Effectiveness and tolerability of antiepileptic drugs in 104 girls with Rett syndrome

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A B S T R A C T

Approximately 60–80% of girls with Rett Syndrome (RTT) have epilepsy, which represents one of the most severe problems clinicians have to deal with, especially when patients are 7–12 years old. The aim of this study was to analyze the antiepileptic drugs (AEDs) prescribed in RTT, and to assess their effectiveness and tolerability in different age groups from early infancy to adulthood.

We included in this study 104 girls, aged 2–42 years (mean age 13.9 years): 89 had a mutation in MECP2, 5 in CDKL5, 2 in FOXG1, and the mutational status was unknown in the remaining 8. Epilepsy was present in 82 patients (79%). Mean age at epilepsy onset was 4.1 years.

We divided the girls into 5 groups according to age: <5, 5–9, 10–14, 15–19, 20 years and older.

Valproic acid (VPA) was the most prescribed single therapy in young patients (<15 years), whereas carbamazepine (CBZ) was preferred by clinicians in older patients. The most frequently adopted AED combination in the patients younger than 10 years and older than 15 was VPA and lamotrigine (LTG).

Seizures in the group aged 10–14 years were the most difficult to treat, requiring a mean of three different AEDs, often used in combination and mostly including VPA. Seizures in fifteen patients (18%) were considered drug-resistant. VPA was reported as the most effective AED in younger girls (in 40% of the patients aged <5 years, in 19% of the girls aged 5–9 years), and CBZ the most effective in the patients 15 years or older. Adverse reactions did not differ from expected: agitation, drowsiness, and weight loss were the most frequently reported. In our sample, LTG was the least tolerated AED. We did not find correlations with MECP2 mutations in terms of effectiveness or adverse reactions.

Conclusion: in this study we observed different effectiveness of AEDs based on age, and suggest that clinicians consider age-dependency when prescribing appropriate AEDs in the RTT population.

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1. Introduction

Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder mostly affecting females, caused by mutations in the MECP2 (methyl-CpG binding protein 2) gene (classic form). Prevalence is approximately 1:10,000 girls [1,2]. The classic form is characterized by normal development in the first months of life, followed by regression of acquired motor and language skills, appearance of hand stereotypes, and epilepsy. MECP2 mutations are identified in up to 95% of patients with the classic form. Non-classic forms include the preserved-speech (Zappella) variant, the early-seizure (Hanefeld) variant (frequently associated with CDKL5-cyclin-dependent kinase-like 5-mutations), and the congenital (Rolando) variant (often caused by FOXG1-fork-head box protein G1-mutations) [3,4].

Epilepsy is one of the main symptoms in RTT, affecting 60–80% of girls, with onset between 2 and 5 years of age in most patients (mean 4 years) and evidence of age-dependency. Seizure frequency is higher between 7 and 12 years, and decreases in severity in late adolescence [4,5]. The presence of seizures is associated with worse clinical outcome regarding hand use, ambulation, and communication [6].

All seizure types have been reported except for typical absences and clonic seizures. The most frequently reported were focal seizures, followed by generalized tonic-clonic, tonic, and myoclonic [4,7].

Genotype-phenotype correlations are still controversial, even though some mutations are associated with a higher prevalence of epilepsy or severity of seizures [8].

Seizures are drug-resistant in approximately 30% of cases, and polytherapy with three or more anti-epileptic drugs (AEDs) is necessary in 18% of the patients [4,8].

Only a few studies report on effectiveness of AEDs in these patients, and no definite recommendations are currently available. Small series with limited numbers of patients have been described, reporting that...
the most frequently used AEDs were valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), and carbamazepine (CBZ) [9]. Tolerability represents another open issue, with few reports available. Adverse events seem to be similar to the ones observed in the general population [4].

Even though the age-dependency of effectiveness and tolerability profile of AEDs seems evident in clinical practice, this aspect has not been investigated in patients with RTT thus far.

In this study, we analyzed the AEDs prescribed, the effectiveness of treatment, and the adverse reactions in five age groups of RTT girls from early infancy to adulthood.

2. Methods

This retrospective study was carried out at the Epilepsy Center of the San Paolo Hospital, University of Milan (Italy). Data were obtained from a dedicated database of RTT patients, meeting the diagnostic criteria proposed by Neul in 2010 [3]. The institutional review board of San Paolo Hospital, Milan, approved the study.

We collected data on genetic tests performed, mutations revealed, motor skills, and clinical problems. Epilepsy characteristics (presence, age of onset, seizure type, frequency, and EEG abnormalities) and pharmacologic treatment (monotherapy, combination of treatment, effectiveness, adverse events) were reviewed.

We classified epileptic seizures according to the 2010 International Classification of Seizures, proposed by ILAE in 2010 [10]. As proposed by ILAE, we considered drug resistance as the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (either as monotherapies or in combination) to achieve sustained seizure freedom [11].

Effectiveness was determined considering clinical data and caregivers’ reports for a minimum follow-up period of one year [11].

We decided to evaluate antiepileptic treatment in different age groups: <5 years (Group 1), 5–9 years (Group 2), 10–14 years (Group 3), 15–19 years (Group 4), 20 years and older (Group 5).

We divided MECP2 mutations into three groups based on type and localization on the gene: early truncating (within the Nuclear Localization Signal–NLS-domain), late truncating (after the NLS domain), and missense. Based on this classification, we attempted correlations between genotype and AED treatment. We did not consider mutations in CDKL5 and FOXG1, since only seven patients had changes in these genes in our cohort.

3. Statistical analysis

All collected data were transferred into an electronic database and processed using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, U.S.A.) for Macintosh version 22.0. Based on the aforementioned MECP2 classification, we compared patients with and without epilepsy with the non-parametric test χ2. Results were considered statistically significant for p-values < 0.05 (two-sided).

4. Results

We included in this study 104 female patients aged 2–42 years (mean age 13.9 years).

Results of genetic tests were available in 100 patients: 89 girls had a mutation in MECP2, 5 in CDKL5, 2 in FOXG1, and in 4 patients no mutations were identified. Data about genetic analyses were not available in four patients.

83 girls presented classic form of RTT, 6 were classified as Preserved Speech Variant, 5 as early seizure variant, and 2 as congenital variant.

Mean age at RTT diagnosis was 5.95 years. Regression was reported in 76% (80) of the patients; mean age at regression was 16.1 months.

4.1. Epilepsy

Epilepsy was present in 79% (82 pts), with mean age at onset of 4.1 years (7 days–14 years).

Seizures were classified as focal in 47.6% (39) of the patients, generalized tonic-clonic in 18.3% (15), tonic in 15.8% (13), spasms in 5% (4), atonic in 4% (3), atypical absences in 2% (2), and myoclonic seizures in 2% (2).

EEG recordings showed bilateral fronto-centro-temporal abnormalities in 52%, focal abnormalities in 19%, and multifocal spikes in 13%. Slow diffuse rhythms were identified in 5% of the girls, generalized abnormalities in 3% of the patients, and in 7% EEG resulted normal for age.

Data about antiepileptic treatment in each of the five age groups are summarized in Tables 1 and 2.

With respect to MECP2 mutations, 39% of the patients (35) showed Early Truncating changes, 19% (17) had Late Truncating mutations, and 36% (32) carried missense mutations. Mutations were not
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