These relatively well preserved SNAPs and SEPs, and mild T2* posterior column abnormalities on MRI as well as the predominant decrease in small myelinated and unmyelinated fibres in the sural nerve suggest that small sensory neurons are predominantly impaired and large diameter sensory neurons are fairly well preserved in this form of neuropathy.

Patients were followed-up for 1–12 years. Deep sensory impairment developed in three patients over nine years. They showed sensory ataxia in the legs and fingers. Other patients showed persistent painful sensory neuropathy with a gradual extension of the distribution of the neuropathy, without sensory ataxia.

Multiple mononeuropathy

A total of 11 patients showed a form of multiple mononeuropathy (Table 2). The initial symptom of neuropathy was the acute onset of a tingling sensation or painful dysaesthesia in the distal portion of the limbs. Subsequently, motor and sensory symptoms episodically occurred and extended to the distribution of a multiple mononeuropathy pattern mostly restricted to the limbs. Initial progression was acute or subacute in half of the patients. Trigeminal nerves and truncal intercostal nerves were involved in only two patients, respectively. Impairment during one episode subsequently disappeared, and another area of sensory impairment developed in some patients. Sensory impairment involved all modalities of both superficial and deep sensation. Muscle weakness was evident in the involved limbs, but sensory symptoms were generally more pronounced. Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and cryoglobulins were negative in all the patients examined. Systemic autonomic symptoms were relatively rare (Table 3). CMAPs and SNAPs in the involved nerves were markedly reduced (Table 4). Both large and small myelinated fibres were markedly depleted with prominent active axonal degeneration in the sural nerves. The most prominent histological feature was the frequent occurrence of vasculitic lesions associated with perivascular cellular invasions (Table 5).

Multiple cranial neuropathy

Five patients had multiple cranial neuropathy (Table 2). Involvement of the cranial nerves was bilateral VII nerve involvement in one patient, recurrent III and VI nerve involvement in one patient, III, V, VI, VII, IX and X nerve involvement in one patient, V, IX and X nerve involvement in one patient, and V, VII, IX, X and XII nerve involvement in one patient. Abnormal pupils were seen in one patient (Table 3). Three patients had acute onset of the neuropathy. With respect to extra-cranial symptoms, painful dysaesthesia in the limbs was detected in the initial phase in one patient, and truncal and limb sensory impairment developed in two patients during the follow-up. All patients had cranial motor nerve involvement in spite of the fact that the extent and degree of cranial nerve involvement was variable among the patients.

Trigeminal neuropathy

A total of 15 patients had a pure sensory trigeminal neuropathy (Table 2). Nine patients had unilateral involvement and six had bilateral involvement. Numbness or paraesthesia restricted to the trigeminal nerve region was the characteristic feature. Appreciation of pin prick and soft touch was diminished in the trigeminal nerve region, and dysaesthesia was present. Dysaesthesia of the tongue was present in one patient. Motor symptoms referable to trigeminal nerve involvement were not seen. The progression of these symptoms was indolent in most patients. Sensory disturbances in the limbs were seen in two patients. Pupillary abnormalities were seen in three patients, and orthostatic hypotension and hypohidrosis were observed in three and four patients, respectively (Table 3). There were no marked abnormalities in the routine nerve conduction of the limbs (Table 4). Blink reflex tests were performed in three patients with unilateral involvement, which confirmed trigeminal nerve involvement on the affected side (data not shown). Nerve biopsy was obtained from one patient, the findings of which were normal (Table 5).

Autonomic neuropathy

Three patients had predominant and severe autonomic symptoms and were designated as autonomic neuropathy (Tables 2 and 3). All three patients showed Adie's pupils and all patients also showed severe orthostatic hypotension with syncope. Hypohidrosis or anhidrosis also was present in the trunk and all four limbs. All patients developed abdominal pain, constipation and diarrhoea. Cardiac ^{123}I-MIBG uptake was reduced in two patients examined. Lack of plasma norepinephrine increase in response to standing and hypersensitive blood pressure increase beyond 25 mmHg in response to low concentration of norepinephrine infusion at 3 μg/min were seen in two patients examined. These observations suggest that peripheral sympathetic nervous system was severely involved in this form of neuropathy. Limb and truncal sensory impairment was present with sensory ataxia, but without motor involvement. These symptoms appeared chronically. The SNAPs and SEPs were unelicited and high intensity MRI signal in the posterior column of the spinal cord was seen in one patient (Table 4). A moderate reduction in the myelinated and unmyelinated fibre populations was seen in the sural nerve (Table 5).

Radiculoneuropathy

Four patients had this form of neuropathy (Table 2). All patients had chronic sensorimotor polyradiculoneuropathy with progressive sensory impairment and muscle weakness. The sensory disturbance was in a glove and stocking pattern in all of the patients, with an associated sensory ataxia in three patients. Apparent muscle weakness was seen in two patients. Autonomic symptoms were generally absent, except for constipation, hypohidrosis and urinary disturbances (Table 3). The CSF protein concentration was elevated, ranging from

98 to 146 mg/dl, without pleocytosis. F-wave abnormalities, poor occurrence and prolonged latencies, were present in all patients, while motor and sensory nerve conductions were almost normal, except in one patient with mild elongated distal latency and decreased conduction velocities in the median and tibial nerves (Table 4). This nerve conduction feature was unusual in chronic inflammatory demyelinating polyradiculoneuropathy. SEPs were also substantially prolonged. MRI of the lumbar spine showed abnormal gadolinium enhancement predominantly of the dorsal spinal roots and cauda equine, in all four patients. Sural nerve biopsy showed variable degrees of myelinated fibre loss with minor to moderate demyelinating changes in all patients (Table 5). These clincopathological features suggest that the primary lesion in these patients is in the spinal nerve roots or most proximal nerve trunks, consistent with an inflammatory radiculoneuropathy.

Overlapping clinical features among the neuropathic forms

Each neuropathic form had principal and predominant clinical features characterizing each individual neuropathic form, while the clinical symptoms overlapped to some extent with each other. Sensory ataxic neuropathy frequently had painful features, autonomic symptoms and trigeminal nerve involvement. Painful sensory neuropathy also had autonomic and trigeminal nerve involvement, as well as sensory ataxic features. Multiple mononeuropathy had painful and sensory ataxic features. Trigeminal neuropathy had autonomic and painful features. Multiple cranial neuropathy had some degree of trigeminal, painful and autonomic features. Autonomic neuropathy also had sensory ataxic and trigeminal nerve involvement. These overlapping symptoms were the common features in the present analysis, while overlapping symptoms occurred during the long-standing clinical course. For instance, some patients with painful sensory neuropathy without sensory ataxia later developed sensory ataxia, or alternatively, patients with sensory ataxic neuropathy often developed painful dysaesthetic features during the clinical course. These overlapping clinical features strongly suggest that each individual neuropathic form is not the absolute clinical entity, but these individual forms share a common underlying pathological process.

Findings in an autopsied patient with the sensory ataxic form of neuropathy

An 88-year-old woman with the sensory ataxic form of neuropathy was examined at the time of autopsy. She had numbness on the right side of her face since the age of 64 years, and developed unsteadiness of gait and pseudoathetosis in the fingers at 71 years of age. She was diagnosed as having Sjögren's syndrome at the age of 71. Severe sensory ataxia in the limbs was present. A marked segmental distribution of sensory impairment, particularly with respect to a deep sensation and anhidrosis, was noted (Kumazawa *et al.*, 1993) in the limbs and trunk (Fig. 1). Severe orthostatic hypotension, with a decrease of up to 70 mmHg in systolic pressure, and marked decrease in cardiac MIBG uptake was present. T2*-high intensity signal lesions in the spinal dorsal column were observed (Fig. 1). Respiratory failure due to pneumonia was the cause of death. The autopsy was performed 5 h postmortem.

The population of sensory ganglion neurons was severely, but variably, diminished among the spinal segments; 45% of the control value in the C5, 37% in the Th11 and 26% in the L4 segments (Fig. 1). Nageotte's nodules (Fig. 1) and mild cell infiltrations that contained mainly T-cells were seen (Fig. 2). The large sensory ganglion neurons were diminished predominantly. Myelinated fibre density in the dorsal spinal roots was also variably diminished among the spinal segments; 48% of the control value in the C5, 42% in the Th11 and 22% in the L4 segments (Fig. 1). The large myelinated fibres also were depleted predominantly. The extent of fibre loss in the dorsal spinal roots correlated well with the corresponding dorsal root ganglion cell population. The spinal dorsal column fibre population was also markedly depleted (Fig. 1). These observations strongly suggest that ganglioneuronitis affecting the sensory neurons is the major pathological process. The sympathetic ganglion cells also were severely, but variably, diminished among the segments (23–51%), with mild T-cell invasion (Fig. 1). These segmental variations in the extent of sensory ganglion neuron involvement and sympathetic ganglion neuron involvement seem to correspond to segmental variation of sensory and sweat impairments seen in this patient (Fig. 1). These clinicopathological correlates also may support the view that the major responsible lesion is of sensory and sympathetic neurons. The myelinated fibres in the sciatic, median and tibial nerves in the proximal portion of these nerve trunks showed a remarkable multifocal patchy distribution of myelinated fibre loss, present mainly in the large diameter fibres. The sural nerve revealed loss of large myelinated fibres with active axonal degeneration. Multifocal and disseminated perivascular T-cell infiltrations were seen in the endoneurial and perineurial space of the peripheral nerve trunks (Fig. 2), although the extent of cell invasion was mild. Features of arterial vasculitis, mostly in the post-active state, were seen throughout the peripheral nerve trunks (Fig. 2). Examination of the skeletal muscles showed an almost normal appearance and spinal motor neurons and ventral roots also were normal in appearance and in population (Fig. 1). Submandibular and subauricular salivary glands had T-cell invasion and acinar cell destruction (Fig. 2). Relatively mild inflammatory cell invasion in this patient may be due to the extensive therapies including prednisone.

Therapeutic profiles for individual neuropathic forms

Corticosteroids (prednisone, 1 mg/kg/day) and intravenous immunoglobulin (IVIG) (400 mg/kg for 5 days) were

prescribed for some of the patients (Table 6). Definite improvement in the modified Rankin scale measurement or in sensory impairments, including pain and painful dysaesthesias, after treatment was considered a favourable response (Table 6). Presence or absence of favourable response was evaluated 1 month after treatment.

Multiple mononeuropathy and multiple cranial neuropathy showed the most favourable response to corticosteroid therapy. Sensory ataxic neuropathy showed a favourable response to corticosteroid treatment in only 18% of the patients (Table 6). The rate of favourable response to IVIG therapy for radiculoneuropathy, painful sensory neuropathy and sensory ataxic neuropathy was 100, 67 and 23%, respectively, although the number of patients treated was limited (Table 6). This suggests that the rate of favourable response to corticosteroid or IVIG therapy was different among the

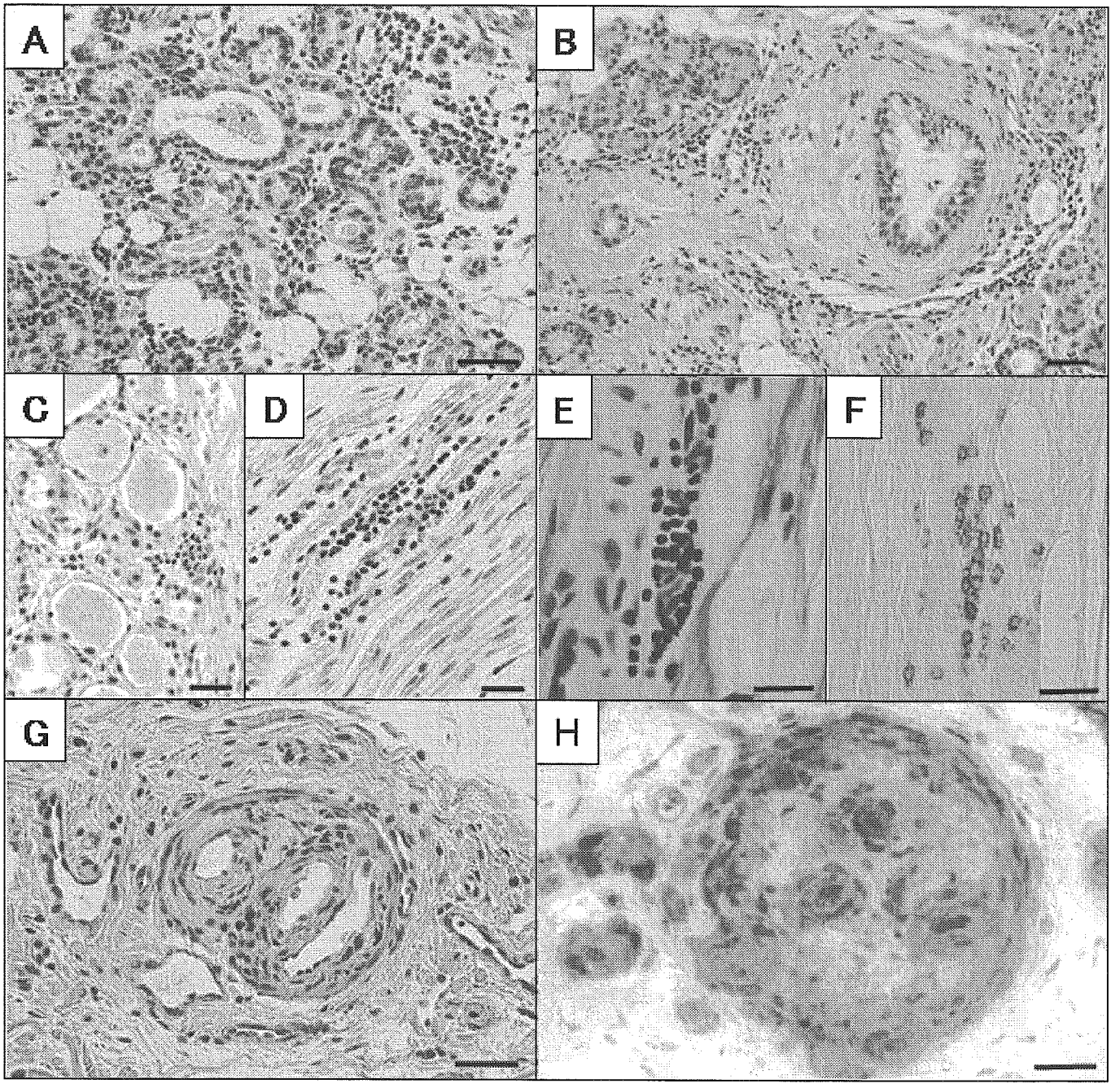

Fig. 2 Inflammatory aspects of the autopsied patient. (**A** and **B**) Lymphocytic infiltration at parotid gland (**A**) and submandibular gland (**B**). Haematoxylin-eosin stain. Scale bar = 40 μm. (**C** and **D**) Lymphocytic infiltration at the L4 dorsal root ganglions on axial section (**C**), and on longitudinal section (**D**). Haematoxylin-eosin stain. Scale bar = 20 μm. (**E** and **F**) Longitudinal section of the median nerve. Perivenular lymphocytic infiltrates in the endoneurium. Klüver–Barrera's stain (**E**) and UCHL-1 positive cells (**F**). Scale bar = 20 μm. (**G** and **H**) Chronic vasculitis in the perineurial space. (**G**) Median nerve. Haematoxylin-eosin stain. (**H**) Sural nerve. Toluidine blue stain. Scale bar = 20 μm.

