these features with the type of MECP2 mutation.

2. Methods

The study was approved by the Multicentre Research Ethics Committee for Wales, UK. We sent letters inviting participation to the parents or carers of 137 patients known to the British Isles Rett Syndrome Survey (BIRSS), each having one of the nine most frequent mutations in the MECP2 gene (comprising ~75% of all known Rett-associated mutations). Parents or their carers gave informed consent to the research and to publication of the results.

We developed a questionnaire to record information about epileptic seizures and autonomic events, and mailed this to participants; we sent a single reminder to non-responders. Two investigators collected further detailed information using semi-structured telephone interviews across the UK and the Republic of Ireland.

2.1. Seizure validation

Three experienced epileptologists analysed the written seizure descriptions obtained from clinical telephone interview. One was an adult neurologist working primarily with non-learning disabled patients, with limited experience of Rett syndrome. Another was a paediatric neurologist, working with children both with and without intellectual disabilities. The third was a psychiatrist in intellectual disability, working mostly with people with intellectual disability and epilepsy. For each case the reviewer was asked to classify the seizure type. This led to one of the following outcomes:

a. Agreement or disagreement that the events were seizures.

b. Agreement or disagreement that the patient had epilepsy.

c. Agreement or disagreement that the events were non-epileptic vacant spells.

where there was disagreement, the majority view was accepted.

2.2. Analysis

Initial analysis was performed using chi square tests, but where patient numbers were insufficient to show clinical differences between phenotype, descriptive data were presented.

3. Results

The parents or carers of 89 patients (65%) responded to the questionnaire. All were female and aged between 5 and 43 years. Sixty of the 89 (67%) received a diagnosis of epilepsy. A total of 199 “episodes” were reported as epileptic seizures by the parents or carers of 60 girls. All three epileptologists agreed with the diagnosis of epileptic seizures in 93 of the 199 reported “episodes” (47%) and in the remainder a majority view was taken, i.e., if 2 out of 3 epileptologists agreed that it was an epileptic seizure, then it was classified as one. There was also similar agreement that 66 of the 89 patients (74%) had non-epileptic vacant spells. There was most variation in the differentiation of non-epileptic vacant spells.

The following data uses the consensus seizure classification agreed, following discussion between the three epileptologists.

3.1. Seizure type and syndrome

62% of patients had generalised tonic–clonic seizures, approximately a quarter had secondarily generalised tonic–clonic seizures, and a quarter had complex partial seizures. Symptomatic focal epilepsy (58%) was more common than symptomatic generalised epilepsy (38%) (Tables 1 and 3).

There was a family history of Rett syndrome in three of the 89 patients, of epilepsy in six of the 89, and of intellectual disability (other than Rett syndrome) in a further six. About three-quarters of
دریافت فوری
متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات