Antiepileptic drugs in Rett Syndrome


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Antiepileptic drugs in Rett Syndrome

Maria Pintaudi a,*, Maria Grazia Calevo b, Aglaia Vignoli c, Maria Giuseppina Baglietto a,d, Yussef Hayek e, Maria Traverso a,d, Thea Giacomini a,d, Lucio Giordano f, Alessandra Renieri g,h, Silvia Russo i, MariaPaola Canevini c, Edvige Veneselli a,d

a University of Genoa, DINOGMI, Italy
b Epidemiology and Biostatistics Unit, Istituto Giannina Gaslini, Genoa, Italy
c Department of Health Science, Epilepsy Centre, St. Paolo Hospital, University of Milan, Italy
d Department of Child Neuropsychiatry, Epilepsy Centre, Giannina Gaslini Institute, Italy
e Pediatric Neuropsychiatric Unit, University Hospital, Policlinico Le Scotte, Siena, Italy
f Pediatric Neuropsychiatric Division, City Hospital of Brescia, Brescia, Italy
h Medical Genetics, University of Siena, Siena, Italy
i Department of Genetics, Istituto Auxologico Italiano, IRCCS, Milan, Italy

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ABSTRACT

Purpose: We investigated drugs most often used to treat epilepsy in Rett Syndrome and their efficacy in a large cohort of Italian patients.

Methods: This is a multi-centre retrospective study. Data of 165 Rett subjects were collected from the patients’ files, and hospital charts. The efficacy of antiepileptic drugs (AEDs) was classified as follows: not effective; decrease in seizure frequency ≥50% for at least 6 months; seizure-free for at least 2 years. Phenotypic and genetic categorization of patients was performed and it was considered in AEDs efficacy evaluation.

Results: There were 130 epileptic patients. Sodium valproate (VPA) was the most commonly administered AED (44.3%) at seizure onset, followed by Carbamazepine (CBZ) (25.4%) and Phenobarbital (PB) (13%). Monotherapy was the first treatment option in most patients. VPA and CBZ proved to be equally effective in Rett patients who presented seizures within the typical age range (4–5 years), while Lamotrigine (LTG) was effective for patients in whom epilepsy started later. Overall, the frequency of side effects was low and the most often observed ones were restlessness and somnolence.

Conclusion: Our study suggests that LTG, VPA and CBZ can be used as drugs of first choice in Rett Syndrome. The association of four drugs should be avoided since it did not result in any significant clinical improvement.

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* Corresponding author. University of Genoa, DINOGMI, Department of Child Neuropsychiatry, Istituto Giannina Gaslini, Largo Gaslini, 5, 16147 Genoa, Italy. Tel.: +39 010 56362432, +39 3292181228 (mobile); fax: +39 010 381303.
E-mail address: mariapintaudi@hotmail.com (M. Pintaudi).
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1. Introduction

Rett Syndrome (RTT) is a rare, severe, X-linked neurodevelopmental disease that affects approximately 1/10,000–15,000 live female births.\(^2\) Classical and atypical forms are well-known, and diagnostic criteria have recently been revised.\(^2\)

In 1999, studies showed that mutations of the MeCP2 gene, encoding methyl-CpG-binding protein 2 and lying on the X chromosome were correlated with RTT and accounted for approximately 80% of cases.\(^3,4\)

Other genes were later found to be involved: CDKL5 gene mutations were found in patients with early seizure onset variant\(^5\) and the FOXG1 gene mutation was associated with the congenital variant.\(^6\)

Although epilepsy affects approximately 80% of Rett patients,\(^7,8\) there are no randomized clinical trials (RCTs) investigating the efficacy of antiepileptic drugs (AEDs) in RTT. This reflects how difficult it is to carry out well-designed, properly conducted RCTs on epileptic drugs.\(^8\) In particular, due to the rarity of the disease, the variability of phenotypes and genetic heterogeneity of RTT, it is not easy to collect homogeneous and large enough cohorts.