Table 6 Therapeutic profiles in prednisone- and IVIG-treated patients

Neuropathic form	Prednisone				IVIG			
	Treated patients (*n*)	Favourable response (*n*)	No response (*n*)	% Response	Treated patients (*n*)	Favourable response (*n*)	No response (*n*)	% Response
Sensory neuropathy								
Ataxic*	22	4	18	18	13	3	10	23
Painful**	6	1	5	17	3	2	1	67
Multiple mononeuropathy*	11	8	3	73	1	0	1	0
Cranial neuropathy								
Multiple***	4	3	1	75	0	ND	ND	ND
Trigeminal***	3	1	2	33	0	ND	ND	ND
Autonomic neuropathy†	2	0	2	0	1	0	1	0
Radiculoneuropathy*	3	0	3	0	4	4	0	100
Total	51	17	34	33	22	9	13	41

IVIG, intravenous immunoglobulin therapy; ND, not determined. Favourable response: *For sensory ataxic neuropathy, multiple mononeuropathy and radiculoneuropathy, positive therapeutic response with reduction of one or more points of the modified Rankin scale. **For painful neuropathy, positive therapeutic response with three or more reduction of Visual Analogue Scale (VAS) rating for pain, ranging from 0 = no pain to 10 = maximal pain intensity. ***For cranial neuropathy, therapeutic response was assessed for the improvement of the symptoms of each cranial nerve. Favourable response was designated as definite subjective and objective improvement. †As for autonomic neuropathy, autonomic symptoms did not show a definite favourable response to the therapy.

neuropathic form, probably reflecting the underlying pathology. However, these favourable therapeutic responses were rather short-lived. In the long-term follow-up, these patients ultimately showed progression of symptoms.

Discussion

Underlying pathological features in each form of neuropathy

In this study, we assessed that Sjögren's syndrome-associated neuropathy has a broad clinical spectrum, including sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy and radiculoneuropathy. Here, we discuss the pathological background underlying several forms of neuropathy. Sensory ganglion cell destruction associated with lymphocytic infiltration detected by dorsal root ganglion biopsy provided direct proof that ganglioneuronitis is responsible for lesions in the sensory ataxic form of neuropathy (Malinow *et al.*, 1986; Griffin *et al.*, 1990). Most of our patients with sensory ataxic neuropathy had lesions of the central rami as well as the peripheral rami of the sensory neurons, as assessed by low amplitude or unelicitable SEPs and SNAPs, dorsal spinal column T2*-high intensity signal lesions and segmental sensory impairment. Furthermore, the autopsy findings of a patient with the sensory ataxic form had severe depletion of large-sized sensory ganglion neurons accompanied by T-cell invasion, which strongly support this view. In addition, substantial preservation of motor nerve function and a lack of axonal sprouting with large axon loss in the sural nerve biopsy specimens also support the view that the sensory neurons are primarily affected.

In contrast, in the painful sensory neuropathy form without sensory ataxia there is predominantly superficial sensory impairment, well preserved motor nerve function and small axon loss with relative preservation of large axons. SEPs are relatively well preserved compared with the sensory ataxic form, but T2*-high intensity signal lesions in the dorsal column of the spinal cord were observed, although the extent of high intensity was smaller than those in sensory ataxic neuropathy. Lack of axonal sprouts in the sural nerve biopsy also argues against the presence of a primary axonal lesion. We did not perform histological examination of the dorsal root ganglion. However, based on our clinical, laboratory, and electrophysiological data, we can speculate that this form of neuropathy is another form of sensory ganglioneuronopathy that affects small ganglion neurons. Some patients with painful sensory neuropathy eventually developed sensory ataxia due to the impairment of deep kinaesthetic sensation during long-term follow-up, although its distribution was restricted. Alternatively, some of the patients with sensory ataxic neuropathy had impairment of superficial sensation with painful dysaesthesias. These overlapping symptoms, observed in these two forms of neuropathy, may also support the hypothesis that these two neuropathies are part of a spectrum of disorders with a similar pathology.

The pathological basis of trigeminal neuropathy is not known. However, isolated sensory deficits along the territory of the trigeminal nerve are characteristic, and motor nerve dysfunction, even trigeminal motor dysfunction, is not present. Furthermore, pure sensory trigeminal neuropathy is occasionally the initial symptom of the sensory ataxic form of neuropathy or can present as one of the subsequent symptoms of sensory ataxic and painful sensory neuropathies. In addition, nature of autonomic symptoms such as pupillary abnormality and orthostatic hypotension, and highly chronic initial progression pattern in trigeminal neuropathy are similarly shared with those in sensory ataxic and painful neuropathy forms. These clinical features would suggest

that trigeminal neuropathy is a cranial nerve version of sensory ganglionopathy, although further evidence is necessary to confirm this hypothesis.

In contrast to sensory ataxic neuropathy, painful sensory neuropathy and trigeminal neuropathy, multiple mononeuropathy and multiple cranial neuropathy often include motor nerve involvement with predominantly acute and subacute onset. Motor nerve involvement can be assessed accurately using the electrophysiological findings in these forms of neuropathy. In some patients with multiple mononeuropathy, evidence of motor nerve denervation on EMG or NCS can be detected. These observations suggest that this form of neuropathy represents a combined sensory and motor neuropathy, rather than an isolated sensory neuropathy. Furthermore, multiple cranial neuropathy and multiple mononeuropathy are not seen in the sensory ataxic and painful sensory forms of neuropathy, suggesting that these neuropathies are distinct from the sensory neuropathies. Vasculitis in the small arteries or arterioles in a sural nerve biopsy were detected in five out of eight patients with multiple mononeuropathy, the frequency of which was significantly higher than those in other forms of sensory neuropathies. Based on these observations, vasculitis and subsequent axonopathy might be the aetiology of multiple mononeuropathy, and possibly of multiple cranial neuropathy.

With respect to the pathological basis of Sjögren's syndrome-associated neuropathy, the autopsy findings of the patient with the sensory ataxic form suggest that there may be a continuous spectrum of pathological processes among the different forms of neuropathy. Sensory and autonomic ganglionitis accompanied by T-cell invasion was present in this patient, while disseminated vasculitis and perivascular T-cell infiltration were also present throughout the peripheral nerve trunks. The patients in whom the ganglionitis process was predominant, as in this autopsied patient, will present with the sensory ataxic form. In contrast, if the vasculitic process in the nerve trunk predominates, the patient would show the features of multiple mononeuropathy, including motor symptoms rather than symptoms of sensory or autonomic ganglionitis. We need further histological studies to confirm these findings, while we may speculate that sensory ganglionopathic lesions would contribute more profoundly to the sensory ataxic, painful sensory and trigeminal neuropathy forms, and vasculitic lesions would result in the multiple mononeuropathy and possibly multiple cranial neuropathy forms.

Neuropathy and other non-sicca symptomatic manifestations of Sjögren's syndrome

The striking feature was that the clinical manifestations of neuropathy preceded the development of sicca syndrome or laboratory findings consistent with Sjögren's syndrome in most patients. Thus, in most patients, neuropathy developed first and then the diagnosis of Sjögren's syndrome was made up to 12 years later, well in agreement with previous studies from our group and other groups (Sobue *et al.*, 1993; Grant *et al.*, 1997; Mori *et al.*, 2001, 2003). This chronological sequence is true for all forms of neuropathy, but is more characteristic in the ganglionitis-related neuropathy forms, such as sensory ataxic and painful sensory neuropathy. Extraneural symptoms, such as pancreatitis and interstitial pneumonia, also can precede the clinical manifestations of Sjögren's syndrome (Garcia-Carrasco *et al.*, 2002). These observations strongly suggest that neural tissues, particularly dorsal root sensory ganglion cells and probably autonomic ganglion cells, are the primary targets in Sjögren's syndrome in addition to the salivary and lacrimal glands (Greenspan *et al.*, 1974), and visceral organs including the pancreas, lung, and thyroid (Swigris *et al.*, 2002).

Antigens primarily responsible for the Sjögren's syndrome, which could be universally present among the target tissues, have been investigated. Whether alpha-fodrin antibody is specific to Sjögren's syndrome or not has been debated (de Seze *et al.*, 2004; Ruffatti *et al.*, 2004), but alpha-fodrin has still been proposed as a candidate antigen (Haneji *et al.*, 1997). We examined anti-alpha-fodrin antibodies in the serum of patients from the present study and found that this antibody is elevated in patients with Sjögren's syndrome-associated neuropathy. However, increases in this antibody were also observed in other types of neuropathy (data not shown) suggesting that this antibody is a candidate marker for Sjögren's syndrome, but its specificity needs to be assessed further. Additional antigens responsible for Sjögren's syndrome that are expressed in all of the target organs need to be identified.

We still do not know why the neuropathic symptoms precede the manifestations of sicca symptoms and other characteristic features in the Sjögren's syndrome-associated neuropathy patients. One possible situation would be that the patients with neuropathic symptoms as the initial symptom would first be referred to a neurology clinic rather than to a rheumatology clinic, while in the case of patients with sicca syndrome they would be referred to a rheumatology clinic. In the case of patients presenting with pancreatitis as the initial symptom, these patients tended to be referred to the gastroenterology clinic rather than to rheumatology clinic. The low prevalence of anti SS-A and SS-B antibodies in our neuropathic patients may also contribute to the earlier occurrence of neuropathies before the diagnosis of Sjögren's syndrome. Taken together, the current diagnostic criteria for Sjögren's syndrome based on the sicca syndrome may need to be re-evaluated.

Autonomic symptoms and the autonomic neuropathy form

Autonomic symptoms are widely present in Sjögren's syndrome-associated neuropathy, particularly in the sensory ataxic, painful sensory and autonomic neuropathy form. Autonomic symptoms may be attributed to a different

pathologic cause, such as autonomic ganglioneuronitis and peripheral autonomic nerve involvement due to direct T-cell attack of the nerves or ischaemia due to vasculitis. The findings from the autopsied patient, including the loss of sympathetic ganglion neurons associated with T-cell invasion, strongly support the view that autonomic ganglion cells are primarily involved, in a fashion similar to the involvement of sensory ganglion cells. In this patient, the segmental distribution of anhidrosis and skin temperature changes corresponded to the segmental variation in the extent of autonomic ganglion cell involvement, also supporting the hypothesis that the primary lesions in autonomic ganglion cells are responsible for autonomic symptoms (Fig. 1). Two of three autonomic neuropathy patients also had sensory ataxia, suggesting that the autonomic ganglionopathy has a similar aetiology as sensory ataxic neuropathy. The presence of Adie's pupils, which is often associated with Sjögren's syndrome-associated neuropathy, is also probably attributable to ciliary ganglion cell involvement (Waterschoot *et al.*, 1991), although further histological assessment is needed. The degree of orthostatic hypotension, anhidrosis, constipation and loss of ^{123}I-MIBG uptake were unexpectedly severe when the autonomic system was involved. Autonomic symptoms in Sjögren's syndrome-associated neuropathy are generally considered mild in their manifestations compared with the sensory symptoms (Wright *et al.*, 1999). Our three patients with autonomic neuropathy were exceptions, since the autonomic symptoms, including bowel dysfunction, were extremely prominent symptoms, suggesting that severe autonomic neuropathy can be present in the spectrum of neuropathies associated with Sjögren's syndrome (Goto *et al.*, 2000; Sakakibara *et al.*, 2004). The present observations suggest that autonomic symptoms are one of the major symptoms in this neuropathy.

Therapeutic approach to Sjögren's syndrome-associated neuropathy

Corticosteroids and immunosuppressants have been employed for the treatment of Sjögren's syndrome, resulting in improvement of non-neuropathic Sjögren's syndrome-associated symptoms, such as sicca syndrome and pneumonitis (Zandbelt *et al.*, 2001; Swigris *et al.*, 2002).

For the therapy of neuropathy associated with Sjögren's syndrome, corticosteroids (Griffin *et al.*, 1990; Noguchi *et al.*, 2003), immunosuppressants (Griffin *et al.*, 1990), plasmapheresis (Chen *et al.*, 2001), D-penicillamine (Asahina *et al.*, 1998), infliximab (Caroyer *et al.*, 2002) and immunoglobulin (Molina *et al.*, 1996; Pascual *et al.*, 1998; Takahashi *et al.*, 2003) administration have been reported anecdotally and suggest a favourable therapeutic response. In the present study, a favourable response to treatment was assessed in an open manner, and both standard corticosteroid and IVIG treatment had similar frequencies of favourable response. Based on the limited number of patients treated, there may be marked differences in the rates of favourable therapeutic response among the neuropathic forms, reflecting major differences in the causes of neuropathy. Corticosteroid therapy is likely a good candidate for multiple mononeuropathy and multiple cranial neuropathy, and favourable improvement may be seen in the painful dysaesthesias of the painful sensory neuropathy and radiculoneuropathy forms with IVIG therapy. Although these symptomatic therapeutic responses were seen in certain patients, overall progression of the neuropathic symptoms as well as of Sjögren's syndrome itself occurred. The findings of this study suggest that IVIG and corticosteroids may be efficacious in treating the neuropathic symptoms of Sjögren's syndrome, although these favourable responses were only seen in certain subpopulations of patients. Randomized controlled studies are needed to assess the efficacy of these treatments for neuropathic symptoms of Sjögren's syndrome.

