SHORT REPORT

Amyotrophic lateral sclerosis with sensory neuropathy: part of a multisystem disorder?

Jeremy D Isaacs, Andrew F Dean, Christopher E Shaw, Ammar Al-Chalabi, Kerry R Mills, P Nigel Leigh

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Sensory involvement is thought not to be a feature of amyotrophic lateral sclerosis (ALS). However, in the setting of a specialist motor neuron disease clinic, we have identified five patients with sporadic ALS and a sensory neuropathy for which an alternative cause could not be identified. In three individuals, sensory nerve biopsy was performed, demonstrating axonal loss without features of an alternative aetiology. These findings support the hypothesis that ALS is a multisystem neurodegenerative disorder that may occasionally include sensory neuropathy among its non-motor features.

Amyotrophic lateral sclerosis (ALS) is characterised by a combination of anterior horn cell and corticospinal tract degeneration. Although dominated by motor dysfunction there is increasing evidence that ALS is a multisystem disorder in which the autonomic system, spinocerebellar tracts, dorsal columns, basal ganglia and extra-motor cortex may also be affected.^{1–5}

In addition, patients with ALS often complain of sensory symptoms, and case series have identified objective sensory signs in 2–10% of patients.^{6–8} However, peripheral sensory neuropathy has not been widely recognised as part of the ALS syndrome. Consequently, the occasional presence of sensory features in ALS has long been a cause of diagnostic uncertainty.⁹

We report five cases of ALS with a coexistent sensory neuropathy for which an alternative cause could not be identified. We propose that sensory nerve degeneration may represent part of the clinical spectrum of ALS.

CASE HISTORIES

Case No 1

A 63-year-old man presented with weakness affecting the right ankle and left hand. Examination revealed lower motor neuron signs in the arms and legs. There were no objective sensory changes. Nerve conduction studies performed 3 months after the onset of weakness demonstrated absent sural sensory action potentials (SAPs) and reduced radial nerve SAPs and conduction velocities (table 1). EMG demonstrated fasciculation in the right arm and widespread chronic partial denervation and reinnervation. Four months after the onset of symptoms he underwent a right sural nerve biopsy, which demonstrated a mild reduction in axons and moderate loss of myelin. There was no response to prednisolone. Ten months after the onset of weakness, upper motor neuron signs were elicited in the left leg. Bulbar function declined and the patient died 24 months after symptom onset.

Case No 2

A 65-year-old man presented with weakness of the right leg, poor balance, numbness in the legs and a burning sensation in

the feet. Examination revealed lower motor neuron signs in the limbs, an ataxic gait and reduced vibration sense in both feet. Nerve conduction studies demonstrated an axonal sensory neuropathy in the lower limbs (table 1). EMG sampling of tibialis anterior and medial gastrocnemius was normal. Repeat nerve conduction studies 24 months after onset demonstrated progression of the neuropathy with absent sural SAPs (table 1). Forty-seven months after symptom onset, he was found to have lower motor neuron features in all limbs with upper motor neuron signs in both legs. His condition progressed and he died 9 months later.

Case No 3

A 49-year-old man presented with fasciculations, decreased limb muscle bulk and paraesthesia in the hands. Initial examination revealed a weak right thumb. EMG performed 12 months after onset demonstrated widespread fasciculation and chronic partial denervation and reinnervation. Nerve conduction studies revealed reduced sural SAPs (table 1). Six months later muscle wasting, weakness and brisk reflexes were present in the upper limbs. Fifty-four months after onset, mild lower motor neuron bulbar features were present with weakness and wasting in all limbs with brisk knee jerks and a brisk adductor jerk. At this time decreased light touch and pinprick sensation was detected in the toes and reduced vibration sense in the feet. Repeat nerve conduction studies approximately 70 months after disease onset confirmed a progressive lower limb axonal sensory neuropathy (table 1). At the last follow-up, approximately 120 months after disease onset, the patient's motor function had declined and he was dependent on nocturnal non-invasive ventilation. Vibration sense was absent to the mid-calf, pinprick was reduced to the ankle and light touch impaired to the high calf.

Case No 4

A 58-year-old man presented with weak hands. He gave a history of restless legs and burning in the feet of approximately 4 years prior to this presentation. On examination, lower motor neuron signs were present in all four limbs, with the upper limbs predominantly affected in the "flail arm" pattern. There were no bulbar signs. Vibration sense was absent in the big toes. Nerve conduction studies demonstrated slightly reduced lower and upper limb sensory SAPs (table 1) with normal conduction velocities. EMG was consistent with motor neuron disease, including widespread profuse fasciculations. Biopsy of the right sural nerve performed 12 months after disease onset demonstrated a mild reduction in myelinated fibres with occasional acutely degenerating fibres and regeneration clusters, and scattered fibres with inappropriately thin myelin sheaths. There was no response to prednisolone. On neurological review