Moreover, the efficacy of epilepsy treatment in Rett patients is difficult to evaluate due to the wide variability in seizure type and drug-responsiveness among subjects and even in the same patient.\(^8,20-12\)

These are likely the reasons why there are so few studies that compare the efficacy of the AEDs that are used in RTT.\(^13-14\)

The choice of the antiepileptic drug is influenced by the type of seizures, the non–epilepsy-related clinical symptomsatology (appetite, sleep quality, tone, irritability, respiratory problems, and so on), and the epileptologist’s experience.\(^51\)

Thus, several different AEDs have been used to treat epilepsy in RTT in the various studies.\(^15,16\)

Moreover, the criteria that are used to evaluate efficacy are not homogeneous. Most studies consider a drug to be effective both when it leads to a decrease in seizure frequency >50% and when it leads to a seizure-free condition, but there is no agreement about the duration of these effects.

In this work we investigated the drugs that are most often used to treat epilepsy and we evaluated their efficacy in a large cohort of Italian patients.

2. Methods

This is a multi-centre, retrospective study that was carried out at the Giannina Gaslini Children’s Hospital, Genoa, Italy. Patients included in the study were evaluated in order to have a diagnosis of Rett Syndrome according to the new diagnostic revised criteria defined in 2010.\(^7\) Molecular analysis of the MECP2 gene was carried out and in negative cases, it was done for the CDKL5 and FOXG1 gene. Furthermore, all patients underwent video/EEG monitoring. On the basis of these criteria, the data concerning 165 subjects were collected from a cohort of patients referred to four Italian Child Neuropsychiatry departments: G. Gaslini Institute, University of Genoa; St. Paolo Hospital, University of Milan; University Hospital, Siena; Spedali Civili, Brescia.

A questionnaire was made up in order to obtain longitudinal data including clinical information on seizures, EEG findings, and treatment. It was filled in by a researcher who collected data from the patients’ files, hospital charts and from the physician in charge of the patients. Phenotypes were categorized as follows: classic, congenital, formes frustes (FF),\(^17,18\) preserved speech variant (PSV),\(^19\) and early-onset seizure type (Hanefeld variant).\(^20\) The genotypes of subjects with a previously identified MECP2 mutation were categorized as follow: late truncating C-terminal deletions, and large gene deletions, were grouped together in two different groups; the other following mutations were analysed separately: T158M, R255X, R270X, R306C, R168X, R294X, R133C, R106W, and P152R mutations.\(^8\)

We evaluated the drugs that were administered at seizure onset and at follow-up. Drugs administered at follow up included the AEDs that were given when the first drug was not effective enough.

AEDs were given according to the physician’s clinical evaluation taking into consideration the semiology and frequency of seizures as well as video-EEG findings. The dosage was determined on the basis of the patient’s weight according to the drug’s chart. AED serum level analyses were performed in order to verify the patient’s compliance.

We assigned the following scores to evaluate the efficacy of AEDs: 0: not effective; 1: decrease in seizure frequency ≥50% for at least 6 months; 2: seizure-free for at least 2 years.

Seizures were classified according to the International classification of Seizures.\(^21\) We considered seizure semiology at epilepsy onset and at last follow-up, as described in a previous paper.\(^8\)

Drug-resistant epilepsy was defined as the failure of two appropriate AEDs, the occurrence of an average of one or more seizures per month for ≥18 months, and no more than a 3-month seizure-free period during those 18 months.\(^22\)

3. Statistical analysis

Data are described as mean and standard deviation (SD) or median and range for continuous variables, and as absolute and relative frequencies for categorical variables.

Non parametric analysis (Mann–Whitney U-test) for continuous variables and the Chi square or Fisher’s exact test for categorical variables were used to measure differences between groups.

P values ≤ 0.05 were considered statistically significant, and all P values were based on two tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois USA).

4. Results

We collected data concerning 165 patients. The clinical and genetic features of these subjects are described in a previous article\(^7\) and are summarized in Table 1. The median age at last follow up was 14 years, ranging from 2 to 40 years.
Among our cohort, 130 (78.8%) subjects had a history of epilepsy. They were subdivided into two groups: patients with drug-responsive epileptic seizures (n = 81, 62.3%), and patients with drug-resistant epileptic seizures (n = 49, 37.7%) (Table 1). There were no significant differences between the groups with respect to age at last follow-up, thus the differences in presence of epilepsy and drug-responsiveness were comparable.

Data concerning the first administered drug were known for 118 patients. Eight different AEDs were used to treat epilepsy at onset: sodium valproate (VPA), carbamazepine (CBZ), phenobarbital (PB), lamotrigine (LTG), clobazam (CLB), vigabatrin (VGB), oxcarbazepine (OXC) and topiramate (TPM).