Acknowledgements

The authors are grateful to Dr Hayashi (Department of Oral Molecular Pathology, The University of Tokushima Graduate School of Dentistry, Japan) for providing us with alpha-fodrin vector, and information on alpha-fodrin. The authors would like to express their deep appreciation to Dr Tsutomu Yanagi (Department of Neurology, Nagoya Daini Red Cross Hospital, Japan), Dr Eiichiro Mukai (Department of Neurology, Nagoya Medical Center, Japan), Drs Kazuhiro Imamura and Yuichi Kawagashira (Department of Neurology, Okazaki City Hospital, Japan), Dr Shigehisa Mitake (Department of Neurology, Tosei General Hospital, Japan), Dr Kenji Mokuno (Department of Neurology, Toyohashi Municipal Hospital, Japan) and Dr Yukihiko Matsuoka (Department of Neurology, Higashi Nagoya Hospital, Japan) for their support in the clinical evaluation of patients and for referring the patients for this study. The authors also are grateful for the expert pathologic technical assistance given by Dr Nozomi Hishikawa and Ms Sugiko Yokoi (Department of Neurology, Nagoya University Graduate School of Medicine, Japan). This study was partly supported by the grants from the Ministry of Health, Labor, and Welfare, Japan.

References

Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjögren's syndrome. Medicine (Baltimore) 1982; 61: 247–57.

Anonymous. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23: 581–90.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315–24.

Asahina M, Kuwabara S, Asahina M, Nakajima M, Hattori T. D-penicillamine treatment for chronic sensory ataxic neuropathy associated with Sjögren's syndrome. Neurology 1998; 51: 1451–3.

Attwood W, Poser CM. Neurologic complications of Sjögren's syndrome. Neurology 1961; 11: 1034–41.

Caroyer JM, Manto MU, Steinfeld SD. Severe sensory neuronopathy responsive to infliximab in primary Sjögren's syndrome. Neurology 2002; 59: 1113–4.

Chen WH, Yeh JH, Chiu HC. Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjögren's syndrome. Eur Neurol 2001; 45: 270–4.

Chu K, Kang DW, Song YW, Yoon BW. Trochlear nerve palsy in Sjögren's syndrome. J Neurol Sci 2000; 177: 157–9.

Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004; 83: 280–91.

Denislic M, Meh D, Popovic M, Kos-Golja M. Small nerve fibre dysfunction in a patient with Sjögren's syndrome. Neurophysiological and morphological confirmation. Scand J Rheumatol 1995; 24: 257–9.

de Seze J, Dubucquoi S, Fauchais AL, Hachulla E, Matthias T, Lefranc D, et al. Autoantibodies against alpha-fodrin in Sjögren's syndrome with neurological manifestations. J Rheumatol 2004; 3: 500–3.

Dyck PJ, Giannini C, Lais A. Pathologic alterations of nerves. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, editors. Peripheral neuropathy. 3rd ed. Philadelphia: WB Saunders; 1993. p. 514–95.

Fujibayashi T, Sugai S, Miyasaka N, Toujou T, Miyawaki S, Ichikawa Y, et al. Revised Japanese diagnostic criteria for Sjögren's syndrome. Annual Report of Research Committee for Immune Disease. Tokyo: Japanese Ministry of Health and Welfare; 1999. p. 135–8.

Garcia-Carrasco M, Ramos-Casals M, Rosas J, Pallares L, Calvo-Alen J, Cervera R, et al. Primary Sjögren's syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002; 81: 270–80.

Gemignani F, Marbini A, Pavesi G, Di Vittorio S, Manganelli P, Cenacchi G, et al. Peripheral neuropathy associated with primary Sjögren's syndrome. J Neurol Neurosurg Psychiatry 1994; 57: 983–6.

Goto H, Matsuo H, Fukudome T, Shibuya N, Ohnishi A, Nakamura H. Chronic autonomic neuropathy in a patient with primary Sjögren's syndrome. J Neurol Neurosurg Psychiatry 2000; 69: 135.

Grant IA, Hunder GG, Homburger HA, Dyck PJ. Peripheral neuropathy associated with sicca complex. Neurology 1997; 48: 855–62.

Greenspan JS, Daniels TE, Talal N, Sylvester RA. The histopathology of Sjögren's syndrome in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol 1974; 37: 217–29.

Griffin JW, Cornblath DR, Alexander E, Campbell J, Low PA, Bird S, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. Ann Neurol 1990; 27: 304–15.

Gross M. Chronic relapsing inflammatory polyneuropathy complicating sicca syndrome. J Neurol Neurosurg Psychiatry 1987; 50: 939–40.

Hamada K, Hirayama M, Watanabe H, Kobayashi R, Ito H, Ieda T, et al. Onset age and severity of motor impairment are associated with reduction of myocardial ^{123}I-MIBG uptake in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003; 74: 423–6.

Haneji N, Nakamura T, Takio K, Yanagi K, Higashiyama H, Saito I, et al. Identification of alpha-fodrin as a candidate autoantigen in primary Sjögren's syndrome. Science 1997; 276: 604–7.

Kachi T, Sobue G, Yamamoto M, Igata A. Sensory conduction study in chronic sensory ataxic neuropathy. J Neurol Neurosurg Psychiatry 1994; 57: 941–4.

Kaltreider HB, Talal N. The neuropathy of Sjögren's syndrome. Trigeminal nerve involvement. Ann Intern Med 1969; 70: 751–62.

Kaplan JG, Rosenberg R, Reinitz E, Buchbinder S, Schaumburg HH. Invited review: peripheral neuropathy in Sjögren's syndrome. Muscle Nerve 1990; 13: 570–9.

Kennett RP, Harding AE. Peripheral neuropathy associated with the sicca syndrome. J Neurol Neurosurg Psychiatry 1986; 49: 90–2.

Kimura J. The blink reflex. In: Kimura J, editor. Electrodiagnosis in diseases of nerve and muscle. Principles and practice. New York: Oxford University Press; 2001. p. 409–38.

Koike H, Mori K, Misu K, Hattori N, Ito H, Hirayama M, et al. Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. Neurology 2001; 56: 1727–32.

Koike H, Misu K, Sugiura M, Iijima M, Mori K, Yamamoto M, et al. Pathology of early- vs late-onset TTR Met30 familial amyloid polyneuropathy. Neurology 2004; 63: 129–38.

Kumazawa K, Sobue G, Yamamoto K, Mitsuma T. Segmental anhidrosis in the spinal dermatomes in Sjögren's syndrome-associated neuropathy. Neurology 1993; 43: 1820–3.

Lafitte C, Amoura Z, Cacoub P, Pradat-Diehl P, Picq C, Salachas F, et al. Neurological complications of primary Sjögren's syndrome. J Neurol 2001; 248: 577–84.

Malinow K, Yannakakis GD, Glusman SM, Edlow DW, Griffin J, Pestronk A, et al. Subacute sensory neuronopathy secondary to dorsal root ganglionitis in primary Sjögren's syndrome. Ann Neurol 1986; 20: 535–7.

Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990; 33: 1094–100.

Mauch E, Volk C, Kratzsch G, Krapf H, Kornhuber HH, Laufen H, et al. Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. Acta Neurol Scand 1994; 89: 31–5.

Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjögren's syndrome. Neurology 1989; 39: 390–4.

Molina JA, Benito-Leon J, Bermejo F, Jimenez-Jimenez FJ, Olivan J. Intravenous immunoglobulin therapy in sensory neuropathy associated with Sjögren's syndrome. J Neurol Neurosurg Psychiatry 1996; 60: 699.

Molina R, Provost TT, Alexander EL. Peripheral inflammatory vascular disease in Sjögren's syndrome. Association with nervous system complications. Arthritis Rheum 1985; 28: 1341–7.

Mori K, Koike H, Misu K, Hattori N, Ichimura M, Sobue G. 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.

Mori K, Iijima M, Sugiura M, Koike H, Hattori N, Ito H, et al. Sjögren's syndrome associated painful sensory neuropathy without sensory ataxia. J Neurol Neurosurg Psychiatry 2003; 74: 1320–2.

Noguchi Y, Tsuchiyama T, Matsumoto T, Fujigasaki H, Inaba A, Yokota T, et al. Two distinct types of neuropathy associated with Sjögren's syndrome developed in one patient. The importance of the selection of an appropriate therapeutic regimen. Rinsho Shinkeigaku 2003; 43: 539–43.

Pascual J, Cid C, Berciano J. High-dose IV immunoglobulin for peripheral neuropathy associated with Sjögren's syndrome. Neurology 1998; 51: 650–1.

Peyronnard JM, Charron L, Beaudet F, Couture F. Vasculitic neuropathy in rheumatoid disease and Sjögren's syndrome. Neurology 1982; 32: 839–45.

Ruffatti A, Ostuni P, Grypiotis P, Botsios C, Tonello M, Grava C, et al. Sensitivity and specificity for primary Sjögren's syndrome of IgA and IgG anti-alpha-fodrin antibodies detected by ELISA. J Rheumatol 2004; 31: 504–7.

Sakakibara R, Hirano S, Asahina M, Sawai S, Nemoto Y, Hiraga A, et al. Primary Sjögren's syndrome presenting with generalized autonomic failure. Eur J Neurol 2004; 11: 635–8.

Sobue G, Hashizume Y, Mukai E, Hirayama M, Mitsuma T, Takahashi A. X-linked recessive bulbospinal neuronopathy. A clinicopathological study. Brain 1989; 112: 209–32.

Sobue G, Yasuda T, Kachi T, Sakakibara T, Mitsuma T. Chronic progressive sensory ataxic neuropathy: clinicopathological features of idiopathic and Sjögren's syndrome-associated cases. J Neurol 1993; 240: 1–7.

Sobue G, Yasuda T, Kumazawa K, Yamamoto K, Mitsuma T. MRI demonstrates dorsal column involvement of the spinal cord in Sjögren's syndrome-associated neuropathy. Neurology 1995; 45: 592–3.

Swigris JJ, Berry GJ, Raffin TA, Kuschner WG. Lymphoid interstitial pneumonia: a narrative review. Chest 2002; 122: 2150–64.

Takahashi Y, Takata T, Hoshino M, Sakurai M, Kanazawa I. Benefit of IVIG for long-standing ataxic sensory neuronopathy with Sjögren's syndrome. IV immunoglobulin. Neurology 2003; 60: 503–5.

Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271–7.

Touze E, Blanche P, Zuber M. A 35-year history of recurrent multiple cranial neuropathy due to primary Sjögren's syndrome. J Neurol 1999; 246: 968–9.

Urban PP, Keilmann A, Teichmann EM, Hopf HC. Sensory neuropathy of the trigeminal, glossopharyngeal, and vagal nerves in Sjögren's syndrome. J Neurol Sci 2001; 186: 59–63.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604–7.

Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, 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.

Watanabe H, Ieda T, Katayama T, Takeda A, Aiba I, Doyu M, et al. Cardiac ^{123}I-meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 70: 781–3.

Waterschoot MP, Guerit JM, Lambert M, de Barsy T. Bilateral tonic pupils and polyneuropathy in Sjögren's syndrome: a common pathophysiological mechanism? Eur Neurol 1991; 31: 114–6.

Wright RA, Grant IA, Low PA. Autonomic neuropathy associated with sicca complex. J Auton Nerv Syst 1999; 75: 70–6.

Yasuda T, Sobue G, Hirose Y, Mimura M, Yanagi T. MR of acute autonomic and sensory neuropathy. AJNR Am J Neuroradiol 1994; 15: 114–5.

Zandbelt MM, van den Hoogen FH, de Wilde PC, van den Berg PJ, Schneider HG, van de Putte LB. Reversibility of histological and immunohistological abnormalities in sublabial salivary gland biopsy specimens following treatment with corticosteroids in Sjogren's syndrome. Ann Rheum Dis 2001; 60: 511–3.

PAPER

Age associated axonal features in HNPP with 17p11.2 deletion in Japan

H Koike, M Hirayama, M Yamamoto, H Ito, N Hattori, F Umehara, K Arimura, S Ikeda, Y Ando, M Nakazato, R Kaji, K Hayasaka, M Nakagawa, S Sakoda, K Matsumura, O Onodera, M Baba, H Yasuda, T Saito, J Kira, K Nakashima, N Oka, G Sobue

J Neurol Neurosurg Psychiatry 2005;**76**:1109–1114. doi: 10.1136/jnnp.2004.048140

See end of article for authors' affiliations

Correspondence to: Dr Gen Sobue, Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466–8550, Japan; sobueg@med.nagoya-u.ac.jp

Received 20 June 2004
Revised version received 28 September 2004
Accepted 18 November 2004

Objective: To clarify age related changes in the clinicopathological features of hereditary neuropathy with liability to pressure palsy (HNPP) in Japanese patients with deletion of 17p11.2, particularly concerning axonal abnormalities.

Methods: Forty eight proband patients from 48 HNPP families were assessed as to clinical, electrophysiological, and histopathological features, including age associated changes beyond those in controls.

Results: Motor conduction studies showed age associated deterioration of compound muscle action potentials in nerves vulnerable to repetitive compression (median, ulnar, and peroneal nerves), but not in others such as the tibial nerve. Sensory conduction studies revealed more profound reduction of action potentials than motor studies with little age related change. Large myelinated fibre loss was seen in the sural nerve irrespective of age at examination.

