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Recurrent Catatonia in Parkinson Disease

To the Editors:

Catatonia is a motor dysregulation syndrome that occurs in various medical conditions.[1] However, few reports have described catatonia in patients with Parkinson disease (PD).[2,3] We present an elderly patient with PD, who developed recurrent episodes of catatonia for a period of 3 years, and discuss the challenges of managing catatonia in this clinical setting.

CASE REPORT

An 80-year-old woman, who had been diagnosed with idiopathic PD 12 years ago, presented to our emergency department with stupor, mutism, and immobility with minimal response to painful stimuli. According to her family, during the previous week, she had been severely agitated and had visual hallucinations. She also became suspicious of her children and believed that her food was poisoned. Therefore, they sought help in an emergency unit of a psychiatric hospital. However, she became increasingly unresponsive afterward and refused food and fluids for the last few days. The patient had been on stable doses of levodopa/benserazide 200/50 mg 4 times daily and pramipexol 2 mg twice daily (BID) in the preceding year, with fairly well controlled motor symptoms. Her daughter also had PD with age of onset at 40 years. She had a medical history significant for hypertension, coronary artery disease, asthma, and hypothyroidism. Further information revealed a history of hospitalization at another center 1 and a half years ago, because of a similar episode of immobility and mutism preceded by a short period of agitation and visual hallucinations. She had been continuously treated with sertraline 50 mg and quetiapine 50 mg once daily afterward.

At our initial examination, patient's eyes and mouth were firmly closed and she had gegenhalten rigidity at her neck and extremities. She had no focal neurological signs or meningeal irritation and was afebrile with normal vital signs. A physical examination revealed findings of dehydration. An initial complete blood count and blood chemistry including a serum creatinine phosphokinase level were in the normal range, except for moderate hypernatremia (150 mEq/L) and hypoglycemia (45 mg/dL). Further laboratory analyses revealed a normal thyroid profile, serum vitamin B12/folic acid levels, and negative serum VDRL/rapid plasma reagin tests. A cranial magnetic resonance imaging showed a moderately severe global cortical atrophy and several small periventricular T2 hyperintensities. After admission, patient's dehydration and hypoglycemia were managed with intravenous fluids. Afterward, a therapeutic trial of diazepam 5 mg intramuscularly followed by lorazepam 1 mg orally was given. This brought about a marked response within 2 to 3 hours; the patient could walk, albeit slowly, sat on a chair, and asked whether the police were after her. However, the response did not persist, and consequently, the dose of lorazepam was gradually increased up to 5 mg/d by the third day. In the following days, she was persistently stuporous, negativistic, and uncooperative and had no oral intake. Electroconvulsive therapy (ECT) was then considered; however, it was deferred because of an acute exacerbation of patient's asthma and concurrent clinical findings of aspiration pneumonia with a moderate degree of hypoxia, which required treatment with a parenteral antibiotic, inhaled bronchodilators, and nasal oxygen. At the tenth day, while the patient was still stuporous, an electroencephalogram revealed generalized low-amplitude theta activity, vertex waves, and positive occipital sharp transients of sleep. Hence, an iatrogenic toxic encephalopathy secondary to lorazepam was suspected, and this agent was discontinued. In the following days, the patient was slightly more responsive; she could open her eyes shortly and occasionally follow simple commands. At the 15th day, on the grounds of resistant catatonic symptoms and a deferred ECT due to clinical instability, memantine at 5 mg daily dose was initiated by enteral route. At the 16th to 18th days, her negativism and immobility resolved markedly, and she began oral intake of food and fluids. At this stage, her mental examination revealed a general mental confusion and incoherence, but no active psychotic symptoms. At the 21st day, with near complete resolution of the initial symptoms, she was discharged. On an outpatient visit a month later, she was better off with memantine 10 mg BID. Her mental examination revealed moderate dementia with a mini–mental state examination score of 18/30.

Five months later, the family reported that the patient had suspiciousness and insomnia and also exhibited a waxing and waning overactivity, which involved some home activities such as cleaning and tidying. The patient was then on a stable antiparkinson regimen arranged at another center 3 months earlier, and it consisted of levodopa/benserazide 50/12.5 mg BID, sustained release levodopa/benserazide 100/25 mg BID, levodopa/carbidopa/entacapone 100/25/200 mg and 150/37.5/200 mg BID, and pramipexol 2 mg BID. She also received memantine 10 mg BID. Soon afterward, she had a loss of interest in daily activities for a period of 3 weeks and became preoccupied with vague abdominal complaints and constipation. According to the family, she was irritable and paranoid and was reluctant to take her medications. At the interview, she was unwilling to respond to questions and had little eye contact. She also demonstrated psychomotor retardation with frequent thought blocking. Her mental examination revealed some depressed mood and anhedonia; thus, duloxetine 30 mg/d and lamotrigine 25 mg/d were prescribed. Two weeks later, however, she had to be hospitalized for recurrence of catatonic stupor with fairly similar symptoms at previous hospitalizations.

