

A true sporadic ALS case carrying a novel de novo p.Q519E FUS heterozygous missense mutation



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Background

FUS mutations account for ~4% of familial ALS (fALS) and 1% of apparently sporadic (sALS) cases (1). Sporadic patients carrying de novo FUS mutations have been already described. We report a true sporadic ALS case carrying a novel de novo p.Q519E FUS heterozygous missense mutation with prevalent lower motor neuron involvement.

Case report.

A Caucasian woman developed progressive weakness and wasting of the right shoulder and the right tibialis anterior. She underwent blood examination, which revealed CPK of 278 IU/L, nerve conduction studies and needle EMG, showing a motor axonopathy and diffuse signs of chronic neurogenic damage without active denervation. Brain and cervical MRI did not reveal significant findings but a small cavernoma in the right occipital lobe, and DTI studies of the corticospinal tracts resulted normal. Lumbar and sacral MRI did not show any sign of compression of nervous structures. Respiratory function assessment showed normal FVC. CSF examination resulted normal and serum anti-GM1 antibodies were absent. Muscle weakness and wasting subsequently involved distal muscles of upper limbs and proximal muscles of lower limbs, without pyramidal and bulbar signs.

Muscle biopsy of the right quadriceps evidenced chronic neurogenic damage. In the hypothesis of an adult-onset spinal muscular atrophy genetic testing of SMN gene was performed and resulted negative. Needle EMG was repeated 16 months after the former assessment, showing active denervation in some muscle of lower and, to a lesser extent, upper limbs. The subsequent genetic analysis of major ALS-related genes revealed a novel p.Q519E heterozygous missense mutation of FUS, which resulted absent in the patient's parents. All the subjects provided written informed consent for genetic analysis. This finding supported the diagnosis of motor neuron disease. Almost three years after the onset the patient is alive, without bulbar and respiratory involvement, with slight pyramidal signs (positive Hoffman sign at the right side; upper limbs reflexes with bilateral synkinesias).

Discussion.

We describe an ALS case carrying a novel de novo p.Q519E FUS heterozygous missense mutation, with prevalent lower motor neuron phenotype resembling spinal muscular atrophy. De novo FUS mutations have been already described (2,3). Nevertheless, further studies are needed to confirm the eventual pathogenic role of the p.Q519E mutation. Biochemical studies suggest that FUS and SMN proteins interact directly and that this interaction can be regulated by FUS mutations (4).

The alteration of the FUS-SMN pathway might be an underlying mechanism of the prevalent lower motor neuron phenotype observed in our case.

References

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