Facial onset sensory motor neuronopathy (FOSMN) syndrome: an unusual amyotrophic lateral sclerosis phenotype?

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Facial onset sensory and motor neuronopathy (FOSMN) syndrome may represent an amyotrophic lateral sclerosis phenotype as indicated by associated with the heterozygous D90A superoxide dismutase-1 (SOD-1) gene mutation.

Facial onset sensory and motor neuronopathy (FOSMN) syndrome is a rare and slowly progressive neurological disorder heralded by development of sensory symptoms within the face (trigeminal nerve distribution), and followed by evolution of sensory and motor deficits in a rostral-caudal direction.[1] The motor deficits are characterised by lower motor neurone features including muscle weakness and wasting, cramps and fasciculations, with absence of upper motor neurone signs.[1 2] The pathophysiological mechanisms underlying FOSMN syndrome remain to be fully elucidated, although neurodegenerative and autoimmune mechanisms have been proposed.[1–5]

Pathologic studies seem to support a neurodegenerative mechanism, with evidence of sensory and motor neuronal degeneration within the trigeminal sensory nucleus, dorsal root ganglion, brainstem and spinal cord motor nuclei along with an absence of tissue inflammation.[1 2] Of further relevance, immunomodulatory therapies seem to exert, at best, a moderate and non-sustained response, thereby further suggesting a predominant role for neurodegenerative processes in the pathogenesis FOSMN syndrome. A link between FOSMN syndrome and amyotrophic lateral sclerosis (ALS) has been recently suggested,[3] raising the prospect of establishing a potential mechanism of neurodegeneration. While some pathological studies have failed to document any features of ALS, including TAR DNA-binding protein 43 (TDP-43) intraneuronal inclusions, Bunina bodies or ubiquitin inclusions,[1 2] thereby arguing against an association, a recent study reported widespread TDP-43 inclusions with the implication being that FOSMN syndrome may represent a spectrum of motor neurone disease like TDP-43 proteinopathy syndromes.[6]

In the article by Dalla Bella[7] and colleagues, a heterozygous D90A mutation in the superoxide dismutase-1 (SOD-1) gene was reported in a single case of FOSMN syndrome and proposed as further evidence to suggest that FOSMN syndrome may be an unusual ALS phenotype. While the pathogenicity of the homozygous D90A SOD-1 mutation is well established,[8] that of the heterozygous D90A mutation is less certain, being detected in unaffected ALS family members[9] and co-occurring with other ALS related genetic mutations.[10] Importantly, the heterozygous D90A mutation may form part of an oligogenic pattern, which could result in unusual phenotypes under specific conditions. In contrast, the identification of non-ALS related genes in FOSMN syndrome, namely the oculopharyngeal muscular dystrophy trinucleotide repeat expansion,[2] may also argue for a chance association. The notion that FOSMN syndrome represents an unusual ALS phenotype remains to be established, and further genotype-phenotype studies incorporating larger numbers of FOSMN patients would be essential to establish any such associations.

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