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CASE REPORT

Pregabalin-associated acute psychosis and epileptiform EEG-changes

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Summary Pregabalin is a novel anticonvulsive and analgesic drug that has been marketed in Europe for more than a year. The typical side effects are dizziness, somnolence and weight gain. We present a patient who, after unintended rapid up-titration of pregabalin, experienced psychotic symptoms associated with rhythmic EEG-changes resolving completely after discontinuation of pregabalin and benzodiazepine administration.

Introduction

Pregabalin is effective in patients with partial seizures, neuropathic pain and generalized anxiety disorders in several placebo-controlled trials. Somnolence and dizziness are the most frequent side effects among patients receiving pregabalin. Psychiatric symptoms have not been reported to date as typical side effects, and there is no evidence for proconvulsive effects, even in patients receiving high dosages.[1] We describe a patient with chronic neuropathic pain who developed a psychotic episode associated with rhythmic epileptiform EEG-changes after the initiation of pregabalin treatment.

Case report

A 44-year-old female patient was admitted to our department because of progressive spasticity of unknown etiology. The symptoms started 5 years ago with increasing numbness in her hands and legs. Then the patient experienced neuropathic pain in her hands, feet, and neck. At admission, the neurological examination revealed asymmetric spasticity in all four limbs, more on the right than the left. There were bilateral Babinski's signs as well as distal hypesthesia and allodynia in the legs.

The MRI examination of the brain and spine was normal, except for two old lesions on the right side of the putamen and the ventral side of the left lateral ventricle. Analysis of the cerebrospinal fluid (CSF) showed mild pleocytosis and mildly elevated protein level. Antibodies for borreliosis were not detectable. Electrodiagnostic studies revealed a predominantly sensory, distal symmetrical axonal

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polyneuropathy. There were no signs of acute or chronic denervation on the electromyographic examination. The EEG was normal, without slowing or epileptiform discharges (Fig. 1a). Initially she was treated with oxycodone 160 mg per day and ibuprofen 800 mg per day without sufficient reduction of the neuropathic pain. Because of the CSF findings, additional antibiotic therapy with ceftriaxone sodium i.v. was initiated but had no effect on the symptoms. Pain modulating therapy with amitryptiline (50 mg per day) was initiated and was well-tolerated. In addition, we recommended pregabalin starting with 150 mg per day and increasing in steps of 150 mg every 4 days. The patient was discharged with a prescription for pregabalin. Besides baclofen (30 mg per day) and flunitrazepam (1 mg per day), no further drug affecting the CNS was administered.

Two days later, the patient started taking 600 mg pregabalin per day without any titration. Subsequently, she became somnolent and developed psychotic symptoms consisting of affective disturbance, visual hallucinations, agitation and paranoid ideation. There was no previous history of psychotic symptoms. She was admitted to our intensive care unit by her general practitioner 3 days after she had started taking pregabalin. On admission, she was disoriented, agitated and experienced visual hallucinations. There were no other abnormalities in the general physical and neurological examination. The EEG showed rhythmic slowing and epileptiform discharges in both posterior head regions (Fig. 1b) that disappeared after the intravenous administration of 4 mg of lorazepam (Fig. 1c). The CSF revealed no cells, a slightly elevated protein level (511 mg/l), and no evidence for the local synthesis of antibodies. Blood-count, extended blood-chemistry including electrolytes, liver enzymes and blood urea nitrogen were normal. The pregabalin plasma level was 7.7 μg/ml on admission and 1.9 μg/ml 12 h later. The patient was diagnosed with pregabalin-associated ictal and postictal psychosis. We discontinued

