Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD): clinical features including sphincter disturbance in a large pedigree

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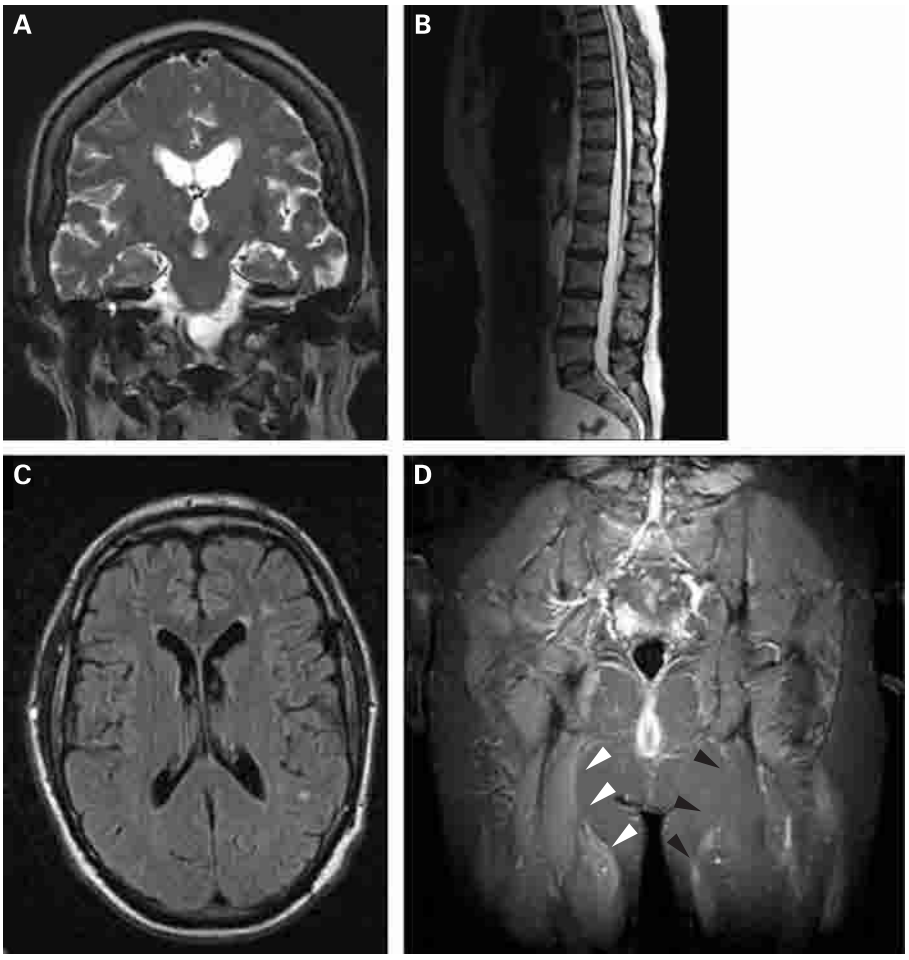

Figure 1 MRI from members of the reported pedigree. (A) T2-weighted coronal image of II:18. There is moderate atrophy of the left temporal lobe cortex. (B) T2-weighted sagittal image of the thoracolumbar spine in the same subject showing marked atrophy of the distal cord. (C) FLAIR axial image of III:14 demonstrating scattered white matter high signal in the white matter. (D) Fat suppressed T2 coronal imaging of the pelvis and upper thigh in III:14 demonstrating marked asymmetrical wasting of the adductor and hamstring muscles on the left side (black arrowheads) compared with the more normal right side (white arrowheads).

Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD): clinical features including sphincter disturbance in a large pedigree

Autosomal dominant inclusion body myopathy (IBM) associated with Paget disease of bone (PDB) and frontotemporal dementia (FTD), or IBMPFD, is a rare recently described multisystem disorder caused by missense mutations of the valosin-containing protein (VCP) gene on chromosome 9p13–p12 (OMIM 605382).[1] Recognised features include proximal and distal weakness, early-onset PDB, early-onset FTD and cardiomyopathy.[1–3] Here we report the clinical features of a large affected kindred.

PATIENTS AND METHODS

A large extended British family was identified with the condition (VS and AJ). Clinical information was obtained by interviewing patients, neurological examination of five living patients and reviewing medical records. Patients were investigated where possible with MRI of brain, spine and pelvic muscles, neurophysiology and anorectal physiology, muscle biopsy, Addenbrookes Cognitive Examination—Revised, skull, lumbar spine and pelvic *x* rays, creatine kinase and alkaline phosphatase. Mutation analysis of VCP was performed on four affected members and one unaffected reference member from this family. Genomic DNA, extracted from peripheral blood via standard methods, was analysed in duplicate for each subject.

