Perverted Head-Shaking and Positional Downbeat Nystagmus in Patients With Multiple System Atrophy

Jee-Young Lee, MD,1,4 Woong-Woo Lee, MD,1 Ji Soo Kim, MD, PhD,2 Hee Jin Kim, MD,1,4 Jin-Kyung Kim, BS1,3 and Beom S. Jeon, MD, PhD1,3,4*

1 Department of Neurology, Seoul National University Hospital, Seoul, South Korea
2 Department of Neurology, Seoul National University Bundang Hospital, Seoul, South Korea
3 Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, South Korea
4 Clinical Research Institute and Movement Disorder Center, Seoul National University Hospital, Seoul, South Korea

Abstract: The diagnosis of multiple system atrophy (MSA) is mainly based on the clinical criteria, which are often of little assistance in the early stages of the disease. Positional downbeat nystagmus (pDBN) and perverted head-shaking nystagmus (pHSN), possible signs of cerebellar dysfunction, may be useful in differentiating MSA from other parkinsonian disorders. To investigate the occurrences of pDBN and pHSN in patients with MSA compared with those in patients with Parkinson’s disease (PD). A total of 127 consecutive patients with MSA and 274 patients with PD underwent a video-oculographic recording of head-shaking and positional nystagmus over a year. The occurrences of pDBN and pHSN were higher in MSA than in PD. pDBN was more frequently observed in MSA with overt cerebellar signs than in those without, but the occurrence of pHSN did not differ between the MSA groups. pHSN was more frequently observed in MSA-p without overt cerebellar signs than in PD, but there was no difference in the occurrence of pDBN between them. The presence of pHSN and pDBN may be a clue for the diagnosis of MSA, and pHSN may be helpful in differentiating MSA-p from PD when the patients do not have overt cerebellar features.

Key words: multiple system atrophy; Parkinson’s disease; perverted head-shaking nystagmus; positional downbeat nystagmus

Multiple system atrophy (MSA) is a neurodegenerative disorder without biological markers for antemortem diagnosis. Because the sensitivity and positive predictive value of the current clinical diagnostic criteria are low during the first few years of the disease, differentiation of MSA in its early features from idiopathic Parkinson’s disease (PD) remains a diagnostic challenge. Prominent cerebellar pathology is a unique feature of MSA among the parkinsonian neurodegenerative disorders and abnormal ocular motilities from cerebellar dysfunction are occasionally observed in MSA patients without other cerebellar features. In this regard, the detection of subclinical cerebellar dysfunction would aid in the differential diagnosis of MSA.

Positional downbeat nystagmus (pDBN) primarily originates from lesions involving flocculonodular lobes or posterior vermis of the cerebellum. Perverted head-shaking nystagmus (pHSN) refers to vertical nystagmus induced by horizontal head oscillation, sustained horizontal rotation in a chair, or caloric irrigation. Although the pathophysiology of pHSN remains unclear, it is usually attributed to lesions in the central vestibular pathways, including the vestibulocerebellum. Therefore, pDBN and pHSN may be useful in...
detecting subclinical cerebellar dysfunction. Furthermore, these types of nystagmus can be easily observed at the bedside by applying Frenzel goggles. However, there has been no report on pHSN in MSA and only a few reports concerning pDBN in MSA.4,7,8

To determine whether the presence of pDBN and pHSN can aid in differentiating MSA from PD, we investigated pDBN and pHSN in patients with clinically diagnosed MSA as well as in patients with PD.

METHODS

Patients

A total of 127 patients with MSA (34 cerebellar dominant [MSA-c, clinically possible 10, and probable 24] and 93 parkinsonian dominant [MSA-p, clinically possible 52, and probable 41] type by Quinn criteria1,9) and 274 patients with PD (by criteria of UK PD Society Brain Bank10) participated in this study. The patients with MSA included 70 women and 57 men who ranged in age from 43 to 81 years (mean ± SD = 64.1 ± 8.3). The mean duration of the disease was 3.5 ± 2.2 years. The patients with MSA-p were divided into two groups based on the presence of overt cerebellar signs. Of the 274 patients with PD, 129 were men. The PD patients ranged in age from 25 to 85 (mean ± SD = 63.3 ± 9.4) with the mean duration of disease at 3.9 ± 3.4 years.

