Facial onset sensory and motor neuronopathy (FOSMN syndrome): a novel syndrome in neurology

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A ‘syringomyelia-like’ syndrome has been infrequently reported in neurological disorders such as Tangier disease and lepromatous leprosy. This study reports a novel ‘syringomyelia-like’ syndrome in four adult male patients, which we have termed facial onset sensory and motor neuronopathy, or FOSMN syndrome, that appears to have a neurodegenerative aetiology. Clinical, neurophysiological and pathological data of four patients were reviewed, including the autopsy in one patient. Four male patients (mean age at onset 43), initially developed paraesthesiae and numbness in a trigeminal nerve distribution, which slowly progressed to involve the scalp, neck, upper trunk and upper limbs in sequential order. Motor manifestations, including cramps, fasciculations, dysphagia, dysarthria, muscle weakness and atrophy developed later in the course of the illness. Neurophysiological findings revealed a generalized sensory motor neuronopathy of caudally decreasing severity in all four patients. Autopsy in one patient disclosed loss of motoneurons in the hypoglossal nucleus and cervical anterior horns, along with loss of sensory neurons in the main trigeminal sensory nucleus and dorsal root ganglia. FOSMN syndrome appears to be a slowly progressive neurodegenerative disorder, whose pathogenesis remains to be determined.

Keywords: FOSMN syndrome; syringomyelia; motoneuron disease; sensory neuropathy


Introduction

Dissociated sensory loss in the cranial, cervical and brachial dermatomes accompanied by wasting and weakness of intrinsic hand and cranio-bulbar muscles is the classic presentation of syringomyelia and syringobulbia (Victor and Adams, 1993; Levine, 2004). The interruption of centrally located spinothalamic fibres by a syrinx results in loss of pain and temperature sensations, while the involvement of anterior horns and bulbar nuclei results in muscle wasting and weakness.

A “syringomyelia-like” syndrome has been reported in the setting of peripheral nerve degeneration secondary to Tangier disease (Dyck et al., 1987; Pietrini et al., 1985; Gibbles et al., 1985; Schmalbruch et al., 1987; Antoine et al., 1991). Tangier disease is an autosomal-recessive disorder of lipid metabolism characterized by markedly reduced high-density lipoprotein (HDL) and apolipoprotein A-I. Recently, mutations in the ATP-binding cassette transporter 1 (ABCA1) gene were reported in Tangier disease (Brousseau et al., 2000; Iida et al., 2001; Zuchner et al., 2003).

In addition to Tangier disease, lepromatous leprosy can also produce a “syringomyelia-like” syndrome (Gibble et al., 1985). Leprosy is an infectious disorder of intracutaneous nerves, preferentially affecting pain and temperature sensations in areas of low skin temperature. Consequently, the aim of this study was to report clinical, neurophysiological and pathological features of a novel “syringomyelia-like” syndrome, termed facial onset sensory and motor neuropathy (FOSMN syndrome), that appears to be a slowly progressive neurodegenerative disorder.

Patients and methods

Study population

Four patients of Caucasian descent, who were referred to the neuromuscular clinic at the Massachusetts General Hospital with a
slowly progressive sensorimotor syndrome, beginning with sensory dysfunction in a peri-oral distribution, were the subjects of this study. Patients underwent clinical, laboratory, neurophysiological and pathological examination, including an autopsy study in one patient who died from a pulmonary embolus.

**Neurophysiology**

Nerve conduction studies (NCS), electromyography, blink reflexes and cervical nerve root stimulation were performed according to methods previously described (Berger et al., 1987; Kimura, 2001; Vucic et al., 2006). All nerves were studied bilaterally, and normative values used those established in our laboratory (Vucic et al., 2005).

**Neuropathology**

**Autopsy**

A full autopsy was performed on Patient 1, 12 hours post-mortem. Brain, spinal cord, dorsal root ganglia at multiple levels, muscle and peripheral nerves were fixed in 10% phosphate-buffered formalin for 2 weeks. Representative blocks were embedded in paraffin wax. Five-micron thick sections were stained with Luxol fast blue and haematoxylin and eosin for brain, spinal cord and dorsal root ganglia, or haematoxylin and eosin for muscle and peripheral nerves. Selected sections were immunostained for GFAP using diaminobenzidine (DAB) tetrahydrochloride as the chromogen.

