TO THE EDITOR

Delirium After Gabapentin Withdrawal. Case Report

Gabapentin is an antiepileptic drug useful in inhibiting focal seizures and is also utilized for several off-label applications. While the use of gabapentin can be associated with dizziness, drowsiness, and coordination problems, drug discontinuation rarely induces a withdrawal syndrome.

Here we report the occurrence of delirium in a woman who was not previously diagnosed with any mental disorder, after the discontinuation of low doses of gabapentin. The authors suggest that pre-morbid psychiatric conditions should be carefully assessed before prescribing any drug with a potential effect on mood.

CASE REPORT

A 76-year-old woman with good past health other than diabetes mellitus was on diet control. No psychiatric illness was reported, although her relatives described the patient as a strong-willed woman, with a propensity to break social rules. Moreover, she showed short sleep patterns and a tendency to hyperactivity, with periodic episodes of melancholy.

At 55 years-of-age, the patient had had an episode of mental confusion, which occurred during a severe pulmonary infection. During that time, she was disoriented and alternated between conscious and unconscious states several times during the course of the day. However, her son reported that, during these episodes, she was aware of what was happening around her and could react aggressively if awakened abruptly. When the patient was awake, her relatives noticed excessive distractibility, restlessness, and unexpected changes of mood. Routine blood tests, brain MRI, transcranial Doppler, and 24-hour electrocardiogram were normal and no other neurological deficits were observed. This condition persisted for several days after the infection and disappeared without any specific therapy in about three weeks.

Recently, the patient has been complaining of postural instability when walking, and a tingling sensation in the lower extremities.

A neurological examination detected reduction of tendon reflexes in the lower limbs.

Electroneurography showed a mild sensory axonal polyneuropathy and gabapentin (900 mg/day) was then introduced, with resolution of symptoms.

After two years, the patient suddenly decided to terminate the therapy with gabapentin without any medical consultation.

The day after, she was referred to our department with an episode of mental confusion and incoherent speech. The patient had exhibited bizarre behaviour consisting of wandering around, entering private properties, and eating without cutlery, using only her hands. Moreover, she was strongly convinced of having “identified the way to transform garbage into gold” and therefore had started to accumulate rubbish at home. She rapidly developed a delirium of persecution, believing that others were conspiring against her, and suspecting that a nurse had injected a metal bar into her arm.

The patient was not cooperative with a formal mental status examination and had difficulty in sustaining attention. She had temporal but not spatial disorientation, she was agitated and anxious and complained of past doctors’ conduct which, according to her, would have forced her to take useless medication for a long time.

No major axial or segmental deficit of strength was detected. Tendon reflexes were symmetrically diminished in the lower extremities.

An electroencephalogram was normal. Performed under compulsory sedation, complete blood counts, electrocardiogram and brain MRI were not significant.

After introducing haloperidol (up to 3 mg/three times per day), the delirium quickly disappeared and the psychiatric symptoms markedly improved. She showed normal orientation in time and space, slight ideomotor slowing and somnolence. MMSE scored 30/30. PNSS score was 65 (range 30-210).

DISCUSSION

Gabapentin is an anti-epileptic drug with a low side-effects profile and versatile employment in the management of neuropathic pain and several diseases.

Here, we reported on a woman without any previously diagnosed psychiatric disorder, having acute delirium after gabapentin withdrawal. This reaction was induced after long treatment with low doses of the drug.

We hypothesized that the previous episode of confusion, which occurred several years ago, was an undiagnosed brief psychotic disorder (DSM IV-TR criteria) and that this patient had had hypo-maniacal behaviour during her entire life alternating with several depressive episodes.

Gabapentin is generally considered to be a well-tolerated drug, but isolated case reports have suggested that withdrawal may induce several complications.

To date, no author had described a delirium after gabapentin discontinuation. This molecule reduces the expression of α2δ-1 and α2δ-2 voltage-gated calcium channels in the limbic forebrain and frontal cortex, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability.

The prolonged use of gabapentin in this woman may have acted as a mood stabilizer and the abrupt discontinuation could have caused a rapid up-regulation of the fronto-limbic circuiting mediated by calcium channels.

We suggest carefully checking pre-morbid mental status of candidates to the use of gabapentin and considering slow drug tapering, independently from a previous diagnosis of psychiatric disorder.

