

A Rare Case of Zellweger Syndrome Associated with Neonatal Ischemic Stroke

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Abstract: The Zellweger disorders (ZSDs) is a prototype of the peroxisome biosynthesis disorders described as a cerebro-hepato-renal syndrome. It is an autosomal recessive systemic disorder characterized clinically by severe neurologic dysfunction such as profound hypotonia, weakness, neonatal seizures, craniofacial abnormalities, and liver dysfunction. Biochemical screening shows the absence of peroxisomes. Brain MRI finds cortical and white matter abnormalities, but it is not known to be associated with ischemic stroke. Here we report a rare case of a newborn presenting with a profound persistent hypotonia, bilateral clubfeet, and refractory seizure, who is diagnosed with Zellweger syndrome associated with ischemic stroke. Because ischemic neonatal stroke has not yet been described in Zellweger Syndrome, this specific association could lead to even greater diagnosis delay, making the situation harder on the medical team and of course the parents. We believe acknowledging the possibility of ischemic stroke in Zellweger Syndrome could help physicians achieve a diagnosis faster if they encounter a similar case. When we are confronted to refractory seizures in a newborn with an ischemic stroke, physicians must keep searching for arguments in favor of a differential diagnosis, and Zellweger Syndrome is one that should not be overlooked.

Keywords: Zellweger Syndrome, Stroke, Hypotonia, Refractory Neonatal Seizure

1. Introduction

Zellweger syndrome (ZS); also known by the following names: Generalized Peroxisomal Disorders, Peroxisomal Biogenesis Disorders, Zellweger Syndrome Spectrum ZSS, cerebrohepatorenal syndrome [1]; constitute a heterogeneous group of autosomal recessive disorders characterized by a defect in peroxisome formation and caused by mutations in one of 13 PEX genes [2, 3]. ZS is mainly characterized by craniofacial abnormalities, severe weakness, hypotonia and hepatic dysfunction [4, 5]. Brain MRI typically shows neuroanatomical characteristics such as abnormal cortical gyration or white matter abnormalities [1, 6, 7]. Ischemic stroke is a rare phenomenon in neonatal period, with a higher occurrence in perinatal period characterized by non-specific symptoms ranging from profound hypotonia, seizures to coma with a diagnosis mainly based on brain MRI [8]. To

our knowledge, ischemic neonatal stroke has not been described in ZS.

In this article we present a case of full-term newborn found to have Zellweger syndrome associated with a neonatal ischemic stroke, who presented with profound hypotonia and refractory seizure.

2. Case Report

Full term baby boy born at 39 weeks and 4 days with a birth weight of 2740 g (6th percentile) to a G3P2 B+ mother, with a medical history of chronic thrombocytopenia and factor VII deficiency treated by steroids before pregnancy. We note a second-degree consanguinity between parents, and isolated renal agenesis in the first sibling, who was otherwise symptom free. Prenatal ultrasound scanning showed growth retardation associated with bilateral clubfeet, and amniocentesis showed normal karyotype and normal array CGH.

Mother presented with spontaneous labor, and received intravenous continuous morphine for pain control, because an epidural was not an option, due to her mild thrombocytopenia. Prolonged fetal heart rate decelerations resulted in an urgent C-section under general anesthesia. At birth, E. had an APGAR score of 3, 5 and 6 at one, five and ten minutes respectively with corrected cord ABGs showing pH 7.27 and lactate 1.8. Initial assessment found remarkable hypotonia and hypoventilation. He was admitted to the neonatal intensive care unit (NICU) due to persistent hypotonia and need for respiratory support despite one dose of intramuscular naloxone, with low efficacy.

