LETTER TO THE EDITOR

Hereditary spastic paraplegia caused by a mutation in the VCP gene

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Sir, The hereditary spastic paraplegias constitute a genetically and clinically heterogeneous group of disorders of which the main clinical feature is progressive lower limb spasticity due to pyramidal tract dysfunction. The cardinal signs result from a ‘dying back’ degeneration of the corticospinal tracts and dorsal column, predominantly due to disturbed axonal transport within the longest fibres that innervate the lower extremities. Currently, among the 52 known hereditary spastic paraplegia genetic loci named SPG1–52, at least 28 genes have been identified.

One of the rarer autosomal dominant forms of hereditary spastic paraplegia, SPG8, is caused by mutations in the KIAA0196 gene on chromosome 8, encoding the protein strumpellin. In an interesting report in Brain by Clemen et al. (2010), strumpellin was demonstrated to interact with the valosin-containing protein (VCP), suggesting a complementary biological function. Also, strumpellin was detected in several pathological protein aggregates, including those seen in autosomal-dominant inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD; OMIM 605382) (Clemen et al., 2010). Mutations in the human VCP gene itself cause either IBMPFD or amyotrophic lateral sclerosis with or without frontotemporal dementia (Watts et al., 2004; Haubenberger et al., 2005; Guyant-Marechal et al., 2006; Gidaro et al., 2008; Bersano et al., 2009; Johnson et al., 2010; Fanganiello et al., 2011; Jesus-Hernandez et al., 2011; Nalbandian et al., 2011). Although the paper by Clemen et al. (2010), based on this interaction between VCP and strumpellin, could suggest that VCP mutations may perhaps lead to an hereditary spastic paraplegia phenotype, this has not yet been reported.

We recently saw two brothers, both affected by a slowly progressive spastic paraplegia and Paget’s disease of bone, in whom we identified a pathogenic mutation in the VCP gene (NM_007126.3) c.475 C>T (p.Arg159Cys). The Arg159Cys mutation affects an arginine residue highly conserved during evolution, located in the N-terminal (CDC48) domain, which is involved in substrate binding (e.g. ubiquitin) and lies within the mutational hot spot (Watts et al., 2004). To date, this missense mutation has only been identified in a sporadic Italian patient with the above mentioned phenotype of adult-onset inclusion body myopathy, who developed frontotemporal dementia 18 years after inclusion body myopathy onset (Bersano et al., 2009).

