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LETTER TO THE EDITORS

Ataxia oculomotor apraxia type 2: course over 27 years and a novel stop mutation in the senataxin gene

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Sirs,

Ataxia with oculomotor apraxia type 2 (AOA2) is an autosomal recessive cerebellar ataxia associated with mutations in the senataxin (*SETX*) gene coding for the ortholog of a yeast DNA/RNA helicase [7]. The disorder is characterized by adolescent age at onset, spinocerebellar gait ataxia, cerebellar atrophy, peripheral sensorimotor neuropathy, areflexia, elevated α-fetoprotein, saccadic ocular pursuit, and occasionally oculomotor apraxia. Mild cognitive impairment, involuntary movements, γ-globulin, and creatine phosphokinase elevation may also occur [1–7]. Here we report the documented course over 27 years of a case of AOA2 and a novel homozygous stop mutation p.R1778X in the *SETX* gene.

This 47-year-old woman was born to consanguineous parents (first cousins). After normal delivery and childhood she first noticed gait problems at the age of 15 years. Unsteadiness gradually worsened and she has essentially been wheelchair-bound from the age of 30. Mild mental and psychomotor decline became evident after graduating from junior high school at age 16. Severe myopia evolved from the age of 8. As reported in other AOA2 cases [2, 5, 6], this patient developed secondary amenorrhoea in early adulthood, indicating an important role of senataxin not only in neuron survival but also in germ line cell survival [2].

The patient was examined in our institute at age 20 (1981) and at age 47 (2008). On both occasions, mild cognitive impairment was obvious. Dysarthria was rated mild at age 20, and moderate at age 47. Eye movements were full with marked saccadic pursuit at both dates, and there was no oculomotor apraxia. There were no muscle weakness or foot deformities. Deep tendon reflexes were normal at age 20 but absent at age 47. There was no extensor plantar response. Vibration and position senses were not documented at age 20 but impaired in her upper and absent in her lower extremities at age 47. Touch sensation was normal. Finger-to-nose and heel-to-shin testing was mildly dysmetric at age 20 and 47 without major progression. Choreic movements were apparent in 1977 and a severe kinetic tremor described in 1981 decreased over the course of the disease. At age 20, her gait was wide-based and Romberg's sign was positive. At age 47, our patient presented with severe gait ataxia and standing instability, and was confined to a wheelchair.

At age 20, electromyography (EMG) and muscle biopsy from tibialis anterior muscle showed severe neurogenic changes while nerve conduction velocity (NCV) was spared (peroneal nerve: 42 m/s). At age 47, neurophysiological testing revealed a sensorimotor neuropathy. EMG showed chronic neurogenic remodelling with single motor unit discharge patterns, pathologic spontaneous activity, and pseudomyotonic discharges. Median nerve showed prolonged distal latency (6.0 ms), and reduced NCV (33.4 m/s) and amplitude (1.9 mV). Sensory NCV was not reproducible in the radial, median, and ulnar nerves. Brain CT at age 47 revealed severe cerebellar atrophy affecting predominantly the vermis (Fig. 1). Her general physical and gynaecological examination was unremarkable without

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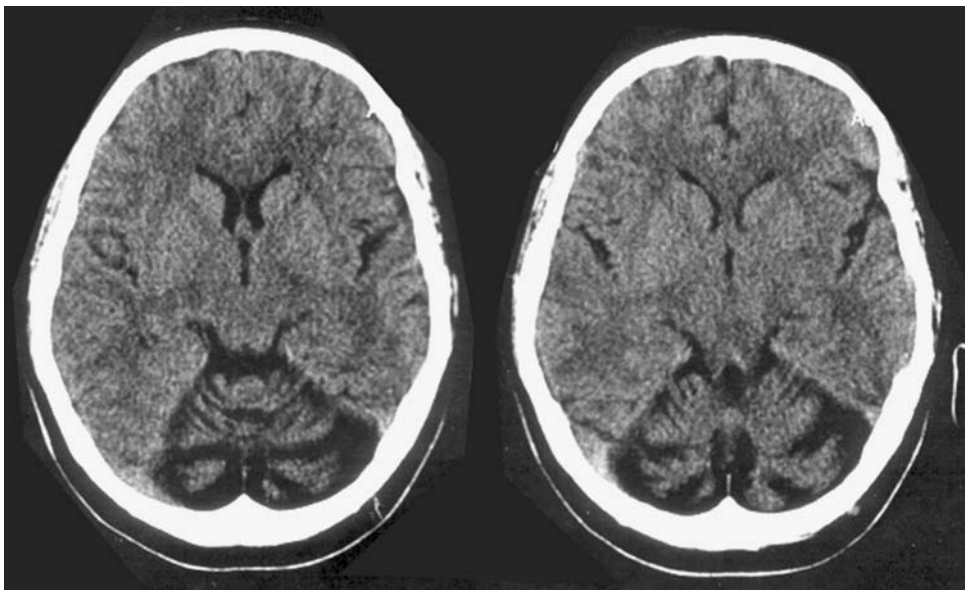

Fig. 1 Brain CT at age 47 revealed severe cerebellar atrophy

ocular telangiectasias or skin findings. Echocardiograms and electrocardiograms were normal at both times.

