Aripiprazole Associated with Severe Exacerbation of Parkinson's Disease

Psychotic symptoms in Parkinson's disease (PD) can be benign, reversible adverse effects of dopaminergic medication, particularly dopamine agonists. Less commonly, they can be more severe, related to the disease process itself.[1] Treatment can be problematic, as typical and newer atypical antipsychotics may worsen PD due to dopamine receptor blockade. Only clozapine, an atypical antipsychotic, possesses a license for treatment of psychotic symptoms in PD because of its low risk of aggravating motor symptoms,[2] but use is limited by the risk of agranulocytosis,[3] necessitating regular hematological monitoring for the duration of treatment. Aripiprazole is a novel atypical antipsychotic with an apparently unique mechanism of action—a dopamine system stabilizer with partial agonist effect at D2 and 5HT1a receptors. It was hoped this drug would treat psychotic symptoms in PD with fewer extrapyramidal side effects.[4]

We report an initial experience of aripiprazole in a 48-year-old PD patient with acute psychosis. She developed an asymmetric, left-sided tremulous akinetic–rigid syndrome at 38 years of age. Magnetic resonance imaging scans of brain, serum copper, and ceruloplasmin were normal. Morbid thoughts and visual hallucinations complicated pergolide treatment, prompting discontinuation. Levodopa was commenced and ropinirole added 9 months later. Two years after starting L-dopa, she developed mild dyskinesias and motor fluctuations with clear therapeutic response. Three years later, she developed paranoid delusions about her neighbors. She reported auditory and visual hallucinations and was overtly withdrawn. After urgent psychiatric assessment, which suggested the possibility of a severe depressive episode with psychotic symptoms, she responded to olanzapine 10 mg and Cipramil 20 mg but suffered a steady deterioration in her PD, prompting discontinuation of olanzapine 4 months later. Her psychosis relapsed, and quetiapine 600 mg was commenced and Cipramil increased to 60 mg. At 5 months, despite increased dosages of quetiapine (800 mg), her psychosis worsened and she was readmitted after an attempted suicide. She continued to experience paranoid ideation and auditory hallucinations, believing staff were filming pornographic videos of her and her family. On day 4 of admission, aripiprazole was started at 15 mg/day (after clozapine was discussed as a possible treatment but declined by the patient) and quetiapine was withdrawn (over 2 weeks), leading to complete resolution of psychosis. However, within a week she became unable to walk, dress, or feed herself due to her severe akinetic–rigid state (Unified Parkinson's Disease Rating Scale [UPDRS] III 84/108). Dysphagia and anarthria necessitated nasogastric feeding for over 2 weeks. Aripiprazole was discontinued immediately, a UK adverse drug report was filed, and Co-beneldopa (Madopar) was increased from 125 mg q.d.s. to 250 mg q.d.s. with slow improvement in mobility and successful discharge 3 weeks later (UPDRS III 22/108). At 3-month follow-up, she remained in remission of psychosis (off antipsychotics) and was ambulant and self-caring with good functional movement.

Two other published articles describe deterioration in motor symptoms in patients with PD after aripiprazole use. The first report is a case report of a 70-year-old man with a 16-year history of PD treated for drug-induced psychosis.[5] He developed a severe akinetic–rigid state within a week of aripiprazole treatment, requiring parenteral nutrition and hydration without improvement of psychosis. The second report[6] describes 8 cases of probable PD and drug-induced psychosis treated with aripiprazole. There were 2 patients who were antipsychotic naive, 5 had failed with quetiapine, and 1 with olanzapine. Only 2 patients experienced near-complete resolution of psychosis on aripiprazole, 6 discontinued the drug within 40 days and 2 due to motor deterioration of PD.

Despite its novel mode of action as a dopamine system stabilizer, the experience of aripiprazole in patients with PD has been disappointing. Product literature[7] states that in patients with schizophrenia the incidence of extrapyramidal side effects is similar to placebo. It has also been suggested that improvements in extrapyramidal side effects occur when patients are switched to aripiprazole from other atypical antipsychotics.[8] However, our experience and that of others suggests that extreme caution must be exercised when using aripiprazole in patients with pre-existing PD.

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Tremors Associated with an Inferior Olivary Lesion That Developed After a Pontine Hemorrhage

Although palatal tremor remains the only dyskinesia consistently related to hypertrophic olivary degeneration (HOD), some uncommon dyskinesias may occur with HOD. We present 2 cases with a predominantly axial tremor, without visible palatal tremor that developed from an inferior olivary lesion after pontine hemorrhage.

