

Case Reports

Memantine-induced Myoclonus in a Patient with Alzheimer DiseaseAditya A. Murgai¹ & Mark S. LeDoux^{1*}¹Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA**Abstract**

Background: Myoclonus can be a clinical manifestation of numerous neurodegenerative disorders and an adverse drug reaction to medications used in their treatment.

Case Report: Herein, we report memantine-induced myoclonus in a patient with Alzheimer disease. The myoclonus seen in our patient was generalized (proximal limbs and trunk), present at rest and with action, and stimulus sensitive. A structured evaluation with the Unified Myoclonus Rating Scale showed that the myoclonus had no significant effect on functional capacity. After discontinuation of memantine, myoclonus slowly resolved over the course of several weeks.

Discussion: Memantine may cause myoclonus in susceptible individuals.

Keywords: Memantine, myoclonus, Alzheimer disease, adverse drug reaction

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Introduction

Myoclonus is a clinical sign defined as sudden, brief, shock like, involuntary movements caused by muscular contractions or inhibitions. Myoclonus can be seen in dementing neurodegenerative disorders of varied etiologies including Creutzfeldt–Jakob disease, Alzheimer disease, dementia with Lewy bodies, and frontotemporal dementia.¹ Myoclonus is also one known, albeit rare, side effect of drugs used to treat dementia and other neurological disorders. The possibility of drug-induced myoclonus in subjects with dementia and related neurodegenerative disorders may be ignored. Here we present a case of myoclonus in a patient with Alzheimer dementia whose myoclonus recovered completely after withdrawal of memantine.

Written informed consent was obtained for publication of the case report and accompanying videos.

Case report

An 89-year-old male presented to us with a 7-year history of progressive cognitive decline and 5-year history of myoclonus. The

myoclonus was generalized in distribution, mainly in the trunk and limbs, and present both at rest and with activity. There were no associated falls or notable functional limitations due to the myoclonus. At the time of initial evaluation, he was receiving memantine 10 mg twice daily for cognitive impairment, previously diagnosed as Alzheimer disease. Myoclonus was being treated with levetiracetam 1000 mg twice daily, clonazepam 0.25 mg daily, and divalproex sodium extended release 500 mg twice daily. Over the course of approximately 2 years, there was minimal subjective or documented clinical benefit from levetiracetam, in isolation, or the combination of levetiracetam, clonazepam, and divalproex sodium. He was also receiving medications for essential hypertension (amlodipine and hydralazine), hypercholesterolemia (simvastatin) and hypothyroidism (levothyroxine). Upon detailed review of historical events, the patient's wife confirmed that the appearance of myoclonus was temporally associated with initiation of therapy with memantine. She had failed to recognize this association during clinic visits with the referring general neurologist.



Video Segment 1A. Baseline. This video shows generalized myoclonus present at rest, with action, and in response to stimuli. Myoclonus is maximal in the proximal legs followed by the trunk and arms. **Segment 1B. Video at 3-month Follow-up.** No myoclonus seen at rest or with stimuli.

Prior to the addition of memantine, the patient's Alzheimer disease was initially treated with transdermal rivastigmine up to 13.3 mg daily. Rivastigmine was discontinued due to apparent lack of efficacy with steady decline in cognition over several years. Magnetic resonance imaging of the brain showed moderate generalized atrophy and mild microangiopathy. Electroencephalography (EEG) obtained with the patient awake and asleep was mildly abnormal due to frequent left temporal slowing in the delta range. Although myoclonus was present during the EEG, there were no apparent neurophysiological correlates. No epileptiform activity was noted on EEG. The EEG background was slow and disorganized with mixed alpha and theta frequencies and absence of a well-recognized posterior alpha rhythm. Bilateral upper limb somatosensory evoked potential studies (SSEPs) were normal.

On physical examination, the pulse was 68/minute and regular, and blood pressure was 130/60 mmHg. The Mini-Mental State Examination score was 20 out of 30 with marked deficits in recall (0/3) and orientation (3/10). Cranial nerve examination was normal: there was no weakness or sensory loss, deep tendon reflexes were normal, and planters were down. A snout reflex was present. The Unified Myoclonus Rating Scale (UMRS)² was videotaped. Myoclonus was most prominent in the proximal legs followed by the trunk and arms without facial involvement (Video Segment 1A). The following UMRS scores were obtained: patient questionnaire (6/44), patient global disability assessment (1/4), myoclonus at rest

(10/128), stimulus sensitivity (10/17), myoclonus with action (5/160), functional tests (0/28), and physician global disability score (1/4). Myoclonus was elicited by unexpected handclaps, nose taps, jaw jerks, pin pricks to the bottom of the feet, toe flicks, and taps to the biceps tendons. There was no evidence for negative myoclonus on examination. The patient's myoclonus exerted mildly deleterious effects on eating, drinking, dressing, rising from a seated position, standing, and walking.

Laboratory studies showed normal blood glucose, vitamin B12, folate, serum electrolytes, and liver function tests. Mild anemia (hematocrit 37.6%, reference range 39–55%), and mild elevations in serum creatinine (1.47 mg/dL, reference range 0.6–1.3 mg/dL), blood urea nitrogen (34 mg/dL, reference range 7–25 mg/dL) and thyroid stimulating hormone (5.88 uIU/mL, 0.35–5.5 uIU/mL) were noted.

