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A 6-Month Longitudinal Study of Early-Onset Tardive Dyskinesia

Association With Olanzapine Treatment and Mild Cognitive Impairment in an Elderly Woman

To the Editors:

Tardive dyskinesia (TD) is a common and potentially irreversible hyperkinetic movement disorder resulting from long-term treatment with antipsychotic drugs that are antagonists at dopamine D_2 receptors.[1–3] Tardive dyskinesia is one of the most serious iatrogenic neurological complications of the first-generation antipsychotics. We present a case study of an elderly woman without a history of psychiatric disorders or previous typical antipsychotic use who developed TD after only 1 month exposure to olanzapine while on chronic treatment with galantamine. Notably, a cerebral magnetic resonance scan revealed cortical and subcortical multiple infarctions in chronic stage. During her hospitalization and 6 months prospective follow-up, several therapeutic approaches were introduced, but the patient did not exhibit remarkable and sustained improvement of her dyskinesia. We are aware of only limited previously reported cases of early-onset TD associated with olanzapine. We suggest that the risk for TD is not limited only to individuals with schizophrenia—it may also potentially develop in at-risk patient populations with ischemic brain lesions exposed to atypical antipsychotic drugs.

CASE STUDY

A 71-year-old Turkish woman from western Turkey (Aegean coast) with a chief complaint of forgetfulness visited her physician. Mild cognitive impairment was determined by the treating physician, and olanzapine treatment was started at a fixed 10-mg/d dose for 1 month. At the end of the 1-month treatment with olanzapine, she presented with involuntary movements of orofacial region. These progressed over the next month until her speech became dysarthric. She returned to the original physician in the beginning of the third month after olanzapine treatment has been started, and a diagnosis of TD was established. Examination at that time showed constant orofacial dyskinesia, and olanzapine was discontinued and quetiapine was started at a 50-mg/d dosage. Two weeks after the initiation of quetiapine treatment, she developed dyskinesia of the upper and lower extremities, whereas the orofacial dyskinesia persisted at an apparently fixed severity. One month after the initiation of quetiapine treatment (ie, month 4 of our case study with respect to first exposure to olanzapine), quetiapine was discontinued due to emergence of this dyskinesia in upper and lower limbs. At the beginning of month 5 of our prospective follow-up, she was admitted to our clinic (Ataturk Training and Research Hospital, Izmir, Turkey), and the abnormal involuntary movement scale score was determined as 25.[4] Tardive dyskinesia diagnosis was formally established at this time as well.

On admission to our clinic, the general physical examination was normal. Neurological examination showed an alert patient with dysarthric speech. There were continuous oro–bucco–linguo-masticatory dyskinesias. These included chewing and smacking of the mouth and lips, rolling of the tongue in the mouth or pushing against the inside of the cheek, and periodic protrusion of the tongue. Alternating protrusion and retraction of the tongue at rest were diminished by active tongue protrusion, of which there was no impersistence. Chewing movements of the jaws were abolished by voluntary mouth opening. There were involuntary choreoathetoid movements of the feet (greater on the left side) and slight dyskinesias of the left upper limb as well. Dystonia, rigidity, and parkinsonism signs were absent. Motor, sensory, and cerebellar functions were normal. She had no history of abnormal movements, toxin exposure, and was not on any concomitant pharmacological treatment. There was no history of psychiatric disorder as determined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. No history of medical disorder such as kidney or liver failure nor substance abuse or dependence was noted. The patient did not use any herbal or traditional medicines, nor was she exposed to chronic prescription medications. There was no family history of movement disorders, and she had no previous neurological and psychiatric symptoms either. Magnetic resonance imaging of the brain identified multiple chronic infarcts in right occipital lobe, left frontal lobe, bilateral periventricular area, and thalamus. Neurocognitive tests could not be carried out because of severe dysarthria and orolingual dyskinesia. Serum ceruloplasmin level and 24-hour urinary copper excretion were normal. Genetic testing for Huntington disease was negative. Acanthocytes were not seen in peripheral blood smear.

Subsequently, diazepam (10 mg/d, PO) for 10 days did not provide relief for TD symptoms, nor the initiation of valproate for 1 month afterwards at a dose of 500 mg. During month 6, valproate dose was increased to 1500 mg/d, but again, TD symptoms did not diminish. Notably, the abnormal involuntary movement scale score was again 25 at that time. Starting on month 3 of our follow-up (with respect to olanzapine start date), patient had a trial of treatments sequentially by about monthly intervals (baclophen, 30 mg/d; memantine, 20 mg/d; gabapentine, 1200 mg/d), but again, there was no change in TD clinically. Six months later, a follow-up magnetic resonance imaging revealed the same lesions.

