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# Abnormal Ocular Movement in the Early Stage of Multiple-System Atrophy With Predominant Parkinsonism Distinct From Parkinson's Disease

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**Background and Purpose** The eye-movement examination can be applied as a noninvasive method to identify multiple-system atrophy (MSA). Few studies have investigated eye movements during the early stage of MSA with predominant parkinsonism (MSA-P). We aimed to determine the characteristic oculomotor changes in the early stage of MSA-P.

**Methods** We retrospectively selected 17 patients with MSA-P and 40 with Parkinson's disease (PD) with disease durations of less than 2 years, and 40 age-matched healthy controls (HCs). Oculomotor performance in the horizontal direction was measured in detail using videonystagmography.

**Results** We found that the proportions of patients with MSA-P and PD exhibiting abnormal eye movements were 82.4% and 77.5%, respectively, which were significantly higher than that in the HCs (47.5%, $p<0.05$). Compared with HCs, patients with MSA-P presented significantly higher abnormal proportions of fixation and gaze-holding (17.6% vs. 0%), without-fixation (47.1% vs. 0%), prolonged latency in reflexive saccades (29.4% vs. 5.0%), memory-guided saccades (93.3% vs. 10.0%), and catch-up saccades in smooth-pursuit movement (SPM, 41.2% vs. 0) (all $p<0.05$). Compared with those with PD, patients with MSA-P presented a significantly higher proportion of catch-up saccades in SPM (41.2% vs. 2.5%, $p<0.001$).

**Conclusions** MSA-P presented the characteristic of catch-up saccades in SPM in the early stage, which may provide some value in differentiating MSA-P from PD.

**Keywords** multiple-system atrophy; Parkinson's disease; oculomotor deficits; smooth-pursuit movement; catch-up saccades.

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## INTRODUCTION

Parkinsonism is a type of clinical syndrome characterized by rigidity and bradykinesia, including idiopathic Parkinson's disease (PD), atypical parkinsonism, and secondary parkinsonism.[1,2] Atypical parkinsonism includes multiple-system atrophy (MSA). PD and atypical parkinsonism, especially MSA with predominant parkinsonism (MSA-P), have similar clinical manifestations. In particular, the misfolded alpha-synuclein accumulated in the brain in both MSA and PD, and nonmotor symptoms such as constipation and rapid-eye-movement sleep behavior disorder were found to be similar among these conditions,[3] which poses a great challenge for doctors in making correct diagnoses in the early stage. Neurologists experience difficulties in the differential diagnosis of these two diseases, especially in the early stage. The misdiagnosis rate of patients with PD was found to be as high as 24%, and approximately 33.3% of patients with MSA remain incorrectly diagnosed at death, even for diagnoses performed by experienced neurologists specializing in movement disorders.[4]

The correct diagnosis can affect patient expectations of the disease, and can also somewhat affect the treatment effect. Identifying biomarkers or auxiliary examinations that can be applied to the early diagnosis of parkinsonism has therefore become an urgent need in clinical practice.

The gold standard of diagnosing both MSA-P and PD is a pathological assessment. However, the clinical application of this method is restricted by difficulties in obtaining materials and high costs. Diagnostic biomarkers for MSA-P and PD have recently become a research focus. Biomarkers that have been used in clinical practice or research include those of structural or functional imaging, blood/cerebrospinal fluid, genes, oxidative stress, neuroprotection, and inflammation.[5,6] The high costs of special instruments and equipment and the invasive procedures have affected the wide application of the above inspection method. In contrast, an eye-movement examination can be applied as a noninvasive method to identify MSA-P and PD.

