Amelioration of spinal myoclonus with levetiracetam

Spinal myoclonus has been associated with various spinal cord insults, including mass lesions, ischaemia, infection, and as part of a paraneoplastic syndrome.[1] It has been postulated that it occurs as a result of deficient inhibitory glycinergic transmission in the spinal cord and subsequent "release" of synchronous motor neurone oscillations within segments of the cord. Levetiracetam (UCB Pharma, Smyrna, Georgia, USA) is a new antiepileptic drug that has been shown recently to reduce the effect of glycinergic inhibitors. We describe three patients whose spinal myoclonus was markedly ameliorated by levetiracetam.

Case reports

Patient 1: spinal epidural compression

A 62 year old woman with known diffuse large cell lymphoma presented to her oncologist with progressive back pain accompanied by a band-like sensation around her waist. In the preceding four weeks, she had also been troubled by spontaneous involuntary abdominal contractions, and in the preceding two weeks these were accompanied by involuntary jerks of her legs. The patient could not suppress these spontaneous movements; moreover, as voluntary leg movements often precipitated them, she was unable to walk safely because of numerous falls. She denied any limb weakness and bladder or bowel incontinence.

On examination, she had a mild spastic paraparesis with 4+/5 MRC grade power in a pyramidal pattern in the lower extremities (quadriceps, hamstrings, and tibialis anterior), 3+ knee and ankle jerks, and extensor plantar responses bilaterally. There were frequent resting myoclonic jerks of her lower extremities, involving both proximal and distal musculature, occurring at a rate of 150–250/min. There were also occasional, infrequent resting myoclonic jerks affecting the trunk. The myoclonic jerks were exacerbated in amplitude during attempts to perform purposeful movements, suggesting the phenomenonology of action myoclonus. The abnormal movements, rather than weakness, made it impossible for her to stand or walk unassisted. Magnetic resonance imaging (MRI) of the spine revealed malignant infiltration of the lower thoracic vertebrae with evidence of cord compression at T11. An EEG was normal.

She was treated with a maximum tolerated dose of clonazepam (1 g/day) with minimal improvement. She was then started on levetiracetam 250 mg twice daily, and within three days the resting and action myoclonus subsided markedly, such that she was able to walk with no assistance. On examination, the myoclonic jerk frequency in her lower extremities had decreased to 5–10/min, and the jerk amplitude was markedly diminished.

Patient 2: zoster myelitis

An 85 year old woman presented with a three month history of involuntary trunk movements. The movements consisted of sudden extensor jerks of her back. They were spontaneous, occurring several times a day with no obvious provoking factors. Of note, two months before the onset of the movements, she had been diagnosed as having thoracic herpes zoster (at T8) and had subsequent postherpetic neuralgia. The back movements began as the pain was subsiding. The movements were not painful, but were distressing to the patient as they were socially embarrassing. She was unable to suppress the movements voluntarily. She had been seen by another neurologist who had treated the movements with sodium valproate. She unfortunately received no benefit from this despite a maximum tolerated dose of 2000 mg/day. Past medical history was notable for cardiac arrhythmia and pacemaker placement.

On examination, she had brief, irregular, extensor movements of her thoracic spine, occurring every 10–30 seconds. An EEG was normal. MRI of the thoracic spine was precluded because of her pacemaker. The patient was given levetiracetam at a dose of 250 mg twice a day. Within 24 hours of starting this treatment, the myoclonic movements completely ceased. Two months later, she began to have clusters of repetitive movements once to twice daily for periods of 20–60 minutes. Her dose of levetiracetam was increased to 500 mg twice a day. The movements again ceased, but because of sedation and dizziness at this higher dose, the dosage was reduced to 375 mg/day. At this well tolerated dose, she has been having brief clusters of myoclonic movements two or three times a week.

Patient 3: transverse myelitis

A 12 year old boy presented with a three month history of rhythmic spasms of his right thigh. One month before this symptom, he had had onset of bilateral leg weakness and paraesthesiae and was diagnosed as having acute transverse myelitis. The paraparesis largely resolved within two weeks of onset, but one month later he began having constant, rhythmic jerks of his right quadriceps and hamstrings. These jerks could not be suppressed voluntarily and made walking difficult. Cerebrospinal fluid analysis and an MRI of the spinal cord were normal. An EEG did not show any epileptiform activity. Sodium valproate (1000 mg/d), phenytoin (300 mg/d), and intravenous lorazepam (as often as 2 mg every 4 hours) failed to relieve the constant myoclonus. A trial of botulinum toxin A injections into the right quadriceps did not ameliorate the movements.

