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Case report

Novel valosin containing protein mutation in a Swiss family with hereditary inclusion body myopathy and dementia

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Abstract

Inclusion body myopathy associated with Paget's disease of the bone and frontotemporal dementia is a rare but highly penetrant autosomal dominant progressive disorder linked to mutations in valosin containing protein (VCP). Here, we characterize a novel mutation in the linker 1 domain of VCP leading to inclusion body myopathy and/or frontotemporal dementia in 3 generations of a Swiss family. A detailed history of several years of clinical follow-up and electrophysiological, radiological and pathological findings are presented. Five out of 6 individuals suffered from progressive myopathy and 2 out of 6 from frontotemporal dementia, respectively. A radiologically suspected Paget's disease of the bone could not been confirmed at autopsy. This case study illustrates that only a subset of individuals shows the full triad of the disease complex and that clinicopathological findings are – when interpreted apart from familial history – hard to distinguish from sporadic inclusion body myositis.

Keywords: Hereditary inclusion body myopathy; Paget's disease of the bone; Frontotemporal dementia; Valosin containing protein

1. Introduction

Inclusion body myopathies form a heterogeneous group of hereditary and sporadic myodegenerative disorders. Histopathologically, hereditary inclusion body myopathies (h-IBM) usually lack the lymphocytic inflammation found in sporadic forms (s-IBM) [1]. In 2004, mutations in the gene encoding valosin containing protein (VCP, p97 or CDC48) have been described to be responsible for autosomal dominant and highly penetrant human inclusion body myopathy associated with Paget's disease of the bone (PDB), and frontotemporal dementia (FTD, IBMPFD) [2].

VCP plays a central role in the ubiquitin dependent protein degradation pathway, being involved in the transport of misfolded ER proteins to the cystosol where proteasomal degradation takes place. Recent studies highlight

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VCP's central role in autophagy [3]. VCP mutations can lead to ubiquitin-positive intracellular inclusions in various tissues, such as skeletal muscle, bone and brain. Further, these inclusions were shown to contain TAR DNA binding protein 43 (TDP-43), β-amyloid, and phosphorylated tau protein, also found in other neurodegenerative diseases including amyotrophic lateral sclerosis [4–6]. To date, up to 26 different mutant alleles in VCP gene have been identified [6–11]. Here, we describe the phenotype of a novel heterozygous mutation (I206F) of VCP in a family of European (Swiss) origin.

2. Case report

2.1. History and clinical phenotype

From 1993 to 2006, 3 brothers independently presented with muscular weakness of varying degree (Fig. 1).

Patient III 1 experienced muscular weakness of all four extremities around the age of 45 years. Initial electromyographic studies suggested a generalized denervation process, whereas repeated examination 5 years later demonstrated myopathic changes. Nerve conduction studies were normal. Serum creatine kinase was 308 U/l. A muscle biopsy showed changes compatible with the diagnosis of inclusion body myositis (Fig. 2A). By that time, his siblings had not yet developed muscular weakness, so a hereditary disorder was not taken into account. Treatment trials with steroids and repeated IVIG infusions had no beneficial effect. About 8 years after disease onset, he became wheelchair-bound. He showed bilateral scapular winging, atrophy and weakness of shoulder girdle, biceps, triceps muscles, hand and finger flexors and hip girdle, quadriceps and tibialis anterior weakness. Echocardiography revealed slight left ventricular hypertrophy but no signs of dilative cardiomyopathy. Later, head drop and weakness of respiratory muscles developed and nocturnal ventilation was introduced. Cognitive decline was suspected due to personality changes and perseveration in thinking. He died of respiratory failure caused by acute bronchopneumonia at the age of 63.

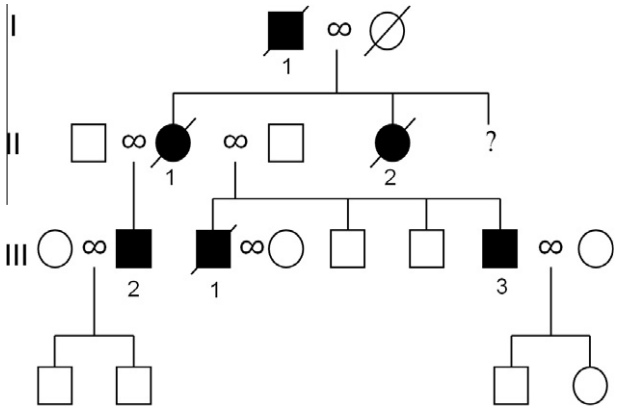

Fig. 1. Family tree shows affected individuals in three generations. The three affected brothers (III 1–3) whose clinical data are presented belong to the third generation. The mother (II 1) suffered from early onset dementia with death in her early 50s. An aunt (II 2) and the grandfather (I 1) from the mother's side suffered from an unknown muscle disease leading to walking disability and death in their 50s. (?) Information on additional members of generation 2 was not conclusive.

Patient III 2, a half brother of patient III 1, experienced asymmetrical proximal paraparesis of the lower limbs and foot drop around the age of 50 years. Electromyographic studies revealed only slight myopathic changes. A muscle biopsy showed changes compatible with inclusion body myositis. Neither he (loss of contact) nor we (different family name) were aware of this similarly affected (half-) brother. A treatment trial with IVIG did not result in any beneficial effect. About 9 years later, he became dependent on a cane and a splint as walking assistance. He showed bilateral scapular winging, weakness of biceps, finger flexors and quadriceps, a foot drop and positive Trendelenburg's sign. Echocardiography was normal. He declined follow-up.

Patient III 3 first realized difficulties with climbing stairs at the age of 55 years. 1 year later, carrying luggage became difficult because of weakness of finger flexors. He presented with slight bilateral scapular winging, marked atrophy and weakness of shoulder and hip muscles, biceps, quadriceps and deep finger flexors. EMG showed signs of chronic denervation as well as myopathic features. A muscle biopsy showed similar findings as in his brother and half-brother. A cardiac pacemaker was implanted due to atrioventricular nodal block five years prior to the onset of the muscular symptoms.

By history, Patient II 1, the mother of the three affected brothers, suffered from early onset dementia (onset in her fifties) with personality changes leading to permanent residency in a psychiatric hospital. She had no reported muscular symptoms. She died at the age of 57 years.

Patient II 2 and patient I 1, the aunt and the grandfather of patients III 1–3, were all reported to have suffered from an unknown muscle disease with progressive walking disabilities. They all died in their early 50s.

2.2. Muscle biopsy

Muscle biopsies of quadriceps were analyzed from patient III 1 in 1998, patient III 2 in 2000 and patient III 3 in 2007. All biopsies revealed similar features: fiber size variation, centralized nuclei and a varying degree of focal perivascular and endomysial lymphocytic infiltrates. Conventional staining revealed intracellular rimmed vacuoles. Immunohistochemistry against leukocyte antigens confirmed focal inflammatory infiltrates (Fig. 2A, biopsy of III 1). These findings were interpreted as inclusion-body myositis.

2.3. Radiographic findings

2.3.1. Imaging studies

MRI imaging of the lower extremities was performed in patient III 1 and 2. A CT scan was performed in patient III 3 (Fig. 2B). All three individuals showed a similar pattern