are no more consistent with depolarization (which invariably increases refractoriness) than with hyperpolarization.

Comparison with other chronic demyelinating neuropathies

The results of the axonal excitability measures in the present study are different from those previously described in acquired demyelinating neuropathies, namely CIDP, multifocal motor neuropathy and Guillain–Barré syndrome, as described in the Introduction. Interestingly, a more recent study has found that a subset of CIDP patients, corresponding to those with a diffuse pattern of demyelination, exhibit features rather similar to those in CMT1A, namely increased thresholds, early fanning-out of TE, with increased activity of inward rectification on hyperpolarization (Sung *et al.*, 2004). There may be a contribution from endoneurial inflammation to the findings in these demyelinating neuropathies (Redford *et al.*, 1997), but it is unlikely that this plays a major role in CMT1A. It remains to be determined whether there are any consistent differences between the abnormal excitability properties in CMT1A and CIDP that could relate to the different aetiologies of demyelination.

Decreased nerve conduction velocity in CMT1A

Many factors may contribute to the decreased nerve conduction velocities typically seen in CMT1A, including axon diameter, myelin thickness and internodal distance. Recently, a few molecules, such as contactin, have been shown to play an important role in segregating nodes and juxtaparanodes and in anchoring Schwann cells to paranodes (Boyle *et al.*, 2001). The disruption of the paranodal junction alone in contactin mutant mice may account for the impaired conduction velocity (Boyle *et al.*, 2001). The disruption of the paranode is expected to reduce R_{II} (Fig. 6A), with consequent effects on excitability parameters, as found in CMT1A, as well as on conduction velocities (Boyle *et al.*, 2001; Kaji, 2003). An alternative explanation for the reduction in velocity is decreased Na^+ channel function (e.g. decreased density) (Kazarinova-Noyes *et al.*, 2001). However, our results did not support abnormal Na^+ channel function, as strength–duration time constant, a sensitive measure of persistent Na^+ current at the node, showed no significant change.

In summary, our data indicate that CMT1A patients exhibit a consistent pattern of abnormal nerve excitability properties. This pattern indicates increased access of applied currents to the internodal compartment of the axon and increased activation of fast K^+ channels. This is the first time that abnormal excitability properties have been found in a neuropathy that are logically attributable to altered myelination, and which may therefore aid the interpretation of excitability abnormalities in other conditions. However, the resemblance of the TE recordings to those in immature rats raises the possibility that the changes are related more specifically to nodal dysmaturity, and may differ in some respects from those in other demyelinating neuropathies.

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LETTERS

An unusual phenotype of McLeod syndrome with late onset axonal neuropathy

McLeod syndrome is a rare multisystem disorder defined by weak expression of the Kell glycoprotein antigens and the absence of a red blood cell surface antigen, Kx.[1 2] The gene responsible for McLeod syndrome, *XK*, was cloned in 1994.[1] The XK protein contains the Kx antigen missing in patients with McLeod syndrome. Mutation analysis of the *XK* gene has shown different deletions or point mutations in families with this condition.[2 3]

Clinical features of McLeod syndrome are reported to be heterogeneous.[2 4 5] Clinical manifestations include acanthocytosis, an increased level of serum creatine kinase (CK), progressive muscular atrophy, seizures, and involuntary movement. As the symptoms and signs of this syndrome seem to be variable even among siblings, it is sometimes difficult to distinguish the condition from other neuromuscular disorders by clinical features and conventional examination.

We report here two cases of McLeod syndrome in brothers and emphasise the variable features of the disease. Phenotypic variability was obvious in the two patients, and one case was unusual because the clinical features greatly resembled an axonal form of Charcot-Marie-Tooth disease.

Case reports

Case 1

A 50 year old man had been complaining of weakness and paraesthesiae in both legs. He first noted weakness in the right leg at the age of 37. Subsequently, the symptom extended to both legs, and he began to be unsteady on his feet. At age 47, he noticed muscular atrophy in his legs. There was no consanguinity in the family. A neurological examination in August 2000 revealed sensorimotor neuropathy with severe weakness and atrophy in both calves and shins (fig 1A). Deep tendon reflexes were diminished in the lower limbs. The ability to sense pinprick and light touch was mildly impaired in the distal parts of the lower extremities. Vibration sense was impaired in both feet. Abnormal involuntary movement was not seen.

Laboratory investigations were unremarkable except for a raised serum CK concentration (1510 IU/l, normal <255). Serum levels of thyroid hormones, vitamin B-12, vitamin E, antinuclear antibody, anti-DNA antibody, and anti-SS-A/SS-B antibodies were normal. In nerve conduction studies, neither compound motor action potentials (CMAP) nor sensory nerve action potentials (SNAP) were elicited in the patient's lower extremities.

Histopathological features of a sural nerve biopsy specimen showed moderate myelinated fibre loss and abundant axonal sprouting in residual myelinated fibres (fig 1B), while onion bulb formation was absent. No apparent amyloid deposits or inflammatory cell infiltrates were seen in the epineurial and endoneurial tissues. An axonal form of Charcot-Marie-Tooth disease was strongly suspected from the clinical features and pathological findings. Although mutation analysis available for the peripheral myelin protein zero and connexin-32 was done, no mutation was detectable in these genes.

Case 2

A 62 year old man, an elder brother of case 1, was admitted for evaluation of a progressive movement disorder in December 2001. On neurological examination, he had choreic involuntary movement of the extremities, mild weakness in the thighs, and hyporeflexia in all limbs. Pathological reflexes were not elicited, and he showed no sensory disturbance. No personality change or cognitive impairment was seen.

A peripheral blood smear showed acanthocytes in 4% of the red blood cells by May-Giemsa staining. Serum CK was raised to 1710 U/l, with predominant MM isozyme. Brain magnetic resonance imaging showed mild atrophy of the bilateral frontal lobes and caudate nuclei (fig 1C). Nerve conduction studies of the lower limbs suggested mild sensory neuropathy, showing reduced SNAP in the sural nerves (left 2.3 μV, right 3.6 μV).

A muscle biopsy specimen taken from the left biceps brachii showed increased variability in fibre diameter. The most striking findings were some scattered necrotic fibres, several basophilic fibres, and an increased number of central nuclei (fig 1D).

An evaluation of Kell antigen expression was subsequently undertaken. Expression of Kell antigens (K2, K4, and K7) on red blood cells was reduced, a result consistent with McLeod syndrome.

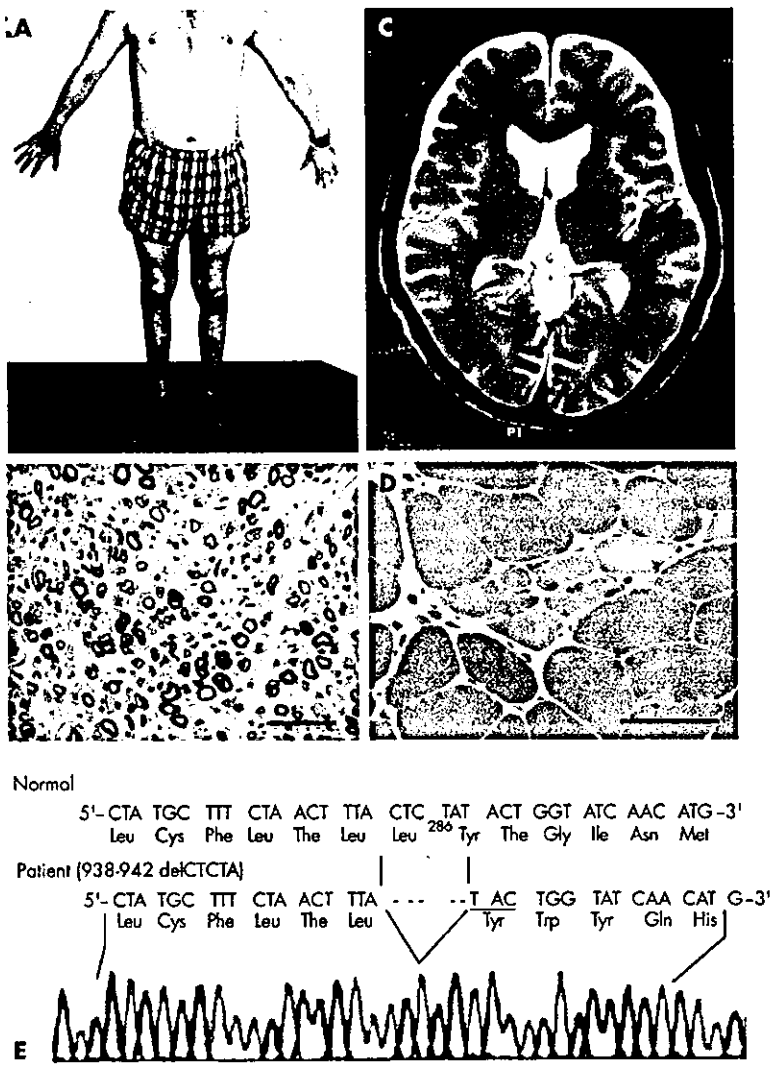

Figure 1 (A) Marked amyotrophy of both legs in case 1. (B) Sural nerve specimen obtained from case 1 showing moderate loss of myelinated fibres. Onion bulb formation is not observed. Toluidine blue stained transverse semithin section. Bar = 50 μ. (C) Axial T2 weighted magnetic resonance image of case 2, showing atrophy of the heads of the caudate nuclei. (D) Muscle biopsy specimen obtained from the left biceps brachii of case 2. The specimen shows increased variability of fibre diameter, and a group of basophilic fibres. Bar = 100 μ. (E) Direct DNA sequencing of the *XK* gene. A five base deletion in exon 3 is present at nt position 938 to 942 from the 5' end of the cDNA.

