Late-onset hereditary ataxia with global thermoanalgesia and absence of fungiform papillae on the tongue in a Japanese family

T. Fukutake, K. Kita, R. Sakakibara, K. Takagi, Y. Tokumaru, S. Kojima, T. Hattori and K. Hirayama

Department of Neurology, Chiba University School of Medicine, Chiba, Japan

Correspondence to: T. Fukutake, Department of Neurology, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260, Japan

Summary
Two Japanese male siblings, aged 68 and 59 years, affected by late-onset progressive ataxia distinguished by extensive sensory and mild autonomic disturbances are described. They had global thermoanalgesia, positive Romberg signs, sensorineural deafness, canal paresis and ageusia. Their autonomic disturbances consisted of absence of overflow tears with usual stimuli, dysphagia, blood pressure and vasomotor instability, diarrhoea/constipation, and urinary frequency. Sensory nerve action potentials were completely absent, whereas motor conduction velocity was slightly reduced only in the lower extremities. Sural nerve biopsy on the younger brother demonstrated a marked loss of myelinated fibres and a reduction in the number of unmyelinated axons. Tongue histology revealed absence of fungiform papillae and taste buds. Autonomic function tests showed widespread but mild sympathetic and parasympathetic failures. Neuro-imaging studies revealed atrophy of the spinal cord, cerebellum, brainstem and corpus callosum, and enlargement of the lateral, third and fourth ventricles. These siblings represent a previously unrecognized variant of late-onset hereditary spinocerebellar degeneration with global thermoanalgesia and absence of fungiform papillae on the tongue.

Keywords: hereditary sensory and autonomic neuropathy; familial dysautonomia (Riley–Day syndrome); hereditary ataxia; thermoanalgesia; fungiform papillae on the tongue (or ageusia)

Abbreviations: ANA = antinuclear antibody; FD = familial dysautonomia

Introduction
This report describes a variant of late-onset ataxia with extensive sensory and mild autonomic disturbances similar to those of Type II or III hereditary sensory and autonomic neuropathy (Dyck, 1993), especially global thermoanalgesia and absence of fungiform papillae on the tongue, in two Japanese adult male siblings.

Case reports
The family originated in Chiba Prefecture, near Tokyo, Japan, and there was no history of Jewish descent and no history of consanguinity (Fig. 1). The patients' grandfathers and grandmothers (I-1-4) died in their sixth or seventh decade, but their medical histories are unclear. The patients' father (II-4), who died age 70 years, had suffered from staggering gait, stuttering speech, defective lacrimation and neurotic depression later in life; their mother (II-6) died age 82 years from 'old age'. Their elder brother (III-1) died age 73 years from a cerebrovascular accident. Their elder sister (III-2) died in her sixth decade, suicide. The other siblings (III-4 and -6), the next generation (IV) and the descendants, as far as we know, are alive and normal.

Case 1 (III-3)
H. T., the proposita, a 68-year-old Japanese man (Fig. 1), presented with an 8-year history of staggering gait. This had been slowly progressive and had been exaggerated in the dark. He had also noted stuttering speech from childhood, which had been overwhelmed by slurred speech for 8 years, a tendency to easily get burned on the foot for 30 years, hearing loss and urinary frequency for 8 years, dysgeusia, dysphagia, constipation/diarrhoea and cold feeling on the legs in winter for 3 years, and numbness on the forehead.

© Oxford University Press 1996
and electrical pain in the lower body for 2 years. Frequently he had got chest infections or unexplained fever. He had had no exposure to toxins and had never taken alcohol in excess.

