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Improvement of myoclonic epilepsy in Down syndrome treated with levetiracetam

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ABSTRACT – Late Onset Myoclonic Epilepsy in Down Syndrome (LOMEDS) is a recognized entity usually preceded by cognitive deterioration. We report two patients with LOMEDS and cognitive decline, aged 52 and 44 years. Continuous video-EEG recording showed generalised spike and slow wave complexes as an ictal correlate of the myoclonic jerks in both patients. Low dose levetiracetam resulted in rapid, sustained seizure freedom in both patients with no reported adverse events. As for other myoclonic epilepsies, levetiracetam appears to be effective for the treatment of LOMEDS, and may be considered as a first line agent for this disorder.

Key words: trisomy 21, Alzheimer-type dementia, myoclonic epilepsy, Down syndrome, levetiracetam

The percentage of people with Down Syndrome (DS) and Alzheimer's disease (AD) varies in some of the epidemiologic studies presented. A review of these studies showed that of patients with DS, AD-type dementia was present in 10-25% aged 40-49 years, 20-50% aged 50-59 years, and 60-75% older than 60 years (Schweber, 1989). The incidence of dementia in Down syndrome (DS) is estimated to be greater than 25% in individuals over 35 years of age. This number has been shown to increase with advancing age (Schweber, 1989), presumably in relation to the increased probability of triplication and over-expression of the amyloid precursor gene on chromosome 21 (Schupf and Sergievsky, 2002). Descriptions of late-onset epilepsy in DS patients are rare.

Nearly all patients with DS after the age of 40 years have histopathological evidence of cerebral neurofibrillary proteins, identical to those seen in AD (Sisodia and St George-Hyslop, 2002). It is in this subset of patients with DS that late myoclonic seizures have been reported, usually after the development of dementia (De Simone *et al.*, 2006; Möller *et al.*, 2001; Crespel, 2007).

Whether the neuropathological changes associated with AD predispose to myoclonic seizures remains to be established. Myoclonic seizures are more common in such disorders as post-hypoxic and spongiform encephalopathy, as well as in juvenile myoclonic epilepsy. For all kinds of myoclonic epilepsies, levetiracetam has shown good efficacy in controlling seizures (Van Zandijcke, 2003). We report two additional cases of myoclonic epilepsy following cognitive decline in older individuals with DS who experienced an optimal response to moderate doses of levetiracetam as monotherapy.

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Case 1

A 52-year-old left-handed man with DS presented with a six-month history of cognitive decline, consistent with dementia. His behavioural changes included a decline in previously marginal language abilities and more dependence on caregivers for activities of daily living, such as dressing and using public transportation. Two to three months after the onset of his cognitive symptoms, brief, intense, single extremity or whole body jerks were noted that were occasionally accompanied by a loud scream. His whole-body jerks resulted in falls and injury. There was no apparent loss of consciousness and the patient resumed his activities after the jerks. The jerks were more prominent in the morning or after a mid-day nap. Phenytoin treatment was initiated by the primary care physician with no change in the frequency or intensity of these events.

He was admitted to our epilepsy monitoring unit and phenytoin was discontinued. His EEG revealed a posterior basic rhythm of 5-6 Hz, with generalised intermittent slowing. Photic stimulation did not elicit abnormal responses. More than 20 episodes of myoclonic seizures were recorded, ranging from subtle, single extremity jerks to full-body violent jerks. All seizures were associated with generalised spikes and polyspike-and-wave discharges, which were maximum in the anterior head regions *(figure 1)*. The duration ranged between 0.5 to 1 second and occurred every 5-10 minutes. Oral levetiracetam was then administered at a dose of 250 mg twice a day with complete resolution of myoclonic seizures. Two days after initiation of levetiracetam treatment, the patient's family noted some improvement in his cognition back to what they estimated to be 50-60% of his pre-dementia baseline.

Case 2

A 44-year-old right-handed man with DS was diagnosed with dementia. Eight months after he was diagnosed with dementia, he started to have episodes of upper body and bilateral arm jerking. Occasionally, the jerks involved the left arm alone. He experienced falls secondary to severe and violent jerks. At times, his myoclonic jerks would interfere with such daily activities as eating and dressing. On examination, he was not able to count beyond 10 or spell any words. No formal neuropsychological evaluation was done. The patient was placed on 10 mg per day memantine without any clear improvement.

