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Oculomotor Function in Multiple System Atrophy: Clinical and Laboratory Features in 30 Patients

Tim Anderson, MD,[1]* Linda Luxon, MD,[2] Niall Quinn, MD,[3] Susan Daniel, MD,[4] C. David Marsden, DSc,[†] and Adolfo Bronstein, MD[2,5]

[1]*Van Der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand*
[2]*Department of Neuro-otology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom*
[3]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London, United Kingdom*
[4]*Queen Square Brain Bank for Neurological Disorders, Institute of Neurology, Queen Square, London, United Kingdom*
[5]*Division of Neurosciences and Mental Health, Medicine, Imperial College, London, United Kingdom*

Abstract: We reviewed the clinical and laboratory oculomotor features in 30 patients with probable multiple system atrophy (MSA), 22 with MSA-P and 8 with MSA-C. Six patients were also examined post mortem, MSA being confirmed in four and excluded in two (Parkinson's disease and progressive supranuclear palsy). Clinical examination showed the following abnormalities; excessive square wave jerks—21 of 30 patients; mild vertical supranuclear gaze palsy—8 of 30; gaze-evoked nystagmus—12 of 30 patients, three of whom had no extraocular evidence of cerebellar dysfunction; positioning downbeat nystagmus—10 of 25; mild or moderate saccadic hypometria—22 of 30; impaired ("broken up") smooth pursuit—28 of 30; reduced VOR suppression—16 of 24. Electro-oculography and caloric testing did not add significant extra information. In patients presenting with an akinetic-rigid syndrome it can be difficult to differentiate idiopathic Parkinson's disease from MSA-P and other causes of atypical parkinsonism. Our findings suggest that the presence of excessive square wave jerks, mild – moderate hypometria of saccades, impaired VOR suppression, spontaneous nystagmus or positioning downbeat nystagmus may be oculomotor "red flags" or clues to the presence of MSA. Further, the presence of clinically slow saccades, or moderate-to-severe gaze restriction, suggests a diagnosis other than MSA.

Key words: multiple system atrophy (MSA); oculomotor; positioning downbeat nystagmus (pDBN); saccades; vestibular; pathology

Multiple system atrophy (MSA) is a sporadic neurodegenerative adult onset disease of unknown aetiology. Prevalence is 4.4/100,000,[1] mean age of onset is 57 years[2] and average survival 7–9 years.[2,3]

Ancillary investigations have either been not sufficiently sensitive or specific, or not sufficiently accessible, to encourage routine application in the differential diagnosis of MSA.[4–10] We aimed to characterize the oculomotor features of MSA in an attempt to identify potential oculomotor "red flags" of the condition to supplement the traditional motor and non motor "red flags"[11,12] by reviewing the clinical and laboratory oculomotor examination of 30 patients with clinically probable MSA. Preliminary results have been previously published in abstract form.[13]

*Correspondence to: Tim Anderson, Van Der Veer Institute for Parkinson's and Brain Research, 16 St Asaph Street, Christchurch, New Zealand. E-mail: tim.anderson@cdhb.govt.nz
[†]Deceased; formerly Institute of Neurology, Queen Square, London, UK
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PATIENTS AND METHODS

Patients

Thirty patients with clinically probable MSA were included, 22 with predominantly akinetic-rigid (MSA-P) phenotype, and 8 with a cerebellar (MSA-C) phenotype. Classification was under the original Quinn criteria[11] as they were studied before the introduction of

Gilman et al., criteria.[14] Under the Quinn criteria, "probable MSA" was defined as either sporadic adult onset non/poorly responsive parkinsonism plus severe symptomatic autonomic failure, and/or cerebellar signs and/or pyramidal signs (parkinsonism predominant), or sporadic adult-onset cerebellar syndrome with or without pyramidal features, with severe symptomatic autonomic failure and/or parkinsonism. 24 were male and 6 female, with mean age of 58 (SD, 9.7 years) and mean disease duration of 6.6 years (SD, 3.7). In retrospect 6 of the 30 patients would not have been classified as MSA under the later Gilman et al., criteria[14]—all of these not fully satisfying the required autonomic or urinary dysfunction criterion.

Procedures

Patients were assessed in the Neurootology Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square. Oculomotor examination was undertaken as follows.

Clinical.