**Muscle biopsies**

Muscle biopsies were divided into two parts processed for enzyme histochemical and ultrastructural analysis. The tissue for histochemical analysis was snap frozen in liquid nitrogen-chilled isopentane for 10 s and kept at −80°C. Five-micron thick sections were stained with haematoxylin–eosin, Gomori’s modified trichrome, periodic acid Schiff (PAS), oil-red-O, nicotinamide adenine dinucleotide dehydrogenase (NADH), and adenosine triphosphatase (pH 4.3, 4.6 and 9.4). The tissue for electron microscopy was fixed in 2% paraformaldehyde and processed according to the standard protocol.

**Nerve biopsy**

Sural (Patient 2), superficial peroneal (Patient 3) and left lateral antebrachial cutaneous (Patient 4) nerve biopsies were divided into three parts for histological examination, teased fibre preparation and ultrastructural studies. For histological studies, the nerve was fixed in 4% formalin overnight and embedded in paraffin. The sections were stained with haematoxylin–eosin, Gomori’s trichrome and toluidine blue. The teased fibre preparation was performed after fixation in 1% paraformaldehyde and 1.25% glutaraldehyde fixed in osmium tetroxide, dehydrated and infiltrated with epoxy resin. Thin cross sections of the nerve were examined with a Philip 400 electron microscope.

**Results**

**Case report**

**Patient 1**

At age 42, this patient developed paraesthesiae and numbness in a peri-oral distribution, with loss of taste sensation. Five years later, at age 47, the numbness and paraesthesiae progressed to involve the face, scalp and posterior aspects of the head and neck. In addition, he reported dysarthria and hoarseness. By age 50, he developed dysphagia with weakness of neck flexor and shoulder girdle muscles. Numbness and paraesthesiae progressed to the anterior aspect of the trunk (T6 level) and both upper limbs. At age 51, a gastric feeding tube was inserted because of marked weight loss (12 kg over 6 months). Generalized cramping and fasciculations were noted. He was empirically treated with prednisone and azathioprine for 6 months, and then with mycophenolate mofetil for 6 months. Despite the immunosuppressive therapy, the sensory and motor symptoms progressed. At age 52, the patient was hospitalized with aspiration pneumonia. On the second hospital day he suffered a massive pulmonary embolus and died. An autopsy was performed.

Cranial nerve examination revealed absent pinprick and temperature sensation in the trigeminal nerve distribution bilaterally, absent corneal reflexes, symmetrical facial weakness, Medical Research Council (MRC) grade 4, loss of taste sensation in the anterior two-thirds of the tongue, absent gag reflexes, hoarseness, tongue atrophy with fasciculations and weakness. Upper limb examination revealed the presence of generalized fasciculations with atrophy and weakness in the following muscle groups bilaterally: neck flexion, MRC grade 4; shoulder abduction, internal and external rotation, MRC grade 4; elbow flexion and extension, MRC grade 4; wrist flexion and extension, MRC grade 4; finger flexion and extension, MRC grade 4; thumb and finger abduction, MRC grade 4. Muscle strength was normal in the lower limbs. Deep tendon reflexes were reduced or absent in the upper limbs, but normal in the lower limbs. Plantar reflexes were flexor. Pinprick and cold temperature sensations were impaired in the scalp, upper limbs, and anterior and posterior trunk. Vibration and proprioception sensations were normal. There were no upper motoneuron, extrapyramidal, cerebellar or autonomic signs. Systemic examination was unremarkable. Specifically the tonsils were not enlarged or discoloured.

