Movement Disorders
CLINICAL PRACTICE

CASE SERIES WITH LITERATURE REVIEW

Amantadine-Induced Craniofacial Myoclonus: Distinctive Iatrogenic Dysarthria in Parkinson's Disease

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ABSTRACT: Background: Amantadine is a widely prescribed medication in Parkinson's disease (PD). A distinctive craniofacial distribution of myoclonus with speech impairment is an underrecognized iatrogenic complication in amantadine-treated patients with PD.

Cases: We report 7 patients with idiopathic PD (disease duration, 6–21 years) who developed speech-induced craniofacial-predominant myoclonus with "stuttering-like" dysarthria and speech arrests days to months after amantadine initiation or dose increase. Renal insufficiency was identified as a risk factor in 4 cases. In all cases, reduction or discontinuation of amantadine markedly attenuated the myoclonus and restored speech intelligibility.

Literature Review: Amantadine can induce subcortical segmental or generalized myoclonus. A report in 1996 of "vocal myoclonus" in an amantadine-treated patient with PD was the first observation of a focal distribution of myoclonus, particularly affecting speech. Since then, few cases of craniofacial myoclonus with speech impairment have been reported, none with accompanying video. With 1 exception, the craniofacial distribution was part of a generalized pattern of amantadine-induced myoclonus. Comorbid renal insufficiency is a recognized risk factor.

Conclusions: Speech-induced craniofacial myoclonus, with marked "stuttering-like" dysarthria and speech arrests, is a disabling iatrogenic complication in PD that resolves upon amantadine discontinuation.

Myoclonus is a movement disorder with a large differential diagnosis depending on origin (cortical, subcortical, brainstem reflex, and spinal), distribution, and temporal course and whether it appears alone or in combination with other movement disorders.[1] Craniofacial myoclonus consists of involuntary, arrhythmic, very brief shock-like "jerks" of the face or cranial musculature (eg, tongue, pharynx, larynx, diaphragm).[2] Isolated speech-induced craniofacial action myoclonus is rare; this distribution is more commonly described in the context of generalized myoclonus.[2] In 7 cases, we highlight an unusual phenomenon that may arise in amantadine-treated patients with Parkinson's disease (PD): craniofacial action myoclonus as the primary complaint, triggered or worsened by speech and leading to marked "stuttering-like" dysarthria and speech arrests.[2–4] The prompt recognition of this iatrogenic complication, which warrants discontinuation of amantadine, is critical to the overall care of patients with PD.

Case Series

Table 1 summarizes the key demographic variables, medications, and laboratory abnormalities, if present, of 7 patients with PD (range, 6–21 years of disease duration). In most cases, amantadine

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TABLE 1 *Demographics and accompanying data for patients on amantadine with craniofacial myoclonus*

Case Number, Age (Years), Sex	PD Duration (Years)	Renal Disease	Myoclonus Distribution	Relevant Medications at Myoclonus Onset	Laboratory Abnormality Values (Normal Range)	Myoclonus Outcome
Case 1, 75, female	6	No	Craniofacial Upper extremity	Amantadine 300 mg/day Levodopa 600 mg/day Amitriptyline, unknown dose	None obtained	Resolution 3 days after discontinuation
Case 2, 73, female	8	No	Craniofacial Upper extremity	Amantadine 300 mg/day Levodopa 750 mg/day Entacapone 1000 mg/day Sertraline 200 mg/day Clonazepam 0.75 mg/day	None obtained	Improvement 1 week after discontinuation, with reinitiation per patient preference
Case 3, 59, male	8	No	Craniofacial Upper extremity torso	Amantadine 200 mg/day Levodopa 1200 mg/day Hydrochlorothiazide 25 mg/day	GFR 90 mL/min/1.73 m^2 BUN 30 mg/dL (7–25)	Resolution 3 days after discontinuation
Case 4, 66, female	16	No	Craniofacial Upper extremity torso	Amantadine 300 mg/day Levodopa 1000 mg/day Diphenhydramine 25 mg/day Norfloxacin	GFR 60 mL/min/1.73 m^2 BUN 7.8 mmol/L[3–7]	Resolution 2 weeks after discontinuation
Case 5, 77, female	10	No	Craniofacial	Amantadine 200 mg/day Levodopa 500 mg/day	None obtained	Resolution after discontinuation, unclear timing
Case 6, 60, male	21	Yes	Craniofacial Upper extremity	Amantadine 300 mg/day Levodopa 1500 mg/day	Initial GFR 47 mL/min/1.73 m^2 BUN 8.3 mmol/L[5–8] Follow-up: GFR 92 mL/min/1.73 m^2	Resolution 5 months after reduction to 200 mg/day
Case 7, 74, female	16	Yes	Craniofacial	Amantadine 200 mg/day Levodopa 800 mg/day	Polycystic kidney disease and UTIs, but no documented renal dysfunction	Improvement after reduction to 100 mg/day, with recurrences with renal impairment

Abbreviations: PD, Parkinson's disease; GFR, glomerular filtration rate; BUN, blood urea nitrogen; UTI, urinary tract infection.