Abbreviations: ALS, amyotrophic lateral sclerosis; MGUS, monoclonal gammopathy of unknown significance; SAP, sensory action potential

Table 1 Summary of clinical features and investigations

Case No	Investigations*	El Escorial category	Sensory action potential (μ V)	Sensory conduction velocity (m/s)	Outcome
1	ESR, B12, folate, immunoglobulins, lead, antineuronal and Purkinje antibodies, Kennedy's mutation, glucose. CSF protein 0.924 g/l. MRI spine—mild degenerative lumbar spine disease only	Clinically probable laboratory supported	Sural absent Radial 10	Radial 33–36	Died 2 years after onset
2	ANA, ANCA, ESR, HbA1c, TFTs, CRP, B12, folate, TPHA. CSF IgG 0.04 g/l (<0.026 g/l). MRI cervical and lumbar spine.	Clinically possible	Initial: Sural 3 Radial 9 Follow-up: Sural absent Radial 12	Sural 41 Radial 59	Died 4.5 years after onset
3	Immunoglobulins, ESR, serum protein electrophoresis, CRP, ANA, anti-dsDNA, ANCA, anti-GM1, glucose, CSF. MRI spinal cord.	Clinically probable laboratory supported	Initial: Sural 5–7 Radial 16 Median 24 Follow-up: Sural absent Median 9.2	Radial 50 Sural 51 Radial ND Median 57	Alive 10 years after onset
4	Immunoglobulins, serum protein electrophoresis, B12, folate, ESR, autoantibodies, ANCA, glucose, CSF.	Pure LMN syndrome	Sural 5 Median 5 Ulnar 2	Sural 33 Median 40 Ulnar 48	Alive 4.5 years after onset
5	Glucose, urine Bence-Jones protein. IgM paraprotein 12.2 g/l. MRI whole spine.	Clinically probable laboratory supported	Median 2 Ulnar 3 Radial 9 Sural 5 Superficial peroneal 3	Median 53 Ulnar 54 Radial 56 Sural 47 Superficial peroneal 48	Died 2.5 years after onset

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GM1, ganglioside GM1; HbA1c, glycated haemoglobin A1c; LMN, lower motor neuron; ND, not determined; TFTs, thyroid function tests; TPHA, Treponema pallidum haemagglutination assay.

*Normal or negative unless stated.

48 months after onset, the patient had continued to progress but without bulbar or upper motor neuron involvement. At 55 months he had further deteriorated being just able to transfer with assistance.

Case No 5

A 64-year-old man presented with weakness of the right leg. On examination, upper limb fasciculations and wasting and weakness of the right leg were observed. Reflexes were brisk in all limbs with extensor plantars. There were no bulbar signs. Sensory examination revealed a loss of pinprick and vibration sense in both feet. Nerve conduction studies demonstrated small or absent SAPs in all limbs with normal conduction velocities (table 1). EMG showed denervation in all limbs with thoracic sparing. Investigations revealed an IgM paraprotein with a titre of 12.2 g/l without evidence of haematological malignancy. A superficial radial nerve biopsy showed

Figure 1 Superficial radial nerve biopsy from case No 5.

mild–moderate loss of large myelinated fibres and the occasional inappropriately thin myelin sheath (fig 1). Of the six fascicles examined, each contained 5–6 regeneration clusters (supplementary fig 1; supplementary fig 1 can be viewed on the *JNNP* website at <http://www.jnnp.com/supplemental>). No IgM deposition on myelinated fibres was demonstrated and no amyloid or vasculitis was seen. A course of treatment with chlorambucil did not result in any motor or sensory improvement. His condition deteriorated and he died 2.5 years after disease onset.

DISCUSSION

The five cases presented here were identified from a database of more than 1000 individuals seen in a specialist motor nerve clinic. All were male and had limb onset ALS. Four patients developed upper motor neuron signs in at least two limbs. Case No 4 had the “flail arm” syndrome, a recognised presentation of ALS that in a significant minority of patients is associated with only lower motor neuron signs.¹⁰ Case No 2 did not have EMG evidence of denervation when examined early in the course of his illness but the clinical features and rapid progression of his disease were felt to be entirely consistent with the diagnosis of ALS. Case No 3 was still alive 10 years after disease onset, an outcome atypical of ALS but not incompatible with the diagnosis; 4% of ALS patients in our clinic have survived >10 years.¹¹ None of the patients had a family history of ALS, thus SOD1 genotyping was not performed. Cognitive decline was not reported in any case. Not all patients had probable or definite ALS (at their final documented clinical assessment), according to the El Escorial criteria (table 1), and autopsy material was not available. However, the progression of the disease (rapid in three cases), confirmatory neurophysiological examination in four patients and lack of evidence for an alternative diagnosis strongly suggest that ALS was the cause of the motor syndrome in all cases.

