J Neurol (2009) 256:1926–1928
DOI 10.1007/s00415-009-5237-9

LETTER TO THE EDITORS

Rare association of motor neuron disease and spinocerebellar ataxia type 2 (SCA2): a new case and review of the literature

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Received: 21 April 2009 / Revised: 25 June 2009 / Accepted: 1 July 2009 / Published online: 31 July 2009

Abstract We report a rare association of spinocerebellar ataxia and motor neuron disease (MND) in a woman with genetically confirmed SCA2 who subsequently developed a rapidly progressive and fatal form of MND. Considering the rarity of these two neurological conditions, it is interesting to note that the concomitant occurrence of SCA mutations and MND have been previously observed in three cases: in one patient affected by SCA6 and two other cases with SCA2.

Keywords Spinocerebellar ataxia type 2 (SCA2) · Amyotrophic lateral sclerosis (ALS) · Motor neuron disease (MND)

Sirs,

We describe a case of an Italian woman with spinocerebellar ataxia type 2 (SCA2) who, several years after the onset of the cerebellar symptoms, developed a rapidly progressive and fatal form of motor neuron disease (MND). SCA2 is one of the genotypes causing familial autosomal dominant cerebellar ataxia, with a worldwide frequency of 13–18%. The disease is particularly frequent in Italy, South Africa, India, USA and Cuba [10].

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The proband developed, at 50 years, gait instability, mild urinary incontinence, and lumbar pain. In her family an uncle was affected by Parkinson disease, while the parents died at the age of 80 and 53 without manifesting neurological symptoms. Neuroradiological investigations showed severe cerebellar and brainstem atrophy. Genetic tests demonstrated SCA2 mutation (39 CAG repeats).

At the age of 65, she had dysarthria, slow saccades, mild limb and gait ataxia, bradykinesia, unilateral extensor plantar reflex, and reduced vibration sensation in the lower limbs. Muscle strength was normal and neither muscle atrophy nor fasciculations were observed.

At the age of 66 she had a fracture of the left arm and a few months later she developed severe hypotrophy of the first interosseus muscle in the left hand. In the same period, she underwent appendicectomy for acute peritonitis. After surgery, the ataxic symptoms worsened and the patient developed rapidly progressive muscle weakness and atrophy, prevalently at the left arm, with evidence of fasciculations in the face area and upper limbs.

At the age of 68, the patient had slow saccades, vertical and lateral ophthalmoplegia, severe dysarthria and dysphagia, muscle weakness in upper and lower limbs, diffuse fasciculations, mild spastic rigidity in lower limbs, hyporeflexia in upper limbs, and bilateral extensor plantar reflex. Electromyography (EMG) revealed diffuse fibrillation and fasciculation potentials and decrease of motor units with reduced recruitment pattern. Electroneurography showed normal motor and sensory nerve conduction velocities and reduced amplitude of motor and sensory potentials. Motor evoked potentials revealed abnormalities in central motor conduction. She had elevated creatine kinase (198 U/L, nv <150). Thyroid-stimulating hormone was normal, paraneoplastic antibodies and syphilis serology were

Table 1 Clinical and genetic characteristics of patients with SCA2 and motor neuron disease

Patient/sex	First clinical diagnosis	SCA2 mutation CAG repeat expansion	Cerebellar/extrapyramidal symptoms	Motor neuron symptoms	References
Case 1/F	Idiopathic late-onset ataxia/multiple system atrophy	22/35	Onset at 61 years with gait ataxia, dysarthria, dysphagia, urinary urgency, bradykinesia. Bradykinesia benefits from levodopa treatment	Onset at 62 years with progressive generalized weakness, amyotrophy, fasciculations. The patient died of respiratory failure 2 years after the onset of motor neuron involvement.	Infante et al. [5]
Case 2/M	Parkinsonism and motor neuron symptoms	22/33[a]	Onset at 70 years with resting tremor, rigidity, bradykinesia, dysarthria. Extrapyramidal symptoms improved with levodopa treatment	Onset at 70 years with distal weakness in upper limbs, diffuse fasciculations and atrophy of the right-hand intrinsic muscles.	Furtado et al. [6]
Present Case/F	Spinocerebellar ataxia	22/39	Onset at 50 years with gait ataxia	Onset at 66 years with progressive weakness in upper and lower limbs and evidence of fasciculations in face and upper limbs. The patient died of respiratory failure 2 years after the onset of motor neuron involvement.	Present study

[a] In symptomatic SCA2 patients the number of CAG repeats ranges from 33 to 77

negative. Molecular test for *SOD1* gene mutations (Super-Oxide Dismutase) was negative.