The two Dutch brothers described here developed a slowly progressive gait impairment in their sixth decade (ages at onset: 54 and 57 years, respectively), limiting their maximum walking distance. Around the same time, Paget’s disease of bone was diagnosed. Sensory complaints or sphincter disturbances were not reported, and neither were dysarthria, dysphagia, behavioural changes or cognitive decline (confirmed by their relatives). The family history revealed another, older brother with Paget’s disease of bone, who became wheelchair-bound at age 57 after 10 years of gait impairment, but unfortunately refused any medical examination or investigation. One younger brother with Paget’s disease of bone just started to notice some gait problems. Their deceased father was said to have had gait problems for a long time, attributed to his diagnosis of Paget disease of bone, but he did show lower limb weakness and was wheelchair-bound for the last 25 years of his life. He died at age 75 without signs of swallowing difficulties or respiratory problems. Two of their father’s brothers had gait impairment without a clear diagnosis. Neurological
examination in the two index patients showed a spastic paraplegia with decreased strength in the anterior tibial muscles (MRC 4), increased muscle tone and hyper-reflexia in the lower extremities with Babinski signs. In the eldest brother, fasciculations were encountered in his tongue and calf muscles, without clinical evidence of bulbar or arm involvement. No proximal muscle weakness, extrapyramidal or cerebellar signs were seen. Cognitive function was normal in both cases. Serum alkaline phosphatase level was increased to 208 U/l in one, and 283 U/l in the other brother (normal: 0–120 U/l), as well as the urinary excretion of galactosyl-hydroxylysine. Additional laboratory investigations (including creatine kinase, vitamins E, B1, B6, B12 and folic acid) and serological tests for Borrelia, Lues and HIV were all normal or negative. A 99mTc bone scintigraphy (as well as a chest and abdominal CT) showed sclerotic lesions in L2, the left ileum and corpus sterni in the youngest brother, with subsequent histological proof of Paget pathology in the ileum. Brain and spinal MRI were normal in both patients. EMG (nerve conductin studies combined with comprehensive needle EMG) showed no myopathic changes and no evidence of peripheral neuropathy, but did reveal lower motor neuron involvement with signs of active denervation in two regions; according to the Awaji-Shima criteria and combined with the upper motor neuron signs in the legs, these data are formally in keeping with a diagnosis of possible amyotrophic lateral sclerosis (Douglass et al., 2010). However, both brothers clinically only showed an isolated slowly progressive spastic gait for at least 10 years and the family history revealed an even longer duration of up to 25 years of gait impairment without developing any upper- or lower motor signs in the other regions. Together with such a long survival, these findings argue against a diagnosis of amyotrophic lateral sclerosis, and we interpret the distal muscle weakness and the EMG findings as evidence of co-existing lower motor neuron involvement. One could speculate whether one of the patients with amyotrophic lateral sclerosis described thus far, had in fact this complex hereditary spastic paraplegia phenotype (without the Paget disease of bone), because of the relatively benign course with 12 years survival (Johnson et al., 2010). However, patients from another Italian kindred with the same Arg191Gln mutation, who seemed to be second degree relatives, did show a clear progressive amyotrophic lateral sclerosis-like course (Johnson et al., 2010). In another report, one VCP patient has been described with bilateral pyramidal tract dysfunction, in whom mutations in SPAST (SPG4), ATL1 (SG3A) and NIPA1 (SPG6) were first excluded, although the arms seemed more affected than the legs (Kumar et al., 2010). Molecular analysis in our family excluded mutations in SPAST (SPG4), SPG7, KIF5A (SPG10), BSC12 (SPG17) and REEP1 (SPG31), before the VCP mutation was identified.

We can only speculate on why this VCP mutation has led to the hereditary spastic paraplegia phenotype. VCP is a ubiquitously expressed member of the AAA-ATPase family with multiple cellular functions (including vesicular trafficking and degradation of proteins by the ubiquitin-proteasome system) and has a wide variety of binding partners, among which strumpellin, as reported by Clemen et al. (2010). VCP not only has the same diffuse cytosolic as well as endoplasmatic reticulum membrane distribution as strumpellin, but was also shown to directly interact with strumpellin (Clemen et al., 2010). This interaction might be necessary for a normal functioning of strumpellin and may become disturbed by mutant VCP. Alternatively, pathogenic VCP positive inclusions, as described in diverse neurodegenerative disorders (e.g. Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis and spinocerebellar ataxia type 3) (Kakizuka, 2008) and myofibrillar myopathies (Hubbers et al., 2007), could sequester strumpellin to such an extent that it might lead to a depletion of strumpellin. Since strumpellin has also been described as a subunit of a large multi-protein complex involved in fission of endosomes (Derivery et al., 2009), it is tempting to speculate that its depletion may interfere with this fission process. A last possibility is a strumpellin-independent pathway of VCP gene mutations causing hereditary spastic paraplegia, due to either a direct effect of mutant VCP (toxic gain of VCP function) (Hubbers et al., 2007) or with a more indirect effect via other hereditary spastic paraplegia-associated proteins, e.g. spastin or paraplegin, which are also members of the AAA-ATPase family. The AAA-ATPase domain of spastin even shares 36% sequence identity with murine p97/VCP (Pantakani et al., 2008). The fact that our patients showed evidence of lower motor neuron loss not restricted to the legs on EMG and that both had Paget’s disease of bone implies, at least partly, direct VCP-induced pathology, because strumpellin mutations have thus far only been linked to uncomplicated forms of hereditary spastic paraplegia. Further investigations are needed to clarify the precise mechanisms through which VCP mutations give rise to progressive lower limb spasticity.

In summary, we here extend the clinical spectrum of VCP-associated diseases with a complex form of hereditary spastic paraplegia. Our finding of a VCP mutation in an hereditary spastic paraplegia family might be the clinical embodiment of the biological interaction between strumpellin and VCP as found by Clemen et al. (2010), although this requires confirmation.

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