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Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam

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***Purpose*:** To investigate the prevalence and psychopathological features of psychiatric adverse events (PAEs) in patients with learning disabilities (LD) in therapy with levetiracetam (LEV).
***Method*:** From a population of 517 consecutively patients with epilepsy started on LEV, we identified 118 patients with epilepsy and LD.
***Results*:** Fifteen patients (12.7%) experienced PAEs during LEV therapy. Two (1.7%) developed an affective disorder, nine (7.6%) aggressive behaviour, two (1.7%) emotion lability and two (1.7%) other personality changes such as agitation, anger and hostile behaviour. We observed a significant association with a previous history of status epilepticus and a previous psychiatric history. We did not find a statistically significant association with epilepsy diagnosis, age at onset or duration of the epilepsy, EEG or MRI features. The titration schedule of LEV appeared not to be relevant.
***Conclusions*:** LEV therapy was well tolerated in patients with epilepsy and LD and the main problems were related to aggressive behaviour. The titration schedule of LEV was not relevant and a subgroup of patients appeared to be biologically more vulnerable.

Key words: epilepsy; levetiracetam; learning disability; depression; psychosis; adverse events.

INTRODUCTION

Levetiracetam (LEV) has been recently approved for the treatment of partial epilepsy and preliminary evidence suggests that it can also be effective in generalised epilepsies[1]. Controlled clinical trials reported a good tolerability profile and a low rate and mild severity of the adverse events[2].

Adults with learning disabilities (LD) have a higher incidence of all types of epilepsy than the general population and up to a forth of patients with epilepsy have LD[3]. Moreover, the presence of psychiatric comorbidity in patients with epilepsy and LD has been widely described and might represent an important variable complicating the management of the patients[4].

The aim of our study was to evaluate the prevalence and psychopathological features of psychiatric adverse events (PAEs) in patients with LD in therapy with LEV, to assess their relationship to seizure pattern and frequency, titration schedule and prescription time of LEV and to identify significant predictive and prognostic factors.

METHODS

LEV was available in UK at the end of 2000. Data were collected from a population of consecutive patients with epilepsy taking LEV, prospectively collected from the National Hospital for Neurology and Neurosurgery (Queen Square and Chalfont Center sites).

The diagnosis of LD (mental retardation or intellectual disability) was made if patients had an intelligent quotient (IQ) less than 70.

PAEs were assessed by evaluating patients at each visit and were defined as a psychiatric manifestation that occurred during LEV therapy and were not related to other AEDs changes, physical illness or personal

events, in patients without a psychiatric disorder when LEV was started.

PAEs have been classified according to the DSM IV classification, while other behavioural changes have been arbitrarily classified as anger/hostile behaviour, aggressive or agitated behaviour, irritability, anxiety and emotional lability.

The following items were investigated: age when LEV was started, gender, epilepsy and seizure diagnosis (according to ILAE classification)[5], age at onset and duration of epilepsy, family history of epilepsy and/or psychiatric disorder, previous psychiatric history, personal history of febrile convulsions, MRI and EEG features, seizure frequency before LEV therapy (classified as 1–10, 11–20 or >20 seizure/month), antiepileptic drug prescribed, starting dose of LEV (classified as 250, 500 or 1000 mg), titration schedule (classified as 1000 mg every 2 weeks, slower or faster), at least 50% seizure reduction after LEV, seizure freedom attained.

The χ^2 analysis or Fisher's exact test was used for categorical data, while ordinal and linear variables were assessed by non-parametric tests and one-way ANOVA. Difference and correlation were considered statistically significant at $P < 0.05$. Subsequently, a regression analysis was used to test whether these factors were related to PAEs. Following the significant likelihood ratio test for the full model, a backward selection method was used to reduce the number of variables. A variable was eliminated if its removal statistic had a probability ≥ 0.10.

RESULTS

Follow up information were available for 118 patients with epilepsy and LD. The M/F ratio was 64/54 and the mean age ± SD was 31.1 ± 9.3 years. There were 21 patients with a diagnosis of cryptogenic partial epilepsy, seven with idiopathic generalised epilepsy, 18 with others, e.g. Lennox–Gastaut or West Syndrome, 12 with symptomatic generalised epilepsy and 57 with symptomatic partial epilepsy. The duration of the epilepsy ± SD was 26.7 ± 10.3 years.

Fifteen patients (12.7%) experienced PAEs during LEV therapy. Two (1.7%) developed an affective disorder, nine (7.6%) aggressive behaviour, two (1.7%) emotional lability and two (1.7%) other personality changes such as agitation, anger and hostile behaviour. Ten (8.5%) patients discontinued LEV because of PAEs, three (2.5%) received a dose reduction and two (1.7%) patients remained on the same dose. The mean dose of LEV at PAEs onset was 1516 ± 1006 mg/day while the time of onset of PAEs was 87.6 ± 85.2 days after LEV was started. PAEs occurred 15.7 ± 11.3 days after a change in LEV dose.

Table 1: Demographic data and distribution of variables associated with PAEs.

Variables	LD with PAEs (15)	LD without PAEs (103)
Gender (male/female)	10/5	54/49
Age (mean ± SD, years)	30 ± 7.9	31.2 ± 9.5
Duration of epilepsy (mean ± SD, years)	26.3 ± 6.5	26.7 ± 10.8
History of status epilepticus	10**	22
Titration schedule (1000 mg every 2 weeks/faster/slower)	4/2/9	36/6/61
50% seizure reduction	8	31
Seizure freedom attained	3	7
Past psychiatric history	9*	21

* $P = 0.009$; ** $P = 0.001$.

Table 2: Regression analysis of variables for PAEs in patients with LD in therapy with LEV.

Variables	Wald	OR (95% CI)	*P*-value
Previous psychiatric history	9.256	5.8 (1.87–18.29)	0.002
Previous history of status epilepticus	8.432	6.4 (1.83–22.54)	0.004

Psychotropic drug prescription was required in three (2.5%) patients while only one (0.8%) patient was admitted to hospital because of PAEs.

We did not find a specific seizure pattern associated to PAEs onset. Three (2.5%) patients were seizure free during PAEs, one (0.9%) was seizure free but behaviour deteriorated after a cluster of seizures, five (4.2%) experienced no change in seizure frequency, five (4.2%) had seizure reduction and only one (0.9%) patient experienced seizure worsening.

Comparing patients with and without PAEs, we found a significant association with the previous psychiatric history and a previous history of status epilepticus (Tables 1 and 2).

DISCUSSION

In clinical practice, it is often difficult to recognize potential side effects of AEDs. Patients with LD may be unable to express what they feel, and changes in mood and behaviour may be all that is apparent.

In our study, the prevalence of PAEs was similar to that described in previous controlled clinical studies of LEV involving general population of patients with epilepsy[2] and suggests that patients with LD are not more prone to develop psychopathology taking LEV. Moreover, the low percentage of psychotropic drug prescription and hospitalisation because of the PAEs, suggests that the prognosis of these episodes was good.

The identification of previous psychiatric history and previous history of status epilepticus as risk