Physical examination on admission, November 29, 1991, revealed a skinny man (height 163 cm, weight 43 kg) with scoliosis, hammer toes and claw feet. Blood pressure was 150/90 mmHg supine and 120/70 standing. His hands and feet were very cold because of freezing weather. There was neither skin ulcers nor mutilating acropathy. No enlargement of the liver and spleen was found. On neurological examination, his cognitive functions were normal. He walked with a stick on a broad base with marked titubation. His speech was slurred and scanning. The pupils were equal, round and slightly sluggish to light. Ocular saccades were hypometric and smooth pursuit movements were saccadic. A fine jerk nystagmus was present on horizontal gaze to either side. His conjunctiva and cornea were moist, but overflow tears were absent with usual stimuli. Corneal sensitivity and reflexes were almost lost. The fundi were normal. Hearing was decreased, associated with tinnitus; audiometric testing showed a threshold to air conduction of 80 dB. Vestibular response to caloric stimulation was absent. The tongue appeared smooth, free from fungiform papillae; taste was lost. The movements of the tongue were normal. Hyposmia was also noted. Difficulty in swallowing water was present.

Mild muscular wasting was globally present, with slight hypotonus and no fasciculation; there was no obvious weakness. Tendon reflexes were normal in the arms, but increased at the knees. The right ankle jerk was decreased, and the left absent. Both plantar reflexes were unresponsive. Pain and temperature sensation were lost globally up to the buccal membranes, with the exception of mild impairment in the lower eye lids, scrotum and central parts of the palms (Fig. 2, left). Touch sensation was normal. Vibration sense was decreased below the elbows and knees, but position sense was preserved. Graphaesthesia and 'proprioceptive localization' (Hirayama et al., 1986; Fukutake and Hirayama, 1992) were mildly impaired in the feet. Periphera nerves were neither palpably nor tender. Moderate dysmetria and terminal oscillation were noted in both finger–nose and heel–knee testings; rapid alternating movements were arrhythmic. On a Revised Wechsler Adult Intelligence Scale test of Japanese version, he scored an IQ of 61; verbal IQ 62 and performance IQ 65.

Laboratory examinations
Routine haematology revealed mild anaemia with a red blood cell count of 324X10⁴ and a haemoglobin of 10.9 mg dl⁻¹. Immunoglobulin (Ig) G was slightly elevated to 2179 mg dl⁻¹ but IgA and IgM were normal. Erythrocyte sedimentation rate was 85 mm h⁻¹ and C-reactive protein was 1.4 mg dl⁻¹. The following determinations were normal: routine biochemical tests and electrolytes, thyroid function with microsome and thyroid tests, serum protein electrophoresis, complements, rheumatoid factor, antinuclear antibody (ANA) tests, syphilis serology, fasting blood sugar, phytanic acid, leukocyte lysosomal enzymes (arylsulfatase A, alpha-galactosidase A, beta-galactosidase, N-acetyl-beta-glucosaminidase A and B), and serum very long chain fatty acids. CSF contained 1 cell mm⁻³, 20 mg protein dl⁻¹ and 60 mg glucose dl⁻¹.

General radiology
A chest X-ray showed pleural scarring and non-homogeneous shadow in the left lung, consistent with old pneumonia. A skull X-ray was normal.

Case 2 (III-4)
N. T., a 59-year-old brother of the proposita (Fig. 1), had his first experience of staggering gait at the age of 49...
years. This had slowly worsened and had been exaggerated in the dark. He was still able to walk without support on a broad base. He had also noted stuttering speech from childhood, dry sensation of the eyes for 7 years, finger tremor in action and urinary frequency for 5 years, dysgeusia, constipation/diarrhoea, and cold feeling in the hands in winter for 3 years, and numbness on the hands and a tendency to easily get burned on the feet for 1 year. He had lost 7 kg in weight over 2 years. He had occasional respiratory infections.

