Original Article

Clinical Characteristics of Patients with Multiple System Atrophy in Singapore

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Abstract

Introduction: Our study aimed to describe the clinical features of multiple system atrophy (MSA) in Singapore and verify its diagnosis using the consensus statement in the diagnosis of MSA. Materials and Methods: All patients suspected to have MSA between 1995 and March 2005 were identified from the Movement Disorders database and the autonomic function testing results. The medical records were reviewed using a standardised data collection form. The diagnosis of MSA was verified using the consensus statement. Disease progression was evaluated using 2 pre-determined events: aid-requiring walking and wheelchair use. Results: Seventy-two per cent (33/46) fulfilled the consensus statement. There were 85% Chinese, 9% Malays, and 6% Indians. The mean age at onset of the disease was 60 ± 10 years. We found a predominance of males (M:F = 1.5:1) as well as MSA-C cases (67%). The most common initial presenting features were parkinsonism and cerebellar signs (27% each). Abnormal neuroimaging was seen in 29 patients (91%). Autonomic function testing was abnormal in 58% (7/12). The risk for aid-requiring walking and wheelchair use at 3 years from onset of the disease was 31% and 17%, respectively. By 5 years, this had increased to 45% and 30%, respectively. There was no difference in the events rate between MSA subtypes. Conclusions: The clinical characteristics of MSA in Singapore are presented. Our study revealed a predominance of MSA-C patients as well as a later age at onset of disease and longer median time to aid-requiring walking and wheelchair use compared to Japanese patients.

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Key words: Autonomic dysfunction, Cerebellar diseases, Orthostatic hypotension, Parkinsonism, Urinary incontinence

Introduction

Multiple system atrophy (MSA), a term introduced in 1969, is a progressive neurodegenerative disease which occurs sporadically and is characterised by parkinsonism, cerebellar dysfunction, and autonomic insufficiency in various combinations.[1-3] It usually begins in the fifth decade and affects both sexes. MSA now includes the disorders previously called Shy-Drager syndrome, olivopontocerebellar atrophy (OPCA), and striatonigral degeneration (SND). The discovery of glial cytoplasmic inclusions (GCI) in the brain of patients with these conditions confirmed that SND, OPCA, and Shy-Drager syndrome are the same disease with different clinical expressions.[4] Several diagnostic criteria have been proposed but no consistent guidelines have been developed.[2,5,6] A consensus conference was held in 1998 and a new diagnostic criteria was adapted.[3] It was then recommended that patients be designated as having MSA-C if cerebellar features predominate and MSA-P if parkinsonian features predominate, instead of using the old terms SND and sporadic OPCA, respectively.[3] The term Shy-Drager syndrome was found to be no longer useful since autonomic failure is invariably present.

While the data from the west were conflicting (some reported a predominance of MSA-P[5,7,8] and others reported a predominance of MSA-C[9,10]), a predominance of MSA-C cases was reported in Japan.[11] The clinical features of MSA using the current consensus statement on the diagnosis of MSA have not been evaluated in Southeast

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Asia, an ethnically and linguistically diverse region with a population of 443 million.[12] We therefore investigated the clinical spectrum and characteristics of MSA in Singapore, a multi-ethnic Southeast Asian country with a population of 4 million people comprising 76% Chinese, 14% Malays, and 8% Indians.[13]

Materials and Methods

All patients identified and managed as MSA sufferers between 1995 and March 2005 at the Movement Disorders (MD) Clinic of the Department of Neurology, Tan Tock Seng Hospital (TTSH), which in 1999 became part of the new National Neuroscience Institute (NNI). The TTSH/NNI provides tertiary care to patients with neurological disorders in Singapore. An MD specialist (AKYT) started the MD database and service at TTSH in 1995. From 1995 to 2001, a single MD specialist ran a weekly MD clinic. Since then, this has increased to 3 MD clinics run weekly by 3 MD specialists. The autonomic function test results from the Neurodiagnostic Laboratory were also reviewed and all non-diabetic patients with documented postural hypotension, abnormal results, or a diagnosis of MSA were included.