On admission, her physical neurological examination was unremarkable except for a generalized rigidity, and an extensive biochemical workup of plasma and urine revealed normal results. A standard paraneoplastic panel and a test for anti-N-methyl-D-aspartate receptor antibodies were also negative. Because of the anticipated medical risks related to immobility and lack of oral intake, modified ECT treatment was started promptly with family's consent on hospital day 3. Electroconvulsive therapy was repeated on the 2 consecutive days and continued biweekly thereafter. Meanwhile, levodopa/benserazide 100/25 mg 6 times a day, pramipexol 1 mg BID, and memantine 10 mg BID were administered by nasogastric tubing. A mild to moderate

response to ECT appeared after the fourth session (on day 10) as demonstrated by spontaneous opening of eyes, after some simple commands and the rare "yes/no" answers. During this period, on several occasions, she had horrifying complex visual and auditory hallucinations, which were accompanied by persecutory delusions ("thieves coming up" and "bombs exploding outside"). Therefore, quetiapine 25 mg at bedtime was started, whereas pramipexol was gradually discontinued and total daily dose of L-dopa was increased up to 900 mg in 5 days. A significantly greater improvement of patient's negativism was observed after the sixth and the final ECT session (15th day). Nevertheless, at this point, the patient appeared severely apathetic and exhibited prolonged immobility when left unattended. She did not initiate any motor acts by herself, ask for food or fluids, or change position in bed, yet she tended to follow most commands without any hesitation (symptoms of severe passivity). Furthermore, her speech was nonspontaneous, perseverative, and incoherent with occasional echolalia. Consequently on day 22, a therapeutic trial with oral amantadine (started at 50 mg and titrated in 50 mg daily increments) was initiated. A mild resolution of the residual catatonic symptoms was noted by the 24th day with this treatment, and a major improvement followed on day 27 at a daily dose of 200-mg amantadine. At that time, her mini–mental state examination score was 22/30. She was discharged on day 30.

DISCUSSION

Catatonic stupor is a life-threatening medical emergency, which should be differentiated from other causes of general unresponsiveness and treated urgently to prevent associated complications.[4] Nonetheless, catatonia remains to be a widely underrecognized phenomenon.[5] Its diagnosis might be even more problematic in the elderly patients and in presence of neurodegenerative diseases, where catatonia-related symptoms can be easily ascribed to the primary neurological syndrome or some unrelated/secondary medical conditions. To our knowledge, only 2 case reports described catatonia in patients with PD. In 1 reported case, catatonic symptoms developed after a switch in the ongoing dopaminergic treatment (after withdrawal of pramipexol and talipexol due to hallucinations and delusions),[2] and in the other, these followed a state, which resembled neuroleptic malignant syndrome.[3] In our case, catatonia was recurrent and these episodes followed an acutely psychotic and agitated period. According to further information gathered from medical records and the family, patient's agitation was treated with parenteral followed by oral olanzapine several days before the second episode, and an unknown parenteral sedative agent was administered before the first. On these 2 occasions, a neuroleptic malignant-like syndrome or acute akinesia in Parkinson disease was an important diagnostic alternative. However, this could be effectively ruled out by the absence of hypertermia, severe rigidity, autonomic symptoms, and serum creatinine phosphokinase elevation. In the last catatonic episode, where the patient was for a long time under our follow-up; symptoms emerged gradually for weeks without an intervening dopamine antagonist; hence, we had an initial impression that these were associated with an underlying major depressive disorder. However, further observation of the patient's mental state over the treatment course yielded no appreciable depressive symptoms, and visual hallucinations and persecutory delusions were predominant after resolution of the initially severe negativism. These together with the prodromal period of overactivity and punding-like phenomena indicate that the patient's catatonia might be a severe motor manifestation of psychosis and a late complication of PD, which were accentuated by the moderate cognitive impairment and excessive dopaminergic dosing. Nevertheless, it is possible that in the initial and the second episodes of catatonia, emergency administration of dopamine receptor antagonists might have also contributed.

Catatonia is hypothesized to reflect a "top-down" (frontal) dysregulation of basal ganglia in severe psychiatric states and a GABAergic deficiency and/or an increased glutamergic activity have been suggested as underlying neurochemical dysfunction.[6–8] Similarly, a severe blockade of dopamine at these brain regions has also been proposed.[6,7] In our case, both top-down and "bottom-up" mechanisms of dysregulation of the frontal-basal ganglionic system might have played a role, as suggested by active psychotic symptoms and the presence of PD, which is primarily a disease of basal ganglia. N-methyl-D-aspartate receptor antagonists memantine and amantadine were found effective in alleviation of our patient's catatonic symptoms on the separate episodes. However, it is interesting that the third catatonic episode emerged despite the ongoing treatment with memantine. On this occasion, an ECT course was effective in reducing negativism and unresponsiveness, although amantadine was required eventually for recovery from the particularly severe amotivational state. Amantadine has a moderate dopaminergic affinity,[9] and this might have brought about the additional clinical benefit. Both of these agents have been successfully used in treatment of lorazepam-resistant catatonic symptoms, ECT unresponsive catatonia, and apathy associated with neurological insults.[8,10–12]

Our final observation was that lorazepam should be administered cautiously for catatonia in the elderly patients with neurodegenerative diseases such as PD, because higher doses might result in a severe encephalopathy or deep sedation, and it might be particularly challenging to distinguish this complication in presence of catatonic stupor. It should be recognized that a general recommendation of benzodiazepines for the treatment of catatonia was reached after reports largely from young patients with primary psychiatric disorders.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

Written informed consent was obtained from patient's next-of-kin (her daughter) for publication of this case report.