On examination, on January 29, 1992, the patient appeared poorly nourished with a height of 166 cm and a weight of 49 kg. Blood pressure was 145/78 supine and 125/69 standing. His hands and feet were very cold. He was alert and cooperative. There was mild stuttering and scanning of speech. Ocular saccades were slightly slow and smooth pursuit movements were saccadic. Bilateral horizontal gaze-evoked nystagmus was present. His conjunctiva and cornea were moist, but overflow tears were absent with usual stimuli. Corneal sensitivity and reflexes were impaired. Hearing was mildly decreased, below a level of 40 dB. Caloric tests gave no response. The tongue was smooth, free from fungiform papillae; taste was lost. Swallowing was normal. Mild muscular wasting was globally present, with normal muscle strength and tone without fasciculation. Tendon reflexes were preserved except for decreased ankle jerks. Both plantar responses were flexor. Pain and temperature sensation were lost globally (Fig. 2, right). Light touch and vibration sense were decreased below the wrists and ankles, but position sense was preserved. Graphaesthesia and 'proprioceptive localization' were mildly impaired in the feet. There was moderate ataxia in all limbs. On a Revised Wechsler Adult Intelligence Scale test of Japanese version, he scored an IQ of 72; verbal IQ 82 and performance IQ 62. In a Mini-Mental State Test of Japanese version he had a score of 25/30.

Laboratory examinations
The following were normal: routine haematology and chemistry, electrolytes, erythrocyte sedimentation rate, thyroid function, serum protein electrophoresis, complement factors, rheumatic factor, ANA tests, syphilis serology, fasting blood sugar, serum vitamins B₁ and B₁₂, leukocyte lysosomal enzymes and serum very long chain fatty acids. Cerebrospinal fluid contained 1 cell mm⁻³, 21 mg protein dl⁻¹ and 65 mg glucose dl⁻¹.

Neurophysiological investigations
Peripheral nerve conduction (Table 1)
In both cases, median, ulnar and sural sensory action potentials were not evoked. Median and ulnar motor conduction velocities were normal, but tibial and superficial peroneal motor conduction velocities were mildly decreased. F-wave latencies of the examined nerves of the legs were also prolonged. These findings suggested that they had sensory predominant neuropathy.

Needle EMG
The studies showed normal neuromuscular units in biceps brachii, triceps brachii, brachioradialis and small hand muscles in both cases, neurogenic neuromuscular units with long durations and giant spikes in quadriceps femoris, tibialis anterior and gastrocnemius muscles in Case 1 and equivocal
Table 2  Results of autonomic function tests in the siblings

<table>
<thead>
<tr>
<th>Test</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Expected responses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head-up tilting (80°)</td>
<td>BP (−19 mmHg)</td>
<td>BP (−16 mmHg)</td>
<td>No BP change</td>
</tr>
<tr>
<td>Plasma NA (supine/head-up)</td>
<td>323/432 pg/ml</td>
<td>368/536 pg/ml</td>
<td>200–600/300–1000 pg/ml</td>
</tr>
<tr>
<td>Cold pressor</td>
<td>No BP change</td>
<td>No BP change</td>
<td>BP (−10–30 mmHg)</td>
</tr>
<tr>
<td>Carotid sinus massage</td>
<td>Normal</td>
<td>Low response</td>
<td>Normal</td>
</tr>
<tr>
<td>Valsalva manoeuver ratio</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal (BP overshoot)</td>
</tr>
<tr>
<td>NA infusion (0.1 μg kg⁻¹ min⁻¹)</td>
<td>BP (−20 mmHg)</td>
<td>BP (−25 mmHg)</td>
<td>BP (−20 mmHg)</td>
</tr>
<tr>
<td>IP infusion (0.02 μg kg⁻¹ min⁻¹)</td>
<td>BP (−14 mmHg)</td>
<td>BP (−16 mmHg)</td>
<td>BP (−15–+5 mmHg)</td>
</tr>
<tr>
<td>Coefficient of variation in R–R interval</td>
<td>1.2</td>
<td>1.6</td>
<td>3.5–7.5</td>
</tr>
<tr>
<td><strong>Pupillary responses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% cocaine</td>
<td>No change</td>
<td>Slight dilatation</td>
<td>Dilatation</td>
</tr>
<tr>
<td>1.25% NA</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>5% tyramine</td>
<td>Dilatation</td>
<td>Dilatation</td>
<td>Dilatation</td>
</tr>
<tr>
<td>2.5% methacholine</td>
<td>Constriction</td>
<td>Constriction</td>
<td>No change</td>
</tr>
<tr>
<td>Schirmer test (5 min)</td>
<td>2 and 2 mm</td>
<td>4 and 5 mm</td>
<td>&gt;15 mm</td>
</tr>
<tr>
<td>Gum test (10 min)</td>
<td>11 ml</td>
<td>16 ml</td>
<td>&gt;10 ml</td>
</tr>
<tr>
<td>Thermal sweating</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>Cold in distal</td>
<td>Cold in distal</td>
<td>Normal</td>
</tr>
<tr>
<td>Thermography</td>
<td>n.e.</td>
<td>Insufficient</td>
<td>Normal</td>
</tr>
<tr>
<td>Plethysmography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urodynamic study</td>
<td>Uninhibited</td>
<td>Uninhibited</td>
<td>Normal</td>
</tr>
<tr>
<td>Cystometry</td>
<td>0 ml</td>
<td>0 ml</td>
<td>0 ml</td>
</tr>
<tr>
<td>Residual urine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA = noradrenaline; IP = isoproterenol; BP = blood pressure; HR = heart rate; n.e. = not examined; ↑ = increase; ↓ = decrease; .prevented increase;  = mild decrease; → = little or no change

