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Clozapine-Induced Negative Myoclonus is not Cataplexy

To the Editor: Desarkar et al.[1] describe a patient who developed negative motor symptoms (sudden knee-buckling and dropping of objects) while taking clozapine. Similar cases have been reported by others,[2] and I have seen several cases as well. This phenomenon has been termed incorrectly cataplexy. True cataplexy is "specific to narcolepsy and . . . characterized by a sudden drop of muscle tone triggered by emotional factors."[3] Because clozapine-related intermittent loss of muscle tone is not preceded by strong emotion, and occurs in patients demonstrating no other evidence of narcolepsy (nor any evidence of a brainstem or hypothalamic lesion known to produce rare cases of secondary cataplexy[3]), it is inaccurate on purely semantic grounds to call this phenomenon cataplexy. A more accurate term is negative myoclonus, which has been defined as "a motor phenomenon characterized by involuntary jerky movement due to brief, sudden interruption of muscle activity."[4] Negative myoclonus can be seen in clinical conditions ranging from epilepsy to toxic-metabolic encephalopathies such as hepatic encephalopathy (in which case it is known as asterixis).[4]

Accurate terminology points the way toward better understanding the pathophysiology of clozapine-induced negative myoclonus. It is important to consider the possibility that clozapine-induced negative myoclonus, like clozapine-induced positive myoclonus, could be an epileptic phenomenon predictive of the development of other seizure types including generalized tonic-clonic convulsions.[5] In Desarkar et al.'s[1] study, the patient's nonepileptiform EEG does not rule out epilepsy; EEG is incompletely sensitive for epilepsy, and specialized back-averaged electromyography/EEG studies (not widely available) may sometimes be necessary to detect subtle epileptic discharges associated with negative or positive myoclonus.[4] If clozapine-induced negative myoclonus is actually an epileptic phenomenon, it might be expected to improve with certain antiepileptic medications (e.g., ethosuximide) but worsen with others (e.g., carbamazepine, phenytoin).[6]

Nonepileptic etiologies for clozapine-induced negative myoclonus must also be considered. As noted by Desarkar et al.,[1] abnormalities in neurotransmitter systems, including the orexin system known to be associated with narcoleptic cataplexy,[3] may also play a role in clozapine-induced negative myoclonus. Asterixis is also a potential explanation for Desarkar et al.'s patient, whose high serum valproate level (assuming the units were μg/ml—not μg/dl as printed) either alone or in combination with clozapine could have contributed to a subtle toxic-metabolic encephalopathy.

It is hoped that this clarification of terminology will facilitate integration of research findings from different areas of neurology (epilepsy, sleep disorders, movement disorders) to provide further insight into the pathophysiology of clozapine-induced negative myoclonus.

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Generalized Peripheral Nerve Hyperexcitability Associated With Lithium

To the Editor: Approximately one out of every 1,000–1,500 people in Western countries are receiving lithium treatment, mainly for a diagnosis of bipolar disorder.[1] The overall incidence of side effects on the CNS ranges from 35% to 50%, with lithium serum levels within the therapeutic range.[2] They often include an acute encephalopathy with cognitive impairment, hallucinations, insomnia, movement disorders, seizures, cerebellar signs, nystagmus, and ocular motor defects. Among the neuromuscular side effects, myopathy, axonal neuropathy, and a myasthenic syndrome were reported.[3] In the majority of cases, drug discontinuation implies complete recovery. Here we describe a patient presenting with an acquired generalized peripheral nerve hyperexcitability associated with lithium treatment.

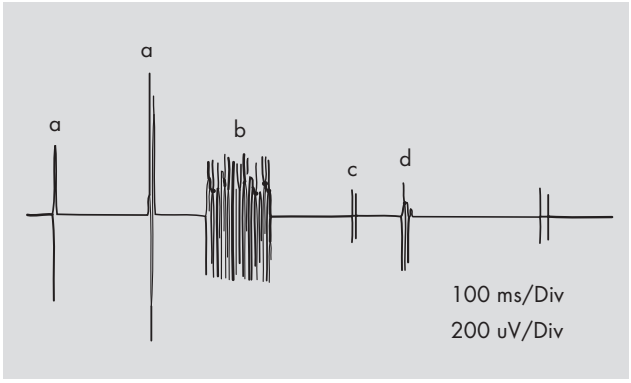
Case Report

A 73-year-old man with a long-standing history of bipolar II disorder was admitted to our neurology department for acute onset of confusion, dysarthria, gait disturbances, muscle stiffness with cramps, and widespread twitching. He reported a fever 3 days before admission. There was no previous history of neurological or neuromuscular disorders. The patient had been taking lithium carbonate (600 mg daily) and venlafaxine (75 mg/day) in the last 3 years. Neurological examination showed an unsteady gait, dysarthria, resting and postural tremor of the upper and lower limbs, mild bradykinesia and rigidity, and prominent muscle twitching of the tongue and the four limbs. Reflexes were symmetrical. Mini-Mental State Examination (MMSE) and Milan Overall Dementia Assessment (MODA) were 24.3 and 89.8, respectively. Routine blood tests including inflammation indexes, electrolytes, renal and thyroid function, creatine kinase, glucose, vitamin B_{12}, folate, and ammonium were normal. Lithium serum level was within the normal range (0.8 meq/liter). Voltage-gated potassium channel antibodies and acetylcholine receptor antibodies were negative. A brain CT scan showed a vascular encephalopathy. An EEG showed a widespread slowing of the background activity with outbursts of generalized theta-delta abnormalities. Motor and sensory nerve conductions were in the normal range. Repetitive stimulation of the motor nerves revealed no myasthenic defect. The needle electromyogram (EMG) disclosed no neuropathic or myopathic features. However, widespread spontaneous motor unit discharges were recorded in the form of doublets, triplets, or multiplets with high intraburst frequencies (50 Hz–160 Hz), occurring at irregular intervals. They were interposed by fasciculation potentials and myokymic discharges (Figure 1). The overall neurophysiological picture met the criteria suggested by Maddison[4] for the diagnosis of the peripheral nerve hyperexcitability "neuromyotonia phenotype." Since the extensive search for other peripheral nerve hyperexcitability causes was negative, lithium was hypothesized to be responsible for the picture. Indeed, after lithium withdrawal the patient experienced a complete clinical recovery with disappearance of the neurological signs. The treatment with venlafaxine was kept unchanged. Two months later, the EMG and neuromuscular picture remained normal.

Discussion

Our patient presented several predisposing factors for lithium toxicity: elderly age, fever, and vascular encephalopathy.[5] Side effects in the CNS such as confusional state, dysarthria, extrapyramidal signs, and EEG abnormalities may occur within lithium therapeutic range.[2]

FIGURE 1. Needle Electromyography



Recording of fasciculations (a), myokymic discharges (b), doublets (c), and multiplets (d) from the right tibialis anterior muscle.