**Clinical features**

**Symptoms**

There were four males with the mean age of onset being 43 years (42–46, Table 1). The mean duration of illness was 13.5 years (8–21). The presenting feature in all patients was numbness and paraesthesiae in the lower face and oral cavity. Over a mean period of 4 years (2–6), the sensory symptoms progressed to involve the entire face, scalp, upper back, upper limbs and upper chest (T6–T8 levels). Patient 2 reported numbness in the feet 14 years after symptom onset. Dysphagia was reported in 2 (50%) patients, at a mean of 5 years after symptom onset. Dysarthria and hoarseness were seen in 3 (75%) patients, at a mean of 7.7 years after symptom onset. Weakness and atrophy of proximal and distal upper limb muscles was noted in all patients, at a
Clinical features in four patients with FOSMN syndrome

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Onset facial symptoms</th>
<th>Dysphagia</th>
<th>Dysarthria and hoarseness</th>
<th>Upper limb weakness</th>
<th>Lower limb weakness</th>
<th>Cramping and fasciculations</th>
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All patients were males with mean age of disease onset being 43 years. The mean duration of illness was 13.5 years. Facial sensory symptoms were the initial symptom in all patients. Motor symptoms invariably developed. One patient died from a pulmonary embolus, 8 years after symptom onset.

Signs

Cranial nerve examination was remarkable for decreased pinprick and temperature sensations in the distribution of all three branches of the trigeminal nerve bilaterally. The corneal reflexes were absent in two patients. Masseter muscle atrophy and weakness was documented in one patient. Facial nerve palsy of the lower motoneuron type was seen in one patient. Loss of taste sensation was seen in three patients. Absent gag reflex, hoarseness and a bovine cough were noted in three patients. Tongue atrophy and fasciculations were seen in two patients. Neck flexion weakness was noted in three patients, MRC score 4. The other cranial nerves were normal.

Motor examination revealed generalized fasciculations in three patients. Muscle weakness and atrophy in the upper extremities were noted in three patients and included: shoulder abduction, internal and external rotation, MRC grade 4; elbow flexion and extension, MRC grade 4; wrist volar flexion and dorsiflexion, MRC grade 4; finger flexion and extension, MRC grade 4; thumb abduction, MRC grade 4; finger abduction, MRC grade 4. One patient exhibited lower extremity weakness which included the following muscles: hip flexion, extension, abduction and adduction, MRC grade 4; knee flexion and extension, MRC grade 4; ankle dorsiflexion, plantarflexion, eversion and inversion, grade 2; toe flexion and extension grade 0–1. Deep tendon reflexes, in the upper extremities, were reduced or absent in all patients. Knee and ankle reflexes were absent in one patient. Plantar reflexes were flexor in all patients. The perception of pinprick, temperature and light touch was absent in the scalp, upper limbs, anterior and posterior upper trunk in all patients. In addition, pinprick, temperature and light touch were reduced in the distal lower limbs bilaterally in Patient 2. Proprioception and vibration sensations were normal in the upper and lower extremities in all patients. Romberg test was negative in all patients. There were no upper motoneuron, extrapyramidal, cerebellar or autonomic signs. Systemic examination was normal in all patients.

Treatment

All the patients were treated with immunosuppressive or immunomodulator therapy, for at least 6 months. Patient 1 was treated with prednisone and azathioprine, while patients 2, 3 and 4 were treated with intravenous immunoglobulin therapy (IVIg). In addition, Patient 3 was treated with a combination of plasmapheresis and rituximab for at least 1 year. There were no benefits from therapy and all patients continued to progress despite being treated.