Conclusions: Irreversible axonal damage may occur at entrapment sites in motor nerves in HNPP patients, progressing with aging. Sensory nerves may show more profound axonal abnormality, but without age association. The electrophysiological features of HNPP are presumed to be a mixture of abnormalities occurring from early in life and acquired features caused by repetitive insults at entrapment sites. Unlike Charcot-Marie-Tooth disease type 1A, age associated axonal damage may not occur unless the nerves are subjected to compression.

Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant disorder characterised by recurrent transient nerve palsies associated with compression at the typical anatomic sites of potential nerve entrapment.[1 2] Tomacula, which represent focal thickening of the myelin sheath, characteristically are seen in both sensory and motor nerves in HNPP.[3–6] This disorder usually is associated with a 1.5 Mb deletion of locus 17p11.2, which contains the gene for peripheral myelin protein 22 (PMP22).[7–9] HNPP therefore appears to represent a reciprocal product of Charcot-Marie-Tooth disease type 1A (CMT1A), which is associated with duplication of PMP22.[10] PMP22 is an important factor for regulation of Schwann cell proliferation and apotosis.[11] As the Schwann cell plays an important role in maintenance of the axon, axonal loss associated with demyelination has been reported to occur in patients with CMT1A.[12–15] Age associated reduction of compound muscle action potential (CMAP) amplitude resulting from large-axon loss has been reported in CMT1A[15] and is closely related to clinical manifestations and functional impairment.[14 15]

In Western countries, the clinical and electrophysiological features of HNPP have been described on a large scale.[16–20] Characteristic electrophysiological findings are multifocal slowing of conduction at sites of entrapment, prolonged distal latency (DL), mild slowing of motor nerve conduction velocity (MCV), and diffuse abnormality of sensory nerve conduction velocity (SCV).[16 18–20] However, there have been no similar large scale investigations of the clinical and electrophysiological features of HNPP in Asian subjects. Furthermore, it has not been clarified whether electrophysiological and histopathological abnormalities, particularly axonal features, worsen with aging in HNPP as happens in CMT1A.

The present investigation was carried out in Japan and we studied HNPP including its electrophysiological and histopathological features, especially in relation to aging.

METHODS

Patients and DNA diagnosis

An HNPP survey was conducted by the study group for hereditary neuropathy in Japan under the auspices of the Ministry of Health, Labor, and Welfare.[15 21] A total of 48 proband patients from 48 HNPP families, whose 17p11.2 deletion was confirmed, were investigated. The mean age (SD) of the patients at examination was 41.8 (18.5) years (table 1). All subjects underwent clinical examination by at least one neurologist. Patients with chronic alcoholism or vitamin deficiency were not included. Four patients manifested mild glucose intolerance. To confirm the diagnosis of HNPP, DNA analyses for the presence of a chromosome 17p11.2–12 deletion, which includes a 1.5 Mb region containing the PMP22 gene between CMT1A-REP repeats, were performed in all patients. For most patients these analyses were performed at the Department of Neurology at Nagoya University Graduate School of Medicine as described previously,[22] while DNA was analysed at other institutions for the rest. The characteristic deletion in HNPP was detected by Southern analysis, probing with PMP22 cDNA, and CMT1A-REP fragments as described previously.[22–24] Hybridisation with PMP22 cDNA and pNEA102, pHK1.0P, and pHK5.2 probes, which map within the CMT1A-REP, was carried out

Abbreviations: CMAP, compound muscle action potential; CMT1A, Charcot-Marie-Tooth disease type 1A; DL, distal latency; HNPP, hereditary neuropathy with liability to pressure palsy; MCV, motor nerve conduction velocity; PMP22, peripheral myelin protein 22; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential

to determine the gene dose of the 1.5 Mb region containing PMP22. Deletion of one copy of the PMP22 gene, compared to the presence of two copies in normal controls, was genetically identified as HNPP. Informed consent was obtained in all patients, and the study as a whole was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

Electrophysiological study

Motor and sensory conduction was measured in the median, ulnar, tibial, peroneal, and sural nerves, using a standard method with surface electrodes for stimulation and recording.[25 26] Motor conduction was investigated in the median, ulnar, tibial, and peroneal nerves, recording from the abductor pollicis brevis, abductor digiti minimi, abductor hallucis brevis, and extensor digitorum brevis muscles, respectively. The following nerve segments were used for calculating MCV: wrist to elbow for the median nerve, wrist to distally at the elbow for the ulnar nerve, ankle to popliteal fossa for the tibial nerve, and ankle to distally at the fibular head for the peroneal nerve. Sensory conduction was investigated in the median, ulnar, and sural nerves, using antidromic recording from ring electrodes at the second and fifth digit for the median and ulnar nerves respectively, and bar electrodes at the ankle for the sural nerve. SCV was calculated for the distal segment. Amplitudes of CMAP and sensory nerve action potential (SNAP) were measured from the baseline to the first negative peak. Waveforms also were analysed to assess temporal dispersion. For motor nerves, we measured duration from the onset to the first crossing of the baseline in the CMAP.[27] For sensory nerves, duration from the onset of the SNAP to the first negative peak rather than to the first crossing of the baseline was measured to avoid artefacts from overlapping muscle action potentials.[25] This was necessary because some motor axons have thresholds similar to those of large myelinated sensory axons, resulting in superimposition on the SNAP that modifies the waveform, especially when abnormal nerves are examined.[28 29] Because of a delay at the neuromuscular junction, the initial phase of the waveform of SNAP is less likely to be affected by muscle action potentials than the later phase.[29]

Control values were obtained in 171 normal volunteers (51.0 (SD 16.3) years of age; male:female, 89:82) for the median nerve, 170 (51.2 (SD 16.4) years of age; male:female, 88:82) for the ulnar nerve, 161 (51.8 (SD 16.6) years of age; male:female, 85:76) for the tibial nerve, 171 (54.2 (SD 16.7) years of age; male:female, 92:79) for the peroneal nerve, and 163 (52.2 (SD 16.7) years of age; male:female, 85:78) for the sural nerve.

Table 1 Characteristics of 48 Japanese HNPP probands with deletion of 17p11.2–12

Clinical features	n (%)
Age at onset, years	33.1 (SD 19.3)
Age at examination, years	41.8 (SD 18.5)
Men/women	38/10
Family history	24 (50%)
Athletic impairment during childhood	1 (2%)
Pes cavus or hammer toe	2 (4%)
Atrophy in the legs	6 (13%)
Pattern of neuropathy	
Multiple mononeuropathy	41 (85%)
Symmetric polyneuropathy	7 (15%)
History of transient nerve palsy	
Median nerve	11 (23%)
Ulnar nerve	18 (38%)
Radial nerve	7 (15%)
Peroneal nerve	29 (60%)
Brachial plexus	10 (21%)
Activity of daily living	
Able to walk	46 (96%)
Unable to walk	2 (4%)
Bedridden	0

Age at onset, age at first awareness of neuropathic symptoms; Family history, obvious family history of recurrent transient nerve palsies.

Histopathological study

Sural nerve biopsy was performed in 14 patients as described previously.[30 31] Informed consent was obtained beforehand. Specimens were divided into two portions. The first portion was fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4) and embedded in epoxy resin for morphometric study. The density of myelinated fibres was assessed in toluidine blue stained semithin sections using a computer assisted image analyser (Luzex FS; Nikon, Tokyo, Japan) to calculate the densities of small and large myelinated fibres as described previously.[32–34] A fraction of the glutaraldehyde fixed sample was processed for a teased fibre study, in which at least 100 single fibres were isolated; their pathologic condition was assessed microscopically according to criteria described previously.[32 35] The second portion of the specimen was fixed in 10% formalin solution and embedded in paraffin. Sections were cut by routine methods and stained with haematoxylin and eosin as well as by the Klüver-Barrera and Masson trichrome methods. Control values were obtained from 13 autopsy cases in which patients died of non-neurologic diseases (48.5 (SD 23.5) years of age; male:female, 7:6). Specimens were processed in the same manner as for HNPP patients.

Statistical analysis

Quantitative data are presented as the mean (SD) and were compared with control values using the Mann-Whitney U test. To determine the relationship of electrophysiological and histopathological indices and age at examination, Pearson's correlation coefficient analysis was carried out. To determine whether worsening of these indices in HNPP patients with aging was significantly greater than in normal controls, regression slopes of patient and control groups were compared. Values of p less than 0.05 were considered to indicate significance.

RESULTS

Clinical features

The age at first awareness of neuropathic symptoms in the 48 probands was 33.1 (SD 19.3) years (table 1). The male:female ratio was 38:10. An obvious family history of recurrent transient nerve palsies was present for 24 patients (50%). Only one patient (2%) reported athletic impairment during childhood. Deformity in the distal part of the lower limbs such as hammer toe or pes cavus was present in two patients (4%). Atrophy was noted in the leg in six patients (13%). The pattern of neuropathic symptoms was multiple mononeuropathy associated with recurrent transient nerve palsies in 41 patients (85%), while the other seven (15%) manifested mainly a symmetric polyneuropathy pattern. A history of transient nerve palsy was noted in the median, ulnar, radial, and peroneal nerves in 11 (23%), 18 (38%), seven (15%), and 29 (60%) patients, respectively. Signs of brachial plexus palsy were reported in 10 (21%). With respect to the activities of daily living, all patients were non-disabled or only mildly disabled, except for two (4%) who became unable to walk.

Electrophysiological features

Motor conduction studies showed variable degrees of abnormality in individual nerves (table 2). For the median nerve, MCV was significantly slowed compared to normal controls ($p<0.0001$). This slowing of MCV was present regardless of age at examination, and there was no

significant difference in regression slopes in the correlation between MCV and age at examination (regression slope −0.073 for HNPP *v* −0.064 for controls). DL was very prolonged (179% of controls) and prolongation tended to worsen as age at examination increased (r = 0.47). The CMAP was reduced to various degrees in most patients and showed further reduction with advancing age (r = −0.67; fig 1). Worsening of both DL and CMAP with age was significantly more prominent than in controls, as evident from comparison of regression slopes ($p<0.0001$ and <0.01, respectively).

For the ulnar nerve, mild to moderate slowing of MCV and prolongation of DL were noted regardless of age at examination, while CMAP decreased with advancing age (r = −0.65). CMAP diminution with aging was significantly worse in patients than in controls (regression slope −0.109 for HNPP *v* −0.021 for controls; $p<0.0001$). For the tibial nerve, slowing of MCV and prolongation of DL also were mild to moderate in most patients of all ages. Reduction of CMAP was also present in all ages examined but, in contrast to other nerves, the relationship of reduction to aging was indistinguishable from that in controls (regression slope −0.062 for HNPP *v* −0.069 for controls). For the peroneal nerve, the age associated decrement in CMAP was significantly greater than in controls ($p<0.05$). Slowing of MCV and prolongation of DL were present in patients of all ages, but no significant worsening with aging was seen in comparison with controls.

As for sensory conduction studies, slowing of conduction velocity was present as in motor nerves. SCV of the median nerve tended to slow with increasing age at examination (r = −0.41). This age associated worsening was significantly greater than in controls ($p<0.05$), while SCV of the ulnar and sural nerves did not show a correlation with age. Reduction of SNAP was conspicuous in the median (24% of control amplitude), ulnar (28%), and sural (42%) nerves. Age associated reduction of SNAP was seen in the median (r = −0.50), ulnar (r = −0.45), and sural (r = −0.37) nerves, but the rate of change was not worse than in controls.

Duration of CMAP and SNAP was prolonged in all nerves examined compared to normal controls, suggesting the presence of temporal dispersion.[27] Compared to controls, significant age associated worsening was seen only in the SNAP of the median nerve ($p<0.0001$).

Histopathological features

Average total myelinated fibre density in patients' sural nerves was mildly, but not significantly, reduced compared to normal controls (7738 (SD 1253) *v* 8561 (SD 1289) fibers/mm^2; table 3). The density of large myelinated fibres was significantly reduced from that in controls (2458 (SD 730) *v* 3258 (SD 736) fibers/mm^2; $p<0.01$) but that of small myelinated fibres was not (5280 (SD 1025) *v* 5302 (SD 655) fibers/mm^2). Axonal sprouting was not conspicuous in any case. Although the density of large myelinated fibres decreased as age at examination increased (r = −0.70), the rate of reduction was indistinguishable from that in controls (regression slope −27.1 for HNPP *v* −26.0 for controls) because large myelinated fibres were reduced even at younger ages. Teased fibre preparations revealed frequent tomacular change (41.5% (SD 15.8%)). The frequency of segmental

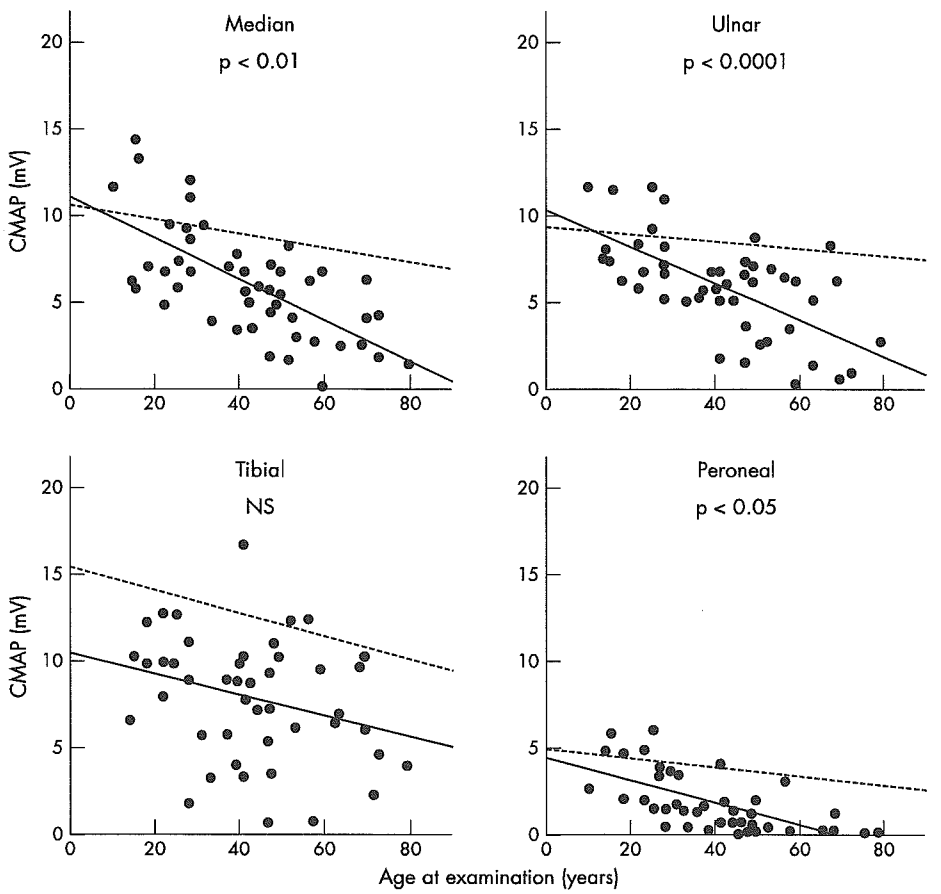

Figure 1 Correlation between CMAP and age at examination in HNPP patients and normal controls. Filled circles represent indices in HNPP patients, bold lines represent regression lines for HNPP patients, and broken lines represent regression lines for normal controls. Comparing regression slopes of normal controls and HNPP patients, CMAP of the median, ulnar, and peroneal nerves, but not the tibial nerve, in HNPP patients were significantly more reduced with increasing age at examination.