The patient was admitted to the epilepsy monitoring unit for two days. His posterior basic rhythm was of medium-amplitude and symmetric at 7-8 Hz. Photic stimulation and hyperventilation did not induce abnormal clinical or electrographic responses. More than 50 myoclonic jerks were recorded which appeared most prominent in the left arm, but clearly affected both arms and the head at other times. Nearly all of the myoclonic jerks correlated with generalised spike-and-wave complexes *(figure 1)*. These myoclonic jerks occurred every 10-30 minutes and were more frequent during sleep and when he was tired. The myoclonus was eliminated both clinically and electrographically after starting levetiracetam treatment and the patient was discharged with a course of 500 mg twice a day of levetiracetam. Upon follow-up six months later, the family reported recurrence of some subtle, occasional jerks. The jerks abated after increasing his levetiracetam dosage to 750 mg twice a day for a follow-up period of five months.

Discussion

Trisomy 21, or Down syndrome, is a relatively common genetic condition with an incidence that is dependent on maternal age. DS occurs in one in every 725 term pregnancies in mothers aged 32 years, and one in every 12 in mothers aged 49 years (Schweber, 1989). The prevalence of dementia in DS patients older than 35 years has been reported to be greater than 25% (Bartolomei *et al.*, 1995). Previously reported cases share remarkable similarities with our cases in the presentation of dementia, that preceded myoclonic jerks by months to years. In the report of Crespel *et al.* (2007), similarities are apparent both in terms of age of onset and precedence of dementia, as well as similar seizure semiological and electrographic manifestations.

Levetiracetam was instituted for both patients. Myoclonic jerks as well as EEG abnormalities resolved one to two days after treatment. The patient of the first case study remained seizure free until the last follow-up about four months later. His cognition remained poor with one to two-word sentences, and difficulty following commands. He continues to take levetiracetam, 250 mg twice a day. The second patient required a higher dose for optimal seizure control.

Levetiracetam has been shown in open-label trials and multiple case reports to have anti-myoclonic activity (Van Zandijcke, 2003). Levetiracetam is well tolerated, has no interaction with other drugs, does not require titration, and is excreted unchanged in the urine. It has been shown to be useful in patients with myoclonus, including juvenile myoclonic epilepsy (for which it is FDA-approved), severe post-anoxic myoclonus (Krauss *et al.*, 2001) and Unverricht-Lundborg disease (Genton and Gélisse, 2000). The mechanism of action of levetiracetam is unknown, but does not appear to be based on any inhibitory or excitatory neurotransmission (Striano *et al.*, 2005). Use of levetiracetam in myoclonic epilepsies is based on past experience with piracetam, a structurally related compound that has shown effective anti-myoclonic activity at high doses (Noachtar *et al.*, 2008).

