

## SHORT REPORT

## Sjögren's syndrome associated painful sensory neuropathy without sensory ataxia

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Sensory neuropathy with prominent ataxia reflecting kinesthetic sensory impairment is a well recognised form of neuropathy associated with Sjögren's syndrome.<sup>1–4</sup> Pathologically, T cell invasion of dorsal root ganglia, loss of large sensory neurons, and secondary large fibre degeneration is seen in this neuropathy.<sup>4</sup> However, a form of neuropathy associated with Sjögren's syndrome, presenting with pain and superficial sensory involvement without sensory ataxia has been described anecdotally<sup>5</sup> and in a case report.<sup>6</sup> Clinicopathological details of the second form of neuropathy have not been elucidated. In this report we describe seven patients with Sjögren's syndrome showing painful sensory neuropathy without sensory ataxia.

Patients studied were referred for painful neuropathy to Nagoya University Hospital and its affiliated institutions. All seven patients fulfilled diagnostic criteria for Sjögren's syndrome by the American-European Consensus Group<sup>7</sup> and showed painful peripheral neuropathy (table 1). Patients included six women and one man, ranging from 25 to 72 years old. In all patients initial symptom of neuropathy was paraesthesia or painful dysaesthesia in the most distal portions of the extremities, later extending proximally to involve the entire legs and arms. The trunk became involved in three patients, and the trigeminal nerve was impaired in three patients. Asymmetry in sensory impairment was present in four patients. None of the patients showed sensory ataxia in the initial phase. Most patients retained essentially normal muscle strength, but patient 1 showed slight weakness in distal limb muscles. Painful sensation was the most characteristic, and this symptom compromised activities of daily living in all patients. Superficial sensation for pinprick and temperature was prominently impaired. Deep sensation such as joint position and vibratory sense was substantially well preserved. Sensory ataxia and Romberg's sign was not seen. Autonomic dysfunction was seen in four patients including Adie's pupils, urinary disturbance, and loss of <sup>123</sup>I-MIBG cardiac accumulation; however, orthostatic hypotension was not present. Apparent hypohidrosis was seen in three patients. Thermal stimulation in two patients, resulted in absent sweating on the forehead, trunk, arms, and legs, with preserved sweat gland function on pirocarpine test. Thermography showed abnormal skin temperature gradient in four patients. Deep tendon reflexes were comparatively well preserved except in two patients. Motor nerve conduction studies showed no slowing (mean (SD) 52.3 (3.9) m/s in the median, 44.8 (6.1) m/s in the tibial nerves) and preserved compound muscle action potentials (CMAPs) (7.5 (3.5) mV in the median, 9.0 (6.3) mV in the tibial nerves). Sensory nerve conduction (50.1 (6.0) m/s in the median, 47.2 (10.4) m/s in the sural nerves) and sensory nerve action potentials (SNAPs) (13.6 (11.7) uV in the median and 9.0 (6.3) uV in the sural nerves) were generally well preserved; only in patient 4, SNAPs were not evoked. Somatosensory evoked potentials (SEPs) were also well preserved (mean (SD) 20.0 (1.1) ms at N20, 13.7 (1.2) ms at N13, and 9.3 (0.4) ms at N9).

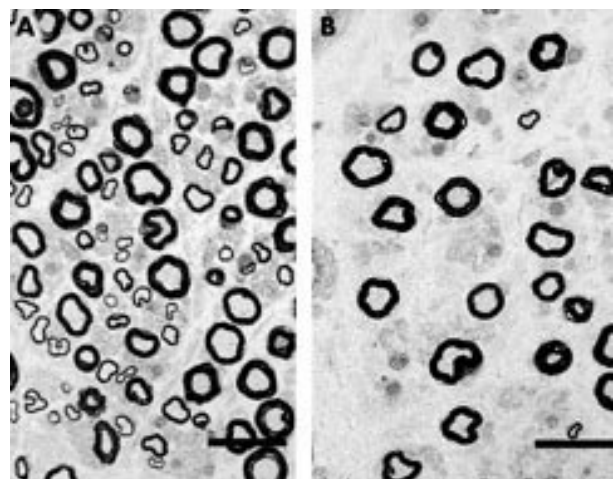
Sural nerve biopsy in five patients showed a variable degree of myelinated fibre loss, predominantly affecting small diam-

eter fibres (table 1, fig 1). Unmyelinated fibre density was severely reduced. Axonal sprouting was essentially absent in all patients. In teased fibre preparations, degeneration was seen in 32% to 55% of axons, predominantly small diameter fibres. Vasculitis was not seen.

