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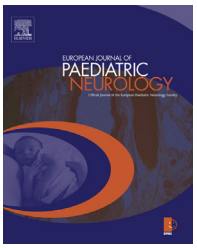

Original article

Antiepileptic drugs in Rett Syndrome

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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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1. Introduction

Rett Syndrome (RTT) is a rare, severe, X-linked neurodevelopmental disease that affects approximately 1/10,000–15,000 live female births.[1] 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.[9] 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.[8,10–12]

These are likely the reasons why there are so few studies that compare the efficacy of the AEDs that are used in RTT.[12–14]

The choice of the antiepileptic drug is influenced by the type of seizures, the non–epilepsy-related clinical symptomatology (appetite, sleep quality, tone, irritability, respiratory problems, and so on), and the epileptologist's experience.[11] 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.[2] 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 $\geq$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 $\geq$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 $\leq$ 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[8] and are summarized in Table 1. The median age at last follow up was 14 years, ranging from 2 to 40 years.

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Table 1 – Characteristics of patients with Rett Syndrome. All data are available in (8).

Patients' characteristics	All	No epilepsy	Drug responsive epilepsy	Drug resistant epilepsy - DRE -
	N (%)	N (%)	N (%)	N (%)
N	165	35 (21.2)	81 (49.1)	49 (29.7)
Phenotype				
Classic forms	140 (84.8)	25 (18)	73 (52)	42 (30)
Preserved speech variant	15 (9.1)	8 (53.3)	5 (33.3)	2 (13.3)
Formes frustes	3 (1.8)	2 (67)	1 (33)	–
Hanefeld variant	6 (3.6)	–	1 (17)	5 (83)
Congenital variant	1 (0.6)	–	1 (100)	–
Genotype				
MeCP2 +	147 (89.1)	30 (20.4)	75 (51)	42 (28.6)
CDKL5 +	5 (3)	–	1 (20)	4 (80)
FOXG1 +	1 (0.6)	–	1 (100)	–
Negative at genetic investigations	12 (7.3)	5 (41.7)	4 (33.3)	3 (25)
Mecp2 mutations				
Late truncating C terminal deletions	29 (19.7)	10 (34.5)	17 (58.6)	2 (6.9)
Large deletions	10 (6.8)	1 (10)	7 (70)	2 (20)
T158M	17 (11.6)	3 (17.6)	6 (35.3)	8 (47.1)
R255X	16 (10.9)	2 (12.5)	7 (43.8)	7 (43.8)
R270X	14 (9.5)	3 (21.4)	8 (57.1)	3 (21.4)
R306C	14 (9.5)	2 (14.3)	8 (57.1)	4 (28.6)
R168X	10 (6.8)	2 (20)	4 (40)	4 (40)
R294X	9 (6.1)	1 (11)	4 (44.5)	4 (44.5)
R133C	6 (4.1)	2 (33.3)	3 (50)	1 (16.7)
R106W	6 (4.1)	–	3 (50)	3 (50)
P152R	5 (3.4)	1 (20)	3 (60)	1 (20)
Others[a]	11 (7.5)	3 (27)	5 (46)	3 (27)
Age at epilepsy onset				
Mean ± SD	4.7 ± 3.7	–	5.3 ± 4.2	3.6 ± 2.5
Median (range)	4 (0.1; 21)		4 (0.1; 21)	3.2 (0.1; 12)
Age at last follow-up				
Mean ± SD	14.9 ± 8.5	13.7 ± 10.4	15 ± 7.9	16 ± 8.2
Median (range)	14 (2; 40)	14 (3; 37)	14 (2; 37)	15 (3; 40)

[a] Others include one patient for each of the following mutations: E14fs, P251fs, P302L, Q297X R111G, R306H, R453X, T322A, L124F, Y141X, D156E.

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)

Table 2 – Efficacy of first AEDs in Rett patients.

