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Research Paper

Zellweger syndrome -Biopsychosocial intervention

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ABSTRACT
Zellweger syndrome is a rare autosomal recessive, congenital disorder characterized by the reduction or absence of functional peroxisomes in the cells of an individual. It is caused by the reduction or absence of peroxisomes, which rid the body of toxic substances in the liver, brain, and kidneys. The most common features of Zellweger syndrome include enlarged liver, high levels of copper and iron in the blood, and vision disturbances. Other symptoms include unusual facial features, mental retardation, seizures, and the inability to suck, and/or swallow, Jaundice and gastrointestinal bleeding may occur. This disorder results from the inheritance of two mutant genes for one of the receptors (PXR1) needed to import proteins into the peroxisome. A baby with Zellweger syndrome will die within six months to a year after it is born. 1 in 50,000 babies are diagnosed with Zellweger syndrome. Treatments focus on symptomatic therapy, and may include; gastrostomy to provide adequate calories, hearing aids, cataract removal in infancy, glasses, vitamin supplementation, primary bile acid therapy, anti-epileptic drugs, and possibly monitoring for hyperoxaluria.
KEY WORDS*: Zellweger syndrome, Peroxisomal disorders, and psychosocial intervention.*

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I. INTRODUCTION

Zellweger syndrome is a rare congenital disorder characterized by the reduction or absence of functional peroxisomes in the cells of an individual [1]. It is one of a family of disorders called Zellweger spectrum disorders , which are leukodystrophies. Because of the defect in peroxisome formation, multiple metabolic (both catabolic and anabolic) pathways are impaired resulting in metabolic abnormalities. Typically, ZSD patients accumulate very long chain fatty acids (VLCFAs), phytanic- and pristanic acid, C27-bile acid intermediates and pipecolic acid in plasma and have a deficiency of plasmalogens in erythrocytes [4]. Clinically, Zellweger Spectrum Disorders are highly heterogeneous, but the core features are: liver dysfunction, developmental delay and other neurological abnormalities, adrenocortical dysfunction and hearing- and vision impairment [4]. Before the biochemical and molecular basis of Zellweger Spectrum Disorders was known, they were clinically described as three distinct disorders: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD). These phenotypes are currently recognized as presentations within a clinical spectrum (with ZS being at the most severe end of the spectrum) which are now collectively referred to as Zellweger Spectrum Disorders, in order to appreciate the wide variations in presentation [5]. Recently, Heimler syndrome was recognized as a peroxisome biogenesis disorder within the Zellweger spectrum and added to the (very) mild end of the clinical spectrum [6]. This review provides a clinical overview of Zellweger spectrum disorders and focuses on management of patients with a ZSD. New developments in the field of management are discussed.

Historical information

Bowen et al. described a syndrome with failure to thrive, congenital glaucoma and craniofacial dysmorphic features with early death (before 2 years of age) [4]. In 1965 Smith et al. described two siblings with comparable multiple congenital malformations, but also polycystic kidneys and intrahepatic biliary dysgenesis [7]. In 1967, Passarge et al. introduced the term cerebro-hepato-renal syndrome. Since Hans Zellweger, a pediatrician, contributed two of the originally described patients it was later called Zellweger syndrome [8]. It was not until 1973 that the causal link between ZS and peroxisomes was made, when Goldfischer et al. described the absence of peroxisomes in hepatocytes and renal proximal tubules [9]. Although the clinical presentation is different, the discovery of similar biochemical abnormalities revealed that the earlier

described entities infantile Refsum disease and neonatal adrenoleukodystrophy were also peroxisomal disorders [10, 11]. Based on these findings, peroxisomes which were once considered unimportant organelles, were now connected to a group of diseases and became the object of intensive scientific investigations. It turned out that peroxisomes are important organelles in the eukaryotic cell, and are involved in many catabolic and anabolic metabolic pathways [3, 12]. At present more than 15 different peroxisomal disorders have been identified. The genetic basis of Zellweger Spectrum Disorders has largely been resolved and now includes 13 different PEX genes [13, 14]. The group of diseases is now referred to as Zellweger spectrum disorders and include the old disease entities of ZS, NALD, IRD but also Heimler syndrome which was recently recognized as a ZSD [6, 15].