On examination, he had constant, semi-rhythmical myoclonus of his right quadriceps at 120–150 beats/min with his knee extended, and of his right hamstrings with his knee flexed. The myoclonus was not suppressed by patellar fixation, but did improve slightly with concentration on mental tasks. On power testing, there was 4+/5 MRC grade power in the right quadriceps and right hamstrings. A repeat EEG was again unremarkable. He was started on levetiracetam at 250 mg daily and the dose increased over a four week period to 1250 mg/d. No clinical change was noted until the 1250 mg dose was reached, at which point the myoclonus slowed and then completely stopped over a seven day period, allowing independent ambulation. Other than mild initial sedation, no side effects were experienced.

Discussion

Glycine is a major inhibitory neurotransmitter in the spinal cord, and it has been postulated that deficient inhibitory glycinergic transmission results in dysfunction of segmental spinal cord circuitry, and hence a myoclonic focus in the spinal cord. This postulate is based on studies of animal models of myoclonus[2] and an in vitro model of spinal myoclonus.[3] The latter study showed that blockade of glycine receptors in isolated spinal cord preparations from neonatal rats enhanced a central pattern generator responsible for 5 to 15 Hz synchronous motor neurone oscillations. Interestingly, these oscillations—generated from as few as two isolated segments—were synchronised over at least six spinal cord segments, suggesting extensive excitatory commissural connections.

It is possible that the effectiveness of levetiracetam in our patients may be related to these glycinergic mechanisms. Levetiracetam has been shown to reverse inhibition of glycine and GABA gated currents induced by negative allosteric modulators, such as zinc and β-carbolines.[4] It may therefore conceivably be of benefit in patients with spinal myoclonus by augmenting glycinergic transmission in the spinal cord and thus dampening down myoclonic foci.

In a recent open labelled trial of levetiracetam in eight patients with chronic myoclonus, three of five patients with cortical myoclonus experienced reduction in their myoclonus severity, as assessed by the unified myoclonus rating scale.[5] The one patient in this study with spinal myoclonus showed no improvement with levetiracetam. However, the average duration of symptoms in these patients was 7.6 years, ranging from one to 17 years, in contrast to our three patients whose symptoms were one to three months in duration before levetiracetam treatment. It is therefore possible that the differential responsiveness to levetiracetam was because the aforementioned non-responder had a chronic fixed condition whereas our responders had subacute evolving spinal cord injuries.

In a recently published study, levetiracetam was used successfully to treat three patients with posthypoxic and postencephalitic myoclonus, two of whom had failed to respond to valproic acid and clonazepam.[6] Add-on therapy with levetiracetam was shown to suppress disabling post-hypoxic cortical reflex myoclonus in a 16 year old boy.[7] In another study, severe action myoclonus was suppressed by levetiracetam in three patients, of whom two had Unverricht–Lundborg disease and one had postanoxic myoclonus.[8]

Our cases, as well as the abovementioned reports of suppression of post-hypoxic and postencephalitic myoclonus with levetiracetam, suggest that this agent is promising for the treatment of both non-cortical and cortical myoclonus. These observations will need to be confirmed in additional patients. Furthermore, the proportion of responders needs to be determined in a larger group of patients, ideally in the setting of a randomised, double blind, placebo controlled trial.

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Hyperthyroidism with increased factor VIII procoagulant protein as a predisposing factor for cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is a rare disorder, with an incidence of approximately 4/1 000 000 per year, occurring more frequently in women than in men (ratio of 1.29:1).[1] CVT is a multifactorial condition, known predisposing factors include venous stasis, hypercoagulability, vasculitis, systemic lupus erythematosus, and trauma. Mortality after CVT ranges from 5% to 30%.[1] The optimal treatment consists of anticoagulation for six months and should only be maintained beyond this time if known risk factors for CVT persist. Treatment should not be discontinued in case of an asymptomatic haemorrhagic transformation of the associated venous infarct.[2]

In recent years, a few thyrotoxic patients with CVT have been reported. An association between hyperthyroidism and increase of FVIII has also been described,[3] and recent data suggest an increased incidence of venous thrombosis in patients with hyperthyroidism and high FVIII levels.[4] Here we report a patient with increased FVIII levels and an autoimmune hyperthyroidism, who developed a CVT complicated by venous infarction.

