

PAPER

When is Onuf's nucleus involved in multiple system atrophy? A sphincter electromyography study

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Background: External anal sphincter (EAS) electromyography (EMG) abnormalities can distinguish multiple system atrophy (MSA) from Parkinson's disease in the first five years after disease onset. However, the prevalence of the abnormalities in the early stages of MSA is unknown.

Objectives: To present EAS-EMG data in the various stages of MSA.

Methods: 84 patients with "probable" MSA were recruited (42 men, 42 women; mean age 62 years (range 47 to 78); mean disease duration 3.2 years (0.5 to 8.0; <1 year in 25%); 50 cerebellar form (MSA-C), 34 parkinsonian form (MSA-P)). EAS motor unit potential (MUP) analysis and EMG cystometry were carried out in all patients.

Results: The overall prevalence of neurogenic change of the EAS MUP was 62%–52% in the first year after disease onset, increasing to 83% by the fifth year ($p < 0.05$); it also increased with severity of gait disturbance ($p < 0.05$), storage and voiding disorders, and detrusor sphincter dyssynergy (NS). The neurogenic change was not correlated with sex, age, MSA-P/C, postural hypotension, constipation, erectile dysfunction in men, underactive or acontractile detrusor, or detrusor overactivity. In 17 incontinent patients without detrusor overactivity or low compliance, urinary incontinence was more severe in those with neurogenic change than in those without ($p < 0.05$).

Conclusions: Involvement of Onuf's nucleus in MSA is time dependent. Before the fifth year of illness, the prevalence of neurogenic change does not seem to be high, so a negative result cannot exclude the diagnosis of MSA.

One of the distinguishing hallmarks in the pathology of multiple system atrophy (MSA) is neuronal loss in the sacral Onuf's nucleus.^{1–3} Onuf's nucleus plays a key role in urinary continence and the micturition reflex.⁴ Neurones in this nucleus receive not only cortical inputs but also noradrenergic and serotonergic facilitatory inputs by way of interneurons from various brain stem structures, including the pontine urine storage centre.^{5,6} External anal sphincter (EAS) electromyography (EMG) is an established method for detecting neurogenic change of motor unit potentials (MUP), which reflects denervation and reinnervation of the sphincter muscle.⁷ The significance of the EAS EMG is well known in MSA,^{7–15} and it is reported that EAS MUP abnormalities can distinguish MSA from Parkinson's disease in the first five years after disease onset.^{7–9} However, the prevalence of the abnormalities in the early stages of MSA is unknown. We present our EAS EMG data in the various stages of MSA.

METHODS

We recruited 84 patients with "probable" MSA¹⁶: 42 men, 42 women; mean age 62 years (range 47 to 78); mean disease duration 3.2 years (0.5 to 8.0 years; <1 year in 21 patients (25%)); 50 MSA-C (cerebellar form), 34 MSA-P (parkinsonian form). We added an imaging study to ensure the diagnosis of the early cases; all patients had magnetic resonance imaging (MRI) abnormalities including pontocerebellar atrophy, abnormal signal intensity in the cerebellar peduncle, cross sign in the pons, and abnormal signal intensity in the posterolateral putamen, all of which were consistent with MSA and helped to exclude Parkinson's disease and progressive supranuclear palsy.¹⁷ Genetic analyses were carried out as far as possible to exclude hereditary

spinocerebellar ataxia. No patient had abnormalities of blood chemistry (including blood sugar) or urinalysis. None had abnormal findings on digital examination or ultrasound echography of the pelvic organs.

After inserting a concentric needle electrode into the EAS, we carried out single MUP analysis in all patients, using an EMG computer (Neuropack Sigma; Nihon Kohden, Tokyo, Japan).¹⁵ We sampled at least 10 single MUPs per patient, manually examining the automatically sampled waves to ensure that the MUPs were indeed single. Neurogenic change was diagnosed when at least one of the following abnormalities was seen:

- more than 20% of MUPs had a duration of >10 ms;
- the average duration of MUP was >10 ms, including the late components in particular.^{14,18}

We carried out standard EMG cystometry with a pressure–flow analysis in all patients.^{15,19,20} The filling phase abnormalities include detrusor overactivity and low compliance detrusor. The voiding phase abnormalities include detrusor–sphincter dyssynergy. In the Schäfer's nomogram test,²⁰ we obtained detrusor contractility classed as strong, normal, weak, or very weak; the latter two were designated as underactive detrusor in this study. The detrusor is classed as acontractile when patients with large post-void residuals (PVR) cannot contract the detrusor at all without urinary flow.

