J Neurol (2014) 261:1442–1443
DOI 10.1007/s00415-014-7400-1

LETTER TO THE EDITORS

A case of amyotrophic lateral sclerosis with intermediate *ATXN-1* CAG repeat expansion in a large family with spinocerebellar ataxia type 1

Rossella Spataro · Vincenzo La Bella

Received: 4 May 2014 / Revised: 3 June 2014 / Accepted: 4 June 2014 / Published online: 11 June 2014

Dear Sirs,

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder, with a genetic contribution to its pathogenesis [1].

It has been demonstrated that poly-Q intermediate expansions of ATXN-2 (SCA2) and ATXN-1 (SCA1) are a genetic risk factor for the disease [2, 3], even though the latter finding was not confirmed in another study [4]. The relationship between the two SCAs and ALS is further supported by the evidence that typical SCA1 or SCA2 patients may develop signs and symptoms of motor neuron (MN) degeneration [5–8]. Finally, a report showed the co-existence, in the same SCA2 family, of ALS bearing intermediate poly-Q expansions and SCA2, with a full expansion [9].

Here, we describe a patient with ALS, carrying an intermediate ATXN-1 poly-Q expansion, who belonged to a large SCA1 family.

A 47-year-old worker (IV-19, Fig. 1) was referred with a history of progressive weakness of the right hand. His family history was positive for SCA1 (Fig. 1), but he never showed signs or symptoms of ataxia.

The neurological examination showed weakness and muscular atrophy in both upper limbs, with fasciculations, cramps and brisk reflexes in both upper and lower limbs. Speech, swallowing, and respiratory function were normal. Sensory function was within normal range.

An extensive biochemical and immunological work-up, including a CSF analysis, was negative. A brain and spine MRI demonstrated a bilateral corticospinal tract hyperintensity. EMG showed diffuse polyphasic MUPs, fibrillation potentials and PSWs in all limbs. Nerve conduction studies were normal. A genetic screening (SOD1, C9orf72, FUS, TARDPB, angiogenin) was negative.

Analysis of ATXN-1, showed in the patient IV-9, intermediate CAG expansions in both alleles (33/33) with no CAT interruptions.

A clinical diagnosis of ALS was made. The progression rate (ΔFS) was calculated following Kimura et al. [10] and gave a value of 3.33, indicating a rapidly progressing disease. Ten months after diagnosis, he died because of a myocardial infarction.

We clinically examined and performed genetic testing in three other members of this family (IV-12, IV-18 and IV-24; Fig. 1).

IV-18 was the proband's brother. When he was 30 years old, unsteadiness when walking, truncal titubation and slurred speech occurred. Genetic testing revealed an expanded CAG repeat of 33/54 in ATXN-1. At the age of 45, he developed a severe cerebellar ataxia, proximal and distal muscle atrophy with marked weakness, brisk reflexes in all four limbs, anarthria and dysphagia, atrophy of the tongue with fasciculations. He died at the age of 46 years because of a respiratory failure.

The other two SCA1 members of the family (IV-12 and IV-24) showed, respectively, a clinical onset at age of 41 and 32 with an ataxic-spastic phenotype but without lower MN signs or symptoms. Genetic testing revealed expanded ATXN-1 CAG repeats of 30/49 for IV-12 and 28/51 for IV-24.

In this report, we have described a SCA1 family in which a member, bearing an intermediate ATXN-1 repeats, was affected by a clinically-definite ALS. There is only another report describing, in a SCA2 family, the co-existence of SCA and ALS in two members [9]. Note that the

R. Spataro (✉) · V. La Bella
ALS Clinical Research Center, Bio.Ne.C., University of Palermo, via G La Loggia 1, 90129 Palermo, Italy
e-mail: rossellaspataro@libero.it

