COULD IT BE AN ATYPICAL CASE OF JUVENILE ALEXANDER DISEASE?

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OBJECTIVES

The term leukoencephalopathy refers to a group of conditions characterized by the progressive destruction or failed development of myelin. The most common of these disorders are inherited and have a metabolic origin. Onset is usually in early childhood but the heterogeneous presentation may delay their recognition; furthermore few cases may also present in adulthood. Among this group of diseases, Alexander disease (AxD) is caused by heterozygous mutations in the gene encoding for the glial fibrillary acidic protein (*GFAP*); several molecules of this protein bind together to form intermediate filaments, which provide support and strength to cells. Mutations in the *GFAP* gene lead to the production of altered proteins which impair the formation of normal filaments, thus leading to their accumulation in the astrocytes and to the formation of the so called Rosenthal fibers, the pathologic hallmark of the disease. The condition is inherited in an autosomal dominant manner but *de novo* mutations may also occur. In the majority of cases the onset is before 2 years; such infantile forms typically present with macrocephaly, seizures and rapid neurologic deterioration leading to early death; brain MRI shows a leukoencephalopathy with frontal predominance and can be diagnostic when specific neuroradiological criteria are fulfilled[1] (Table). Patients with juvenile or adult variant of AxD present with bulbar signs (including speech abnormalities, swallowing difficulties and vomiting), pyramidal signs (more often involving lower limbs) and cerebellar dysfunction (ataxia), with a slower progressive course. MRI can be critical for the diagnosis, showing white matter changes and atrophy involving the medulla oblongata and upper cervical spinal cord; however, atypical MRI findings are common in juvenile- and adult-onset forms. Signs of involvement of peripheral nervous system, such as reduced deep tendon reflexes and muscular atrophy, are not typical in AxD, being more frequently reported in other leukoencephalopathies, such as metachromatic leukodystrophy, cerebrotendinous xanthomatosis, Krabbe disease, adult polyglucosan body disease as well as in peroxisome biogenesis disorders and in mithocondrial diseases.

CASE DESCRIPTION AND DISCUSSION

A 18-year-old boy was evaluated because of progressive weakness and muscular atrophy with gait difficulty and sphincter dysfunction since age 7; his parents were first cousins and there was no family history of neurological diseases, despite two young second cousins living in Pakistan with no better specified disease. Neurological examination revealed a global weakness with diffuse muscular atrophy, with a main distal involvement, absence of deep tendon reflexes and no sensitive abnormalities. Mild dysarthria and nystagmus were also present, as well as slow saccades. EMG revealed neurogenic abnormalities with absent nerve motor and sensory action potentials at lower limbs. CSF examination was normal. MRI showed diffuse hyperintensity of the periventricular white matter (with posterior predominance) on T2WI, scattered abnormalities in the subcortical white matter, abnormal signal in the medulla and in the hilum of the dentate nuclei, medulla and spinal cord atrophy (Figures). Based on these findings, a molecular analysis of the *GFAP* gene was performed at first, showing a heterozygous missense nucleotide substitution (c.883G>A) in exon 5 causing the amino acid change p.D295N. So far, such mutation has been described in a single patient affected by adult onset AxD who also carried another *GFAP* mutation[2] and in other neurologic diseases[3]. Mutation is predicted to be damaging *in silico*, but in some other database it is described as a polymorphic change The molecular analysis of the *GFAP* gene was then performed on both the proband's relatives: his mother, who is apparently healthy, turned out to carry the same mutation. Therefore, the role of this variant remains uncertain: some epigenetic mechanisms can cause a different clinical expression and incomplete penetrance. However, we can not exclude that the Alexander-like neuroradiological picture could be related to a different mutation in a different unknown gene.

CONCLUSIONS

Leukoencephalopathy are a group of diseases with heterogeneous and often overlapping clinical and neuroradiological findings. In our patient, although neuroradiological findings strongly suggest a form of juvenile AxD, clinical picture and genetic assessment remain uncertain. An extensive diagnostic work up by biochemical assays and next generation sequencing approach is on going.

Table. MRI diagnostic criteria for Alexander disease

Alexander disease is diagnosed if four of the five following criteria are fulfilled:

1. Extensive white matter abnormalities with a frontal preponderance
2. A periventricular rim of decreased signal intensity on T2-weighted images and elevated signal intensity on T1-weighted images
3. Abnormalities of the basal ganglia and thalami that may include any of the following:
   - elevated signal intensity and swelling
   - atrophy
   - elevated or decreased signal intensity on T2-weighted images
4. Brain stem abnormalities, particularly involving the medulla and midbrain
5. Contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, brain stem.