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Diffuse Maculopapular Rash With Increasing Dosage of Methylphenidate

To the Editors:

There have been several reports of methylphenidate hydrochloride (MPH)-related skin reactions in children and adolescents with attention-deficit hyperactivity disorder treated with this medication.[1–6] Here we present an 11-year-old boy who developed diffuse nonpruritic maculopapular skin rash with increasing dosage of MPH.

CASE

E is an 11-year-old boy who has been followed up with diagnosis of social and generalized anxiety and attention deficit disorders for the last 2 years. His developmental history and intellectual capacity were within normal limits. He had no significant medical or neurological history but had several episodes of itching and mild and local skin eruptions on his arms and chest which were considered psychological in origin by a dermatologist and pediatrician. He had no known drug allergy but had a few episodes of skin eruptions possibly related to food.

He was first started on sertraline 25 mg. He used this dosage for 3 months without any significant side effects. Then sertraline was increased to 50 mg/d. He generally tolerated it well except he developed itching and mild skin eruptions on his arms and upper chest. Sertraline was discontinued by the family for 1 month, during which time, there were no skin eruptions and itching. On the next visit, it was revealed he had some problems in his school due mainly due to attention problems. His recent episode of itching and mild and local skin eruptions were considered as stress related, and we decided to restart sertraline 50 mg and add MPH 27 mg/d. His anxiety and attention problems showed moderate to much improvement during 4 months of treatment. There were no significant side effects except some level of decreased appetite during the day and rebound increased appetite at nights without any significant weight change. His weight was 58 kg, and we decided to increase MPH to 54 mg/d. After 1 week of treatment, he developed nonpruritic maculopapular skin rash first on his face and chest and then the rash spread all over the body within 1 day (Fig. 1). We discontinued sertraline and MPH. He received a short-term antihistaminic and steroid treatment. His skin rash resolved within 10 days of discontinuation. He denied using any other medication or unusual food. We obtained verbal consent from both the patient and his family to publish this report and to include his photograph.

DISCUSSION

Methylphenidate has been the first-line psychopharmacological treatment in children and adolescents with attention-deficit hyperactivity disorder and results in significant improvement in 70% to 80% of affected children.[7] Nausea, decreased appetite, weight loss, and sleep disturbances are among the most frequently reported adverse effects during MPH treatment.[7] Besides these common adverse effects, MPH has also been reported to cause some unusual adverse effects, such as hallucinations,[8,9] hypersexuality or inappropriate sexual behaviors,[10,11] skin eruptions,[1–6] obsessive-compulsive symptoms,[12,13] gynecomastia,[14] and painful muscle cramps.[15]

A review of the literature regarding MPH-related skin eruptions revealed that skin eruptions were usually local or included several parts (such as face, neck, arms, scrotum, chest, or trunk) of the body in these reports.[1–5] Skin eruptions in these reports included pruritic maculopapular,[1,4] pruritic raised edematous circular

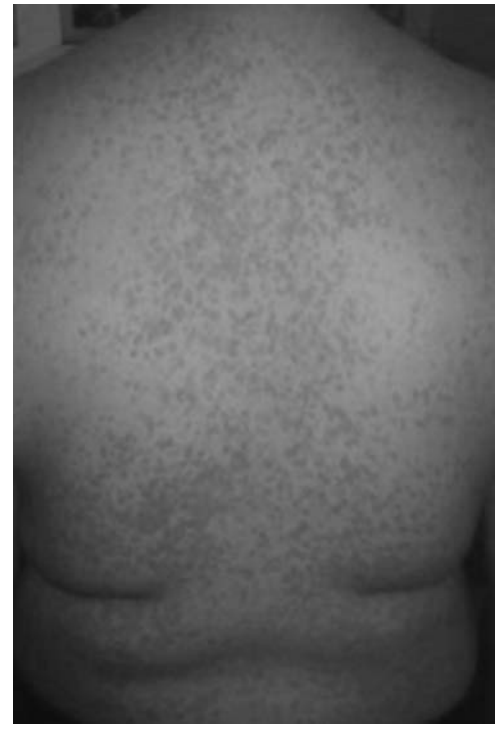

FIGURE 1. Diffuse maculopapuler rash after increasing dosage of OROS-methylphenidate.