At the first and follow-up visit before performing a video-oculographic recording, the presence of overt cerebellar signs, such as cerebellar dysarthria, dysdiadochokinesia, limb, and gait ataxia, were examined by patients’ speech, rapid alternating hand movement, finger-to-finger, finger-to-nose, heel-to-shin, tandem gait, and Romberg tests. At the same time, patients were also examined for ocular motor abnormalities such as spontaneous or gaze-evoked nystagmus, rebound nystagmus, and saccadic hypometria.

All of the patients underwent video-oculographic recording of head-shaking and positional nystagmus between February 2007 and January 2008. They met the following conditions: (1) absence of a structural lesion in the cerebellum and brainstem on brain magnetic resonance images (MRI) or computed tomography (CT) scans except for alleged degenerative signal changes or atrophy in parkinsonian disorders,11 (2) no history of concurrent peripheral vestibulopathy, (3) no medications that could affect the vestibular and cerebellar function, and (4) no neck problems causing difficulty in head-shaking or positioning maneuvers. All of the patients were examined by the senior author (J.B.S.) at the Movement Disorders Clinic of Seoul National University Hospital.

Prior to this study, normative data were obtained from 25 healthy volunteers (7 men and 18 women with the age ranging from 30 to 81 [mean ± SD = 56.8 ± 12.9]). The Institutional Review Board of Seoul National University Hospital approved this study.

Head-Shaking Test

Nystagmus was induced using a passive head-shaking maneuver according to the method described previously.12 In a dark room, patients were asked to sit upright with their eyes closed and their head tilted forward about 30 degrees to bring the horizontal semicircular canals into the plane of stimulation. The head was shaken horizontally by an examiner in a sinusoidal manner at a rate of 2.5 Hz with an amplitude of 10 degrees for 10 s. Immediately after the head-shaking, the patients were instructed to open their eyes and look straight ahead. Post head-shaking nystagmus was observed via video goggles with removal of fixation. Eye movements were recorded with an infrared camera (resolution of 640 × 480 pixels, frame rate of 60 Hz) and displayed on a computer monitor (SLMED, Seoul, Korea). The recording continued until the nystagmus resolved or for 20 s if nystagmus was absent. The presence of pHSN was defined when the median slow-phase velocity (SPV) of the first 3 beats of the induced vertical nystagmus was 3 degrees/s or more, with or without a horizontal component.12

Positioning Test

pDBN was induced by the Dix-Hallpike and straight head-hanging maneuvers. During each positioning, the patients were instructed not to close their eyes. When the nystagmus was evoked, the position was maintained until it resolved. The positioning nystagmus mostly developed without latency and dissipated gradually, even though the provoking position was maintained. pDBN was also recorded using a video-oculography system as described earlier. The presence of pDBN was defined when the median slow phase velocity (SPV) of the first 3 beats of the induced vertical nystagmus was 5 degrees/s or more.

Interpretation of the Nystagmus

The presence of pHSN or pDBN was also confirmed by three neurologists (J.B.S., L.J.Y., and K.H.J.) who reviewed the video recordings and oculography findings. An example of a patient who underwent head-shaking (Video Segment 1) and positioning test (Video...
Statistical Analysis

In comparisons of the occurrences of pDBN and of pHSN between the two groups, $\chi^2$ test was used. The statistical analyses were conducted using the SPSS software (version 12.0; SPSS, Chicago, IL), with the limit of significance set at 0.05 (two-tailed).

RESULTS

Among the 93 patients with MSA-p, 56 had no overt signs of cerebellar dysfunction. During the video-oculography, primary position downbeat nystagmus was absent in all of the subjects. Opsoclonus was present in one patient with probable MSA-p, and ocular flutter was present in two patients (one with probable MSA-p and the other with probable MSA-c).