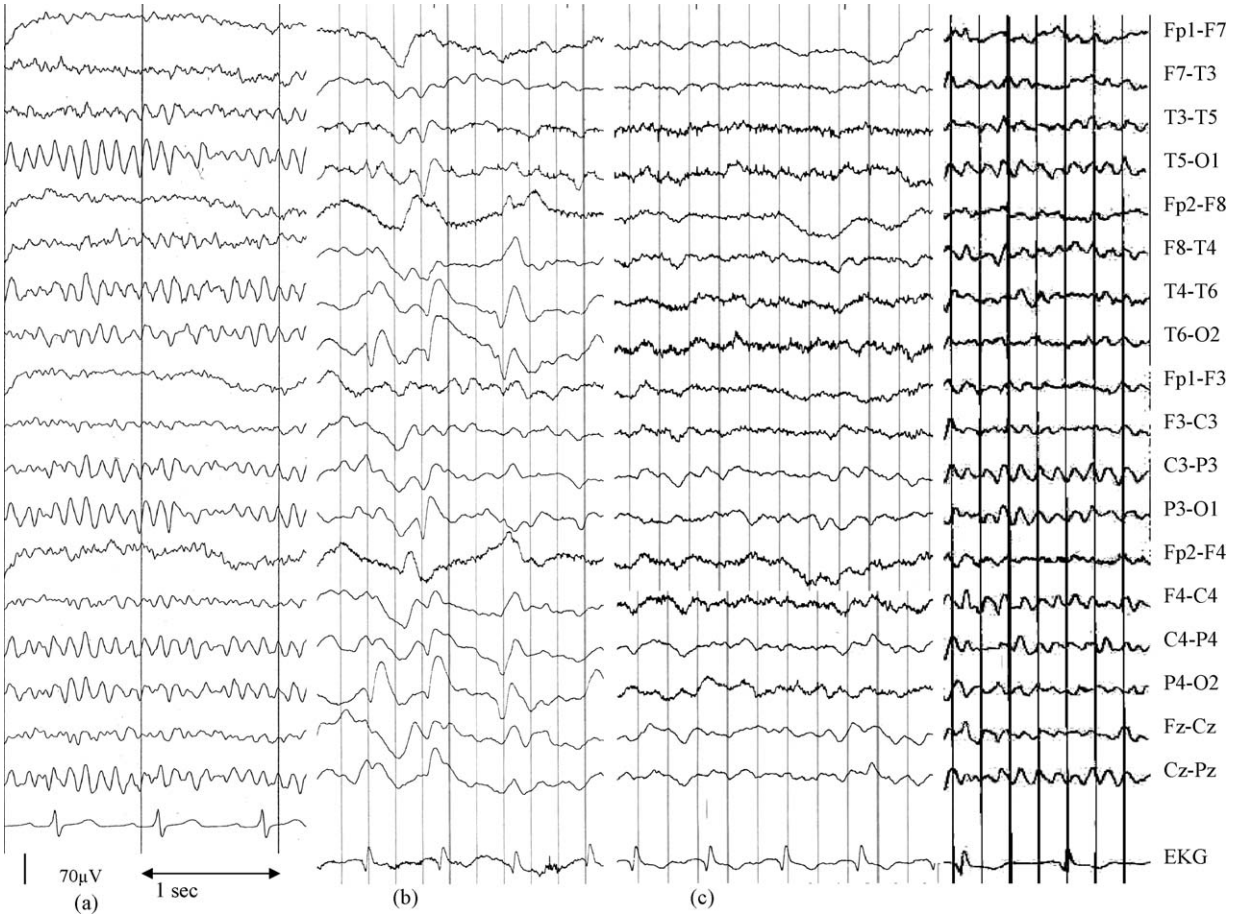

Figure 1 (a) Normal EEG 2 weeks before onset of pregabalin treatment; (b) EEG 2 days after the onset of the psychotic episode: generalized slowing, epileptiform discharges in both posterior head regions, maximum on the right; (c) EEG after the intravenous administration of 4 mg of lorazepam: restored background activity, with intermittent slowing in right posterior head region; and (d) EEG 2 weeks after onset of the psychotic episode, with resolution of the clinical symptoms: normal background activity.

pregabalin and treated her with lorazepam for 2 weeks. During this time, the patient gradually recovered and the EEG became normal again (Fig. 1d).

Discussion

The patient suffered from a sudden psychotic episode immediately after rapid titration of a relatively large dose of pregabalin. The episode was associated with rhythmic and epileptiform EEG changes that resolved after the administration of lorazepam. The symptoms disappeared within 2 weeks of anticonvulsant treatment and did not recur again. The clinical examination, routine blood tests and CSF analysis did not show evidence for an alternative explanation of the patient's symptoms. The close temporal relationship between the start of pregabalin therapy and the onset of the symptoms as well as the singularity of the episode suggest a causative role for pregabalincrucial role of pregabalin.

Anticonvulsant-associated psychotic symptoms are relatively rare.Vigabatrin may induce or worsen psychosis and depression.[2] Topiramate may induce both psychosis and depression, but these are less likely to occur at the currently recommended starting doses.[2] Gabapentin most likely has relatively little effect on behaviour but may exacerbate behavioural problems in some children with pre-existing difficulties.[2] In addition, there is a single case report on a gabapentin-induced paradoxical exacerbation of psychosis in a patient with schizophrenia.[3]

The rhythmic EEG changes and newly developed epileptiform discharges that subsided after anticonvulsant treatment suggest an epileptic nature of the episode. The paradoxical effects of anticonvulsants are well-recognized. They usually occur sporadically and in association with overdose or intoxication[4] but may also occur at normal doses and drug levels.[5] In our case, the patient took a high but normal dose, and her serum drug levels were within the normal range seen in the drug-approval studies.[6] However, the patient did not gradually increase the daily dose but immediately took the target dose of 600 mg per day. The sudden administration of a relatively high drug dose may have played a crucial role.

The pathophysiological mechanism of the patient's symptoms remains unclear. Although pregabalin is structurally related to GABA, it does not interact with either $GABA_A$ or $GABA_B$ receptors, it is not converted to GABA or to a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.[7] Pregabalin (as well as gabapentin) interacts with an auxiliary subunit (the $alpha_2$-delta subunit) of presynaptic voltage-gated calcium channels in the CNS. Potent binding at this site attenuates depolarization-induced calcium influx at nerve terminals, with a subsequent reduction in the release of excitatory neurotransmitters, including glutamate, noradrenaline, and substance P.[7] In predisposed persons, a sudden increase of pregabalin plasma levels might result in relative over-attenuation of inhibitory systems, and thus in paradoxical over-synchronization. However, there is no data available yet to elucidate this phenomenon.

Pregabalin is an effective anticonvulsant and analgesic drug. In the vast majority of patients, central nervous system side effects are rare, mild and transient in nature.[1] However, physicians should be aware that in some patients, even a normal dose of pregabalin may be associated with psychotic symptoms. More data is needed to estimate the risk and relevant risk factors for this phenomenon.

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