neurogenic neuromuscular units in the same leg muscles in Case 2.

**Somatosensory evoked potentials**
In both cases, somatosensory evoked potentials after tibial nerve stimulations revealed conduction delay within the peripheral nerves, roots and posterior columns.

**Brainstem auditory evoked potentials**
These demonstrated, in both cases, delayed latency of wave I and normal conduction time between waves I and V, consistent with hearing loss of sensorineural type.

**Autonomic functions**
Table 2 shows the results of autonomic function tests.

**Cardiovascular function**
Head-up tilting (80°), after 1 min, revealed 19 and 16 mmHg drop in systolic blood pressure in the two subjects, Cases 1 and 2, respectively, with only slight elevation in heart rate. Measurement of plasma noradrenalin in supine position and 10 min after tilting showed normal basal values and low orthostatic increases. Cold pressor tests done by immersing the patient’s one hand in ice water at 4°C for 1 min demonstrated no rise in blood pressure. Carotid sinus massage tests were normal in Case 1, but gave a low response in Case 2. Valsalva manoeuver tests gave normal blood pressure overshoot in phase IV (Valsalva ratio: 1.37 in Case 2). Noradrenalin infusion tests, 0.05–0.15 μg kg⁻¹ min⁻¹, did not show exaggerated increases in blood pressure in either case. Isoproterenol infusion tests, 0.02 μg kg⁻¹ min⁻¹ revealed slight decreases in blood pressure but no exaggerated increases in heart rates. Coefficients of variation of R–R intervals on EKG, calculated by feeding 100 successive beats three times through an arrhythmia computer (Automatic R-100, M. E. Commercial Corp., Tokyo, Japan) while the patients lay quietly at least 15 min, were low, 1.1 and 1.6, respectively, suggesting parasympathetic dysfunction. In Case 1, serum homovanillic acid and vanillyl-mandelic acid were normal; mean excretion rates of homovanillic acid and vanillyl-mandelic acid in the 24 hour urine were also normal.

**Pupillary responses to a series of agents**
In both cases, defective pupillary dilatation to 5% cocaine and exaggerated pupillary constriction to 2.5% methacholine...
were observed, indicating both sympathetic and parasympathetic dysfunctions.

**Lacrimation**
Schirmer filter-paper tests showed 2 and 2 mm, and 4 and 5 mm of tear flow in each eye at 5 min, respectively, indicating deficiency of tear secretion.