Patient 2 developed sensory ataxia in the legs over the next nine years, and more details of this patient are given below. Patient 4 developed localised sensory ataxia in the fingers of the right hand over 11 years. Other patients showed persistent painful sensory neuropathy with gradual extension of distribution over 4 to 11 years of follow up.

## CASE REPORT

A 68 year old man had painful dysaesthesia and numbness in the feet for about 10 years, with spread to the proximal of the legs and arms. When he was 56 years old, he noticed painful dysaesthesia in the legs, and subsequently in the hands. Neurological examination demonstrated light touch and pinprick were disturbed, and painful dysaesthesia was elicited in glove and stocking distribution. Vibration and joint position sense was comparatively well preserved for the first time. Sensory ataxia and Romberg's sign were not seen. Deep tendon reflexes were well preserved in upper limbs, but mildly decreased in lower limbs. Muscle strength was normal. Autonomic disturbance was not present. Nerve conductions were nearly normal except for sensory conduction in the median nerve, 40 m/s. SNAPs were well preserved. Result of routine blood haematology and biochemistry screening tests were normal. CSF protein was 33 mg/dl with no cells. A sural nerve biopsy specimen revealed myelinated fibre loss predominantly involving small diameter fibres with axonal degeneration.



**Figure 1** (A) Transverse section of a sural nerve specimen from a control subject. (B) Specimen from a patient of painful sensory neuropathy with predominant small fibre loss associated with Sjögren's syndrome (patient 1). Small diameter myelinated fibres are more noticeably involved and no axonal sprouting. Bars=25 µm.

**Table 1** Clinical symptoms and histopathological findings

Patient Age/sex	Sjögren's syndrome, positive test	Neurological symptoms							Sural nerve biopsy			Follow up (y)
		Motor involvement Muscle atrophy/ strength	Sensory involvement				Sensory ataxia	Romberg's sign	Autonomic signs	Myelinated fibre density large, 9 small (no/mm <sup>2</sup> ), Small/large ratio	Unmyelinated fibre density (no/mm <sup>2</sup> )	
Distribution	Painful sensation		Nociception	Vibration/ position sense								
1 72/F	SS-A SS-B Sialography	+1 / +1	TL	+3	-3	-1 / -	-	-	1, 2, 4	axonal degeneration 1159, 921, 0.79	3463	6
2 68/M	SS-A Lip biopsy RB	-/-	L	+2	-3	-1 / -1	-*	-*	4	axonal degeneration 922, 448, 0.49 79, 169, 2.14‡	ND	2
3 36/F	Lip biopsy RB	-/-	TL	+3	-3	-/-	-	-	3	axonal degeneration 1876, 1332, 0.71	2585	6
4 71/F	SS-A Sialography RB	+1 / -	L	+3	-3	-2 / -2	-†	-	1, 2, 4	axonal degeneration 1158, 1553, 1.34	8312	11
5 48/F	Lip biopsy Gum test	-/-	FL	+3	-3	-/-	-	-	-	axonal degeneration 2541, 1528, 0.62	3232	11
6 25/F	SS-A RB	-/-	FL	+3	-3	-/-	-	-	1	ND	ND	6
7 62/F	Lip biopsy Schirmer's test	-/-	FL	+3	-3	-/-	-	-	-	ND	ND	4
Controls (mean (SD), n=9)									3068 (294),	5122 (438), 1.7 (0.2)	29913 (3457)	

+, Positive findings; -, negative findings. Muscle weakness, atrophy, and painful sensation: +3, severe; +2, moderate; +1, mild; -, absent. Distribution of sensory involvement: F, facial; T, trunk; L, limbs. Sensory signs: -3, severe; -2, moderate; -1, mild; -, absent. Nociception was evaluated by pin pricking. Autonomic dysfunction: 1, Adie's pupils; 2, loss of <sup>123</sup>I-MIBG cardiac accumulation; 3, urinary disturbance; 4, hypohidrosis. SS-A, anti-SS-A antibody; SS-B, anti-SS-B antibody; RB, Rose Bengal test for Sjögren's syndrome. For nerve biopsy findings, large >6.73 µm; small <6.73 µm in fibre diameter; As for typical sensory ataxic neuropathy with Sjögren's syndrome, large myelinated fibre density was 660 (714) (mean (SD)), small myelinated fibre density was 3263 (2390), and small/large fibre ratio was 14.6 (19.0) for 20 cases. ND, not determined. \*, †Sensory ataxia developed in the legs 9 years later, in the right hand 11 years later respectively. ‡Result of second sural nerve biopsy examined 12 years later.