Upon admission, the physical exam showed mild facial dysmorphism, bilateral club feet, bilateral cryptorchidism, central and peripheral remarkable hypotonia associated with a lack of eye contact. EEG revealed recurrent seizures, frontal right crisis, that were non responsive to phenobarbital and clonazepam. Due to his status epilepticus, he was intubated at Hour 20 of life, sedated and he received IV continuous clonazepam, and vitamins B1, B6 and B9. Despite normal brain ultrasound, brain MRI was performed on day of life 4 and showed large right Sylvian ischemic stroke reaching the basal ganglia and a large polymicrogyria at left side (gyration of the right hemisphere was non analyzable due to the large stroke) (Figure 1). Echocardiography was done to rule out any associated embolisms or abnormalities of the heart or the great vessels, and it turned out to be normal.

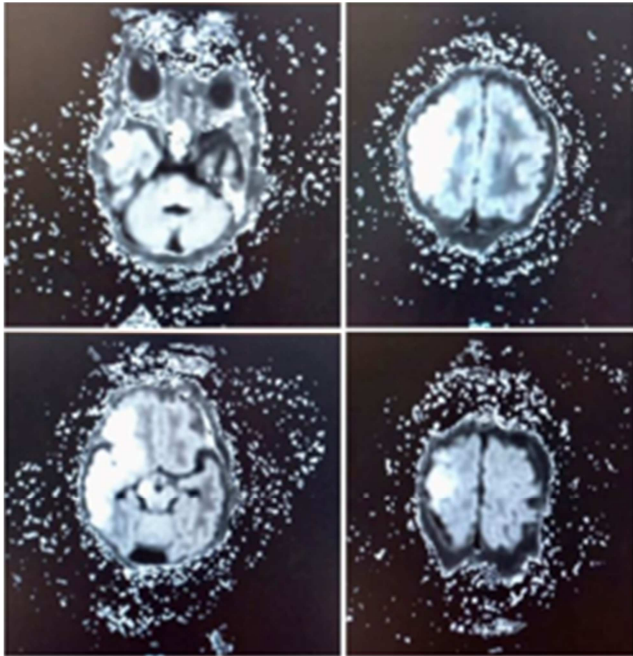


Figure 1. MRI brain showing large right sylvian ischemic stroke.

Based on the patient's symptoms and physical exam, a neurologic and metabolic consultations were needed. A complete metabolic screening was prescribed and showed elevation in long chain fatty acids mainly C22, C26 in favor of peroxisome disease. Genetic testing ruled out Steinert

disease, spinal amyotrophy and Prader-Willi. Hormonal screening for cryptorchidism was normal. Therefore, the baby was diagnosed to have an ischemic neonatal stroke of the right sylvian artery associated with a Zellweger disease, confirmed later on with molecular studies on cultured fibroblast showing a mutation of c.574C > T PEX26 gene.

At day 7, seizures were mostly controlled; clonazepam was replaced by levetiracetam and vigabatrin. E. was extubated with gradual withdrawal from ventilatory support to end with a spontaneous ventilation without any support. The physical exam showed an extremely hypotonic baby with a lack of eye contact, and a recently increased head circumference. Transfontanellar ultrasound was repeated at day 10 and showed a dilatation of the lateral ventricles and the third ventricle.

Because of the severe prognosis, palliative care was proposed after a multidisciplinary ethics discussion, and E. was discharged with levetiracetam and vigabatrin, pain killers if needed, physiotherapy, and gastric tube feeding. Follow up was organized with a specialized medico-social care center and the parents were informed for the importance of a genetic counseling for future pregnancies.

3. Discussion

The neonatal seizure constitutes an emergent condition, which needs an immediate intervention to determine the possible treatable etiologies, and prevent death or related long-term neurologic disabilities when it's possible [9, 10].