While diagnosis remained unclear in 1981, AOA2 was suspected at the current presentation, and accordingly, the serum α-fetoprotein level was found markedly elevated (58.3 ng/ml). Sequence analysis of the complete *SETX* gene showed the novel homozygous nonsense mutation p.R1778X resulting from a C to T transition at nucleotide 5,332 in exon 11, causing a premature truncation of the protein. Friedreich ataxia had previously been excluded by molecular analysis.

AOA2 may represent up to 8% of non-Friedreich recessive ataxias [5]. The disorder was first described in Japanese [11] and Pakistani [8] families, later reports included six families from different Mediterranean areas and the West Indies [5], ten French–Canadian families known as the Quebec cluster [3], four families from Italy [2], one German [10] and one Cypriot family [9]. Although included in the disease name, oculomotor apraxia is not obligatory for diagnosis of AOA2 and was absent in our patient [3–5]. Age of onset, phenotype, CT, and laboratory findings were consistent with previous series. We had the unique opportunity to compare the documented clinical signs in this patient over a course of 27 years. This shows the pace of progression, particularly of gait ataxia, dysarthria, sensorimotor neuropathy, and areflexia in this patient. Although AOA2 resembles Friedreich ataxia in many respects, the course of AOA2 is much milder than in most cases of Friedreich ataxia, and can be differentiated by elevated α-fetoprotein and severe cerebellar atrophy.

The case presented highlights the importance of revisiting patients with disorders of previously unknown aetiology using new information and the extended spectrum of diagnostic methods in molecular genetics.

References

1. Asaka T, Yokoji H, Ito J, Yamaguchi K, Matsushima A (2006) Autosomal recessive ataxia with peripheral neuropathy and elevated AFP: novel mutations in SETX. Neurology 66(10):1580–1581
2. Criscuolo C, Chessa L, Di Giandomenico S, Mancini P, Sacca F, Grieco GS, Piane M, Barbieri F, De Michele G, Banfi S, Pierelli F, Rizzuto N, Santorelli FM, Gallosti L, Filla A, Casali C (2006) Ataxia with oculomotor apraxia type 2: a clinical, pathologic, and genetic study. Neurology 66:1207–1210
3. Duquette A, Roddier K, McNabb-Baltar J, Gosselin I, St-Denis A, Dicaire MJ, Loisel L, Labuda D, Marchand L, Mathieu J, Bouchard JP, Brais B (2005) Mutations in senataxin responsible for Quebec cluster of ataxia with neuropathy. Ann Neurol 57(3):408–414
4. Fogel BL, Perlman S (2006) Novel mutations in the senataxin DNA/RNA helicase domain in ataxia with oculomotor apraxia 2. Neurology 67(11):2083–2084
5. Le Ber I, Bouslam N, Rivaud-Péchoux S, Guimarães J, Benomar A, Chamayou C, Goizet C, Moreira MC, Klur S, Yahyaoui M, Agid Y, Koenig M, Stevanin G, Brice A, Dürr A (2004) Frequency and phenotypic spectrum of ataxia with oculomotor apraxia 2: a clinical and genetic study in 18 patients. Brain 127(Pt 4):759–767
6. Lynch DR, Braastad CD, Nagan N (2007) Ovarian failure in ataxia with oculomotor apraxia type 2. Am J Med Genet A 143(15):1775–1777
7. Moreira MC, Klur S, Watanabe M, Nemeth AH, Le Ber I, Moniz JC, Tranchant C, Aubourg P, Tazir M, Schols L, Pandolfo M, Schulz JB, Pouget J, Calvas P, Shizuka-Ikeda M, Shoji M, Tanaka M, Izatt L, Shaw CE, M'Zahem A, Dunne E, Bomont P, Benhassine T, Bouslam N, Stevanin G, Brice A, Guimaraes J, Mendonca P, Barbot C, Coutinho P, Sequeiros J, Durr A, Warter JM, Koenig M (2004) Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. Nat Genet 36:225–227
8. Németh AH, Bochukova E, Dunne E, Huson SM, Elston J, Hannan MA, Jackson M, Chapman CJ, Taylor AM (2000) Autosomal recessive cerebellar ataxia with oculomotor apraxia (ataxia-telangiectasia-like syndrome) is linked to chromosome 9q34. Am J Hum Genet 67(5):1320–1326

9. Nicolaou P, Georghiou A, Votsi C, Middleton LT, Zamba-Papanicolaou E, Christodoulou K (2008) A novel c.5308_5311delGAGA mutation in senataxin in a Cypriot family with an autosomal recessive cerebellar ataxia. BMC Med Genet 14(9):28
10. Schöls L, Arning L, Schüle R, Epplen JT, Timmann D (2008) "Pseudodominant inheritance" of ataxia with ocular apraxia type 2 (AOA2). J Neurol 255(4):495–501
11. Watanabe M, Sugai Y, Concannon P, Koenig M, Schmitt M, Sato M, Shizuka M, Mizushima K, Ikeda Y, Tomidokoro Y, Okamoto K, Shoji M (1998) Familial spinocerebellar ataxia with cerebellar atrophy, peripheral neuropathy, and elevated level of serum creatine kinase, gamma-globulin, and alpha-fetoprotein. Ann Neurol 44(2):265–269