Based on symptoms and/or diagnoses identified from both sources (MD database and autonomic function test results), patients suspected to have MSA were identified. Their available medical records were then retrospectively reviewed by an MD fellow (RDGJ) to obtain demographic and clinical characteristics using a standardised data collection form to verify the diagnosis of MSA using the consensus statement on the diagnosis of MSA.[3] The progression of the disease was evaluated using 2 pre-determined events: aid-requiring walking and wheelchair use. Aid-requiring walking was defined as the use at all times of a walking aid (stick, quad-cane, etc) or holding onto someone or something (a companion's arm, wall, furniture, etc) for support. Wheelchair use was defined as the time the patient started using a wheelchair as noted by the physician in the medical records. We treated the onset of aid-requiring walking or wheelchair-bound state as the "failure" event with the time to event measured in months from the time of onset of first symptom attributable to MSA.

Quantitative variables were expressed as means ± standard deviations (SDs) while qualitative variables were expressed as percentages. The χ^2 test was used to compare qualitative variables and the Student's *t*-test to compare means between groups. Survival curves were plotted using the Kaplan-Meier survival analysis for events (aid-requiring walking and wheelchair use). The log-rank test was used to compare the rate of events between MSA-P and MSA-C patients. The data were analysed using SPSS ver 11.5 (SPSS Inc., Chicago).

Results

We reviewed the medical records of 46 patients with suspected MSA who were then evaluated based on the consensus statement on the diagnosis of MSA.[3] Thirteen patients who did not fulfill the criteria for probable or possible MSA were excluded. Thirty-one patients (94%) were identified from the MD database and 2 patients (6%) were identified from the autonomic function test results review. The majority (94%) were diagnosed and being managed by MD specialists, 1 (3%) by a neurologist, and 1 (3%) by a geriatrician.

The 33 patients included in this study all met the criteria for probable MSA, consisting of 20 males and 13 females (M:F ratio = 1.5:1) (Table 1). The mean age at onset of the first symptom was 60 ± 10 years (range, 41 to 76 years). There were more MSA-C patients (67%). Seven patients (21%) did not have any comorbidity. Of the remaining 79%, the most common comorbid conditions were hypertension (n = 13), stroke (n = 6), dyslipidaemia (n = 5) and anxiety/depression (n = 4). The racial composition of Chinese, Malays, and Indians in our study was comparable to that of the general population in Singapore ($\chi^2 = 1.49$, $P = 0.47$).

The initial presenting clinical features of the disease were parkinsonism and cerebellar signs in 27% (9 patients each) (Fig. 1). Fifteen patients (45%) had features involving more than 1 system. None presented with pure autonomic failure initially. By the last clinical visit, 79% had parkinsonism, autonomic failure and cerebellar and pyramidal signs.

Parkinsonism was documented in all patients (Table 1). Levodopa (maximum dose achieved, range: 100 mg/day to 800 mg/day) was started in 67% of the patients. Some degree of subjective improvement was noted in 50% of MSA-P and in 25% of MSA-C patients. Selegiline (5 mg/

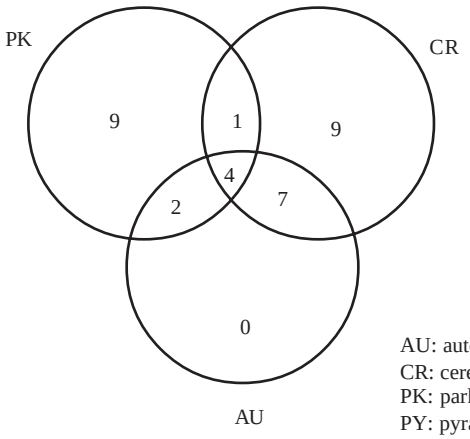

Fig. 1. Frequency of various combinations of initial clinical features in 33 cases of probable MSA.

