Muscle wasting, bone pain and cognitive decline: a unifying diagnosis

Introduction

Muscle wasting and weakness has a very broad differential diagnosis. Associated clinical and investigative features may sometimes assist in diagnosis. This article reports a patient in whom the definitive diagnosis of a proximal myopathy was achieved by targeted genetic testing following the development of early onset cognitive decline.

Discussion

Inclusion body myopathy-Paget's disease-frontotemporal dementia is an autosomal dominant disorder associated with valosin-containing protein gene mutations, with a variable phenotype encompassing three clinical features: myopathy, Paget's disease and frontotemporal dementia. The full spectrum of disease is seen in only around 10% of patients. Phenotypic heterogeneity is the norm, even within families harbouring the same mutation. Muscle weakness with onset from the third decade of life onwards is the presenting symptom in more than half of patients, and may occur in isolation in around 30%. Weakness may be proximal, being mistaken for facioscapulohumeral muscular dystrophy or a limb girdle muscular dystrophy, or distal.

The diagnosis of inclusion body myopathy-Paget's disease-frontotemporal dementia should be considered in the differential diagnosis of any patient with muscular weakness with a personal or family history of Paget's disease. The latter may manifest as a history of musculoskeletal pain and/or pathological fractures, requiring assay of markers of bone turnover such as blood alkaline phosphatase,

Ms L St John *is Final Year Medical Student and* **Dr AJ Larner** *is Consultant Neurologist in the Walton Centre for Neurology and Neurosurgery, Liverpool L9 7LJ*

Correspondence to: Dr AJ Larner (a.larner@thewaltoncentre.nhs.uk)

Case Report

A 63-year-old right-handed man was referred to the cognitive clinic. The history was mostly obtained from his wife; the patient displayed the 'head turning sign' when asked for details of his memory difficulties, a highly specific sign for the presence of cognitive impairment (Larner, 2012). The wife reported 6–12 months of repetitive questioning, and having to take over the supervision of her husband's various medications. There was a past medical history of muscle disease. Since his mid-fifties the patient had developed progressive painless leg weakness with a tendency for the legs to give way, with walking distance now reduced to about 50 metres. Upper limb weakness had also developed, with difficulty lifting the arms above the head. There was no history suggestive of ocular or bulbar involvement.

There was a prior history of chronic obstructive pulmonary disease, gout and Paget's disease of bone. The latter was diagnosed incidentally at the age of 54 years following radiological imaging for a separate indication which showed Pagetic change in the pelvic bones. A technetium bone scan confirmed these changes and also revealed foci in two vertebrae, the left femoral shaft and the left humerus. Blood tests showed high bone turnover, with raised levels of alkaline phosphatase (330 IU/litre, normal range 35–125 IU/litre), procollagen type 1 N-terminal propeptide (a marker of bone formation; 367 μg/litre, normal range 20–76 μg/litre) and C-terminal telopeptide of type 1 collagen (a marker of bone resorption; 0.88 μg/litre, normal range 0.1–0.5 μg/litre). This was treated with zoledronate infusion at the time of diagnosis, and then again some years later when he developed bone pain in one thigh.

In the family history, his father died in his late forties with an unspecified muscular atrophy of some 10 years duration, and a brother had Paget's disease.

Neurological examination showed intact cranial nerve function, but in the limbs there was proximal wasting and weakness (shoulder abduction and hip flexion power both Medical Research Council grade 3/5) with scapular winging. Reflexes were depressed but preserved other than the ankle jerks, plantar responses were downgoing, and sensation was intact.

On performance-based cognitive testing, the patient scored 27/30 on the Mini-Mental State Examination. On a more extensive test, the Addenbrooke's Cognitive Examination-III (ACE-III; Hsieh et al, 2013), he scored 57/100, with impaired subscores for attention (12/18), memory (7/26), fluency (7/14) and language (16/26), but with relative preservation of visuospatial skills (15/16), findings corroborated on the mini-Addenbrooke's Cognitive Examination (M-ACE; Hsieh et al, 2015; Larner, 2015a) on which he scored 18/30. On the AD8, an informant-based cognitive screening instrument completed by his wife, he scored 6/8, where a score of ≥2/8 is interpreted as 'cognitive impairment is likely to be present' (Galvin et al, 2005; Larner, 2015b). Brain imaging (both computed tomography and magnetic resonance imaging) showed reduced volume in the temporal lobes (L>R). The cognitive profile was thought to be more in keeping with a frontotemporal lobar degeneration syndrome than Alzheimer's disease.

Previous blood investigations showed a mildly elevated creatine kinase (>500 U/litre). Electromyography and nerve conduction studies were reported normal. Initial neurogenetic testing investigating his muscular problems proved negative for facioscapulohumeral muscular dystrophy, and spinal and bulbar muscular atrophy (Kennedy's syndrome).

Because of the combination of muscle disease, Paget's disease and cognitive decline, further neurogenetic testing was undertaken targeting the valosin-containing protein gene on chromosome 9p13.3, mutations in which have been shown to cosegregate with the disorder of inclusion body myopathy-Paget's disease-frontotemporal dementia. This showed a heterozygous point mutation (p.Arg191Gln), which has previously been described in other cases (Watts et al, 2004), hence establishing the diagnosis of inclusion body myopathy-Paget's disease-frontotemporal dementia, also known as valosin-containing protein disease (Weihl et al, 2009).

© 2015 MA Healthcare Ltd

procollagen type 1 N-terminal propeptide and C-terminal telopeptide of type 1 collagen, as well as radiological studies of bone to establish the diagnosis. To the authors' knowledge, there are no reports of cognitive screening in cohorts of patients with Paget's disease to assess how common valosin-containing protein disease might be. Dementia related to hydrocephalus has also been reported in Paget's disease (Roohi et al, 2005).