Laboratory investigations

Anti-sulfatide (IgG) antibody [Athena Diagnostics, Worcester, MA] titres were elevated in 2 (50%) patients (Patient 1, 10350 IU/L; Patient 2, 4521 IU/L; normal <1500 IU/L) and anti-GD1b antibodies in one patient. Creatine-kinase was mildly elevated in three (75%) patients (mean 297, 21–232 IU). Serum HDL, low density lipoprotein (LDL), very-low density lipoprotein, triglyceride and total cholesterol assays were within normal limits in all four patients. Enzyme-linked immunosorbent assay revealed normal apolipoprotein A-I and A-II levels. In addition to the normal lipid profile, the following investigations were normal or negative in all patients: genetic testing for Kennedy’s disease, electrolytes, renal and liver function tests, full blood count, vitamin B12 and folate levels, thyroid function tests, parathyroid and testosterone hormone levels, autoantibodies and paraneoplastic antibodies, including antinuclear antibody, anti-dsDNA, anti-Ro, anti-La, anti-Smith, anti-ribonucleoprotein, anti-neutrophil cytoplasmic antibody, rheumatoid factor, angiotensin converting enzyme, cryoglobulins, anti-GM1 antibody, anti-myelin associated glycoprotein antibody, acetylcholine receptor antibody, antinuclear nucleolar antibody-I and II, Purkinje cell antibody-I, amphiphysin, anti-striated muscle, P/Q calcium channel, and N-type calcium channel, serum protein electrophoresis and immunofixation, urine electrophoresis, transferrin mutation testing [Athena Diagnostics, Worcester MA]; serology testing including HIV, hepatitis B and C, syphilis (RPR), Lyme disease, HTLV I and II, hexosaminidase A and B activity; and very-long-chain fatty acids.
Fat pad biopsy was negative for amyloid. SOD-1 mutation testing was negative. Duodenal biopsy in Patients 1 and 3 was normal. Specifically, the biopsy did not reveal features of Tangier disease (presence of lipid-laden macrophages), Whipple’s or coeliac disease. A submandibular gland biopsy in Patient 1 was normal.

**Neuroimaging**
Contrast MRI imaging of the spinal cord revealed mild-to-moderate atrophy of the mid cervical spinal cord, in three (75%) patients. There was no evidence of a syrinx in any of the patients. Brain MRI was normal in all patients.

**CSF analysis**
CSF opening pressure, glucose, protein and white cell count were normal in all patients. Local synthesis of oligoclonal bands was not detected in any of the patients. CSF assessment for Lyme disease, cryptococcus, syphilis, sarcoidosis and malignancy was negative. Polymerase chain reaction, in Patient 1, did not reveal the presence of *Tropheryma whippelii*.

**Neurophysiological findings**
NCS revealed reduced median, ulnar and superficial radial sensory nerve action potential (SNAP) amplitudes, with preserved sural SNAP amplitudes. Median, ulnar, common peroneal and tibial nerve F-response latencies and tibial H reflex latencies were prolonged or absent in three (75%) patients. Tibial and common peroneal nerve CMAP amplitudes were reduced in Patient 2. There was no evidence of conduction block to the cervical nerve roots bilaterally. Blink reflexes were abnormal (absent or delayed latency) in all patients. Needle EMG revealed fibrillation potentials and positive sharp waves in muscles of the upper and lower extremities bilaterally, paraspinal muscles at three levels (cervical, thoracic and lumbar), tongue and facial muscles in all patients. Denervation–reinnervation changes (large amplitude, polyphasic motor unit potentials of increased duration) were documented in the muscles of the upper and lower extremities. The neurophysiological findings were in keeping with a generalized sensorimotor neuropathy of caudally decreasing severity in all four patients.

**Neuropathology**
Autopsy findings, in Patient 1, revealed a brain weight of 1600 g with evidence of global hypoxic–ischaemic brain injury. Macroscopic examination revealed atrophy of cranial nerves V and IX–XII. Anterior cervical roots were atrophied bilaterally. Cerebral and cerebellar hemispheres, ventricular system, midbrain, pons, medulla and pituitary gland were grossly unremarkable.

Microscopic sections through the brainstem revealed a neuronal loss with reactive astrocitosis in the main sensory nucleus of the trigeminal nerve, facial nerve nucleus (Fig. 1A), nucleus of the solitary tract and hypoglossal nucleus. Spinal cord sections revealed pallor and loss of axons in the nucleus fasciculus, bilaterally. Dorsal root
neurium or endoneurium. Electron microscopy revealed loss of large and small myelinated fibres, along with a loss of unmyelinated fibres. Staining of nerve and muscle tissue with cell markers CD8 and CD45, in Patients 2, 3 and 4, was negative.

