Infantile Alexander Disease: A Genotype-Phenotype Correlation

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Introduction

Alexander disease (AD) is a progressive brain white matter disorder (leukodystrophy) and in most instances, presents at the onset of childhood. It is caused by a mutation in the gene that encodes for glial fibrillary acidic protein (GFAP). The location and nature of the mutation will have noticeable effects on the phenotype of the patient [1,2].

Three age-dependent clinical categories have been described. The infantile form presents before 2 years of age and is characterized by developmental delay, seizures and megalencephaly. The juvenile form begins between 2 to 14 years of age with a clinical picture of bulbar symptoms, ataxia and progressive cognitive deterioration; and the adult-onset presents with an unspecified and variable disease pattern and consequently there is diagnostic delay. The earlier the age of the patient, the higher the rates are for severe illness [1,3,4]. Brain magnetic resonance imaging (MRI) shows abnormalities, particularly in the deep frontal white matter, suggestive of hypo/demyelination [5,6].

We report the case of a child with delayed psychomotor development and seizures diagnosed with Alexander disease.

Case Report

The patient was a 4½ years old boy with no history of note during gestation, birth or the neonatal period. At 14 months, he presented generalized febrile seizures and was hospitalized; his parents had not observed any neurologic illness during his development. On examination, generalized floppiness without any focal neurological deficits was observed and head circumference (HD) was 50.8 cm (+2.55 SD). Antibiotics and acyclovir were empirically prescribed. The electroencephalogram (EEG) showed no abnormalities. MRI of the brain, T2-weighted and fluid attenuated inversion recovery (FLAIR) images revealed hyperintense lesions in the frontal white matter (Figure 1a). As post-infectious encephalopathy was suspected, a high dose of corticosteroids were prescribed without causing seizure recurrence. However, biochemical, microbiological and immune studies, including oligodendral banding, were normal. The values of blood, urine and CSF organic acids and amino acids, including very long chain fatty acids and N-Acetilaspartic acid concentrations, were normal.

Serial MRIs, T2-weighted images clearly detected some deep and diffusion white matter frontal predominance (black asterisks), with small extent at subcortical U-fibers, subtle hyper intense abnormalities at the head of the caudate nuclei head and lenticular nucleus compared to thalamic signal changes (white asterisks), and hypo-intense rings adjacent to anterior horn of lateral ventricles (arrows).

The child started walking at 18 months of age. At 23 months, he had two febrile seizures, and the EEG showed generalized background slowing and frontal bilateral theta waves; therefore, valproic acid was given. At 2 years 4 months, he could say self-referential words of two syllables, follow simple commands and HD was 52.2 cm (+2.01 SD). Serial MRIs, T2-weighted images clearly detected some deep and apparent hyperintense lesions with bilateral and symmetric hyper intense lesions, involving mainly the frontal lobes and anterior third of both external capsules (Figure 1b). MR spectroscopy showed decreased N-acetyl-aspartate (NAA) levels in centrum semiovale particularly in the frontal lobe and highly raised choline-containing compounds (Cho) and lactate (Lac) levels, associated with hyper metabolism in the posterior area of the centrum semiovale. Myo-inositol (Ins) and lipid peaks were also noted (Figure 2).

In view of the above findings which could be suggestive of AD, a molecular analysis was made confirming a mutation R79H (c.236G>A, exon 1), in GFAP on chromosome 17. At 4 years of age, the child received physiotherapy and speech therapy support. Language delays

Figure 1: a) Brain MRI, axial T2-weighted image, performed at 14 months, diffuse bilateral and symmetric hyperintense lesions, with deep and superficial white matter frontal predominance (black asterisks); b) Brain MRI, axial T2-weighted image, performed at 3½ years, diffuse bilateral and symmetric hyper intense lesions, with deep and superficial white matter frontal predominance (black asterisks), with small extent at subcortical U-fibers, subtle hyper intense abnormalities at the head of the caudate nuclei head and lenticular nucleus compared to thalamal signal changes (white asterisks), and hypo-intense rings adjacent to anterior horn of lateral ventricles (arrows)
in comprehension as well as expression and unsteady gait were observed. The HD was 56.8 cm (+4.8 SD). He has been taking valproic acid as prescribed without recurrence of seizures in the last 2½ years.

Discussion

Alexander disease is a very rare and serious illness and only approximately 300 cases have been reported. This disorder is caused by a mutation in the gene that encodes for GFAP which is a type III intermediate filament protein located on chromosome 17q21, along with vimentin and nestin and is a part of the cytoskeletal fibers [7]. The clinical phenotype is caused by a sequence of cellular events such as a mutation in GFAP, sequestration of protein chaperones, hyperactivation of the stress response and subsequent accumulation of GFAP, together with αβ-crystallin and HSP27 that result in the formation of Rosenthal fibers [8-10]. In AD, they are particularly in perivascular, subependymal or subpial location and, with electron microscopy, appear as eosinophilic cytoplasmic inclusions within perivascular astrocyte processes [11,12]. They may be observed in other neurological conditions, such as pyleocitic astrocytome, multiple sclerosis or syrinx cavities, but differ with regard to the quantity and location [13].

The main neuroimaging finding is a diffused change in white matter, predominantly in frontal areas, because of an expansion of dendritic fields and an increase in capillary density in these cerebral lobes. Also observed are a periventricular rim of decreased signal intensity on T2-weighted images and elevated signal intensity on T1-weighted images, abnormalities of the basal ganglia and thalamus, brain stem deficits and contrast enhancement of one or more of those previously mentioned [5,14,15]. In AD, the frontal white matter disruptions in the first 2 years of life are very distinctive and as in our case, permit distinguishing between different types of leukodystrophy [5,9].

MRI spectroscopy receives the signal from cerebral metabolites. Decreased NAA and elevated Cho, Lac, Ins and lipid levels are suggestive of active demyelination. Decreased NAA correlates with axonal loss, as shown in the frontal area of our patient. Rising Cho concentration is due to increase in white matter density and Lac is related to raise non-oxidative glycolysis. Ins is a glial marker that enhances in the event of gliosis or reactive astrocitosis and increased acquisition of lipids means severe brain injury [6].

A correlation genotype-phenotype in AD has been described. The most common mutations are R239, R79, R416 and R88. R79 mutation, as in the present case, is more likely to happen in males and predicts an early onset of the disease which manifests as seizures, progressive megalencephaly, psychomotor delay and gait disturbance [1,9]. Nevertheless, this phenotype is much less severe than the R239 mutation and life expectancy is higher. It has outlined infantile AD patients who may live from 20 or 48 years of age [16].

The disease’s debut may present with febrile status epilepticus. In the cases we have reviewed and, as in our case, medication helped control seizures and it was not even necessary to prescribe antiepileptic drugs [3,17]. However, patients who develop refractory epilepsy are usually associated with other mutations in the GFAP gene.

Even though AD is considered as a progressive infantile illness, some mutations in GFAP, as R79 variation, confer a more stable evolution and can be confused with a neurodevelopmental disorder. In such cases it may therefore be necessary to perform MRI to demonstrate frontal white matter abnormalities which lead to a suspicion of Alexander disease which can then be confirmed by molecular analysis.

Author Contributions

Particularly remarkable is the participation of LLV and GLS. LLV is first author and wrote the draft and completed final editing of the article. GLS is the first author’s mentor, proofread the draft and offered his professional comments.

Declaration of Conflicting Interests

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