Neuroleptic Malignant Syndrome Induced by Combination Therapy with Tetrabenazine and Tiapride in a Japanese Patient with Huntington’s Disease at the Terminal Stage of Recurrent Breast Cancer

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Abstract

We herein describe the case of an 81-year-old Japanese woman with neuroleptic malignant syndrome that occurred 36 days after the initiation of combination therapy with tiapride (75 mg/day) and tetrabenazine (12.5 mg/day) for Huntington’s disease. The patient had been treated with tiapride or tetrabenazine alone without any adverse effects before the administration of the combination therapy. She also had advanced breast cancer when the combination therapy was initiated. To the best of our knowledge, the occurrence of neuroleptic malignant syndrome due to combination therapy with tetrabenazine and tiapride has not been previously reported. Tetrabenazine should be administered very carefully in combination with other neuroleptic drugs, particularly in patients with a worsening general condition.

Key words: Huntington’s disease, tetrabenazine, tiapride, neuroleptic malignant syndrome, dopamine

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Introduction

Huntington’s disease (HD) is a genetic neurodegenerative disease characterized by hypotonic muscles, various involuntary movements, psychiatric signs and cognitive decline. The prevalence of HD is 0.1-0.4 per 100,000 Japanese individuals in the general population; HD is a rare disease in Japan compared with the U.S.A (approximately 4-8 per 100,000 individuals) or European countries (approximately 3-9 per 100,000 individuals), except for Belgium, Finland and Spain (0.5-1.6 per 100,000) (1). To date, neuroleptic drugs that block dopamine receptors (e.g., haloperidol or tiapride) have been primarily used to treat the involuntary movements of patients with HD in Japan. Tetrabenazine was approved as a new therapeutic drug for HD in Japan in December 2012 and has been on sale since February 2013. This drug is a reversible monoamine-deleting drug that prevents the uptake of monoamine into presynaptic vesicles by inhibiting vesicular monoamine transporter 2 (VMAT2) and deleting monoamine in synaptic clefts, particularly dopamine in the striatum, which is the most affected site in HD (2). Tetrabenazine is effective in controlling involuntary movements in patients with HD by inhibiting dopaminergic neurons with relative safety (at a daily dose of 12.5-100 mg) (2). Neuroleptic malignant syndrome (NMS) is a rare adverse event of neuroleptic drugs and extremely rare in patients treated with tetrabenazine (3-6). We herein present the case of a Japanese patient with HD presenting with NMS induced by tetrabenazine combined with tiapride.

Case Report

A Japanese woman who underwent resection of left breast cancer at 63 years of age gradually developed difficulty in writing letters starting in 2001 at 69 years of age. She could not remain still, although she became slovenly in 2007. Starting in 2009, she sometimes left without paying at res-
A 38-year-old Japanese woman was admitted to our hospital with involuntary twisting movements of the neck and limbs. She had a relevant family history: her grandmother, father, aunt, sister, elder brother and younger brother all had HD. In 2010, she received a diagnosis of HD based on the results of a genetic analysis of the huntingtin gene, in which the CAG trinucleotide repeat was found to be increased to 41, and treatment with tiapride was started at a dose of 75 mg daily.

Thereafter, she was admitted to our hospital for a phase III clinical trial of tetrabenazine in June 2011. A neurological examination revealed cognitive dysfunction, explosive speech, hypotonic limb muscles, facial grimacing and occasional quick twisting involuntary movements of the neck and extremities. Magnetic resonance imaging of the head demonstrated mild atrophy of the bilateral caudate nucleus on axial T2-weighted imaging (Figure A) and coronal T1-weighted imaging (Figure B). Contrast-enhanced computed tomography (CE-CT) of the chest showed a homogenously enhancing mass in the left chest wall of the axilla (Figure C). After discontinuing tiapride (326 days of treatment), the patient was given tetrabenazine, with the dose increased by 12.5 mg every seven days to 62.5 mg per day. Although her involuntary movements improved, somnolence and unsteadiness of gait developed; therefore, the dose was decreased in a stepwise fashion to 25 mg per day. Part of the skin on the axilla became reddish, and a skin biopsy of a lesion in this area identified on CE-CT (Figure C) revealed recurring metastatic breast cancer. The serum levels of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3), tumor markers of breast cancer, were elevated to 22.6 ng/mL (normal limit <5) and 44.1 U/mL (normal limit <27), respectively. The clinical trial of tetrabenazine was discontinued for 86 days because breast cancer was one of the exclusion criteria; no severe adverse effects were observed during the clinical trial. After the clinical trial, the patient was again given tiapride, the dose of which was gradually increased to 125 mg per day. Other medications included anastrozole for the recurrence of breast cancer and alendronate for osteoporosis. In February 2013, at 81 years of age, tetrabenazine was added at a dose of 12.5 mg daily, with a decrease in the dose of tiapride to 75 mg per day due to the gradual deterioration of involuntary movements. The treatment proved beneficial, and the patient’s liver and renal functions were normal, with a serum creatine phosphokinase (CPK) level of 70-80 U/L (normal limit <136). The recurrent breast cancer gradually deteriorated, and CE-CT of the

