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A New Observation of The Zellweger Syndrome Spectrum: How A D Eleterious Mutation of The PEX 2 Gene Severely Affects The phenotype of A 3 Month Old Infant.

[1]Dr. Y. LANDA, Pediatric service P2, Rabat Souissi Children's Hospital.

[2]Dr. FZ OUDGHRI, Head of service, Pediatric Neuropediatrics and Neurometabolism Unit, P2 Pediatric Department, Souissi Children's Hospital in Rabat.

[3]Dr. Y. KRIOUILE, Neuropediatrician, Liberal sector – Rabat

[4]Dr. A. MDAGHRI ALAOUI, Congenital Anomalies Research Team, Faculty of Medicine and Pharmacy, Mohammed V Rabat University.

Corresponding Author: Dr. Y. LANDA, Pediatric service P2, Rabat Souissi Children's Hospital.

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Abstract

Peroxisome biogenesis (PBA) abnormalities are an heterogeneous group of autosomal recessive abnormalities encompassing two distinct clinical spectra; The spectrum of Zellweger syndrome (SZ) and The rhizomelic punctate chondrodysplasia (CPR). We report the case of a 3-month-old child, whose genetic test revealeda mutation in the PEX2 gene. Referring to Zellweger syndrome. she is the only child of a family, with no history of consanguinity. The delivery was by cesarean section due to nuchalcord. the newborn adaptation to extra uterine life was difficult. Birth weight was 2kg800. The infant was born with respiratory distress due to perinatal asphyxia, and was therefore hospitalized in neonatal intensive care for two weeks. During her stay, the patient presented convulsive crises. As crises persisted, she was re-hospitalized at 30 days-old for convulsive mal states. Clinical examination showed the following: hypotonicity, absence of contact, no eye tracking, dysmorphic syndrome, hypertelorism type, flat forehead, retrognathism with plagiocephaly, hepatosplenomegaly, the cerebral magnetic resonance imaging found a small cavity in T2 hypointense, left paraventricularhyposignal flair related to a Virchow and Robin space (variant of normal). The electroencephalogram showed myoclonic epilepsy with partial component. Metabolically, two amino acid chromatography exams were inconclusive. The genetic study with sequencing of the exome, confirmed the diagnosis of abnormalities of biogenesis of the peroxisome with mutation on the gene Pex2 .c.88G> T P (glu30) and Pex2 c.750G> A p (trp250). The patient was treated with anti-epileleptique. The outcome was fatal 4 months later.

Keywords: Peroxin; Zellweger syndrome; Pathogenic gene.

Introduction

Peroxisome biogenesis (PBA) abnormalities are an heterogeneous group of autosomal recessive abnormalities encompassing two distinct clinical spectra : The spectrum of Zellweger syndrome (SZ) and the spectrum of rhizomelic punctate chondrodysplasia (CPR). These anomalies are the consequence of the mutation of one of the genes (PEX genes) encoding proteins called peroxins involved in the transport of matrix and membrane enzymes to the organism. Zellweger syndrome or cerebro-hepato-renal syndrome is the more severe form of the spectrum of (SZ) compared to the more moderate variants such as

neonatal adrenoleukodystrophy (ALDN) or infantile refsum disease (MRI). We report the case of a 3-month-old infant with a mutation in the PEX2 gene.

Case report

Infant Hiba was admitted to the hospital at the age of 3 months. She was the only child in a family; with no history of consanguinity. During her continuing pregnancy of approximately 41 weeks, the mother reported abnormal fetal movements in the uterus. Ultrasound obstetrics were reassuring. The delivery was by cesarean section due to a nuchal cord. Weight at birth of 2kg800 and difficult adaptation to extra uterine life. Facing respiratory distress due to perinatal asphyxia, Hiba was hospitalized on the first day of life in neonatal intensive care for two weeks. During her stay, the patient also presented convulsive seizures which reduced with the injection of gardenal.

Two weeks after her discharge, the 30 days-old patient was re-hospitalized for states of convulsive pain, such as myoclonus with fixity of the gaze, which afterwards became tonic-clonic hemi-bodily, and sometimes generalized. She was treated with bolus of gardenal, and then put on depakine syrup at a dose of 30 mg / kg / day; at this stage the patient had a cytolysis score 4 times the normal, with a low rate of trambine (65%).Upon her admission, the following observations were made: was very hypotonic, no contact, no eye tracking, with a dysmorphic syndrome, hypertelorism type, flat forehead, retrognathism with plagiocephaly, and hepatosplenomegaly.

Biologically, she had hepatocellular insufficiency, cytolysis at 3 times the normal, low rate of trambine, no acidosis on the ionogram or on the gas measurement, a normal amonemia and lactatemia (91-81), the spot test was without anomaly, the lumbar puncture with lactate dosage was also without anomaly, the cerebral scanner returned without abnormalities; cerebral magnetic resonance imaging however showed a small cavity in the T2 hypo signal, hypo signal left par ventricular flair in connection with a space of Virchow and Robin (variant of the normal). In addition, he electroencephalogram showed myoclonic epilepsy with partial component. Her ophthalmologic examination with fundus was normal, suggesting a potential returned to normal.

