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A patient carrying a homozygous p.A382T *TARDBP* missense mutation shows a syndrome including ALS, extrapyramidal symptoms and FTD

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Abstract

We have recently published data showing that a founder mutation of the *TARDBP* gene (p.A382T) accounts for approximately one third of ALS cases on the Mediterranean island of Sardinia (Chiò et al, 2011). In that report, we identified 53 years-old man carrying a homozygous A382T missense mutation of the *TARDBP* gene with a complex neurological syndrome including ALS, parkinsonian features, motor and vocal tics, and frontotemporal dementia (FTD). Due to the uniqueness of this case, here we provide a detailed clinical description, as well as

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neurophysiological, neuropsychological and neuroimaging data for that case and his extended family.

1. Introduction

We recently published data showing that approximately one third of amyotrophic lateral sclerosis (ALS) cases on the Mediterranean island of Sardinian ancestry arise from a single founder mutation of the *TARDBP* gene, namely the c.1144G>A (p.A382T) missense mutation (Chiò et al, 2011). In that publication, we identified:

“a 48-year-old man who also presented with upper motor neuron–predominant ALS that was followed 3 years later by the onset of rigid hyperkinetic parkinsonism. Neuropsychological testing confirmed frontal lobe dysfunction consistent with fronto-temporal dementia (FTD). Of note, the patient had a history of a vocal and motor tics disorder since childhood that had been treated with haloperidol for less than 2 years when aged 18 years. This patient carries a homozygous A382T missense mutation and was alive 4 years after the onset of ALS.”

The purpose of the current article is to provide additional clinical details and neuroimaging data for this case and his extended family.

2. Case report

The pedigree of the family is reported in Figure 1. The index case (III-1) is currently a 53 year old man, who is homozygous for the p.A382T missense mutation of the *TARDBP* gene. He developed progressive spasticity at upper and lower limbs, with hyperreflexia and Babinski sign at the age of 49 followed by the development of slurred speech, and difficulty swallowing fluids with episodes of glottis spasm. Neurophysiological examination showed chronic and active denervation in distal muscles of his upper and lower limbs, with normal motor and sensory conduction velocities. Motor evoked potentials revealed absence of the motor evoked response at the left upper limb and at the lower limbs, and a reduction of the amplitude at the right upper limb both at rest and after facilitation. Neuropsychological examination showed impairments in tests for selective attention, verbal phonological and semantic fluency, and in the frontal assessment battery (FAB), consistent with a diagnosis of mild frontotemporal dementia (FTD). A diagnosis of probable laboratory supported ALS was made.

Six months after the onset of ALS, the patient developed parkinsonism, characterized by rigidity of upper and lower limbs and of neck and trunk musculature with bradyphrenia. Tremor was not observed. Dystonic movements of the fingers of both hands and of the right foot were also noted. Magnetic resonance imaging (MRI) of the spinal cord was normal. Brain MRI with fiber tracking showed a bilateral reduction of corticospinal tract fibers. No abnormalities of the basal ganglia were found with single photon emission computed tomography (SPECT) with ¹²³I-Ioflupane (DaT-SCAN®). Perfusion SPECT with ⁹⁹Tc-ECD (ethylene cystine dimer) showed a marked reduction of the uptake in the frontotemporal regions bilaterally and in the right parietal lobe (Figure 2), confirmed by the ¹⁸F-FDG-PET (Figure 3). The patient was treated with levodopa/benserazide (200/50) b.i.d., which was withdrawn soon after due the occurrence of psychomotor retardation and worsening of speech disturbances. Four years after the onset of symptoms the patient is wheelchair-bound and shows a severe worsening of the mixed (pyramidal/extrapyramidal) hypertonia. His ALS Functional Rating Scale - Revised (ALSF-RS-R) score was 25.

The patient reported a history of vocal and motor tic disorder when he was 6 years-old. The motor tics were characterized by lifting of the left shoulder, leg extension, shaking of the diaphragm and movements of the peribuccal muscles. His vocal tics were consisted of guttural, sometimes explosive, sounds. The tic syndrome was treated for less than one year with haloperidol when the patient was 18. The motor tics disappeared when the patient developed the actual motor symptoms, while the vocal tics still persist.

The patient has one sister and two brothers, who are 51, 49 and 43 years-old. They are healthy and do not show any neurological sign or symptom. The father of the index case (II-4) died at 85 after having been affected by predominant behavioral FTD (indicated by pathological scores for the FAB and the Neuropsychiatric Inventory [NPI] tests) for 5 years. He had no signs of motor neuron dysfunction, tics or extrapyramidal impairment. The mother of the index case (II-5) is 82 years old and healthy. Both the father and the mother of the index case are heterozygous for the p.A382T missense mutation of the *TARDBP* gene.

