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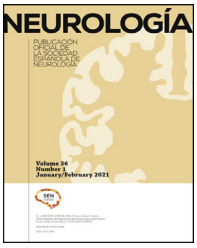

LETTER TO THE EDITOR

Complex regional pain syndrome and palmar fibromatosis secondary to treatment with primidone

Síndrome de Dolor Regional Complejo y fibromatosis palmar secundarios a tratamiento con primidona

Dear Editor,

Treatment with primidone is not usually associated with complex regional pain syndrome (CRPS); however, 6 cases of CRPS and fibromatosis have been described in several regions (palmar, plantar, and shoulder) in association with phenobarbital.[1,2]

We present the case of a patient diagnosed with CRPS in the left hand and receiving treatment with primidone.

Clinical case. Our patient was a 70-year-old man with type 2 diabetes and dyslipidaemia, a smoker of 7—11 cigarettes per day, and diagnosed 5 years previously with essential tremor, who was being treated with ascending doses of primidone; the patient's current treatment was Mysoline (1—1—1/2). He was under follow-up by the rheumatology department due to CRPS and was referred to our neurology department for assessment of a possible interaction with primidone.

The patient reported that he had been experiencing motor slowing in the 6 preceding months, which manifested with pain, flushing, tumefaction, and limitation to flexion and extension of the left fingers; he was diagnosed with CRPS. In the physical examination, he presented significantly limited flexion and extension due to very pronounced rigidity, suggesting palmar fibromatosis and onset of bilateral Dupuytren contracture, predominantly involving the left hand. Pain was treated with median nerve block and physiotherapy.

The neurological examination revealed bradyphrenia, mild akinesia in the left hand, no tremor, and smooth gait with appropriate arm swing.

Based on these findings, and suspecting encephalopathy and palmar fibromatosis associated with primidone use, we discontinued this treatment; after laboratory tests, brain MRI, and DaTSCAN, we ruled out primary neurological causes.

One month after discontinuation of the drug, the patient showed significant improvement of the encephalopathy, palmar fibromatosis, and CRPS; he was practically asymptomatic at 6 months.

Metabolic, primary rheumatological, and neurodegenerative causes were reasonably ruled out.

The relevance of the possible effects and interactions of primidone resides in the fact that it is one of the drugs of first choice for the treatment of essential tremor. The action mechanism of primidone is not fully understood, but it is believed to be due to the effect of one of its metabolites, phenobarbital. It acts by increasing the duration of opening of the chloride channels in GABA-A receptors, resulting in an increase in seizure threshold.[3] Hurst et al.[4] suggest that treatment with antiepileptic drugs causes a decrease in prostaglandin E, which in turn may enable contraction of palmar myofibroblasts and cause Dupuytren contracture. Recent studies have suggested that this disease may involve neuroinflammatory mechanisms associated with cell immunity (proinflammatory cytokines, TNF-α, etc), and some modulating mechanism of these same neuroinflammatory processes has been suggested.[5] Therefore, inhibition of TNF-α may prevent progression or recurrence of Dupuytren contracture. The pathophysiological mechanism of this side effect of primidone is currently unknown.

Primidone presents some known side effects, including dizziness, confusion, and difficulties in motor control. Patients under treatment with primidone for epilepsy are known to be less intolerant to the drug than patients treated due to essential tremor. One of the most widely accepted hypotheses to explain this phenomenon is age difference, as patients treated due to epilepsy are generally younger. Anti-seizure drugs are believed to influence liver and kidney function, body water, and even cognitive function in these patients.[6]

Although the association between the use of barbiturates and the onset of joint rigidity has been known since 1925,[5] it was not until 1941 that Lund[7] demonstrated this association. Furthermore, phenobarbital has been shown to be able to cause several connective tissue disorders, such as Ledderhose disease or other associated syndromes, such as Dupuytren contracture, frozen shoulder, Peyronie disease, or CRPS. These effects have been observed to occur from

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3 months to 20 years after the introduction of the drug, with this condition being dose-dependent and disappearing after discontinuation of the medication.[1] In the 3 cases showing a possible interaction, side effects were observed to manifest at 20, 5, and 6 years, respectively, after onset of phenobarbital treatment.[1]

As mentioned previously, we have found no cases of CRPS associated with primidone, although we did identify cases of other connective tissue diseases, such as the case reported by Vasconcellos et al.[8] in 2019. These authors describe the case of a 71-year-old patient who experienced palmar fascia fibrosis (Dupuytren contracture), plantar fascia fibrosis (Ledderhose disease), and tunica albuginea fibrosis (Peyronie disease), which remitted one year after discontinuation of primidone treatment for essential tremor.

In 1989, Mattson et al.[9] reviewed 622 cases of patients treated with antiepileptics who developed connective tissue disorders. Up to 6% of the patients treated with barbiturates developed such disorders. Of these, 4 were receiving primidone and were aged between 43 and 67 years. Three presented frozen shoulder between 8 and 28 months after treatment onset. The remaining patient developed Dupuytren contracture at 3 months after treatment onset. All patients improved in the first 4 months after treatment discontinuation. A spontaneous partial improvement of this side effect over time has been observed in patients treated with phenobarbital. Our literature search yielded only one study reporting 4 patients with reflex sympathetic dystrophy (now known as CRPS) and antiepileptic treatment[2]: phenobarbital in 3 and carbamazepine and valproate in one. All patients presented shoulder and hand impairment, which was bilateral in 2; one patient presented ipsilateral foot impairment. Two patients did not respond to treatment switch, but all improved with a course of prednisone. One patient with reflex sympathetic dystrophy associated with phenobarbital presented a relapse after inadvertent exposure to secobarbital.

We would like to draw attention to this side effect (CRPS) of primidone, which may manifest as late as 5 years after treatment onset and is potentially reversible when detected early.

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