Previous studies have found that MSA and PD have different degrees of abnormal eye movement.[7-9] Due to the overlap and specificity of their pathological changes, their abnormal eye movements had both similarities and characteristic changes.[10] Our previous studies suggested that combined eye movements were useful in the differential diagnosis of MSA and PD, and MSA subtypes also have their own abnormal eye-movement characteristics.[9,11] For example, PD may be associated with typical multistage saccades, and MSA-P may be associated with hypermetria and abnormal smooth pursuit.[7,10,12] Brooks et al.[13] found that increased antisaccade errors combined with slowed prosaccade latencies might serve as a useful marker for early differentiation between MSA and PD in mid-stage patients. Eye movements may therefore have certain value in identifying MSA and PD. It should be noted that because cerebellar ocular symptoms mostly remain subtle, it was more difficult to distinguish MSA-P from PD, especially in their early stages. There is controversy about the utility of eye movements in the differential diagnosis of early MSA-P and PD. According to Linder et al.,[14] saccade and smooth-pursuit tests could not separate the different forms of early-stage PD and MSA-P. However, Terao et al.[15] found that saccades in MSA-P were characterized by both prolonged acceleration and deceleration periods with reduced peak velocity, while the velocity profile of patients with PD was mostly characterized by the prolonged deceleration period. The saccade velocity profiles might be helpful in differentiating between early MSA-P and PD. Pinkhardt et al.[16] found that although MSA-P was associated with a significantly lower smooth-pursuit movement (SPM) gain than was PD, the difference was not helpful in differentiating these conditions at the individual patient level due to a large data overlap. However, catch-up saccades accumulated during SPM epochs and anticipatory saccades in MSA were sufficiently significant for differentiating between MSA and PD, while anticipatory saccades were not specific enough since they could also be observed in PD.

Few studies have investigated eye movements during the early stages of MSA-P and PD, and the usefulness of eye movements in differentiating between these conditions still needs to be verified. This study therefore explored the characteristics of eye-movement changes in the early stages of MSA-P and PD.

## METHODS

### Clinical assessments of participants

This was a retrospective cohort study. All participants were patients at Peking University First Hospital (PKUFH) Movement Disorders Clinic between June 2018 and October 2022. Three movement-disorder neurologists (Z.X.W., W.S., and J.C.) performed the diagnoses according to certain criteria for MSA-P or PD.[1,17] Patients with MSA-P were assessed using the Unified Multiple System Atrophy Rating Scale,[18] and those with PD were assessed using the Unified Parkinson Disease Rating Scale.[19] We collected the clinical data of all individuals who were diagnosed with parkinsonism at their first visit and also at every follow-up visit, including their basic information, symptoms, and complications. The auxiliary examination mostly included an olfactory examination (China-Germany version of the Sniffin' Sticks test) with a score range of 0−12,[20] brain magnetic resonance imaging (MRI), and an autonomic nerve assessment (including orthostatic hypotension and/or urogenital features). Orthostatic hypotension was confirmed using the head-up tilt test, in which blood pressure and heart rate were measured in the supine position and after 70° of tilting at 1, 3, 5, 10, 15, and 20 min. The postvoid residual volume of urine was measured using ultrasound in the morning. All patients with MSA-P or PD received appropriate treatment if needed, and all patients were followed up to confirm the diagnosis accuracy (Y.C.S.). We reviewed the data of patients with MSA-P (probable) or PD (clinically established) with initial symptoms within 2 years and their related eye-movement examinations. The sample finally included 17 patients with MSA-P and 40 with PD. We also selected 40 healthy individuals as controls. All healthy controls (HCs) presented no signs of nervous system disease and were no taking any medication for movement-disorder-related diseases. They also had no vestibular system disease, substance abuse or dependence, or psychiatric disorders according to the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders.[21] The Mini

Mental State Examination (MMSE) was used to assess cognitive function. We excluded patients who could not complete eye-movement tests for any reason or who had poor-quality eye recording data. This study was approved by the ethics committee of PKUFH (IRB No. 2019210) and was performed in accordance with the principles of the Declaration of Helsinki. All participants were fully aware of the study details and provided written informed consent.