RESULTS

VCP mutation analysis of four affected individuals (II:18, III:13, III:14, III:15; online figure 1) showed a heterozygous c.464G→A nucleotide substitution in exon 5 of the VCP protein (p.R155H), a substitution not detected in an unaffected maternal brother (II:20) confirming mutation segregation within the family. This mutation has been previously identified.[1]

CLINICAL FEATURES

The pedigree of this five-generation IBMPFD family with 18 affected members (12 men, six women) is consistent with an autosomal dominant pattern of inheritance (online fig 1). Affected members presented with proximal and axial weakness diagnosed as motor neuron disease (MND) or other muscular dystrophies (online table 1). Eight members then proceeded to develop dementia. PDB was not found in the retrospective notes. The mean age of muscle weakness onset was 34 (n = 9; range 20–49). The mean duration of the illness to death, when recorded, was 17 years (n = 8; range 10–30). A detailed summary of the current clinical features and investigations and those from the retrospective notes for this large pedigree are presented in online table 1. Four members of the pedigree were found to have dilated cardiomyopathy following echocardiography, two with mild shortness of breath on exertion. All affected members have been treated with angiotensin-converting enzyme inhibitors, one patient with symptomatic improvement.

Five members of the extended pedigree had symptoms of sphincter disturbance presenting as urge incontinence (n = 5),

faecal incontinence (n = 4) or erectile dysfunction (n = 3; all male patients). Anorectal electrophysiology was performed in two patients, both consistent with bilateral pudendal neuropathies (Web table 1). MRI studies (fig 1) showed: scattered cerebral white matter hyperintensities in all three patients in whom this test was performed; asymmetrical left frontotemporal atrophy consistent with clinical FTD and an atrophic cord especially around the conus in II:18; and fatty change and atrophy of the gluteal muscles and low muscle volume in the quadriceps and hamstring groups in III:14. A muscle biopsy from II:14 is shown in online fig 2.

DISCUSSION

IBMPFD presents as a multisystem disorder affecting brain, skeletal and cardiac muscle,[3] spinal cord and bone.[1 4] The R155H mutation, an arginine-to-histidine substitution in the N-terminal CDC48 domain of the VCP protein, results in loss of VCP function[5] and is found exclusively in individuals affected with IBMPFD.[1] Clinical reports of this disease are scarce.[1 2 4] Family members usually presented with proximal weakness, progressing to wheelchair disability and premature death. The average age of muscle weakness onset, as a familial average, was 34, contrasting with previous studies (43[2] and 57[4]). The dementia frequency within this pedigree was 44% compared with 30%,[1] 70%,[4] and 100%[4] in other studies. As some patients may have prematurely died of myopathy- or cardiomyopathy-related complications, it was difficult to assess FTD penetrance.

Four out of five investigated members of this pedigree had echocardiographic features of cardiomyopathy.[3] This is the first clinical description of cardiomyopathy in a molecularly confirmed VCP mutation. Recent postmortem findings have found a dilated and hypertrophic cardiomyopathy in one patient with IBMPFD.[3]

The new observation in this pedigree is the presence of prominent sphincter disturbance involving bladder, bowel and erectile function in all five assessed pedigree members. Other factors could partially explain these symptoms: for example, functional obstructive defaecation may be partly responsible for the clinical picture of pudendal neuropathy seen in III:13. However, this is associated with a reduction in sphincter tone, a feature not seen during anorectal physiology. Moreover, III:15 had pudendal neuropathy with no history of longstanding constipation. In III:13, III:14 and III:15, erectile failure may be partly explained by psychogenic factors. Nonetheless, the similarity of sphincter symptoms between all patients and in particular four relatively young patients (III:3, III:13, III:14, III:15) is striking. We therefore conclude that IBMPFD is likely to be associated with sphincter disturbance. The presence of spinal cord atrophy in one patient (II:18) and previous work showing ubiquitin-positive nuclear inclusion bodies in the spinal cord in IBMPFD[4] suggest that sphincter disturbance in IBMPFD could arise from both spinal cord and nerve pathology.

Brain MRI demonstrated a mild excess of white matter abnormalities in all three examined. Right temporal lobe atrophy and cord atrophy were seen in an older patient, correlating with her clinical FTD. This is in agreement with one other MRI brain study of IBMPFD,[3] while another described progressive cerebral atrophy with prominent callosal and frontal white matter loss.[5] Spinal cord atrophy is a previously undescribed feature of IBMPFD and is consistent with pathological findings of spinal cord inclusion bodies.[4] A recent report describes MRI muscle findings in IBMPFD of "fatty degeneration" throughout predominantly proximal muscle groups,[3] in agreement with current findings.

Members of this pedigree had been previously given other diagnoses including various muscular dystrophies and spinal muscular atrophy. MND had been diagnosed in some patients because of denervation on neurophysiology (online table 1).

In conclusion, IBMPFD is a multisystem disorder, which should be considered in the differential diagnosis of autosomal dominant neuromuscular disorders, especially when there is a prominent history of dementia or "MND." Sphincter involvement is a likely associated clinical feature of the disease.

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CORRECTION

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M P T Lunn, H J Willison. Diagnosis and treatment of inflammatory neuropathies (*J Neurol Neurosurg Psychiatry* 2009;**80**:249–58). There is a dosage error in this paper. In the last paragraph on page 255 the dose of prednisolone should be 1mg/kg not 1g/kg as printed.