Memantine was tapered off over the course of 4 weeks with moderate reduction in the frequency and severity of myoclonus. According to the patient's spouse, myoclonus did not completely resolve until several weeks after the final dose of memantine. Follow-up examination with repeat UMRS 3 months after the initial UMRS showed complete resolution of stimulus-sensitive, rest and action myoclonus (Video Segment 1B). Upon resolution of myoclonus, levetiracetam and divalproex sodium were discontinued without consequence. The patient continued to take an occasional dose of 0.25 mg of clonazepam for sleep. Resolution of myoclonus was

associated with mild improvements in the subject's ability to eat, drink, dress, stand, and walk.

A total score of 4 was obtained upon applying the Naranjo Adverse Drug Reaction Probability Scale,³ suggesting that the myoclonus in our patient was a possible adverse reaction to memantine. The Naranjo score is derived from a 10-item questionnaire and scores range from 0 to ≥ 9 . The probability of an adverse drug reaction is assigned as definite (≥ 9), probable (5–8), possible (1–4), or doubtful (0).

Discussion

Memantine is a low-to-moderate affinity, uncompetitive (open-channel), voltage-dependent, NMDA (N-methyl-D-aspartic acid)-receptor antagonist with fast on/off kinetics that inhibit excessive calcium influx induced by chronic overstimulation of the NMDA receptor. Memantine is approved in the United States for the treatment of patients with moderate-to-severe dementia of the Alzheimer type.⁴ Memantine is largely excreted unchanged by the kidney and caution should be used in patients with significant renal impairment. Overall, drugs used for dementia cause approximately 4% of drug-induced myoclonus, and cholinesterase inhibitors are the most common culprits.⁵ Drug-induced myoclonus can be cortical or subcortical origin. In patients with drug-induced myoclonus, a cortical origin is supported by the presence of EEG spikes and large amplitude SSEPs.^{6,7}

Our review of the literature identified only three reports of myoclonus associated with memantine.^{8–10} All three of these previously described patients had Alzheimer disease and two of the three had renal impairment, which may have contributed to the toxicity of memantine.^{8–10} Although one report included a video that documents myoclonus,¹⁰ myoclonus was not robustly characterized in these reports and the UMRS was not employed as part of the neurological evaluations. However, as seen in our patient, memantine-induced myoclonus was described as generalized in these earlier publications. The normal SSEPs, normal EEG, stimulus sensitivity, and predominant involvement of the proximal limbs and trunk are most compatible with a subcortical origin. In addition, a subcortical origin is supported by the lack of improvement with medications that act principally to suppress cortical myoclonus.

Myoclonus is a common clinical manifestation of Alzheimer disease.¹¹ In one study, 8% of patients with Alzheimer disease had a myoclonic variant characterized by presenile onset with severe cognitive deterioration, mutism, and early-onset myoclonus.¹² Myoclonus is more commonly seen in early-onset and rapidly progressive Alzheimer disease, where its prevalence may be as high as 75%.¹³ Myoclonus in Alzheimer disease can be classified into cortical and subcortical types. The cortical variety is more common.^{14,15} Subcortical myoclonus may have its origin in the brainstem, and autopsy studies have shown reduced numbers of neurons in the locus coeruleus and raphe nucleus in these patients.¹⁶ The myoclonus in Alzheimer disease may be multifocal or generalized and it can occur at rest, action, or in response to stimuli.¹⁷

The cellular and network origins of myoclonus in patients taking memantine are not known. Amantadine, which has a similar

mechanism of action to memantine, has been shown to produce myoclonus. Both drugs act by blocking NMDA glutamate receptors. There have been reports of amantadine-induced myoclonus in patients with Parkinson disease and progressive supranuclear palsy.^{18,19}

Myoclonus slowly disappeared over a period of 3–4 weeks after withdrawal of memantine, suggesting that some neuronal changes induced by memantine persist long after the drug has been cleared from the system. It is possible that memantine induces long-term changes in neuronal firing properties by altering the expression of secondary- or delayed-response genes. In this regard, memantine has been shown to alter the expression of genes in rat brain encoding kinases, phosphatases, G-protein coupled receptors, vesicle and synaptic proteins, and neuropeptides.²⁰

Based on clinical examination alone it can be difficult to differentiate drug-induced myoclonus from the myoclonus of degenerative dementias. An acute onset and clear temporal association with initiation of medication would point towards drug-induced myoclonus. Additional evidence for drug-induced myoclonus includes previous valid reports of causality in the referred literature, resolution with discontinuation of the medication, and correlations between myoclonus severity and drug dosage.

To conclude, myoclonus may be seen as an adverse reaction to memantine in patients with Alzheimer disease and, perhaps, other neurodegenerative disorders. Given that myoclonus is relatively common in Alzheimer disease, clinicians must maintain a high index of suspicion of an adverse drug reaction when myoclonus appears in this patient population. Moreover, myoclonus may take weeks to resolve after discontinuation of memantine.

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