### Protocol and ocular evaluation

We performed eye-movement examinations (H.Z. and X.W.) using a binocular EyeLink system (Bao Runtong Research, Beijing, China), as described in our previous studies.[9,11] In brief, there were six eye-movement tests: 1) without-fixation, 2) fixation and gaze-holding, 3) reflexive saccades, 4) SPM, 5) optokinetic nystagmus (OKN), and 6) memory-guided saccade (MGS) tests. The following eye-movement recording parameters were analyzed: quantitative data including 1) latency, peak velocity, and saccade accuracy, and 2) the gains in the SPM and OKN tests (quantitative data were analyzed automatically and generated using computer software); and qualitative data including 1) hypometria/hypermetria and saccade intrusions in reflexive saccades, 2) anticipatory saccades, catch-up saccades, and saccade intrusions in SPM; 3) gaze-evoked nystagmus, square-wave jerks (SWJs), and macro-SWJs in fixation and gaze-holding tests, 4) spontaneous nystagmus and SWJs in the without-fixation test, and 5) gains in SPM or OKN lower than 0.60, which were judged as abnormal (qualitative data were judged by three eye-movement experts; H.Z., X.W., and G.P.Z.). Any abnormal manifestations of any eye-movement type were judged as abnormal in both the quantitative and qualitative analyses.

### Statistical analyses

Statistical analyses were performed using SPSS software (version 22.0 for Windows, SPSS, IBM Corp., Armonk, NY, USA). The measurement data were expressed as mean±standard deviation values for normally distributed continuous variables and as median and interquartile-range values for skewed variables. The numeric data were described using proportions. The independent-samples *t*-test was used to performed intergroup comparisons of normally distributed measurement data. ANOVA was used to compare the mean values between multiple groups, and the parameters of two groups were compared if significant differences were determined. The chi-square test was used to assess the differences in the distribution of categorical variables according to disease. We used the Bonferroni method to correct the results for multiple comparisons. Significance was set at $p<0.05$ (two-tailed).

## RESULTS

### Demographics

The clinical data and characteristics of the patients with MSA-P and PD are listed in Table 1. There were no significant differences in age, sex, or MMSE among patients with MSA-P and PD, and HCs ($p>0.05$) (Table 1). There were significant differences in the results from olfactory examinations, autonomic nerve assessments, and brain MRI between MSA-P and PD (Supplementary Table 1 in the online-only Data Supplement).

### Oculomotor recordings in MSA-P and PD

The overall proportions of abnormal eye movements in MSA-P and PD were significantly higher than in HCs (82.4%, 77.5%, and 47.5%, respectively; $p<0.05$), while there were no significant differences between the MSA-P and PD groups (Table 2).

#### Fixation and gaze-holding tests

In the fixation and gaze-holding tests, the proportions of abnormal eye movements in MSA-P and PD were significantly higher than in HCs (17.6%, 15.0%, and 0%, respectively;

**Table 1.** Demographic and clinical characteristics of the participants

| Characteristic | MSA-P (*n*=17) | PD (*n*=40) | HCs (*n*=40) | Test statistics |
|---|---|---|---|---|
| | | | | Overall group difference |
| Age, years | 68.12±8.82 (52–85) | 66.50±7.1 (53–82) | 66.71±8.8 (53–83) | F=0.25, *p*=0.77 |
| Sex, male/female | 7/10 | 16/24 | 18/22 | $\chi^2$=31.22, *p*=0.22 |
| Disease duration, years | 1.64±0.54 | 1.27±0.61 | - | *t*=2.17, *p*=0.034* |
| UPDRS/UMSARS score | 22 [16–41] | 15 [8–24] | - | - |
| Hohen & Yahr stage | - | 1.89±0.78 | - | - |
| MMSE score | 26.57±3.10 | 27.12±3.19 | 28.22±1.11 | F=1.62, *p*=0.21 |

Data are mean±standard deviation (range), *n*, or median [interquartile range] values.
*$p<0.05$ between PD and MSA-P.
HCs, heathy controls; MMSE, Mini Mental State Examination; MSA-P, multiple-system atrophy with predominant parkinsonism; PD, Parkinson's disease; UMSARS, Unified Multiple System Atrophy Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