The Presence of pDBN and pHSN in Patients With MSA and PD

The occurrence of pDBN was 15.7% (n = 20) in MSA and 2.6% (n = 7) in PD, while that of pHSN was 31.5% (n = 40) in MSA and 9.5% (n = 27) in PD. Both pDBN and pHSN were more common in patients with MSA than in those with PD ($P < 0.001$, Table 1). Among the 84 (51 MSA and 33 PD) patients with either pDBN or pHSN, 9 patients with MSA and 1 patient with PD had both pDBN and pHSN. The presence of both types of nystagmus was a significant indicator of MSA rather than PD (specificity of 99.3%).

pDBN was observed more frequently in patients with MSA-c (32.4%, 11 of 34) than in patients with MSA-p (9.7%, 9 of 93, $P = 0.004$). The occurrence of pHSN was 20.6% (7 of 34) in patients with MSA-c and 35.5% (33 of 93) in patients with MSA-p, but there was no significant difference between the groups ($P = 0.133$). When we compared the occurrences of the nystagmus in the MSA groups according to the presence of cerebellar signs, the occurrence of pDBN was higher in the patients with cerebellar signs (both MSA-c and MSA-p with cerebellar signs) than in those without, i.e., MSA-p without cerebellar signs ($P = 0.004$), but the occurrence of pHSN did not differ between the two groups ($P = 0.806$, Table 1).

The occurrence of pHSN in MSA-p without cerebellar signs was 30.4% (17 of 56), which was higher than that in PD ($P < 0.001$, Table 1), but the occurrence of pDBN did not differ between the groups (5.4 vs. 2.6%, $P = 0.383$). The sensitivity and specificity of pHSN in differentiating MSA-p from PD was 30.4% and 90.5%, and the positive and negative likelihood ratios were 3.2 and 0.77, respectively.

Clinical Features of PD With pDBN or pHSN

Thirty-three (12%) patients with PD had either pDBN or pHSN. The clinical profiles of the patients are summarized in Supplementary Table. All patients, except for patient 5, demonstrated three or more supportive features of PD according to the diagnostic criteria of the UK PD Society Brain Bank, such as unilateral onset of symptoms, good L-dopa response, the presence of resting tremor, persistent asymmetry, and the presence of L-dopa-induced dyskinesias. Features suggestive of MSA were not observed on brain images of any of the patients, except for patient 16. Patient 16 showed subtle atrophic changes in the right putamen on magnetic resonance imaging, but her parkinsonian features were symmetric.

DISCUSSION

The results of this study showed that pDBN and pHSN were more common in MSA than in PD. pDBN was more frequently observed in MSA-c, but there was no difference in the occurrence of pHSN between MSA with cerebellar signs and those without. Because the mean disease duration was relatively short (less than 5 years in 81.7%) in MSA, the occurrence of both types of nystagmus might increase with progression of the disease. The importance of our study lies in the inclusion of a considerable number of MSA-p patients without cerebellar features. Interestingly, the occurrences of pDBN in MSA-p without cerebellar features and in PD (5.4% vs. 2.6%) were similar, whereas pHSN was more frequently observed in MSA-p without overt cerebellar features (30.4% vs. 9.5%). This might be due to the fact that in MSA, the cerebellar Purkinje cells in the vermis are more affected than those in the hemisphere, and advanced cerebellar pathology is required for the development of detectable cerebellar ataxia, compared with less severe striatonigral pathology for the expression of parkinsonism. Therefore, it is supposed that the anatomical substrates for pDBN and pHSN may differ and that pDBN is more likely to be related to the expression of cerebellar ataxia.

