Effectiveness of Levodopa in Patients with Multiple System Atrophy and Associated Clinicopathological Features

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Abstract:
Objective To determine the clinicopathological features of levodopa or dopamine agonist (DA) responders with multiple system atrophy (MSA), an autopsy-confirmed diagnosis is vital due to concomitant cases of MSA and Parkinson’s disease (PD). We therefore aimed to investigate the effectiveness of levodopa and DA in autopsy cases of MSA without PD and thereby clarify the clinical course, magnetic resonance imaging (MRI) findings, and pathological features of levodopa-responsive MSA cases.

Methods The medical records (clinical data, MRI findings, and pathological findings) of 12 patients with MSA were obtained, and the patients were pathologically confirmed to not have PD. The clinical diagnoses of the patients were MSA with predominant parkinsonism (MSA-P) (n=7), MSA with predominant cerebellar ataxia (MSA-C) (n=4), and progressive supranuclear palsy (PSP) with a concomitant pathology of MSA (n=1).

Results Nine patients received a maximum dose of 300-900 mg of levodopa as treatment, which was effective in two MSA-P patients and mildly effective in another two MSA-P patients. DA was mildly effective in one MSA-C patient. The levodopa responders showed marked autonomic dysfunction relatively late and became bedridden after 10 years. Additionally, they exhibited bilateral hyperintense putaminal rims in MRIs after six and nine years, respectively, after disease onset. One levodopa responder and one DA mild responder showed relatively mild neurodegeneration of the putamen.

Conclusion Levodopa responders, despite having MSA-P, may show a relatively slow progression in putaminal neurodegeneration, and might maintain prolonged daily life activities in cases without an early occurrence of autonomic dysfunction.

Key words: dopamine agonist, levodopa, magnetic resonance image, multiple system atrophy, putamen

[Intern Med 60: 367-372, 2021]
(DOI: 10.2169/internalmedicine.4836-20)

Introduction

The approximate rate of effectiveness of levodopa in multiple system atrophy (MSA) has been reported as 30-65% in both clinical and pathological cases (1-3). The pathological background in which levodopa is effective has mainly been studied with a focus on putaminal lesions (4, 5). However, to investigate the effectiveness of levodopa in MSA, an autopsy-confirmed diagnosis is vital as there are concomitant cases of MSA and Parkinson’s disease (PD) (6). Additionally, no studies have previously examined the effectiveness of levodopa through sequential magnetic resonance imaging (MRI) findings in relation to the pathological findings. We therefore investigated the effectiveness of levodopa and dopamine agonist (DA) in autopsy cases of MSA without PD and aimed to clarify the clinical course, MRI findings, and pathological features of levodopa-responsive MSA cases.

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Received: March 11, 2020; Accepted: July 27, 2020; Advance Publication by J-STAGE: September 19, 2020
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Materials and Methods

Patients

This study was approved by the ethics committee of the National Hospital Organization Iou National Hospital, Japan. Among the consecutive autopsy cases from the hospital from January 2008 to January 2017 (10 years), 12 patients were pathologically diagnosed with MSA without PD (male/female, n=6/6). The pathological diagnosis of MSA was based on the following: (1) the neurodegenerative findings in the substantia nigra-striatal system and the olivoponto-cerebellar system, (2) a large number of α-synuclein-positive glial cytoplasmic inclusions, characteristic of MSA and recognized in a wide area, and (3) to exclude PD in this study, we confirmed that the presence of many Lewy bodies was not observed (7).

Methods

We retrospectively extracted the following datasets from our medical records and examined their relevance.

Clinical and pathological diagnosis of the patients

The patients were clinically diagnosed to have either MSA with predominant parkinsonism (MSA-P), MSA with predominant cerebellar ataxia (MSA-C), or progressive supranuclear palsy (PSP) (8). In addition, they were pathologically confirmed to have either MSA or PSP (7, 9).