Abbreviations: EAS, external anal sphincter; MSA, multiple system atrophy; MSA-C, cerebellar form of multiple system atrophy; MSA-P, parkinsonian form of multiple system atrophy; MUP, motor unit potential; PVR, post-void residual

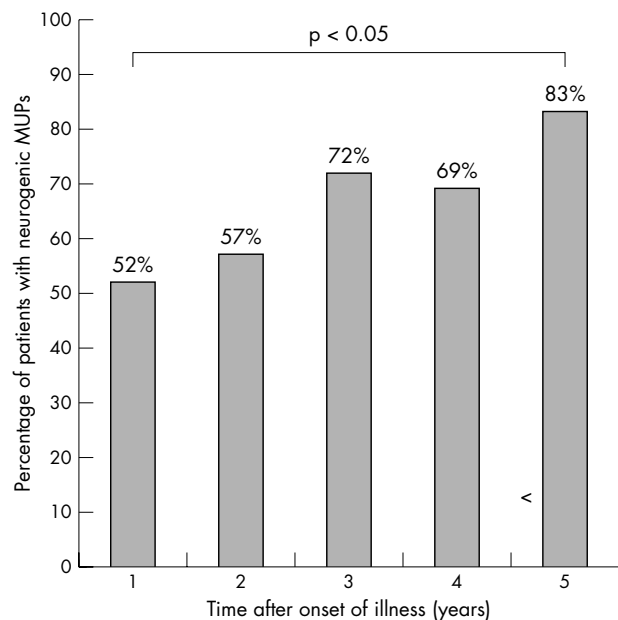


Figure 1 Neurogenic sphincter EMG and duration of illness. The prevalence of neurogenic sphincter EMG increased during a course of illness. MUP, motor unit potential.

All patients gave their informed consent before participating in the study. Statistics were analysed using the χ^2 test.

RESULTS

Patients' functional ability and urinary disorders were as follows. Gait disorder (as measured by the international cooperative ataxia rating scale, walking capacities subscale²¹) was absent (score of 0) in none, independent walking (score 1–3) in 23, walking with one stick (score 4–5) in 22, walking with aid (score 6–7) in 28, and wheelchair bound (score 8) in 11. All patients except for two had urinary symptoms. Urinary incontinence (storage disorder) was never experienced in 25, monthly in 14, weekly in 13, and daily in 32. The PVR volume measured by transurethral catheterisation was <100 ml in 35, 100–200 ml in 27, and >200 ml in 22.

The overall prevalence of neurogenic change was 62% in our patients—52% in the first year after disease onset, and 83% by the fifth year. Thus the prevalence of neurogenic change increased during the course of the illness ($p < 0.05$) (fig 1). Changes in the percentage of MUPs with a duration of more than 10 ms, including patients undergoing repeated studies, are shown in fig 2. Many of the patients who underwent repeated studies had normal to mild abnormality at the initial assessment, and this became marked during the

course of the illness, although in two cases the EAS EMG findings remained normal. The prevalence of neurogenic change was 47% in patients who walked independently, but 82% in those who were wheelchair bound ($p < 0.05$) (table 1). Similar but non-significant changes were found for urinary incontinence (59% of patients without urinary incontinence had neurogenic change v 63% with incontinence); post-void residual (58% with PVR <200 ml v 73% in those with PVR >200 ml); and detrusor sphincter dyssynergy (60% in patients without detrusor sphincter dyssynergy v 73% in those with dyssynergy). The neurogenic sphincter EMG results were not clearly correlated with sex, age, MSA-P/C, postural hypotension, constipation, erectile dysfunction in men, underactive or acontractile detrusor, or detrusor over-activity.

Seventeen of the 56 incontinent patients (seven men, 10 women) lacked abnormal bladder contraction during the filling phase, although 12 of the 17 also had PVR (mean 135 ml (range 30 to 500)). In the 17 patients, urinary incontinence was more severe in those with neurogenic change ($n = 8$; monthly, 0; weekly, 1; daily, 7) than in those without ($n = 9$; monthly, 4; weekly, 2; daily, 3) ($p < 0.05$).

DISCUSSION

Results of the EAS EMG in over 500 MSA patients have already been reported, with an abnormality rate of more than 70% in many studies.^{7–15} Compared with those findings, the overall prevalence rate of neurogenic change in the present study was slightly lower (62%). This is presumably because up to 25% of our patients had a disease duration of one year or less, as early referral to our department has increased recently, and patients are able to come to us without referral. Thus the diagnosis of MSA in such early cases should be made with extreme caution. In addition to the clinical diagnostic criteria,¹⁶ we added an imaging study to ensure the diagnosis in all patients, and we carried genetic analyses as far as possible. Although the EAS MUP abnormalities allow one to distinguish MSA from Parkinson's disease in the first five years after disease onset,^{7–9} the prevalence of the abnormalities in the early stages of MSA (or, conversely, the false negative rate) has not been established up to now. We report here for the first time that in our patient cohort the prevalence of neurogenic change was 52% in the first year after disease onset, increasing to 83% by the fifth year ($p < 0.05$). Among the patients who underwent repeated studies, many were normal or had only mild abnormality at the initial examination, but the abnormality became marked during the course of their illness. Therefore, as expected, the involvement of Onuf's nucleus in MSA is time dependent. In the early stages of illness, the prevalence of neurogenic change in MSA does not seem to be high. In two patients who underwent repeated studies, the EAS EMG findings remained normal. We do not know whether there are some