With regard to drugs used at seizure onset, monotherapy was the first treatment in all cases: VPA (44.9%) was found to be the most commonly used first AED, followed by CBZ (25.4%), PB (13.6%) and LTG (10.2%). Other drugs were given in 5.9% of patients and included CLB, VGB, OXC and TPM (Table 2). In particular, patients with classic forms (N = 104) and preserved speech variant (N = 8) had the highest incidence of drug resistance.

<table>
<thead>
<tr>
<th>AED</th>
<th>Seizure free for at least 2 years</th>
<th>More than 50% reduction in seizure frequency</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>8 (27)</td>
<td>18 (60)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>LTG</td>
<td>7 (58.3)</td>
<td>4 (33.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>PB</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>VPA</td>
<td>13 (24.5)</td>
<td>23 (43.4)</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>Other (VGB/OXC/TMP/CLB)</td>
<td>3 (43)</td>
<td>2 (28.5)</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (28)</td>
<td>49 (41.5)</td>
<td>36 (30.5)</td>
</tr>
</tbody>
</table>

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received VPA (45.2%), CBZ (27.9%), LTG (11.5%), PB (10.6%) and other drugs (4.8%); patients with PSV (N = 6) took VPA (83.3%) and CBZ (16.7%); patients with Hanefeld variant (N = 6) were given PB (66.7%), VPA (16.7%) and VGB (16.7%), while the one subject with forma frusta received PB and the patient with the congenital form was given CLB.

Overall, the first AED had a positive effect on epilepsy in 69.5% (N = 82) of RTT patients: no seizures occurred in 33 (28%) subjects for the following two years, and a more than 50% decrease in seizure frequency was observed in 49 (41.5%) subjects (Table 2). In particular, VPA was used in 53 patients and resulted in a decrease in seizure frequency of at least 50% in 23 subjects (43.4%) and in a two year seizure-free condition in 13 (24.5%) others. Of the thirty patients who received CBZ, 18 (60%) showed a decrease in seizure frequency ≥50%, while seizures disappeared in 8 (27%). PB was given in 16 cases, leading to an overall positive effect (scores 1 and 2) in only 4 subjects (25%). LTG was used in 12 patients and led to a decrease in seizure frequency ≥50% in 4 (33.3%) subjects and to a two year seizure-free condition in 7 (58.3%) (Table 2). LTG was observed to be the most effective AED among these girls respected to PB (p = 0.002). No difference was observed between VPA and CBZ efficacy. Significative differences in efficacy were found even when comparing VPA vs PB (p = 0.006) and CBZ vs PB (p = 0.001).

In order to analyse a homogeneous population, we evaluated the patients with classic form separately since Hanefeld forms are often drug resistant, and PSVs are often drug responsive. The efficacy of AEDs was found for 104 subjects in this group (Table 3). LTG was found to be the most effective AED among these girls: 58.3% of subjects were seizure-free at 2 years and 33.3% showed a reduction in seizure frequency. PB again proved to be less effective, and in fact it had no effect in 63.6% of cases and in 18.2% of its effects it led to a decrease in seizure frequency ≥50% (LTG vs PB p = 0.02). A significant difference in drug efficacy was found even when comparing CBZ vs PB (86.2% vs 36.4% p = 0.004). VPA proved to be more efficacious (scores 1 and 2) than PB (66% vs 36.4%; it did not reach statistical significance) but less efficacious than LTG (66% vs 91.7%; p = 0.05).

In order to evaluate whether PB is actually not effective, we then focused on classic drug-responsive patients. We observed that PB was given to three subjects and only one responded to therapy (scores 1 and 2), unlike the 100% (N = 10) response rate (RR) observed in subjects treated with LTG, the 90% RR (N = 18) in subjects treated with CBZ (N = 20), and the 77.4% (N = 24) RR in subjects treated with VPA (N = 31). Due to the small number of patients, we were not able to perform statistical analysis.

With regards to genotype, as previously described, CDKL5 mutations resulted associated with drug-resistant epilepsy in most cases (80%). Specifically, in terms of first administered drug, four CDKL5 patients took PB and no effect (score 0) was observed. One patient was administered VPA that resulted in a decrease of seizures frequency. The patient with FOXG1 mutation took CLB that lead to a disappearance of seizures.