Clinical manifestations, and levodopa or DA effectiveness for the patients

The patients were assessed for the use and effectiveness of anti-PD drugs (levodopa and DA), clinical symptoms (initial symptoms, autonomic disorders and the time of appearance), and clinical course until the death of each patient. The effectiveness of anti-PD drugs was evaluated as effective, mildly effective, or ineffective according to the medical records.

Appearance of abnormal findings on MRI

A 1.5-Tesla MRI was used to check for the presence or absence of bilateral hyperintense putaminal rims (Fig. 1A) and the characteristic “hot cross bun” sign of MSA in the pons (10) (Fig. 1B).

Evaluating the grade of neurodegeneration in the putamen

The microscopic findings of the putamen were observed in three coronal planes: the mammillary body, anterior commissure, and nucleus accumbens. The putaminal neurodegeneration of each plane was then qualitatively classified into 4 levels as either “almost normal”, “mild”, “moderate”, or “severe” (Fig. 2).

Datasets were further graded from G0-G3 as follows: G0, “almost normal” in all three planes; G1, “mild” to “moderate” in the mammillary body and anterior commissure planes, and “almost normal” in the nucleus accumbens plane; G2, “moderate” to “severe” in the mammillary body and anterior commissure planes, and “mild” in the nucleus accumbens plane; and G3, “moderate” to “severe” in all three planes.

Results

Clinical and pathological diagnosis of the patients (Table 1)

Among the 12 patients, 7 were clinically diagnosed as MSA-P, 4 as MSA-C, and 1 as PSP with features of early onset of easy falling, postural instability, and vertical supranuclear gaze palsy. The patient who was clinically diagnosed to have PSP further showed the concomitant pathology of both MSA and PSP with wide-spread phosphorylated...
was started within 3 years after the onset and it was found proved for up to 2 years. Levodopa treatment of MSA-P4 started to wear-off after 7 years. MSA-P3 was treated with therapy to 350 mg, but the effect of levodopa 350 mg thereafter showed mild effectiveness (MSA-P3 and MSA-P4) in 4 of 12 (33%) patients (Table 2). Levodopa therapy had no effect on three patients (Table 2). Levodopa therapy began in MSA-P1 8 years after the onset of the disease, and the effectiveness was observed within the 3 coronal planes, i.e. the mammillary body, anterior commissure, and nucleus accumbens. A: almost normal findings; B: mild neuronal loss with gliosis; C: moderate neuronal loss with gliosis; D: severe neuronal loss and gliosis. Bar=100 μm.

Table 1. Clinical and Pathological Diagnosis of the Patients.

| Clinical diagnosis | Patient numbers (M/F) | Age at onset (year-old) | Disease duration (years) | Numbers of treated patients | Pathological diagnosis |
|--------------------|-----------------------|-------------------------|--------------------------|-----------------------------|-----------------------|
|                    |                       |                         |                          | G | T | V |
| Total              | 12 (6/6)              | 61.1±8.3                | 8.8±4.6                  | 10 | 5 | 2 |
| MSA-P              | 7 (3/4)               | 61.0±9.7                | 9.6±5.4                  | 5  | 4  | 2 |
| MSA-C              | 4 (2/2)               | 58.3±2.9                | 8.7±3.3                  | 4  | 0  | 0 |
| PSP                | 1 (1/0)               | 73                      | 3.9                      | 1  | 1  | 0 |

M: Male, F: Female; G: Gastrostomy, T: Tracheostomy, V: Artificial ventilation
1Mean±Standard deviation
2One patient with tracheostomy and invasive ventilation (TIV) and the other one with noninvasive ventilation (NIV).

tau-positive neurofibrillary tangles, coiled bodies, and tufted astrocytes.

