Focal limb weakness (monoparesis): when family history holds the key to diagnosis

Introduction

Focal single limb weakness, monoparesis or monoplegia, has a broad differential diagnosis, extending neuroanatomically from the cerebral cortex to the neuromuscular junction and muscle. History of onset (acute, subacute, chronic) may suggest the underlying pathological process, while the pattern of signs, originating from upper or lower motor neurone pathology, may assist in lesion localization. Cerebral and cord lesions produce upper motor neurone weakness accompanied by increased muscular tone (spasticity) and pathologically brisk reflexes (hyperreflexia); pathology in nerve roots, plexus or peripheral nerves produces lower motor neurone weakness (wasting, reduced tone, hyporeflexia or areflexia).

This article reports a patient presenting with focal upper limb weakness in whom the family history provided important clues to diagnosis and directed appropriate investigation.

Discussion

Focal (monomelic) disorders are described in clinical classifications of motor neurone diseases. Hirayama disease (possibly cognate with O'Sullivan–McLeod syndrome; Ghadiri-Sani et al, 2014) is a juvenile onset muscular atrophy of the upper limb, characterized by unilateral progressive wasting and weakness over years followed by spontaneous arrest. Hirayama disease was considered in this patient, but it occurs predominantly in males and the weakness is usually distal. The current patient progressed rapidly and had a family history of motor neurone disease, neither typical features of Hirayama disease.

A positive family history occurs in around 15–20% of patients with amyotrophic lateral sclerosis. Mutations which determine familial amyotrophic lateral sclerosis syndromes occur in several genes (*Table 1*) and more continue to be identified (Chia et al, 2018). Many overlap with genetic causes of frontotemporal dementia syndromes (e.g. FUS, TDP-43, VCP, C9orf72; St John and Larner, 2015). Of the familial amyotrophic lateral sclerosis deterministic genes, the C9orf72 hexanucleotide repeat expansion on chromosome 9p21.2 is the most commonly identified (Majounie et al, 2012), and hence should be the first tested in suspected familial amyotrophic lateral sclerosis. C9orf72 expansion is also a common cause of sporadic amyotrophic lateral sclerosis, and of frontotemporal dementia either with or without amyotrophic lateral sclerosis (Larner, 2013; McCormick and Larner, 2018).

Mutations in the FUS gene, first identified in 2009 (Vance et al, 2009), include the point mutation p.Pro525Leu (Kwiatkowski et al, 2009) found in this family. This mutation is consistently associated with early onset

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CASE REPORT

A 23-year-old right-handed woman presented with a 5-month history of progressive, painless, proximal left arm weakness. She was otherwise well. Examination showed left arm wasting, especially shoulder girdle musculature, with a corresponding pattern of limb weakness. No fasciculation was seen. Reflexes were depressed in the left arm, but pathologically brisk in the right. Cranial nerves and lower limbs were intact. No sensory deficit was identified.

Differential diagnostic possibilities included compressive cervical radiculopathy and brachial plexopathy, although the absence of pain or sensory deficit made these diagnoses unlikely. Multifocal motor neuropathy with conduction block might explain the exclusively motor findings; this condition can have very focal presentations. A focal (right) cerebral lesion might produce contralateral upper limb weakness but muscle wasting and reflex depression would not be expected.

The family history pointed to another possibility. The patient's mother died at the age of 35 years with motor neurone disease. Her presentation was with slurred speech, unsteady gait and limb weakness over a few months. Her diagnosis was based on the findings of neurophysiological studies.

In light of the family history, the possibility of a focal upper limb presentation of amyotrophic lateral sclerosis or another form of motor neurone disease was considered, despite the patient's young age.

Magnetic resonance imaging of the brain and cervical spine and CSF analysis were all normal. There was neither cervical cord atrophy nor symmetrical T2-weighted high signal in the anterior horns ('snake eyes'). Neurophysiological studies showed active denervation in muscles of both arms and tongue, consistent with a diagnosis of amyotrophic lateral sclerosis.