Neonatal seizures have many etiologies, mainly neonatal encephalopathy and hypoxic-ischemic encephalopathy (HIE), acquired structured brain lesions including ischemic and hemorrhagic stroke, metabolic disturbance (hypoglycemia, hypocalcemia, hyponatremia, hypomagnesemia...), inborn error of metabolism, and central nervous system (CNS) or systemic infection [11]. Ischemic stroke associated with metabolic disorders is a specific entity described in several inborn error of metabolism [12, 13]. It is caused by decompensation of underlying metabolic disorder and in those cases; MRI shows large vessel or lacunar strokes potentially in any vascular distribution [14]. In our case, although ZS is a metabolic disease, the MRI findings were not those expected in a metabolic disorder, and we found a regular large right sylvian ischemic stroke. T2WI shows increased signal intensity (SI) in the affected cortex and white matter [15]. (Figure 1). Angiography didn't show any signs of thrombus or arterial malformation (Figure 2). In ZS, in addition to the clinical features, brain MRI shows bilateral frontoparietal pachygyria, caudothalamic germinolytic cysts, and bilateral perisylvian polymicrogyria [6], along with neocortical dysplasia, abnormal deep central sulcus and non-specific myelination delay of the supratentorial white matter [7]. In our patient, along with the stroke, we found hypersignal diffusion associated with restriction of diffusion coefficient in right cortico sub-cortical temporo-frontoparietal region with also a lesion of same type in caudate and lenticular nuclei (Figure 1). We found no cause for ischemic

stroke in E's screening. It is possible that the severe hypotonia made it difficult for E to progress in the birth canal, and this long labor might have resulted in ischemic brain damage. This theory is supported by the presence of growth retardation since recent data shows that abnormally developed placenta may predispose to intrapartum fetal hypoxia. In the neonatal ischemic stroke, seizure can be focal or generalized. It usually responds well to antiepileptic treatment. [16, 17]. In inborn error of metabolism, seizure can occur prepartum, per partum or post-partum, after a symptom-free period. It can be associated with organomegaly, or metabolic disturbances like the hypoglycemia, hypocalcemia, or even hypomagnesemia. In peroxisome disorders, seizures are typically refractory [14], like in ZS, with seizure characterized by its resistance to treatment, and association with severe profound hypotonia, dysmorphic facial features and hepatic dysfunction [18]. This is what we experienced in our patient, and his crisis only partially subsided after seven days. It is important to remember that even with an ischemic stroke diagnosis on the brain MRI, differential diagnosis must still be considered if seizures fail to subside rapidly. Since they can lead to specific treatments, inborn errors of metabolism are especially important to consider and a complete metabolic screening must not be overlooked in case of resistant seizures, even with a stroke diagnosis.



Figure 2. Normal cerebral angioplasty.

Usual care for ZS consists in treating epilepsy and assessing comfort in order to provide adequate pain control and comfort care, and support feeding to avoid consequences of severe undernourishment.

Other approach under investigation is to normalize the concentration of docosahexaenoic acid (DHA). DHA

concentration is low in brain, retina, and other tissues in this disorder, and may contribute to abnormalities in neurologic function. In one report, 20 individuals with Zellweger spectrum peroxisome biogenesis disorders were treated with DHA ethyl ester [19]. Beneficial effects included normalization of DHA levels and liver function, improved vision in approximately one-half of those treated, and increased muscle tone. Myelination improved on MRI in nine patients. Clinical improvement was greatest in those who started treatment before age six months. Nevertheless, whether DHA treatment is beneficial or not is still very much in debate [15, 19].

Although E left our unit with a palliative care plan, we associated early physiotherapy to his treatments because stiffness in his left side caused by the stroke would later cause further unnecessary discomfort. Even in a severe prognosis such as ZS with an expected early childhood death, associated diagnosis should not be overlooked, in order to provide maximal comfort to our patients.

4. Conclusion

ZS is a rare peroxisome biogenesis disorder characterized by craniofacial abnormalities, severe hypotonia, hepatic dysfunction and seizures. Associated causes of seizures must be researched and be taken into consideration in order to provide the best care for our patients. Also, routine investigations, associated to long-term follow-up are recommended to improve outcomes.

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