DISCUSSION

Tardive dyskinesia is characterized by involuntary, repetitive, purposeless movements that vary in localization and form and can occur in 8 main areas: the tongue, jaw, lips, face, trunk, upper extremities, lower extremities, and respiratory system. Whether persons with coarse brain disease or damage are at higher risk for TD is a challenging research question particularly in elderly patients who are already at an elevated risk due to advanced age. Moreover, the pathophysiology of TD remains poorly understood; numerous theories have been proposed, including dopamine receptor supersensitivity, catecholamine hyperactivity, γ-aminobutyric acid (GABA) hypoactivity, hyperactivite glutamatergic neurotransmission, genetic predisposition, and free radicals.[1,3,5,6]

Typical antipsychotics pose a risk for TD, which is generally considered greater than that of atypical antipsychotics.[7] Atypical antipsychotics seem to display a hierarchical risk from least to greatest as follows: clozapine has a lower risk than quetiapine, which has a

lower risk than olanzapine and ziprasidone; risperidone carries a lower risk than the latter 2 drugs at low doses but an elevated risk at high doses.[8] Prevalence rates for TD increase with age due to a higher incidence and a lower remission rate in older patients. Older women seem to be the most vulnerable group.[6,7] Other proposed risk factors include a greater total drug exposure, preexisting drug-induced parkinsonism, treatment for an affective rather than a psychotic disorder, diabetes mellitus, mental retardation, organic brain damage, alcoholism, and smoking.[1,5–7,9] Exposure to the offending dopamine-receptor blocking agent must be for at least 3 months or 1 month if aged 60 years or older.[9] Most patients reported in the literature have taken the offending drug for at least 1 year, but our case developed manifestations of TD after as little as 1 month of exposure to olanzapine. Atypical antipsychotics have a low frequency of extrapyramidal side effects and TD. Moreover, they have been found to be effective in the treatment of TD. Quetiapine may especially have symptomatic benefit for TDs even when used as an adjunctive agent to another antipsychotic.[8,10] In 1 review of 11 studies, the atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) were associated with a mean annual incidence of new-onset TD of 0.8% in adults as compared with 5.4% in adults treated with haloperidol.[9] Data regarding the long-term impact of olanzapine and quetiapine on TD are limited. In the published case reports[9] that involved patients with olanzapine-associated TD, 1 patient experienced TD after only 4 months of olanzapine therapy and had no previous typical antipsychotic use, whereas 4 patients developed TD after olanzapine therapy and had a history of conventional antipsychotic use. In the same review,[9] TD associated with quetiapine use was documented; 1 case had TD who had a history of conventional antipsychotic use. In another case report,[11] a patient with bipolar disorder who received quetiapine along with lithium and gabapentine developed TD and had only previous short-term exposure to olanzapine (1 month) and risperidone (1 week).

We note that the risk for TD is not limited only to individuals with a psychotic illness. It may also develop in patient populations treated with antipsychotics for other conditions. It is noteworthy that our patient did not fully meet the diagnostic criteria of dementia and had no indication provided to us for using both antipsychotic and cholinergic drugs by the original treating physician, but she notably developed manifestations of TD after a short time of exposure. Antipsychotic drugs have many potentially troublesome adverse neurologic effects, particularly movement disorders. Therefore, physicians must use judicious therapeutic drug monitoring and, when necessary, should consider alternative medications particularly in patients with nonpsychotic disorders.

It has been proposed that TD can have a component of central cholinergic deficiency. Cholinergic drugs have been used to treat TD. The theory is that there may be a deficiency in acetylcholine underlying the psychopathology of TD, and this can be corrected by increasing acetylcholine effect through a centrally acting cholinesterase inhibitor.[12] On the basis of this hypothesis, galantamine, a cholinesterase inhibitor, would inhibit the development of TD in our case. In most studies, however, cholinergic drugs did not result in any substantial improvement in TD symptoms when compared with placebo.[13] On the other hand, a recent meta-analysis concluded that clinical trials of cholinergic agents in the treatment of TD conducted to date have insufficient statistical power to draw a firm conclusion on their effectiveness.[14]

Tardive dyskinesia is an important public health problem because there is no definitive curative therapy, nor are there clinically reliable biomarkers or predictive tests that can estimate the individual patient risk before initiation of antipsychotic therapy. It has been reported that TD may be associated with GABA hypoactivity and hyperactivite glutamatergic neurotransmission. The inhibitory effect of GABA on dopamine neurons provides the rationale for treating TD with drugs that increase GABAergic influences.[1,3,5,6] It has been also suggested that

the antagonists showing selectivity for *N*-methyl D-aspartate receptors may be particularly efficacious as novel therapeutic agents for the treatment of TD.[15] However, GABAergic drugs (diazepam, valproate, baclophen, and gabapentine) and *N*-methyl D-aspartate receptor antagonist (memantine) medications have failed to significantly provide sustained improvement, and the symptoms of TD in our patient were persistent and remained constant during our 6-month follow-up period.

