Objective: To delineate the frequency and nature of dystonia in multiple system atrophy (MSA).

Methods: A cohort of 24 patients with clinically probable MSA over the past 10 years were prospectively followed up. Motor features were either dominated by parkinsonism (MSA-P subtype, n=18) or cerebellar ataxia (MSA-C, n=6). Classification of dystonic features and their changes with time was based on clinical observation during 6–12 monthly follow up visits. Parkinsonian features and complications of drug therapy were assessed. Most patients (22/24) died during the observation period. Neuropathological examination was confirmatory in all of the five necropsied patients.

Results: At first neurological visit dystonia was present in 11 (46%) patients all of whom had been levodopa naive at this time point. Six patients (25%) exhibited cervical dystonia (antecollis) (MSA-P n=4, MSA-C n=2), five patients (21%) showed unilateral limb dystonia (MSA-P n=4; MSA-C n=1). A definite initial response to levodopa treatment was seen in 15/18 patients with MSA-P, but in none of the six patients with MSA-C. A subgroup of 12 patients with MSA-P developed levodopa induced dyskinesias 2.3 years (range 0.5–4) after initiation of levodopa therapy. Most patients had peak dose cranio-cervical dystonia; however, some patients experienced limb or generalised dystonia. Isolated peak dose limb chorea occurred in only one patient.

Conclusion: The prospective clinical study suggests that dystonia is common in untreated MSA-P. This finding may reflect younger age at disease onset and putaminal pathology in MSA-P. Levodopa induced dyskinesias were almost exclusively dystonic affecting predominantly cranio-cervical musculature. Future studies are required to elucidate the underlying pathophysiology of dystonia in MSA.
The levodopa responder group consisted of 15 (83%) patients with MSA-P in whom initial response to levodopa therapy was scored as excellent in four (27%), good in seven (47%), or moderate in four patients (27%) (table 1). After 2 years of dopaminergic treatment only nine (60%) patients were still considered responsive and this percentage declined to 13% (two patients) after 4 years. Levodopa induced motor fluctuations emerged in all 15 patients with MSA-P in the responder group. Unilateral limb dystonia was improved by levodopa in all patients presenting with this feature.

Three patients with MSA-P (4, 5, 6) who showed a clear initial response to levodopa treatment never developed dyskinesias. They deteriorated rapidly due to severe autonomic failure and pyramidal involvement, and died 3–4 years after disease onset.

Levodopa induced dystonia and dyskinesias

A subgroup of 12 (80%) patients with MSA-P developed dyskinesias on average 2.3 (SD 1.1) years after the initiation of levodopa therapy. The levodopa induced dyskinesias were predominantly (n=2) or purely (n=9) dystonic in all but one of these patients. Dyskinesias were interdose in all but one patient (14) who exhibited end of dose dystonia.

As shown in table 1, levodopa induced dyskinesias were confined to the neck and consisted of “on period” phasic dystonic posturing in seven of the 12 responsive patients with MSA-P. This group comprised all three patients with antecollis as presenting symptom in whom levodopa exposure induced phasic rotational head movements. Additional facial dystonia was present in five patients and consisted predominantly of spasms of the lower part of the face, lips, and eventually the platysma. In three patients levodopa induced dyskinesias were confined to the limbs, another two patients exhibited generalised dyskinesias.

DISCUSSION

Dystonia is typically encountered as a levodopa induced phenomenon in PD. Except from a literature review limited by poor documentation of clinical features dystonia has never been systematically studied in patients with MSA. Our study suggests that dystonia is more common in MSA than previously reported, occurring in 42% of levodopa naive patients. Although there are no prospective series assessing the frequency of dystonia in untreated PD, dystonia has been reported in 16% of levodopa naive patients with PD in a retrospective survey. This suggests that dystonia is more common in untreated MSA compared with untreated PD.

In keeping with previous reports dystonia in the present series of patients predominantly affected craniocervical muscles with antecollis being present in 25% of cases. Importantly, unilateral limb dystonia was also seen, albeit in a minority of five (21%) patients.

