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Clinical/Scientific Notes

A Case of Tetrabenazine-Induced Neuroleptic Malignant Syndrome After Prolonged Treatment

We report the case of a patient with tardive dystonia and a history of psychiatric illness who showed signs of neuroleptic malignant syndrome (NMS) after chronic treatment with tetrabenazine. The first symptom was a mental status change consisting of confusion, disorganized thinking, paranoid delusions, and hallucinations. The patient was initially diagnosed with a psychiatric illness until other clinical features of NMS developed, including low-grade fever, autonomic instability, elevated creatine phosphokinase (CPK) level, and rigidity. After initiating treatment for NMS, motor and autonomic signs resolved, and mental status returned to normal. NMS may appear with initial signs of psychosis; in patients with psychiatric illness this fact may cause a delay in the early recognition of NMS and the initiation of appropriate treatment. In addition, though tetrabenazine is generally considered a safe drug, tetrabenazine-induced NMS may appear after long-term treatment.

Neuroleptic malignant syndrome is a rare, but potentially fatal complication of neuroleptic treatment. It usually occurs within 4 weeks of starting medication, but it can develop at any time during treatment (1). The four major characteristic features of NMS include rigidity, hyperpyrexia, autonomic dysfunction, and mental status changes. Mental status changes, such as mutism or stupor, and psychomotor agitation may be the initial manifestations of this toxic condition (2). Prominent early mental status and behavioral changes in NMS present a diagnostic challenge in patients with chronic psychiatric disorders.

Three previous reports have attributed NMS to tetrabenazine, a catecholamine-depleting agent and dopamine receptor blocker used to treat hyperkinetic movements (3). All three cases have been reported in Huntington's disease patients (4–6). We now report a case of NMS in a patient with tardive dystonia, who showed signs of this disorder after receiving long-term and stable treatment with tetrabenazine. This case illustrates two additional points: insidious mental and behavioral changes may be the first signs of NMS, and during the course of illness, there may be clinical features that resemble those typical of the serotonin syndrome.

Case Report

In 1985, at age 23, the patient experienced depression and delusional ideations. She was treated with thiothixene (1–2 mg/day intermittently) from 1985 until 1991, and psychiatric symptoms resolved. During this same period, in December of 1990, while on thiothixene, she experienced involuntary movements that consisted of repetitive and rapid arm flexion, back arching, blepharospasm, and facial grimacing. After laboratory testing (serum copper, ceruloplasmin, 24-h urine copper, thyroid function, and brain magnetic resonance imaging) found no abnormalities, tardive dystonia was diagnosed. Shortly thereafter, the patient received short trials of alprazolam, benztropine, and diphenhydramine, but without benefit. Because lorazepam (4 mg) provided only marginal improvement of the dyskinesias, tetrabenazine was added in 1991 and gradually increased to a dose of 150–175 mg/day by 1993. Benztropine (4 mg/day) was also restarted to treat mild parkinsonism due to tetrabenazine. Before hospitalization, she remained on relatively stable doses of tetrabenazine with moderate control of her tardive dystonia. Several attempts to reduce her tetrabenazine dose led to an exacerbation of dystonia.

Four days before hospitalization in January of 1995, the patient's family noted a change in her condition characterized by generalized slow movements and delayed and occasionally confused verbal and behavioral responses. Tetrabenazine was decreased from 175 mg/day to 100 mg/day. She continued to be confused and was admitted to the hospital. Her family felt that her mental status was similar to her previous psychosis in 1985.

On admission, her blood pressure was 114/70 mm Hg, and her pulse was 120 beats/min. She was hallucinating, delusional, agitated, and inattentive and her thoughts were tangential, and disorganized. Slight facial grimacing was evident, and occasional quick dystonic-myoclonic flexion movements of the elbows and wrists were present, along with a slight upper-extremity tremor. Motor strength and coordination were normal, with mild rigidity. Her gait was slow but not ataxic, and her arm flexion increased with walking. The examination was otherwise normal. Over the next 3 days tremulousness of all muscles increased, accompanied by intermittent limb rigidity, confusion, and diaphoresis. Her pulse rate varied from 80 to 130 beats/min, her temperature rose to 101.3°F, and her CPK level (mm isoenzyme) on hospital day 2 was elevated, at 1,380 IU/L.

Tetrabenazine and benztropine were discontinued. NMS was diagnosed on hospital day 3, and dantrolene (80 mg i.v. four times daily) and bromocriptine (5 mg per nasogastric tube four times daily) were started. Investigation found myoglobinuria; mild leukocytosis; normal head computed tomography and lumbar puncture results; negative culture results (blood, urine, and cerebrospinal fluid); normal thyroid and renal functions; normal B12, folate, and antinuclear antibody levels; a normal erythrocyte sedimentation rate; and initially normal liver function. Serum CPK levels reached a peak of 5,700 IU/L on hospital day 8, and there were mild elevations of transaminases and alkaline phosphatase.