Clinical manifestations, and levodopa or DA effectiveness for the patients

The mean age at the onset of disease was 61.1±8.3 [44-73] years, and the mean disease duration was 8.8±4.6 [3-19] years (Table 1). Levodopa, administered at a maximum dose of 300-900 mg, was effective (MSA-P1 and MSA-P2) or mildly effective (MSA-P3 and MSA-P4) in 4 of 12 (33%) patients (Table 2). Levodopa therapy had no effect on three patients (MSA-P5, MSA-P6 and MSA+PSP1). Although two patients (MSA-C1 and MSA-C2) were treated with levodopa, there was no report of the levodopa’s effectiveness. There was no information concerning levodopa administration in three patients (MSA-P7, MSA-C3, and MSA-C4).

Levodopa therapy began in MSA-P1 8 years after the onset of the disease, and the effectiveness was observed within 2 years of its administration. MSA-P1 was diagnosed with PD by neurologists, in the levodopa-responsive phase, although the details of the levodopa-responsiveness were not recorded. MSA-P2 was treated with levodopa 4 months after disease onset, and was seen to have a decrease in hand tremors and motor dysfunction. The dose was escalated further to 350 mg, but the effect of levodopa 350 mg thereafter started to wear-off after 7 years. MSA-P3 was treated with levodopa from the onset, and gait abnormality mildly improved for up to 2 years. Levodopa treatment of MSA-P4 was started within 3 years after the onset and it was found to be mildly effective, based on the mild improvement in forward-leaning posture and bradykinesia. Three patients (MSA-P5, MSA-P6, and MSA+PSP1) were treated with levodopa from the early stage of the disease. However, it was found to be ineffective until 2.5 years, 1 year, and 2 years from the beginning of the treatment in MSA-P5, MSA-P6, and MSA+PSP1, respectively.

Treatment with DA was performed in five patients (MSA-P1, MSA-P2, MSA-P5, MSA-C1, and MSA-C4). The dopamine agonist was only mildly effective in a single patient (MSA-C4) (Table 2) whose motor function slightly improved with the administration of pramipexole 1.5 mg until 5 years after the onset; however, it was unclear when the treatment had begun. Although the other four patients (MSA-P1, MSA-P2, MSA-P5, and MSA-C1) had records of DA administration, there were no reports describing DA’s effectiveness.

Clinical course, appearance of abnormal findings in MRI, and putaminal neurodegeneration of the patients (Fig. 3)

In the levodopa responders (MSA-P1 and MSA-P2), the onset of autonomic dysfunction was slow (more than 6 years), and the period until being bedridden was long (more than 10 years) (Fig. 3). Two patients, MSA-P1 and MSA-P2, showed MRI abnormalities after 6 and 9 years of the onset of the disease, respectively, and these abnormalities had not been confirmed during their levodopa-responsive phase. In addition, MSA-P2 showed mild neurodegeneration.
Table 2. Levodopa- or Dopamine Agonist-responsibilities and Clinical Manifestations of the Patients.

| Patients | Age at onset (year-old)/ Sex | Levodopa maximum dose (mg) / Effectiveness | DA administration/ Effectiveness | Initial symptoms or signs | Autonomic dysfunctions (time of appearance from the onset, years) |
|----------|-----------------------------|---------------------------------------------|---------------------------------|--------------------------|---------------------------------------------------------------|
| MSA-P1   | 61/M                        | N.D./R                                      | +/-N.D.                         | Bradykinesia, difficulty of walking | Urinary retention, OH (11)                                     |
| MSA-P2   | 44/F                        | 900/R                                       | +/-N.D.                         | Hand tremor              | Urinary incontinence, constipation (7)                        |
| MSA-P3   | 70/M                        | 600/mR                                      | N.D.                           | Bradykinesia             | Dysuria, OH (2)                                               |
| MSA-P4   | 52/M                        | 450/mR                                      | N.D.                           | Instability of walking   | Dysuria, constipation (5)                                     |
| MSA-P5   | 64/F                        | 300/nR                                      | +/-N.D.                         | Difficulty of walking, postural instability          | OH (<1)                                                      |
| MSA-P6   | 70/F                        | N.D.                             | N.D.                           | Difficulty of limb movement | OH (2)                                                       |
| MSA-P7   | 66/F                        | N.D.                             | N.D.                           | Difficulty of hand movement, easy falling       | OH (<1)                                                      |
| MSA-C1   | 56/M                        | 500/N.D.                                 | +/-N.D.                         | Instability              | OH (<1)                                                      |
| MSA-C2   | 59/M                        | 450/N.D.                                 | N.D.                           | Instability              | Details unknown (<1)                                         |
| MSA-C3   | 59/M                        | N.D.                             | N.D.                           | Difficulty of speaking and walking             | Urinary retention, OH (4)                                    |
| MSA-C4   | 62/F                        | N.D.                             | +/-DA-mR                        | Dysuria, delusion, instability, difficulty of limb movement | Dysuria (0)                                                  |
| MSA+PSP  | 73/M                        | 300/nR                                 | N.D.                           | Easy falling, instability                  | Pollakisursia (2)                                             |

