up and walk by herself. One year after MCS, she presented remarkable improvement. She came to walk much faster with wide steps without freezing and falling.

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An Open Trial of Levetiracetam for Segmental and Generalized Dystonia

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Abstract: **Local botulinum toxin injections represent the treatment of choice for most patients with focal dystonia. However, patients with segmental or generalized forms require additional pharmacologic treatment which is often ineffective or limited by intolerable side-effects. An animal study and three case reports suggested antidystonic effects of levetiracetam, a pyrrolidone derivate, whereas a recent open-label study found no improvement in 10 patients with primary idiopathic cervical dystonia. We studied the efficacy of levetiracetam in a daily dose of 3000 mg in 10 consecutive patients with otherwise therapy refractory segmental or generalized dystonia. At 4-week follow-up, none of the patients showed improvement of dystonia, mild side-effects were observed in 3 patients.** © 2007 Movement Disorder Society

Key words: dystonia; levetiracetam; botulinum toxin

Dystonia is one of the most prevalent movement disorders with a minimum prevalence of about 100/100,000.[1] Local injections with botulinum toxin (BTX) are the treatment of choice for the majority of patients with dystonia. However, the use of BTX may be limited by the development of neutralizing antibodies against the toxin. In addition, patients with more widespread symptoms usually require additional oral medication to alleviate their symptoms. Drugs currently available to treat dystonia include anticholinergics, dopamine antagonists, benzodiazepines, baclofen, riluzole, or clozapine.[2,3] Nevertheless, in the majority of patients the above-mentioned drugs are only partially effective or their use is limited by intolerable side-effects.

Levetiracetam (LEV, Keppra), an S-enantiomer pyrrolidone derivate used in the treatment of epilepsy, has shown antidystonic effects in an animal model of paroxysmal dystonia.[4] In addition, isolated case reports have suggested beneficial effects of LEV in patients with

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Meige's syndrome,[5,6] or generalized dystonia.[7] However, a recent open-label study by Tarsy et al. found no improvement in 10 patients with primary idiopathic cervical dystonia (CD).[8]

The aim of this open-label pilot study was to examine the efficacy and safety of LEV in 10 adults with otherwise pharmacologically refractory segmental and generalized dystonia.

PATIENTS AND METHODS

Ten patients with dystonia (7 primary, 3 secondary), seven women, median age 51 years [range 33–67], median disease duration 22 years [range 8–39] were included. Among those with primary dystonia, three had generalized dystonia (one DYT1 positive), and four segmental dystonia involving face, head and trunk/upper extremity. Secondary dystonia was segmental in one patient with tardive dystonia and generalized in two following perinatal injury. Four patients showed additional symptoms including myoclonic jerks (n = 2) or tremor (n = 2). Patients were diagnosed according to standardized criteria[9] by a neurologist with expertise in the diagnosis and treatment of movement disorders.

Prior treatments included BTX injections (10/10) trihexyphenidyl (10/10), tiapride (10/10), tetrazine (10/10), benzodiazepines (10/10), riluzole (4/10), or intrathecal baclofen (1/10). BTX and other medications were largely unsuccessful with improvements on the movement subscale of the Burke–Fahn–Marsden-Dystonia-Rating scale (BFMDRS) not exceeding 30% in any of the patients.

Patients had not received BTX injections for at least 4 months prior to starting treatment with LEV. Five patients received additional antidystonic medication that remained unchanged throughout the study period (trihexyphenidyl [n = 4, dose-range 3–12 mg/day], tetrabenazine [n = 3, dose-range 25–75 mg/day], clonazepam [n = 1, 3 mg/day], intrathecal baclofen [n = 1, 300 μg/day]). Informed consent was given by all patients. The movement subscale of the BFMDRS served as primary outcome measure.[10] A self-rating instrument (−3 [marked worsening]/−2/−1/0 [no change]/+1/+2/+3 [marked improvement]) was completed by the patient at follow-up. LEV was started at 500 mg twice daily and increased by 500 mg every 5 days to a maintenance dose of 3000 mg daily. Follow-up assessments were performed after continuous treatment with 3 × 1000 mg/day LEV for 4 weeks in all patients. Side-effects were documented as reported by the patients. All patients were assessed by the same investigator (JM).

RESULTS

Nine of 10 patients (90%) completed the study. One patient with primary segmental dystonia stopped LEV after 3 weeks on 3000 mg/day because of somnolence and lack of improvement.

At baseline, the median BFMDRS motor score was 51 [range 10–86]. With treatment, the score did not improve (follow-up median BFMDRS motor score = 55, n.s.), nor did severity of myoclonic jerks and tremor. One patient reported mild worsening of dystonia (−1) and one mild improvement (+1), the remaining patients experienced no subjective change of dystonia at follow-up. There were no severe side-effects, 3 patients reported mild side-effects (nausea, n = 1; dizziness, n = 1; somnolence, n = 1).

DISCUSSION

The present study failed to provide evidence for any beneficial effect of LEV on segmental or generalized dystonia. Our findings are consistent with those of Tarsy et al. who reported no improvement in CD and a high drop-out rate due to adverse effects in 10 patients after treatment with 2000 mg/day LEV for 4 weeks.[8] The absence of even a slight placebo-response is remarkable but similar to the observation by Tarsy et al. Another possible reason is presumably a selection bias of patients who had been through numerous drug-treatment attempts and remained resistant.

However, 6 of the 10 patients (3 primary generalized, 2 primary segmental, 1 tardive dystonia) have meanwhile received bilateral pallidal deep brain stimulation (DBS) with moderate to excellent benefit (50–90% BFMDRS improvement).

Previous case reports and small open-label studies suggested that LEV may have beneficial effects in the treatment of hyperkinetic movement disorders, including tardive dyskinesia,[11–14] chorea,[15–20] and posthypoxic cortical myoclonus.[21]

Prior studies in the field of levodopa-induced dyskinesia have had conflicting results: In an animal study published by Betard et al., LEV significantly reduced levodopa-induced chorea but had no effect on dystonia in the MPTP-treated macaque,[22] while two open-label studies in 25 PD patients reported no improvement of levodopa-induced dyskinesia combined with a high drop-out rate.[23,24] Accordingly, LEV showed a significant decrease in severity of dystonic attacks following i.p. injection of LEV in a genetic hamster model of paroxysmal dystonia,[4] but failed to be effective in clinical studies.

We do not believe that methodological limitations hold responsible for the totally negative result of the present study. Despite the fact that LEV plasma concen-

trations were not measured, the daily dose of 3000 mg and the treatment duration of 4 weeks should be sufficient to generate stable LEV plasma and CNS concentrations as was shown in several patients with epilepsy.[25] In addition, the animal study showed a significant antidystonic efficacy of LEV with a dose of 27 mg/kg body weight,[4] corresponding to about 1900 mg in the average 70 kg human adult. Therefore, the discrepancy between animal and human antidystonic effects of LEV cannot be explained by a dose-dependent effect.

A possible weakness of this study could be that it included patients with primary as well as secondary dystonia. Still, given that an open-label design usually induces bias favoring "efficacy," the present results and those recently published by Tarsy and coworkers make it seem unlikely that LEV might work in a larger controlled trial of dystonia.

In conclusion, this preliminary open trial indicates that LEV, in a daily dose of 3000 mg, is ineffective in patients with segmental and generalized dystonia. To date, pallidal DBS is the most effective treatment modality for patients with severe medically refractory primary dystonia.[26]

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