Molecular analysis

After informed consent had been obtained from the brothers, genomic DNA was extracted from peripheral blood by standard procedures. Exons of the *XK* gene were subsequently amplified by polymerase chain reaction as described by Ho *et al*.[1] The analysis showed a five base deletion in exon 3 at nt positions 938 to 942 from the 5′ end of the cDNA. This mutation results in a frame shift at codon 286 and the premature stopping of translation at codon 301, as reported previously.[2] This mutation was found in both cases 1 and 2, whose clinical phenotypes were extremely different.

After mutation analysis of the *XK* gene, we confirmed the presence of acanthocytes in a peripheral blood smear of case 1.

Comment

To date, the clinical features of McLeod syndrome have been reported to be heterogeneous.[2 3] The clinical features and conventional pathological findings in this condition are sometimes difficult to distinguish from other neuromuscular disorders because the expression of symptoms and signs seems to be variable, even among siblings.[2 3] In many cases, chorea, seizures, or muscular atrophy are the most frequently presented symptoms. Danek *et al* recently reported clinical features of 22 affected patients with mutation analysis of the *XK* gene.[2] In their investigations, limb chorea—which reflects CNS involvement in McLeod syndrome—was described in all patients. It is extremely difficult to make a diagnosis of this disease where the symptoms and signs are restricted to the peripheral nervous system.

In the present investigation, case 2 was characterised clinically by choreic movement and mild muscular atrophy, frequently seen in the reported cases of McLeod syndrome. In contrast, the symptoms in case 1 were extremely rare. Case 1 showed late onset of symptoms, slowly progressive weakness and amyotrophy of the lower extremities, areflexia, glove and stocking type sensory impairment, an increased level of serum CK, and pathological features with axonal degeneration of the nerve biopsy specimen. He showed no apparent central nervous system involvement 14 years from onset.

Our case 1 was clinically and pathologically indistinguishable from an axonal form of Charcot-Marie-Tooth disease without McLeod serology.

McLeod syndrome should be considered in patients with axonal sensorimotor neuropathy and high CK activity. Abnormal red cell morphology may be a clue to the diagnosis.

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NHS Direct for headache

NHS Direct is a government sponsored, nurse led, telephone helpline available throughout the United Kingdom, offering confidential medical advice without recourse to a doctor by using computerised assessment systems based on clinical algorithms.[1] As algorithms for the management of headache have been formulated, this might be construed as a condition for which NHS Direct would be well suited to offer an appropriate service. Following a protocol used in previous studies of the use of NHS Direct by patients attending neurology outpatient clinics,[2–4] patients with headache were specifically asked about their use of this service.

Of 1000 consecutive unselected patients seen in 118 general neurology outpatient clinics over a period of approximately 10 months by one consultant neurologist, headache was the principal reason for referral or patient complaint during consultation in 208 (21%), a frequency similar to that previously reported by others.[5] The neurologist's diagnoses, using standard diagnostic criteria,[6] were: chronic daily headache of tension type (157), drug overuse headache (12), episodic tension type headache (3), and migraine (34); one patient had a cerebral neoplasm, with typical postural features and visual obscurations, and one had coital cephalalgia. Of these 208 patients, 120 (58%) had heard of the NHS Direct telephone helpline. Of these 120 patients, 36 (30%; or 17% of all headache patients) had used the service; only three patients volunteered this information spontaneously. Of the 36 users, in 14 the call to NHS Direct related to headache (39% of NHS Direct users, or 6.7% of all headache patients); two volunteered this information spontaneously. The percentages for awareness and use of NHS Direct in this cohort are similar to those previously reported for an unselected general neurology outpatient clinic surveyed in 2002.[3]

Of those calling NHS Direct for advice about their headache, five of the 14 reported that they were told to go to hospital or call an ambulance immediately. The neurologist's diagnoses in these five patients were chronic daily headache of tension type in three, episodic tension type headache in one, and migraine without aura in one (in whom the reported NHS Direct diagnosis was cerebral haemorrhage). One patient was told to go to a local NHS walk-in centre (final diagnosis: chronic tension type headache), and another two patients were told to attend their general practitioner (both with chronic tension type headache). NHS Direct diagnosed transient ischaemic attack in a man thought by the neurologist to have migraine without headache (migraine equivalent). One patient with chronic tension type headache was told to lie in a dark room. One patient phoned for information about side effects of analgesic medication. Three could not recall the outcome of their call to NHS Direct.

Proposals for changes in the primary care of headache in the UK, issued by the British Association for the Study of Headache (BASH), described the role of NHS Direct in headache management as "uncertain," as "algorithms in use cannot provide for the taking of an adequate history to inform advice given."[7] The current study, although hospital based and reliant on patient report, with all their inherent biases, has provided no evidence to contradict that view. The suggestions emanating from NHS Direct were neither dangerous nor useful. Hence the study does not suggest that NHS Direct can currently replace clinical assessment by a practitioner trained in the diagnosis and management of headache disorders.

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Isolated total tongue paralysis as a manifestation of bilateral medullary infarction

Isolated acute bilateral hypoglossal nerve (CXII) paralysis is a very rare clinical condition which has been described in the context of traumatic mechanical injuries to the nerves.[1] The two nuclei of CXII, located at the tegmentum of the medulla oblongata, are in close proximity and may be damaged at the same time.[2] However, isolated bilateral CXII paralysis has not been described in cases of medullary infarction. We report a patient presenting with isolated complete tongue paralysis and a small ischaemic area in the medulla affecting both CXII nuclei exclusively.

CASE REPORT

A 49 year old woman with a history of primary biliary cirrhosis presented to the emergency room with acute dysarthria, swallowing difficulty, and inability to protrude her tongue. She was unable to eat, drink, or handle saliva. She denied vertigo, dizziness, nausea, unsteady gait, numbness, or weakness.

Examination showed that she was alert and responsive but was dysarthric and unable to initiate a swallow. Pupils were 3 mm in diameter, equal, and reactive to light and accommodation Extraocular movements were full. There was no ptosis and the corneal reflex was present bilaterally. Sensation was intact to light touch and pin prick. There was no spontaneous or gaze nystagmus, saccadic pursuit, or ocular dysmetria. Facial symmetry was noted, with no signs of weakness. The gag reflex was present with symmetric palatal elevation. Her tongue had limited protrusion and no side to side movement. The remainder of the cranial nerve examination was normal.

Neuromuscular strength was preserved. There were no sensory deficits to touch, pain, temperature, vibration, or position sense. Deep tendon reflexes were normal and there were no pathological reflexes. Coordination of the extremities was intact. Gait was not ataxic.

Clinical laboratory tests proving normal included an echocardiogram, chest *x* ray, repetitive nerve stimulation and single fibre electromyography, erythrocyte sedimentation rate, full blood count, serum electrolytes, fasting lipid profile, angiotensin converting enzyme, protein S, protein C, lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), plasma homocysteine levels, C3 and C4 complement, anti-ENA (anti-Sm, SS-A/anti-Ro, SS-B/anti-La, and anti-RNP), antinuclear antibodies, antiacetylcholine antibodies, serum syphilis serology, and cerebrospinal fluid findings. Magnetic resonance imaging (MRI) showed a region of increased signal intensity on T2 weighted and fluid attenuated inversion recovery images, involving only the two CXII nuclei; no further lesions were observed (fig 1). Figure 2 is a schematic drawing of the lesion. Conventional cerebral angiography showed a narrow basilar artery as well as tortuosity of the vertebral artery at the cervical level. The patient required a nasogastric tube for feeding.

Aspirin 300 mg daily was initiated. Four days after the onset of symptoms, the patient began suffering from sustained paroxysmal hiccups. Chlorpromazine 75 mg daily and valproic acid 500 mg daily were then given orally for 10 days, but the hiccups continued. She was then given 5 mg of baclofen orally three times a day, and the hiccups abated within 48 hours. The baclofen was discontinued after one week of treatment, and the hiccups did not recur.

The condition of the patient improved within the following weeks. Two months after onset, she reported the return of some tongue mobility. She began to eat and drink without a nasogastric tube. On examination, her tongue had limited ability to protrude but there was some side to side movement. No tongue atrophy was observed. Five months later, she presented with acute diplopia and right facial weakness which lasted for 14 days. Examination showed a right lateral rectus nerve paralysis along with a right peripheral facial nerve paralysis. Further cranial MRI showed no new lesions apart from the previous evidence of brain stem ischaemia. The patient was then switched to warfarin.

Figure 1 T2 weighted magnetic resonance image at the level of the tegmentum of the upper medulla oblongata, showing hyperintensity confined to the two CXII nuclei.

A two year follow up examination showed that her tongue mobility had returned to normal. The tongue had full side to side motion and full protrusion. No further strokes occurred and she continues taking warfarin.