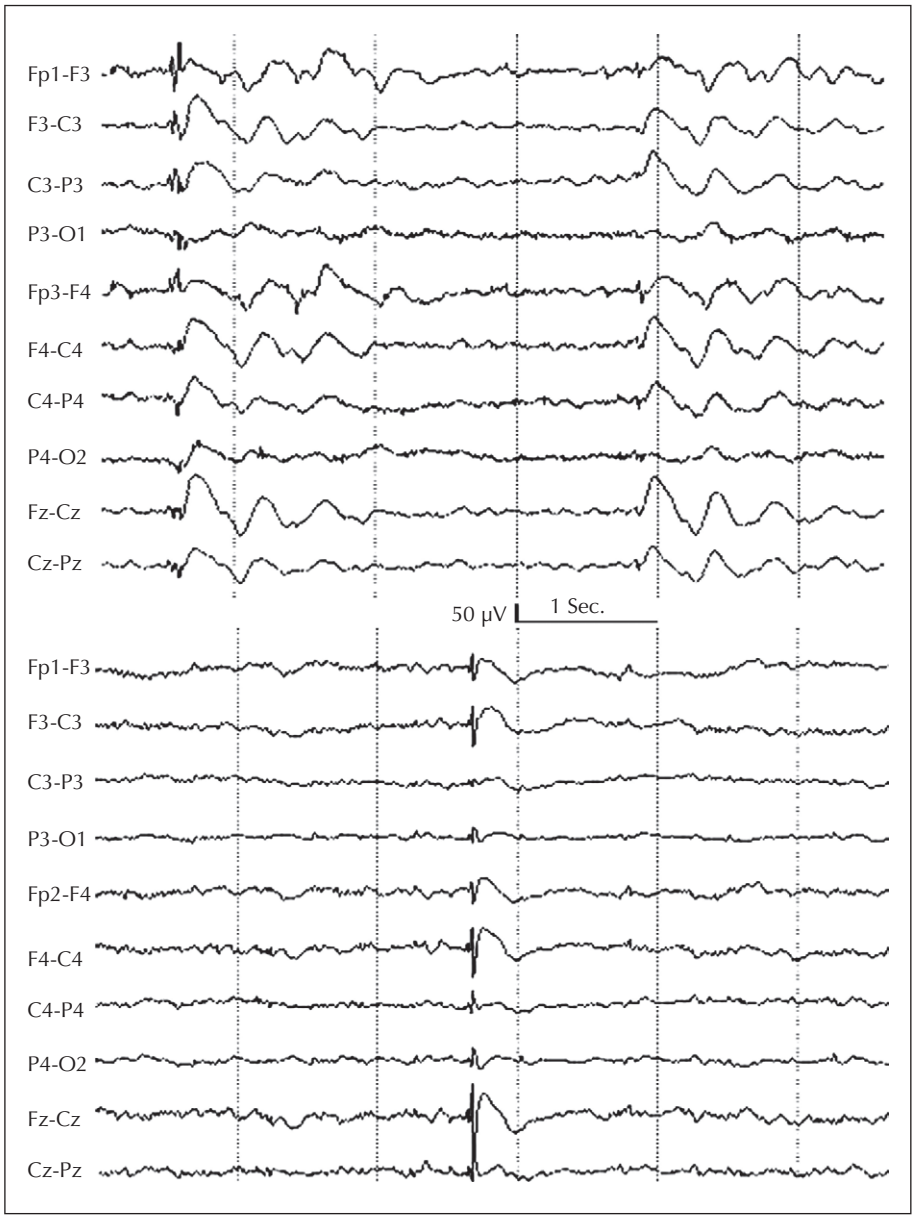

Figure 1. Generalized spike-and-wave discharges in the 2 patients associated with myoclonic jerks.

Electrophysiological studies report that myoclonic seizures are produced through a cortical generator *via* a polysynaptic mechanism acting on the muscles (Auvin *et al.*, 2008). Apparently, the epileptiform discharges stimulate the motor cortex resulting in myoclonic jerks (Auvin *et al.*, 2008). The specific mechanisms underlying myoclonus in DS are not yet fully understood.

Late Onset Myoclonic epilepsy in Down Syndrome (LOMEDS), as described by Möller *et al.* (2001), should be suspected, or at least anticipated in individuals with Down syndrome over the age of 35 years. Dementia may precede the onset of myoclonic jerks by months to years. The semiology, time of day, and electrographic findings are similar to those of juvenile myoclonic epilepsy.

De Simone *et al.* (2006) reported a clear improvement of jerks after starting levetiracetam treatment in a similar case of LOMEDS. The patients in our study responded well to low doses of levetiracetam with complete seizure freedom, although cognition continued to decline. This may suggest that a decline in cognition is independent of seizure frequency, however this was based on subjective reporting and formal neuropsychological testing before and after the treatment of epilepsy may be

warranted for a more accurate report. Although low dose levetiracetam was very effective in the two cases reported here, as well as a case of LOMDES reported by De Simone *et al*. (2006), definite conclusions can not be made from small numbers of case reports. We suggest that long-term efficacy of levetiracetam should be verified in larger controlled studies. □

Disclosure.
None of the authors has any conflict of interest to disclose.

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