During the next 2 weeks the patient's neurological condition fluctuated between an agitated and hypervigil state to one of akinesia and stupor. When agitated, she was tremulous, diaphoretic, and unable to sleep for several days at a time. Her tardive dystonia was mild and consisted of clonic upper-extremity jerks. In contrast, during her stuporous state she manifested no evidence of tardive dystonia and was sleepy, akinetic, and responded slowly when awakened. She also had sialorrhea and dysphagia. In both conditions there was intermittent muscle rigidity, and her reflexes were brisk. Her temperature ranged from 99 to 102.6°F, her pulse ranged from 80 to 139, and her blood pressure ranged from 100/56 to 156/98 mm Hg.

Her condition worsened with attempts to change parenteral dantrolene to the oral form. Aspiration pneumonia developed on hospital day 9 and deep venous thrombosis on day 11. She

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was treated with i.v. ceftazadime, clindamycin, and heparin. Over the next 2 weeks she gradually improved, and her laboratory values normalized. She was discharged on hospital day 32, at which time the tardive dystonia was mild and consisted of intermittent quick elbow flexion and minimal upper-facial contractions. Only lorazepam was prescribed at discharge. At 8 months after discharge, her mental state was normal, and only mild arm dystonia was present. By 12 months her tardive dystonia returned to her pre-NMS state, and clonazepam was added. Tetrabenazine has not been restarted.

Discussion

We report a fourth case of NMS associated with tetrabenazine. Unlike the case of our patient, who had tardive dystonia, the other three patients with NMS had Huntington's disease (4–6). Burke et al. described a patient who had NMS and dystonic movements in the context of alphamethylparatyrosine and high doses of tetrabenazine (350 mg/day). NMS was treated with supportive therapy only and resolved in 6 days (4). The second report, by Mateo et al., described the case of a patient in whom NMS developed after rapid administration of tetrabenazine (100 mg/day) and discontinuation of haloperidol (5). The patient was treated with dantrolene with equivocal response. In the case report of Osserman et al., a patient was found to have NMS 2 weeks after a moderate increase of tetrabenazine (100–131 mg/day) and 2 months after an accidental overdosage (6). Despite normalization of CPK with bromocriptine and dantrolene, the patient died 2 months later from pneumonia and septicemia.

All patients experienced resolution of chorea with NMS but reemergence of chorea as NMS resolved. Two patients were restarted on tetrabenazine, and NMS did not recur (4,5). In these three reports NMS developed in the context of (a) a moderate dosage increase of tetrabenazine, (b) after a moderate dose increase and 2 months following an accidental overdosage (500 mg), or (c) when other dopaminergic agents (dopamine-blocking agent or dopamine-depleting agent) were also used. In our case, tetrabenazine was used for a prolonged period and maintained at a relatively stable dosage before the onset of NMS and was the only antidopaminergic agent administered. Our patient also differed in her complicated and protracted course, which clearly benefited from parenteral dantrolene. In addition, her movement disorder, which initially improved with NMS, remained minimally symptomatic at 8 months and did not require reinstitution of tetrabenazine.

This case illustrates several clinical points concerning tetrabenazine-induced NMS. Similar to dopamine receptor–blocking agents, tetrabenazine-induced NMS may develop years after treatment begins. One possible explanation for the particularly delayed development of NMS in our case may have been the absence of other dopamine receptor–blocking or –depleting agents. In addition, the development of tetrabenazine-induced NMS appears to be associated with improvement of the underlying movement disorder (e.g., chorea, dystonia), which in our case lasted for 8 months. Although tardive dystonia has occasionally been reported to improve as a natural course of the disease, we do not believe that this possibility could account for the improvement seen in our patient for three reasons: (a) several attempts to reduce tetrabenazine, up to the time of admission, led to an exacerbation of her movements, (b) the improvement of her dystonia coincided with the development of NMS, and (c) her tardive dystonia returned after 8 months.

Although the etiology of tardive dystonia has been linked to dopamine antagonists, the pathophysiology of the disease is not well understood. Animal models have supported the possible roles of pre- and postsynaptic dopamine hypersensitivity and/or decreased GABAergic transmission in the striatum (7–9). Agents such as dopamine depletors, capable of decreasing dopaminergic activity, are commonly used to treat tardive dystonia. The basis for the improvement in our case is unclear. Levels of dopamine metabolites in the cerebrospinal fluid of patients with NMS have been reported to be decreased both during the attack and for $\geq$1 month after the episode. Possible explanations for the improvement of tardive dystonia in our patient may include long-term pharmacological effects of tetrabenazine due to the depletion of presynaptic dopamine storage and pharmacological alterations of dopaminergic neural transmission due to NMS (10,11).