Likewise, the diagnosis of inclusion body myopathy-Paget's disease-frontotemporal dementia should be considered if there is a personal or family history of early-onset cognitive decline or dementia. This may require cognitive assessment using commonly available performance-based (e.g. ACE-III, M-ACE) and informant-based (e.g. AD8) screening instruments as well as brain imaging.

Mutations in several genes are recognized to be deterministic for frontotemporal dementia syndromes (*Table 1*). Of these, the hexanucleotide repeat expansion in C9ORF72 is reported to be the most commonly encountered, followed by tau and progranulin mutations (Warren et al, 2013), as has been the experience in this clinic (Larner, 2014). Most of the other genetic mutations are rare, with the possible exception of valosin-containing protein.

Currently there is no specific treatment for valosin-containing protein disease, other than supportive care for weakness (assistive devices, wheelchair) and cognitive decline. However, the long course of the disease means that it would be an ideal candidate for early intervention with disease-modifying drugs when such become available, hence the importance of early diagnosis which may be facilitated by increased awareness of the clinical phenotype. Genetic counselling of at-risk family members may be undertaken following diagnosis.

Conclusions

Undiagnosed muscular weakness may be caused by valosin-containing protein disease. Consideration of this diagnosis should be prompted by a personal or family history of Paget's disease and early cognitive decline. **BJHM**

Galvin JE, Roe CM, Powlishta KK et al (2005) The AD8. A brief informant interview to detect dementia. *Neurology* **65**: 559–64

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013) Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* **36**: 242–50 (doi: 10.1159/000351671)

Hsieh S, McGrory S, Leslie F et al (2015) The Mini-Addenbrooke's Cognitive Examination: a new assessment tool for dementia. *Dement Geriatr Cogn Disord* **39**: 1–11 (doi: 10.1159/000366040)

Larner AJ (2012) Head turning sign: pragmatic utility in clinical diagnosis of cognitive impairment. *J Neurol Neurosurg Psychiatry* **83**: 852–3 (doi: 10.1136/jnnp-2011-301804)

Larner AJ (2014) *Dementia in clinical practice: a neurological perspective. Pragmatic studies in the Cognitive Function Clinic.* 2nd edn. Springer, London: 163–4, 224–7 (doi: 10.1007/978-1-4471-6371-8)

Larner AJ (2015a) Mini-Addenbrooke's Cognitive Examination: a pragmatic diagnostic accuracy study. *Int J Geriatr Psychiatry* **30**: 547–8 (doi: 10.1002/gps.4258)

Larner AJ (2015b) AD8 informant questionnaire for cognitive impairment: pragmatic diagnostic test accuracy study. *J Geriatr Psychiatry Neurol* **28**: 198–202 (doi: 10.1177/0891988715573536)

Roohi F, Mann D, Kula RW (2005) Surgical management of hydrocephalic dementia in Paget's disease of bone: the 6-year outcome of ventriculo-peritoneal shunting. *Clin Neurol Neurosurg* **107**: 325–8

Warren JD, Rohrer JD, Rossor MN (2013) Clinical review. Frontotemporal dementia. *BMJ* **347**: f4827 (doi: 10.1136/bmj.f4827)

Watts GD, Wymer J, Kovach MJ et al (2004) Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet* **36**: 377–81

Weihl CC, Pestronk A, Kimonis VE (2009) Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and fronto-temporal dementia. *Neuromuscul Disord* **19**: 308–15 (doi: 10.1016/j.nmd.2009.01.009)

Table 1. Currently recognized genes in which mutations may be deterministic for familial frontotemporal lobar degenerations

Protein/gene	Chromosomal location	Online Mendelian inheritance in man (OMIM) catalogue number
Microtubule-associated protein tau (MAPT)	17q21.31	OMIM#600274
Progranulin (GRN or PGRN)	17q21.31	OMIM#607485
Valosin-containing protein (VCP)	9p13.3	OMIM#167320
Charged multivesicular body protein 2B (CHMP2B), also known as chromosome 3 linked FTD or FTD3	3p11.2	OMIM#600795
TAR-DNA binding protein 43 (TDP-43), also known as ALS10	1p36.22	OMIM#612069
Fused in sarcoma protein (FUS), also known as ALS6	16p11.2	OMIM#608030
Ubiquilin 2 (UBQLN2), also known as ALS15	Xp11.21	OMIM#300857
C9ORF72, also known as FTDALS	Non-coding region hexanucleotide repeat expansion on chromosome 9p21.2	OMIM#105550

LEARNING POINTS

- If dementia is diagnosed before the age of 65 years then it is said to be early onset. Although common things are common, such as Alzheimer's disease, it is important to be aware that rarer causes of dementia have a higher prevalence in younger patients and should therefore be considered.
- Mutations in the valosin-containing protein gene may produce a constellation of clinical features including myopathy (proximal or distal), Paget's disease of bone and frontotemporal dementia.
- In a patient with unexplained myopathy, screening for a personal history (musculoskeletal pain, pathological fractures) or a family history of Paget's disease, or for early-onset cognitive impairment, may be indicated as a prelude to genetic testing for valosin-containing protein gene mutations.
- The diverse symptomatology of inclusion body myopathy-Paget's disease-frontotemporal dementia means input may be required from different specialties, including neurology, memory services, metabolic medicine, rheumatology and genetics, in order to optimize patient care.

© 2015 MA Healthcare Ltd