The paternal uncle (II-3) of the index case is heterozygous for the p.A382T missense mutation of the *TARDBP* gene. He is 81 and has been affected from childhood by a motor and vocal tic syndrome similar to that of the index case; he also developed cognitive impairment (FTD) (indicated by pathological FAB scores) at 76 years of age. The maternal aunt of the index case (II-11) is 83 years-old and developed FTD at 77. She is heterozygous for the p.A382T missense mutation of the *TARDBP* gene. Another maternal aunt (II-3) developed resting tremor at both hands and head at 75 and died at 81. DNA was not available for this subject. The maternal grandfather (I-3) developed dysarthria at 65, followed by walking disturbances and dementia. He was diagnosed as having ALS. He died at 82, after being bedridden for 7 years. DNA was not available for this subject. The paternal grandfather (II-1) developed dementia at 70 and deceased 6 years later. No DNA is available of this subject.

3. Discussion

In this current paper, we provided an exhaustive clinical description, neurophysiological, neuropsychological and neuroimaging data for a patient that we previously identified as carrying the p.A382T missense pathogenic variant of the *TARDBP* gene (Chiò et al, 2011). Highlighting the unique clinical aspects of this case may facilitate the identification of similar cases by other neurologists. The index case is affected by a predominant upper motor neuron ALS (Gordon et al, 2009; Sabatelli et al, 2009), associated with a motor and vocal tic syndrome since childhood, extrapyramidal features consistent with a rigid-akinetic parkinsonism, and a mild FTD. None of his relatives, who also carry the same p.A382T missense mutation of the *TARDBP* gene, albeit heterozygous, have clinical features of ALS, with the exception of his paternal grandfather, who developed of ALS and dementia and died 17 years after the onset of ALS. The patient's father and one of his maternal aunts had FTD, while one of his paternal uncles has a motor and vocal tic syndrome from childhood and later-onset FTD. It is not clear whether the tic syndrome identified in the index case and in one of his paternal uncles is related to the p.A382T missense mutation of the *TARDBP* gene. To the best of our knowledge, *TARDBP* mutations have not been assessed in patients with tic syndrome.

TARDBP mutations have been described as being related to typical ALS (Sreedharan et al, 2008), ALS with FTD (Chiò et al, 2010), ALS with extrapyramidal symptoms (Chiò et al, 2011), ALS and supranuclear palsy (Chiò et al, 2011), supranuclear palsy, FTD and chorea (Kovacs et al, 2009), and FTD without motor neuron disease (Borroni et al, 2009). In this family we have found that the same mutation can manifest with broadly different neurological phenotypes. Interestingly, the index case, who carries a homozygous mutation,

has a clinical syndrome summarizing all the constellation of symptoms found in his family, but nevertheless he has a relatively mild ALS, with relatively slow progression over a four year period. Our previously published data demonstrated the founder nature of the p.A382T mutation in the Sardinian population (Chiò et al, 2011). Thus, it is highly likely that the p.A382T mutation in both the maternal and paternal sides of the kindred shared the same common ancestor.

As already observed in our previous paper (Chiò et al, 2010), the penetrance of this mutation is not complete, since the 82 years-old mother of the index case, who carries the p.A382T *TARDBP* missense mutation, is neurologically healthy.

TARDBP encodes for the TDP-43 protein, which has been found to be deposited in neurons in several neurological disorders, such as ALS, FTD with or without ALS, Parkinson's disease and Alzheimer's disease (Geser et al, 2009), conditions that are now grouped under the general heading of multisystem TDP-43 proteinopathies. Moreover, post-mortem analysis of ALS cases shows the diffusion of TDP-43 pathology beyond the motor system to involve the nigro-striatal system, the neocortical and allocortical area and the cerebellum (Geser et al, 2008). Therefore, the heterogeneity of clinical features associated to *TARDBP* missense mutations may not be surprising. It is perhaps more surprising the presence of a marked phenotypic heterogeneity in members of same family, all carrying the same missense mutation. This finding indicates that other factors influence the phenotype related to *TARDBP* mutations. While these factors remains unknown, it can be hypothesized that these can be genetic, epigenetic, post-translational, or environmental in nature (Simpson & Al Chalabi, 2006). The unveiling of the mechanisms underlying the variability of the clinical phenotype in patients carrying pathogenic mutations may be of importance for identifying new pathways for targeted therapeutic interventions in ALS.

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Figure 1. Family pedigree. Square indicates male; circle, female; slash, deceased; and arrow, index patient. The red square indicates ALS; the blue square, vocal and motor tics; the yellow square, FTD; the green square, parkinsonism; and the violet point, tremor.

Figure 2.

(A) Perfusion SPECT with ^{99}Tc -ECD (ethylene cystine dimer), patient III-1. The transversal scans show a marked reduction of the uptake in the frontotemporal regions bilaterally and in the right parietal lobe. (B) The patient's SPECT is compared to a that of a normal subject with the same age as patient III-1.

Figure 3.

(A) ^{18}F -FDG PET scan, patient III-1. The sagittal scans show the reduction of the ^{18}F -FDG uptake on the right frontal precentral gyrus, on the right and left parietal postcentral gyrus and on the right insula. (B) ^{18}F -FDG PET scan of a normal subject with the same age as patient III-1.