In the next nine years, involvement of deep sensation gradually developed. At 68 years old, he showed sensory ataxia in the legs and positive Romberg's sign without muscle weakness. The deep tendon reflexes were almost absent. Motor nerve conduction velocities were still preserved, but sensory nerve action potentials were not elicited in the median and sural nerves. At this time, sicca symptoms were obvious, and a Rose Bengal test was positive. A lip biopsy specimen showed periacinar lymphocytic infiltration. Second sural nerve biopsy on the other side showed severe large fibre loss as well as small fibre loss without axonal sprouts.

## DISCUSSION

The most well recognised form of Sjögren's syndrome associated neuropathy has been sensory ataxic neuropathy associated with profound impairment of kinesthetic sensation.<sup>1-4 8-10</sup> Neuropathologically, T cell invasion in the dorsal root ganglion as well as loss of large ganglion neurons and their large axons have been verified.<sup>4</sup> However clinicopathological findings in our patients differed remarkably from those of sensory ataxic neuropathy. Painful sensation and hyperalagia in our patients suggested involvement of small nociceptive nerve fibres as has been demonstrated.<sup>11</sup>

Indeed, in sural nerve of our patients, small myelinated and unmyelinated fibres were predominantly involved; electrophysiologically, amplitudes of SNAPs were comparatively preserved, particularly in contrast with sensory ataxic neuropathy. Findings in the dorsal root ganglion in this neuropathy have not been described, but predominant small fibre loss, extremely rare axonal sprouts, lack of vasculitis, lack of motor involvement, and fairly well preserved SEPs suggest that small dorsal root ganglion neurons can be involved.

As demonstrated by the clinical course of our patients, some patients show persistent symptoms or a slowly progressive course while remaining limited to a painful small fibre type of neuropathy, while others, including one of our patients, may later develop sensory ataxic neuropathy presumably involving large sensory neurons. Additionally, one of our patients developed localised unilateral sensory ataxia in the fingers, suggesting that some patients may develop localised sensory ataxia. These observations suggest that painful sensory neuropathy with predominant small fibre loss and sensory ataxic large fibre neuropathy are elements of a spectrum of sensory neuropathy in Sjögren's syndrome.

In summary, these patients suggest that painful sensory neuropathy with predominant small fibre loss is an identifiable subtype of Sjögren's syndrome associated neuropathy.

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## REFERENCES

- 1 **Kennett RP**, Harding AE. Peripheral neuropathy associated with the sicca syndrome. *J Neurol Neurosurg Psychiatry* 1986;**49**:90-2
- 2 **Graus F**, Pou A, Kanterewicz E, et al. Sensory neuronopathy and Sjögren's syndrome: clinical and immunologic study of two patients. *Neurology* 1988;**38**:1637-9.
- 3 **Gemignani F**, Marbini A, Pavesi G, et al. Peripheral neuropathy associated with primary Sjögren's syndrome. *J Neurol Neurosurg Psychiatry* 1994;**57**:983-6.
- 4 **Griffin JW**, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 1990;**27**:304-15.
- 5 **Grant IA**, Hunder GG, Homburger HA, et al. Peripheral neuropathy associated with sicca complex. *Neurology* 1997;**48**:855-62.
- 6 **Denislic M**, Meh D, Popovic M, et al. Small nerve fibre dysfunction in a patient with Sjögren's syndrome. Neurophysiological and morphological confirmation. *Scand J Rheumatol* 1995;**24**:257-9.
- 7 **Vitali C**, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**:554-8.
- 8 **Sobue G**, Yasuda T, Kachi T, et al. Chronic progressive sensory ataxic neuropathy: clinicopathological features of idiopathic and Sjögren's syndrome-associated cases. *J Neurol* 1993;**240**:1-7.
- 9 **Kumazawa K**, Sobue G, Yamamoto K, et al. Segmental anhidrosis in the spinal dermatomes in Sjögren's syndrome-associated neuropathy. *Neurology* 1993;**43**:1820-3.
- 10 **Mori K**, Koike H, Misu K, et al. Spinal cord magnetic resonance imaging demonstrates sensory neuronal involvement and clinical severity in neuronopathy associated with Sjögren's syndrome. *J Neurol Neurosurg Psychiatry* 2001;**71**:488-92.
- 11 **Wokke JH**, van Dijk GW. Sensory neuropathies including painful and toxic neuropathies. *J Neurol* 1997;**244**:209-21.