This case emphasizes the importance of considering the diagnosis of NMS in psychiatric patients who are taking tetrabenazine and other dopamine receptor–blocking agents and then show a change in mental status, including signs of psychosis. Mental status changes, such as mutism, catatonia, stupor, coma, and agitation, have been reported to be a common clinical presentation of this syndrome, whereas delusional thinking and paranoia, as seen in our patient, are not considered common (2,12). The early agitation, hallucinations, and delusional thinking observed in our patient initially suggested a primary psychiatric illness. The diagnosis of NMS became evident only after rigidity, tremulousness, elevated CPK levels, and fever appeared. We believe that her psychiatric symptoms were early manifestations of NMS because they occurred shortly before the development of other classic features of NMS (rigidity, hyperpyrexia, and CPK elevation) and they resolved with the treatment of motor and autonomic signs. Psychiatric manifestations of NMS may arise independently of previously diagnosed psychiatric illness and yet go unrecognized owing to the concurrent and confounding underlying psychiatric illnesses typically encountered in patients receiving neuroleptics.

The etiology of NMS in this patient could be tetrabenazine's action as a dopamine depletor or as a dopamine receptor–blocking agent or both (4,11,13). To our knowledge, neither alphamethylparatyrosine alone nor reserpine, both capable of disrupting presynaptic dopamine content, have been associated with NMS. Most reports support a central hypodopaminergic mechanism in the development of NMS based on several factors: (a) NMS is associated with drugs that block dopamine receptors, (b) NMS may occur in patients with Parkinson's disease upon the rapid withdrawal of dopaminergics, and (c) dopamine agonists appear to treat NMS (14) . A hypodopaminergic state, however, does not account for all the clinical features of NMS. For example, low dopamine levels do not explain the idiosyncratic manner in which NMS develops nor the attendant psychosis or confusion. Therefore, the pathogenesis underlying this syndrome is likely to be more complex. Other mechanisms that have been proposed involve prostaglandins, calcium, iron, or neurotransmitters, such as catecholamines, gamma-aminobutyric acid, and excitatory amino acids (glutamate) (12,14–18).

The differential diagnosis of NMS includes a variety of medical (e.g., sepsis) and neurologic conditions (malignant hyperthermia and lethal catatonia) that may be accompanied by fever and rigidity. In this case, we were impressed by the clini-

cal similarity of certain features in our patient, namely restlessness, agitation, myoclonus, diaphoresis, hyperreflexia, and tremulousness, to another toxic neurologic condition, the serotonin syndrome. These symptoms were most apparent during our patient's hypervigil state and were less obvious in her stuporous state. The clinical overlap between NMS and the serotonin syndrome has been reported by others and includes hyperthermia, autonomic instability, mental status changes, and dyskinesias (19–22). These two conditions may be distinguished by their different triggering agents. NMS has been associated with drugs that decrease dopamine transmission, and the serotonin syndrome has been attributed to drugs that increase serotonin transmission, such as serotomimetic agents alone or in combination with monoamine oxidase inhibitors. In addition, the serotonin syndrome typically evolves over a shorter period of time and is less commonly associated with extrapyramidal signs, cardiac changes, high temperature, or elevated CPK levels (19–22).

It has been proposed that the clinical similarities between NMS and serotonin syndrome may be explained by a common underlying neurochemical change (19,23,24). For example, clinical reports have associated a number of drugs (phenelzine, fluoxetine, lithium, and 3,4-methylenedioxymethamphetamine) with both the serotonin syndrome and the neuroleptic malignant syndrome (12,14,19,20,22–25). The confusion between these two syndromes may be due to the close association between the dopaminergic and serotonergic systems in the central nervous system (CNS). It has been shown, for example, that increased serotonin activity in the CNS can inhibit dopaminergic neurons (26). One may postulate that any drug creating a relative imbalance between dopamine and serotonin (low dopamine relative to serotonin) may be capable of eliciting a clinical state where features of both NMS and the serotonin syndrome occur. In our patient the resemblance to the serotonin syndrome may be due to tetrabenazine's interaction with both the serotonergic and dopaminergic systems. Tetrabenazine depletes both dopamine and serotonin by disrupting vesicular storage, but it also blocks presynaptic and postsynaptic dopamine receptors (11,13); thus there may be a relative increase in serotonergic function. Understanding the mechanisms of serotonin and dopamine interaction in the CNS may help elucidate the pathogenesis underlying these two syndromes.

