Clinical and MRI features of two novel unrelated patients with Alexander Disease

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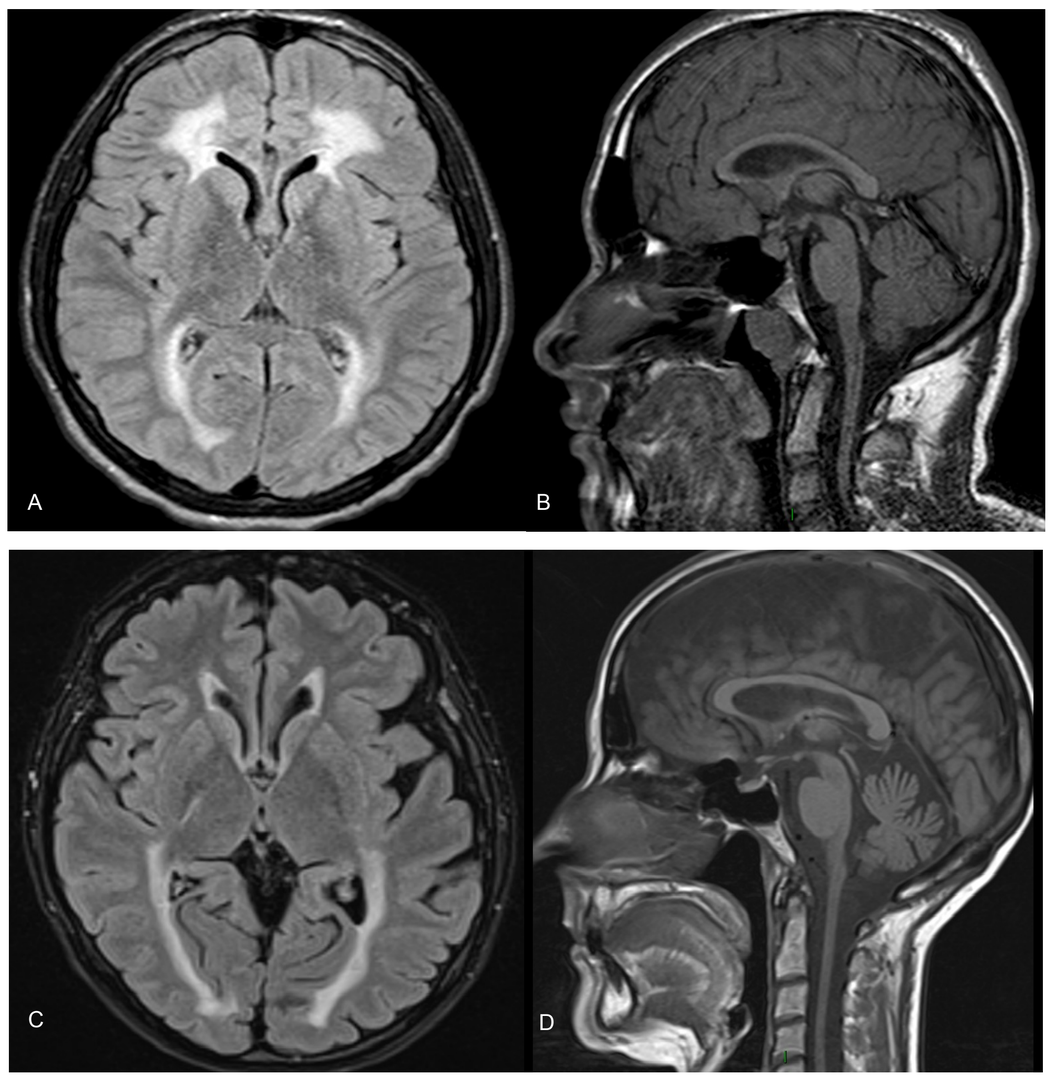
Background

Alexander disease (AD) is a rare cerebral genetic white matter disease resulting from mutations in the glial fibrillary acidic protein (GFAP) gene. De novo mutations are commonly reported. Different subtypes of AD based on the age of onset are recognized: the severe infantile, often fatal within a few years, the juvenile and adult form with a more protracted course [1]. Neuroradiological features play a crucial role in the diagnosis. In infantile cases, MRI usually shows extensive white matter signal hyperintensities in T2-weighted images, mainly in the periventricular regions, involvement of basal ganglia, thalami and brainstem and contrast enhancement particularly of periventricular areas and brainstem. Conversely, in the adult form, MRI displays significant bulbar and upper spinal cord atrophy, hilum of dentate nuclei involvement with less frequent cerebellar white matter changes, and pial FLAIR signal and cerebellar peduncles abnormalities. Supratentorial periventricular white matter hyperintensities and areas of post-contrast enhancement range from absent or minimal to moderate. Juvenile cases show an intermediate phenotype [2]. While classic infantile form has a well recognized clinical and MRI pattern, juvenile and adult cases may be easily misdiagnosed, mimicking common neurodegenerative disorders in the absence of evident leukodystrophy. Here, we present clinical/ radiological findings of two new AD cases with different age at onset.

Case reports

Case 1: a 19 year-old boy with mild macrocephaly and marked kyphoscoliosis was referred to us for dysphagia and speech disturbances since age 8 years. Neurological examination showed mild gait and limb ataxia, dysarthria, hypophonia, and dysphagia. MRI findings showed diffuse leukoencephalopathy, hyperintensities of dentate nuclei and moderate atrophy of medulla oblongata and cervical spinal cord **(A,B).** Genetic analysis revealed the heterozygous c.1246C>T mutation in the GFAP gene. **Case 2:** a 46 year-old woman complained of progressive walking difficulties and repeated falls from three years. Neurological examination disclosed moderate gait and limb ataxia, dysarthria and pyramidal signs. The neuro-ophthalmological examination shows saccadic dysmetria, impairment of smooth pursuit, vestibule-ocular reflex cancellation and gaze-evoked nystagmus. Brain and cervical MRI showed mild hyperintensities of the subcortical white matter, midbrain and cerebellum and severe atrophy of medulla oblongata and cervical spinal cord **(C,D).** GFAP gene was sequenced and the heterozygous c.1193C>T mutation found.



Discussion

The first heterozygous missense mutations of the GFAP gene was identified in 2001[3]. The availability of genetic diagnostic tests has increased diagnostic possibility of Alexander disease, expanding the understanding of clinical phenotype, radiological features and genetic mechanism. AD is a challenging diagnosis, especially in the adulthood, for the wide spectrum of clinical and MRI features. While infantile subtype typically displays marked leukoencephalopathy with clinical signs of cortical and subcortical white matter involvement, the adult AD patients have a prominent atrophic pattern in the posterior fossa at MRI with ataxia, bulbar signs and ocular movement abnormalities. As also here we reported, an intermediate clinical and radiological pattern is typical of the juvenile-onset cases. In conclusion, our case reports confirm the presence of age-related phenotypic peculiarities and suggest that the clinical phenotype of the disease can be considered as a continuum with a rostro-caudal gradient of abnormalities from infantile to adult cases.

References.
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