COMMENT

Medial medullary infarcts represents less than 0.5% of all cerebral infarcts.[3 4] They may be unilateral or, rarely, bilateral. The clinical features of bilateral medial medullary infarctions are flaccid quadriplegia sparing the face, bilateral disturbance of deep sensation, weakness of the tongue, and respiratory failure.[3 4] The case here reported broadens the spectrum of the medial medullary syndrome. The isolated bilateral CXII paralysis in our patient was the only manifestation of a bilateral medullary infarct. Tongue paralysis is caused either by involvement of the fibres of the hypoglossal nerve, which are located just lateral to the medial lemniscus and the pyramid, or by involvement of the nucleus.[3] The CXII nucleus is placed in the dorsomedial medulla and depends on the territory of the anteromedial arteries, which, in addition, supply the medial portion of the pyramidal tract and its decussation, the medial lemniscus, and the medial longitudinal fasciculus. The anteromedial arteries usually arise from the anterior spinal artery to the caudal medulla and from the distal vertebral artery or proximal basilar artery to the rostral medulla.[3 4]

With regard to aetiology, the vertebrobasilar system was found to be hypoplastic. We feel that an anomalous branch of a vertebral artery supplied both sides of medial medullary area. Distal occlusion of this rostral branch at the level of the dorsal medulla resulted in a restricted bilateral CXII infarct. Our patient had a further vertebrobasilar stroke and was switched to warfarin. Patients with ischaemia in the territory of a hypoplastic vertebrobasilar system may be treated with either antiplatelet agents or warfarin.[5] However, recurrent transient ischaemic attacks may be more common in patients given antiplatelet agents. In a recent series, for example, two of four patients with symptomatic vertebrobasilar hypoplasia who were initially treated with an antiplatelet agent developed recurrent transient ischaemic attacks. In contrast, none of the patients treated with warfarin had recurrent symptoms.[5]

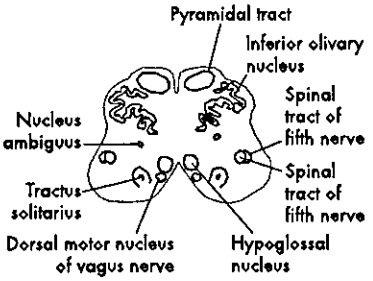

Figure 2 Schematic drawing of the lesion at the mid-medullary level. The shadowed area indicates the lesion.

In conclusion, this case shows that an isolated complete tongue paralysis can be produced by bilateral medullary infarction, a finding that broadens our understanding of the spectrum of medial medullary syndrome.

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Chronic inflammatory demyelinating polyneuropathy presenting with features of GBS

Abstract—The authors report five patients with inflammatory demyelinating polyneuropathy with a Guillain–Barré syndrome (GBS)–like onset and initial clinical features, but with persistent symptoms similar to chronic inflammatory demyelinating polyneuropathy (CIDP). Patients in the chronic phase improved with corticosteroid or IV immunoglobulin therapy. Patients with apparent GBS who show persistent symptoms may benefit from corticosteroids or other treatment that is beneficial in the management of CIDP.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by chronic, progressive onset with or without exacerbations and recurrences.[1] Patients may benefit from corticosteroid, plasma exchange (PE), or IV immunoglobulin (IVIg) therapy .[2-4] Guillain–Barré syndrome (GBS) is characterized by acute onset of symptoms, and frequently a preceding infectious event such as flu-like or diarrheal symptoms; corticosteroid therapy is not considered beneficial,[5] but PE or IVIg therapy shortens disability.[6] CIDP and GBS are considered separate clinical entities, and specific diagnostic criteria have been established.[7,8]

We describe five patients with acute motor paralysis with GBS-like onset in whom symptoms persisted. They then become clinicopathologically similar to CIDP in the chronic phase.

Case reports. *Patient 1.* A 13-year-old boy had fever and cough for 3 days. Ten days later, he developed distal muscle weakness and numbness in all four extremities. These symptoms worsened rapidly, and he needed support to stand and walk at 7 days from onset of neurologic illness.

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Table 1 Clinical features

Patient no.	Age at onset, y/sex	Preceding event	Initial progression, d*	Peak clinical grade†	Motor symptoms	Sensory symptoms	CSF protein (mg/dL)	
							Acute phase	Chronic phase
1‡	13/M	URI	7	7	U = L distal	Distal limb numbness	77	134
2§	31/M	None	7	8	U = L proximal	Distal limbs	49	127
3	53/M	Diarrhea	9	7	U < L proximal	Distal limbs	74	75
4	26/M	URI	7	7	U = L distal	None	41	141
5	44/F	URI	10	8	U = L diffuse	Distal limb numbness	50	183

* Rapidly progressive period from the onset.

† Clinical grading scale for functional assessments: 0 = normal; 1 = no disability, minor sensory signs or areflexia; 2 = mild disability, ambulatory for >200 m, mild weakness in one or more limbs and sensory impairment; 3 = moderate disability, ambulatory for >50 m without cane, moderate weakness Medical Research Council (MRC) grade 4 and sensory impairment; 4 = severe disability, able to walk >10 m with support of cane, motor weakness MRC grade 4 and sensory impairment; 5 = requires support to walk 5 m, marked motor and sensory signs; 6 = cannot walk 5 m, able to stand unsupported and able to transfer to wheelchair, able to feed self independently; 7 = bedridden, severe quadriparesis, maximum strength MRC grade 3; 8 = respirator-dependent and/or severe quadriparesis, maximum strength MRC grade 2; 9 = respirator dependent and quadriplegia; 10 = dead.

‡ Patient 1 had mild facial nerve palsy.

§ Patient 2 had mild facial and bulbar palsy, and also had tachycardia and very mild dyspnea.

URI = upper respiratory infection; U = upper limb; L = lower limb for motor symptoms.

Subsequently, he could not rise or remain standing by himself. Neurologic examination revealed severe muscle weakness in all four extremities and mild bilateral facial nerve palsy. Muscle tone was decreased, but muscle bulk was well preserved. Deep tendon reflexes were diffusely absent. Pathologic extensor plantar reflexes were absent. Numbness was noted in the fingers and feet, but objective sensory dalities were well preserved (table 1). Motor nerve conduction velocity was 25.1 m/s in the tibial nerve. CSF protein was elevated to 77 mg/dL, with a cell count of 1 lymphocyte/mm^3. The patient was diagnosed with GBS and was admitted to a hospital affiliated with Nagoya University. He was observed without specific treatment, because symptoms appeared to be slowly subsiding after admission. One year later, he began to

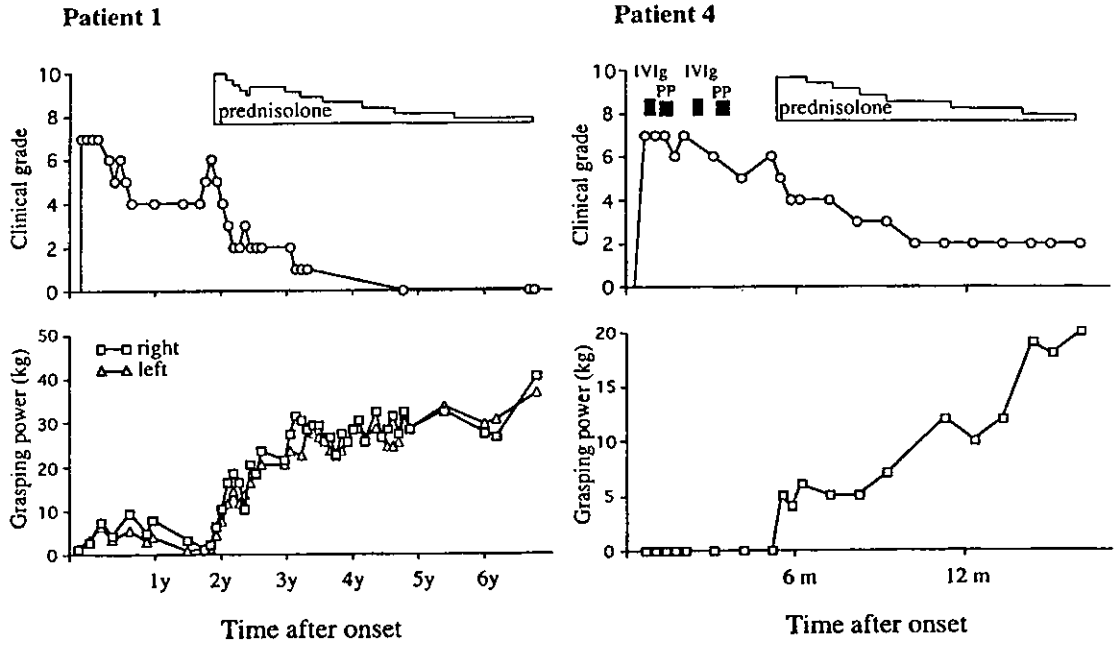

Figure. Clinical course and treatment of the two representative patients. Clinical grades, grasping power, and treatment were semiquantitatively plotted in terms of duration from onset. Clinical grading for functional assessment was performed by the method described previously.[3] Details are described in the footnotes for table 1. Grasping power was assessed using an ordinary hand dynamometer. Each patient used the same dynamometer throughout the course. Generally, 30 kg for men represent the lower limits of normal, although values vary somewhat depending on individual dynamometers. IVIg = IV immunoglobulin therapy at 0.4 g/kg/d × 5 consecutive days; PP = plasmapheresis at 5 sessions of double-filtration or plasma exchange; prednisolone = prednisolone orally at 1 mg/kg/d for the initial 4 to 6 weeks, with subsequent gradual reduction.