Our patient had multiple cerebral infarctions. It may be more likely that cerebral lesions can exert an effect on cortical and subcortical functions by alteration in levels of bilaterally distributed neurotransmitters with various potential effects on movement. We conclude that the risk of TD is greater in elderly patients, and the existence of cerebral ischemia may even increase this risk. Taken together, we suggest that close clinical monitoring of elderly women with neuroradiological studies may be warranted before introducing atypical antipsychotic pharmacotherapy with olanzapine and quetiapine. This may help to identify individuals who may be at an elevated risk for early-onset TD.

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Aripiprazole and Neuroleptic Malignant Syndrome

To the Editors:

Neuroleptic malignant syndrome (NMS) is a rare, but potentially life-threatening, side effect of neuroleptic treatment (mortality rate, 4%–30%).[1–3] It was first described by Delay et al[4] in 1960, and the frequency of its occurrence with conventional antipsychotics has been reported to vary from 0.02% to 2.4%.[5] Mann et al[3] have proposed clinical diagnosis criteria. Neuroleptic malignant syndrome is usually characterized by the association of fever, extrapyramidal rigidity, disturbances of consciousness and autonomic function, increased level of creatine kinase (CK), and increased white blood cell count.[2]

The physiopathology remains controversial even if D_2 dopamine receptor antagonism is considered as a contributing factor. However, some authors have suggested a common factor for NMS, catatonia, and serotonin syndrome.[6] A sympathoadrenal hyperactivity associated with hypodopaminergic activity has also been hypothesized.[7]

Several predisposing factors such as male sex, young age, organic brain disorder, mental retardation, or affective disorders were described.[2,3,8]

In approximately two thirds of the cases, the onset of NMS occurred within 2 weeks of neuroleptic treatment initiation or major change.[9] It was not related to dose or previous exposure. Concomitant use of lithium has been considered as a risk factor for NMS.[2,3]

Neuroleptic malignant syndrome has usually been associated with conventional neuroleptic medication (especially high-potency neuroleptics and depot forms), but case reports of atypical antipsychotic–associated NMS have been described. Atypical antipsychotic agents can be associated with NMS as they are also D_2 dopamine receptor antagonists. But considering that they have a lower propensity to induce extrapyramidal symptoms (EPS), it has been reported that the atypical antipsychotic–associated NMS may be qualitatively and quantitatively different from the NMS induced by typical neuroleptics.[10]

A Medline search conducted in 2003 by Ananth et al[11] yielded 82 cases of NMS (clozapine, 21; risperidone, 23; olanzapine, 19; and quetiapine, 19). The authors reported that the mortality rate was lower with the atypical antipsychotic drugs than with the conventional ones and that no NMS case was reported with aripiprazole.

Recently, some cases of NMS associated with aripiprazole have been published. One additional case of a possible NMS with the association fluoxetine-aripiprazole (30 mg/d) was described by Duggal and Kithas.[12] Chakraborty and Johnson[13] reported one neuroleptic-induced catatonia-NMS with aripiprazole without any fever or autonomic dysfunction in a patient with treatment-resistant schizophrenia. Spalding et al[14] have described a case of aripiprazole-associated atypical NMS (15 mg/d) without any EPS side effects in an adolescent previously treated with other atypical antipsychotics. Srephichit et al[15] have reported another NMS case in a drug-naive patient with methamphetamine dependence and a recent-onset psychosis; the patient was treated with 30 mg/d of aripiprazole. Ali et al[16] have described a typical moderate case of NMS occurring (within 3 weeks of initiation of treatment) in a bipolar patient who was being treated with lithium (lithium level, 0.93 mmol/L) and aripiprazole (30 mg/d). In this case, valproic acid was discontinued 1 or 2 weeks before.

We report a new case of NMS occurring during a treatment switch from risperidone to aripiprazole.