**Salivation**
Chewing gum yielded a normal volume of saliva in both cases.

**Swallowing**
 Videofluoroscopic swallowing examination in Case 1 revealed marked aspiration.

**Sweating**
Thermal sweat tests showed normal sweating on whole body in both cases.

**Vasomotor function**
Thermographic examinations showed abnormally cold areas in the distal parts of four extremities. A plethysmographic test on the right middle finger in Case 2 revealed insufficient response.

**Urodynamic study**
Cystometric examinations demonstrated uninhibited contraction of the bladder with storage disorder in both cases. No residual urine was measured.
Histamine flare test
Skin flare testing, with 0.03 ml (1 mg ml"^{-1}"") of histamine injected intradermally into the forearm, showed normal wheals and areola in both cases, but diminished flare responses (8 and 9 cm², respectively); the flares were less than half the size of normal controls (20 cm²) and of normal flares reported previously. The patients experienced no pain.

Neuro-imaging studies
Brain
CT of the brain in Case 1 showed moderate atrophy of the cerebellum and brainstem, and moderate dilatation of the lateral, third and fourth ventricles (Fig. 3A). MRI of the brain in both cases revealed moderate atrophy of the cerebellum, brainstem and corpus callosum (Fig. 3B).

Spinal cord
Metrizamide myelogram and CT myelogram disclosed marked atrophy of the spinal cord with flattening of the posterior aspect, suggesting posterior column pathology (Fig. 4).

Morphological investigations
Tongue biopsies
Methods
With informed consent, biopsy specimens were taken in both patients from the lateral part of upper surface of the tongue at the anterior one-third line. These were fixed in formaldehyde solution and embedded entirely in paraffin. Histological examinations were performed employing haematoxylin-eosin stain.

Results (Fig. 5)
In both cases, neither fungiform papillae nor taste buds could be found in step sections. In Case 2, illiform papillae were present, although they were reduced in number, whereas in Case 1 the absence of illiform papillae, thinning of ectoderm and poor papillary formation were confirmed.

Sural nerve biopsies
A whole sural nerve biopsy was performed on Case 2 at ankle level without the use or need of a local anaesthetic. Control biopsies came from three patients being investigated for neuromuscular disease, who proved to have myopathy. The patient and control patients gave informed consent to the procedure.

Methods
The specimen was fixed in phosphate buffered 2.5% glutaraldehyde for 24 h. After osmication and dehydration it was embedded in epoxy plastic. Semi-thin transverse sections were stained with toluidine blue for light microscopy. Thin sections for electronmicroscopy were examined in a Hitachi H700H. Quantitative analysis of myelinated and unmyelinated nerve populations was carried out.

Results
Light microscopy revealed a marked reduction in density of the number of small and large myelinated fibres, which was 1246 mm"^{-2}" (normal range 7000–11 000) (Figs 6 and 7). There were no amyloid deposits and no inflammatory changes.

Quantitative electron microscopy showed a significant but less severe reduction in the densities of unmyelinated nerve fibres which was 12 000 mm"^{-2}" (normal range 25 000–50 000). The histogram of the diameters of unmyelinated sural nerve fibres shows a selective decrease of density in fibres of <1 μm diameter (Fig. 8). There were numerous Schwann cell clusters and collagen pockets (12 400 mm"^{-2}" and 19 900 mm"^{-2}", respectively) (Fig. 9) but no excess of lipofuscin and no endoneurial cytoplasmic inclusions were
evident on electron microscopic examination of the sural nerve.

These findings were consistent with a chronic, relatively inactive, genetically acquired axonal neuropathy.

**Discussion**

The reported siblings are affected by a similar, but uncommon, clinical disorder, a slowly progressive spinocerebellar ataxia beginning in the fifth or sixth decade, associated with extensive sensory and mild autonomic disturbances. Their father might also have suffered from the same disease; autosomal dominant inheritance is therefore probable.