Table 2 Nerve conduction studies

	HNPP							Controls		
	Nerve conduction measures				Correlation to aging				Correlation to aging	
	n	Mean (SD)	% of controls	p Values for controls*	r †	Regression slope	p Values for controls‡	Mean (SD)	r †	Regression slope
Motor conduction										
Median nerve										
MCV (m/s)	47	46.0 (5.3)	80	<0.0001	−0.25	−0.073	NS	57.6 (3.8)	−0.27	−0.064
DL (ms)	47	6.1 (1.8)	179	<0.0001	0.47	0.046	<0.0001	3.4 (0.4)	0.19	0.005
CMAP (mV)	48	6.3 (3.2)	77	<0.0001	−0.67	−0.122	<0.01	8.2 (2.9)	−0.24	−0.042
Duration (ms)	32	5.4 (0.8)	115	<0.001	0.13	0.006	NS	4.7 (0.9)	−0.07	−0.004
Ulnar nerve										
MCV (m/s)	47	46.9 (8.3)	81	<0.0001	0.04	0.018	NS	58.0 (4.6)	−0.22	−0.062
DL (ms)	47	3.8 (0.8)	146	<0.0001	0.17	0.009	NS	2.6 (0.3)	0.06	0.001
CMAP (mV)	48	6.0 (3.0)	81	<0.001	−0.65	−0.109	<0.0001	7.4 (1.8)	−0.20	−0.021
Duration (ms)	28	5.9 (1.2)	116	<0.0001	−0.22	−0.016	NS	5.1 (0.7)	−0.01	−0.001
Tibial nerve										
MCV (m/s)	45	39.6 (4.5)	86	<0.0001	−0.02	−0.006	NS	46.0 (3.8)	−0.34	−0.079
DL (ms)	45	5.5 (1.3)	138	<0.0001	0.15	0.011	NS	4.0 (0.6)	0.11	0.004
CMAPs (mV)	45	7.9 (3.7)	67	<0.0001	−0.29	−0.062	NS	11.8 (3.5)	−0.33	−0.069
Duration (ms)	25	5.7 (1.3)	114	<0.01	−0.18	−0.012	NS	5.0 (0.7)	−0.17	−0.008
Peroneal nerve										
MCV (m/s)	38	35.7 (5.7)	76	<0.0001	−0.11	−0.042	NS	47.4 (4.5)	−0.38	−0.101
DL (ms)	38	7.7 (2.3)	167	<0.0001	−0.002	−0.00004	NS	4.6 (1.1)	0.04	0.002
CMAP (mV)	41	1.9 (1.8)	56	<0.0001	−0.65	−0.067	<0.05	3.4 (2.0)	−0.22	−0.027
Duration (ms)	16	6.4 (0.9)	131	<0.0001	−0.09	−0.006	NS	4.9 (0.9)	−0.17	−0.009
Sensory conduction										
Median nerve										
SCV (m/s)	42	38.6 (10.1)	69	<0.0001	−0.41	−0.235	<0.05	56.3 (5.3)	−0.26	−0.085
SNAP (μV)	48	6.8 (6.2)	24	<0.0001	−0.50	−0.178	NS	28.0 (11.5)	−0.45	−0.327
Duration (ms)	26	0.9 (0.4)	150	<0.0001	0.56	0.011	<0.0001	0.6 (0.1)	−0.11	−0.001
Ulnar nerve										
SCV (m/s)	41	36.8 (8.4)	68	<0.0001	−0.13	−0.069	NS	54.5 (5.5)	−0.28	−0.093
SNAP (μV)	48	6.6 (6.4)	28	<0.0001	−0.45	−0.170	NS	23.8 (10.3)	−0.37	−0.240
Duration (ms)	26	0.9 (0.2)	150	<0.0001	0.08	0.001	NS	0.6 (0.1)	−0.05	−0.00004
Sural nerve										
SCV (m/s)	43	36.4 (6.9)	74	<0.0001	−0.13	−0.052	NS	49.2 (4.8)	−0.12	−0.035
SNAP (μV)	48	7.1 (5.9)	42	<0.0001	−0.37	−0.124	NS	16.8 (7.8)	−0.38	−0.177
Duration (ms)	21	0.9 (0.3)	129	<0.05	0.23	0.004	NS	0.7 (0.1)	0.21	0.002

*Mann-Whitney U test; †Pearson's correlation coefficient; ‡regression slopes of HNPP and controls were compared.
Control values were obtained in 171 normal volunteers for the median nerve, 170 for the ulnar nerve, 161 for the tibial nerve, 171 for the peroneal nerve, and 163 for the sural nerve.
CMAP, compound muscle action potential; DL, distal latency; Duration, duration from the onset to the first crossing of the baseline in the CMAP and duration from the onset of the SNAP to the first negative peak; MCV, motor nerve conduction velocity; NS, not significant; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential.

de/re-myelination also was significantly high (25.6% (SD 13.9%), $p<0.001$). Axonal degeneration was slightly increased (3.6% (SD 3.8%)) and was seen even in young patients in contrast to controls.

DISCUSSION

This study demonstrated clinical, electrophysiological, and histopathological features of Japanese HNPP patients with the 17p11.2 deletion. Although recurrent transient nerve palsies are the characteristic feature of this disease, a minority of patients showed a symmetric polyneuropathy pattern, as previously reported.[16–18 36] Electrophysiological features of slowing of conduction velocities and varying degrees of abnormality among individual nerves, agreed well with previous reports of Western populations.[16–20] Slowing of MCV in our series seemed more marked than in previous reports.[16–18 20] The fact that we only examined probands of HNPP families and did not include affected siblings could

Table 3 Histopathological study of the sural nerve

	HNPP (n = 14)					Controls (n = 13)		
			Correlation to aging				Correlation to aging	
	Mean (SD)	p Values for controls*	r †	Regression slope	p Values for controls‡	Mean (SD)	r †	Regression slope
Myelinated fibre density (no./mm²)								
Total	7738 (1253)	NS	−0.45	−29.6	NS	8561 (1289)	−0.73	−39.9
Large	2458 (730)	<0.01	−0.70	−27.1	NS	3258 (736)	−0.83	−26.0
Small	5280 (1025)	NS	−0.05	−2.5	NS	5302 (655)	−0.50	−13.9
Teased fibre study (%)								
Tomacular change	41.5 (15.8)	–	−0.21	−0.18	–	–	–	–
Segmental de/re-myelination	25.6 (13.9)	<0.001	0.39	0.30	NS	6.9 (6.5)	0.82	0.22
Axonal degeneration	3.6 (3.8)	NS	−0.35	−0.07	<0.05	1.6 (1.8)	0.81	0.06

*Mann-Whitney U test; †Pearson's correlation coefficient; ‡regression slopes of HNPP and controls were compared.
NS, not significant.

account for the difference, or greater slowing might be characteristic of Japanese patients. In the peroneal nerve, it seems that the amplitude of CMAP is lower and the distribution of DL is wider than in Western populations even in normal controls.[26] Japanese people usually sit on the floor at home, rather than on chairs, and sometimes sit with their legs folded underneath them. This traditional Japanese sitting position may induce peroneal nerve injury.

A striking finding in our study was a reduction in CMAP with increasing age at examination. This feature was observed in the median, ulnar, and peroneal nerves but not in the tibial nerve. The median nerve passes through the carpal tunnel, predisposing it to entrapment injury, while the ulnar and peroneal nerves are vulnerable to repetitive compression injury at the cubital tunnel and fibular head, respectively, as suggested by the high frequency of episodic palsy of these nerves compared with the tibial nerve. Repetitive movement and nerve stretching at these sites also may contribute to injury. Thus, individual nerve-specific CMAP reduction with increasing age probably resulted from the cumulative effects of repetitive damage; conduction slowing caused by demyelination would be prominent at entrapment sites, as previously reported.[16–18 20] In the present study, demyelination also showed progression over time as demonstrated by age associated prolongation of DL and SCV in the median nerve for conduction through the entrapment site. However, in the ulnar and peroneal nerves, where electrophysiological indices were recorded distally from sites vulnerable to compression, no age associated worsening of MCV, SCV, or DL was observed, suggesting that myelin abnormality distal to the entrapment site does not worsen with advancing age. Thus, CMAP reduction in the median, ulnar, and peroneal nerves would reflect secondary axonal involvement complicating demyelination at the entrapment site. This age associated axonal involvement in a primarily demyelinating condition is similar to that observed in CMT1A with PMP22 duplication.[12 14 15] However, unlike CMT1A, axonal damage may not occur unless the nerves are subjected to compression. PMP22 duplication in Schwann cells results in disturbance of axonal cytoskeletal organisation, resulting in distal axonal degeneration and fibre loss.[13] However, the effect of PMP22 deletion on the axonal cytoskeleton is less severe.[13] PMP22 deletion in itself may not cause progressive axonal involvement associated with aging, though compression induced demyelination may elicit secondary axonal loss because of deficient Schwann cell signalling to the axonal cytoskeleton.[37]

SNAP of the median, ulnar, and sural nerves showed marked reduction even in nerves relatively free from compression and tended to decrease with increasing age at examination. Unlike findings for CMAP, however, rates of reduction with aging did not differ significantly from those in normal controls. Sensory axons may be less susceptible than motor nerves to changes caused by entrapment.

Reduction in CMAP and SNAP may be at least partly attributed to dispersion with phase cancellation as a result of demyelinating change, as suggested by significant prolongation of waveform duration.[27 38] Sural nerve biopsy specimens showed a reduction in large myelinated fibre density irrespective of age, which may indicate a developmental abnormality of axons or a loss of axons relatively early in life. This axonal loss also may contribute to reduction in amplitudes. At any rate, reduction in myelinated fibres of sensory nerves in HNPP patients did not appear to be associated with acquired damage at the entrapment sites. Thus, the electrophysiological features of HNPP are a mixture of abnormalities occurring from an early stage in life and acquired features caused by repetitive insults at entrapment sites. One therapeutic strategy in HNPP patients may be directed toward prevention of axonal damage associated with entrapment.

Authors' affiliations
H Koike, M Hirayama, M Yamamoto, H Ito, N Hattori, G Sobue, Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan
F Umehara, K Arimura, Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Japan
S Ikeda, Third Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan
Y Ando, Department of Laboratory Medicine, Kumamoto University School of Medicine, Kumamoto, Japan
M Nakazato, Third Department of Internal Medicine, Miyazaki Medical College, Miyazaki, Japan
R Kaji, Department of Clinical Neuroscience, University of Tokushima, Tokushima, Japan
K Hayasaka, Department of Pediatrics, Yamagata University School of Medicine, Yamagata, Japan
M Nakagawa, Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto, Japan
S Sakoda, Department of Neurology, Osaka University Graduate School of Medicine, Suita, Japan
K Matsumura, Department of Neurology, Teikyo University School of Medicine, Tokyo, Japan
O Onodera, Department of Neurology, Niigata University School of Medicine, Niigata, Japan
M Baba, Department of Neurology, Hirosaki University School of Medicine, Hirosaki, Japan
H Yasuda, Department of Medicine, Shiga University of Medical Science, Otsu, Japan
T Saito, Department of Rehabilitation, Kitasato University School of Allied Health Sciences, Sagamihara, Japan
J Kira, Department of Neurology, Kyushu University Graduate School of Medicine, Fukuoka, Japan
K Nakashima, Department of Neurology, Tottori University School of Medicine, Yonago, Japan
N Oka, Department of Rehabilitation, National Minami-Kyoto Hospital, Joyo, Japan

This work was supported by grants from the Ministry of Health, Labor, and Welfare of Japan.