The first patient is a 54-year-old woman, admitted to our neurosurgical clinic because of disturbance of consciousness. Neurologic examination at that time showed stuporous mentality, left hemiplegia, dysconjugate gaze, and fixation of the oculocephalic reflexes. Hemorrhage throughout the pontine tegmentum was observed on magnetic resonance imaging scans (Fig 1A). The patient slowly improved over the following months.

Five months after the hemorrhage, a tremor of the head was noted and gradually increased in amplitude to affect the trunk. Four weeks after its onset, the tremor was present in all extremities, and the patient was readmitted. On examination, she had a coarse tremor of the head and trunk with a frequency of 3 to 5 Hz measured clinically. The tremor was present at rest, increased with posture, and was further amplified during intentional movements. Dystonic posture of the distal part of all limbs was also noted. There was no tremor of palatine structures. Ocular abnormalities included mild ptosis, left horizontal gaze palsy, and impaired convergence. Speech was dysarthric but intelligible. Muscular strength and tone were normal. Follow-up MRI scans of the brain showed increased signal intensification in the area of the inferior olivary nuclei in T2-weighted images (Fig. 1B). The red nucleus, substantia nigra, cerebellum, and basal ganglia appeared normal (Fig. 1C).

The second patient was a 61-year-old right-handed woman with a 7-year history of hypertension. She was admitted to a private medical clinic because of a sudden onset of dizziness, dysarthria, diplopia, and left hemiparesis. Neurologic examination at that time demonstrated horizontal gaze paralysis, dysarthria, and mild left hemiparesis. Hemorrhage throughout the right pontine tegmentum was seen on computed tomography. In the ensuing months, her neurologic status slowly improved and the hypertension was controlled by medication.

After 6 months, the patient noticed a very slight occasional trembling of the head. The tremor progressed slowly to the extent that she was not able to manage self-care. Six weeks after its onset, the tremor persisted when lying down and caused difficulties falling asleep. The patient was admitted to our movement clinic. On examination, she had a coarse flexion–extension tremor of the head with a frequency of ~2 to 3 Hz measured clinically. The tremor was present when lying down, increased with sitting, and was further amplified during intentional movements. There was no tremor of the extremities and the palatine. Muscular strength and tone was normal. Ocular abnormalities included left horizontal gaze palsy, right temporal gaze palsy, and impaired convergence; nystagmus was absent. The patient was incapable of independently standing or walking. MRI scans of the brain showed hemosiderin deposits, indicative of a previous hemorrhage in the pontine tegmentum and increased signal intensification in the area of the inferior olivary nuclei in T2-weighted images. The red nucleus, substantia nigra, cerebellum, and basal ganglia appeared normal (Fig. 2).

In our cases, there are some noteworthy characteristics: the absence of palatal tremor, and a delayed onset of tremor with evidence of inferior olivary lesions by MRI. Case 1 had dystonic posturing and tremors of the extremities at rest that intensified with movement, which is referred to as a midbrain tremor. Although pontine hemorrhage is among several common causes of HOD,[1,2] the occurrence of a midbrain tremor without palatal myoclonus associated with an olivary lesion is rare.[2] As Homes' elucidation, it could be suggested that the midbrain tremor is related to disruption of the cerebellar outflow pathways at the superior cerebellar peduncle and the rubroolivary tract in the central tegmentum.[3]

In case 2, the tremor was a "yes–yes" head nodding without appendicular or palatal tremor. This characteristic is similar to axial tremors associated with cerebellar pathology.[4] The cerebellar axial tremor has been suggested to be a release phenomenon that results from damage to the cerebellum and its outflow pathway.[5] There have been few cases reported with cerebellar axial postural tremor accompanied by secondary olivary change[5]; however, cerebellar axial tremor associated with HOD has not been reported previously. The pathogenesis of this tremor is obscure and remains speculative. Cerebellar cortical atrophy, after injury to the inferior olivary nucleus, has been reported in animal experiments and in humans.[6,7] In addition, a degenerative process involving the dentate nucleus and the cerebellar cortex has been associated with HOD, and has been demonstrated by MRI.[8] This evidence suggests that involvement of the cerebellar–olivary system or damage to the cerebellar outflow tract, by bilateral interruption of the rubro-olivo-cerebello-rubral loops, may be a reasonable explanation for the findings in our patient; although it may not contribute directly to the generation of the cerebellar axial tremor.

To our knowledge, there are few reports to date of uncommon dyskinesias, akin to midbrain tremor and cerebellar axial tremor, associated HOD. The cases presented here suggest that the involvement of the cerebellar–olivary system, and its outflow pathways, may lead to two distinct tremors.

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