The occurrence of NMS in our patient after 3.5 years of tetrabenazine treatment and its primary symptom of mental status changes contributed to the relative delay in diagnosis. Tetrabenazine is considered safe and effective treatment for hyperkinesia, but this important and life-threatening complication needs to be considered regardless of the duration of treatment. Furthermore, the insidious emergence of mental status changes, including psychosis, must be carefully evaluated, particularly in patients with a history of psychiatric illness.

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References

1. Jahan MS, Farooque AI, Wahid Z. Neuroleptic malignant syndrome. *J Natl Med Assoc* 1992;84:966–970.
2. Velamoor VJ, Norman RMG, Caroff SN, Mann SC, Sullivan KA Antelo RE. Progression of symptoms in neuroleptic malignant syndrome. *J Nerv Ment Dis* 1994;182:168–173.
3. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology* 1988;38:391–394.
4. Burke RE, Fahn S, Mayeux R, et al. Neuroleptic malignant syndrome caused by dopamine depleting drugs in a patient with Huntington's disease. *Neurology* 1981;31:1022–1026.
5. Mateo D, Munoz-Blance JL, Gimenez-Roldan S. Neuroleptic malignant syndrome related to tetrabenazine introduction and haloperidol discontinuation in Huntington's disease. *Clin Neuropharmacol* 1992;15:63–68.
6. Osserman M, Sindic CJM, Laeterre C. Tetrabenazine as a cause of neuroleptic malignant syndrome. *Move Disord* 1996;11:95–114.
7. Clow A, Theodorou A, Jenner P, Marsden CD. Cerebral dopamine function in rats following withdrawal from one year of continuous neuroleptic administration. *Eur J Pharmacol* 1980;63:145–157.
8. Calabresi P, De Murtas M, Mercuri NB, Bernardi G. Chronic neuroleptic treatment: D2 dopamine receptor supersensitivity and striatal glutamatergic transmission. *Ann Neurol* 1992;31:366–373.
9. Gunne LM, Haggstrom JE, Sjoquist B. Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. *Nature* 1984;309:347–349.
10. Nisijima K, Ishiguro T. Neuroleptic malignant syndrome: a study of CSF monoamine metabolism. *Biol Psychiatry* 1990;27:280–288.
11. Reches A, Burke RE, Kuhn CM, et al. Tetrabenazine, an amine-depleting drug, also blocks dopamine receptors in rat brain. *J Pharmacol Exp Ther* 1983;225:515–521.
12. Schneiderhan ME, Marken PA. An atypical course of neuroleptic malignant syndrome. *J Clin Pharmacol* 1994;34:325–334.
13. Burke RE, Avionam R, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. *Ann Neurol* 1985; 17:200–202.
14. Caroff SN, Mann SC. Neuroleptic malignant syndrome. *Med Clin North Am* 1993;77:185–203.
15. Kornhuber J, Weller M. Neuroleptic malignant syndrome. *Curr Opin Neurol Neurosurg* 1994 Aug:7(4):353–357.
16. Millnamow GA. Neuroleptic malignant syndrome: a clinical conundrum. *J Okla State Med Assoc* 1995;88:256–258.
17. Weller M, Kornhuber J. A rationale for NMDA receptor antagonist therapy of the neuroleptic malignant syndrome. *Med Hypoth* 1992; 38:329–333.
18. Ebadi M, Pfeiffer RF, Murrin LC. Pathogenesis and treatment of neuroleptic malignant syndrome. *Gen Pharmacol* 1990;21:367–386.
19. Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. *Neurology* 1995;45:219–233.
20. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991;148: 705–713.
21. Graber MA, Hoehns TB, Perry PJ. Sertraline-phenelzine drug interaction: a serotonin syndrome reaction. *Ann Pharmacother* 1994; 28:732–735.
22. Kline SS, Mauro LS, Scala-Barnett DM, Zick D. Serotonin syndrome versus neuroleptic malignant syndrome as a cause of death. *Clin Pharm* 1989;8:510–514.
23. Halman M, Goldbloom DS. Fluoxetine and neuroleptic malignant *Syndr Biol Psychiatry* 1990;28:518–521.
24. Ammes D. Ecstasy, the serotonin syndrome, and neuroleptic malignant syndrome: a possible link? [Letter]. *JAMA* 1993;69:869.
25. Brennan D, MacManus M, Howe J, McLoughlin J. "Neuroleptic malignant syndrome" without neuroleptics. *Br J Psychiatry* 1988; 152:578–579.
26. Baldessarini RJ, Marsh E. Fluoxetine and side effects. *Arch Gen Psychiatry* 1990;47:191–192.