Patients were assessed by clinicians (TA, LL, AB) experienced in eye movement examination for abnormalities of fixation, gaze, convergence, saccades, smooth pursuit, optokinetic nystagmus (OKN) elicited with a handheld drum, doll's eyes-head manoeuvre, VORS (vestibulo-ocular reflex suppression[15]), and positioning (Dix-Hallpike manoeuvre, with eyes remaining in primary gaze position). Positioning nystagmus was defined as that which occurred with positioning but dissipated on maintenance of that position (i.e. fatigued or adapted), and positional nystagmus that which emerged with positioning and sustained for as long as the position was maintained.[16] Oculomotor features were graded on a clinical basis as normal, or mildly, moderately, or severely abnormal. Further specific information for each oculomotor function is provided under "Results."

Electro-oculography.

Patients underwent the following laboratory tests, with quantitative results compared to the laboratory normative data[17-19]—primary and horizontal lateral gaze ($\pm 30^\circ$) evoked nystagmus, full field OKN (constant velocity 40°/S), sinusoidal smooth pursuit (40°/S; 0.2 Hz), VOR step (40°/S angular velocity steps) and VOR sinusoidal (40°/S, 0.2 Hz) in the dark, and VOR suppression by visual fixation (40°/S, 0.2 Hz). Age was accounted for when interpreting abnormalities. Caloric responses to warm (44°) and cold (30°) water irrigation[20] were assessed.

RESULTS (TABLE 1)

Fixation, Gaze, and Positioning

Fixation instability was present in 21. 23 of these exhibited excessive square wave jerks clinically, confirmed on EOG in 13 of 25 (more than 9 per minute[21]). Downbeat nystagmus (DBN), defined as nystagmus present in the primary position of gaze with the head upright, was present in one patient with MSA-C though one MSA-P patient with positioning DBN (pDBN) developed primary position DBN later.

Vertical supranuclear gaze palsy, defined as conjugate gaze limitation for saccades but overcome by pursuit or doll's eye-head manoeuvre, was apparent in 8, always mild, with upgaze always more affected than down gaze. Gaze-evoked horizontal nystagmus was present in 12, with rebound nystagmus in three of these. There was positioning nystagmus in 12 of 23 so examined, with pDBN in 10 of these. Three of the 12 had no cerebellar limb signs and six did not exhibit horizontal gaze evoked nystagmus. One of these 12 later developed head upright DBN. The pDBN habituated (i.e. it disappeared on repeated positioning testing) in five.

Saccades, Smooth Pursuit, and OKN

Severity of saccadic inaccuracy was graded qualitatively;[22] two to three corrective saccades deemed mild-moderate hypometria, and multiple small steps ("staircase"), severe hypometria. Horizontal saccades were mild or moderately hypometric in 26 of the 30 clinically and 22 of 25 examined with EOG. Only one had moderately slowed saccades (in all directions) clinically, confirmed on EOG (135°/S for 15° saccade; MSA group mean for 20° saccades, 359°/S, SD, 40°/S; control mean, 450°/S, SD, 50°/S). Vertical saccades were mildly or moderately hypometric in 26. Two MSA-C patients had hypermetria of horizontal saccades, and one, mild unilateral internuclear ophthalmoplegia.

Horizontal smooth pursuit was clinically impaired ("broken up") in 27 of the 30, with reduced gain (i.e. ratio of eye velocity/stimulus velocity) in 22 of 25 with EOG (MSA mean gain, 0.45, SD, 0.17; control mean gain, 0.84, SD, 0.11). OKN was judged clinically impaired if restorative quick phases were reduced in number and/or size based on the experience of the

TABLE 1. *Clinical and horizontal electro-oculographic abnormalities*

Eye movement	Oculomotor abnormality	Clinical examination	EOG recording
Fixation	Square wave jerks	21/30[a]	13/25
	Downbeat nystagmus	1/30	NA
Gaze	Vertical gaze restriction	8/30	NA
	Gaze evoked nystagmus	12/30	12/30
Positioning	Downbeat nystagmus	10/23	NA
(Dix Hallpike)	Ageotropic nystagmus	2/23	
Saccades	Horizontal saccades mild/mod hypometria	26/30	22/25
	slow velocity	1/30	2/25
	Vertical saccades mild/mod hypometria	26/30	NA
Pursuit	Reduced smooth pursuit	27/30	22/25
Optokinetic nystagmus (OKN)	Horizontal OKN		
	Reduced	17/28	24/26
	Vertical OKN		NA
	Reduced	13/28	
	Absent	7/28	
Vestibulo-ocular response (VOR)	Doll's eye-head manoevre		
	absent VOR	1/29	
	Step rotation		
	increased gain		7/22
	absent VOR		1/22
	Sinusoidal rotation		
	increased gain		5/20
VOR suppression (VORS)	Impaired	18/23	20/22