AED	First Drug's efficacy score			Total
	Seizure free for at least 2 years	More than 50% reduction in seizure frequency	No effect	
	N (%)	N (%)	N (%)	N (%)
CBZ	8 (27)	18 (60)	4 (13.3)	30 (25.4)
LTG	7 (58.3)	4 (33.3)	1 (8.3)	12 (10.2)
PB	2 (12.5)	2 (12.5)	12 (75)	16 (13.6)
VPA	13 (24.5)	23 (43.4)	17 (32.1)	53 (44.9)
Other (VGB/OXC/TMP/CLB)	3 (43)	2 (28.5)	2 (28.5)	7 (5.9)
Total	33 (28)	49 (41.5)	36 (30.5)	118 (100)

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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[8,10,20,23] and PSVs are often drug responsive.[8,10,19] The efficacy of AEDs was known 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 cases 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,[8] 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 (4.8 ± 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.[8] Data concerning drug efficacy as related to seizure semiology were known for 103 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 3 – Efficacy of first AEDs in Rett patients with classic form.

AED	First Drug's efficacy score			Total
	Seizure free for at least 2 years	More than 50% reduction in seizure frequency	No effect	
	N (%)	N (%)	N (%)	N (%)
CBZ	7 (24.1)	18 (62.1)	4 (13.8)	29 (27.9)
LTG	7 (58.3)	4 (33.3)	1 (8.3)	12 (11.5)
PB	2 (18.2)	2 (18.2)	7 (63.6)	11 (10.6)
VPA	11 (23.4)	20 (42.6)	16 (34)	47 (45.2)
Other (VGB/OXC/TMP/CLB)	2 (40)	2 (40)	1 (20)	5 (4.8)
	29 (27.9)	46 (44.2)	29 (27.9)	104 (100)

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Table 4 – AED side effects.

Side effects	N° cases
Somnolence	11
Decrease in appetite	3
Restlessness	10
Hand tremor	1
Hair loss	2
Hypotonia	6
Gastrointestinal disorders	1
Decrease in platelets	1
Weight increase	1
Skin rash	1
Anorexia	1
Hyperammonemia	1
Total	39

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 (Table 4) 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).[8,10] 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[8] 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[12] and from other authors.[13–16]

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.[24] Moreover, PB is described as an effective drug in partial onset seizures in adults and children, similarly to CBZ, PHT and VPA.[9,24]

PB is one of the barbiturate drugs that depress neuronal excitability by enhancing the c-aminobutyric acid receptor-mediated chloride current.[25] A possible, though not exhaustive, explanation for our results could be that the dendrite-synaptogenic developmental failure, which is one of the physiopathogenetic mechanisms believed to be involved in RTT Syndrome,[26] 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[11,12,14,27,28] but one,[13] with regard to both seizure control and interictal epileptiform activity reduction.[11]

Several studies have shown that CBZ is very effective[12–14] despite the possible worsening of generalized spike and wave discharges.[11]

Lamotrigine has been reported as being effective in some studies,[14,29–31] with a positive effect on alertness and concentration.[30] Nevertheless, one paper reports a less favourable effect.[13]

Huppke et al.[13] 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[32] and LEV.[33] Some small studies suggest that treatments such as ketogenic diet[34,35] and vagus nerve stimulation[36] 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.[14,33]

Seventy-five different drug associations were given to our cohort at follow up. The most frequently used ones were: CBZ and LTG, CBZ and PB, 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[13] 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.[13–15]

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

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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 treatment of epilepsy in Rett Syndrome. The association of four drugs should be avoided since it did not result in any significant clinical improvement.

Conflicts of interest

The authors have no financial interest in any of the products or instruments used in this study.

The authors declare that they have no conflicts of interest concerning this article.

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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.