Table 2 Nerve conduction study

Patient no.	Duration from onset	Median MCV, m/s/ms/mV	Median SCV, m/s/uV	Tibial MCV, m/s/ms/mV	Sural SCV, m/s/uV	F-wave velocity, median, m/s	Conduction block	Temporal dispersion
Acute phase								
1	13 d	ND	ND	25.1/ND/ND	ND	ND	ND	ND
2	7 d	56.2/4.2/10.5	58.6/4.0	52.9/6.3/13.7	53.1/10.8	65.4	−	−
3	10 d	49.8/5.2/9.8	ND/ND	36.9/4.4/6.9	23.5/1.5	ND	−	−
4	7 d	59.6/3.9/3.8	53.4/27	51.7/6.2/3.4	52.1/15.1	40.3	+	+
5	—	ND	ND	ND	ND	ND	ND	ND
Chronic phase								
1	24 mo	8.3/19.0/2.5	NE	22.3/12.0/5.8	34.6/7.1	NE	−	+
2	3 mo	15.5/16.7/2.6	NE	NE	NE	NE	−	+
3	3 mo	21.3/5.2/5.9	NE	40.1/8.5/0.3	NE	ND	−	+
4	5 mo	45.3/4.5/5.7	56.0/21.1	30.2/7.5/0.1	48.2/19.0	30.0	+	+
5	5 mo	32.6/4.5/4.7	40.5/21.2	46.1/7.2/5.2	35.3/10.6	NE	−	−
Control values, mean (SD)		57.8 (3.7)/3.4 (0.4)/10.7 (3.5)	57.8 (4.7)/ 23.5 (8.4)	46.9 (3.5)/4.5 (0.8)/ 10.9 (3.8)	51.0 (5.1)/ 11.5 (4.7)	54.5 (3.5)	−	−

Control values were obtained in 191 healthy volunteers (mean age (SD), 48.7 (16.5) years; males/females 97/94) for the median nerve, 121 (mean age (SD), 49.9 (15.0) years; males/females 64/57) for the tibial nerve, and 133 (mean age (SD), 50.6 (15.6); males/females 74/59) for the sural nerve. Motor nerve conduction velocity (MCV) values are described as conduction velocity (m/s)/distal latency (ms)/ muscle action potential (mV) on median or tibial nerve recordings. Sensory nerve conduction velocity (SCV) values are described as conduction velocity (m/s)/sensory nerve action potential (uV) on median or sural nerve recordings.

NE = not evoked; ND = not determined; + = present; − = absent.

walk with support from a cane, but his overall neuromuscular state had not sufficiently improved (figure). At 2 years after onset, he noted progressive muscle weakness in the limbs and was admitted to our hospital.

He could not stand or walk by himself because of severe muscle weakness. CSF protein was 134 mg/dL without elevation of the cell count. A nerve conduction study showed severely compromised conduction with demyelinative features (table 2). A sural nerve biopsy specimen revealed endoneurial edema and active demyelination in a teased fiber preparation. Prednisolone (1 mg/kg/d) was administered orally. After initiation of corticosteroid therapy, recovery was remarkable. In 3 months, muscle weakness dramatically recovered, and the patient could walk unaided.

Patient 4. A 26-year-old man developed fever and cough for approximately 10 days. Nine days later, he noted muscle weakness and had difficulty walking. He needed support to stand and walk by 5 days, and could not rise by 7 days. The patient was diagnosed with GBS. IVIg therapy and plasmapheresis were performed (see the figure) with no significant recovery. At 4 months, muscle weakness was severe in the distal portions of all 4 extremities, and he could not stand or walk by himself. Prednisolone was administered orally. After initiation of corticosteroid therapy, muscle strength gradually improved (see the figure). In 2 months, he could walk by himself without support, and had no relapses in the following year.

In summary, four of the five patients had a preceding event, two had cranial nerve involvement, and one had autonomic and mild respiratory distress. All patients showed rapid progression of muscle weakness and sensory impairment, becoming unable to walk or peak impairment in 7 to 10 days. All patients were diagnosed with GBS in the initial phase. Nerve conduction studies showed more profound demyelinating abnormalities including conduction block and temporal dispersion in the chronic phase than in the acute phase (table 2). Sural nerve biopsy from four patients in the chronic phase showed endoneurial edema and variable degree of demyelinating fibers. Perivascular lymphocyte invasion was seen in one patient.

For initial treatment, two patients were closely observed and three received plasmapheresis or IVIg therapy, but none showed a notable remission. In the chronic stage, three patients received corticosteroid therapy and two received IVIg therapy, which were not used in the early phase, and all showed dramatic response. Two patients showed recurrence in the follow-up period, but the other patients had no relapses during the follow-up years.

Discussion. The five patients showed characteristic features of GBS in the acute phase with rapid progression of symptoms over days and a preceding infectious episode in four patients. In addition, all patients partially recovered in 3 to 4 months of initial treatment or observation, although the degree of recovery was not sufficient. In the chronic phase, they were experiencing continued muscle weakness and sensory impairment, with severe demyelinating changes in nerve conduction studies and sural nerve biopsies. The most striking observation was a re-

markable response to corticosteroid treatment in three patients, which was not attempted in the acute phase, considering the diagnosis of GBS. In the chronic phase, when corticosteroid treatment was effective, these patients were expected to have a pathophysiology similar to that of CIDP rather than GBS. In the other two patients, IVIg treatment was selected in the chronic phase and was remarkably effective.

How should these five patients be classified? Initial progression in days to a plateau of severity does not fit the diagnostic criteria for CIDP.[7] However, in large series or anecdotal reports in the early era of CIDP studies, some patients were noted to progress rapidly in days during the early period and remain symptomatic in the chronic phase.[9] Although detailed information is lacking, some of them could be similar pathophysiologically to the current patients.

Conversely, a subgroup of patients with GBS have been known to show chronic persistent symptoms after recovery phases have concluded.[8] Although they were considered residual symptoms of GBS, some of these patients may have included a true chronic inflammatory phase like CIDP. Corticosteroid responsiveness of "residual" symptoms has not been well assessed, because corticosteroid therapy may not be considered once diagnosis of GBS has been established.

A subacute form of idiopathic demyelinating polyneuropathy (SIDP) has been proposed.[10] SIDP is a monophasic illness with progression of weakness for 4 to 8 weeks, a profile intermediate between GBS and CIDP and corticosteroid responsive.[10] However, initial progression over days, frequent preceding infectious events, followed by a chronic persistent phase including relapses differs from SIDP. Recurrent GBS has been defined as two or more episodes of acute monophasic neuropathy followed by near complete recovery between two or more acute episodes, being different in our patients.

In our patients, because no corticosteroids were administered in the acute phase, the corticosteroid responsiveness during the acute phase is unknown. Two alternative pathophysiologic sequences can be proposed in these five patients. One possibility, reflecting the changes in clinical manifestations and course, would be chronic persistent transformation of GBS. The second view is that these patients had CIDP pathophysiology in the initial phase even though they showed a GBS-like onset. If this is true, corticosteroid therapy could be applicable to the acute phase. However, in the initial 2 months, all of our patients were indistinguishable from GBS by clinical and electrophysiologic features, so this was not tested.

Although the current patients cannot easily be classified, these cases are therapeutically informative. After initial treatment, most of the patients diagnosed with GBS are followed up without consideration of any alternative treatment, particularly corticosteroid therapy. However, even a diagnosis of GBS should not preclude consideration of corticosteroid therapy if persistent or recurrent symptoms suggest a chronic phase of neuropathy.

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CME Familial transthyretin-type amyloid polyneuropathy in Japan

Clinical and genetic heterogeneity

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Abstract—Familial amyloid polyneuropathy (FAP) was once considered a disease peculiar to endemic areas, but it is now recognized not to be a rare disease among hereditary neuropathic disorders in Japan. FAP in Japan, the majority of which is caused by transthyretin (TTR)-related amyloid deposition, shows a wide spectrum of clinical pictures. This variability can be explained on the basis of the many causative gene mutations of TTR, but even in the same TTR type of FAP, the clinical phenotypes seem to vary in different kindreds or individuals. Especially in the case of the Val30Met TTR type, the sex ratio and the age at onset are considerably different between patients in endemic foci and those in nonendemic areas. It is also noteworthy that serious cardiac amyloidosis is commonly seen in patients with FAP of the non-Val30Met TTR type. In addition to TTR gene mutation, unknown factors may play an important role in the development of FAP. At present, liver transplantation is the only life-saving treatment, but this therapy is always associated with great stress for the patient and the donor, particularly in living-related transplantation. Less invasive treatments for this disease are required.

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Familial amyloid polyneuropathy (FAP) is one form of hereditary generalized amyloidosis, initially showing polyneuropathy and autonomic dysfunction but later involving many visceral organs. This disorder was first clearly described in Portugal in 1952,[1] where the disease is endemic; up to 1994, 1,233 FAP patients from 489 pedigrees were diagnosed at Centro de Estudos de Paramidoidose in Porto.[2] In the 1960s and 1970s, two other large foci of patients were found in Japan[3] and Sweden,[4] and the origin of all Japanese and Swedish FAP patients was long considered to be related to the Portuguese kindreds. However, during the past 20 years, the understanding of FAP, including the molecular pathogenesis and diagnostic technology, has greatly progressed. The discovery of transthyretin (TTR) as a main constituent of amyloid deposits in FAP was an initial advance,[5] and the complete amino acid sequence of TTR-related amyloid fibril protein in this disorder was reported in 1983,[6,7] showing one amino acid substitution (a valine-to-methionine change at position 30). Since then, with use of DNA analysis or protein chemistry techniques, more than 80 mutations[8] have been identified as causative gene abnormality in FAP. Corresponding to this variety of TTR gene mutations, FAP seems to consist of significantly different clinical phenotypes.

FAP kindreds are now known to exist in many nations worldwide. In Japan, where people with a relatively uniform genetic background have been living in an isolated island country, a number of FAP families were reported with different TTR gene mutations. In this article, we present and summarize the current clinicopathologic aspects of TTR-related FAP in Japan.