Reports on ocular motor abnormalities have been sparse in MSA. A recent comprehensive study of 30 patients with clinically diagnosed MSA documented that excessive square wave jerks, hypometric saccades,
impaired suppression of the vestibulo-ocular reflex, and spontaneous nystagmus as well as pDBN may give clues for the diagnosis of MSA. However, the study did not classify the abnormal features of MSA according to the presence of cerebellar signs, and they did not compare the ocular motor findings with those in PD either. Furthermore, as the authors acknowledged, the interval from symptom onset to the study was long (6.6 ± 3.7 years), so that some ocular motor abnormalities may not have been apparent during the early stage when the differential diagnosis is most challenging.4

pDBN is a well-known sign of cerebellar dysfunction and the putative anatomical substrates are flocculonodular lobes or posterior vermis of the cerebellum.5

In a retrospective study analyzing 50 consecutive patients with pDBN, 13 had MSA and five had predominant parkinsonism, suggesting that pDBN may be a useful sign in the differential diagnosis of parkinsonian disorders.15 pDBN was later found in 10 of 25 patients with MSA (7 MSA-c and 3 MSA-p).6 In our study, pDBN was more frequently present in MSA than in PD. However, the presence of pDBN does not seem to be useful in differentiating MSA-p without cerebellar features from PD. It also should be noted that in another report, pDBN was found in one of 20 (5%) patients with PD as well as in normal subjects in the prone position without fixation,5 which suggests that pDBN may not be useful in the differential diagnosis of parkinsonian disorders in general.

Although the pathophysiology of pHSN is poorly understood, it might be explained by abnormal cross-coupling of the vestibular storage system in the central vestibular pathways.5 Responsible anatomical locations have been suggested in just a few reports. Experimentally, pHSN is evoked by destroying the vestibular nuclei in monkeys.16 In humans, pHSN has been reported in a patient with a demyelinating plaque in the caudal medulla,6 a patient with focal cerebellar infarction17 and in patients with lateral medullary infarction.12 Dysfunction of the vestibulocerebellum may cause cross-coupling of the vestibular responses. The nodulus and ventral uvula participate in velocity storage during head tilt,18 and damage to these areas may induce cross-coupling during horizontal head oscillation, resulting in pHSN.17 It was also suggested that lesions interrupting connections to the vestibulocerebellum produce pHSN.17

The nucleus of Roller and the nucleus intercalatus are the precerebellar nuclei that project to the cerebellum. A recent study reported that the precerebellar nuclei are involved in MSA19 and showed that the nucleus of Roller and the inferior olivary complex were severely involved (the involvement of the nucleus intercalatus was not mentioned in this paper). The nucleus of Roller and the nucleus intercalatus located in the caudal medulla have reciprocal connections with both the nucleus prepositus hypoglossi and the interstitial nucleus of Cajal.6 Thus, in the presence of lesions in this region, ephaptic transmission of the vestibular signal from the horizontal to vertical plane across the fiber tracts may take place and produce pHSN.6 On the other hand, the nucleus of Roller and the nucleus intercalatus also project to the vestibulocerebellum,20,21 and another hypothesis for pHSN is disinhibition of the central pathways from the anterior semicircular canals, which are normally inhibited by the Purkinje cells of the flocculus.5,6 It remains to be determined whether the frequent appearance of pHSN in MSA-p patients without cerebellar features is related to the pathology in the precerebellar nuclei in the lower brainstem.

Another unexplained issue is the observation of pHSN or DBN in PD. In our study, 12% of patients with PD had pHSN or pDBN. A misdiagnosis of MSA as PD has been consistently reported in 13 to 19% of clinically diagnosed PD cases by several autopsy studies, even those involving the use of strict

| TABLE 1. The occurrences of pDBN and pHSN in patients with PD and MSA |
|-------------------------|------------------|------------------|------------------|------------------|------------------|
| Nystagmus               | PD (n = 274)     | MSA-c (n = 34)   | MSA-p (n = 93)   | pDBN with cerebellar signs (n = 37) | pHSN with cerebellar signs (n = 56) |
|                        | p               | p               | p               | p                | p                |
|                        | DBN             | HSN             | DBN             | HSN              | DBN             | HSN              |
|                        | (n = 274)       | (n = 34)        | (n = 93)        | (n = 37)         | (n = 56)        | (n = 56)         |
| pDBN                   | 2.6             | 32.4            | 16.2            | 5.4              | <0.001          | 0.265            | 0.004            |
| pHSN                   | 9.5             | 20.6            | 43.2            | 30.4             | <0.001          | <0.001           | 0.806            |

Data is shown as percent of the patients having a nystagmus.