The first, most striking feature of the siblings exists in the absence of fungiform papillae on the tongue. This unusual unique sign has been considered to be a major diagnostic, almost pathognomonic feature for Type III of hereditary sensory and autonomic neuropathy, i.e. familial dysautonomia (FD) (Dancis, 1983). Tongue pathology in the siblings is also consistent with those in FD (Smith et al., 1965b; Pearson et al., 1970). Absence of the papillae has not been reported in any other condition, except following a defect of the chorda tympani (Bull, 1965) and in some cases of congenital sensory neuropathies (Barry et al., 1974; Kien et al., 1981; Nordborg et al., 1981; Axelrod and Pearson, 1984; Ouvrier

---

**Fig. 5** Tongue biopsies in both cases (Case 1, upper; Case 2, lower) showing loss of fungiform papillae and taste buds. ×20.
Fig. 6 Transverse section of sural nerve from Case 2 showing marked reduction of myelinated fibres. Horizontal bar = 100 μm.

Fig. 7 Histograms showing diameter distribution of myelinated sural nerve fibres from Case 2 (left) and controls (right).

Fig. 8 Histogram showing diameter distribution of unmyelinated sural nerve fibres from Case 2 (left) and controls (right).

Fig. 9 Electron microscopic examination of sural nerve from Case 2 showing numerous Schwann cell clusters (upper) and collagen pockets (lower). Horizontal bar = 2 μm.
### Table 3 Diagnostic criteria in our patients and in Type II and III hereditary sensory and autonomic neuropathy

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial occurrence</td>
<td>+(AD?)</td>
<td>+(AD?)</td>
<td>+(AR)</td>
</tr>
<tr>
<td>Jewish extraction</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age at onset</td>
<td>5th decade</td>
<td>5th decade</td>
<td>Birth to 3rd decade</td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>±</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>Skin blotching</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vasomotor instability</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Defective lacrimation</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Impairment of taste</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Impairment of salivation</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Excessive sweating</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Episodic vomiting</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Constipation/diarrhoea</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Disorder of micturition</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal temperature control</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Recurrent chest infection</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Episodic fevers</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Motor-sensory-mental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of intelligence</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Emotional instability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypoactive tendon reflex</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Hypotonus</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Insensitivity to pain or thermoanalgesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Corneal insensitivity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Canal paresis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Body weight loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pes cavus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Absent fungiform papillae</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Sural nerve biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelinated fibres</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Unmyelinated fibres</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

\[\text{†} = \text{marked decrease}; \downarrow = \text{mild or moderate decrease. Adopted from Riley et al. (1949); Riley and Moore (1966); Mahloudji et al. (1970); Pearson et al. (1971); Solitare (1975, 1991) and Dyck (1993).}\]

and McLeod, 1991). The former is generally unilateral and excluded by history. The latter is seen in infants and children.

The second remarkable finding in the siblings is global thermoanalgesia, which is a prominent feature of hereditary sensory and autonomic neuropathy but rarely associated with spinocerebellar degenerations. The unusual combination of ataxia and thermoanalgesia was reported in some sporadic diseases, such as 'chronic sensory and autonomic neuropathy' (Yamamura et al., 1975; Kobayashi et al., 1979) and 'sensory polyneuropathy accompanied by generalized insensitivity to pain' (Nokura et al., 1991), but these cases had no evidence of CNS involvement. The majority of patients with late onset ataxia have no sensory symptoms. Even when sensory impairments develop, they are of a minor degree with sensory signs usually restricted to vibration and proprioceptions (Harding, 1982). Some authors have reported patients with adult onset spinocerebellar degeneration associated with peripheral neuropathy (McLeod and Evans, 1981; Bennett et al., 1984; Nousiannen, 1988), but the degree of peripheral damage was less severe than in this investigation. Recently Pollock and Kies (1990) described three siblings aged 79, 71 and 67 years, from a New Zealand family affected by late onset hereditary cerebellar ataxia, distinguished by the development of near global thermoanalgesia. The evaluation of sural nerve biopsies revealed a marked loss of axons, especially of those with diameters 1–7 μm and 0.2–1.5 μm. These cases are distinguished from our patients in the preservation of hearing, taste, proprioception and autonomic function. A number of hereditary spinocerebellar syndromes with neuropathy, namely Refsum’s disease, adult chronic GM2 gangliosidosis (Rapin et al., 1976), adrenomyeloneuropathy (Marsden et al., 1982). Krabbe’s disease (Thomas et al., 1984) and ceroid lipofuscinosis (Wisniewski et al., 1988) were excluded by the clinical history and laboratory results. Sensory impairment in the brothers of this study was noted not only in somatic sensation but also in special sensations;
they had sensorineural hearing loss, canal paresis and loss of taste. The latter two are common in FD (Siggers et al., 1975), but hearing is intact in FD.