Case report

A 39 year old woman was admitted to the emergency room after a brief episode of convulsions, preceded by a short period of perseveration, verbal aggressiveness, and disorientation. Four days before admission, she had developed a sudden, pulsatile left sided headache, which was unresponsive to paracetamol and ibuprofen. Personal and family medical histories were unremarkable. She had been taking oral contraceptive medication for several years and smoked two cigarettes a day. Neurological examination was normal, except for a temporary confusional state that lasted less than 24 hours. Electroencephalography demonstrated a slow arrhythmia in the left temporal region, without epileptic activity. Brain computed tomography revealed a left temporal hypodense lesion, with moderate contrast enhancement. Magnetic resonance imaging of the brain performed 24 hours later, showed a non-specific hyperintense lesion on the T1 weighted images. The magnetic resonance venography (fig 1) revealed an extensive thrombosis of the left lateral sinus with involvement of the distal part of the jugular vein. The diagnosis of a temporal venous infarct was made. Treatment with unfractionated heparin was started promptly and maintained for one week, followed by oral anticoagulation with an INR between 2 and 3. Oral contraceptive treatment was discontinued and the patient was advised to stop smoking. Extensive screening for coagulopathies including antiphospholipid syndrome, dysfibroginaemia, deficiencies in antithrombin, protein C and S, hyperhomocysteinaemia, and activated protein C resistance revealed no abnormalities. The G20210A prothrombin gene mutation was absent. Autoimmune tests including ANF, ANCA, complement and rheumatoid factors were negative. Further analysis revealed a state of hyperthyroidism with a TSH value below 0.015 mIU/l (normal: 0.27–4.2), free triiodothyronin of 12.1 ng/l (normal: 9.3–18.0 ng/l), and an increased free thyroxin of 28.8 ng/l (normal: 9.3–18.0 ng/l). Anti-TSH receptor antibodies were found consistent with Graves-Basedow's disease. The patient was treated with thiamazole (3×10 mg/day), followed by the administration of radioactive iodine (9 mCi). One month after discontinuation of oral contraceptives, thyroid tests remained increased. FVIII procoagulant protein showed a marked increase: 1680 IU/l (normal levels: 500–1500 IU/l) and remained slightly raised five weeks later. Meanwhile the patient developed a hypothyroidism, necessitating a substitution treatment with LT4. After a further six months both thyroid tests and FVIII levels normalised and anticoagulants were stopped.

Discussion

Increase of clotting FVIII occurs in several conditions such as strenuous exercise, fever, pregnancy, renal failure, adrenaline (epinephrine) infusion, prednisone treatment, and intravascular haemolysis.[3] Hyperthyroidism, whatever its origin, also induces a significant increase in FVIII levels, with a comparatively short activated partial thromboplastin time, while other clotting factors remain within normal limits.[3] Moreover, correction of thyroid function results in a normalisation of FVIII levels. In patients with recurrent hyperthyroidism, levels of FVIII are known to fluctuate with thyroid function. The physiopathological mechanism involved remains unclear. Excessive adrenergic activity occurring in hyperthyroid patients could have a direct effect on the production of FVIII. The fact that administration of propanolol inhibits the increase of FVIII in patients with hyperthyroidism supports this theory.

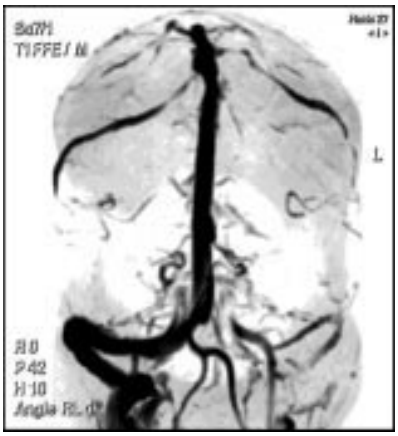

Figure 1 Magnetic resonance venography confirms complete occlusion of the left lateral sinus.

In 1995 a large study was performed on 301 case-control pairs, younger than 70 with a first episode of deep vein thrombosis.[4] Patients with malignant disorders were excluded. The authors showed that high levels of FVIII contribute to the development of venous thrombosis in a dose dependent manner. In multivariate analysis FVIII concentrations above 1500 IU/l result in a 4.8-fold higher risk of developing venous thrombosis. It was also shown that this is not an acute phase reaction, and that high levels of FVIII persist for months after the thrombotic event. Recently, it was calculated that the reported incidence of CVT and hyperthyroidism is significantly higher than expected by chance alone.[5] A small number of case reports mention the concomitant occurrence of thyrotoxicosis and CVT. To our knowledge, this is the first reported case of CVT of the left lateral sinus associated with clinically silent hyperthyroidism and increased FVIII levels. Correction of thyroid function resulted in normalisation of FVIII levels. This report emphasises the need for thyroid evaluation in every patient with CVT and other venous thromboembolic events, even in the absence of clinical signs of hyperthyroidism. Every patient with hyperthyroidism, especially if immobilised, has a significantly higher risk of developing venous thromboembolism and should benefit from maximal preventive measures.

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Coma with focal neurological signs caused by *Datura stramonium* intoxication in a young man

Intoxication with *Datura stramonium*, which contains a variety of tropine alkaloids, produces atropine-like effects. The seeds of *D stramonium* (semen stramonii) in particular contain hyoscyamine, scopolamine, and atropine. Symptoms include agitation, disorientation, hallucination, flushed skin, dilatation of