Two patients had no sensory symptoms; only one had no sensory signs although nerve conduction studies showed

unequivocal sensory axonal dysfunction in this case. Three underwent nerve biopsy and in all cases there was evidence of axonal loss without features suggesting an alternative cause.

Could neuropathy in these patients have been attributable to other causes? In none of the cases is it likely that vasculitis, alcohol or other toxins, or a paraneoplastic syndrome could account for the neuropathy. None of the patients had manifest diabetes and although glucose tolerance tests were not performed, evidence that impaired glucose tolerance is a risk factor for axonal neuropathy is conflicting.¹² Furthermore, in each case where corticosteroids were prescribed, the sensory features were present prior to the commencement of therapy.

Case No 5 had a serum IgM paraprotein. Monoclonal gammopathy of unknown significance (MGUS) is usually associated with a demyelinating neuropathy and it has been argued that the co-presentation of MGUS with axonal neuropathy may be coincidental in a large proportion of cases.¹³ Case No 1 had slightly elevated CSF protein; however, raised CSF protein has been reported in a pathologically confirmed case of ALS in which a sensory neuronopathy was present.¹⁴

Although subjective sensory symptoms are common in ALS, objective sensory signs are seen less frequently. In a series of 111 ALS patients, up to 50% had sensory symptoms whereas 10% were documented to have sensory signs.⁶ Frequencies of 5% for pain and temperature disturbance in a glove and stocking distribution, 2% for impairment of vibration sense and 1% for impaired joint position sense have been reported in large series of ALS cases.^{7,8}

Electrophysiological studies in ALS suggest a high incidence of subclinical yet progressive sensory dysfunction.^{15,16} One study reported significant reductions in sural nerve conduction velocity and sensory action potentials over a 6 month period in 50 ALS patients. Over 60% of this group had neurophysiological dysfunction of at least one afferent pathway.¹⁷

Loss of myelinated fibres and axonal degeneration have been demonstrated in dorsal roots and sensory nerves from cases of ALS.^{18–20} One study reported a 30% reduction in the total number of sural nerve myelinated fibres in ALS patients compared with controls.²⁰ A reduction in large diameter neurons in the dorsal root ganglia has also been reported.¹⁹

It has been proposed that the initial insult to the sensory system in ALS results in a dorsal root ganglia neuronopathy followed by progressive sensory axonal atrophy, secondary demyelination-remyelination and finally axonal loss.²¹ The presence of regeneration clusters in two of the three nerve biopsies in our series suggests a coexistent axonopathy. Interestingly, regeneration clusters have been reported in phrenic, common peroneal and hypoglossal nerves in ALS.^{20,22} Bradley *et al* have argued that although motor neuron degeneration in ALS is primarily caused by a neuronopathy, focal axonopathic features due to a “sick” perikaryon can occur.²⁰ This may also be the case with respect to sensory nerve involvement.

A relatively high prevalence of symptoms or signs suggestive of sensory neuropathy has been reported in familial ALS.^{8,23} Sensory involvement has been demonstrated clinically or pathologically in a number of individuals and pedigrees with SOD1 mutations.^{24–26} The association between SOD1 dysfunction and sensory neuropathy is supported by recent work demonstrating sensory axonal degeneration in transgenic mice expressing mutant SOD1.²⁷

We have described five ALS patients with an otherwise idiopathic sensory neuropathy. We acknowledge that our patients were drawn from an uncontrolled series and that there is a low incidence of idiopathic neuropathy in the general population, which could account for its occasional co-presentation with ALS.²⁸ However, we believe that our observations

support the concept of ALS as a multisystem disorder and may extend the phenotype of ALS to include clinical or subclinical axonal sensory neuropathy. Indeed, where the disease course is prolonged through use of invasive ventilation, atypical features such as ophthalmoplegia can emerge, suggesting that additional neuronal populations may ultimately be vulnerable to degeneration in ALS if the disease continues for sufficient time.²⁹ As average disease duration increases as a consequence of advances in supportive care and pharmacology, we anticipate that a wider spectrum of pathology in ALS will become clinically apparent, challenging the standard clinical descriptions of the disease.

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Supplementary fig 1 can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>.

Authors' affiliations

Jeremy D Isaacs, Christopher E Shaw, Ammar Al-Chalabi, P Nigel Leigh, King's College London MRC Centre for Neurodegeneration Research, Department of Neurology, Institute of Psychiatry, London, UK
Andrew F Dean, Department of Histopathology, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
Kerry R Mills

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Correspondence to: Professor P Nigel Leigh, Department of Clinical Neuroscience at King's College London, and MRC Centre for Neurodegeneration Research, Department of Neurology, PO Box 41, Institute of Psychiatry, Denmark Hill, London SE5 3AF, UK; n.leigh@iop.kcl.ac.uk

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