Table 1. Comparison of Demographic and Clinical Data of MSA Patients According to MSA Subtypes

Variable	MSA-P n = 11	MSA-C n = 22	Total n = 33
Males	8 (73)	12 (55)	20 (61)
Age at onset of MSA, years	63 (13)	58 (7)	60 (10)
Age at diagnosis of MSA, years	65 (13)	61 (7)	63 (9)
Race			
Chinese	8 (73)	20 (91)	28 (85)
Malay	2 (18)	1 (5)	3 (9)
Indian	1 (8)	1 (5)	2 (6)
Autonomic and urinary dysfunction			
Orthostatic hypotension	8 (73)	9 (41)	17 (52)
Urinary incontinence	10 (91)	21 (95)	31 (94)
Parkinsonism			
Bradykinesia	10 (91)	19 (86)	29 (88)
Rigidity	11 (100)	16 (73)	27 (82)
Postural instability*	10 (91)	6 (27)	16 (48)
Tremor (postural, rest or both)	7 (63)	4 (18)	11 (33)
Cerebellar dysfunction			
Gait ataxia	3 (27)	22 (100)	25 (76)
Ataxic dysarthria	1 (9)	17 (77)	18 (55)
Limb ataxia	2 (18)	18 (82)	20 (61)
Sustained gaze-evoked nystagmus	0	6 (100)	6 (18)

MSA: multiple system atrophy; MSA-C: MSA with predominant cerebellar features; MSA-P: MSA with predominant parkinsonian features

* Not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

All values are either mean [standard deviation (SD)] or n (%).

day to 10 mg/day) was given to 6 patients (18%) and only 2 patients reported some improvement. Cerebellar signs were present in 26 patients (79%). The most common cerebellar sign was gait ataxia (76%).

All patients had documented autonomic symptoms. Urinary incontinence was reported in 31 patients (94%), occurring more often in males (61%). Postural hypotension was recorded in 17 patients (52%), 4 of whom were started on fludrocortisone. Constipation was reported in 19 patients while syncopal attacks and faecal incontinence were noted in 3 patients. Only 1 patient reported decreased sweating.

Pyramidal signs were noted in 12 patients. Other than nystagmus, other eye signs included saccadic pursuit (n = 7) and slow pursuit (n = 3). Sleep problems were noted in 3 patients (REM sleep behaviour disorder, insomnia, excessive daytime sleepiness). Spasticity was noted in 11 patients, dystonia in 6 patients (4 with anterocollis, 2 with blepharospasm), and myoclonus in 2 patients. Sensory complaints were reported by 5 patients.

Neuroimaging was done in 32 patients (97%), of which 21 (66%) had magnetic resonance imaging (MRI) of the brain and 11 (34%) had computed tomography (CT) of the brain. Three patients (9%) had normal neuroimaging findings. A total of 29 patients (91%) had abnormal neuroimaging. The reported neuroimaging abnormalities were cerebellar/vermian atrophy (29 patients), pontine atrophy (11) and "hot cross bun sign" in the pons (5). None of the patients were reported to have putaminal abnormalities. Only 12 patients (36%) underwent autonomic function testing, 7 of whom showed parasympathetic, sympathetic, or autonomic dysfunction, 2 had inconclusive results and 3 were normal. None had sphincter electromyography.

The rate of aid-requiring walking was 1.5/100 person months and for wheelchair use, the rate was 1.6/100 person months. The risk of aid-requiring walking at 3 years from the time of initial symptom onset was 31% and 17%, respectively. At 5 years, this had increased to 45% and 30% and by 10 years, to 81% and 73%, respectively (Figs. 2a and 2b). The median time to aid-requiring walking was 72 months (95% CI, 33 to 111) and for wheelchair use, 82 months (95% CI, 68 to 96). There was no statistically significant difference in the time to aid-requiring walking (72 months versus 82 months, $P = 0.97$, Fig. 2c) and in the time to wheelchair use (57 months versus 81 months, $P = 0.63$, Fig. 2d) between MSA-P and MSA-C patients.