REFERENCES

1. Hagberg B, Hagberg G. Rett syndrome: epidemiology and geographical variability. *Eur Child Adolesc Psychiatry* 1997;**6**:S5–7.
2. Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK. RettSearch Consortium Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;**68**:944–50.
3. Amir RE, Van dV I, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;**23**:185–8.
4. Bienvenu T, Carrie A, De Roux N, Vinet MC, Jonveaux P, Couvert P, Villard L, Arzimanoglou A, Beldjord C, Fontes M, Tardieu M, Chelly J. MECP2 mutations account for most cases of typical forms of Rett syndrome. *Hum Mol Genet* 2000;**9**:1377–84.
5. Scala E, Ariani F, Mari F, Caselli R, Pescucci C, Longo I, Meloni I, Giachino D, Bruttini M, Hayek G, Zappella M, Renieri A. CDKL5/STK9 is mutated in Rett syndrome variant with infantile spasms. *J Med Genet* 2005 Feb;**42**(2):103–7.
6. Ariani F, Hayek G, Rondinella D, Artuso R, Mencarelli MA, Spanhol-Rosseto A, Pollazzon M, Buoni S, Spiga O, Ricciardi S, Meloni I, Longo I, Mari F, Broccoli V, Zappella M, Renieri A. FOXG1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet* 2008 Jul;**83**(1):89–93. Epub 2008 Jun 19.
7. Jian L, Nagarajan L, de Klerk N, Ravine D, Bower C, Anderson A, Williamson S, Christodoulou J, Leonard H. Predictors of seizure onset in Rett syndrome. *J Pediatr* 2006 Oct;**149**(4):542–7.
8. Pintaudi M, Calevo MG, Vignoli A, Parodi E, Aiello F, Baglietto MG, Hayek Y, Buoni S, Renieri A, Russo S, Cogliati F, Giordano L, Canevini M, Veneselli E. Epilepsy in Rett syndrome: clinical and genetic features. *Epilepsy Behav* 2010 Nov;**19**(3):296–300. Epub 2010 Aug 21.
9. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006 Jul;**47**(7):1094–120 [Review].
10. Guerrini R, Parrini E. Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene –related encephalopathies. *Epilepsia* 2012 Dec;**53**(12):2067–78.
11. Nissenkorn A, Gak E, Vecsler M, Reznik H, Menascu S, Ben Zeev B. Epilepsy in Rett syndrome–the experience of a National Rett Center. *Epilepsia* 2010 Jul;**51**(7):1252–8. Epub 2010 May 13.
12. Jian L, Nagarajan L, de Klerk N, Ravine D, Christodoulou J, Leonard H. Seizures in Rett syndrome: an overview from a one- year calendar study. *Eur J Paediatr Neurol* 2007 Sep;**11**(5):310–7. Epub 2007 Apr 11.
13. Huppke P, Köhler K, Brockmann K, Stettner GM, Gärtner J. Treatment of epilepsy in Rett syndrome. *Eur J Paediatr Neurol* 2007 Jan;**11**(1):10–6. Epub 2006 Dec 18.
14. Krajnc N, Župančič N, Oražem J. Epilepsy treatment in Rett syndrome. *J Child Neurol* 2011 Nov;**26**(11):1429–33. Epub 2011 Jun 2.
15. Bao X, Downs J, Wong K, Williams S, Leonard H. Using a large international sample to investigate epilepsy in Rett syndrome. *Dev Med Child Neurol* 2013;**55**(6):553–8.
16. Dolce A, Ben Zeev B, Naidu S, Kossoff EH. Rett syndrome and epilepsy: an update for child neurologists. *Pediatr Neurol* 2013 May;**48**(5):337–45.
17. Hagberg B. Rett syndrome: clinical peculiarities and biological mysteries. *Acta Paediat* 1995;**84**:971–6.
18. Hagberg BA, Skjeldal OH. Rett variants: a suggested model for inclusion criteria. *Pediatr Neurol* 1994 Jul;**11**(1):5–11.
19. Renieri A, Mari F, Mencarelli MA, Scala E, Ariani F, Longo I, Meloni I, Cevenini G, Pini G, Hayek G, Zappella M. Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain Dev* 2009 Mar;**31**(3):208–16.
20. Artuso R, Mencarelli MA, Polli R, Sartori S, Ariani F, Pollazzon M, Marozza A, Cilio MR, Specchio N, Vigevano F, Vecchi M, Boniver C, Dalla Bernardina B, Parmeggiani A, Buoni S, Hayek G, Mari F, Renieri A, Murgia A. Early-onset seizure variant of Rett syndrome: definition of the clinical diagnostic criteria. *Brain Dev* 2010 Jan;**32**(1):17–24. Epub 2009 Apr 10.
21. Engel J. for the International League against Epilepsy ILAE. A proposed diagnostic scheme for people with epileptic

