Epilepsy in Rett syndrome

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Epilepsy is common in Rett syndrome. Many, but not all, individuals experience seizures. The estimates of epilepsy prevalence in Rett syndrome range from 48% in the cross-sectional examination of the Natural History study (Glaze et al. 2010) to 94% over the lifespan in other studies (Steffenburg et al. 2001, Jian et al. 2007, Vignoli et al. 2012, Halbach et al. 2013, Anderson et al. 2014, Tarquinio et al. 2017).

Epilepsy natural history

Mean age at the onset of epilepsy is 4.68 ± 3.5 years, but this age varies widely from 1 to 16 years (Steffenburg et al. 2001, Jian et al. 2007, Vignoli et al. 2012, Halbach et al. 2013, Anderson et al. 2014, Nissenkorn et al. 2015, Tarquinio et al. 2017).The course of seizure occurrence and remission is strikingly variable among Rett patients. Some subjects never attain even moderate seizure control, whereas in others, seizures completely remit and they are able to withdraw medication treatment.

The most common scenario, however, reflects a remitting and relapsing tendency, waxing and waning over the lifespan. Notably, active epilepsy is most common in late adolescence (Tarquinio et al. 2017).

Difficulties in diagnosing epileptic and non-epileptic events in Rett syndrome

One of the challenging issues in Rett syndrome is to make the proper diagnosis of epilepsy. Because non-epileptic paroxysmal events are common in Rett syndrome, even epileptologists disagree on the classification of spells as seizures. However, clinical diagnosis by an experienced paediatric neurologist remains the gold standard for diagnosis of epilepsy (Aaberg et al. 2017). Indeed, in the absence of an evaluation by an expert in conjunction with video-EEG, parents misclassify non-epileptic spells as seizures in as many as 82% of cases (Glaze et al. 1998).

All seizure types may be present in Rett syndrome with no characteristic “first seizure” semiology. Compared with the general population, early febrile seizures may be more frequent (12% vs. 2-5% overall) (Nissenkorn et al. 2010). The most common reported seizure types include complex partial, generalized tonic-clonic, tonic, and myoclonic seizures, with absences and clonic seizures being less frequent. Focal epilepsy (58%) seems to be more common than generalized epilepsy (38%) (Cardoza et al. 2011). The severity of epilepsy is not significantly correlated with any particular type of seizure (Steffenburg et al. 2001).

'Non-seizure' events include episodes of motor activity, such as twitching, jerking, head turning, falling forward, and trembling, unusual eye movements (oculogyric movements, blinking episodes), oral facial dyskinesias, unwarranted bouts of laughing or screaming, and motor abnormalities (tremor, dystonia, jerking, spasticity, and episodic atonia) as well as episodes of staring, laughing, pupil dilatation, breath holding and hyperventilation.

EEG findings

The electroencephalogram (EEG) is an important diagnostic tool in Rett syndrome because it allows for the distinction between true seizures and nonepileptic behavioral characteristics.

The EEG findings in Rett syndrome follow an evolution that similarly progresses through the four clinical stages of the disease. It is invariably abnormal and shows characteristic, though not diagnostic, changes:

- before 18 months, the EEG is usually normal although some cases may show slowing of the posterior background rhythm; loss of expected developmental features - observed during the regression - usually between 18 months-3 years;
- the appearance of focal initially rolandic epileptiform abnormalities that can evolve towards pseudoperiodic delta activity and generalized rhythmic spike discharges are seen most prominently during sleep between 2 and 10 years;
- then, after 10 years the EEG show multifocal, and generalized epileptiform abnormalities and rhythmic slow (theta) activity primarily in the frontal-central regions (Hagne et al. 1989) (Glaze 2002).

Importantly, these epileptiform activities on electroencephalography are frequent in Rett syndrome and occur without any clear evidence of corresponding clinical seizures.