Discussion

We found that 72% (33/46) of our patients fulfilled the consensus statement for the diagnosis of MSA.[3] This was slightly lower than the 80% (230/286) reported in a Japanese study, which used the same criteria.[11] There may be some difficulty in the diagnosis of MSA partly due to the fact that 10% to 20% of MSA cases present with relatively pure parkinsonism (asymmetry, levodopa-responsiveness, development of levodopa-induced dyskinesias and motor fluctuations).[14] While the use of the current diagnostic criteria for MSA may improve the accuracy of diagnosis at first visit, at the last visit they are no more accurate than the neurologist's final diagnosis.[15] The reported sensitivity of the consensus statement using neuropathologically examined cases ranges between 63% and 88%.[14,15]

Our study showed a male predominance (M:F, 1.3:1), as seen in previous studies (range, 1.2 to 2.0:1).[11,15-19] We also noted a predominance of MSA-C cases (67%) compared to MSA-P (33%), which is similar to the series from Japan.[11]

Another difference in our study was the later mean age of onset of MSA in our patients (60 years) compared to that in published data (54.2 years to 55.4 years).[11,17,19] Our median time from symptom onset to aid-requiring walking and wheelchair use was 2 times and 1.4 times longer respectively, when compared to Japanese patients.[11] These differences are difficult to explain. It is tempting to speculate that our MSA patients may have a more benign course compared to