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seizures and with epilepsy: report of the ILAE Task Force on classification and terminology. *Epilepsia* 2001;**42**:796–803.
22. Berg AT, Kelly MM. Defining intractability: comparisons among published definitions. *Epilepsia* 2006;**47**:431–6.
23. Bahi-Buisson N, Kaminska A, Boddaert N, Rio M, Afenjar A, Gérard M, Giuliano F, Motte J, Héron D, Morel MA, Plouin P, Richelme C, des Portes V, Dulac O, Philippe C, Chiron C, Nabbout R, Bienvenu T. The three stages of epilepsy in patients with CDKL5 mutations. *Epilepsia* 2008 Jun;**49**(6):1027–37.
24. Pal DK. Phenobarbital for childhood epilepsy: systematic review. *Paediatr Perinat Drug Ther* 2006 May;**7**(1):31–42.
25. Kikuchi K, Hamano S, Oritsu T, Koichihara R, Tanaka M, Minamitani M, Ida H. Effectiveness and safety of non intravenous high-dose phenobarbital therapy for intractable epilepsy during childhood. *Brain Dev* 2011 May;**33**(5):379–83. Epub 2010 Aug 17.
26. Armstrong DD. Neuropathology of Rett syndrome. *J Child Neurol* 2005 Sep;**20**(9):747–53 [Review].
27. Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. *Acta Paediatr* 2001;**90**:34–9.
28. Glaze DG, Percy AK, Skinner S, Motil KJ, Neul JL, Barrish JO, Lane JB, Geerts SP, Annese F, Graham J, McNair L, Lee HS. Epilepsy and the natural history of Rett syndrome. *Neurology* 2010 Mar 16;**74**(11):909–12.
29. Uldall P, Hansen FJ, Tonnby B. Lamotrigine in Rett syndrome. *Neuropediatrics* 1993;**24**:339–40.
30. Stenbom Y, Tonnby B, Hagberg B. Lamotrigine in Rett syndrome: treatment experience from a pilot study. *Eur Child Adolesc Psychiatry* 1998;**7**:49–52.
31. Kumandas S, Caksen H, Ciftçi A, et al. Lamotrigine in two cases of Rett syndrome. *Brain Dev* 2001;**23**:240–2.
32. Goyal M, O'Riordan MA, Wiznitzer M. Effect of topiramate on seizures and respiratory dysrhythmia in Rett syndrome. *J Child Neurol* 2004;**19**:588–91.
33. Specchio N, Balestri M, Striano P, Cilio MR, Nardello R, Patanè S, Margiotta ML, D'Orsi G, Striano S, Russo S, Specchio LM, Cusmai R, Fusco L, Vigevano F. Efficacy of levetiracetam in the treatment of drug-resistant Rett syndrome. *Epilepsy Res* 2010 Feb;**88**(2–3):112–7. Epub 2009 Nov 14.
34. Haas RH, Rice MA, Trauner DA, Merritt TA. Therapeutic effects of a ketogenic diet in Rett syndrome. *Am J Med Genet Suppl* 1986;**1**:225–46.
35. Liebhaber GM, Riemann E, Baumeister FA. Ketogenic diet in Rett syndrome. *J Child Neurol* 2003;**18**:74–5.
36. Wilfong AA, Schultz RJ. Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. *Dev Med Child Neurol* 2006 Aug;**48**(8):683–6.

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