Advances in diagnostic techniques. In addition to clinical symptoms and proven amyloid deposition in biopsy specimens, demonstration of TTR abnormality at the protein or DNA level is necessary to make a definite diagnosis of FAP. Among the many TTR mutations, the most common one, involving the substitution of methionine for valine at position 30 (Val30Met), causes the classic phenotype of FAP, which has been called type I FAP. To detect this variant form of TTR in serum, a specific radioimmu-

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noassay was developed in 1984[9]; Southern blot DNA analysis[10] also became available in the same year. Since the PCR for allele-specific enzymatic amplification of genomic DNA started to be employed,[11] both restriction fragment length analysis and DNA sequencing can be carried out more rapidly and easily, which has made it possible to find varied mutations of the TTR gene related to the development of FAP.

Application of mass spectrometry[12,13] also allows the variant form of TTR to be easily identified. This system can demonstrate a mass difference between a wild type and a variant type of TTR using immunoprecipitated TTR obtained from patient serum. Testing serum TTR by mass spectrometry alone does not make it possible to specify the site and kind of substitution of an amino acid in a number of FAP-related TTR gene mutations, and thus subsequent direct DNA sequencing is usually required.[13] However, this method is very useful for screening FAP patients with unknown TTR gene mutations.

To confirm amyloidosis, including FAP, the demonstration of amyloid deposition on biopsied tissues is essential. In FAP, biopsy samples are obtained from the sural nerve, skin, or rectal and gastric mucosa,[14] and it is necessary to show that these amyloid deposits are specifically immunolabeled by anti-TTR antibodies. In practice, aspiration biopsy of abdominal fat tissue[15] is the most recommended. This biopsy can be easily performed and is very sensitive for detecting amyloid deposition in patients with FAP.

Epidemiology and geographic distribution of FAP kindreds. There are two large foci of FAP in Japan: One is Arao city in Kumamoto prefecture,[3] and the other is Ogawa village in Nagano prefecture.[16,17] Both foci consist of patients with the Val30Met TTR type of FAP,[18] but no consanguineous relationship between the Arao and Ogawa families has been found. Over the last 20 years, we have examined 165 patients in Arao city and 172 patients in Ogawa village and its neighboring area.[19,20] In addition to both endemic foci, 43 FAP kindreds with Val30Met TTR were traced[21]: They were genealogically independent and were geographically scattered throughout Japan (figure 1A).

Non-Val30Met TTR-type FAP is being increasingly recognized. In 1990, three different TTR mutations causing FAP (Glu42Gly, Ser50Arg,[22] and Tyr114Cys[23]) were identified, and since then, a total of 19 TTR mutations have been found among Japanese that relate to the development of FAP. The families with these mutations were composed of 27 kindreds widely distributed in our country (see figure 1B). Among them was a rare form of double mutation of the TTR gene showing a compound heterozygote for Val30Met and Arg104His.[24] A family with Tyr114Cys TTR,[23,25] which originated in Kunimi, Nagasaki prefecture, in Kyushu Island, had many patients (12 affected members in five generations were confirmed). Concerning Asp38Ala,[26,27] Ser50Arg,[22] and Tyr114His[28,29] TTR types, three di-

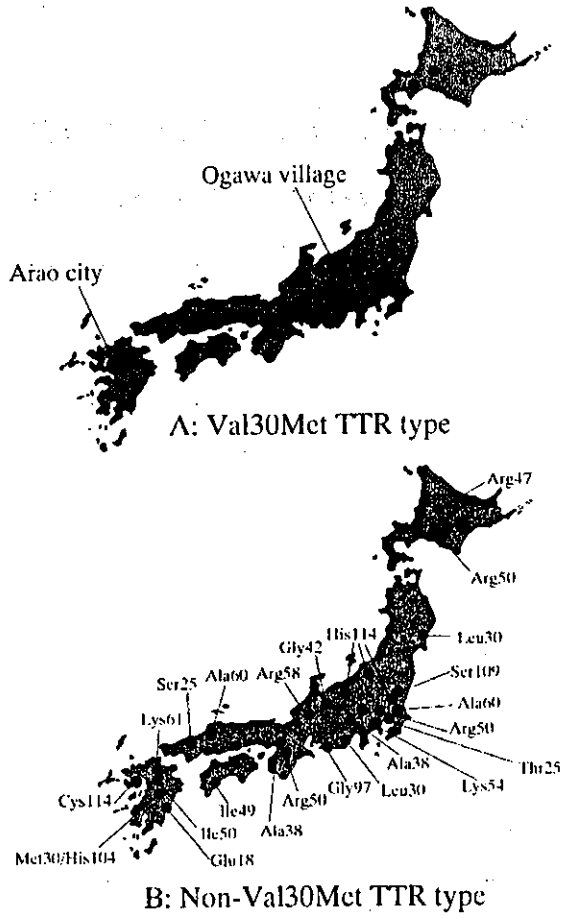

Figure 1. Geographic distribution of familial amyloid polyneuropathy (FAP) kindreds in Japan. (A) Val30Met transthyretin (TTR)-type families. (B) Non-Val30Met TTR-type families.

verse kindreds in each type were reported, and a pair of families with Val30Leu[11] and Thr60Ala[30] TTR types were also identified. However, no genealogical relationship was found among these families. According to a recent survey[31] of hereditary neuropathic disorders in Japan, Charcot–Marie–Tooth disease is the most common (prevalence ratio 1.5/100,000), and the next is FAP, although the exact prevalence ratio of this disease has not been determined yet.

Clinical pictures and pathologic findings. *Val30Met TTR type.* The clinical concept of this disease consists of the following four features[1,19]: 1) The disorder is inherited as an autosomal dominant trait with equal sex distribution; 2) the age at onset is late twenties to early forties, leading to death from cachexia in 10 to 15 years; 3) polyneuropathy with sensory dissociation starts in the legs and progresses in an ascending fashion; and 4) manifestations of

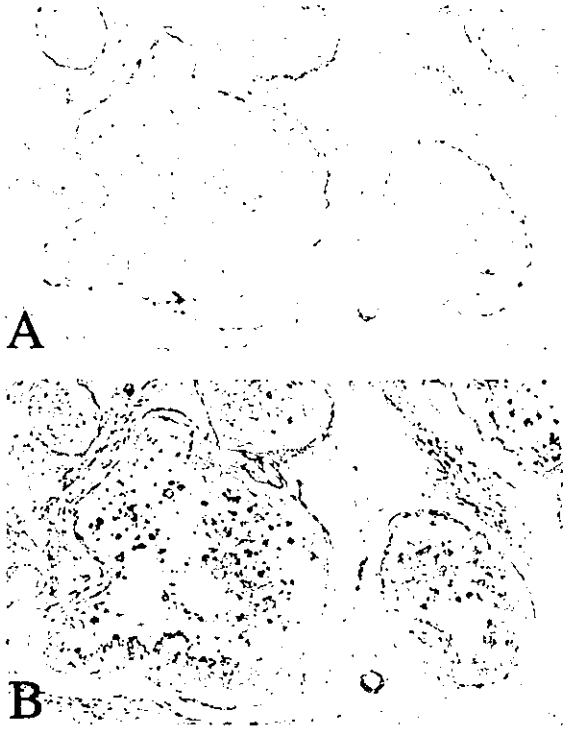

Figure 2. Transthyretin (TTR)-derived amyloid deposition on peripheral nerve. Transverse sections of sciatic nerve in an autopsied patient with familial amyloid polyneuropathy with Val30Met TTR were stained by alkaline Congo red (A) and immunohistochemical techniques with an anti-human TTR antibody (B). Heavy deposition of amyloid is seen in the endoneurium and perineurium, and all these amyloid deposits were positively immunolabeled with an anti-TTR antibody. Original magnification ×45.

various autonomic dysfunctions such as severe orthostatic hypotension, disturbed bowel movement with alternating constipation and diarrhea, impotence, and dysuria invariably appear in the course of the disease. This clinical picture of FAP is clearly seen in the patients originating from the Arao and Ogawa areas. Conversely, FAP patients who had no genealogical relationship with the two endemic foci showed different clinical features.[21] In the 43 kindreds examined, the probands consisted of 39 men and 4 women (the sex ratio was 10:1, being male dominant) and the age at onset was 46 to 80 years. The probands who were proved to have symptomatic siblings were 14 of 43 families, so other patients with no family history seemed to be sporadic.

Nervous system. Most patients showed chronic progressive sensorimotor neuropathy, usually accompanied by autonomic failure. Massive deposits of amyloid, occurring predominantly both in the endoneurium of the peripheral nerves[32] (figure 2) and in the interstitium of autonomic ganglia,[33] cause nerve degeneration. However, neither dissociated sensory loss nor autonomic failure was prominent in the patients with a late age at onset, especially in those originating from nonendemic areas. Severe nausea and vomiting, which periodically appear and profoundly waste the affected FAP patients, were not seen in any of these older patients. Lower cranial neuropathy with bulbar palsy[19,34] occurred infrequently.

Heart. In patients with the Val30Met TTR type of FAP in the Arao and Ogawa foci, amyloid deposition on the myocardium is localized to the subendocardial area including the conduction system, so various types of conduction block frequently appear, requiring the implantation of a pacemaker.[19] However, heart failure caused by severe myocardial amyloid deposition rarely occurs until the terminal stage. Recently, it has been noted that a small number of patients with Val30Met TTR who developed the illness at an older age commonly experienced serious cardiac amyloidosis with heart failure.[35,36]

Other organs. In the postmortem examination, the kidney was found to be consistently involved by marked deposition of amyloid, but most patients show well-preserved renal function, even in the more advanced stages. On rare occasions, patients with Val30Met TTR-type FAP in the Ogawa area were affected by severe nephropathy with heavy proteinuria from an early stage.[19] On the other hand, three older patients who originated from nonendemic areas showed slight amyloid deposition on renal tissues at postmortem examinations. Amyloid deposition on the digestive tract wall is a common finding in systemic amyloidosis, including primary immunoglobulin light chain amyloid (AL) and secondary serum amyloid A protein (AA) amyloidosis, and FAP. Among them, FAP is characterized pathologically by predominant involvement of gastrointestinal autonomic nerves: Denervation of extrinsic sympathetic nerves,[37] severe nerve fiber loss in the vagus nerve,[33] and degeneration of intramural ganglion cells[14] were demonstrated. These amyloid-induced disorders in the enteric nervous system may cause the characteristic bowel symptoms in FAP.