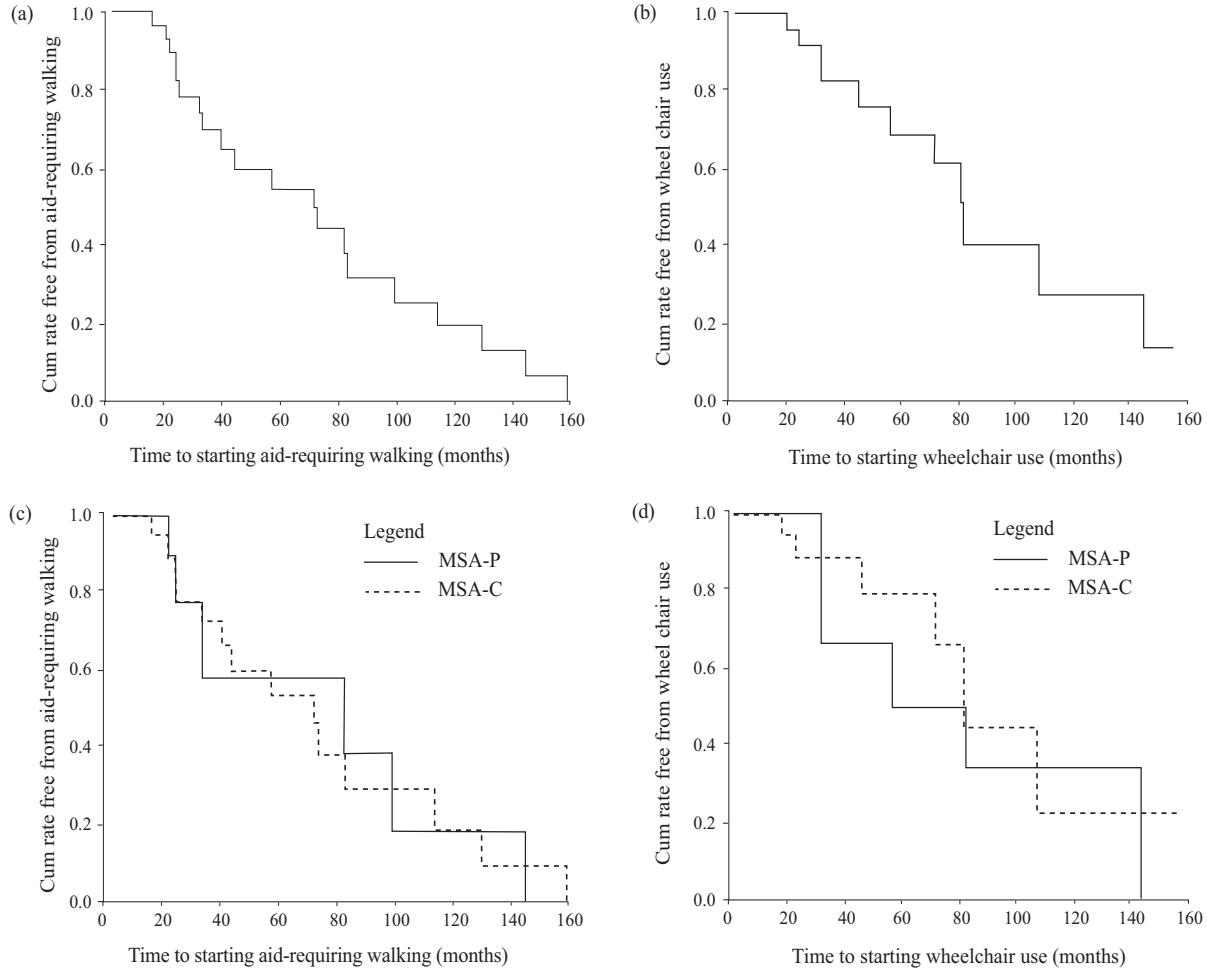

Fig. 2. Overall cumulative rate free from aid-requiring walking (a) and wheelchair use (b) in MSA patients from the onset of symptoms, stratified according to MSA subtype (c, $P = 0.97$ and d, $P = 0.63$).

other patients. Another reason could be that these patients were seen in a movement disorders clinic of a specialised institution, where a rehabilitative service like physiotherapy was readily available. Thus, patients were able to receive advice on falls prevention and undergo gait and balance training, which may have contributed to their continued independence. A further possibility could be that our patients, in their efforts to remain independent, delayed the use of walking aids and wheelchairs. While financial constraints could be another factor causing delayed wheelchair usage in our patients, all patients needing any form of assistance would have been referred to the institution's social worker for financial assistance.

While Japanese MSA-P patients had significantly earlier aid-requiring walking and wheelchair dependence,[11] we found these event rates for our MSA-P and MSA-C patients to be similar. We also saw an equal number of patients presenting with pure cerebellar or parkinsonian features while other studies reported a predominance of motor disturbance.[11,17] In terms of autonomic features, we also found a greater number of patients with urinary disturbance as compared to orthostatic hypotension, in agreement with previous studies.[20,21]

Autonomic function testing and neuroimaging are not part of the consensus criteria but are often used to support the diagnosis of MSA and to exclude other conditions. MRI has also been found to be useful in differentiating MSA from progressive supranuclear palsy.[22] The majority of our patients had cerebellar-pontine atrophy on neuroimaging and none were reported to have putaminal abnormalities. A hyperintense rim at the lateral edge of the dorsolateral putamen was reported in about 32% of MSA patients in one study.[11] Nonetheless, the MRI can be normal in up to 20% of cases.[23] While autonomic function tests have been reported to help differentiate MSA from Parkinson's disease (PD) and idiopathic cerebellar degenerations,[24] a recent

publication reported that autonomic function testing may not distinguish MSA from PD, since the clinical combination of parkinsonism and dysautonomia is as likely to be caused by PD as by MSA.[25]

As our study strictly adhered to the latest consensus criteria for the diagnosis of MSA, there is greater confidence in the accuracy of the diagnosis in our cases. However, missed cases can occur as a result of the early cases misdiagnosed as other types of parkinsonism. Also, not all our patients had MRI of the brain performed and the neuroimaging was not prospectively performed. As such, subtle abnormalities could have been missed by the neuroradiologists. Another limitation is the small number of our study population and that no neuropathological confirmation was available for our patients with MSA.