Figure. Magnetic resonance imaging of the head revealed mild atrophy of the bilateral caudate nucleus on a plain axial T2-weighted image (A) and a coronal T1-weighted image (B). Computed tomography of the chest with contrast enhancement showed a homogenously enhancing mass (white arrowhead) in the chest wall of the left axilla on admission (C). Eighteen months after admission, the number of enhancing masses (white arrowheads) had increased in the chest wall, and right massive pleural effusion (white arrow) was observed (D).
The occurrence of NMS induced by tetrabenazine was first reported in patients with HD in 1981 (3). Since then, only three cases have been reported, including two cases of HD in the English-language literature (4-6) (Table). To our knowledge, this report involves the fourth case of tetrabenazine-related NMS in a patient with HD and the first case in Japan. NMS has been found to be related to the administration of a high dose of tetrabenazine (100-350 mg/day) in previous reports, including cases of tardive dystonia (3-6). Although it has been reported that a daily dose of 25 mg of tetrabenazine can induce NMS-like hyperthermia in patients with tardive dystonia treated with clomipramine (110 mg/day), mianserin (30 mg/day) and lorazepam (2.5 mg/day), the occurrence of hyperthermia cannot be rejected as a form of serotonin syndrome caused by clomipramine, a serotonin reuptake inhibitor (11) (Table). In our patient, the daily dose of tetrabenazine was no more than 12.5 mg, which is the lowest dose associated with NMS based on previous reports. No accidental episodes of overdose occurred during our patient’s clinical course because she was an inpatient whose medications were managed by nurses.
during and after the clinical trial. Therefore, in our patient, the NMS was not induced by an overdose of tetrabenazine.

The administration of tiapride, which blocks dopamine D2 receptors, is also related to NMS, with various cases having been reported (12-14). While NMS developed several days after the intravenous or intramuscular administration of high-dose tiapride (200-1,200 mg/day) in these cases, it took various periods of times, from several days to nine months, and rarely five years, for NMS to develop in the patients treated with an oral daily dose of 20-75 mg of tiapride (12-14). In general, it is possible that NMS may emerge following treatment with tiapride alone without increasing the dose when the general condition of the patient deteriorates; however, in our patient, an additional drug, namely tetrabenazine, was considered to have triggered NMS because the NMS developed soon after the start of tetrabenazine treatment.

In previous reports of NMS induced by tetrabenazine, the only combined use of a drug primarily interrupting dopamine transmission in the striatum involved α-methyltyrosine, which inhibits dopamine synthesis, in a case reported by Burke et al. (3). In the present patient, the NMS was considered to be induced by the lowest dose of tetrabenazine when combined with a drug that blocks postsynaptic dopaminergic receptors (i.e., tiapride), as no severe adverse effects were identified when tetrabenazine or tiapride alone were used for a longer duration than that of the combination treatment. Although the pharmacological action of tetrabenazine is quite different from that of tiapride, both drugs attenuate dopaminergic effects on postsynaptic receptors. The pathogenesis of NMS is considered to be based on the imbalance of dopamine in the central nervous system, particularly in the hypothalamus and basal ganglia (12, 15). In the present case, we speculate that the different mechanisms of these drugs (i.e., dopamine blockade or dopamine depletion) strongly interfered with the dopaminergic system and caused NMS. There have been no reports of NMS resulting from combination therapy with tetrabenazine and a dopamine D2-receptor antagonist; therefore, this case is regarded to be very important. Although tetrabenazine is considered to be relatively safe because the NMS has not recurred since the restart of treatment with tetrabenazine alone in spite of the patient’s worsening general condition, her status must be followed up carefully.

In conclusion, combination therapy with tetrabenazine and tiapride can induce NMS in patients with HD, even if the dose of tetrabenazine is very low. Tetrabenazine should be administered very carefully in combination with other neuroleptic drugs, particularly in patients with a worsening general condition.

The authors state that they have no Conflict of Interest (COI).

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References