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Ciprofloxacin safety is similar to other antibiotic. However, it’s use has been associated with various systemic adverse effects which vary from a mild form like gastroenteritis to a severe one like acute renal failure. The central nervous system (CNS) adverse effects include headache, confusion and seizure. However; there are rare reports of peripheral neuropathies. These patients have experienced parathesia, hypoesthesia, dysesthesias and weakness. The CNS and peripheral nervous system (PNS) side effects of ciprofloxacin can occur even after the first dose. The treatment should be stopped in order to prevent irreversible damage.

CASE REPORT

A 49-year-old patient with a past medical history of hypertension and lumbar spondylosis was treated with regular botulinum toxin injections for detrusor muscle hyperactivity. Three weeks earlier, he had received an intravesical botulinum toxin injection and over the ensuing two weeks he developed fever, rigors and dysuria. His general practitioner prescribed him ten days cefadroxil for a presumed UTI but, as his symptoms remained, the antibiotic was changed to oral ciprofloxacin. Within 24 hours he developed a severe burning sensation in his feet, in the left more than the right, necessitating urgent admission to hospital. His treatment for UTI continued with intravenous ciprofloxacin as the urine culture grew Pseudomonas species sensitive to the antibiotic. On examination, he was oriented and alert but pyrexial. He was unable to stand due to burning feet pain. His cranial nerves and upper limbs were normal. In the lower limbs he had normal muscle bulk and no fasciculation. Power testing was normal proximally but limited distally due to severe pain; tone and reflexes were normal and plantars were down going bilaterally. Sensory examination showed severe allodynia up to mid-calf in the left leg and in the dorsum of the right foot. Joint position and vibration sensation were normal bilaterally.

He had a white cell count (WCC) of 12.7 and a CRP 152, both attributed to the UTI. The rest of his blood tests, including blood glucose, urea and electrolytes, liver function tests, thyroid function tests, immunoglobulins, immunoglobulin electro-phoresis and autoimmune and vasculitis screens, were normal.

Radiological examinations including chest, abdomen and lumbar spine X-rays and abdominal ultrasound, were all normal.

Magnetic resonance imaging (MRI) of thoracic and lumbar spine showed some degenerative changes at the L4/L5 and L5/S1 levels with mild exit narrowing at L4/L5 level but no spinal cord compression, reflecting his background history of lumbar spondylosis. No surgical intervention was deemed necessary.

The standard nerve conduction study (NCS) results performed in the second week of his admission did not show evidence of large fibre neuropathy, nor any evidence of a focal left sciatic or a lumbosacral radiculopathy in his lower limbs. The responses from the sural and superficial peroneal nerves were within normal limits bilaterally. These were slightly asymmetrical, with smaller responses in the left leg probably explained by a mild degree of peripheral oedema. Tibial and peroneal motor responses were within normal limits, with no asymmetry and normal F-waves. Electromyography (EMG) examination from left tibialis anterior and left medial gastrocnemius showed no evidence of active or chronic denervation.

Small fibre assessment with thermal sensation threshold study showed evidence of small fibre impairment in both his upper and lower limbs:
- Cold sensation threshold: elevated in the upper limb 24°C and lower limbs 17.3°C [Normal values are 28.55°C and 25.39°C respectively].
- Warm sensation threshold: elevated in the upper limb 36.4 °C and lower limbs 49.8°C [Normal values 34.89°C and 43.58°C respectively].
- Cold pain threshold: mildly elevated in the upper limbs 0.6°C. [Normal value is 2.39°C]
- In the lower limbs, cold stimulus evoked paradoxical sensations with cold being felt as heat.
- Heat pain threshold: normal in the upper 49.8°C and lower limbs 50.0+°C. [Normal values are 51.53°C and 50.34°C respectively]

Area: S1 Left Foot Dorso-lateral. (Table 1)
Area: C6 left hand Palmar Thenar. (Table 2)

His ciprofloxacin treatment for UTI was stopped five days after his admission, following neurology team review. He had symptomatic treatment for the hyperesthesia. His peripheral neuropathic pain resolved after three weeks.

DISCUSSION AND LITERATURE REVIEW

In 1992, a case report in the Lancet discussed a 37-year-old man who developed peripheral neuropathy whilst taking oral pefloxacin 400mg twice daily for five months. All symptoms were reported in the lower limbs, and all were sensory in nature.

REFERENCES