**Table 2.** Eye movements in PD and MSA-P

| Task | MSA-P (*n*=17) | PD (*n*=40) | HCs (*n*=40) | Test statistics |
|---|---|---|---|---|
| | | | | Overall group difference |
| Comprehensive | | | | |
| Abnormal | 14 (82.4) | 31 (77.5) | 19 (47.5) | $\chi^2$=10.48, $p$=0.005*† |
| Fixation and gaze-holding tests | | | | |
| Abnormal | 3 (17.6) | 6 (15.0) | 0 | $\chi^2$=7.06, $p$=0.03*† |
| Saccade intrusions (SWJs) | 2 (11.8)<br>(1, 5.9) | 1 (2.5)<br>(0) | 0 | $\chi^2$=5.59, $p$=0.06<br>($\chi^2$=4.76, $p$=0.09) |
| Multistep pattern | 0 | 1 (2.5) | 0 | $\chi^2$=1.44, $p$=0.49 |
| Gaze-evoked nystagmus | 1 (5.9) | 0 | 0 | $\chi^2$=4.76, $p$=0.09 |
| Without-fixation test | | | | |
| Abnormal | 8 (47.1) | 12 (30.0) | 0 | $\chi^2$=18.70, $p$<0.001*† |
| Spontaneous nystagmus | 1 (5.9) | 0 | 0 | $\chi^2$=4.28, $p$=0.12 |
| SWJs | 6 (35.3) | 12 (30.0) | 0 | $\chi^2$=11.59, $p$=0.003*† |
| Multistep pattern | 1 (5.9) | 0 | 0 | $\chi^2$=4.04, $p$=0.13 |
| Reflexive saccades | | | | |
| Abnormal | 9 (52.9) | 20 (50.0) | 15 (37.5) | $\chi^2$=1.74, $p$=0.42 |
| Hypometria | 8 (47.1) | 16 (40.0) | 13 (32.5) | $\chi^2$=1.17, $p$=0.56 |
| Hypermetria | 0 | 0 | 0 | - |
| Slow saccades | 4 (23.5) | 5 (12.5) | 13 (7.5) | $\chi^2$=2.83, $p$=0.24 |
| Prolonged latency | 5 (29.4) | 3 (7.5) | 2 (5.0) | $\chi^2$=8.27, $p$=0.02† |
| Multistep pattern | 3 (17.6) | 6 (15.0) | 2 (5.0) | $\chi^2$=2.81, $p$=0.25 |
| MGS test (multistep pattern) | | | | |
| Abnormal | 14 (93.3) ($n$=15) | 31 (81.6) ($n$=38) | 4 (10.0) | $\chi^2$=45.64, $p$<0.001*† |
| SPM test | | | | |
| Abnormal | 10 (58.8) | 24 (60.0) | 7 (17.5) | $\chi^2$=17.12, $p$<0.001*† |
| Catch-up saccades | 7 (41.2) | 1 (2.5) | 0 | $\chi^2$=29.33, $p$<0.001*† |
| Anticipatory saccades | 5 (29.4) | 14 (35.0) | 7 (17.5) | $\chi^2$=3.19, $p$=0.20 |
| Saccade intrusions (SWJs) | 10 (58.8)<br>(1, 5.9) | 24 (60.0)<br>(0) | 5 (12.5)<br>(0) | $\chi^2$=0.64, $p$=0.72<br>($\chi^2$=4.75, $p$=0.09) |
| Gain | | | | |
| Toward left | 0.75±0.13 | 0.75±0.10 | 0.77±0.08 | F=0.49, $p$=0.62 |
| Toward right | 0.68±0.12 | 0.72±0.11 | 0.73±0.09 | F=1.40, $p$=0.25 |
| OKN test | | | | |
| Abnormal | 2 (11.8) | 3 (7.5) | 0 | $\chi^2$=4.14, $p$=0.13 |
| Gain | | | | |
| Toward left | 0.77±0.12 | 0.83±0.16 | 0.85±0.09 | F=2.33, $p$=0.10 |
| Toward right | 0.78±0.12 | 0.81±0.15 | 0.82±0.08 | F=0.66, $p$=0.52 |

Data are mean±standard deviation or *n* (%) values.
*$p$<0.05 between PD and MSA-P; †$p$<0.05 between PD and HCs; ‡$p$<0.05 between MSA-P and HCs.
HCs, heathy controls; MGS, memory-guided saccade; MSA-P, multiple-system atrophy with predominant parkinsonism; OKN, optokinetic nystagmus; PD, Parkinson's disease; SPM, smooth-pursuit movement; SWJs, square-wave jerks.

$p$<0.05). There was no significant difference between MSA-P and PD ($p$>0.05). Gaze-evoked nystagmus (in 5.9%) and SWJs (5.9%) were noted in patients with MSA-P but not in those with PD, with no significant difference between the two (Table 2).