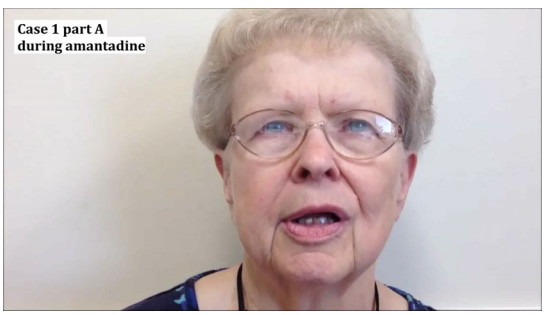
was used to treat peak-dose dyskinesia, but also in some *off*-related tremor or *off*-related foot dystonia.

Case 1

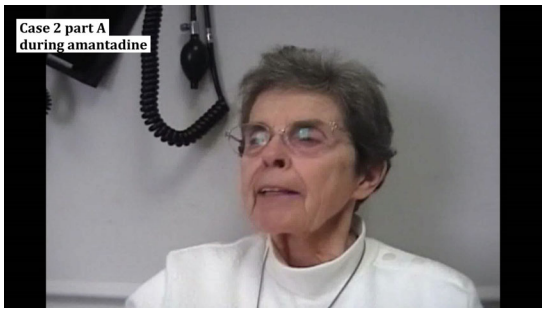
A year after amantadine initiation and 3 days after a dose increase to 100 mg 3 times a day (t.i.d.), this 75-year-old woman with normal cognition developed intermittent "stuttering and stammering" and "involuntary twisting and twitching around the mouth," with words "coming out garbled." In addition, she reported visual hallucinations, worsened balance, and more frequent falls. An urgent evaluation showed speech impairment associated with myoclonus affecting the orofacial musculature, and hand myoclonus (Video 1, part A), with an *on*-state Movement Disorders Society–sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) motor subscale score of 29. At 3 days after amantadine discontinuation, she returned to baseline (*on*-state MDS-UPDRS III score of 22), with resolution of the hallucinations and improvement in balance (Video 1, part B).

Case 2

About 4 months after amantadine initiation, this 73-year-old woman with normal cognition noted "ragged, stuttering, jumbled" speech. To further improve dyskinesia control, the dose of amantadine was increased to 100 mg t.i.d. She developed "speech arrests," slurring, "jerking of the mouth," and "stumbling over words" 9 days later. Examination revealed speech impairment with brief arrests and mild myoclonus around the perioral region and hands (Video 2, part A) (*on*-state MDS-UPDRS III score of 12). A week after amantadine discontinuation, she reported a clearer speech although with worsening of dyskinesia. At her request, amantadine was reinitiated at the dosage of 100 mg twice a day (b.i.d.), which improved dyskinesia without re-emergence of speech problems (*on*-state MDS-UPDRS III score of 12). She self-titrated the dosage back to 100 mg t.i.d., trying to further improve dyskinesia control, leading again to severe speech stuttering and craniofacial myoclonus. As she perceived dyskinesia to yield a greater disability than dysarthria, she opted to continue long-term amantadine (Video 2, part B).



Video 1. Case 1. Part A: during amantadine therapy; part B: 1 month after amantadine cessation.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828



Video 2. Case 2. Part A: during amantadine therapy; part B: after long-term use of amantadine (approximately 8 years after part A).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

Case 3

This 59-year-old man with normal cognition had dyskinesia with an *on*-state MDS-UPDRS III score of 23. Amantadine was initiated, and 13 days after reaching 100 mg b.i.d., as well as concurrent initiation of hydrochlorothiazide to treat his hypertension (by his primary care physician), he experienced an abrupt onset of "twitching and jerking" of the torso and "chattering" of the jaw approximately 12 hours after the last dose. The movements interfered with his ability to speak. There was no change in mental status. The patient discontinued amantadine, but movements worsened, reaching a maximum intensity about 36 hours after the last dose. Evaluation in the emergency department showed trunk and left shoulder myoclonus with asterixis of his hands and rhythmic myoclonus of the jaw (Video 3). Workup showed high blood urea nitrogen (Table 1). Approximately

