Treating Epilepsy in Patients with Rett Syndrome - Options and Challenges

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Abstract

Rett syndrome is a frequent neurodevelopmental disorder that manifests in infancy with the regression of previously acquired motor and verbal skills. The specific brain areas are affected with the arrest of the neuronal growth and their connectivity.

The majority of patients has epilepsy in the early clinical stages of the disease which usually becomes less active in the adolescent age. Besides epilepsy other paroxysmal events are present in majority of Rett patients and may mimick epileptic seizures. Antiepileptic drug treatment is successful and the prevalence of drug resistant epilepsy is about equal to patients with other newly-diagnosed epilepsy. Valproate, carbamazepine and lamotrigine were the most frequently used and reported effective. The epilepsy usually becomes less active in the adolescence and the common guidelines for withdrawal of antiepileptic drugs could be implemented also in Rett patients.

Keywords: Rett Syndrome; Epilepsy; Treatment

Abbreviations

RTT: Rett Syndrome; MECP2: Methyl-CpG-Binding Protein 2 Gene; EEG: Electroencephalogram; TMS: Transcranial Magnetic Stimulation; CMCT: Central Motor Conduction Time; CMT: Cortical Motor Threshold; CSP: Cortical Silent Period; AED: Antiepileptic Drugs; US: United States of America

Highlights

- Clinical and EEG evolution of epilepsy in RTT.
- Mechanisms of epileptogenesis based on TMS studies.
- Epilepsy treatment options and outcomes.

Introduction

Rett syndrome (RTT) is a rare disorder according to its incidence but it is the second major cause of learning disability in girls following Down syndrome. It occurs in 1:10000 - 15000 girls worldwide [1,2]. The clinical course with the regression of acquired motor skills, loss
of purposeful activity and acquired spoken language suggest degenerative disorder but neuroanatomical findings confirmed that this is developmental brain disorder which affects selected brain areas in a critical period of its development. Hand stereotypies, gait abnormalities, loss of hand skills and spoken language are the necessary four main criteria to support the clinical diagnosis of the classical (typical) form of RTT. Supportive criteria are helpful to establish the variant (atypical) forms of RTT where at least two of four main criteria and a half of eleven accepted supportive criteria should be fulfilled. Possibility of secondary causes as brain trauma, neurometabolic disease or infection as well as grossly abnormal psychomotor development in first six months of life are exclusive for the clinical diagnosis [3]. The period of apparently normal early development is followed by the regression and some recovery or stabilization in its later course [4].

RTT was first described about 60 years ago and the methyl-CpG-binding protein 2 (MECP2) gene mutation, discovered in 1999, is associated with up to 95% of classical RTT patients [3,5]. The diagnosis of RTT still remains clinical because presence of the mutation alone is not sufficient to make the diagnosis of RTT, nor does its absence exclude it.

Epilepsy in RTT

Epilepsy is present in up to 80% of patients with the classical form of the disease. Seizures usually start in a period of deterioration, around 4 years of age [6]. The electroencephalogram (EEG) is usually normal in the early stage, but slowing of the background activity and epileptiform abnormalities occur later.

The EEG is typically normal or shows some slowing of occipital background activity in the awake state in the early clinical stage with apparently normal psychomotor development. Loss of non-REM sleep characteristics and focal spikes or sharp waves in sleep and then in the awake state are observed in the stage of clinical deterioration. Additional slowing of background activity, absence of non-REM sleep characteristics, multifocal epileptiform discharges, generalized slow spike-wave and rhythmic delta over the central regions during sleep and in the awake state are present in the stage of pseudo-stabilization. Marked slowing of the background activity with delta rhythms, multifocal epileptiform activity in the awake state and generalized slow spike-wave activity in sleep are frequent in the stage of late motor deterioration [7] (Figure 1 and 2).
**Figure 1**: EEG of 10y old Rett patient in a clinical stage II (clinical deterioration).

B: Monomorphic rhythmic theta activity over frontocentral regions in drowsiness.

C: Multifocal central spikes in sleep, no sleep structure.
A: Slow background activity, non reactive to eye-opening (and muscle artifacts).

B: Rhythmic theta activity over frontocentral regions in awake with eyes closed.
However, the EEG patterns are neither diagnostic nor pathognomonic of RTT, and correlation between clinical and EEG staging is not a constant finding, although frequently observed. EEG abnormalities also develop in RTT patients who do not have seizures.

Other paroxysmal events such as hand stereotypies, breathing abnormalities in awake state, laughing or screaming episodes, vacant spells with staring gaze and gait dyspraxia are frequent in RTT. They could easily be misinterpreted as epileptic seizures if evaluated only with the observation so video-EEG recording is helpful in establishing the diagnosis and it is mandatory in difficult to manage cases.

The mechanisms of epileptogenesis

The neuroanatomical findings of Rett brains disclosed that the frontal lobe, anterior temporal lobe and anterior caudate nucleus are selectively affected, with cortical thinning, immature small neurons and reduced dendritic branching with higher neuronal density [8,9].

A higher prevalence of epilepsy associated with certain mutation types was reported in some studies but there were no correlation between genotype and phenotype in the others. The information on genotype is generally not used for the prediction of epilepsy severity or the clinical course in a given patient [10].