### Without-fixation test

In the without-fixation test, the proportion of abnormal eye movements was significantly higher in MSA-P and PD than in HCs (47.1%, 30.0%, and 0%, respectively; $p$<0.001). The patients with MSA-P and PD had higher proportions of SWJs than did the HCs (35.3%, 30.0%, and 0%, respectively; $p$<0.05), with no significant difference between MSA-P and PD ($p$>0.05). Spontaneous nystagmus was noted in 5.9% of patients with MSA-P but not in those with PD, but with no significant difference between them (Table 2).

**Table 3.** Reflexive saccade parameters in MSA-P, PD, and HCs

| | −5° | −10° | −15° | −20° | −25° | −30° | +5° | +10° | +15° | +20° | +25° | +30° |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Latency, ms | | | | | | | | | | | | |
| MSA-P | 248±193 | 213±62 | 213±102 | 243±125 | 235±118 | 206±90 | 141±38 | 173±59 | 205±91 | 246±89 | 263±107 | 261±118 |
| PD | 223±163 | 224±66 | 182±78 | 218±80 | 203±64 | 207±88 | 155±52 | 171±62 | 182±69 | 203±75 | 258±143 | 226±74 |
| HCs | 224±48 | 270±56†† | 231±49† | 267±67† | 264±65† | 246±66 | 209±48†† | 227±58†† | 235±50† | 237±53*† | 273±61 | 264±51 |
| Accuracy, % | | | | | | | | | | | | |
| MSA-P | 109±36 | 94±19 | 78±22 | 76±21 | 78±20 | 79±13 | 94±29 | 83±13 | 86±14 | 84±10 | 79±20 | 81±14 |
| PD | 103±43 | 94±15 | 81±19 | 82±17 | 84±22 | 81±20 | 100±23 | 86±16 | 88±17 | 82±18 | 82±21 | 81±17 |
| HCs | 97±20 | 89±11 | 87±15 | 86±9 | 84±10 | 81±12 | 92±16 | 88±13 | 89±11 | 86±11 | 85±15 | 84±13 |
| Velocity, °/s | | | | | | | | | | | | |
| MSA-P | 127±29 | 176±35 | 213±48 | 253±72 | 318±82 | 319±76 | 116±26 | 183±29 | 231±50 | 298±56 | 314±88 | 344±84 |
| PD | 123±29 | 188±38 | 236±74 | 280±58 | 351±82 | 340±77 | 119±19 | 202±39 | 255±59 | 297±67 | 325±81 | 350±79 |
| HCs | 117±15 | 189±33 | 254±51 | 279±54 | 332±66 | 343±66 | 115±14 | 194±29 | 250±44 | 303±49 | 340±62 | 362±66 |

Data are mean±standard deviation values.
*$p$<0.05 between PD and MSA-P; †$p$<0.05 between PD and HCs; ‡$p$<0.05 between MSA-P and HCs.
HCs, heathy controls; MSA-P, multiple-system atrophy with predominant parkinsonism; PD, Parkinson's disease; –, left; +, right.

The SWJs in most patients with MSA-P had a frequency of 2–3 Hz and an amplitude of 2°, while three of those patients had a frequency of 2–4 Hz and an amplitude of 5°–7°. The SWJs in PD had a frequency of 2–4 Hz and an amplitude of 2°–3°.

**Reflexive saccade test**

There were no significant differences among patients with MSA-P, PD, and HCs (52.9%, 50.0%, and 37.5%, respectively; $p$>0.05) in the qualitative analysis. Patients with MSA-P had higher proportions of prolonged latency than HCs (29.4% vs. 5.0%; $p$<0.05). There was no significant difference in hypometria among patients with MSA-P and PD, and HCs (47.1%, 40.0%, and 32.5%, respectively; $p$>0.05). Hypermetria was not found in any group (Table 2).

The latency, accuracy, and velocity of the saccades from the quantitative analysis of all participants are listed in Table 3. Compared with HCs, the patients with MSA-P had shorter latencies at the locations of +5°, +10°, and -10°, and those with PD had shorter latencies at the locations of +5°, +10°, +15°, -10°, -15°, -20°, and -25° ($p$<0.05). MSA-P only had a longer latency than PD at +20° ($p$<0.05). There were no significant differences in accuracy and velocity among the three groups ($p$>0.05) (Tables 2 and 3).