Since the little number of patients with other mutations than MeCP2 (5 subjects with CDKL5 mutation and 1 with FOXG1), we could not perform any statistical analysis regarding correlation between genotype (MECP2, CDKL5, FOXG1) and AEDs efficacy.

Considering patients with MECP2 mutation, no differences in frequency and efficacy of first administered drug were found among various groups of mutation.

Mean age at seizure onset in patients who received CBZ, VPA and PB was similar (4.6 ± 2.2, 3.7 ± 1.9, 4 ± 2.4 yrs, respectively), while it was 9.4 ± 6.5 yrs for patients who were administered LTG.

Seizure semiology is described elsewhere. Data concerning drug efficacy as related to seizure semiology were known for 104 patients. No difference in AED efficacy was found both for partial seizures (N = 51) and generalized seizures (N = 52).

Several different drugs were given at follow up: VPA, CBZ, PB, LTG, CLB, VGB, OXC and TPM were administered, as was clonazepam (CZP), ethosuximide (ESM), levetiracetam (LEV), nitrazepam (NZP), phenytoin (PHT), zonisamide (ZNS), Adrenocorticotropic hormone (ACTH), Ketogenic diet (KD), primidone (PRM), hydrocortisone. They were combined in 75 different drug associations.

Evaluation of efficacy at follow-up only included drugs that had been administered frequently enough to perform statistical analysis i.e., CBZ (n = 18), CBZ and LTG (n = 19), CBZ and PB (n = 12), CBZ and VPA (n = 12), VPA (n = 14), VPA and LTG (n = 13).

No statistically significant differences in efficacy were found among these associations, however VPA and LTG proved to be the most effective association and led to a decrease in seizure frequency of at least 50% in 11 (85%) subjects and to a two year seizure-free period in 2 (15%) subjects.

Considering drugs at onset and at follow-up, most drug-responsive patients responded to monotherapy (69%) and to the association of two drugs (27%), while a small percentage (4%) required a third drug and none a fourth AED.

<table>
<thead>
<tr>
<th>AED</th>
<th>First Drug’s efficacy score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizure free for at least 2 years</td>
<td>More than 50% reduction in seizure frequency</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>CBZ</td>
<td>7 (24.1)</td>
<td>18 (62.1)</td>
</tr>
<tr>
<td>LTG</td>
<td>7 (58.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>PB</td>
<td>2 (18.2)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>VPA</td>
<td>11 (23.4)</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td>Other (VGB/OXC/CLB)</td>
<td>2 (40)</td>
<td>2 (40)</td>
</tr>
<tr>
<td></td>
<td>29 (27.9)</td>
<td>46 (44.2)</td>
</tr>
</tbody>
</table>
The poor effectiveness of PB is a particular finding of our study since there is no evidence in the literature of a difference in antiepileptic efficacy between PB and any other AED it has been compared to. Moreover, PB is described as an effective drug in partial onset seizures in adults and children, similarly to CBZ, PHT and VPA.

PB is one of the barbiturate drugs that depress neuronal excitability by enhancing the c-aminobutyric acid receptor-mediated chloride current. A possible, though not exhaustive, explanation for our results could be that the dendritesynaptogenic developmental failure, which is one of the physiopathogenetic mechanisms believed to be involved in RTT Syndrome, leads to a decrease in GABA receptor activity.

Nonetheless, this does not explain the significant difference in efficacy between PB and the other drugs, such as VPA, that, albeit indirectly, act on the GABA.

In the literature, VPA has been reported as one of the most often used and effective drugs in all clinical studies but one, with regard to both seizure control and interictal epileptiform activity reduction. Several studies have shown that CBZ is very effective despite the possible worsening of generalized spike and wave discharges.

Lamotrigine has been reported as being effective in some studies, with a positive effect on alertness and concentration. Nevertheless, one paper reports a less favourable effect.

Huppke et al. described sulthiame as being very effective in RTT, nevertheless, it was not administered to any of our patients since it is not available in Italy. Other drugs that are reportedly effective in RTT are TPM and LEV. Some small studies suggest that treatments such as ketogenic diet and vagus nerve stimulation may be beneficial, but no clinical data are available on RTT, and in our cases they were not given frequently enough to allow us to compare them to other AEDs.