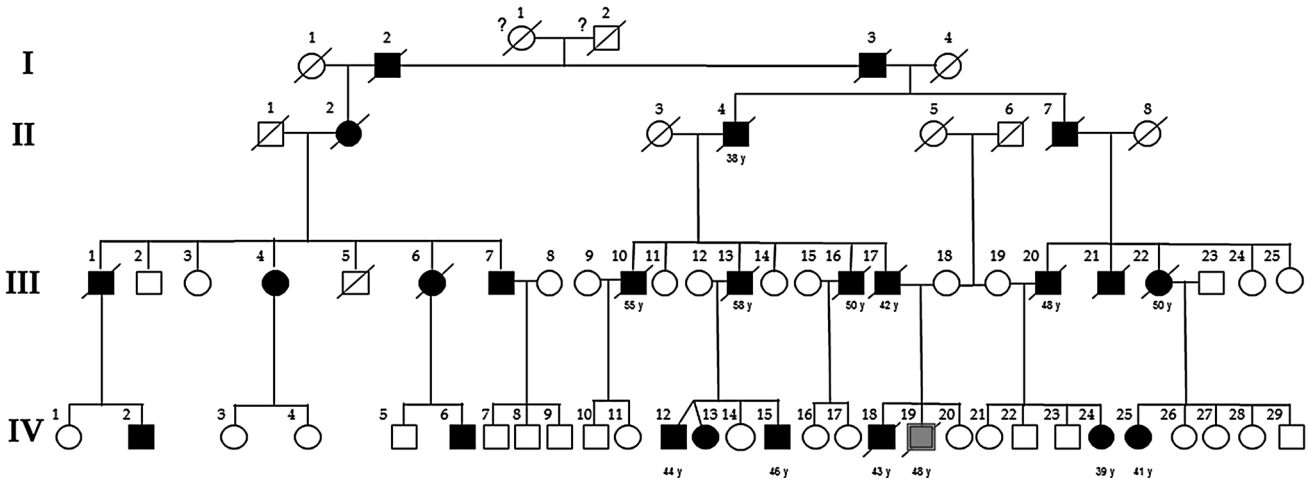

Fig. 1 SCA1-ALS family pedigree. *Square* indicates male; *circle* female; *slash* deceased; *black symbols* indicate patients affected by SCA1; *gray symbol* indicates the patient affected by ALS

SCA1 case IV-18 showed at later stages a full MN disease-like phenotype.

We speculate that an unknown MN-specific genetic factor may have played a role in driving a full ALS phenotype in the proband and an ALS-like phenotype in the SCA1 brother.

The role of ataxins in ALS pathogenesis remains unclear. The poly-Q binding protein 1, which interacts with ATXN-1, when overexpressed in mice induces a progressive MN-like phenotype [11]. Furthermore, ATXN-2 intermediate repeats contribute to the pathological cascade involving FUS and TDP-43, two ALS-related proteins [12, 13].

Although rare, the co-occurrence of ALS and SCA in the same family reinforces the putative pathogenic link between the two disorders.

Conflicts of interest The authors declare no financial or other conflicts of interest.

Ethical standard This report was reviewed and approved by the internal Ethic Commitee of BioNeC, University of Palermo. All patients described in the report gave their informed consent to make genetic analysis and use clinical information for research purposes.

References

1. Al-Chalabi A, Jones A, Troakes C et al (2012) The genetics and neuropathology of amyotrophic lateral sclerosis. Acta Neuropathol 124:339–352
2. Elden AC, Kim H-J, Hart MP et al (2010) Ataxin-2 intermediate-length polyglutamine expansions are associated with increate risk for ALS. Nature 466:1069–1075
3. Conforti FL, Spataro R, Sproviero W et al (2012) Ataxin-1 and ataxin-2 intermediate-length poly-Q expansions in amyotrophic lateral sclerosis. Neurology 79:2315–2320
4. Lee T, Li Y-R, Chesi A et al (2011) Evaluating the prevalence of polyglutamine repeat expansions in amyotrophic lateral sclerosis. Neurology 76:2062–2065
5. Magana JJ, Velasquez-Perez L, Cisneros B (2013) Spinocerebellar ataxia type 2: clinical presentation, molecular mechanisms, and therapeutic perspectives. Mol Neurobiol 47:90–104
6. Goldfarb LG, Vasconcelos O, Platonov FA et al (1996) Unstable triplet repeat and phenotypic variability of spinocerebellar ataxia type 1. Ann Neurol 39:500–506
7. Fukazawa SH, Yanagihara T, Yanagihara T et al (1996) Clinical features and natural history of spinocerebellar ataxia type I. Acta Neurol Scand 93:64–71
8. Nanetti L, Fancellu R, Tomasello C et al (2009) Rare association of motor neuron disease and spinocerebellar ataxia type 2 (SCA2): a new case and review of the literature. J Neurol 256:1926–1928
9. Tazen S, Figueroa K, Kwan JY et al (2013) Amyotrophic lateral sclerosis and spinocerebellar ataxia type 2 in a family with full CAG repeat expansions of ATXN2. JAMA Neurol 70:1302–1304
10. Kimura F, Fujimura C, Ishida S et al (2006) Progression rate of ALSFRS-R at the time of diagnosis predicts survival time in ALS. Neurology 66:265–267
11. Okuda T, Hattori H, Takeuchi S et al (2003) PQBP-1 transgenic mice show a late-onset motor neuron disease-like phenotype. Hum Mol Genet 12:711–725
12. Farg MA, Soo KY, Warraich ST et al (2013) Ataxin-2 interacts with FUS and intermediate-length polyglutamine expansions enhance FUS-related pathology in amyotrophic lateral sclerosis. Hum Mol Genet 22:717–728
13. Nihei Y, Ito D, Suzuki N (2012) Roles of ataxin-2 in pathological cascades mediated by TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS). J Biol Chem 287:41310–41323