A familial ALS case carrying a novel p.G147C *SOD1* heterozygous missense mutation with non-executive cognitive impairment

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease causing progressive muscle weakness and wasting. Death usually occurs within 3–5 years from respiratory failure. Approximately 10% of cases are familial (fALS).The frequency of *SOD1* gene mutations in patients with fALS varies among populations, from 0% in Ireland to 13.6% in Italy and 23.5% in Scandinavia.[1] *SOD1* encodes for the Cu/Zn Superoxide Dismutase 1. Mutations are usually autosomal dominant, but the p.D90A and the p.D96N may be autosomal recessive.[2]

Performing the genetic screening of an Italian fALS series, we found a novel c.442g>t heterozygous missense mutation of *SOD1* gene leading to a substitution of cysteine for glycine (p.G147C). Such mutation was absent in healthy controls (n=130). The patient provided written informed consent.

The index case displayed progressive weakness and wasting of both hands when he was 52 years old. One year after the onset he also exhibited tongue hypotrophy with fasciculations, spastic paraparesis, impairment of feet extension and brisk jaw jerk and lower limbs reflexes. Plantar response was absent bilaterally. He referred diffuse cramps and fasciculations. Dysphagia, dysarthria, dysphonia and dyspnoea were absent. The amyotrophic lateral sclerosis funcional rating scale revised (ALSFRS-R) was 44/48. Needle electromyography (EMG) showed chronic and active denervation in bulbar and spinal regions. Forced vital capacity was 106%. The neuropsychological evaluation showed an impaired performance in the Rey-Osterrieth Complex Figure (ROCF) Test, in copy and recall task, while other tests had normal scores. Brain MRI showed selective atrophy of the right supramarginal gyrus (figure 1A), slight hyperintensity of the corticospinal tracts in T2-weighted scans, reduced fractional anisotropy along the right corticospinal tract in diffusion tensor imaging (DTI) scans. Cervical cord MRI was normal. ^{18}F-FDG cerebral PET revealed reduced uptake (p=0.001) in the right supramarginal gyrus (Brodmann area (BA) 40) (figure 1B). Brain MRI and 18F-Fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and neuropsychological assessment were repeated 6 months later. The focal atrophy of the right supramarginal gyrus resulted unchanged at MRI. ^{18}F-FDG PET showed slight extension of the area of hypometabolism previously observed at this site and the appearance of a new area in the right frontopolar region (p=0.01) (figure 1C). A relative reduction of the uptake in the right caudate nucleus, probably due to deafferentation, seems to support the significativity of the frontopolar hypometabolism. The neuropsychological evaluation confirmed the deficit in the ROCF and demonstrated a reduction of the scores of mini mental state examination (MMSE), trail making test (TMT)-A and TMT-B, Clock Test and frontal assessment battery (FAB), although they were still normal.

Two brothers of the proband died from ALS. The former showed muscle weakness and wasting at upper limbs when he was 46 years of age. He had a rapid worsening and died from respiratory failure 10 months after the onset. The latter reported cramps at lower limbs when he was 48 years of age, followed by weakness of the left upper limb. He showed a classic ALS phenotype and died from respiratory failure 27 months after the onset. Two siblings were 46 years and

50 years and healthy. His father died when he was 76 years from chronic kidney failure without any neurological impairment; his mother was 83 years and healthy. No other relatives with neurological impairment were reported. The index case showed a p.G147C missense mutation of *SOD1* (mutations of other ALS-related genes were excluded). The same mutation was found in the latter affected sibling. DNA of other family members was unavailable. A diagnosis of clinically definite fALS with genetic confirmation was made. The patient is still alive, 24 months after the onset. He also shows slight dysarthria and occasional dysphagia. The disease is slowly progressive and respiratory involvement is absent. The autonomy in daily living activities is good. ALSFRS-R is 41/48.