**Discussion**

We report a novel syndrome in four male patients, characterized by facial onset of sensory abnormalities and subsequent development of motor deficits (FOSMN syndrome). FOSMN syndrome is a chronic progressive disorder, which is sporadic, with the mean age of onset being 43 years. The presenting symptoms include paraesthesiae and numbness in the trigeminal nerve distribution that slowly progress to affect the scalp, neck, upper trunk and upper extremities. Motor symptoms, which become manifest after the onset of sensory features, include muscle cramping, weakness and atrophy, fasciculations, dysphagia, dysarthria and hoarseness. Neurophysiological findings in FOSMN syndrome include low SNAP amplitudes in the upper limbs, with preserved sural SNAP amplitudes, and evidence of widespread axonal loss on needle EMG testing. The MRI findings of cervical cord atrophy taken together with the neurophysiological features, suggested that the underlying pathological process was a neuronopathy. This was confirmed on pathological studies that revealed a loss of dorsal root ganglion and anterior horn neurons.

Prior to proposing that the clinical features exhibited in the present series represent a novel syndrome, secondary disorders that can resemble the FOSMN phenotype need to be excluded. Specifically, adult-onset forms of Tangier disease share the same clinical phenotype (syringomyelia-like syndrome) as the reported patients (Gibbles et al., 1985; Pietrini et al., 1985; Dyck et al., 1987; Schmalbruch et al., 1987; Antoine et al., 1991; Zuchner et al., 2003). Tangier disease is a disorder of lipid metabolism characterized by absent or markedly reduced HDL and apolipoprotein A-I levels, together with reduced serum cholesterol, normal or elevated triglyceride and normal apolipoprotein A-II levels (Herbert, 1983; Pareyson, 2003). Pathologically, Tangier disease is characterized by accumulation of cholesteryl esters in many tissues, including tonsils, lymph nodes, skin, liver, spleen, Schwann cells, neurons and intestinal mucosa (Assmann et al., 1989; Lachaux et al., 1998). In addition, a distinctive pattern of axonal degeneration characterized by (i) loss of unmyelinated and small myelinated fibres; (ii) excessive endoneurial collagenization and (iii) the appearance of distinctive linear bands of closely packed osmiophilic and clear droplets in degenerating axons has been reported in Tangier disease (Kocen et al., 1973; Dyck et al., 1978; Pollock et al., 1983; Schmalbruch et al., 1987).

Although small fibre loss was prominent in our patients, the normal lipid profile including normal HDL and apolipoprotein A-I levels, along with the absence of the other characteristic neuropathological findings exclude Tangier disease.
In addition to Tangier disease, other lesions affecting the sensory and motor neurons including Kennedy’s disease (Kenny et al., 1968; Harding et al., 1982; La Spada et al., 1991; Ferrante and Wilbourne, 1997), motoneuron disease (Ince et al., 1996; Wakabayashi et al., 1998; Rezania et al., 2003), syringomyelia and syringobulbia (Victor and Adams, 1993; Levine, 2004), leprosy (Gibbles et al., 1985), amyloidosis (Pareyson, 2003), neurosarcoïdosis (Zumiga et al., 1991; Said et al., 2002), Fabry’s disease (Pareyson, 2003) and autoimmune disorders such as Sjogren’s syndrome (Griffin et al., 1990; Chu et al., 2000; Urban et al., 2001; Mori et al., 2005) and CANOMAD syndrome (Willison et al., 2001) are important differential diagnoses. These conditions were excluded in the present series on the basis of clinical investigation, including pathological, laboratory and genetic testing, neuroimaging of the brain and cervical spine and neurophysiological studies.

Although the pathogenesis of FOMSN syndrome remains unclear, the presence of antisuflhatide antibodies in two patients and anti-GD1b antibodies in one patient, suggested an autoimmune process. The absence of inflammatory cells in tissue biopsies along with an absence of positive tissue staining with inflammatory cell markers CD8 and CD45 and an absence of a clinical response to immunosuppressive therapies argue against an autoimmune process. Rather, a neurodegenerative process is more likely and further neuropathological studies may yet prove useful in unlocking this clinical mystery.

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References