Homozygosity. It is well known that the vast majority of FAP patients are heterozygous for the mutant Val30Met TTR gene. However, five individuals with homozygosity of this mutant gene were identified in three families[38-40]: Three were symptomatic individuals aged 56, 65, and 69 years, and the 65-year-old man also had vitreous opacity in the left eye. The remaining two were asymptomatic carriers aged 49 and 59 years. The 49-year-old man[39] developed vitreous opacity in both eyes at age 59 but lacked any symptoms ascribable to peripheral somatic and autonomic neuropathy. Up to now, a total of 18 homozygous individuals including our 5 have been reported in the literature[41]: Ten of them originated from kindreds in nonendemic areas, and 15 developed symptoms after the age of 50. It is concluded that the double dose of the mutant gene does

Table Clinical pictures of non-Val30Met TTR type of FAP

Gene mutation (no. of codon)	Substitution of amino acid	No. of patients	Polyneuropathy	Autonomic dysfunction	Cardiopathy
T→G (18)	Asp→Glu	1	−	+	+++
G→T (25)	Ala→Ser	1	+	−	++
G→C (25)	Ala→Thr	1	++	−	−
G→A (30)/G→A (104)[24]	Val→Met/Arg→His	1	+	++	++
G→C (30)[11]	Val→Leu	2	+++	++	+++
A→C (38)[27]	Asp→Ala	3	++	+	+++
A→G (42)[22,76]	Glu→Gly	3	+++	++	++
G→C (47)[77]	Gly→Arg	1	+++	++	+
C→T (49)[78]	Thr→Ile	1	+++	++	++
G→T (50)[53]	Ser→Ile	4	+	++	+++
T→G (50)[22,49]	Ser→Arg	3	+++	+++	+++
G→A (54)[50]	Glu→Lys	1	+++	+++	+++
T→G (58)[43]	Leu→Arg	2	++*	++	/
A→G (60)[80]	Thr→Ala	2	++	+	+++
G→A (61)[79]	Glu→Lys	1	++	++	/
C→G (97)[80]	Ala→Gly	1	++	−	+
G→C (109)[81]	Ala→Ser	1	++	+	/
A→G (114)[23,25]	Tyr→Cys	12	+++	+++	+++
T→C (114)[28,29]	Tyr→His	4	+*	−	−

Severity of symptoms: − = none; + = slight; ++ = moderate; +++ = severe; / = not evaluated.

* Polyneuropathy starts as a carpal tunnel syndrome.

TTR = transthyretin; FAP = familial amyloid polyneuropathy.

not affect the clinical phenotype of the disease, apart from the high frequency of vitreous opacity.[42]

Non-Val30Met TTR types. The clinical pictures of the patients with non-Val30Met TTR types of FAP are summarized in the table.

Nervous system. Clinical manifestations of polyneuropathy and autonomic dysfunction in these patients closely resembled those of Val30Met TTR-type FAP patients with a late age at onset. In some patients, dissociated sensory loss was not noted and autonomic dysfunctions seemed to be less serious in the early phase of the disease. In Leu58Arg[43] and Tyr114His TTR[28,29] types, the disease started as a carpal tunnel syndrome. Amyloid deposition on the subarachnoid vessels and leptomeninges was found to be a consistent finding in FAP,[44] but in the Val30Met TTR type, this amyloid deposition is clinically insignificant except for two reported patients[45,46] in whom amyloid-induced thickened leptomeninges compressed the spinal cord. In Ala25Thr and Tyr114Cys TTR types, thickening of the leptomeninges through amyloid deposition was demonstrated either on biopsy or at autopsy.[25]

Heart. Serious cardiac amyloidosis was commonly seen in non-Val30Met TTR-type FAP. This disorder is hemodynamically classified as restrictive cardiomyopathy, and echocardiographic assessment showed thickened walls with greatly refractile echoes (so-called granular sparkling appearance) and impaired diastolic function.[47] Highly positive myocardial uptake was seen on the ^{99m}Tc-pyrophosphate scintigram.[48] At necropsy, diffuse and/or globular deposits of amyloid were seen to involve the whole myocardial layer.[27,49] Clinically, intractable heart failure was the predominant manifestation, leading directly to death.

Other organs. Vitreous opacity was seen in Glu54Lys,[50] Leu58Arg,[44] and Tyr114Cys[25] TTR types. The patients with Asp38Ala TTR[27] frequently had shortness of breath, and the postmortem pathologic examination revealed diffuse pulmonary amyloid deposition involving the alveolar septa and the vascular walls. Bronchopulmonary amyloidosis is usually seen in patients with primary AL systemic amyloidosis[51] and has been rarely reported in patients with FAP.[52] When investigating the cause of dyspnea in patients with FAP, much attention is given to cardiac amyloidosis, but the possibility of pulmonary involvement with TTR-derived amyloid needs to be kept in mind. The gastrointestinal tract was wholly affected and the pattern of amyloid deposition was very similar to that seen in Val30Met TTR-type FAP. In the kidney, small amounts of amyloid deposition were observed only in the perivascular areas on autopsy examinations in Asp38Ala[27] and Tyr114Cys[25] TTR types.

Considering the clinical features in each variant of TTR, cardiac dysfunction was the main symptom in Asp18Glu and Ser50Ile[53] TTR types, so the term "FAP" is not suitable for these forms of TTR-related hereditary amyloidosis. In the Ala25Thr TTR type, the pattern of peripheral nerve lesion was unique, showing progressive motor weakness with no involvement of sensory and autonomic functions. The Glu54Lys[50] TTR type is an aggressive form of FAP, showing rapid progression of polyneuropathy and autonomic dysfunction and fatal cardiomyopathy. A Thr60Ala TTR was first identified in a large kindred of Appalachian origin,[54] in which cardiac amyloidosis was apparent. In our family with the same variant of TTR,[30] polyneuropathy starting in the legs was another clinical manifestation. The Tyr114Cys[25] TTR type of FAP is associated with amyloid deposition on the leptomeninges and vitreous opacity, so its clinicopathologic findings partly resemble those of familial oculoleptomeningeal amyloidosis with Val30Gly[55] TTR or Hungarian-type familial meningocerebrovascular amyloidosis with Asp18Gly[56] TTR. However, the latter two disorders mainly cause CNS symptoms and lack apparent polyneuropathy or autonomic failure. The disease with Tyr114His TTR is characterized by late-onset bilateral carpal tunnel syndrome and very slow progression.[28,29] Although amyloid deposition was histologically demonstrated in the peripheral nerves,[29] polyneuropathy and autonomic failure did not appear, so the prognosis of patients with this type of FAP is good.

Treatment. FAP was long considered to be an incurable disease, but a new therapeutic approach was developed 10 years ago. As the liver produces most of the TTR in serum,[57] it was assumed that the replacement of a liver expressing an abnormal TTR gene should stop the production of the variant TTR, the serum amyloid precursor in FAP. The first successful liver transplantation for a patient with FAP was performed in Sweden in 1990,[58,59] and since then this operation has become widely used. By June 2000, liver transplantation records of 460 FAP patients had been sent to the FAP World Register office in Sweden,[60] and the 5-year survival rate is about 80%. Several follow-up studies[61-64] have shown beneficial therapeutic effects: The serum concentration of Val30Met TTR rapidly decreased, reaching near zero after operation.[58] The progression of FAP symptoms certainly stopped, and patients who were in an early stage of FAP and underwent successful operations showed considerable improvement in their quality of life.[64]

In Japan, full-liver transplantation is uncommon because brain death has not been widely accepted as a definition of death. As an alternative, in 1993, we started to perform partial liver transplantation using grafts from living donors.[65,66] More than 20 patients with FAP have had this operation in Japan, with the donors consisting of parents, siblings, or husbands. Recently, a two-step operation using a technique called auxiliary partial orthotopic liver transplantation[67] has been employed to compensate for the very small size of the liver graft. In a series of 16 patients at Shinshu University Hospital,[68] all had Val30Met TTR and their ages at surgery were 25 to 47 years. The postoperative follow-up ranged from 3 months to 7.5 years. Their courses, including slight relief of polyneuritic and autonomic symptoms in patients with shorter durations of illness, were very similar to those reported from other countries.[61-63] In addition, no recurrence of periodic attacks of severe nausea and vomiting has been noted in three patients. Among the 16 patients, 3 had unfavorable outcomes: One woman developed acute liver failure 1 week after surgery, resulting in no recovery, while the remaining two patients died 3 and 21 months after transplantation.[69] Both had longer preoperative histories of FAP (7 years in one patient and 10 years in the other) and were significantly disabled by polyneuropathy and autonomic dysfunctions, which frequently required the use of a wheelchair. It is now generally accepted that earlier intervention (<5 years after onset) provides a better chance of improvement following liver transplantation.[64]

Although liver transplantation is very promising, unexpected postoperative findings have recently been noted. One is amyloid deposition on ocular tissues.[70,71] This amyloid might be derived from the de novo production of variant TTR in the retinal epithelium. Another is a life-threatening cardiac complication shown by serial echocardiograms[72,73]: Myocardial amyloid deposition with thickened ventricular wall might progress rapidly in some patients after transplantation, although polyneuropathy and autonomic failure stabilize or improve slightly. These were all patients with non-Val30Met TTR-type FAP who possibly had substantial amyloid deposition on the myocardium before operation. In the pathogenesis of this form of cardiac amyloidosis, wild-type TTR is regarded as playing an important role.[73] Wild-type TTR is known to be itself amyloidogenic and causes senile cardiac amyloidosis.[74] It was also demonstrated that amyloid fibrils isolated from the hearts of patients with FAP contained considerable amounts of wild-type TTR regardless of the types of TTR mutations and that patients who died after liver transplantation had more abundant wild-type TTR in deposited cardiac amyloid fibrils.[75] It is presumed that amyloid heart disease can be accelerated by enhanced deposition of wild-type TTR on a template of amyloid derived from variant TTR. Cardiac amyloidosis is a fatal visceral lesion in FAP patients, so it is critical to clarify the severity of cardiac amyloid deposition when considering liver transplantation in patients with this disease.