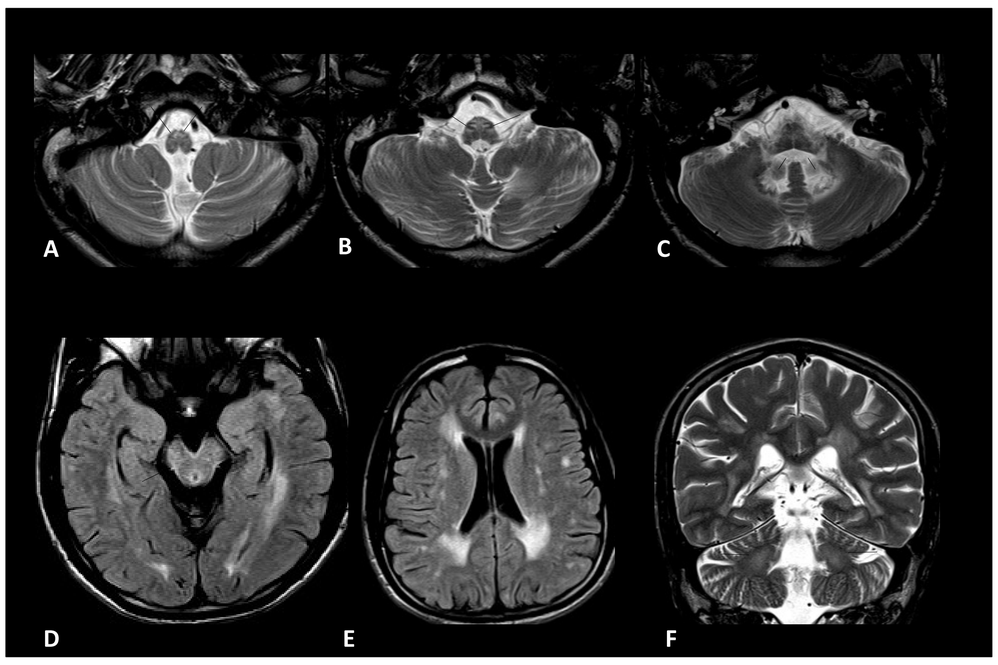

Figure 1. Brain MRI, axial T2WI (A, B, C) , axial FLAIR (D, E), coronal T2WI (F). Bilateral symmetric hyperintensities in the ventral medulla oblongata especially involving the pyramids (red arrows in **A**), the hilum of the olivary nuclei (purple arrows in **B**) and the hilum of the dentate nuclei (yellow arrows in **C**); there is involvement of the medial lemniscus and central tegmental tract as well (in B);); the medulla oblongata is clearly atrophic. A thin peripheral rim of hyperintensity is visible along the surface of the mesencephalon (orange arrows in **D**). Scattered hyperintensities in the peripheral supratentorial white matter and confluent hyperintensities in the periventricular white matter, prevailing posteriorly (**E**). Subtle symmetric signal abnormalities in the middle cerebellar peduncles (blue arrows in **F**).

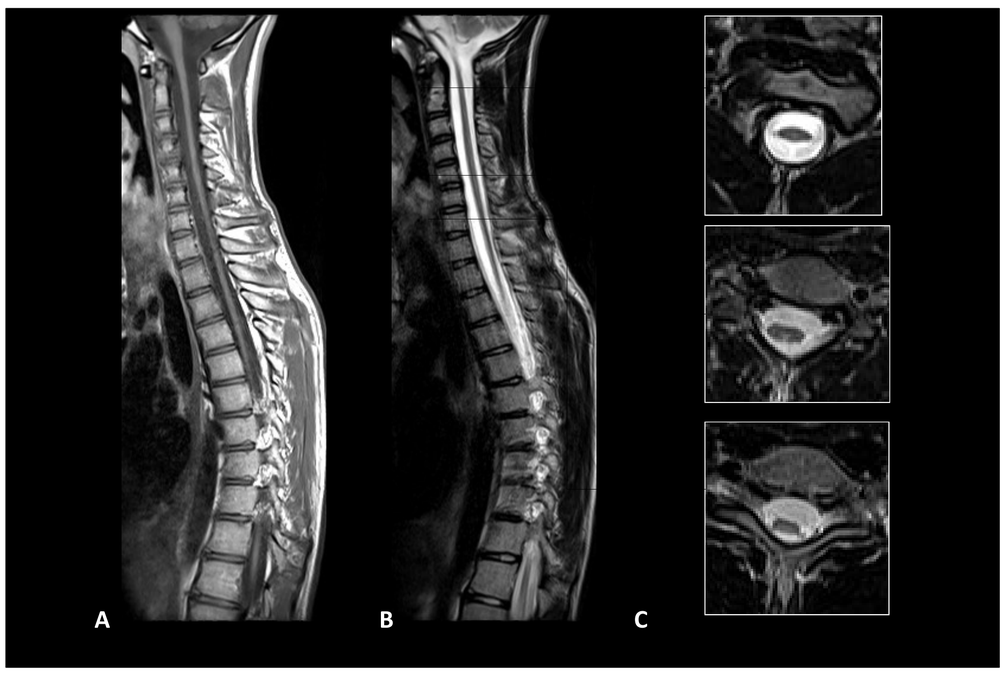

Figure 2. Spine MRI, sagittal T2WI (A) and T1WI (B), axial T2WI (C) (there are some movement artifacts). The atrophy of the medulla oblongata extends downward to the entire cervicodorsal spinal cord (**A**, **B**), that appear "flattened" in the axial images (**C**). There are no clearcut signal abnormalities in the atrophic spinal cord (the subtle hyperintensity in the central cord, better visible at C5 level, is probably related to the normal gray matter signal).

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