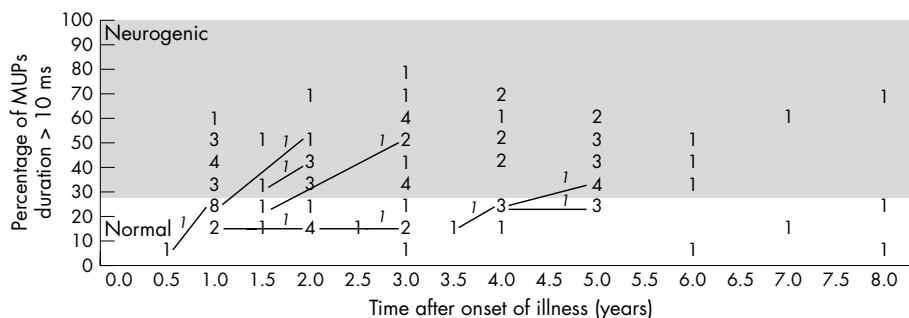


Figure 2 Change in percentage of motor unit potentials (MUPs) of duration >10 ms with duration of illness. Roman figures = the number of the patients; italic figures = the number of the patients who underwent repeated study.

Table 1 Neurogenic sphincter EMG and clinical variables other than duration of illness

	Patients with neurogenic sphincter EMG			Patients with neurogenic sphincter EMG		
	No	%		No	%	
Male	27/42	65	Female	25/42	59	NS
Age <60 years	22/39	56	Age >60 years	30/45	66	NS
MSA-C	29/50	58	MSA-P	23/34	68	NS
Independent walking (1–3*)	11/23	48	Wheelchair bound(6–7*)	9/11	82	p<0.05
Postural hypotension –	30/48	63	Postural hypotension +	22/36	60	NS
Constipation –	40/66	61	Constipation +	12/18	67	NS
Erectile dysfunction –	4/5	80	Erectile dysfunction +	19/30	63	NS
Continent	15/25	59	Incontinent	37/59	63	NS
RU <200 ml	36/62	58	RU >200 ml	16/22	73	NS
Detrusor overactivity –	14/26	55	Detrusor overactivity +	38/58	65	NS
UD/AD –	29/52	56	UD/AD +	20/32	63	NS
DSD –	44/73	60	DSD +	8/11	73	NS

*International cooperative ataxia rating scale, walking capacities subscale.

AD, acontractile detrusor; DSD, detrusor sphincter dyssynergy; MSA, multiple system atrophy; RU, residual urine volume; UD, underactive detrusor.

MSA patients who never develop neurogenic change during the course of their illness. However, Wenning *et al* reported three patients with normal EAS EMG and necropsy confirmation of MSA.²² Thus the negative result cannot exclude the diagnosis of MSA.

The prevalence of neurogenic change also increased with the severity of gait disturbance ($p < 0.05$) in the present study. However, it was not related to postural hypotension (reflecting adrenergic nerve dysfunction),¹⁷ erectile dysfunction in men (presumably reflecting cholinergic and nitrate oxidergic nerve dysfunction),²³ detrusor overactivity (reflecting central type of detrusor dysfunction),^{12, 15} constipation (presumably reflecting both peripheral and central types of autonomic and somatic dysfunctions),²⁴ or sex. Changes in the EAS MUP were slightly more common in patients with detrusor sphincter dyssynergy (reflecting central type of sphincter dysfunction).¹³ It has previously been reported that neurogenic change does not correlate directly with a clinically obvious functional deficit.⁷ Patients with marked abnormalities of the EAS MUP may have no faecal incontinence²² although in such patients anal sphincter weakness is not uncommon.²⁴ In the present study, the prevalence of neurogenic change slightly increased with the severity of storage disorder (incontinence) and voiding disorder (large PVR). The latter may only reflect a parallel and not a causative relation. In the former, the most common urinary incontinence in MSA is urge incontinence, which mostly results from the detrusor (bladder) overactivity. However, we noted urinary incontinence in 17 patients without detrusor overactivity or a low compliance detrusor, which might have a sphincter aetiology. Urinary incontinence was more severe in the patients with neurogenic change than in those without ($p < 0.05$). These results are in agreement with observations by Beck *et al*,¹² and with our previous findings that neurogenic change of the EAS MUP led to a low urethral pressure and sphincter incompetence, particularly in women in the middle to advanced stages of MSA (inability to hold urine, “intrinsic sphincter deficiency”, or stress urinary incontinence type 3).²⁵ The function of Onuf's nucleus is not confined to the innervation of the EAS—that is, it innervates external urethral sphincter as well. As we do not carry out EMG of the external urethral sphincter routinely, the present study results may represent only one aspect of the nucleus. However, our findings may contribute to the differential diagnosis of parkinsonism and ataxic cerebellar disorders.

In conclusion, the results of the present study suggest that the involvement of Onuf's nucleus in MSA is time dependent.

In the early stages of the illness, the prevalence of neurogenic change does not seem to be high, so a negative result cannot exclude a diagnosis of MSA.

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