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Progression and prognosis in multiple system atrophy
An analysis of 230 Japanese patients

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Summary
We investigated the disease progression and survival in 230 Japanese patients with multiple system atrophy (MSA; 131 men, 99 women; 208 probable MSA, 22 definite; mean age at onset, 55.4 years). Cerebellar dysfunction (multiple system atrophy–cerebellar; MSA-C) predominated in 155 patients, and parkinsonism (multiple system atrophy–parkinsonian; MSA-P) in 75. The median time from initial symptom to combined motor and autonomic dysfunction was 2 years (range 1–10). Median intervals from onset to aid-requiring walking, confinement to a wheelchair, a bedridden state and death were 3, 5, 8 and 9 years, respectively. Patients manifesting combined motor and autonomic involvement within 3 years of onset had a significantly increased risk of not only developing advanced disease stage but also shorter survival ($P < 0.01$). MSA-P patients had more rapid functional deterioration than MSA-C patients (aid-requiring walking, $P = 0.03$; confinement to a wheelchair, $P < 0.01$; bedridden state, $P < 0.01$), but showed similar survival. Onset in older individuals showed increased risk of confinement to a wheelchair ($P < 0.05$), bedridden state ($P = 0.03$) and death ($P < 0.01$). Patients initially complaining of motor symptoms had accelerated risk of aid-requiring walking ($P < 0.01$) and confinement to a wheelchair ($P < 0.01$) compared with those initially complaining of autonomic symptoms, while the time until confinement to a bedridden state and survival were no worse. Gender was not associated with differences in worsening of function or survival. On MRI, a hyperintense rim at the lateral edge of the dorsolateral putamen was seen in 34.5% of cases, and a 'hot cross bun' sign in the pontine basis (PB) in 63.3%. These putaminal and pontine abnormalities became more prominent as MSA-P and MSA-C features advanced. The atrophy of the cerebellar vermis and PB showed a significant correlation particularly with the interval following the appearance of cerebellar symptoms in MSA-C ($r = 0.71$, $P < 0.01$, $r = 0.76$ and $P < 0.01$, respectively), but the relationship between atrophy and functional status was highly variable among the individuals, suggesting that other factors influenced the functional deterioration. Atrophy of the corpus callosum was seen in a subpopulation of MSA, suggesting hemispheric involvement in a subgroup of MSA patients. The present study suggested that many factors are involved in the progression of MSA but, most importantly, the interval from initial symptom to combined motor and autonomic dysfunction can predict functional deterioration and survival in MSA.

Keywords: multiple system atrophy; progression; survival; activities of daily living; early symptoms

Abbreviations: ADL = activities of daily living; CC = corpus callosum; CV = cerebellar vermis; MISS = midline internal skull surface; MPF = midline posterior fossa; MSA = multiple system atrophy; MSA-C = multiple system atrophy–cerebellar; MSA-P = multiple system atrophy–parkinsonian; OPCA = olivopontocerebellar atrophy; PB = pontine basis; SND = striatonigral degeneration

Introduction

Olivopontocerebellar atrophy (OPCA), Shy–Drager syndrome and striatonigral degeneration (SND) were described as independent clinicopathological neurodegenerative entities in 1900, 1960 and 1961, respectively (Déjerine and Thomas, 1900; Shy and Drager, 1960; Adams *et al.*, 1961). Subsequently, concurrence of OPCA with SND, and of OPCA with Shy–Drager syndrome was reported (Adams *et al.*, 1964; Johnson *et al.*, 1966; Takahashi *et al.*, 1969). At that time, Graham and Oppenheimer (1969) suggested that OPCA, Shy–Drager syndrome and SND often co-exist clinicopathologically and proposed the term multiple system atrophy (MSA). Following this paper, many other clinicopathological studies supported this view (Bannister and Oppenheimer, 1972; Borit *et al.*, 1975; Spokes *et al.*, 1979; Gosset *et al.*, 1983; Polinsky 1984; Riku *et al.*, 1984). The subsequent discovery of glial cytoplasmic inclusions then allowed the clear definition of MSA as a clinicopathological entity (Papp *et al.*, 1989; Nakazato *et al.*, 1990). Neuronal loss and gliosis in the cerebral cortex, putamen, caudate nucleus, external pallidum, substantia nigra, locus coeruleus, pontine nuclei, inferior olives, cerebellar Purkinje cells, corticospinal tracts and intermediolateral cell columns of the spinal cord have been assessed so far (Riku *et al.*, 1984; Sobue *et al.*, 1986, 1987, 1992; Kume *et al.*, 1991, 1993; Terao *et al.*, 1994; Wenning *et al.*, 1995, 1997; Lowe *et al.*, 1997). Based on these clinicopathological analyses, diagnostic criteria were proposed by a Consensus Conference in 1998 (Gilman *et al.*, 1999). This statement recommended designating patients as having MSA-P if parkinsonian features predominated or MSA-C if cerebellar features predominated, in lieu of the older designations SND and OPCA, respectively. The designation Shy–Drager syndrome was considered to have lost practical meaning because of wide misuse of the term. Furthermore, almost all MSA patients develop autonomic dysfunction at some point during their course.

The presence of autonomic failure/urinary dysfunction plus either parkinsonism poorly responsive to levodopa or cerebellar ataxia is necessary to establish a clinical diagnosis of MSA and distinguish it from other diseases (Litvan *et al.*, 1997; Mathias and Bannister, 1999; Gilman *et al.*, 1999). However, MSA patients often show motor impairment or autonomic symptoms in isolation during the initial phase, followed by additional features during the course of the illness. Recently, Gilman *et al.* (2000) reported that 17 of 51 sporadic OPCA patients evolved to MSA within 5 years, and that this transition carried a poor prognosis for survival. Since the prognosis of MSA is less favourable than that of hereditary ataxia or Parkinson's disease, defining the interval from onset of first symptom to concurrent multiple system impairment is important for making an accurate diagnosis, for counselling patients and family members with respect to prognosis, and for designing therapeutic trials. Furthermore, variability has been observed concerning patterns of MSA signs, symptoms and progression, specifics of autonomic failure, MRI findings and ultimate prognosis. Many studies have suggested several risk factors that influenced progression and survival in MSA (Saito *et al.*, 1994; Schulz *et al.*, 1994; Wenning *et al.*, 1994; Testa *et al.*, 1996; Ben-Shlomo *et al.*, 1997; Klockgether *et al.*, 1998). However, some of these investigations involved small numbers of patients and, with the exception of three studies (Wenning *et al.*, 1994; Ben-Shlomo *et al.*, 1997; Klockgether *et al.*, 1998), diagnostic criteria were not uniform; thus proposed risk factors for progression and prognosis such as phenotype, gender or age of onset have shown disagreement between reports.

In addition, several reports have suggested that OPCA (MSA-C) is relatively more frequent and SND (MSA-P) less frequent among Japanese MSA patients than is the case in Western populations, but this generalization has not been assessed by current diagnostic criteria (Kita, 1993; Saito *et al.*, 1994). These observations, however, have raised the possibility that phenotypic manifestations of MSA may be influenced by ethnic background.

In this study, we investigated the initial clinical manifestation of MSA and subsequent evolution and outcome in 230 Japanese patients with probable or definite disease.

Methods

Selection of patients

We reviewed the medical records of 286 patients with a clinical diagnosis of MSA who were referred to the Nagoya University Hospital, Aichi Medical University Hospital or one of four affiliated hospitals in Aichi prefecture between 1985 and 1999. We evaluated these patients based on the Consensus Conference statement concerning MSA diagnostic criteria (Gilman *et al.*, 1999), and excluded 56 patients who did not fulfil criteria for probable or definite MSA. These excluded patients comprised: eight patients with cerebellar ataxia and parkinsonism but no autonomic involvement; 15 with orthostatic hypotension but failing to fulfil diagnostic criteria; and 11 with severe autonomic failure who did not develop parkinsonism or cerebellar signs during the follow-up period (two with mild rigidity and no gait disturbance; two with only postural tremor; three with nystagmus and mild limb ataxia; and four with extensor plantar responses and normoreflexia or hyper-reflexia). We also excluded 14 patients for whom we could not obtain the necessary information from medical records and interviews. Of the 230 MSA patients ultimately included in this study, all were followed-up by least one of the six institutions for a total period of 1–17 years (mean, 4.0 ± 2.8).