Three other missense mutations of codon 147 of *SOD1* have already been found. Andersen and colleagues reported an Icelandic case with a p.G147R mutation and a patient carrying a p.G147D mutation.[3] Two families with a p.G147D mutation were identified in a series of French fALS cases: age of onset ranged from 45 years to 73 years, with spinal onset for three of four; tested subjects had no cognitive impairment; disease duration ranged from 10 months to 49 months.[4] The p.G147S mutation was described in an apparently sporadic case with bulbar onset at the age of 56 years and death from respiratory failure in 8 months.[5 6] Codon 147 encodes a highly conserved aminoacidic residue across species. This change was predicted to affect protein function by molecular modelling studies.

We report the first ALS case carrying a p.G147C heterozygous missense mutation of *SOD1*. Noteworthy, the impairment of the ROCF is in agreement with the reduced uptake of the tracer in the right supramarginal gyrus (BA 40) and the right middle frontal gyrus (BA 10) at ^{18}F-FDG PET and with the atrophy at MRI in the right supramarginal gyrus (BA 40). A ^{18}F-FDG PET study in patients with probable AD showed a significant positive association between ROCF performance and cortical metabolism in the following regions: the widest area was situated in the posterior part of the right hemisphere and included the supramarginal gyrus; other significant clusters were found in the right frontal lobe and included the middle frontal gyrus.

Cognitive impairment is rare in *SOD1* mutations carriers. *SOD1* fALS subjects seem less vulnerable to cognitive dysfunction than non-*SOD1* fALS.[1] The follow-up including neuropsychological tests and ^{18}F-FDG PET showed a trend to progression of cognitive impairment with frontal lobe involvement. This finding supports the hypothesis that cognitive impairment is related to ALS rather than to other causes (ie, developmental anomalies).

Most of the cases carrying mutations of codon 147 show a rapid worsening, while our patient displays a slower trend. His affected siblings had a faster course. We need further data to establish possible genotype-phenotype correlations.

Although genetic data were unavailable for one of the affected siblings and healthy relatives, the presence of the p.G147C mutation in two ALS cases supports the hypothesis that it is pathogenic. Nevertheless, the presence of healthy aged parents and the absence of other affected relatives raise the possibility of an incomplete penetrance. Further studies are necessary to highlight its pathogenic role and its clinical manifestation.

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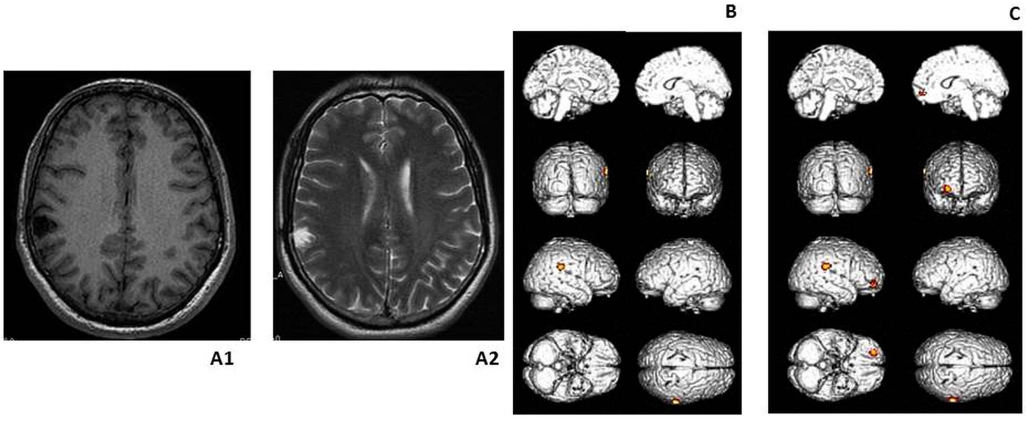

Figure 1 (A) MRI axial T1 (A1) and T2 (A2) images show a focal atrophy of the right supramarginal gyrus (Brodmann area (BA) 40). (B) ^{18}F-FDG cerebral PET parametric study confirmed this finding, showing a reduced uptake (p=0.001) in the right supramarginal gyrus (BA 40). (C) A ^{18}F-FDG cerebral PET parametric study performed 6 months after the previous study showed an extension of reduced uptake in the middle frontal gyrus (BA 10) (at p=0.01).

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