CASE REPORT

A 43-year-old schizoaffective patient (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria) was being treated with haloperidol. In April 2003, he was admitted to an inpatient psychiatric service because of manic symptoms and delusions, where haloperidol was discontinued, and he was then started on divalproex sodium and amisulpride (400 mg PO once daily). In September 2003 and March 2004, he was readmitted because of a manic episode associated with psychotic symptoms. In March 2004, amisulpride was replaced with risperidone (4 mg PO BID), and divalproex sodium was increased to 2000 mg/d. The patient's adherence to the medication was uncertain. In September 2004, he was readmitted after a suicide attempt, where he exhibited psychomotor inhibition and hallucinations. Divalproex sodium and risperidone were reduced to 1000 and 6 mg/d, respectively. Six months later, he was readmitted for increasing symptoms of psychomotor inhibition, social withdrawal, and hallucinations. Divalproex sodium was discontinued. In June 2005, a switch from risperidone to aripiprazole was decided to improve these negative

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symptoms. Risperidone was gradually decreased while the patient was started on aripiprazole (June 27, 2005) (10 mg PO once daily).

On day 11 (July 7, 2005), aripiprazole was increased to 15 mg (PO once daily); risperidone was still prescribed at a dose of 2 mg PO once daily, without much improvement. On day 22 (July 18, 2005), the patient became markedly withdrawn. He was lying in bed all day long, mute, refusing either to eat or to drink. He also had keratitis and palpebral blink. Within 48 hours (July 20, 2005), he developed agitation, hyperthermia (38.7°C; with no evidence of infection), tachycardia (140 bpm), labile blood pressure (from 130/90 to 160/80 mm Hg), muscle rigidity, dysphagia, urinary incontinence, and altered consciousness (fluctuating level of consciousness with periods of agitation and periods of stupor). There was an absence of diaphoresis, diarrhea, shivering, myoclonia, or tremors. The CK level was 1768 U/L (reference range, 50–171 U/L), there was a leukocytosis of 13,000/μL (reference range, 4000–10,000 cells/μL), and the alanine aminotransferase level was 189 U/L (reference range, 10–45 U/L). Serotonin syndrome was ruled out as hyperthermia, and elevated CK was present; his symptoms appeared progressively, and shivering, diarrhea, and myoclonia were not present. The symptoms observed were consistent with a diagnosis of NMS; therefore, the antipsychotic treatment was abruptly interrupted, and the patient was transferred to an intensive care unit, where treatment by dantrolene was used intravenously (2.5 mg/kg initial, followed by 4 mg/kg per day).

Within 24 hours, hyperthermia and extrapyramidal symptoms disappeared. Biological parameters returned gradually during the next few days to baseline levels (CK level was 279 U/L on day 4). A bilateral pulmonary atelectasis, which was considered as a possible dantrolene side effect, occurred and was treated with respiratory physical therapy and antibiotic treatment. One week later, the patient was transferred back to the psychiatric unit without any significant physical symptoms.

DISCUSSION

This case raises several questions about the pathophysiology of NMS, mainly thought to be the result of a hypodopaminergic state (induced by striatal dopamine D_2 receptor antagonism). Aripiprazole acts as a potent partial dopamine D_2 receptor agonist, a partial serotonin 5-hydroxytryptamine (5-HT) 1A agonist, and a 5-HT_{2A} receptor antagonist.

Little is known about the clinical features of NMS associated with the atypical antipsychotic agents. Some authors have reported ''atypical'' NMS cases, which are milder than NMS cases observed with conventional neuroleptics.[10] Nevertheless, Ananth et al[11] have found that incidences of extrapyramidal symptoms associated with NMS induced either by typical or atypical antipsychotics were approximately the same (95% with the typicals vs. 78% with the atypicals). In our case, the patient exhibited a marked extrapyramidal rigidity, also reported in former cases of NMS associated with aripiprazole,[13] whereas aripiprazole, with its pharmacological profile, is usually associated with a lower incidence of EPSs.[17] However, Sharma and Sorell[18] have reported a case of aripiprazole-induced parkinsonism. The effect of a partial agonist (such as aripiprazole) depends on the ambient concentration of the endogenous neurotransmitter (ie, dopamine), which is difficult to determine in any given patient, and may vary depending on brain region.