[a]Number exhibiting sign/number examined. Note that not all of the 30 patients were examined for each oculomotor feature.
NA; not applicable.

examiners. Horizontal OKN was impaired clinically in 17 and on EOG in 24 of 26 assessed (MSA mean gain, 0.51, SD, 0.21; control mean gain, 0.68, SD, 0.07). Vertical OKN was absent in seven and impaired in a further 13 (Table 1).

Vestibulo-Ocular Response (VOR) and VOR Suppression (VORS)

During doll's eye-head manoeuvre (head on trunk sinusoidal oscillation whilst patient fixates on the examiner's nose) the VOR appeared normal in 29 and absent (i.e. "broken up" compensatory eye movements) in one (confirmed with absent caloric and rotational responses). When assessed with EOG on a rotating chair, five exhibited increased gain (i.e. ratio of eye velocity/chair velocity), whilst the other 15 of the 20 examined had normal VOR gains (control mean, 0.66, SD, 0.07; MSA mean, 0.69, SD, 0.28). With step rotation, seven of 22 revealed increased gain, and the other 15 normal gain (control mean, 0.80, SD, 0.20; MSA mean, 0.85, SD, 0.31, the patient with absent vestibular function not included). VORS was elicited clinically by rotating the patient side-to-side in a swiveling chair with the patient fixating his/her own thumb within clasped hands held locked out in front, the elbows hugged tightly into the side, the presence of corrective saccades denoting impairment (see Stell and Bronstein[22]). It was clinically impaired in 18 of 23 assessed and abnormal in 20 of 22 assessed by EOG.

Caloric testing was undertaken in 24. The majority (16/24) exhibited brisk responses but with no or minimal enhancement of nystagmus with removal of fixation (Frenzel's glasses), suggesting retained vestibular function and reduced VOR suppression. One (the same subject who had clinically absent rotational VOR) had absent responses. Three had unilateral canal paresis and one a directional preponderance.

Pathologically Proven Cases (Table 2)

Autopsy neuropathological information subsequently became available in six of the 30 cases. The diagnosis of MSA was confirmed in four whilst a fifth had Parkinson's disease, and a sixth PSP (Table 2).

DISCUSSION

The near-ubiquitous oculomotor abnormalities found in the 30 patients with a diagnosis of probable MSA (22 MSA-P and 8 MSA-C) demonstrate the potential utility of eye movement examination in this condition and in the differential diagnosis of parkinsonian disorders. Principal findings were: first, most patients (over 70%) exhibited excessive square wave jerks, mild or moderate saccadic hypometria, and impaired VORS or

TABLE 2. *Clinical, oculomotor and neuropathological features in 6 patients with a clinical diagnosis of MSA-P and postmortem examination*

Patient/years of disease*	Clinical features	Fixation and gaze	D-H	Saccade hypometricity	Pursuit	OKN	VORS	VOR	Pathological diagnosis and findings/disease duration to death
55yrs ♀ 12 yrs	akinetic-rigid syndrome orthostatic hypotension finger myoclonus mild pyramidal signs urinary incontinence nil cerebellar partial levodopa response	SWJ +	n	++ horiz and vert	+++	+++	+++	n	MSA widespread glial cytoplasmic inclusions, severe striatonigral and olivopontocerebellar atrophy 14 years
45♂ 7 yrs	erectile failure orthostatic hypotension urinary incontinence akinetic-rigid syndrome nil pyramidal/cerebellar moderate levodopa response	SWJ +	pDBN	++ horiz and vert	+	+++	++	n	MSA widespread glial cytoplasmic inclusions, severe nigral degeneration No atrophy of basis pontis, medulla or cerebellum 8 years
48♂ 9 yrs	akinetic-rigid syndrome urinary incontinence impotence mild pyramidal signs mild cerebellar ataxia moderate levodopa response	n	pDBN	+ up and horiz	+	+	+	n	MSA widespread glial cytoplasmic inclusions, severe nigral and olivopontocerebellar degeneration 14 years
58♂ 7 yrs	impotence orthostatic hypotension akinetic-rigid syndrome cerebellar ataxia no pyramidal signs	n	pDBN	+ horiz and vert	+	n	ND	n	Likely MSA (limited examination due to post mortem artifact) putamen atrophic with gliosis 13 years
61♂ 9 yrs	severe akinetic-rigid syndrome with antecollis marked orthostatic hypotension no cerebellar or pyramidal features modest levodopa response	n	ND	+ horiz and vert	+	+	n	n	Parkinson's disease Depigmented substantia nigra and locus coerulus with Lewy bodies Normal cerebral hemispheres, pons and cerebellum 13 years
61♂ 9 yrs	akinetic-rigid syndrome (without axial rigidity) aphonia marked "apraxia" of eye opening extensor plantar responses absent postural reflexes mild cerebellar signs no levodopa response	SWJ +++ gaze-evoked nystagmus +	n	+ horiz +++ vert slow on EOG	++	++ horiz absent vert	++	n	PSP Neurofibrillary tangles Atrophy of globus pallidus, especially the externa Depigmentation of substantia nigra Normal medulla and cerebellum Severe gliosis of colliculus and periaqueductal grey 12 years