Competing interests: none declared

REFERENCES

1 **Davies DM.** Recurrent peripheral nerve palsies in a family. *Lancet* 1954;**267**:266–8.
2 **Earl CJ,** Fullerton PM, Wakefield GS, *et al.* Hereditary neuropathy with liability to pressure palsies: a clinical and electrophysiological study of four families. *Q J Med* 1964;**33**:481–98.
3 **Behse F,** Buchthal F, Carlsen F, *et al.* Hereditary neuropathy with liability to pressure palsies. Electrophysiological and histopathological aspects. *Brain* 1972;**95**:777–94.
4 **Madrid R,** Bradley WG. The pathology of neuropathies with focal thickening of the myelin sheath (tomaculous neuropathy): studies on the formation of the abnormal myelin sheath. *J Neurol Sci* 1975;**25**:415–48.
5 **Oda K,** Miura H, Shibasaki H, *et al.* Hereditary pressure-sensitive neuropathy: demonstration of "tomacula" in motor nerve fibers. *J Neurol Sci* 1990;**98**:139–48.
6 **Sander S,** Ouvrier RA, McLeod JG, *et al.* Clinical syndromes associated with tomacula or myelin swellings in sural nerve biopsies. *J Neurol Neurosurg Psychiatry* 2000;**68**:483–8.
7 **Chance PF,** Alderson MK, Leppig KA, *et al.* DNA deletion associated with hereditary neuropathy with liability to pressure palsies. *Cell* 1993;**72**:143–51.
8 **Mariman EC,** Gabreëls-Festen AA, van Beersum SE, *et al.* Prevalence of the 1.5-Mb 17p deletion in families with hereditary neuropathy with liability to pressure palsies. *Ann Neurol* 1994;**36**:650–5.
9 **Tyson J,** Malcolm S, Thomas PK, *et al.* Deletion of chromosome 17p11.2 in multifocal neuropathies. *Ann Neurol* 1996;**39**:180–6.
10 **Lupski JR,** de Oca-Luna RM, Slaugenhaupt S, *et al.* DNA duplication associated with Charcot-Marie-Tooth disease type 1A. *Cell* 1991;**66**:219–32.
11 **Sancho S,** Young P, Suter U. Regulation of Schwann cell proliferation and apotosis in PMP-deficient mice and mouse models of Charcot-Marie-Tooth disease type 1A. *Brain* 2001;**124**:2177–87.
12 **Dyck PJ,** Karnes JL, Lambert EH. Longitudinal study of neuropathic deficits and nerve conduction abnormalities in hereditary motor and sensory neuropathy type 1. *Neurology* 1989;**39**:1302–8.
13 **Sahenk Z,** Chen L, Mendell JR. Effects of PMP22 duplication and deletions on the axonal cytoskeleton. *Ann Neurol* 1999;**45**:16–24.

14 **Krajewski KM**, Lewis RA, Fuerst DR, *et al.* Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A. *Brain* 2000;**123**:1516–27.
15 **Hattori N**, Yamamoto M, Yoshihara T, *et al.* Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins (PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. *Brain* 2003;**126**:134–51.
16 **Gouider R**, LeGuern E, Gugenheim M, *et al.* Clinical, electrophysiologic, and molecular correlations in 13 families with hereditary neuropathy with liability to pressure palsies and a chromosome 17p11.2 deletion. *Neurology* 1995;**45**:2018–23.
17 **Pareyson D**, Scaioli V, Taroni F, *et al.* Phenotypic heterogeneity in hereditary neuropathy with liability to pressure palsies associated with chromosome 17p11.2–12 deletion. *Neurology* 1996;**46**:1133–7.
18 **Mouton P**, Tardieu S, Gouider R, *et al.* Spectrum of clinical and electrophysiologic features in HNPP patients with the 17p11.2 deletion. *Neurology* 1999;**52**:1440–6.
19 **Andersson P-B**, Yuen E, Parko K, *et al.* Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. *Neurology* 2000;**54**:40–4.
20 **Li J**, Krajewski K, Shy ME, *et al.* Hereditary neuropathy with liability to pressure palsy: the electrophysiology fits the name. *Neurology* 2002;**58**:1769–73.
21 **Koike H**, Misu K, Ikeda S, *et al.* Type I (transthyretin Met30) familial amyloid polyneuropathy in Japan: early- vs late-onset form. *Arch Neurol* 2002;**59**:1771–6.
22 **Yamamoto M**, Yasuda T, Hayasaka K, *et al.* Locations of crossover breakpoints within the CMT1A-REP repeat in Japanese patients with CMT1A and HNPP. *Hum Genet* 1997;**99**:151–4.
23 **Kiyosawa H**, Lensch MW, Chance PF. Analysis of the CMT1A-REP repeat: mapping crossover breakpoints in CMT1A and HNPP. *Hum Mol Genet* 1995;**4**:2327–34.
24 **Yamamoto M**, Keller MP, Yasuda T, *et al.* Clustering of CMT1A duplication breakpoints in a 700 bp interval of the CMT1A-REP repeat. *Hum Mutat* 1998;**11**:109–13.
25 **Kimura J**. Principles and variations of nerve conduction studies. In: Kimura J, ed. *Electrodiagnosis in disease of nerve and muscle: principles and practice*, 3rd ed. New York: Oxford University Press, 2001:91–129.
26 **Kimura J**. Assessment of individual nerves. In: Kimura J, ed. *Electrodiagnosis in disease of nerve and muscle: principles and practice*, 3rd ed. New York: Oxford University Press, 2001:130–77.
27 **Kimura J**, Machida M, Ishida T, *et al.* Relation between size of compound sensory or muscle action potentials, and length of nerve segment. *Neurology* 1986;**36**:647–52.
28 **Gilliatt RW**, Melville ID, Velate AS, *et al.* A study of normal nerve action potentials using an averaging technique (barrier grid storage tube). *J Neurol Neurosurg Psychiatry* 1965;**28**:191–200.
29 **Kimura J**. The carpal tunnel syndrome: localization of conduction abnormalities within the distal segment of the median nerve. *Brain* 1979;**102**:619–35.
30 **Sobue G**, Yasuda T, Mitsuma T, *et al.* Expression of nerve growth factor receptor in human peripheral neuropathies. *Ann Neurol* 1988;**24**:64–72.
31 **Misu K**, Hattori N, Nagamatsu M, *et al.* Late-onset familial amyloid polyneuropathy type I (transthyretin Met 30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan: clinicopathological and genetic features. *Brain* 1999;**122**:1951–62.
32 **Sobue G**, Hashizume Y, Mukai E, *et al.* X-linked recessive bulbospinal neuronopathy, a clinicopathological study. *Brain* 1989;**112**:209–32.
33 **Hattori N**, Ichimura M, Nagamatsu M, *et al.* Clinicopathological features of Churg-Strauss syndrome-associated neuropathy. *Brain* 1999;**122**:427–39.
34 **Koike H**, Iijima M, Sugiura M, *et al.* Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol* 2003;**54**:19–29.
35 **Dyck PJ**, Giannini C, Lais A. Pathologic alterations of nerves. In: Dyck PJ, Thomas PK, Griffin JW, *et al*, eds. *Peripheral neuropathy*, 3rd ed. Philadelphia, PA: WB Saunders, 1993:514–95.
36 **Korn-Lubetzki I**, Argov Z, Raas-Rothschild A, *et al.* Family with inflammatory demyelinating polyneuropathy and the HNPP 17p12 deletion. *Am J Med Genet* 2002;**113**:275–8.
37 **de Waegh SM**, Lee VM, Brady ST. Local modulation of neurofilament phosphorylation, axonal caliber, and slow axonal transport by myelinating Schwann cells. *Cell* 1992;**68**:451–63.
38 **Rhee E**, England J, Summer AJ. A computer simulation of conduction block: effects produced by actual block versus interphase cancellation. *Ann Neurol* 1990;**28**:146–56.

PAPER

Progression and prognosis in pure autonomic failure (PAF): comparison with multiple system atrophy

N Mabuchi, M Hirayama, Y Koike, H Watanabe, H Ito, R Kobayashi, K Hamada, G Sobue

J Neurol Neurosurg Psychiatry 2005;**76**:947–952. doi: 10.1136/jnnp.2004.049023

See end of article for authors' affiliations

Correspondence to: Dr Gen Sobue, Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466–8550, Japan; sobueg@med.nagoya-u.ac.jp

Received 6 July 2004
In revised form 15 October 2004
Accepted 15 October 2004

Objective: To clarify the progression of autonomic symptoms and functional deterioration in pure autonomic failure (PAF), particularly in comparison with multiple system atrophy (MSA).
Methods: The investigation involved eight patients with PAF (M/F = 7/1; mean age at onset, 57 years) and 22 with probable MSA matched for age at onset (M/F = 14/8; onset 56 years). Subjects were followed up for neurological symptoms, activities of daily living, and autonomic function for more than seven years. Autonomic functional tests were carried out.
Results: In PAF, fainting or sudomotor dysfunction occurred first, followed by constipation and syncope. Urinary dysfunction developed late, and respiratory dysfunction was not evident. This clinical course contrasted sharply with that in MSA, where early urinary dysfunction usually proceeded to sudomotor dysfunction or orthostatic hypotension ($p=0.004$), followed by respiratory dysfunction ($p=0.0004$). Results of pharmacological tests also distinguished PAF from MSA. Progression and prognosis in patients with PAF did not worsen, unlike the steady progressive autonomic dysfunction in MSA ($p<0.0001$, $p<0.0001$, $p=0.0009$, and $p=0.003$, for progression to modified Rankin scale grade III, IV, V, and death, respectively).
Conclusions: The time course and pattern of progression of autonomic failure differed significantly between PAF and MSA. Patients with PAF had slower functional deterioration and a better prognosis.

Pure autonomic failure (PAF) is a sporadic idiopathic neurodegenerative disorder characterised by gradually progressive severe autonomic disturbances without other neurological features. In the past, PAF was defined as severe orthostatic hypotension without other neurological deficits, and was referred to as idiopathic orthostatic hypotension. However, this has proved to be a heterogeneous condition, including diseases such as PAF, acute autonomic neuropathy, the early stages of Shy–Drager syndrome, and Parkinson's disease with autonomic failure.[1–6]

Bannister *et al*[7] classified primary autonomic failure into three categories: Parkinson's disease with autonomic failure, multiple system atrophy (MSA), and pure autonomic failure. In 1996, a consensus statement was established concerning PAF,[8] but it has remained uncertain whether the autonomic failure of PAF can readily be distinguished from those of MSA and Parkinson's disease with autonomic failure. In addition, although the clinical course of both MSA and Parkinson's disease with autonomic failure has been described to some extent, details of the natural history of PAF have not been fully assessed because of its rarity and very slow progression.[9–11] Previous reports have noted longer survival in patients with PAF than in those with MSA.[3 12–15] Orthostatic hypotension and anhidrosis/hypohidrosis are the main clinical symptoms in PAF, but their severity, prognosis, and progression have been only incompletely assessed. To clarify the clinical features, particularly the natural course of PAF, we observed eight patients who fulfilled the PAF consensus statement and maintained a follow up for at least five years. We show that their features are distinct from those of another form of primary autonomic failure, MSA.

METHODS

Patients

We examined eight patients with PAF (seven men, one woman; mean (SD) age at onset, 57 (14) years; mean age at first evaluation, 68 (12) years; mean duration from onset to most recent evaluation, 19 (10) years) who were referred to the Nagoya University Hospital or its affiliated hospitals in Aichi prefecture between 1988 and 1997. We evaluated these patients clinically from onset for between seven and 32 years. We reviewed the clinical records preceding our own follow up period, and also obtained information by interviewing the patients and family members.

According to the consensus statement,[8] PAF is characterised by orthostatic hypotension, various other autonomic signs without more widespread neurological involvement, and a low resting supine plasma noradrenaline concentration. The statement acknowledged that some patients would later prove to have other disorders such as MSA,[8] but did not state how long a period of follow up was required to confirm a diagnosis of PAF. Early MSA with predominant autonomic failure is particularly difficult to distinguish from PAF. We estimated that most MSA patients can be diagnosed by follow up for five years or more after onset,[8 16] and we therefore serially examined putative PAF patients for more than five years from onset to exclude those with MSA. We also excluded patients with acute autonomic neuropathy, Parkinson's disease with autonomic failure, and other diseases presenting with autonomic signs by neurological examination, imaging (magnetic resonance imaging and positron emission tomography), and neurophysiological tests.

We also investigated 22 probable MSA patients[17] matched according to age at onset (14 men, eight women; mean age at onset, 56 (8) years; mean age at first autonomic test, 61 (7) years; mean interval from onset, 8 (3) years) who had detailed clinical information particularly concerning autonomic features, and follow up intervals from over five years to 16 years after onset. All patients with MSA presented with autonomic failure as an initial symptom or with predominant autonomic failure at their first clinical visit, and fulfilled the criteria for a probable MSA diagnosis.[17]

Abbreviations: AVP, arginine-vasopressin; HUT, head up tilt test; MSA, multiple system atrophy; PAF, pure autonomic failure

Table 1 Clinical profiles of eight patients with pure autonomic failure at their first visit

Variable	Patient 1	2	3	4	5	6	7	8
Sex	M	M	M	M	M	M	M	F
Onset age (y)	35	68	72	78	50	52	51	50
Time until first evaluation (y)	17	1	10	5	27	7	5	13
Duration of observation (y)	32	7	12	12	32	14	15	29
Hypohidrosis	+	+	+	+	+	+	+	+
Faintness	+	+	+	+	+	+	+	+
Syncope	−	−	−	−	+	+	+	+
Constipation	+	−	−	−	+	−	+	−
Difficulty in urination	−	−	+	−	+	−	−	−
Incontinence/urinary urgency	−	−	−	−	−	+	+	+
Respiratory disturbance	−	−	−	−	−	−	−	−
Plasma noradrenaline (pg/ml) *	30	43	25	83	50	34	14	10
Orthostatic hypotension	+	+	+	+	+	+	+	+
Denervation supersensitivity	+	+	+	+	+	+	+	+
Modified Rankin scale	0	0	0	0	0	0	0	0

*Normal range 150 to 450 pg/ml.
F, female; M, male; y, years.