# PostScript

## CORRESPONDENCE

### The harsh realities facing the use of SPECT imaging in monitoring disease progression in Parkinson's disease

Dr Snow is right to be cautious in his optimism concerning the use of functional imaging markers in neuroprotection studies in Parkinson's disease<sup>1</sup> as storm clouds gather<sup>2-3</sup> over the methods and interpretation of CALM-PD and REAL-PET. The concerns, however, are not limited to the effect of drug treatment on ligand uptake. Most importantly we need to ask the weight that should be placed on the result of functional imaging studies when they are not supported by the accompanying clinical data. In addition, there are concerns about the ability of the methods for accurately monitoring progression. The key requirements for a PET or SPECT method to be used in assessing progression are sensitivity to clinical change and reproducibility.<sup>4</sup> There are no data concerning either from the study of Winogrodzka and colleagues,<sup>5</sup> the authors quoting reproducibility data from Seibyl *et al.*<sup>6</sup> These data need to be presented for the benefit of the readership. The mean (SD) scan to scan variability in a group (n = 7) of patients with Parkinson's disease was 16.8 (13.3)%. It is surely only in functional imaging that a measurement to measurement variability of  $\pm 43\%$  (mean  $\pm 2$  SD) could be described as highly reproducible<sup>5</sup> or excellent.<sup>6</sup> Sensitivity provides knowledge of the amount a functional imaging marker will change with a given clinical change, and I have yet to be convinced (partly because the data have not been presented) that [<sup>123</sup>I]β-CIT SPECT can provide the necessary sensitivity to outweigh the very strong influence of scan to scan variability. The problems are compounded in studies of L-dopa versus agonist because within the first year a significant number of patients will leave the study or require supplementary L-dopa. The data of Winogrodzka and colleagues<sup>5</sup> illustrate this. In one year mean scan to scan change because of progression is 8% of baseline (or about 4% of normal mean), where mean (SD) scan to scan variability (which may be biological or methodological) is 16.8 (13.3)%. If we are looking for a 25% difference in rate of progression between the two study arms over one year (a difference of 2% progression from baseline) we need a technique that gives a more reproducible measurement than  $\pm 43\%$ . This is the principal problem that needs to be addressed before further "neuroprotection" studies take place using [<sup>123</sup>I]β-CIT SPECT.

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## References

- 1 Snow B. Objective measures for the progression of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;**74**:287.
- 2 Ahlskog EJ. Slowing Parkinson's disease progression: recent dopamine agonist trials. *Neurology* 2003;**60**:381-9.
- 3 Morrish PK. REAL and CALM: What have we learned? *Move Disord* 2003;**18**:839-40.
- 4 Morrish PK, Rakshi JS, Bailey DL, *et al.* Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [<sup>18</sup>F]dopa PET. *J Neurol Neurosurg Psychiatry* 1998;**64**:314-19.
- 5 Winogrodzka A, Bergmans P, Stoof JC, *et al.* [<sup>123</sup>I]β-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;**74**:294-8.
- 6 Seibyl JP, Marek K, Sheff K, *et al.* Test/retest reproducibility of iodine-123-betaCIT SPECT brain measurement of dopamine transporters in Parkinson's patients. *J Nucl Med* 1997;**38**:1453-9.