*Duration of disease at time of examination.

SWJ, square wave jerks; D-H, Dix-Hallpike positioning manoeuvre; pDBN, positioning downbeat nystagmus; ND, not done; horiz, horizontal; vert, vertical; n, normal; +, mildly abnormal; ++, moderately abnormal; +++, severely abnormal.

smooth pursuit; second, pDBN was present in 40% of those examined, including some patients who had no other signs of cerebellar involvement, or spontaneous nystagmus; thirdly, slowed saccades (with one exception) or greater than mild supranuclear gaze palsy were not present.

The majority (73%) had MSA-P and it is pertinent therefore to compare their oculomotor findings with those seen in idiopathic Parkinson's disease (PD) and related conditions (see Fig. 1). It is acknowledged that our patients were studied on average 6 years after symptom onset and some oculomotor features may not

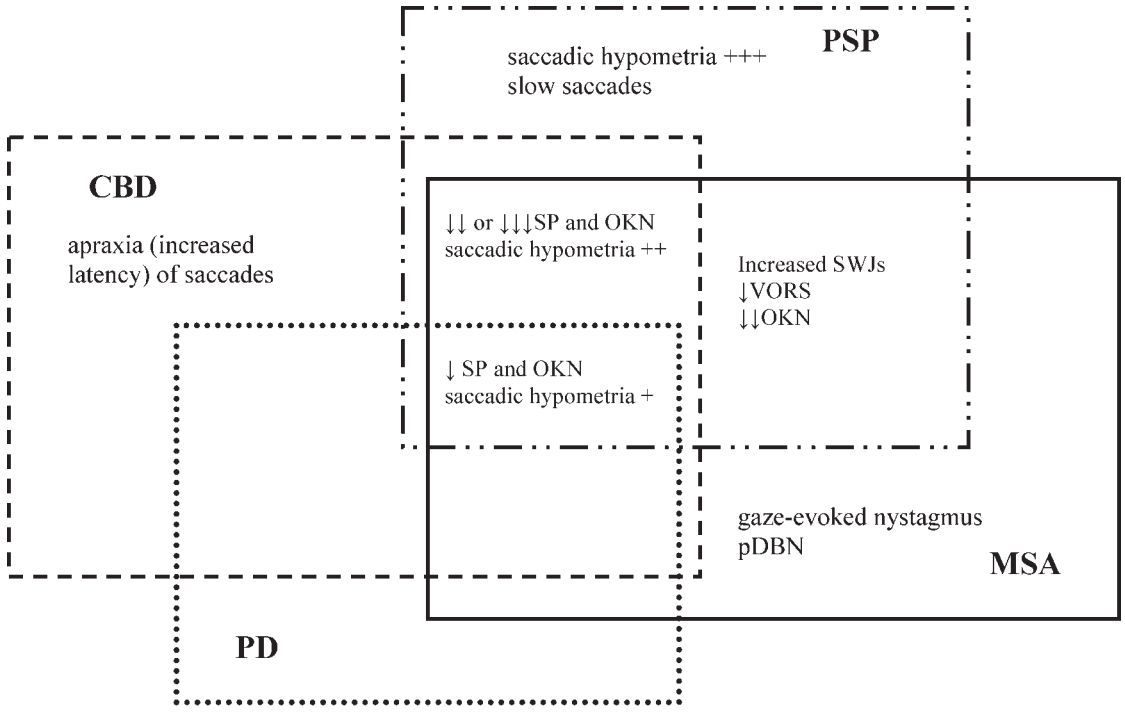

FIG. 1. Oculomotor characteristics of MSA in relation to the other major parkinsonian disorders.[21–32] Unique and shared oculomotor features are expressed in Venn diagram form. Abbreviations and symbols denote the following: PD, Parkinson's disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; SP, smooth pursuit; OKN, optokinetic nystagmus; pDBN, positioning downbeat nystagmus; SWJs, square wave jerks; ↓, mildly impaired; ↓↓, moderately impaired; ↓↓↓ severely impaired; + mild; ++ moderate; +++ severe.

have been apparent earlier when differential diagnosis can be most challenging.

Fixation and Gaze

Fixation abnormalities were common, with square wave jerks noted clinically in 70% and confirmed electrooculographically in 52%. Similarly, Rascol et al.,[21] observed SWJs in 65% of 25 MSA but only 15% of PD patients. In contradistinction, SWJs are a prominent feature of PSP.[21,23,24] Thus SWJs are suggestive of a diagnosis other than PD but do not distinguish MSA from other atypical parkinsonian disorders such as PSP.

Primary position DBN was present in two patients. Horizontal gaze-evoked nystagmus was present in 12 (40%), three of whom also exhibited rebound nystagmus. Notably, three of the 12 did not have evidence of cerebellar involvement outside the oculomotor system. Thus, the presence of gaze-evoked nystagmus is a potentially useful clinical sign in akinetic – rigid (i.e. potential MSA-P) presentations as it clearly identifies involvement outside the nigro-striatal system even in the absence of any other cerebellar features.

Positioning Nystagmus