**MGS test**

The multistep pattern was significantly more common in patients with MSA-P and PD than in HCs (93.3%, 81.6%, and 10.0%, respectively; $p$<0.001) in the MGS test, while there was no significant difference between MSA-P and PD ($p$>0.05) (Table 2).

**SPM test**

The proportion of abnormal eye movements in the SPM test was significantly higher in patients with MSA-P and PD than in HCs (58.8%, 60.0%, and 17.5%, respectively; $p$<0.001), while there was no significant difference between MSA-P and PD ($p$>0.05). Patients with MSA-P had a higher proportion of catch-up saccades than did those with PD (41.2% and 2.5%, respectively; $p$<0.001), while no significant differences were found in anticipatory saccades, saccade intrusions, and SWJs among the three groups ($p$>0.05). There was no significant difference in SPM gains among patients with MSA-P and PD, and HCs ($p$>0.05) (Table 2 and Fig. 1).

**OKN test**

There were no significant differences among the proportions of abnormal eye movements among MSA-P, PD, and HCs (11.8%, 7.5%, and 0%, respectively; $p$>0.05) in the OKN test. There were also no significant differences in OKN gains among MSA-P, PD, and HCs ($p$>0.05) (Table 2).

## DISCUSSION

In this study, 82.4% of patients with MSA-P and 77.5% with PD presented abnormal eye movements at the early disease stages. In the qualitative analysis, patients both with MSA-P and PD had SWJs in the without-fixation test, and had the multistep pattern in MGS. Patients with MSA-P exhibited specific catch-up saccades in SPM with a sensitivity of 41.2% and specificity of 97.5%. Patients with both MSA-P and PD had reduced latency in the reflexive saccade test in the quantitative analysis. The results suggest that ocular-related nuclei are involved in the early stages of MSA-P and PD.