Despite these limitations, this is a review of the clinical characteristics of MSA patients seen in a movement disorders clinic using the consensus criteria in the diagnosis of MSA. Our study revealed a predominance of MSA-C patients as well as a later age at onset of disease and longer median time to aid-requiring walking and wheelchair use compared to Japanese patients.

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REFERENCES

1. Graham JG, Oppenheimer DR. Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. J Neurol Neurosurg Psychiatry 1969;32:28-34.
2. Quinn N. Multiple system atrophy – the nature of the beast. J Neurol Neurosurg Psychiatry 1989;52(suppl):78-89.
3. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999;163:94-8.
4. Lantos PL. Multiple system atrophy. Brain Pathol 1997;7:1293-7.
5. Wenning GK, Ben-Shlomo Y, Magalhães M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 1994;117:835-45.
6. Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology 1996;46:1470.
7. Testa D, Filippini G, Farinotti M, Palazzini E, Caraceni T. Survival in multiple system atrophy: a study of prognostic factors in 59 cases. J Neurol 1996;243:401-4.
8. Ben-Shlomo Y, Wenning GK, Tison F, Quinn NP. Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. Neurology 1997;48:384-93.
9. Schulz JB, Klockgether T, Petersen D, Jauch M, Muller-Schauenburg W, Spieker S, et al. Multiple system atrophy: natural history, MRI morphology, and dopamine receptor imaging with 123IBZM-SPECT. J Neurol Neurosurg Psychiatry 1994;57:1047-56.
10. Klockgether T, Lüdtke R, Kramer M, Abele M, Burk K, Schols L, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain 1998;121:589-600.
11. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002;125:1070-83.
12. World Health Organization. World Health Statistics Annual 1996. Geneva: Office of Publications, 1998:A6-A8.
13. Ministry of Health homepage. Singapore: Ministry of Health; c2004 [updated 2004 July]. Health Facts Singapore 2004. Available at: http://www.moh.gov.sg/corp/publications/statistics/population.do. Accessed 21 April 2005.
14. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861-70.
15. Osaki Y, Wenning GK, Daniel SE, Hughes A, Lees AJ, Mathias CJ, et al. Do published criteria improve clinical diagnostic accuracy in multiple system atrophy? Neurology 2002;59:1486-91.
16. Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, et al. Starnberg trial on epidemiology of parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. Arch Neurol 1995;52:1017-22.
17. Wenning GK, Tison F, Ben-Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. Mov Disord 1997;12:133-47.
18. Chrysostome V, Tison F, Yekhlef F, Sourgen C, Baldi I, Dartigues JF; MSA-Aquitaine Network. Epidemiology of multiple system atrophy: a prevalence and pilot risk factor study in Aquitaine, France. Neuroepidemiology 2004;23:201-8.
19. Vanacore N, Bonifati V, Fabbrini G, Colosimo C, De Michele G, Marconi R, et al; European Study Group on Atypical Parkinsonism (ESGAP). Epidemiology of multiple system atrophy. Neurol Sci 2001;22:97-9.
20. Kaufmann H. Multiple system atrophy. Curr Opin Neurol 1998;11:351-5.
21. Sakakibara R, Hattori T, Uchiyama T, Kita K, Asahima M, Suzuki A, et al. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? J Neurol Neurosurg Psychiatry 2000;68:65-9.
22. Schrag A, Good CD, Miszkiel K, Morris HR, Mathias CJ, Lees AJ, et al. Differentiation of atypical parkinsonian syndromes with routine MRI. Neurology 2002;54:697-702.
23. Schrag A, Kingsley D, Phatouros C, Mathias CJ, Lees AJ, Daniel SE, et al. Clinical usefulness of magnetic resonance imaging in multiple system atrophy. J Neurol Neurosurg Psychiatry 1998;65:65-71.
24. Sandroni P, Ahlskog JE, Fealey RD, Low PA. Autonomic involvement in extrapyramidal and cerebellar disorders. Clin Auton Res 1991;1:147-55.
25. Riley DE, Chelimsky TC. Autonomic nervous system testing may not distinguish multiple system atrophy from Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:56-60.