There are currently few data available in the literature with regard to the efficacy of the association of AEDs in Rett Syndrome.

Seventy-five different drug associations were given to our cohort at follow up. The most frequently used ones were: CBZ and LTG, CBZ and FB, CBZ and VPA, VPA and LTG. No statistically significant differences in efficacy were found among these associations but we observed that VPA and LTG were the most effective ones.

Old drugs were still frequently used among our patients. Differences in efficacy between old and new drugs could not be evaluated since many of the drug associations included both old and new AEDs at the same time.

In most cases, drug-responsive patients responded to the first used drugs and only few subjects required a third drug. The association of four drugs did not improve epileptic outcome.

Overall, the frequency of reported side effects was low. The most frequently observed ones were restlessness and somnolence. This is in agreement with Huppke’s finding and with the data that the spectrum and rate of side effects of AEDs in RTT is comparable to what is seen in other patients with epilepsy.

The strength of this study is the large cohort of patients all coming from facilities that are specialized in RTT and

A 3-drug association was often used in drug-resistant patients and it never led to the disappearance of seizures, but it may have led to a decrease in seizure frequency of at least 50%, while the association of four drugs never improved efficacy.

Physicians reported epileptic status in 11 cases but no additional data regarding semiology and treatment were available. Side effects were reported in 39 (28%) epileptic patients and the most frequently observed ones were restlessness and somnolence. It is not possible to compare the incidence of side effects among drugs since most patients were on poly-therapy when side effects occurred. The effect on EEG was not evaluated. Although all patients underwent video-EEG monitoring, seizures were recorded in subjects with daily or weekly attacks.

### 5. Discussion

In this work we evaluated the drugs that are most often used to treat epilepsy in RTT and their efficacy in a large cohort of patients.

VPA proved to be the most commonly used first AED, followed by CBZ and PB, and monotherapy was the first treatment administered to all patients.

The large number of patients allowed us to compare the efficacy of the most commonly used drugs at seizure onset: LTG proved to be an effective drug for RTT patients, followed by CBZ and VPA both of which resulted equally effective. Nevertheless, we have to consider that among our patients, LTG was most frequently given to those in whom epilepsy started later, i.e., after the typical age (4–5 years). This choice was most likely due to the fact that in Italy, LTG is authorized for use in patients over 12 years of age, and we previously reported that later onset of seizures is more often related to a milder form of epilepsy.

PB was found to be the least effective first administered drug among patients with different phenotype and genotype.

The widespread use of PB is a peculiarity of our Italian cases and may reflect the tendency to use more traditional drugs. This differs from the Australian custom of giving “new” AEDs to children with more severe forms of epilepsy and from other authors.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>N’ cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>11</td>
</tr>
<tr>
<td>Decrease in appetite</td>
<td>3</td>
</tr>
<tr>
<td>Restlessness</td>
<td>10</td>
</tr>
<tr>
<td>Hand tremor</td>
<td>1</td>
</tr>
<tr>
<td>Hair loss</td>
<td>2</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>1</td>
</tr>
<tr>
<td>Weight increase</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperammonemia</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
</tr>
</tbody>
</table>
epilepsy, thus with a great deal of experience in the use of AEDs and the possibility to carry out drug dosage measurement in the blood and video-EEG monitoring. Moreover, the clinicians involved in the study are experts in the clinical characterization and classification of Rett patients. Thus, the wide number of patients and the evaluation of AEDs administration and efficacy considering patient’s phenotype and genotype represent a peculiarity of our study. The limits of this work are the retrospective nature and the heterogeneity of drug associations that were used at follow-up.

Therefore, in conclusion, our study suggests that LTG, VPA and CBZ can be used as drugs of first choice in Rett Syndrome. LTG is particularly effective for patients in whom epilepsy starts later than typical age (4–5 years). The association of VPA and LTG could be considered a good option if patients do not respond to the above mentioned AEDs. PB should not be included among the drugs of first choice for patients do not respond to the above mentioned AEDs. PB administration and efficacy considering patient’s phenotype and genotype represent a peculiarity of our study. The limits of this work are the retrospective nature and the heterogeneity of drug associations that were used at follow-up.

Acknowledgements


Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2015.02.007.

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