On the metabolic level, the first chromatography of the amino acids showed a slight quasi-generalized hypoamonino-acidemia, with an increase in threonine. At this stage, and due to the persistence of crises, the patient was put on depakine with injection of gardenal 2 CP per day, and supplemented with vitamin B1, B6, B12 and folic acid for 2 weeks. As attacks were not improving, a2nd amino acid chromatography with profile of acylcarnitines was done and showed an increase in citrulin, ornithine, and decrease in aspartic acid This can be explained by a deficiency in pyruvate carboxylase, the dosage of which is in progress The profile of l-carnitine did not show abnormalities that could suggest deficiency in beta oxidation mitochondrial fatty acids Besides, the genetic study with sequencing of the exome, had confirmed the diagnosis of anomalies of biogenesis of the peroxisome with mutation on the gene Pex2 .c.88G> TP (glu30) and Pex2 c.750G> A p (trp250) (fig1).Therapeutically this was treated with Keppra 1 ml in 2 doses per day, gardenal 15 mg per day, a laxative and Vit K for his hepatic insufficiency. The evolution was fatal at the age of 7 months with respiratory distress.

Gene	Variant Cordinates	Zygosity	In Silico Parametres	Allele Frequencies	Type and calssification
PEX2	P. (glu30) Exon 4	Het	Pplygene N/A Oligo-GVGD N/A SIFT N/A Mutation tester N/A Conservation NT Modurate	genomAD - ESP - 1000G - CentoMD	Stop Gain (Likely pathogene) (class 2)
PEX2	P. (Trp250) Exon 4	Het	Pplygene N/A Oligo-GVGD N/A SIFT N/A Mutation tester N/A Conservation NT High	genomAD - ESP - 1000G - CentoMD	Stop Gain (Likely pathogene) (class 2)

Figure 1: The Genetic Study of Our Patient.

Discussion

The peroxisome is a cellular organelle bounded by a single membrane. It is present in all cells except erythrocytes. It is abundant in two types of cells, hepatocytes and epithelial cells (1). It does not have a genome but it catalyzes different cellular functions, mainly the biosynthesis of esters and phospholipids and the ß-oxidation of fatty acids for very long chains. Peroxins (PEX) are proteins encoded by a family of PEX genes that are responsible for membrane synthesis, and the import of matrix proteins and organelle division (2).

Many studies have described the important role of peroxisome metabolism in the development of the central nervous system. This explains the severe neurodegeneration of these conditions (2, 3). The clinical expression of these metabolic abnormalities is defined by facial dysmorphia, consisting of a flattened face, broad nose, broad anterior fontanel, bulging forehead, flat occiput, with epicanthus. This was the case of our patient, who presented, as hypertelorism, flat forehead, and retrognathism with plagiocephaly. Neurologically patients present a profound hypotonia, and severe intellectual deficit, associated with epileptic crisis. Magnetic resonance imaging can reveal polymicrogyria, and gyration abnormalities.

On the metabolic level, patients present hepatic and renal dysfunctions. Our patient had liver failure with low Prothrombin. Patients may also have cataracts, glaucoma, retinitis pigmentosa, nystagmus, oroptic nerve atrophy. Visual disturbances occur gradually and are followed by a loss of vision (2); this was the case of our patient. Sensorineural hearing loss may also occur skeletal abnormalities are common.

Zellweger syndrome is known to be caused by many mutations that occur in at least 12 of the PEX gene. Fredrick's study identifies two locations on the PEX2 gene where mutations are responsible for severe impact on the phenotype of the Zellweger syndrome these are 355C> T and c.550del (5). In our case PAX2 mutations were observed in two locations:Pex2 .c.88G> TP (glu30) and the Pex2 c.750G> A p (trp250) to classify pathogenic.

It is noted that the syndrome affects one in 50,000 newborns. Prenatal screening, in particular in cases of risky pregnancy, is important. As all zellweger syndromes are serious disorders that can appear in the neonatal period or later in childhood with the increased risk of death during the first year of life (2). In 2015, after many years of research, a treatment with the combination of chloric acid and primary bile acid, was approved by the FDA (6-7). James E. Heubi in the USA reports 3 cases of children was treated this way. For 15 years the liver disease was stabilized. Associated to a satisfactory psychomotor development with a good quality of life. (6)

Despite the current ranking, clinical, biochemical and genetic overlap is present among the three phenotypes. In addition, only limited sources are available to serve as a background for prognosis. All ZSD are known to be severe disorders with onset of neonatal period or later in childhood and death during childhood or adolescence

Conclusion

Zellweger's syndrome is a very serious and rare pathology with a poor prognosis, thanks to scientific research; it has made it possible to discover treatments capable of

improving the life expectancy and quality of life of patients, hence the interest of genetics for the family.

References

1. Tran C, Hewson S, Steinberg SJ, Mercimek-Mahmutoglu S. Late-onset Zellweger spectrum disorder caused by PEX6 mutations mimicking X-linked adrenoleukodystrophy. Pediatr Neurol. 2014 Aug;51(2):262-5.
2. Braver man NE, Raymond GV, Rizzo WB, Moser AB, et al guidelines. Mol Genet Metab. 2016 Mar;117(3):313-21.
3. Andrea Mignarri. Zellweger Spectrum Disorder with Mild Phenotype Caused by PEX2 Gene Mutations. JIMD Reports- 29 January 2012: 43-46.
4. Krause C, Rosewich H, Gärtner J. Rational strategy diagnosis for Zellweger syndrome spectrum patients. Eur J Hum Genet. 2009 Jun;17(6):741-8.
5. FedickC. Jalas N.R. Treff, A deleterious mutation in the PEX2 gene causes Zellweger syndrome in individuals of Ashkenazi Jewish descent. Clin Genet. 2014 Apr;85(4):343-6.
6. Heubi et al.: Long-Term Cholic Acid Therapy in Zellweger Spectrum Disorders, Case Rep Gastroenterology. 2018 Jun 28;12(2):360-372.
7. Braver man NE, Raymond GV, Rizzo WB, Moser AB, Wilkinson ME, Stone EM, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: an overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016 Mar;117(3):313–21.