Treatment

There is a limited number of reports specifically addressing the anticonvulsant treatment in Rett syndrome, and of those available, most are small series with a limited number of subjects and multiple different anticonvulsants being used. Based on previous publications, medication use is largely based on local prescribing practices rather than efficacy or adverse effects (Bao et al. 2013, Pintaudi et al. 2015).

Given that both partial and generalized seizures may be present in Rett syndrome, drugs selected for use in the literature are often those considered to have broad-spectrum efficacy. Monotherapy is the first treatment option in most patients (Dolce et al. 2013). Common drugs reported in clinical practice as first- or second-line monotherapy for Rett syndrome include valproate and lamotrigine.

Valproate is the most typically reported anticonvulsant for Rett syndrome at this time. Some authors have reported a 75% rate of seizure freedom with valproate as first monotherapy with a reported effectiveness (>50% reduction in seizure frequency) in 59% of the patients, mostly in patients who started seizures at 4-5 years (Nissenkorn et al. 2010, Dolce et al. 2013).

Concerning the effect of Lamotrigine, a significant proportion of Rett syndrome patients have a 50% seizure-free rate, mostly in those who start seizures after 10. Lamotrigine is useful in girls who became happier, more alert, and more able to concentrate. Only mild adverse reactions as rash and tremor are seen. It is concluded that Lamotrigine could be worth trying as an adjunctive treatment in girls with Rett syndrome, being aware of possible adverse reactions and no effect at all (Uldall et al. 1993, Stenbom et al. 1998).

No specific medications are contraindicated in Rett syndrome; however, the issue of bone health is an important consideration when prescribing anti-seizure drugs. One study has found increased risk of fracture in Rett syndrome associated with valproate use, whereas another study has demonstrated that low vitamin D levels, common in Rett syndrome, are not associated with anticonvulsants use (Leonard et al. 2010) (Motil et al. 2011).

When seizures are concluded to be epileptic in origin and anticonvulsants are initiated, the side effect profiles of medications should be considered carefully, and medications, which can cause behavioural issues (e.g. levetiracetam), anorexia and nephrolithiasis (e.g. topiramate), QT interval prolongation (e.g. felbamate), or marked sedation (e.g. benzodiazepines), should be used with caution.

Medication choice in Rett syndrome should be based on consideration of semiology, EEG characteristics, and risk/benefit ratio with respect to adverse effects, and video-EEG should be used to confirm the epileptogenic nature of events.

Vagal nerve stimulation (VNS)

Only one retrospective study has evaluated the outcomes of females with Rett syndrome and medically refractory epilepsy who have been treated with adjunctive VNS therapy for a minimum of 12 months. Patients range in age from 1 to 14 years-old at the time of implantation; they have experienced seizures for a median period of approximately six years, and have failed at least two trials of antiepileptic drugs before receiving VNS. At 12 months, six females have >or=50% reduction in seizure frequency. VNS is safe and well tolerated, with no surgical complications and no patients requiring explanation of the device. Quality of life outcomes among these patients include reports at 12 months of increased alertness among all seven patients. No change in mood or communication abilities is noted (Wilfong and Schultz 2006).

Ketogenic diet

There are three reports in the literature, (respectively 4 cases, and 2 case reports) describing the positive effects of the classical ketogenic diet on seizure frequency and behaviour in Rett syndrome (Haas et al. 1986, Liebhaber et al. 2003, Giampietro et al. 2006). As a result of this research, the consensus statement by the International Ketogenic Diet Study Group has listed Rett syndrome as a condition in which the ketogenic diet has been reported as “probably” particularly beneficial because of at least two publications describing excellent benefit with the ketogenic diet (Kossoff et al. 2009). Many children with Rett syndrome are fed with gastrostomy tubes, also making them good potential candidates for dietary therapy because they can be easily started on the ketogenic diet without compliance issues. At Johns Hopkins Hospital, Rett syndrome is one of the fastest growing subpopulations being treated with the ketogenic diet, especially if the patients have gastrostomy tubes.

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