M: Male; F: Female; DA: dopamine agonist; N.D.: not described; R: levodopa-responsive; mR: mildly levodopa-responsive; nR: levodopa-nonresponsive; DA-mR: mildly DA-responsive; OH: orthostatic hypotension

1 There is a record of treatment with levodopa, although the maximum dose is not described.
2 There is no description whether the patient was treated with levodopa.

Figure 3. Clinical course, appearance of abnormal findings in magnetic resonance imaging (MRI), and putaminal neurodegeneration of the patients. Black and grey bars show the disease period, black bars indicate the onset of the disease and the grey bars indicate the period of a bedridden state for the patients. The large letters above the black and grey bars indicate the following: A: the outstanding or first appearance of autonomic dysfunction; G: gastrostomy; NIV: noninvasive ventilation; T: tracheostomy and TV, tracheostomy and invasive ventilation. White circles and squares indicate the last absent times of the abnormal MRI findings. White circle indicates bilateral hyperintense putaminal rims and the white square indicates hot cross bun sign. Black circles and squares exhibit the first confirmed times of abnormal MRI findings. Dotted lines indicate the periods suggesting the occurrence of those MRI findings. The letters G1, G2, and G3, show the staging of putaminal neurodegeneration. DA-mR: mildly dopamine agonist-responsive, mR: mildly levodopa-responsive, nR: levodopa-nonresponsive, R: levodopa-responsive

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(G1) of the putamen despite a long clinical course (14 years), although the other patients with MSA-P exhibited moderate (G2) or severe (G3) neurodegeneration of the putamen. Patient MSA-P1 showed severe neuropathological change (G3) of the putamen with the longest clinical course (19 years).

The mild levodopa responders (MSA-P3 and MSA-P4) showed a slightly longer period to reach a bedridden state compared to the levodopa nonresponders (MSA-P5, MSA-P6, and MSA + PSP1). Patient MSA-P3 had an early onset of autonomic dysfunction and became bedridden in a short period when compared to MSA-P4. There was no apparent difference between the mild levodopa responders (MSA-P3 and MSA-P4) and the nonresponders (MSA-P5, MSA-P6 and MSA + PSP1) in the time of the occurrence of abnormal MRI findings or in their grades of putaminal degeneration.

Patient MSA-C4, a mild DA responder, showed an early occurrence of autonomic dysfunction and was bedridden in a short time period. Hypointense putaminal rims appeared from 3 to 7 years after the onset and showed mild neurodegeneration (G1) of the putamen. Two MSA-C patients (MSA-C2 and MSA-C3) showed a longer period to reach the bedridden state than did MSA-C4, and MSA-C2 further showed mild neuropathological findings of the putamen. However, MSA-C2 and MSA-C3 had no records on the effectiveness of anti-PD drugs (Fig. 3).