Disproportionate antecollis is considered a rare, but characteristic, “red flag” suggestive of MSA, and usually emerging late in the course of disease. In our study antecollis occurred in 25% of the patients and it often emerged within early disease stages. The discrepancy between the present finding and previous reports may well reflect differences in the clinical classification of abnormal head posturing. We defined antecollis as abnormal neck flexion and may therefore have included patients with moderate posturing. However, there is no validated scale that would have allowed us to define a disproportionate degree of antecollis. In a previous neuropathological study of 10 patients with MSA antecollis was attributed to neuronal loss in the ventral putamen. Furthermore, studies on symptomatic dystonia emphasise the role of the putamen as a major lesion site in dystonia. Additional involvement of interconnections between the basal ganglia and the brain stem or cerebellar structures may contribute towards abnormal axial posturing and, thus, to dystonia in MSA-P.
MSA. 20–24 Recently, marked myopathy of neck extensor muscles was found in patients with clinically probable MSA and antecollis. 25, 26, 27 Further studies are required to determine the relevance of myopathic changes associated with neck muscle abnormalities in MSA.

Our study showed that limb dystonia may occur in levodopa naive MSA, similarly to previous reports in early PD. 28–30 Because levodopa treatment abolished limb dystonia in all levodopa responsive patients with MSA it is likely that dystonia in levodopa naive de novo patients with MSA predominantly reflects early nigrostriatal dysfunction due to a decrease of endogenous dopaminergic stimulation rather than postsynaptic striatal pathology. 31–33

We found a definite initial response to levodopa treatment in 83% of patients with MSA-P which was scored excellent in 27%. This finding is in line with data obtained by Wenning et al, who found a good or excellent response to levodopa treatment in 29% of patients with MSA-P. 34 Levodopa induced dyskinesias developed in 12 out of 15 levodopa responsive patients with MSA-P after an average exposure of 2.3 years. The three patients with MSA-P without levodopa induced dyskinesias despite an initial antiparkinsonian response had rapidly progressive disease with death occurring within a few years, which may have precluded the evolution of motor complications resulting from chronic levodopa delivery. By contrast, recent prospective controlled trials of dopamine agonists versus levodopa in PD reported dyskinesia rates between 20% and 40% in the levodopa treatment arms over 3 to 5 years of treatment. 35–37 Although the latency to onset of dyskinesias is comparable in the PD trials, in our present series patients with MSA-P seem to more prone to develop dyskinesias. Age at onset of disease and disease severity both determine the frequency and severity of dyskinesias in PD. 38 Age at onset is about 1 decade earlier in MSA-P compared with PD, furthermore the motor disability at presentation is clearly more advanced in MSA-P and it progresses more rapidly than in PD. 39 Both findings may partly account for the high rates of levodopa induced dyskinesias in MSA-P.

Our study confirms previous reports of the cranio cervical predilection of levodopa induced dyskinesias. 7, 10, 11, 13 Furthermore, most of the dyskinesias found were dystonic. There is no clear explanation for the topographic predilection and dystonic nature of levodopa induced dyskinesias in MSA. Although the mechanism of levodopa induced dyskinesias is incompletely understood, an abnormal imbalance of activity in the indirect and direct putaminal lateral outflow systems, possibly related to levodopa induced changes in signal transaction in striatal medium spiny neurons, are thought to play an important part. 40 In MSA-P degeneration in the caudal and dorsal part of the putamen, which receives topographical projections from cortical limb areas, may account for the lack of dyskinetic responses in the limbs when such patients are exposed to levodopa. In early disease stages; however, the ventral putaminal region, related to facial projections, is relatively spared providing the substrate for a dystonic face and neck response to levodopa. 41

It is interesting to note that levodopa induced on period dyskinesias when they affect the orofacial region seem to be dystonic both in MSA and PD. 42 This may be linked to the normal motor physiology of cranio cervical muscles, which are predominantly used for slower phasic movements as in physiological grimacing, speaking, or chewing and have to perform less ballistic rapid movements compared with the limbs.

In summary, this prospective clinical study suggests that dystonia is often encountered in untreated MSA-P. The predominant occurrence of levodopa induced dystonia in the cranio cervical region is probably related to the topography of putaminal pathology in this disorder.

Authors’ affiliations
S M Boesch, G K Wenning, G Ransmayr, W Poewe, Department of Neurology, University Hospital, Innsbruck, Austria

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