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Efficacy of levetiracetam in the treatment of drug-resistant Rett syndrome

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Summary Rett syndrome (RTT) is a progressive neurological disorder characterized by a wide spectrum of phenotypes. Epilepsy is reported to occur in 50—90% of patients with RTT; some develop medically refractory epilepsy. The aim of this study is to investigate the efficacy of levetiracetam (LEV) in drug-resistant patients with RTT.

This prospective, pragmatic, open-label study consisted of an 8-week baseline period and a 6-month evaluation period. Efficacy variable was the mean frequency of monthly seizures before, and after 3 and 6 months of treatment with LEV.

Eight female patients, aged 7.5—19 years (M12.8 ± 5) entered the study. Mean age at epilepsy onset was 25.8 ± 14.1 months. All patients showed MeCP2 mutation. Patients had been treated with a mean of 3.4 AEDs (2—7) before LEV. The mean LEV dose was 44.84 ± 18.02 mg/kg/day. The mean monthly seizure frequency for all types of seizures during the baseline period was 21.3 ± 8.1 (range 10—35); after 3 months it was 3.3 ± 4.1 (range 0—9) and after 6 months of LEV treatment it was 1.5 ± 2 (range 0—4), $p < 0.0001$. The mean follow-up period was 20.2 ± 13 months. Mild sleepiness occurred in two patients, one reported intermittent agitation.

Levetiracetam appeared effective in our series of drug-resistant RTT patients. All reported a reduction in seizure frequency and consequently a better quality of life.

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Introduction

Rett syndrome (RTT) is a progressive neurological disorder characterized by a wide spectrum of phenotypes. A classic form and an RTT variant have been reported, which are thought to be caused by mutation in the methyl-CpG binding protein 2 gene (MeCP2) and in another X-linked gene, cyclin-dependent kinase-like 5 (CDKL5), responsible for early-onset epileptic encephalopathy. In the classic form major clinical characteristics are developmental arrest, regression with loss of speech, stereotypic hand movements, ataxia, hand apraxia and epilepsy. Despite the diversity of epileptic seizures in RTT, partial complex seizures are more frequently described (Steffenburg et al., 2001), but generalised seizures are also present such as tonic, generalised clonic, absence atonic and myoclonic seizures (Nieto-Barrera et al., 1999). The EEG is abnormal in the wide majority of patients with RTT. Abnormalities include both slowing and disorganization of background activity with multifocal epileptiform discharges while awake, and intermittent, high-amplitude discharges followed by relative attenuation of background activity during sleep (Trauner and Haas, 1987). Diffuse or bilateral-synchronous spikes or spike—wave complexes have also been found (Niedermeyer et al., 1986).

Epilepsy is reported to occur in 50—90% of patients with RTT. Seizures can be controlled with antiepileptic drugs (AEDs) in many patients; however, some develop medically refractory epilepsy (Steffenburg et al., 2001). Few studies have been performed on the efficacy of antiepileptic drugs in RTT patients. In clinical practice carbamazepine and valproate are the most used drugs although valproate has been found less effective than carbamazepine (Huppke et al., 2007).

Levetiracetam (LEV) is a new antiepileptic drug approved as monotherapy for new onset partial epilepsy from 16 years (Brodie et al., 2007) and as adjunctive treatment for partial epilepsy in children (Glauser et al., 2006). Levetiracetam is also useful as add-on treatment for myoclonic seizures in patients with Juvenile Myoclonic Epilepsy (JME) (Noachtar et al., 2008) and for generalised tonic—clonic seizures in patients with Idiopathic Generalised Epilepsy (IGE) (Berkovic et al., 2007). Moreover, levetiracetam has been found to prevent the photoparoxysmal response (PPR) in the 75% of subjects with photosensitive epilepsy (Kasteleijn-Nolst Trenité et al., 1996).

The aim of this study is to report the efficacy and tolerability of levetiracetam in RTT drug-resistant epilepsy.

Methods

Patient population

Patients were recruited in an add-on, open-label study if they fulfilled with the following inclusion criteria:

- diagnosis of RTT, defined according to consensus criteria established in 2001 (Hagberg et al., 2002);
- presence of epilepsy defined according to the ILAE criteria (Commission on Classification, 2006);
- presence of at least four seizures a month during the last 8 weeks;
- previous use of at least two conventional AEDs;
- parents or caregivers able to comply with drug therapy and complete seizure diary regularly;
- mutational testing of *MeCP2* accomplished.

Concomitant occurrence of acute medical illness or previous exposure to levetiracetam were considered exclusion criteria. The study was conducted according to the Declaration of Helsinki criteria and no pharmaceutical support was obtained. The study was approved from the Institutional Ethic Committee and informed consent signed by the parents was required. Family and personal history was taken and neurological examinations performed in all patients.

Study design

This was a prospective, pragmatic, long-term, open-label treatment study evaluating the efficacy and tolerability of levetiracetam in RTT patients resistant to previous AED treatments. The study consisted of an 8-week baseline period and a 6 months of evaluation period. Concomitant medicines remained at unchanged doses for at least 2 months prior to study entry and throughout the duration of the study. At the investigator's judgement, seizure-free patients could be converted to levetiracetam monotherapy by gradual tapering of concomitant medicines. Levetiracetam was given orally at starting doses of 10 mg/kg/day followed by 10-mg/kg/day increments at 1-week intervals up to a dose of 50—60 mg/kg/day given in two divided doses until the best improvement was reached or adverse events appeared, according to clinical judgement. The titration phase included the week in which target dose was reached. The treatment period was composed of a 5—6 weeks up-titration phase and an observational period of up to 48 months. The use of benzodiazepines was generally avoided during the trial. However, parents and caregivers were allowed to administer oral or rectal benzodiazepines in the event of long-lasting major epileptic seizures. No further adjunctive AED treatments were allowed during the follow-up period.

Safety procedures

Adverse events were recorded in the diary and levetiracetam discontinuation was undertaken if intolerable side effects or seizure aggravation developed. Physical and neurological examinations were performed at each visit.

Evaluation of efficacy and tolerability

Seizure type and frequency were recorded in an epilepsy diary by parents and/or caregivers over an 8-week period before starting levetiracetam treatment (Baseline Period) until the patient remained in the study. Focal, myoclonic, atonic, hemiclonic and tonic—clonic seizures were distinguished. The primary efficacy parameter was the evaluation of seizure frequency after 3 months and after 6 months compared with the baseline period considering the total number of seizures and the types of seizures. The secondary efficacy parameter was the evaluation of the EEG characteristics before and after levetiracetam administration. The following items were considered: (i) background activity (mild and severe impairment) and (ii) presence of epileptiform abnormalities (focal, multifocal, or diffuse). EEGs were performed during the baseline period and after 6 months of levetiracetam treatment. Tolerability was assessed by recording the type, duration and intensity of adverse events at each visit, as reported by parents or caregivers or evidenced by physical and neurological examinations.

Statistical analysis

Statistical analysis was performed using ANOVA for repeated measures.