In this study, levodopa in a maximum dose of 300-900 mg was effective or mildly effective in 4 out of 12 (33%) patients with pathologically confirmed MSA. From another point of view, there were 4 (44%) levodopa responders or mild responders among 9 patients who had been confirmed to receive levodopa treatment. A previous study on levodopa in patients with pathologically confirmed MSA reported 28-37% effectiveness; however, the effect persisted for several years in only 13% of those patients (1). In previous studies on patients with clinically diagnosed MSA, levodopa’s effectiveness was reported range from 31.2-51.6%, with a median effective period of 3.2-3.5 years (2, 3). The results of those reports include MSA-C patients as well as MSA-P patients (1-3). As our study was retrospective and lacked some information, we could not identify the period when levodopa was most effective. Additionally, there is a possibility that the patients in this study might not have received a sufficient dose of levodopa and therefore the effectiveness of levodopa might have been underestimated, since responsiveness should be evaluated by administering 1,000 mg for 3 months (1, 11).

Focusing on the levodopa responders of this study, the time until the onset of autonomic dysfunction was over 6 years and the time to become bedridden was over 10 years. Previous studies have indicated that the prognosis is worse in patients with an early onset of autonomic symptoms or with concomitant early onset movement disorders (12-14) and levodopa-responsiveness is not significantly related to the prognosis (14). On the other hand, it has been reported that 4 autopsy-confirmed MSA-P patients showed long-term survival of over 15 years (15). In the same report, autonomic symptoms appeared 11 years after the disease onset in all patients, 3 of them were responsive to levodopa treatment (15). Therefore, we cannot determine if levodopa-responsive patients with MSA can achieve a good prognosis, however, some patients with MSA-P with long-term survival may show a good response to levodopa.

The abnormal findings of bilateral hyperintense putaminal rims in the MRI appeared more than 6 years after the disease onset in our levodopa-responsive patients. The time of occurrence of the putaminal lesions in the levodopa responders were later than those of MSA-P cases in this study or from the previous study (10). A previous study shows abnormal signals of the outer putamen on both sides of the brain in patients with MSA-P after 3 to 6 years of disease onset and 3 years earlier than those with MSA-C (10). Moreover, the abnormal MRI findings of the hyperintense putaminal rims had not been confirmed in their levodopa-responsive phases. In one levodopa responder of this study, the pathological change of the putamen was mild despite a long clinical course of 14 years. Putamen lesions were noted in the previous pathological study on levodopa responsiveness of MSA (4, 5). The fibers projecting from the putamen to the pallidus were more well preserved in 2 levodopa responders than in 3 non-reactive cases (4). In another pathological study of 57 cases of MSA, levodopa-responsive cases showed a decreased putamen pathology compared to the nonresponsive cases (5). Our current results and those of previous studies of levodopa indicate that putaminal lesions may show slow development and remain relatively well preserved, even at the time of death in the responsive patients. We should refrain from considering DA-responsiveness as having a common pathomechanism as levodopa responsiveness, because the levodopa reactivity of a mild DA responder in this study was unknown and the patient was one of MSA-C. However, the fact that the putamen lesion was relatively well preserved seems to be a remarkable finding.

In the present autopsy-confirmed patients with MSA, levodopa was effective in more than 30% of all cases. Most patients with MSA-P show an early progression of putamen lesions. However, our results indicate that some of MSA-P, in which levodopa is responsive, may have a slow progression of putamen lesions, therefore leaving the putamen relatively preserved at the time of death. Furthermore, with the late-onset of autonomic dysfunction, the activities of daily life may ultimately be maintained for a long time in patients with MSA. Concerning DA, we could not obtain sufficient data in this study. We consider that further research that links sequential MRI findings and pathology to DA as well as levodopa is therefore needed.

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

This work was supported by the National Hospital Organization Iou National Hospital. We are very grateful to Professor Masahito Yamada for collaboration and advice on the neuropathological studies. We are also grateful to Ms. Yumiko Kakuda, Ms. Miyuki Honda, and Ms. Keiko Kawabata for their technical support.

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