*The comparison between total MSA and PD by χ² test.

†The comparison between MSA-p without cerebellar signs and PD by χ² test.

‡The comparison between MSA with cerebellar signs (both MSA-c and MSA-p with cerebellar signs) and MSA-p without cerebellar signs, by χ² test.

pDBN, positional downbeat nystagmus; pHSN, perverted head-shaking nystagmus; MSA, multiple system atrophy; PD, Parkinson’s disease.
clinical diagnostic criteria. In a recent study, 7 of 11 cases with autopsy-confirmed MSA had also been clinically diagnosed with PD, reflecting that MSA-p without cerebellar features is often misdiagnosed as PD. However, our patients still met the clinical criteria for PD, not MSA, even after reviewing the clinical features and performing a repeat examination. Because the cerebellar signs may not be apparent in the early stage of L-dopa responsive MSA, some of these patients may turn out to be MSA with future clinical follow-up. Interestingly, the occurrence of either pHSN or pDBN (12%) in our study is similar to the rate of misdiagnosis (13–19%), and both of the nystagmus were not found in the PD patients with more than 5 years of the disease. Otherwise, the precerebellar nuclei may be involved in PD, but this hypothesis has not yet been investigated.

In view of our study results, evaluation of pHSN or pDBN may aid in the diagnosis of MSA, and pHSN may be helpful in differentiating MSA-p from PD when the patients do not have overt cerebellar features. The potential correlation between these types of nystagmus and other alleged ocular motor abnormalities in MSA needs to be investigated in future studies.

LEGENDS TO THE VIDEO

During the head-shaking and positioning test, patients are asked to put on video goggles with removal of visual fixation. Because the nystagmus can be directly seen by an examiner, Frenzel goggle can be applied instead of video goggles if a videonystagmography system is not provided. Here is an example of pHSN and pDBN in a patient with MSA-p without overt cerebellar features. The subject is a 67-year-old woman with a 5-year-history of right dominant hypokineti-rigid syndrome with atypical posture. Deep tendon reflexes are hyperactive on the right side. Her cognitive function is normal. She has no clinical signs of autonomic or cerebellar system involvement. The response to L-dopa is poor. After 2 years of symptom onset, she develops camptocormia and postural instability. On the brain MRI taken at this time, there is no abnormality. The videonystagmographic examination is performed at the time of 5 years after symptom onset when she still has no overt cerebellar features.

Segment 1. Perverted head-shaking nystagmus. The patient is asked to sit upright with eyes closed and the head tilted forward about 30 degrees to bring the horizontal semicircular canals into the plane of stimulation. The head is shaken horizontally by an examiner in a sinusoidal manner at a rate of 2.5 Hz for 10 s. Immediately after the head-shaking, the patient is instructed to look straight ahead. The typical post head-shaking downbeat nystagmus appears without latency and then spontaneously dissipates over 20 s.

Segment 2. Positional downbeat nystagmus. The positioning test is performed with straight head-hanging followed by right and left Dix-Hallpike maneuvers. The video segment shows straight head hanging maneuver and the pDBN which appears without latency, lasts for a few seconds and dissipates spontaneously with the position maintained. She develops no definite downbeat nystagmus with Dix-Hallpike maneuvers.

Acknowledgments: This study was supported by Seoul National University Hospital Research Grant. We deeply appreciate a generous donation from Mr. Chung Suk-Gyoo and Shinyang Cultural Foundation. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Pf. Jeon BS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Roles: JYL was involved in study design, analysis and interpretation of data, and drafting the manuscript; WWL, HJK, JKK in the acquisition and interpretation of data, JSK in interpretation of data, critical revision of the manuscript for important intellectual content; BSJ in the study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content and the corresponding author.

REFERENCES