Early onset amyotrophic lateral sclerosis with a family history of disease prompted neurogenetic testing. Mutations in several genes are deterministic for familial amyotrophic lateral sclerosis syndromes (*Table 1*). These studies showed a heterozygous point mutation (c.1574C>T) in the fused in sarcoma (FUS) gene on chromosome 16p11.2, with predicted amino acid sequence change p.Pro525Leu in the FUS protein. This FUS mutation had previously been described in other cases of familial amyotrophic lateral sclerosis (Kwiatkowski et al, 2009), hence establishing this patient's diagnosis as ALS6.

The patient continued to deteriorate, despite treatment with riluzole, and developed respiratory failure. She died about 6 months after the original presentation and 1 year after symptom onset.

Five years later her younger sister presented at the age of 26 years with rapidly progressive right arm weakness and wasting, followed by tetraparesis and ultimately death as a result of respiratory failure 6 months after the initial presentation. Diagnostic neurogenetic testing showed that she carried the same p.Pro525Leu point mutation in the FUS gene.

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Table 1. Some genes currently recognized to harbour mutations which cause familial amyotrophic lateral sclerosis

Protein (with abbreviation) and name of gene locus	Chromosomal location	OMIM catalogue phenotype number
Superoxide dismutase-1 (SOD1), ALS1	21q22.11	OMIM#105400
Fused in sarcoma protein (FUS), ALS6	16p11.2	OMIM#608030
Vesicle-associated membrane protein-associated protein B (VAPB), ALS8	20q13.22	OMIM#608627
Angiogenin gene (ANG), ALS9	14q11.2	OMIM#611895
TAR-DNA binding protein 43 (TDP-43), ALS10	1p36.22	OMIM#612069
FIG4 gene, ALS11	6q21	OMIM#612577
Optineurin gene (OPTN), ALS12	10p13	OMIM#613435
Valosin-containing protein (VCP), ALS14	9p13.3	OMIM#613954
Ubiquilin 2 (UBQLN2), ALS15	Xp11.21	OMIM#300857
Charged multivesicular body protein 2B (CHMP2B), ALS17	3p11.2	OMIM#614696
Profilin-1 (PFN1), ALS18	17p13.2	OMIM#614808
V-ERB-B2 avian erythroblastic leukemia viral oncogene homolog 4 (ERBB4), ALS19	2q34	OMIM#615515
Heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), ALS20	12q13.13	OMIM#615426
Matrin-3 (MATR3), ALS21	5q31.2	OMIM#606070
Tubulin, alpha-4A (TUBA4A), ALS22	2q35	OMIM#616208
Annexin A11 (ANXA11), ALS23	10q22.3	OMIM#617839
C9ORF72, FTDALS	Non-coding region hexanucleotide repeat expansion on chromosome 9p21.2	OMIM#105550

OMIM = Online Mendelian Inheritance in Man

disease, beginning in the second or third decade (classified as 'juvenile' if onset before 25 years of age), with an aggressive disease course (Conte et al, 2012; Mochizuki et al, 2012; Leblond et al, 2016). Early onset disease characterized genetically may afford insights into disease pathogenesis (Qamar et al, 2018) which ultimately might afford new treatments for amyotrophic lateral sclerosis and frontotemporal dementia. **BJHM**

LEARNING POINTS

- In amyotrophic lateral sclerosis, enquiry for a family history is positive in around 15–20% of cases; this may prompt discussion about genetic testing.
- Mutations in a number of genes are associated with autosomal dominant familial amyotrophic lateral sclerosis, some presenting very early in life.
- Of these, the C9orf72 hexanucleotide repeat expansion is the most commonly identified cause of familial amyotrophic lateral sclerosis.
- Fused in sarcoma gene mutations may be associated with early onset familial amyotrophic lateral sclerosis with an aggressive clinical course.

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