Valosin-containing protein-related myopathy and Meige syndrome: just a coincidence or not?

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Introduction

Valosin-containing protein (VCP) is a hexameric AAA+-type ATPase with a central role in various cellular activities, including cell cycle control, membrane fusion and the ubiquitin–proteasome degradation pathway. Mutations in the *VCP* gene have been associated with a variety of disorders, including distal myopathy with rimmed vacuoles, Paget's disease of the bone, frontotemporal dementia, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease type 2, cardiomyopathy and Parkinson's disease (PD) [1]. Meige syndrome is a type of cranial dystonia with blepharospasm and oromandibular dystonia sometimes associated with complex movement of lower facial muscles, mouth, jaw, tongue, pharyngeal and cervical muscles [2]. We report a patient with Meige syndrome, a mutation in VCP, and a myopathy

Case report

A 62-year old man presented with a 14-year history of a steppage gait. Clinical evaluation revealed weakness of ankle dorsiflexion, graded as 2/5 on the Medical Research Council scale bilaterally. Creatine kinase (CK) level was mildly elevated at 568 IU/L (normal range 25–190). Needle electromyography (EMG) demonstrated small amplitude, short duration, polyphasic motor unit action potentials, with early recruitment and small amounts of fibrillation potentials and positive sharp waves. Nerve conduction studies were normal. Biopsy of the tibialis anterior muscle revealed a myopathy with rimmed vacuoles (Figure 1). Subsequent genetic testing revealed a heterozygous missense mutation c.476G>A (p.R159H) in exon 5 of the *VCP* gene,

which was previously described in another Greek family with a dominantly-inherited syndrome of myopathy, dementia and an ALS-like syndrome in members of consecutive generations [3]. Our patient had no evidence of Paget's disease of bone and no cognitive deficits on neuropsychological evaluation. His 21-year-old son also had high a CK level (400 IU/L) and an EMG with findings similar to but less severe than those of his father. He declined genetic testing. There was no other family history of myopathy, Paget's disease of bone or cognitive decline. The patient also carries a diagnosis of Meige syndrome with involuntary tonic spasms of the orbicularis oculi and oromandibular muscles, without eyelid opening apraxia. The first symptoms of eye closure spasms appeared at the age of 54 years and slowly spread to involve the oromandibular muscles and the platysma within the next five years. OnabotulinumtoxinA injections had a moderate positive effect on the muscle spasms, but produced ptosis and diplopia. Injection sessions began with small doses (2.5 U at 3 locations in the pretarsal orbicularis oculi muscles of each eye) and were gradually increased to 20 U per eye (5 U in three pretarsal and 2.5 U in two orbital orbicularis oculi sites). The latter dose caused severe bilateral ptosis that lasted 4 weeks.

Discussion

Rare variants in the *VCP* gene may be more clinically important than is usually the case with other genes, because the protein appears to be intolerant to loss of function and missense mutations [1]. For example the I27V missense variant with an allele

frequency of 0.05%, has been described several times as being potentially pathogenic and has been identified in PD [1]. Moreover, immunohistochemical studies have demonstrated the presence of VCP in the peripheral portion of Lewy bodies, in Marinesco bodies that are seen in the nuclei of aged nigral neurons and in Lewy neurites in neuronal processes in PD, suggesting that the protein could be involved in the formation or degradation of various neuronal inclusions in neurodegenerative diseases such as a-synucleinopathies [4, 5]. I VCP is also known to play a pivotal role in TAR DNA-binding protein 43 (TDP-43) dysregulation and is therefore involved in TDP-43 pathology, which is implicated in the mechanisms of neurodegeneration in many Lewy body-related diseases [6, 7]. Based on these findings, it can be hypothesized that VCP variants may confer a risk for common degenerative diseases, including PD. Meige syndrome pathophysiology involves many brain regions and neural networks, mostly sensorimotor cortex, brain stem, and basal ganglia. Neuropathological studies from patients with Meige syndrome have revealed the presence of Lewy bodies in the brainstem and basal ganglia of 25% of autopsied cases [8]. In addition patients with Meige syndrome are more prone to develop PD than aged-matched controls [9]. VCP-related myopathy is an extremely rare disease with a prevalence of 0.66/100,000 population[1], while Meige syndrome has an estimated prevalence of less than 32 per million [10]. In view of their rarity, their coexistence in the same patient may not be coincidental and may be linked to an underlying pathological mechanism. Collectively, these data suggest that at least some patients with Meige disease share a common pathophysiology with PD patients that includes

basal ganglia dysfunction and Lewy body formation [10]. It is possible that VCP mutations lead to the formation of Lewy bodies in basal ganglia, but that in the majority of patients this basal ganglia dysfunction is subclinical. However, in a small proportion of patients, such as the one presented here, this could cause or predispose to the development of Meige syndrome and in a small minority of patients, as the basal ganglia lesion becomes more severe, it could result in PD.

While there are several reports of patients with VCP-related PD [1] and the VCP protein itself is a component of Lewy bodies [4], there has been no association with another movement disorder. The patient presented here demonstrated findings of typical Meige syndrome and carried a VCP gene mutation. The causal relationship between the VCP defect and Meige syndrome cannot be established by this single patient. However, the association of VCP with PD and Lewy bodies in basal ganglia suggests a possible pathological link. Further pathological studies are necessary to validate this hypothesis. This case adds to the increasing body of literature on *VCP* mutations by identifying a possible novel presentation.

Abbreviations

Parkinson's disease, PD; TAR DNA-binding protein 43, TDP-43; Valosin-containing protein, VCP

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Figure legends

Figure 1.Skeletal muscle section from tibialis anterior obtained at age 62 stained using modified Gomori trichrome showing multiple rimmed vacuoles (arrows) (x40). Scale bar = 70 μm.