## Authors' reply

We would like to thank Dr Morrish for his comments on our paper.<sup>1</sup> We agree that it would be of interest to present the data of the longitudinal progression of dopaminergic degeneration (as measured by [<sup>123</sup>I]β-CIT SPECT) in correlation with data on clinical progression. In our study, the patients were drug-naïve when the baseline SPECT scans were obtained. Interestingly, these SPECT data correlated highly with clinical scores (motor UPDRS), which indicate that the SPECT measures may be of value in monitoring progress of nigrostriatal degeneration. Within our study design, however, the patients did not discontinue their dopaminergic drug treatment when the second [<sup>123</sup>I]β-CIT SPECT scan was done (one year after baseline). Consequently, the UPDRS scores were influenced by dopaminergic drug effects and therefore were not suitable to study correlations with [<sup>123</sup>I]β-CIT SPECT measures. Nevertheless, as dopamine transporter imaging will only be a relevant tool for monitoring dopaminergic degeneration if it ultimately reflects meaningful changes in clinical function in patients with Parkinson's disease, future studies should investigate this relation carefully. However, there is still debate on how adequate clinical data can be obtained in patients on drug treatment. For example, it is still unclear whether data obtained in the "defined OFF stage" are adequate enough to assess clinical progression (for a discussion, see Marek *et al.*, 2003<sup>2</sup>).

Concerning the issue of variability and reproducibility of the [<sup>123</sup>I]β-CIT SPECT technique, we of course agree with Dr Morrish that, for the benefit of future neuroprotection studies, all effort should be made to improve analysis methodology to reduce the variance in imaging outcomes. Variability may be reduced, for example, by quantifying radioligand binding automatically on a voxel by voxel basis (three dimensional).<sup>3</sup> Moreover, to reduce variability in SPECT measures for dopamine transporter binding, other tracers than β-CIT

might be of value. For example, FP-CIT SPECT studies in patients with Parkinson's disease have shown reproducibility of the order of 8%.<sup>4</sup> This high reproducibility may stem from the fact that acquisition can be started as soon as three hours after injection for [<sup>123</sup>I]FP-CIT,<sup>5</sup> whereas the optimal time point for acquisition of [<sup>123</sup>I]β-CIT studies is 20 to 24 hours after injection. Consequently, the counts statistics are better for [<sup>123</sup>I]FP-CIT than for [<sup>123</sup>I]β-CIT SPECT studies. Interestingly, a recent preliminary study showed the feasibility of using [<sup>123</sup>I]FP-CIT SPECT for monitoring dopaminergic degeneration in Parkinson's disease.<sup>6</sup> Nevertheless, it would be of major importance that further studies focus on minimising the variability in SPECT measures of dopamine transporter binding, and show which radiotracer is optimal for performing progression studies.

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## References

- 1 Winogrodzka A, Bergmans P, Stoof JC, *et al.* [<sup>123</sup>I]β-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 2003;**74**:294-8.
- 2 Marek K, Jennings D, Seibyl J. Dopamine agonists and Parkinson's disease: what can we learn from neuroimaging studies. *Ann Neurol* 2003;**53**:S160-9.
- 3 Slomka PJ, Radau P, Hurwitz GA, *et al.* Automated three-dimensional quantification of myocardial perfusion and brain SPECT. *Comput Med Imaging Graphics* 2002;**25**:153-64.
- 4 Booij J, Habraken JBA, Bergmans P, *et al.* Imaging of dopamine transporters with iodine-123-FP-CIT in healthy controls and patients with Parkinson's disease. *J Nucl Med* 1998;**39**:1879-84.
- 5 Booij J, Hemelaar JTGM, Speelman JD, *et al.* One-day protocol for imaging of the nigrostriatal pathway in Parkinson's disease by [<sup>123</sup>I]FP-CIT SPECT. *J Nucl Med* 1999;**40**:753-61.
- 6 Winogrodzka A, Bergmans P, Booij J, *et al.* [<sup>123</sup>I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease. *J Neural Transm* 2001;**108**:1011-19.

## CORRECTIONS

There were two mistakes published in the table of the short report, Sjögren's syndrome associated painful sensory neuropathy without sensory ataxia, by K Mori, M Iijima, M Surgiura *et al.* in the September issue of *JNNP* (2003;**74**:1320-2): the digit 9 was added to the eleventh column head by accident and the second entry in the final column should read 12, not 2.

The authors of the letter entitled Meningioma of the optic nerve sheath: treatment with hydroxyurea, published in the September issue of *JNNP* (2003;**74**:1348-50) were listed in the incorrect order. The author order should read as follows: S Paus, T Klockgether, H Urbach, U Schlegel.