The younger brother showed the following pathological features on sural nerve biopsy: (i) a marked diminution of myelinated axons and (ii) a moderate depletion in non-meylinated axons. This morphology corresponds closely with that previously observed in Type II hereditary sensory and autonomic neuropathy (Axelrod et al., 1983; Axelrod and Pearson, 1984; Dyck, 1993) rather than Type III (FD) (Aguayo et al., 1971). No consistent findings in the CNS have been reported in FD, but most patients with FD present with poor coordination or ataxia and some cases, particularly older ones, have cerebellar, brainstem and sometimes posterior column–dorsal root pathology (Cohen and Solomon, 1955; Brown et al., 1964; Fogelson et al., 1967; Sohn and Levine, 1974).

The brothers presented with autonomic disturbances, which are widespread but milder than those in FD (Riley et al., 1949; Riley and Moore, 1966; Mahloujdi et al., 1970; Pearson et al., 1971; Sofitare, 1975, 1991), Shy–Drager syndrome (Shy and Drager, 1960) or acute pandysautonomia (Kita et al., 1984). This mildness may reflect the extent of the diminution in non-meylinated fibres. In the cardiovascular system, there are no findings of alpha and beta-1 post-ganglionic sympathetic disturbances, although pharmacological testing (Isoproterenol infusion) demonstrated slight beta-2 adrenergic denervation supersensitivity. Characteristically they showed low response of heart rate to blood pressure variance in the head-up tilting test, suggesting impairment of cardiovascular sympathetic system. Lack of blood pressure rise on cold stress may reflect somatic sensory disturbance (global thermoanalgnesia), although it can also be the result of a defect in the sympathetic efferents. The levels of noradrenaline in both cases and homovanillic acid/vanillylmandelic acid in Case 1 are distinct from those in FD (Smith et al., 1963; Smith and Dancis, 1964). Low R–R interval variation on ECG, pupillary constriction to methacholine, loss of overflow tears, uninhibited contraction of the bladder, and, possibly, swallowing dysfunction indicated parasympathetic failure. Methacholine supersensitivity has been thought to be one of the ‘cardinal’ findings of FD (Smith et al., 1963a). In the siblings, the moisture of the eyes was normal, although they had hypolacrimation. The defect seems to lie mainly in the production of tears after emotional stimuli (Dancis, 1983, 1963). In conclusion, these siblings represent a previously unrecognized variant of late-onset hereditary spinocerebellar degeneration with predominant involvement of afferent (sensory) components in somatic and cranial–special nerves.

Acknowledgements

We wish to thank Drs T. Numata and T. Hino (Department of Otorhinolaryngology, Chiba University) for carrying out tongue biopsies, Drs N. Amaya and K. Tanaka (Institute of Neurology, Niigata University) for measuring lysosomal enzymes and very long chain fatty acids. The work was supported by the Research Committee on Ataxia of the Ministry of Welfare and Health, Japan.

References


Fukutake T, Hirayama K. Big-toe localizing test—clinical study of

Harding AE. The clinical features and classification of the late onset autosomal dominant cerebellar ataxias: a study of 11 families, including descendants of 'the Drew family of Walworth'. Brain 1982; 105: 1–28.


Accepted January 8, 1996

Hereditary ataxia with thermoanalgesia 1021