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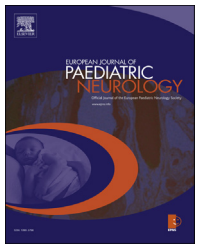

Original article

Diagnosis by whole exome sequencing of atypical infantile onset Alexander disease masquerading as a mitochondrial disorder

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ABSTRACT

Introduction: There are many similarities, both clinical and radiological, between mitochondrial leukoencephalopathies and Alexander disease, an astrogliopathy. Clinically, both can manifest with a myriad of symptoms and signs, arising from the neonatal period to adulthood. Radiologically, both can demonstrate white matter changes, signal abnormalities of basal ganglia or thalami, brainstem abnormalities and contrast enhancement of white matter structures. Magnetic resonance spectroscopy may reveal elevation of lactate in the abnormal white matter in Alexander disease making the distinction even more challenging.

Patient and Methods: We present a child who was considered to have an infantile onset mitochondrial disorder due to a combination of neurological symptoms and signs (developmental regression, failure to thrive, episodic deterioration, abnormal eye movements, pyramidal and cerebellar signs), urinary excretion of 3-methyl-glutaconic acid and imaging findings (extensive white matter changes and cerebellar atrophy) with a normal head circumference. Whole exome sequence analysis was performed.

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Results: The child was found to harbor the R416W mutation, one of the most prevalent mutations in the glial fibrillary acidic protein (GFAP) gene that causes Alexander disease.
Conclusions: Alexander disease should be considered in the differential diagnosis of infantile leukoencephalopathy, even when no macrocephaly is present. Next generation sequencing is a useful aid in unraveling the molecular etiology of leukoencephalopathies.

1. Introduction

Alexander disease is an astrogliopathy caused by dominant mutations in the glial fibrillary acidic protein gene (GFAP), usually characterized on magnetic resonance imaging (MRI) by leukodystrophy with a frontal predominant pattern.[1] Three forms of Alexander disease are recognized, based on age of onset and clinical features.[2] Type I (cerebral) is characterized by infantile onset (birth to 2 years) and features macrocephaly, developmental delay, encephalopathy, seizures, failure to thrive, paroxysmal deterioration and typical MRI findings, mainly superior frontal white matter changes. Type II (bulbospinal) is characterized by later onset, autonomic dysfunction, ocular movement abnormalities, palatal myoclonus, weakness, ataxia, bulbar or pseudo-bulbar symptoms, with preserved motor and cognitive functions and a milder progression than type I. The MRI features in this type are considered atypical and include signal abnormalities and atrophy in the medulla oblongata and upper cervical spinal cord. Type III is an intermediate form which has the characteristics of both.[1,3]

We present an atypical case that was suspected as having a mitochondrial disorder (Leigh-like syndrome) due to a fluctuating deterioration since infancy following infections, no megalencephaly, with subtle signal changes in both basal ganglia and brainstem on the initial MRI and elevated excretion of 3-methylglutaconic acid.

Exome sequencing revealed a heterozygote mutation in the *GFAP* gene consistent with Alexander syndrome.

2. Materials and methods

Case study: The patient is a product of a spontaneous twin pregnancy. She was born at term by caesarian section due to breech presentation; birth weight and Apgar scores were normal.

The family history is noted for hypertrophic cardiomyopathy and several cases of auto-immune thyroid disorders on the maternal side. The patient's older brother had hypotonia and gross motor delay and is now clumsy; her non-identical gender-matched twin is healthy.

Early development was normal until the age of 10 months; then she underwent a febrile illness followed by protracted vomiting. She became lethargic, and abnormal eye movements were noted (alternating esotropia and nystagmus). Gradually, she lost all acquired developmental milestones and failed to thrive. A metabolic workup (ammonia, blood gases, lactate, pyruvic acid, carnitine, acyl carnitine profile, amino acids, very-long-chain fatty acids) was normal except for urinary organic acids that showed mild excretion of ketones, dicarboxylic acids, Krebs cycle intermediates and 3-methylglutaconic acid (suggestive of a mitochondrial disorder). A brain MRI showed hyper-intense T2 signal in the peri-aqueductal area and mild signal changes in the caudate nucleus bilaterally (Fig. 1). She received cyproheptadine (for its appetizing affect) and developmental therapies, and gradually regained weight and developmental milestones.

When examined for the first time in our metabolic-neurogenetic clinic at the age of 2 years 5 months, she had alternating strabismus, pyramidal signs (brisk reflexes, clonus and extensor plantar responses) and a gait abnormality. She showed gross motor and expressive speech delay; formal developmental assessment using the Griffiths developmental scales performed at the age of 20 months found a developmental quotient of 77. An additional MRI performed at the age of 2 years and 7 months demonstrated mild hyper-intense signal changes in the caudate head, diffuse white matter signal changes in the frontal area bilaterally (Fig. 2 top panel) and mild atrophy of the superior vermis (Fig. 3 top panel).

She continued follow up at our clinic and in the next 1.5 years seemed to have a static clinical condition with residual pyramidal and cerebellar signs. Head circumference growth was consistently on the 25th percentile.

At the age of 4 years, she suffered from bacterial pneumonia and a few weeks later, a nonspecific viral illness. During these two febrile illnesses, she had frequent emesis, claimed to be weak and refused to walk. When made to stand, she appeared unstable. When examined at our clinic about a month after the onset of this episode, her neurological examination demonstrated pyramidal signs (that were present before), marked ataxia, tremor and dysmetria, oral dystonia and mild ptosis. A mitochondrial "cocktail" consisting of carnitine, antioxidants and coenzyme Q10 was recommended. She began to recuperate about a week after her visit; she regained walking and the ptosis disappeared. MRI performed at the age of 4 years 2 months (1 month after the onset) demonstrated extensive signal changes in the frontal white matter with a discrete lesion in the left anterior periventricular region, showing a restrictive pattern on diffusion-weight imaging (DWI) and enhancement with gadolinium. Also noted were diffuse, symmetric, bilateral signal changes in the caudate heads, brainstem and white matter including the peri-aqueductal region and in the cerebellar dentate nuclei, with worsening cerebellar atrophy.