Most movement-disorder experts believe that the simi-

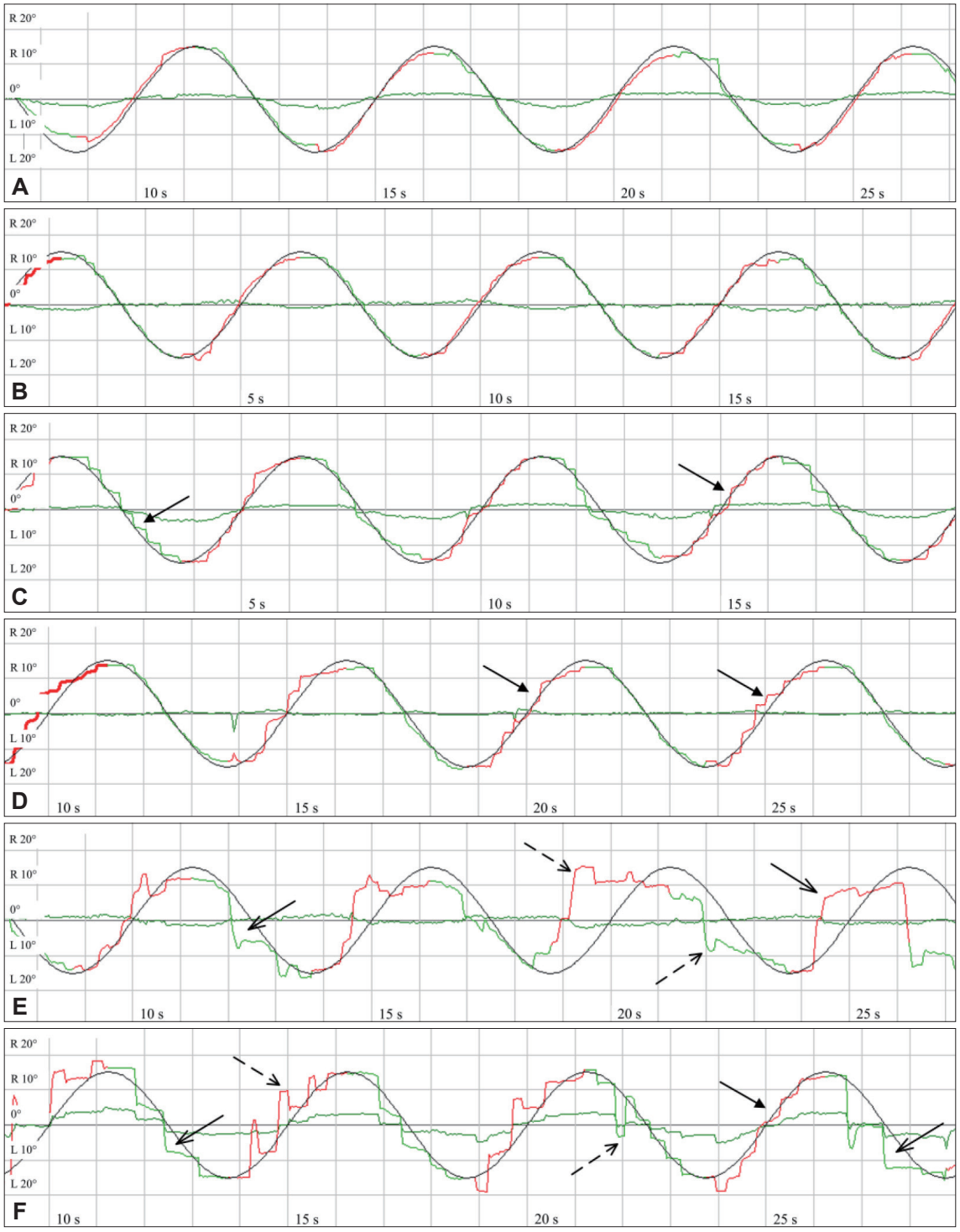


**Fig. 1.** Data from the SPM test in MSA-P. A: Normal SPM with normal gains (left 0.91, right 0.93) in a 65-year-old male with a disease duration of 2 years. B: Normal SPM with slightly decreased gains (left 0.82, right 0.72) in a 60-year-old male with a disease duration of 1 year. C: Catch-up saccades in SPM with unilaterally decreased gain (left 0.65, right 0.71) in a 78-year-old female with a disease duration of 2 years. D: Catch-up saccades in SPM with unilaterally decreased gain (left 0.83, right 0.46) in a 63-year-old female with a disease duration of 1 years. E: Anticipatory saccades and saccade intrusions in SPM with bilaterally decreased gain (left 0.61, right 0.47) in a 64-year-old male with a disease duration of 1 years. F: Catch-up saccades, anticipatory saccades, and saccade intrusions in SPM with bilaterally decreased gain (left 0.61, right 0.47) in a 73-year-old male with a disease duration of 2 years. Catch-up saccades, bold arrow; anticipatory saccades, solid arrow; saccade intrusions, dashed arrow. L, eye movement toward the left; MSA-P, multiple-system atrophy with predominant parkinsonism; R, eye movement toward the right; SPM, smooth-pursuit movement.

larity and overlap of eye-movement manifestations in PD markedly reduces the diagnostic advantage of distinguishing PD from other diseases by using oculomotor movement assessments, especially due to the similar manifestations in early-stage MSA-P.[22-24] Previous studies found that both MSA and PD had abnormal manifestations of saccades (hypometria) and MGS (multistep pattern), SPM (decreased gain), and deficits in ocular positional stability (SWJs).[9,12] The abnormal eye movements in MSA-P were also less obvious than those in MSA with predominant cerebellar ataxia (MSA-C).[11] Considering that the involved ocular nuclei are specific even in the early stages of MSA-P and PD, we speculate that they could present specific eye movements when their clinical manifestations are minimal.