Video 3. Case 3. During amantadine therapy.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

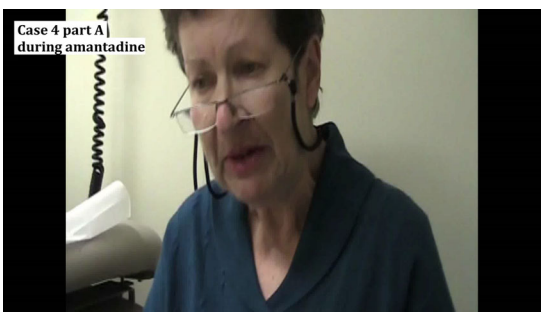
3 days after the last dose of amantadine, he returned to baseline with complete resolution of the myoclonus; on follow-up exam, his *on*-state MDS-UPDRS III score was 20.

Case 4

After 9 years of treatment with amantadine 100 mg b.i.d. and 8 months after a dose increase to 300 mg/day, this 66-year-old woman with normal cognition developed intermittent speech difficulties and visual hallucinations. Her speech was described as "getting stuck with certain words although she knew what she wanted to say." She had 1 episode of loss of consciousness with jerky movements. She was diagnosed with a urinary tract infection and treated with norfloxacin. Her examination (Video 4, part A) showed action-induced orofacial myoclonus with speech interference, probable diaphragmatic involvement as she vocalized with a grunt at times during speech, and a jerky irregular upper limb rest and action tremor with superimposed stimulus-sensitive myoclonus (*on*-state MDS-UPDRS III score of 34). Cognition was impaired (Montreal Cognitive Assessment [MoCA] score of 25/30). She also had a tonic–clonic generalized seizure. Workup demonstrated mild worsening of renal function (Table 1). The norfloxacin was changed to trimethoprim, and amantadine was weaned over 72 hours. About 48 hours after amantadine discontinuation, the patient became confused, paranoid, and disoriented with worsened mobility (Video 4, part B). Myoclonus had resolved completely 2 weeks later, but hallucinations persisted (Video 4, part C). The patient had a full recovery 1 month afterward (*on*-state MDS-UPDRS III score of 25; MoCA score of 29/30), including a resolution of the hallucinations.

Case 5

As a result of worsening bilateral lower extremity edema, this 77-year-old woman had amantadine discontinued, which made previously controlled dyskinesia reemerge. Amantadine was restarted at 100 mg b.i.d., and 1 month later she developed a new speech impairment, jerky facial movements, worsening cognition, and lower extremity edema. Examination showed prominent stimulus and action-sensitive facial myoclonus (Video 5). Following slow amantadine tapering and discontinuation, she returned to baseline (*on*-state MDS-UPDRS III score of 34).

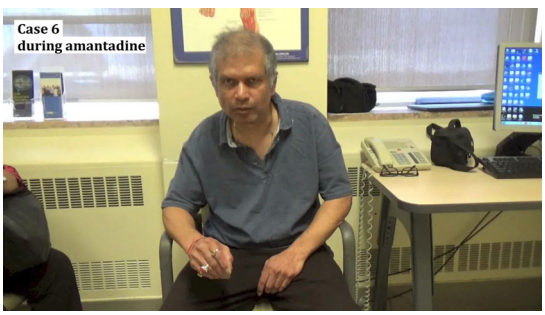


Video 4. Case 4. Part A: during amantadine therapy; part B: 1 week after amantadine cessation; part C: 2 weeks after amantadine cessation.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

Video 5. Case 5. During amantadine therapy.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

Case 6

After 13 years of treatment with amantadine 100 mg t.i.d., this 60-year-old man with normal cognition with a history of diabetes and renal dysfunction was reported by his wife to have occasional mouth "twitching" during the past year. He suffered sudden worsening of abnormal facial movements with speech problems and stuttering, an increase in falls, visual hallucinations, and cognitive decline (MoCA score of 19/30). Examination demonstrated action-induced and stimulus-sensitive facial myoclonus impacting speech (Video 6) as well as stimulus-sensitive action and spontaneous myoclonus in the upper extremities (*on*-state MDS-UPDRS III score of 66). Workup showed renal impairment (Table 1). Amantadine was tapered, but his motor



Video 6. Case 6. During amantadine therapy.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

Video 7. Case 7. During amantadine therapy.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13828

status worsened with new freezing of gait. Subsequent blood work revealed an improvement in renal function. Levodopa dose was adjusted to permit withdrawal of amantadine, and motor status improved but the dyskinesia worsened. Amantadine was eventually reintroduced at 200 mg/day. Myoclonus resolved 5 months later, and he returned to baseline (*on*-state MDS-UPDRS III score of 32; MoCA 28/30).