Procedures

We evaluated all eight patients with PAF and 22 with MSA with a passive multistage head up tilt test (HUT) and a noradrenaline infusion test. The HUT was performed as follows. Blood pressure and heart rate were measured continuously by tonometry (SA-250; Colin, Komaki, Japan). After blood pressure stabilised at the supine stage, changes in blood pressure and heart rate were recorded continuously through 20°, 40°, and 60° head up tilting for five minutes each. Orthostatic hypotension was defined as a fall in systolic blood pressure of more than 30 mm Hg during the 60° head up tilt.[18]

Blood samples were collected at the rested supine stage and after 60° head up tilting from all patients for evaluation of plasma noradrenaline and arginine-vasopressin (AVP). Differences in AVP between after 60° head up tilting and the supine position were calculated as ΔAVP. Additionally, a noradrenaline infusion test was carried out as follows. A very low (0.3 μg/min) or a low (3 μg/min) concentration of noradrenaline was infused intravenously while blood pressure was monitored for changes. If diastolic or systolic blood pressure rose by more than 10 mm Hg or 25 mm Hg, respectively, the patient was considered to have denervation supersensitivity involving the sympathetic nervous system.[19] Four patients were re-evaluated two, five, six, and 11 years later, respectively. We also carried out ^{123}I-metaiodebenzylguanidine (MIBG) scintigraphy and evaluated the heart/mediastinum (H/M) ratio from delayed images, as previously described.[20–22]

We followed up all eight patients and noted the time points when new autonomic symptoms appeared, including hypohidrosis, faintness and syncope, constipation, urinary dysfunction, impotence, and respiratory distress, and considered such clinical features in sequence to assess the natural clinical course. We evaluated hypohidrosis in terms of inspection of the skin and recording of patient symptoms. Dry skin or reduced perspiration was noted on some parts of the body, with compensatory hyperhidrosis elsewhere. Patients often noted their reduced perspiration in summer and felt severe fatigue, which sometimes limited their capacity for outdoor work. Faintness was defined as a floating sensation while in the upright position without loss of consciousness, or as symptomatic orthostatic hypotension during the head up tilt test. Syncope was defined as a blackout or loss of consciousness, including severe blurred vision. Constipation was defined by the passage of stools at intervals of three days or more, or complaints of straining. Urinary dysfunction was defined as urination twice at night or more than five times in the daytime, urinary urgency, incontinence, or difficulty in urination. Impotence was defined as difficulty in achieving normal sexual function. Respiratory disturbances were defined either as the presence of sleep apnoea, including heavy snoring, or as difficulty in respiration. Onset of an autonomic symptom was defined as the time when the patient first noted the symptom.

Statistics

The Mann–Whitney U test for non-parametric statistics was used as appropriate. Kaplan–Meier analyses were employed to estimate the natural course of autonomic features and disease progression, assessed by the modified Rankin scale in both PAF and MSA patients. Log-rank test statistics were used to determine whether the Kaplan–Meier curves differed between PAF and MSA. Calculations were done using the statistical software package Stat View (Abacus Concepts, Berkeley, California, USA). Statistical significance was defined as a probability (p) value of <0.05.

RESULTS

Clinical profiles of PAF on the first visit to the hospitals

Clinical profiles of the eight patients with PAF at their first examination at our hospital are presented in table 1. They had many complaints suggesting autonomic disturbances, but the specific features varied. The earliest age at onset was 35 years, and the latest was 78 years. The interval from onset to presentation at our hospital varied from one to 27 years. Each patient showed various autonomic disturbances at that time, but faintness and hypohidrosis had been experienced by all patients. Other autonomic symptoms were as follows: urinary dysfunction in five, syncope in four, constipation in three, and impotence in two. All patients had very low plasma noradrenaline concentrations, orthostatic hypotension, and denervation supersensitivity according to the noradrenaline infusion test.

Clinical manifestations of MSA

The initial symptoms in all 22 patients with MSA were those of autonomic failure. Median time from onset to the presence of concomitant autonomic and motor manifestations (evolution from onset to probable MSA) was 2.0 years (range 1 to 10). At the first clinical visit, seven of the 22 patients presented with severe autonomic failure but failed to fulfil consensus diagnostic criteria of MSA.

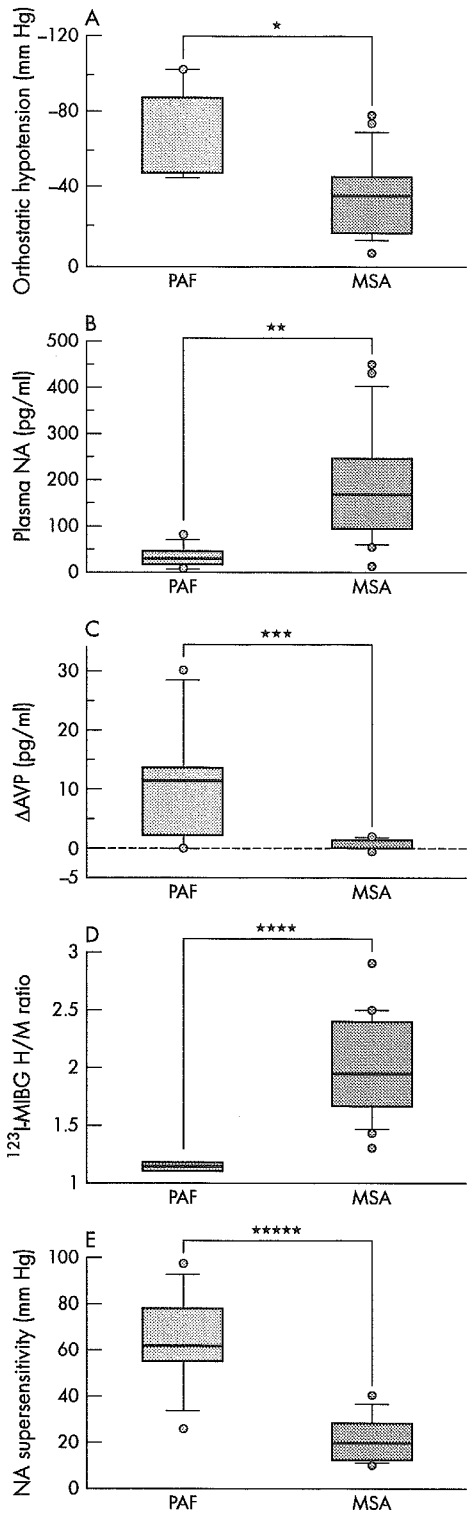

Figure 1 Box and whisker plot of the autonomic nervous testing comparing pure autonomic failure (PAF) with multiple system atrophy (MSA). (A) Systolic blood pressure fall during orthostatic hypotension. (B) Plasma noradrenaline (NA) concentration. (C) Differences in arginine-vasopressin (AVP) concentration between 60° head up tilt and supine posture calculated as ΔAVP. (D) Heart/mediastinum (H/M) ratio from ^{123}I-metaiodobenzylguanidine (MIBG) delayed imaging. (E) Systolic blood pressure increase during noradrenaline infusion test. *p=0.004, **p=0.0003, ***p=0.003, ****p=0.002, *****p=0.0004, Mann–Whitney U test.

Autonomic nervous system testing in PAF and MSA

We found significant differences between PAF and MSA patients with respect to the following:

- *orthostatic hypotension* evaluated by the head up tilt test (mean (SD): PAF, 68.9 (22.5) mm Hg; MSA, 36.3 (20.4) mm Hg; p = 0.004 (fig 1A);
- *noradrenaline concentration*: PAF, 36.1 (23.2) pg/ml; MSA, 189.9 (121.9) pg/ml; p = 0.0003 (fig 1B);
- *ΔAVP*: PAF, (10.7) pg/ml; MSA, 0.34 (0.62) pg/ml; p = 0.003 (fig 1C);
- *H/M ratio*: PAF, 1.15 (0.05); MSA, 2.04 (0.44); p = 0.002 (fig 1D);
- *noradrenaline infusion test*: PAF, 70.1 (23.2) mm Hg; MSA, 23.7 (11.0) mm Hg; p = 0.0004 (fig 1E).

Clinical course of autonomic failure

Kaplan–Meier curves depicting the natural clinical course of PAF and MSA are shown in fig 2. Hypohidrosis, faintness and syncope, constipation, urinary dysfunction, and respiratory disturbance were assessed sequentially.

Hypohidrosis

Six patients noted hypohidrosis or anhidrosis as an initial symptom, and seven became aware of hypohidrosis within five years of onset. Hypohidrosis was one of the earliest and most important symptoms of patients with PAF. In contrast, patients with MSA noted hypohidrosis at a significantly later stage of disease (p = 0.027).

Faintness and syncope

These symptoms represented orthostatic hypotension. Usually faintness preceded syncope. Faintness was often noted as an initial autonomic symptom in PAF. Four of eight patients first noted hypohidrosis in the same year as they first experienced faintness. In our series, five patients complained of faintness as an initial symptom, and seven noted faintness within five years of onset. Syncope appeared at (mean (SD)) 6 (7) years after the onset of faintness, and half the patients had experienced syncope within five years. However, two patients first noted syncope more than 19 years after experiencing faintness. In patients with MSA, faintness was observed later in the course of illness, with risk of progression to syncope differing significantly between the two groups (p = 0.002).

Constipation

Constipation was among the early symptoms of PAF. In our series, three patients noted constipation as an initial symptom, and five noted constipation within five years of onset; all patients complained of constipation within 13 years. Constipation was the second earliest symptom in our PAF patients, while patients with MSA also complained of constipation at a relatively early stage of disease. No significant differences were seen between the two groups in time from onset of first symptom to development of constipation (p = 0.46).

Urinary dysfunction

In the early stages few PAF patients noted urinary dysfunction, while at a later stage most patients had this complaint. In our series, urinary dysfunction appeared at (mean (SD)) 9 (9) years after the onset of hypohidrosis, faintness, and constipation. Only three patients noted urinary urgency, urinary frequency, or incontinence in the first five years. Among types of urinary dysfunction, difficulty in urination was rare in PAF patients. We evaluated the results of urodynamic studies in five of the eight PAF patients, at four,

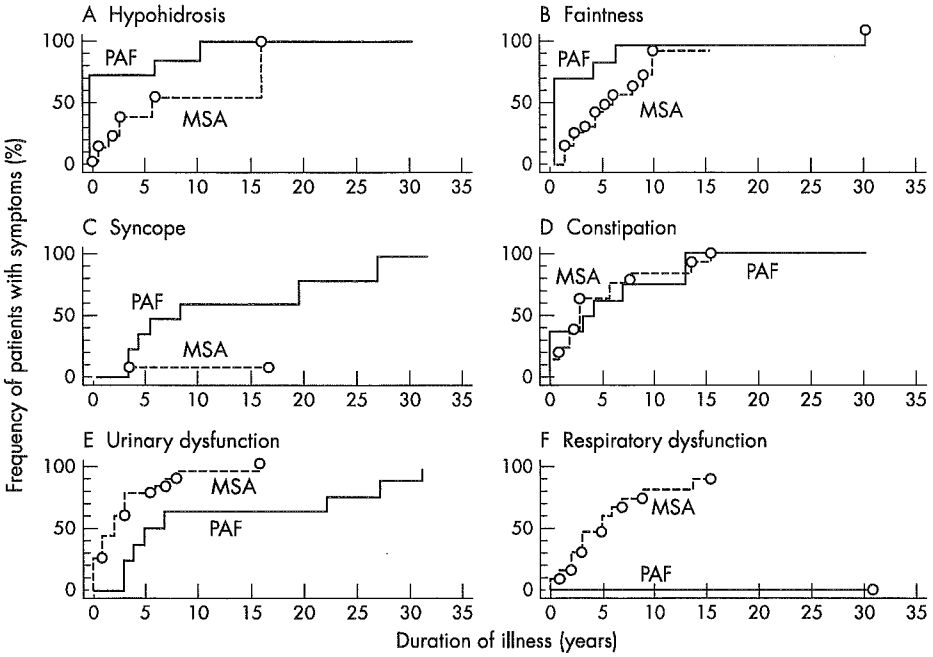

Figure 2 Progression of autonomic symptoms including hypohidrosis (A), faintness (B), syncope (C), constipation (D), urinary dysfunction (E), and respiratory disturbance (F) in patients with pure autonomic failure (PAF) and multiple system atrophy (MSA). Hypohidrosis was an earlier symptom in PAF than in MSA (panel A, $p=0.027$). Faintness and syncope were earlier symptoms in PAF than in MSA (panel B, $p=0.04$; panel C, $p=0.002$). Development of constipation was similar between the two diseases (panel D). Urinary dysfunction was a later symptom in PAF than in MSA (panel E, $p=0.004$). Respiratory disturbance did not occur in our PAF patients, but MSA patients had these problems at an early stage (panel F, $p=0.0004$).

six, 10, 13, and 17 years after the onset of PAF, respectively. Two of the five patients were essentially asymptomatic and had normal study results. Three patients were symptomatic, one of whom had an overactive bladder and the other an underactive bladder; the third had normal results. In our series, all eight patients had urinary dysfunction by 30 years after onset. Thus urinary dysfunction typically emerged in late stage PAF. In contrast, MSA patients developed urinary dysfunction at a very early stage of their disease ($p = 0.004$), often as an initial autonomic symptom in about a quarter of the patients. Within five years, more than 75% of MSA patients had urinary dysfunction, especially difficulty in urination. Thus urinary symptoms occurred early and were particularly prominent in MSA.

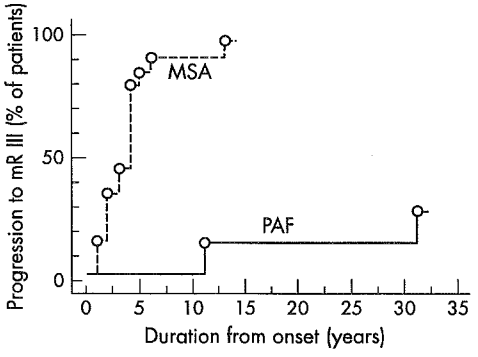

Figure 3 Differences in time remaining independent in activities of daily living (ADL) assessed by the modified Rankin scale between patients with pure autonomic failure (PAF) and multiple system atrophy (MSA). Round symbols represent censored data. Significant differences were seen between PAF and MSA for three ADL milestones and for survival, by Kaplan–Meier analysis and log-rank tests. mR III, modified Rankin scale, grade III (moderate impairment requiring minimal support such as a cane, stair rails, and so on): difference between PAF and MSA significant at $p<0.0001$.

Respiratory disturbances

Respiratory disturbances such as sleep apnoea were uncommon in patients with PAF. Indeed, in our series, no patient had respiratory difficulties in 30 years of follow up. In contrast, respiratory disturbance was one of the most important features in patients with MSA ($p = 0.0004$). About half the MSA patients had this complaint within five years, and subsequently the prevalence of respiratory disturbances increased. More than 80% of the MSA patients had respiratory disturbances by 10 years.