Clinical evaluation

The motor or autonomic symptoms initially noted by patients were considered to represent onset. Time from

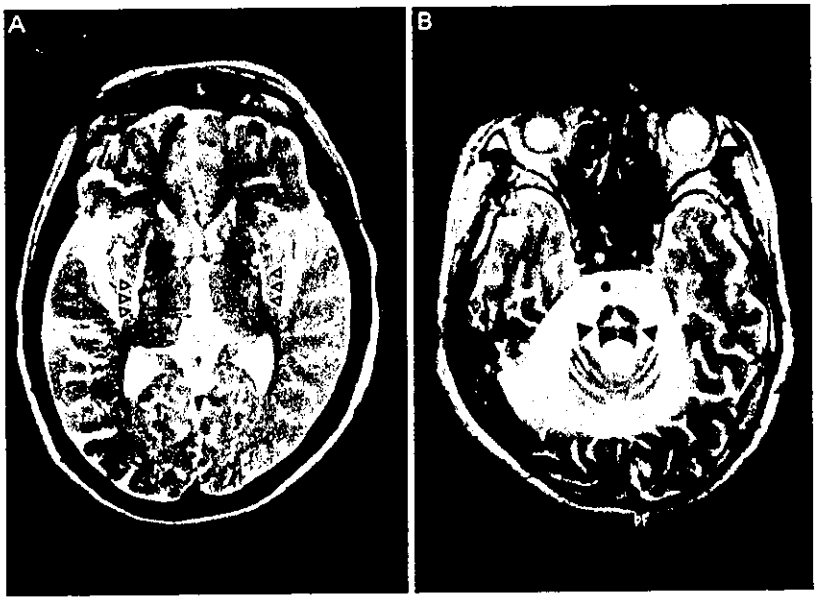

Fig. 1 MRI signal abnormalities in patients with multiple system atrophy. (A) Hyperintense putaminal rim on T_2-weighted images [1.5 T; 4000 ms repetition time (TR), 120 ms echo time (TE)] in the axial plane (arrowheads). (B) Signal change in the pons on T_2-weighted images (1.5 T; TR, 4000 ms; TE, 120 ms) in the axial plane (arrowheads).

Table 1 *Patient characteristics*

Characteristics	MSA	MSA-C	MSA-P
n	230	155	75
Male : female	131 : 99	93 : 62	38 : 37
Age at onset (years)	55.4 ± 8.3	54.8 ± 8.7	56.7 ± 7.2
Time from onset to diagnosis (years)	3.3 ± 2.0	3.2 ± 2.1	3.4 ± 1.7
Follow-up period (years)	4.0 ± 2.8	3.9 ± 2.7	4.0 ± 3.0
Initial symptoms			
Autonomic *n* (%)	64 (27.8)	49 (31.6)	15 (20.0)
Motor *n* (%)[+]	166 (72.2)	106 (68.4)	60 (80.0)

[+]Motor symptoms include either parkinsonism or cerebellar ataxia.

onset to transition or evolution to MSA, requiring both motor and autonomic involvement, was defined as patient awareness of symptoms of both types. Symptoms of all 230 patients were assessed from clinical records, and confirmed by an interview of patients and family if adequate information was not obtained from clinical records. All the autopsy records were assessed for the patients who underwent post-mortem examination. Autonomic symptoms included urinary and orthostatic symptoms. Urinary symptoms were nocturnal or diurnal urinary frequency, a sensation of urgency, urinary incontinence, voiding difficulty and retention. Orthostatic symptoms were postural faintness, blurred vision or syncope associated with an orthostatic drop of 30 mmHg in systolic blood pressure or 15 mmHg in diastolic blood pressure without a corresponding increase in heart rate of >10 beats per minute. While sexual impotence in MSA is a noteworthy symptom, manifesting in an early phase and affecting virtually all male patients, it was not considered here. Organic erectile failure can be difficult to distinguish objectively from psychogenic impotence (Mathias *et al.*, 1999). Furthermore, impotence has low specificity for diagnosis of MSA, as the consensus statement described (Gilman *et al.*, 1999).

We assessed three activities of daily living (ADL) milestones to evaluate disease progression: aid-requiring walking was defined as use at all times of a walking aid or a companion's arm for support; a wheelchair-bound state was defined as use of a wheelchair at all times; and a bedridden state was defined as complete loss of ability for independent movement. We assessed time of onset for each of these states and for death by reviewing the patient's record, by family

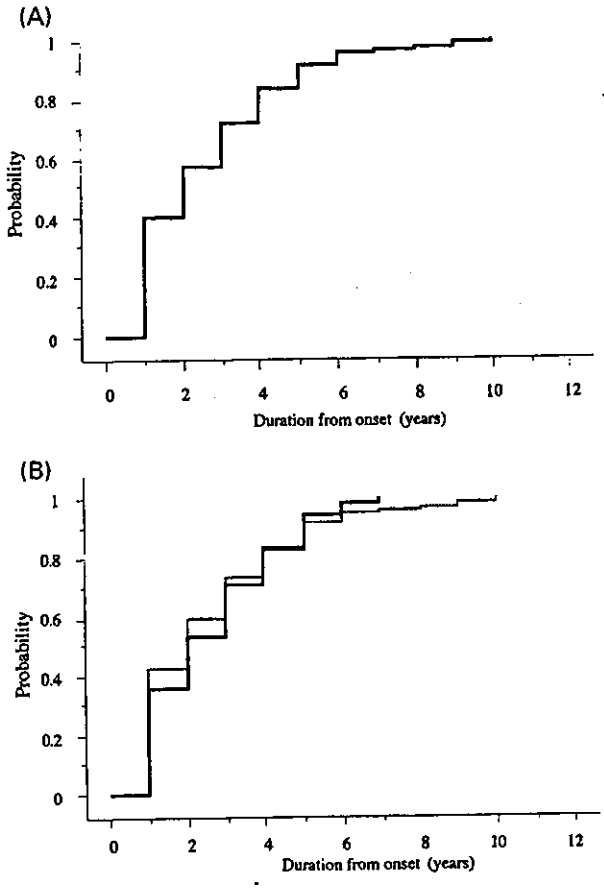

Fig. 2 Time from onset to appearance of concomitant motor and autonomic manifestations calculated by the Kaplan–Meier method. Patients are considered overall in A and by phenotypic group in B. No significant difference in rate of this evolution was noted between predominantly cerebellar multiple system atrophy (MSA-C; thin line) and predominantly parkinsonian (MSA-P; thick line).

interviews and direct examination of the patients in the follow-up hospital.

MRI

We examined MRI findings at the first hospital visit for 139 of 230 patients. Age at MRI examination ranged from 43 to 78 years (mean, 56.9 ± 8.1 years). Among these, 96 MSA patients (59 MSA-C, 37 MSA-P) were examined with a 1.5 T scanner, and 43 patients (26 MSA-C, 17 MSA-P) with a 0.5 T scanner. All MRIs included T_1- and T_2-weighted axial images [2300–4000 ms repetition time (TR), 80–120 ms echo time (TE), 5–8 mm thickness and 1–2.5 mm gap). We evaluated the presence of a hyperintense rim in the dorsolateral putamen (Fig. 1A) and a 'hot cross bun' sign in the pons (Fig. 1B) according to previous reports (Savoiardo *et al.*, 1990; Konagaya *et al.*, 1994; Schrag *et al.*, 1998; Kraft *et al.*, 1999). We also quantified atrophic change of the cerebellar vermis (CV), pontine basis (PB) and corpus callosum (CC) in 52 patients with sufficient information available for assessment (33 MSA-C, 19 MSA-P; mean age, 55.7 ± 8.2 years; range, 42–78 years) compared with 45 age-matched control subjects (mean age, 55.1 ± 7.7 years; range, 42–76 years). A midsagittal T_1-weighted spin-echo image was used for measurement (1.5 T; TR, 350–500 ms; TE, 15–20 ms). Areas of CV, PB and CC were quantified from the computer monitor using US National Institutes of Health image software (version 1.60) as described previously (Abe *et al.*, 1998). Areas of the midline posterior fossa (MPF) and midline internal skull surface (MISS; inner table, foramen magnum, clivus, sellar diaphragm and jugum sphenoidale) were measured to adjust for individual variation in the size of the skull. Ratios of PB/MPF, CV/MPF and CC/MISS were calculated as previously described (Laissy *et al.*, 1993; Abe *et al.*, 1998).

Statistical analyses

Data were entered into a database for further statistical analysis. Kaplan–Meier analyses were used to estimate the disease progression assessed by ADL milestones. Risk factors possibly influencing disease progression included initial symptoms, age of onset, disease phenotype and gender. Log-rank test statistics were used to determine whether Kaplan–Meier transition curves differed among subgroups (Peto *et al.*, 1977). Statistically assessed data for disease progression are expressed as median values. The disease duration from onset to the time when both autonomic and motor impairment was present was also assessed as a risk factor. The Mann–Whitney *U* test was used to compare continuous variables for different subgroups. Contingency tables were analysed with the χ^2 test. Relationships between duration of cerebellar signs and interval from onset to degree of CV, PB and CC atrophy were analysed using Pearson's correlation coefficient. Calculations were performed using the statistical software package Stat View (Abacus Concepts, Berkeley, Calif., USA).

Results

Patient characteristics

Patients consisted of 131 men and 99 women (Table 1). Mean age at onset of the first symptom was 55.4 ± 8.2 years (range, 38–75 years). 155 patients had MSA-C and 75 had MSA-P. No significant differences were noted between these two subgroups for gender distribution, age at onset, interval from onset to MSA diagnosis or follow-up period. 166 patients complained of motor disturbance as an initial symptom before appearance of autonomic failure; cerebellar dysfunction was the initial symptom in