A recent case of NMS associated with aripiprazole was described in an antipsychotic-naive patient.[15] However, in most NMS cases associated with atypical antipsychotics, patients were not drug naive. In our case, D_2 receptor supersensitivity because of chronic risperidone use may be considered. Subsequent reduction of D_2 antagonism as the risperidone dose was reduced may have left hypersensitive D_2 receptors exposed to the partial agonism of aripiprazole. It is possible that introducing a partial D_2 agonist at that point somehow destabilized the overall balance of the D_2/5-HT system in a way that promoted NMS, but this hypothesis is very speculative. A switch or discontinuation of antipsychotics has previously been identified as a potential risk factor for developing NMS.[10] Neuroleptic malignant syndrome was also previously reported during a switch from haloperidol to risperidone.[19]

Some authors have described an overlap in clinical signs between NMS and toxic serotonin syndrome, suggesting that they may be examples of nonspecific generalized neurotoxic syndrome.[3] The hypothesis that aripiprazole may have increased serotonin levels is possible, but not supported by a recent animal study.[20] However, it is possible that aripiprazole was having 5-HT_1 receptor effects without increasing measurable 5-HT levels.

Finally, aripiprazole is metabolized by cytochrome P450 (CYP) enzymes 3A4 and 2D6.[17] Although risperidone is not known to be a significant inhibitor of CYP2D6, it is at least partially metabolized by this enzyme as well as CYP3A4, raising the possibility that risperidone was competing to some degree with metabolism of aripiprazole.

This is a new case of NMS associated with aripiprazole in a patient with psychosis. Physicians should be aware of aripiprazole's potential propensity to induce NMS, especially during the switch period from a previous antipsychotic treatment. The physiopathology of NMS associated with the second-generation antipsychotics requires further investigation.

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Olanzapine-Associated Bilateral Eyelid Edema

To the Editors:

Olanzapine is a potent medication to alleviate positive and negative symptoms of schizophrenic psychoses.[1] Just recently, results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) underlined the high rates of adherence of patients during treatment with olanzapine[2] and superiority compared with other medications after discontinuation of a previous atypical antipsychotic.[3] However, a number of bothersome side effects limit the clinical use of olanzapine.[4] In particular, several cases with peripheral and pedal edema have been reported.[5–7] Here, we report for the first time the occurrence of bilateral eyelid edema during olanzapine therapy of an otherwise medically healthy man.

CASE

Mr K., a 41-year-old previously healthy man, experienced a first psychotic episode and attempted suicide by opening the veins of his forearm. This act was motivated by the delusional idea that he was infected with HIV. He fulfilled the criteria of DSM-IV-R for a schizoaffective, disorder type. After surgical wound repair and transfusion of 2 units of blood due to anemia (hemoglobin was 5.5 g/dL), he was transferred to our psychiatric hospital. During the following weeks, treatment attempts with risperidone, aripiprazole, and venlafaxine failed. With a combination of duloxetine (90 mg/d) and amisulpride (400 mg/d), an improvement of the psychotic and depressive symptoms was achieved. However, the delusional fear to be HIV-infected persisted. The emergence of akathisia precluded any further increase of the amisulpride dose, and an add-on treatment with olanzapine was planned.

The day after the first evening dose of olanzapine (5 mg), the patient complained a "swollen face," and the eyelids were found to be turgid. He showed no signs of rash, fever, or evidence for an allergic reaction. Detailed investigations found no evidence for pedal edema, cardiac, hepatic, renal, or immunological diseases. In particular, serum electrolytes, total serum proteins and serum albumin, a complete blood count, and parameters of renal and thyroid function were within normal limits. Olanzapine was discontinued after 10 days, and the eyelid swelling disappeared completely the next day. The patient did not accept any further changes of his treatment, underwent successful vocational rehabilitation during therapy with amisulpride (400 mg/d) and duloxetine (90 mg/d), and was discharged in complete remission after a total of 6 months of psychiatric therapy.

DISCUSSION

This case report associates antipsychotic treatment with olanzapine and the onset of a bilateral swelling of the eyelids. Detailed clinical assessments failed to detect any other causal condition for the lid edema such as a liability for allergic reactions, dermatological, heart, renal, or thyroid disorders. Based on the precise coincidence in time with olanzapine onset, it seems unlikely to attribute the side effect to duloxetine and amisulpride or to pharmacological interactions.

With regard to possible mechanisms, blockade of serotonin and α_1-adrenergic receptors by olanzapine has to be considered.[6] In addition, olanzapine might influence the renal dopamine system. The renal regulation of electrolyte and fluid homeostasis is under dopaminergic control, and hypodopaminergic states have been associated with the development of idiopathic edema.[8,9] At present, the specific properties of olanzapine resulting in the development of edema cannot be defined. Careful monitoring of patients at risk due to prior episodes of peripheral edema, allergic, renal, or heart diseases seems desirable if antipsychotic treatment with olanzapine is selected.

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