Progression of orthostatic hypotension and noradrenaline supersensitivity

Orthostatic hypotension

Orthostatic hypotension (fig 1A) was a major clinical feature in PAF, being marked even in the early stages of the disease. Blood pressure fall varied from 34 to 108 mm Hg at presentation to our hospital, and the extent of orthostatic hypotension progressed markedly in most patients over the next two to 11 years. In seven patients blood pressure fell by more than 50 mm Hg, and most patients experienced syncope.

Noradrenaline supersensitivity

The noradrenaline infusion test estimates denervation supersensitivity at peripheral noradrenaline receptors, suggesting disease involvement of the peripheral sympathetic nervous system. At an early stage, PAF patients all showed excessive rises in blood pressure of 30 mm Hg or more with infusion of a low concentration of noradrenaline (3 or 0.3 μg/min), indicating the presence of denervation supersensitivity (fig 1E). After two to 11 years, however, the extent of blood pressure rise in response to noradrenaline infusion was smaller than at an early stage, suggesting emergence of some compensatory mechanism or secondarily induced insensitivity of noradrenaline receptors.

Activities of daily living and prognosis

PAF patients did not show diminishing capacity for activities of daily living (ADL) up to a late stage (fig 3). In our series three patients died, but they maintained nearly normal ADL throughout their lives. One patient who died at 90 years, 12 years after disease onset, could walk alone without assistive devices until he was 89 years old (modified Rankin scale, 0 to1); rapid deterioration in the last year of life resulted from a subdural haematoma. Another patient who died at 82 years, 32 years after onset, could perform all his daily activities unassisted until he was 81. He was essentially bedridden for the last year of life because of myelodysplastic syndrome. The third patient, who died aged 84 years 12 years after disease onset, remaining healthy and active (modified Rankin scale 0 to 1) until he died suddenly of a severe stroke.

Although both MSA patients and PAF patients have severe autonomic disturbances, functional and survival prognoses[16] were significantly worse in MSA than in PAF. In our series, median time from onset to modified Rankin scale grade III in MSA was four years ($p<0.0001$ *v* PAF); grade IV, seven years ($p = 0.0009$); grade V, nine years ($p<0.0001$); and death, 11 years ($p = 0.003$). In contrast to MSA, PAF carried a relatively good prognosis for function and survival.

DISCUSSION

PAF is a chronic progressive neurodegenerative disease characterised by severe autonomic failure without other neurological deficits. Uniquely, PAF patients can maintain a long healthy life, in contrast to patients with other types of primary autonomic failure. Pathological reports of PAF have described Lewy bodies in the intermediolateral grey columns of the thoracolumbar spinal cord, suggesting that PAF is a form of Lewy body disease.[23–30]

Our study is the first assessment of long term progression of autonomic symptoms and ADL status in PAF, particularly in comparison with MSA. Although a consensus has been reached over the diagnostic criteria for PAF,[8] long term follow up observation of the clinical features is important to identify the differences between PAF and autonomic failure in other neurodegenerative diseases, particularly MSA and Parkinson's disease with autonomic failure.[7 8 12] We investigated clinical features of eight patients with PAF over follow up periods ranging from seven to 32 years.

It is generally accepted that patients with PAF have autonomic failure resulting in peripheral but not central involvement. The results of supine noradrenaline levels, ΔAVP, ^{123}I-MIBG, and the noradrenaline infusion test clearly confirm this. In contrast, patients with MSA have patterns suggesting a predominantly central involvement, although some patients with probable MSA also have low noradrenaline concentrations, increased ΔAVP, a reduced H/M ratio, and raised blood pressure during the noradrenaline infusion test. These neuropharmacological tests would be useful for differentiating PAF from MSA early in the course of the illness. Further studies are needed to clarify their sensitivity, specificity, and positive predictive value.

In our study, orthostatic hypotension and related faintness and syncope were the most important clinical features of PAF, and developed at a very early stage. Furthermore, orthostatic hypotension worsened gradually as the disease progressed in spite of medical treatment for hypotension. In contrast, MSA patients were less likely to have syncope than PAF patients. Progression of MSA is relatively rapid,[16] so MSA patients are often wheelchair bound or nearly bedridden before showing severe hypotension with syncope.[16] About half the patients with MSA noted faintness by four years after onset, at a time when most of them were wheelchair bound and spent a considerable amount of their waking time lying down. This may limit the exposure of MSA patients to syncope.

Another important autonomic abnormality observed in PAF was sudomotor impairment. Hypohidrosis or anhidrosis was a major complaint in patients with PAF. Emergence of orthostatic hypotension, sometimes with loss of consciousness, and sudomotor dysfunction at a very early stage were striking characteristic features in PAF, in contrast to MSA where these symptoms were absent in the early phase of the disease.

A striking clinical characteristic of PAF was the absence of respiratory dysfunction such as sleep apnoea until a very late phase of disease. This feature again contrasted with MSA, where respiratory dysfunction was a major problem, threatening life in the later phase of disease.

Constipation and urinary dysfunction are among the characteristic symptoms of primary autonomic failure syndrome including PAF, MSA, and Parkinson's disease with autonomic failure.[30 31] Urinary problems have been documented in the past to some extent,[9 11 12] representing a characteristic feature of PAF, especially in the late phase. Sakakibara *et al*[32] reported that all six of their patients with PAF who complained of urinary disturbances showed abnormalities on urodynamic studies. In our series, five of eight patients underwent urodynamic evaluation, and two with urinary symptoms showed a hyperactive or underactive bladder. However, the severity of the urodynamic abnormalities and associated symptoms was mild, in agreement with the previous report.[32] In contrast, patients with MSA have severe urinary dysfunction, especially difficulty in urination[33] and nocturnal urinary frequency, with residual urine, detrusor hyperreflexia, low compliance, and detrusor sphincter dyssynergy on urodynamic studies. Intermittent self catheterisation is often required even early in the course of the illness.

On the basis of these observations, we can assume that orthostatic hypotension and sudomotor dysfunction precede urinary dysfunction and particularly respiratory dysfunction in the development of autonomic disturbances in PAF, while in MSA urinary dysfunction precedes orthostatic hypotension and sudomotor dysfunction, and respiratory dysfunction is a serious problem even at an early stage. Modes of progression of autonomic symptoms seem to be an important way of distinguishing between PAF and MSA.

The evolution of the change in blood pressure during the noradrenaline infusion test in PAF is difficult to explain. While the clinical features became worse over the course of several years in PAF patients, in contrast the degree of blood pressure elevation during the test became smaller with time. The same method was used for the test on each occasion, and no previous reports provide an explanation for this phenomenon. Age related changes such as atherosclerosis or changes in drug treatment might have contributed, but further study is necessary.

Patients with PAF had a better prognosis than those with MSA. Even the three patients with PAF who died during follow up lived independently until one or two years before they died all died of concurrent diseases. Various factors contributed to this advantage in ADL and long term prognosis. First, patients with PAF did not have severe urinary disturbances, which would lessen the risk of recurrent urinary infections, and they also did not have life threatening respiratory failure. Second, while management of orthostatic hypotension remains challenging late in the course of illness, administration of plasma volume expansion fluids, fludrocortisone, and sympathomimetic agents can be effective in ameliorating symptoms and preventing faintness and syncope with resulting head injuries or bone fractures which could compromise ADL and survival. Third, patients

with PAF in this study showed no motor or cognitive impairment. No parkinsonism or dementia, which would have affected daily activities or required additional treatment, was evident during the course of their illness. Further studies are needed to evaluate the significance of the pathological background for temporal features of autonomic, motor, and cognitive involvements.

The precise epidemiology of PAF has not been assessed, either in Japan or in Western countries. To our knowledge, relatively few cases of PAF have been studied or described, and necropsy reports are far less common than for MSA. In our Japanese series, more than 200 patients with MSA were referred to hospital during the course of the study, but only eight patients with PAF were diagnosed during the same period. Although physician referral patterns may have on influence, PAF appears to be uncommon in Japan compared with MSA. Further studies should be undertaken to clarify the incidence and prevalence of PAF worldwide.

Authors' affiliations

N Mabuchi, M Hirayama, H Watanabe, H Ito, K Hamada, G Sobue, Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan
Y Koike, Department of Health Science, Nagoya University Graduate School of Medicine
R Kobayashi, Department of Neurology, National Nagoya Hospital

Competing interests: none declared

REFERENCES

1 **Rosecan M**, Glaser RJ, Goldman ML. Orthostatic hypotension, anhidrosis, and impotence. *Circulation* 1952;**6**:30–40.
2 **Drenick EJ**. Orthostatic hypotension in the presence of hypertensive cardiovascular disease. *Ann Intern Med* 1957;**47**:124–31.
3 **Roessmann U**, van der Noort S, McFarland DE. Idiopathic orthostatic hypotension. *Arch Neurol* 1971;**24**:503–10.
4 **Ochiai J**, Kobayashi T, Gotou I, *et al*. Clinical study of two cases of "pure progressive autonomic failure". *Shinkei Naika* 1986;**24**:297–9.
5 **Tsuboi K**, Nakano K, Tokuhisa H, *et al*. A case of slowly progressive idiopathic orthostatic hypotension. *Junkan Naika* 1983;**3**:1078–86.
6 **Bradbury S**, Eggleston C. Postural hypotension. A report of three cases. *Am Heart J* 1925;**1**:73–86.
7 **Bannister R**, Mathias C, Polinsky R. Autonomic failure. In: *A textbook of clinical disorders of the autonomic nervous system*, 2nd ed. Oxford: Oxford University Press, 1988:267–88.
8 **Consensus committee**. The 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.
9 **Tamura N**, Shimazu K, Yamamoto T, *et al*. Clinical features and nosology of pure autonomic failure. *Jiritsu Sinkei* 1995;**32**:435–42.
10 **Akimitsu T**, Maeda T, Hara M, *et al*. Pure progressive autonomic failure presenting severe orthostatic hypotension. *Intern Med* 1993;**32**:122–7.
11 **Asahina M**, Hattori T. Pure autonomic failure: differential diagnosis and limitations of treatment. *Shinkei Naika* 2002;**57**:29–34.
12 **Davidson C**, Morgan DB. Long survival in orthostatic hypotension. Case report and a review of the literature. *J Chron Dis* 1976;**29**:733–42.
13 **Brigden W**. Postural hypotension. *Br Heart J* 1946;**8**:103–9.
14 **Kaufmann H**. Primary autonomic failure: Three clinical presentation of one disease? *Ann Intern Med* 2000;**133**:382–3.
15 **Bannister R**, Mathias CJ. Autonomic failure. In: *A textbook of clinical disorders of the autonomic nervous system*, 4th ed. Oxford: Oxford University Press, 1999:307–16.
16 **Watanabe H**, Saito Y, Terao S, *et al*. Progression and prognosis in multiple system atrophy. An analysis of 230 Japanese patients. *Brain* 2002;**125**:1070–83.
17 **Gilman S**, Low PA, Quinn N, *et al*. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999;**163**:94–8.
18 **Hirayama M**, Koike Y. Physiological test for autonomic nervous system. *Nippon Rinsho* 1997;**714**:487–90.
19 **Hirayama M**, Koike Y. Pharmacological test for autonomic nervous system. *Nippon Rinsho* 1997;**714**:491–5.
20 **Watanabe H**, Ieda T, Katayama T, *et al*. Cardiac ^{123}I-meta-iodebenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001;**70**:781–3.
21 **Hamada K**, Hirayama M, Watanabe H, *et al*. Onset age and severity of motor impairment are associated with reduction of myocardial ^{123}I MIBG uptake in Parkinson's disease. *J Neurol Neurosug Psychiatry* 2002;**74**:423–6.
22 **Hirayama M**, Hakusui S, Koike Y, *et al*. A scintigraphical qualitative analysis of peripheral vascular sympathetic function with meta-[^{123}I]iodobenzylguanidine in neurological patients with autonomic failure. *J Auton Nerv Syst* 1995;**53**:230–4.
23 **van Ingelghem E**, van Zandijcke M, Lammens M, *et al*. Pure autonomic failure: a new case with clinical, biochemical, and necropsy data. *J Neurol Neurosurg Psychiatry* 1994;**57**:745–7.
24 **Hague K**, Lento P, Morgello S, *et al*. The distribution of Lewy bodies in pure autonomic failure: autopsy findings and review of the literatures. *Acta Neuropathol (Berl)* 1997;**94**:192–6.
25 **Hishikawa N**, Hashizume Y, Hirayama M, *et al*. Brainstem-type Lewy body disease presenting with progressive autonomic failure and lethargy. *Clin Auton Res* 2000;**10**:139–43.
26 **Arai K**, Kato N, Kashiwado K, *et al*. Pure autonomic failure in association with human α-synucleinopathy. *Neurosci Lett* 2000;**296**:171–3.
27 **Miura H**, Tsuchiya K, Kubodera T, *et al*. An autopsy case of pure autonomic failure with pathological features of Parkinson's disease. *Rinsho Shinkeigaku* 2001;**41**:40–4.
28 **Johnson RH**, Lee de JG, Oppenheimer DR, *et al*. Autonomic failure with orthostatic hypotension due to intermediolateral column degeneration. *Q J Med* 1965;**138**:276–9.
29 **Terao Y**, Takeda K, Sakuta M, *et al*. Pure progressive failure: a clinicopathological study. *Eur Neurol* 1993;**33**:409–15.
30 **Noda K**, Katayama S, Watanabe C, *et al*. Pure autonomic failure with motor neuron disease: Report of a clinical study and postmortem examination of a patient. *J Neurol Neurosug Psychiatry* 1994;**57**:745–7.
31 **Niimi Y**, Ieda T, Hirayama M, *et al*. Clinical and physiological characteristics of autonomic failure with Parkinson's disease. *Clin Auton Res* 1999;**9**:139–44.
32 **Sakakibara R**, Hattori T, Uchiyama T, *et al*. Micturitional disturbance in pure autonomic failure. *Neurology* 2000;**54**:499–501.
33 **Sakakibara R**, Hattori T, Uchiyama T, *et al*. Urinary dysfunction and orthostatic hypertension in multiple system atrophy: which is the more common and earlier manifestation? *J Neurol Neurosurg Psychiatry* 2000;**68**:65–9.