Case 7

This 74-year-old woman had been taking amantadine 100 mg b.i.d. for 1.5 years. Without any subjective deficits, she was witnessed to have intermittent "shock-like" movements of the right lower face (*on*-state MDS-UPDRS III score of 25) (Video 7). Amantadine was reduced to once daily, improving her facial movements but worsening her dyskinesia (*on*-state MDS-UPDRS III score of 26). Her medical history was notable for polycystic kidney disease and recurrent urinary tract infections. Although renal function was reported to be normal, recurrence of facial movements was noted during periods of suspected renal impairment. The dose of amantadine 1 year later was eventually increased to 100 mg b.i.d. without recurrence of the facial movements.

Literature Review and Discussion

In 1996, Pfeiffer reported a case of amantadine-induced facial and vocal myoclonus in a patient with PD resulting in speech "stuttering" triggered by attempts to talk, resolving upon cessation of the drug.[3] In 2001, Matsunaga et al described 3 cases of generalized myoclonus in association with amantadine use; of these cases, 2 had facial and tongue involvement.[5] Since then, a handful of other amantadine-associated cases with generalized myoclonus have been reported to also involve the face, jaw, or tongue, at times associated with stuttering of speech or speech arrests.[3–7] Facial or cranial myoclonus in isolation (ie, without myoclonus elsewhere) has been rarely reported.[3,4] In all cases, myoclonus and speech impairment improved or resolved following the discontinuation of amantadine.[3–7]

The pathogenesis of amantadine-induced myoclonus is unclear. Although amantadine is better known as a weak *N*-methyl-D-aspartate receptor antagonist, its lesser-known serotonergic effects may be responsible for the iatrogenic complication reported here, magnified in the setting of renal insufficiency. Amantadine is excreted primarily in the urine and minimally removed through hemodialysis, with its elimination half-life significantly prolonged in patients with even mildly impaired renal function.[8–11] This may explain the vulnerability in cases 3, 4, 6, and 7. Renal impairment is a well-recognized risk for amantadine-induced seizures and generalized myoclonus, encephalopathy, ataxia, and hallucinations.[5,7,8,10,12–14] Serotonin syndrome, in which myoclonus is a key criterion for diagnosis, has been reported due to amantadine in the context of renal failure.[15] Even subclinical renal insufficiency may alter the levels of amantadine and induce toxicity. In some patients with PD on stable amantadine doses (50–300 mg/day), plasma amantadine levels can reach more than 3000 ng/mL.[11] Plasma levels above 1000 ng/mL are sufficient to induce neurological toxicity.[16]

Monitoring of amantadine levels, although not universally available, has been suggested in patients with mild to moderate renal impairment.[8] Subclinical renal impairment can be suspected not only with increasing age but also in cases of dehydration, infection, obstructive urinary tract diseases, and concurrent medications potentially affecting renal function.[11,12] These factors clearly played a role in some of our cases.

Recognition of the full spectrum of amantadine-related central nervous system effects, including myoclonus of the craniofacial region, leading to "stuttering-like" dysarthria and speech arrests, allows clinicians to recognize a reversible source of dysarthria. In selected cases, myoclonus may be minimally bothersome and tolerable or preferable to inadequately controlled dyskinesia, as in case 2. However, we believe that this situation is probably very uncommon, and a decision to continue amantadine in such setting needs to be individualized according to patient preferences.

Although not pursued in any of our cases, neurophysiological testing could have been helpful to better characterize the cortical versus subcortical origin of myoclonus. Also, imaging was not obtained at the time of myoclonus occurrence in any of our cases, which precluded our ability to characterize other risk factors, for example, the comorbid presence of vascular disease.

Conclusions

In conclusion, craniofacial speech-induced myoclonus leading to dysarthria may arise from exposure to amantadine in patients with PD. This complication improves or resolves in all patients following the reduction or cessation of amantadine. Caution should always be exercised when prescribing

amantadine given its unfavorable risk-to-benefit ratio in some patients, especially in the elderly with (or at risk for) renal impairment.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

I.L.: 1B, 1C, 3A
L.A.-G.: 2C, 3B
S.S.: 2C, 3B
G.K.: 2C, 3B
S.H.F.: 2C, 3B
A.E.L.: 1A, 3B
A.J.E.: 1A, 3B

Disclosures

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