The catch-up saccades in SPM were specific to cerebellar lesions. Pinkhardt et al.[16] found that this phenomenon was sufficiently characteristic to allow MSA to be distinguished from PD, which had been confirmed in previous studies.[9] Catch-up saccades are therefore likely to be a feature observed in both MSA-P and MSA-C. More detailed results indicated that about half of patients with MSA (55.6%) had catch-up saccades in SPM, with the proportion among patients with MSA-C being 66.7%. Even in the patients with MSA-P, the proportion of catch-up saccades in SPM was as high as 45.8%.[11] In the present study, we further found that even in the early stage of MSA-P, 41.2% of patients experience this phenomenon. The proportion of catch-up saccades in patients with PD was only 2.5%. It was therefore suggested that catch-up saccades had better differential diagnostic value in the early stages of MSA-P and PD. The pathophysiological basis was the cerebellar vermis, the vestibulocerebellum, and the corresponding pontine nuclei that participate in the SPM pathway.[25] Isozaki found that changes in oculomotor parameters reflected that the dorsal vermis was initially involved in MSA, followed by the flocculus in the cerebellum; the degenerative lesions might then expand to the vestibular nucleus and the cerebral cortex including the vestibular cortex.[26] Our results suggested that the key cerebellar nuclei related to eye movements had been involved in the early stage of MSA-P, which might be useful for differentiating between early MSA-P and PD. It is worth mentioning that the SPM gains did not change significantly in early MSA-P and PD, which indicated that SPM gain was of little use for the differential diagnosis between MSA and PD due to overlap. This conclusion was consistent with those of previous studies.[16]

The multistep pattern in MGS, which was caused by the lesions in the basal ganglia, was previously considered as a biomarker of PD.[12] Previous studies have found that the multistep pattern in MGS could also occur in MSA.[9] Besides, because the MGS multistep pattern in MSA is caused by cerebellum and basal ganglia lesions, its pattern morphology varies.[9] Both early-stage MSA-P and PD presented the multistep pattern in MGS in the present study, and the proportion was higher in MSA-P than in PD. This suggests that eye-movement-related nuclei in the basal ganglia are involved in the early stages of both MSA-P and PD.

The patients with MSA-P exhibited some oculomotor changes in this study, such as gaze-evoked nystagmus, spontaneous nystagmus, and macro-SWJs. Although the incidence rates were low and there were no significant differences between MSA-P and PD, these changes were specific to MSA-P. These abnormal ocular changes might be the specific ocular signs of cerebellar lesions.[27] SWJs could also be caused by enhanced compensatory activity by the frontal lobe, altered inhibitory pathways in the basal ganglia, and enhanced inhibitory function of the superior colliculus (SC). Cerebellar lesions can also lead to large SWJs.[25] Our results therefore suggest that the oculomotor abnormalities in early-stage PD reflect basal ganglia lesions, while those in early-stage MSA-P reflect both basal ganglia and cerebellum lesions. The different pathological changes between these conditions lead to specificity in oculomotor abnormalities.

In the reflexive saccade test performed as part of the quantitative analysis, both MSA-P and PD had shorter average latencies. Previous studies found that shorter latencies in PD might result from the enhanced compensatory function of the frontal lobe.[28] Patients with MSA-P performed similarly in our study. It was speculated that brain function compensation was also enhanced in MSA-P, which needs further brain function research for confirmation. However, Terao et al.[15] found decreased peak velocity of saccades in MSA-P, but normal peak velocity in PD. Our results were inconsistent with that study, which might be attributable to the shorter disease durations in our study, or the larger numbers of samples and differences in the experimental characteristics in the analysis. These findings also indicate that the abnormal saccadic velocity in MSA-P might change significantly as the disease course lengthens. Some patients with MSA-P also showed prolonged latency at particular angles in the qualitative analysis. Combined with the quantitative analysis, the standard deviation of latency was larger in MSA-P, indicating that saccadic latency in MSA-P had greater variability. Previous studies found that the prolonged latency in reflexive saccades might be caused by lesions of burst neurons in the brainstem and those in the connections of the SC, which leaded to delayed saccade initiation.[29] Our results suggest that the functions of the brainstem and SC are normal in the early stages of MSA-P and PD.

Our study had some limitations. It was a single-center study with a small sample, and the ocular and functional MRI find-

ings were not combined. Some patients with MSA-P in this study had mild cognitive impairment (MMSE score <26), and so an influence of cognitive function on their ocular motor performance cannot be excluded, specially that in the MGS and SPM test.[30,31] We will conduct more-detailed studies with larger samples in the future.

In conclusion, patients with early-stage MSA-P presented characteristic catch-up saccades in the SPM test, which may be useful in differentiating MSA-P from PD.

## Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0037.

### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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