She died of acute respiratory failure 24 months after the onset of motor neuron signs. Autopsy was not performed.

Spinocerebellar ataxias and MND are rare, usually late-onset, neurodegenerative diseases: SCAs being hereditary, while 90% of MNDs are represented by sporadic forms [10, 11].

To our knowledge, eleven patients with concomitant SCA and MND have been previously described: one patient had SCA6 mutation [6, 7], two unrelated patients had SCA2 [4, 5], while in the eight remaining cases no molecular defect was identified [8]. Considering the recent availability of genetic tests for SCAs, it is possible that a genetic diagnosis was missed in the past.

Focusing on patients with positive SCA2 genetic tests, all described cases, including our patient, showed clinical features, EMG findings, and disease progression consistent with the diagnostic criteria for probable amyotrophic lateral sclerosis (Table 1) [1]. A simple co-occurrence of two rare disorders is certainly a possibility [7], however it may be noted that no MND has been reported in association with SCA1 or SCA3, which are the most frequent SCA genotypes worldwide. In SCA3, a clinical onset resembling MND has been recently described, however the progression of the symptoms did not further support the diagnosis of MND [9].

It is worth to mention that in SCA2 upper and lower motor neuron semeiology is relatively common, though clinical presentation mimicking MND, as reported here, is exceptional. In fact, as noted by Infante et al., fasciculations of the face, tongue and limb musculatures are common signs in SCA2 pedigrees [2, 5]. Furthermore, a morphometric autopsy study showed reduction of lumbar (33–83% of normal) and thoracic motorneurons (27–64%) [3].

Even though it is not possible to establish a definite correlation between the two disorders, it seems important to monitor the occurrence of these rare cases for a better understanding of this combined multiple system neurodegenerative disease.

References

1. Brooks BR, Miller RG, Swash M, Munsat TL (2000) World Federation of Neurology Research Group on Motor Neuron Diseases (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:293–299
2. Dürr A, Smadja D, Cancel G, Lezin A, Stevanin G, Mikol J, Bellance R, Buisson GG, Chneiweiss H, Dellanave J, Agid Y, Brice A, Vernant JC (1995) Autosomal dominant cerebellar ataxia type I in Martinique (French West Indies): Clinical and

neuropathological analysis of 53 patients from three unrelated SCA2 families. Brain 118:1573–1581
3. Estrada R, Galarraga J, Orozco G, Nodarse A, Auburger G (1999) Spinocerebellar ataxia 2 (SCA2): morphometric analyses in 11 autopsies. Acta Neuropathol 97:306–310
4. Furtado S, Payami H, Lockhart PJ, Hanson M, Nutt JG, Singleton AA, Singleton A, Bower J, Utti RJ, Bird TD, de la Fuente-Fernandez R, Tsuboi Y, Klimek ML, Suchowersky O, Hardy J, Calne DB, Wszolek ZK, Farrer M, Gwinn-Hardy K, Stoessl AJ (2004) Profile of families with parkinsonism-predominant spinocerebellar ataxia type 2 (SCA2). Mov Disord 19(6):622–629
5. Infante J, Berciano J, Volpini V, Corral J, Polo JM, Pascual J, Combarros O (2004) Spinocerebellar ataxia type 2 with levodopa-responsive parkinsonism culminating in motor neuron disease. Mov Disord 19(7):848–852
6. Ohara S, Iwahashi T, Oide T, Hayashi R, Nakajima T, Ishikawa K, Misusawa H (2001) Spinocerebellar ataxia type 6 with motor neuron loss: a follow-up autopsy report. J Neurol 249:633–635
7. Ohara S, Tsuyuzaki J, Hayashi R, Iwahashi T, Nakajima T, Maruyama T, Tokuda T, Nonaka I (2000) Motor neuron loss in a patient with spinocerebellar ataxia type 6: chance co-occurrence or causally related? J Neurol 247(5):386–388
8. Ohta Y, Hayashi T, Nagai M, Okamoto M, Nagotani S, Nagano I, Ohmori N, Takehisa Y, Murakami T, Shoji M, Kamiya T, Abe K (2007) Two cases of spinocerebellar ataxia accompanied by involvement of the skeletal motor neuron system and bulbar palsy. Intern Med 46(11):751–755
9. Pinto S, De Carvalho M (2008) Machado–Joseph disease presenting as motor neuron disease. Amyotroph Lateral Scler 9:188–191
10. Soong BW, Paulson HL (2007) spinocerebellar ataxias: an update. Curr Opin Neurol 20:438–446
11. Wijesekera LC, Leigh PN (2009) Amyotrophic lateral sclerosis. Orphanet J Rare Dis 4:3