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Letter to the Editor

Adult onset Alexander disease presenting with progressive spastic paraplegia

Adult-onset Alexander disease (AOAD) is an underdiagnosed genetic entity, clinically characterized by progressive pyramidal signs, cerebellar ataxia, palatal tremor and bulbar palsy. The disease is caused by glial fibrillary acidic protein (GFAP) gene mutations. Spinal cord and medulla oblongata atrophy are typical features found on neuroimaging [1]. AOAD may present with wide clinical variability, and a genotype–phenotype correlation is a matter of debate.

Here, we describe a patient with AOAD with a previously reported mutation in codon 66 of the GFAP gene, presenting with an unusual phenotype characterized by progressive spastic paraplegia. The correlation between the genotype and phenotype in AOAD is also discussed.

A 67-year-old man presented with progressive gait instability and difficulty walking since the age of 61. He had been wheelchair bound for the previous two years. About four years before he developed slurred speech, together with lower limbs weakness and periods of urinary retention. He had had three recent seizures, and phenytoin had been prescribed. The patient denied memory loss or psychiatric symptoms. Family history was unremarkable. On neurological examination, there was slurred speech, palatal tremor, global spasticity predominately in the legs, severe weakness in the lower limbs, and bilateral ankle clonus and Babinski sign (Video). The patient was unable to stand, owing to muscle weakness in the lower limbs. Magnetic resonance imaging (MRI) of the spine disclosed marked atrophy of the spinal cord and medulla oblongata (Fig. 1). Brain MRI showed mild cerebellar atrophy. Serologic tests for HTLV and HIV were negative. Vitamin E, B12 and copper deficiency were ruled out. Arylsulfatase A and very long chain fatty acids concentrations were normal. Cerebrospinal fluid contained 1 cells/mm^3 and oligoclonal bands were absent.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2013.10.014.

Negative tests for acquired diseases that may present with sporadic spastic paraplegia, together with the presence of palatal tremor and neuroimaging features, prompted testing for AOAD. Molecular analysis was performed looking for mutations in the GFAP gene. The nine exons and adjacent intronic regions of the GFAP gene were sequenced. Mutation analysis revealed a previously reported heterozygous non-synonymous missense mutation at exon 1, c.197G>A (p.Arg66Gln), which changes arginine for Glutamine at the 66th codon. This mutation has been previously reported twice [2,3]. AOAD was confirmed.

The availability of genetic diagnostic tests has greatly increased the number of confirmed cases of AOAD, expanding its clinical phenotype leading to more detailed understanding of the clinical features of late onset subtypes, as well as helping to facilitate more precise correlation between the genotype and phenotype and improved genetic counseling [1,4]. The clinical spectrum of AOAD frequently comprises pyramidal signs, palatal tremor, ataxia, bulbar signs, occulomotor abnormalities, and autonomic dysfunction. Occasionally, seizures, macrocephaly and cognitive deficits may be observed. The clinical pattern usually reflects the topographic localization of the lesions, with adult cases displaying a predominant infratentorial localization of the lesions. Our patient, presented with a marked sporadic spastic paraplegia syndrome. Although spastic paresis has been previously reported in AOAD patients, this phenotype is unusual in AOAD, as a systematic review published in 2010 comprising 56 AOAD patients, failed to identify a single patient with spastic paraplegia phenotype [1,5].

Different GFAP mutations have already been associated with AOAD [4]. The 197G>A (p.Arg66Gln) mutation has been reported twice, by Prust et al. and Hida et al. [2,3]. The patient reported by Hida et al., besides having severe vocal cord paralysis during sleep, also had spastic paresis in all extremities. Our patient's overnight polysomnography showed severe sleep apnea (44 episodes), but laryngoscopy showed no vocal cord paralysis. The patient reported by Prust el al. was diagnosed post-mortem and there is no clear information if she had spastic paresis [2]. It is reported that she had ataxia, dysphonia, dysarthria, palatal tremor and ocular movement abnormalities but not spasticity or spastic paraplegia. She had upper extremity hyper-reflexia (Adeline Vanderver, personal communication).

Although many GFPA mutations do not appear to have a genotype–phenotype correlation, exon 1 mutations like the one described here may be more likely to express as an unusual phenotype of AOAD, spastic paraplegia. Future studies are necessary to determine genotype–phenotype correlations in a larger number of patients with GFAP mutations. Neurologists should test for the diagnosis of AOAD presenting with spastic paraplegia, particularly when associated with palatal tremor and typical neuroimaging features. Additionally, AOAD should be considered as a relevant differential diagnosis in several sporadic diseases presenting with late onset progressive bulbar syndrome associated with brainstem, cerebellar or spinal cord atrophy, such as multiple system atrophy, adult onset cerebellar ataxias and sporadic spastic paraplegias. Testing for the GFAP gene is recommended when the clinical spectrum described above is present, in order to genetically determinate AOAD.

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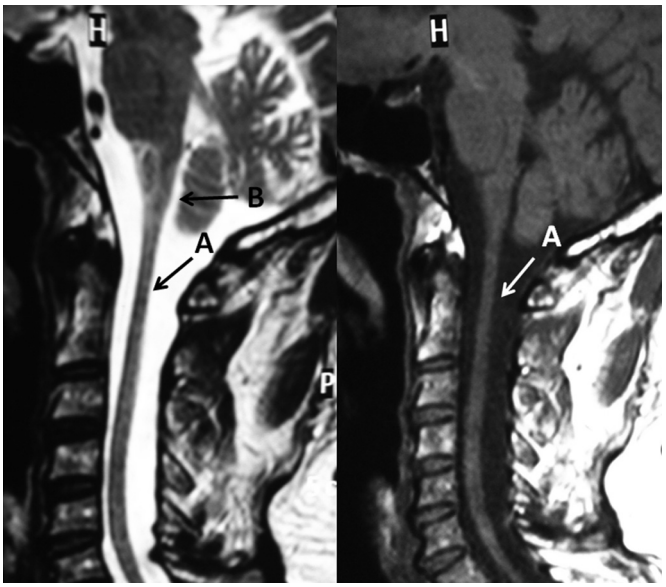

Fig. 1. Sagittal craniocervical transition MRI disclosing marked spinal atrophy (A) and medulla oblongata atrophy (B).

Conflict of interests

We have no conflict of interest.

Financial disclosure

We have nothing to disclose.

Ethical statement

Full consent was obtained from the patient for the case report and video publication.

Authors' roles

1- Case report project: A. Conception, B. Organization, C. Execution;
2- Genetic evaluation: A. Organization, B. Execution;
3- Manuscript: A. Writing of the first draft, B. Review and Critique.

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