A novel finding was the presence of bilateral pDBN in 10 of 25 patients (40%) who underwent Dix-Hallpike positioning. Positioning DBN is indicative of disease of the cerebellum of its brainstem connections.[16] It is noteworthy then that three of these had no features of cerebellar dysfunction outside the oculomotor system, and four exhibited no gaze-evoked nystagmus. The pDBN was usually of immediate onset but otherwise quite variable so that in some but not others it fatigued, and in some it habituated and others it did not. All 10 patients thus exhibited positioning DBN and some of these, positional DBN. The authors have subsequently examined 20 patients with PD and observed pDBN in only one, in whom there was a history of unexplained recurrent vertigo. The presence of pDBN may therefore be another potentially useful discriminating sign in the differential diagnosis of parkinsonism. All 7 MSA-C patients in whom the Dix-Hallpike manoeuvre was performed exhibited pDBN. Amongst the spinocerebellar ataxias (SCAs), pDBN is extremely common in SCA6 but not in SCA1, SCA2, or SCA3.[33] In MSA olivopontocerebellar neuronal loss—the likely cause of the pDBN—primarily encom-

passes inferior olives, pontine nuclei, and Purkinje cells of the cerebellar vermis.[34,35] However degeneration in SCA6 is confined to the cerebellar cortical Purkinje cells and is distinct from the additional olivopontine loss that occurs in SCAs1-3.[36] These observations suggest that pDBN in MSA is due to Purkinje cell dysfunction in cerebellar vermis. Three of the four pathologically confirmed MSA cases (all with MSA-P) had exhibited pDBN (Table 2).

Saccades

The majority of patients (87%) exhibited mild or moderate hypometria of saccades but none had severe hypometria. It was always more marked vertically than horizontally and greater for upward than downward saccades. Mild saccadic hypometria may be observed in PD[22,37] whilst severe hypometria, especially of vertical saccades and greater than exhibited by the MSA patients in this study, is often present in PSP.[23,25] Saccades were not clinically slowed apart from a solitary patient. This finding of a lack of saccadic slowing accords with the observations of Burk et al.,[38] who did not observe it in 17 patients with idiopathic OPCA, and implies that slowing of saccades should be considered an oculomotor "red flag" against the diagnosis of MSA. Slow saccades can be present in PSP[23,24] and some spinocerebellar ataxias, particularly SCA2.[38] Apraxia of saccades, evidenced by delay in initiating saccades, is commonly encountered in corticobasal degeneration,[22,25] but was not seen in our MSA patients. Thus, in patients presenting with a parkinsonian disorder, the presence of moderate or marked hypometria argues against PD, the presence of slow or markedly hypometric saccades argues against MSA but in favour of PSP, and the presence of apraxia of saccades suggests CBD.