C: Sharp and slow activity over frontocentral leads, no sleep structure.

**Figure 2**: EEG of 18y old Rett patient in a clinical stage III (pseudo-stabilization).
The mechanism of increased epileptic activity in RTT is not well understood. The transcranial magnetic stimulation (TMS) is increasingly used in pediatric population as the non-invasive neurophysiological method to study motor pathway. It has been used to study motor pathway maturation and to demonstrate neurophysiological abnormalities in neurological disorders, especially those that influence the integrity of the corticospinal tract and cortical excitability [11,12]. It has been used in RTT patients in early 90s when the method was introduced in the paediatric clinical practice according to the fact that the motor areas are selectively affected in RTT. The following parameters are usually measured in the clinical setting: central motor conduction time (CMCT), cortical motor threshold (CMT) and cortical silent period (CSP).

CMCT reflects central conduction and is obtained by subtracting the peripheral nerve component from the total latency obtained by TMS. CMT reflects the excitability of the corticospinal projection. CSP is a measure of motor cortical inhibition [13].

Short CMCT has been repeatedly reported in early TMS studies performed in RTT as a unique change not observed in any other neurological disorder so far [14-18]. The shorter CMCT was attributed to hyperexcitability of cortical neurons and/or spinal motor neurons, but was not studied further in those studies. There were no data on epilepsy and antiepileptic drug (AED) treatment which could influence the measurements in the studied patients (Table 1).

In a recent TMS study motor cortex excitatory and inhibitory function were systematically evaluated besides measuring CMCT. CMCT was shorter as already reported previously but elevated CMT and shorter CSP were also found, which suggests decreased both, excitatory and inhibitory motor cortical function. The outcome was independent of AED or epilepsy activity and was attributed to the pathogenic mechanism itself [19].

Moreover, the cortical drive could be important in the disordered breathing patterns leading to severe respiratory dysrhythmia in awake in RTT patients which is difficult to treat. This was not systematically studied so far but a single reported clinical case study suggests the possible pharmacological treatment with topiramate which is primarily used in epilepsy treatment in children and in adults [20].

### Table 1: TMS findings in Rett patients.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number</th>
<th>CMCT</th>
<th>CMT</th>
<th>CSP</th>
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<tr>
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<td>3</td>
<td>↓</td>
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<tr>
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<td>↓</td>
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<tr>
<td>Krajnc N, 2016</td>
<td>17</td>
<td>↓</td>
<td>↑</td>
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</table>

Legend: TMS: Transcranial Magnetic Stimulation; CMCT: Central Motor Conduction Time; CMT: Cortical Motor Threshold; CSP: Cortical silent period; AED: Antiepileptic Drugs; -: Not known; +: Known; ↓: Shortened; ↑: Elevated.

In a recent TMS study motor cortex excitatory and inhibitory function were systematically evaluated besides measuring CMCT.

Antiepileptic drug treatment

All seizure types, except for typical absences and clonic seizures were reported in RTT but partial complex, followed by tonic-clonic, tonic and myoclonic were most commonly reported [21]. There are no specific triggering factors reported to contribute to seizures.

Treating Epilepsy in Patients with Rett Syndrome - Options and Challenges

The pharmacological treatment is the main option of the epilepsy treatment in RTT. The treatment of patients having only EEG abnormalities without clearly documented seizures does not seem to be justified. Valproate, carbamazepine and lamotrigine were the most frequently used and reported effective in the European and Australian series but valproate was only rarely used in the US study. The effectiveness of newer AED such as levetiracetam and topiramate was reported only in a small number of patients [10].

It seems that the prevalence of drug resistant epilepsy in RTT is about equal to patients with other newly-diagnosed epilepsy, where 20-40% become refractory to treatment. Other treatment options such as ketogenic diet or vagal nerve stimulation have been used in some refractory RTT cases but there is no report of epilepsy surgery in this syndrome [10]. The long-term video-EEG analysis is recommended in difficult-to-treat patients to differentiate epilepsy from other paroxysmal events and to avoid polytherapy.

The epilepsy usually becomes less active in the adolescence and the common guidelines for withdrawal of AED could be implemented also in RTT [22]. There is no reports on relapse risk rate after AED discontinuation.

Conclusion

Epilepsy in RTT usually starts in a period of clinical deterioration, around 4 years of age and is less active in the later clinical course, usually around adolescence.

The mechanism of increased epileptic activity in RTT is not well understood. EEG abnormalities also develop in some patients who do not have seizures.

Other paroxysmal events such as hand stereotypies, breathing abnormalities in awake state, laughing or screaming episodes, vacant spells with staring gaze and gait dyspraxia are frequent in RTT. They could easily be misinterpreted as epileptic seizures if not carefully evaluated.

Recent TMS study suggests decreased both, excitatory and inhibitory motor cortical function which could be a common mechanism also in evolution of other paroxysmal events as in severe respiratory dysrhythmia.

The pharmacological treatment of epilepsy is the main treatment option in RTT and the prevalence of drug resistant epilepsy is about equal to patients with other newly-diagnosed epilepsy. The decision to stop the AED medication could be implemented, usually in the latter clinical course of the disease.

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Bibliography


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