Pursuit, VOR Suppression, and OKN

These three functions depend upon integrity of the cerebellum, especially vermis, for generation of normal slow phases.[26,39] Smooth pursuit was impaired (broken) in 90% of patients, generally mild to moderate in severity. Smooth pursuit can be mildly impaired in PD[25,27,40] and moderately or severely impaired in CBD and PSP.[23,25] From our MSA data and the literature,[25,28] it seems that clinically impaired pursuit is common in extrapyramidal disorders and therefore not always useful in differential diagnosis. However, patients showing greater than mild pursuit deficit are not likely to have PD. Failure of VORS was easily detected clinically and on EOG in the majority, including seven of the thirteen MSA-P patients who exhibited no clinical cerebellar features. Reduced VORS in MSA has also been noted by others[28] particularly in MSA-C.[41] VORS is normal in PD,[28] but often abnormal in the general spectrum of the degenerative cerebellar ataxias[39] and may be observed in PSP.[23] Thus, the assessment of VOR suppression by fixation may be a helpful clinical tool for distinguishing PD from other parkinsonian disorders, and its presence should be considered an oculomotor "red flag" for MSA.

Impaired OKN, particularly vertical, was present in the majority. OKN has not previously been quantified in a specified MSA group but was abnormal in 86% of 37 patients with OPCA.[42] OKN is normal[29] or mildly abnormal in PD,[37] and can be moderately impaired later in CBD.[30] In PSP, OKN is significantly impaired, particularly in the vertical plane, with the eyes often deviating in the direction of the fast phase due to failure of quick phases.[29,43] Thus, although there are general differences in severity and nature of OKN impairments in these syndromes, the finding of abnormal OKN does not necessarily distinguish between the various akinetic-rigid disorders. However, the observation of OKN that is more than mildly impaired in a patient with an akinetic rigid syndrome might suggest a diagnosis other than PD.

Vestibular Function

Vestibular function was preserved and in a few cases even slightly increased gain above control values was found. Thus the one patient with bilateral absence of vestibular function may well have an alternative or additional diagnosis.[44-46]

Pathologically Confirmed Cases

The diagnosis of MSA was confirmed in 4 of the 6 patients in whom post mortem neuropathological examination findings were available. The two remaining patients had alternative neuropathological diagnoses – PD and PSP. Despite the diagnosis being incorrect in 2 of 6 (i.e one third) of our cases that came to postmortem, the overall false positive rate of MSA diagnosis in the Queen Square Brain Bank was only 14% (including the 2 misdiagnosed cases in our series).[47] Hence it is not likely that the overall misdiagnosis rate in our series is as high as one third. It is pertinent though to review the oculomotor findings in these 2 patients.

The case with PD presented with an akinetic-rigid syndrome, only modest levodopa response, and marked orthostatic hypotension with abnormal cardiovascular

autonomic function tests (probable MSA-P on both Quinn and Gilman et al., criteria). In fact the oculomotor features were entirely compatible with PD and in particular, there was no excess of square wave jerks, saccades were only mildly hypometric, smooth pursuit and OKN only mildly abnormal, and VORS not impaired.

The case with PSP presented with an akinetic-rigid syndrome without axial rigidity and no L-dopa response but later extensor plantar responses and mild limb and gait ataxia, then apraxia of eye opening. There were excessive square wave jerks and gaze-evoked nystagmus but no pDBN. Vertical saccades were markedly hypometric and clinically slowed. On the basis that the cardinal abnormality in PSP is slowing of vertical saccades, and that all bar one of our remaining patients with probable MSA did not exhibit slowed saccades, the eye movement findings in this patient were in retrospect suggestive of a diagnosis of PSP.

In summary, this study shows that examination of eye movements is a useful adjunct in the diagnosis of MSA. In particular, the presence of a cerebellar type eye movement disorder, notably gaze evoked-nystagmus, abnormal VOR suppression and positioning DBN, should raise the possibility of MSA in a patient with a parkinsonian syndrome. Further, the presence of slow saccades or prominent supranuclear gaze palsy suggests a diagnosis other than MSA, usually PSP (Fig. 1). Instrumental analysis of the oculomotor system objectively confirmed the clinical findings, but did not add any additional information. Thus, careful clinical observation alone should be sufficient in identifying key oculomotor features important in the differential diagnosis of the parkinsonian disorders.

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