Pathophysiology

Zellweger Spectrum Disorders are caused by mutations in one of the 13 different PEX genes. PEX genes encode proteins called peroxins and are involved in either peroxisome formation, peroxisomal protein import, or both. As a consequence, mutations in *PEX* genes cause a deficiency of functional peroxisomes. Cells from ZSD patients either entirely lack functional peroxisomes, or cells can show a reduced number of functional peroxisomes or a mosaic pattern (i.e. a mixed population of cells with functional peroxisomes and cells without) [1,24, 25]. Peroxisomes are involved in many anabolic and catabolic metabolic processes, like biosynthesis of ether phospholipids and bile acids, α- and β-oxidation of fatty acids and the detoxification of glyoxylate and reactive oxygen species. Dysfunctional peroxisomes therefore cause biochemical abnormalities in tissues, but also in readily available materials like plasma and urine [2,14] .There is a reasonable genotype-phenotype correlation [22]. Approximately 60 % of ZSD patients have biallelic *PEX1* mutations and almost 90 different mutations in *PEX1* have been reported so far [26]. Detailed and up to date information about *PEX* gene mutations is available through the DBPEX gene database. Symptoms that may be present at birth include a lack of muscle tone and an inability to move. The most common features of Zellweger syndrome include enlarged liver, high levels of iron and copper in the blood, and vision disturbances.

Case Presentation

A newborn 2-day-old male admitted to NICU at Nasser pediatric hospital, in Gaza strip due to history of poor suckling since birth and recurrent abnormal movement he developed recurrent arracks of generalized clonic seizures in both upper and lower limbs and switching of eyes and mouth. He was born at full term by uncomplicated spontaneous vaginal delivery with birth weight of 3 kg antenatal and postnatal histories were unremarkable. The parents were non-consanguineous and there was no known family history of genetic diseases. Physical examination revealed craniofacial dysmorphic features (high forehead, up slanting eyes, flat nasal bridge, wide anterior fontanel and paucity of facial expression. He had generalized hypotonia and hyperreflexia. Systemic examination was otherwise unremarkable. Baseline investigations including CBC, liver and renal function, ammonia and serum electrolytes. were unremarkable . Chest x-ray and brain U/S were normal. Abdominal U/S showed multiple renal cysts. For suspecting of sepsis, septic work up was done. All cultures were negative C-reactive protein CRP was positive +24 for which started on intravenous antibiotic. A clinical diagnosis of Zellweger syndrome was made based on typical facial features, recurrent seizures and generalized central hypotonia. Other work up to confirm the diagnosis like VLCFA and genetic test were not available at Gaza strip. Subsequently the baby developed seizures and was started on Phenobarbital, phenytoin. Medical team at NICU taken the decision if cardic arrest do not resuscitate and allow natural death. The baby died peacefully at age of 22 days.

II. DISCUSSION

Physical examination revealed craniofacial dysmorphic features (high forehead, up slanting eyes, flat nasal bridge, wide anterior fontanel and paucity of facial expression. He had generalized hypotonia and hyperreflexia. Systemic examination was otherwise unremarkable. Baseline investigations including CBC, liver and renal function, ammonia and serum electrolytes were unremarkable. Chest x-ray and brain U/S were normal. Abdominal U/S showed multiple renal cysts. For suspecting of sepsis, septic work up was done. All cultures were negative C-reactive protein CRP was positive +24 for which started on intravenous antibiotic .A clinical diagnosis of Zellweger syndrome was made based on typical facial features , recurrent seizures and generalized central hypotonia . Other work up to confirm the diagnosis like VLCFA and genetic test were not available at Gaza strip. Baseline investigations including CBC, liver and renal function, ammonia and serum electrolytes were unremarkable. All cultures were negative C-reactive protein CRP was positive +24 for which started on intravenous antibiotic.

Diagnosis

A diagnosis of a Zellweger syndrome usually suspected when characteristic signs and symptoms are present at birth, including the distinctive facial features. Tests that measure or detect specific substances in blood or urine samples can confirm a diagnosis of Zellweger syndrome. For example, detection of elevated levels of very long chain fatty acids (VLCFA) in the blood is the most commonly used screening test. Additional tests on blood and urine samples to find other substances associated with the condition may performed. An ultrasound may used to look for cysts on the kidneys or an enlarged liver. [1.26]. A genetic test to find a mutation in one of the genes associated with Zellweger spectrum disorders may also be used to confirm the diagnosis.

Yes. Clinical genetic testing is available for the twelve genes known to cause Zellweger syndrome. Carrier testing for at-risk relatives and prenatal testing are possible if the two disease-causing mutations in the family known. [1.24.25]. The Genetic Testing Registry (GTR) is a centralized online resource for information about genetic tests. The intended audience for the GTR is health care providers and researchers. Patients and consumers with specific questions about a genetic test should contact a health care provider or a genetics professional.

Epidemiology

The incidence of Zellweger Spectrum Disorders estimated to be 1 in 50.000 newborns in the United States [16]. It presumed that Zellweger Spectrum Disorders occur worldwide, but the incidence may differ between regions. For example, the incidence of (classic) Zellweger syndrome in the French-Canadian region of Quebec was estimated to be 1 in 12 [17]. A much lower incidence reported in Japan, with an estimated incidence of 1 in 500.000 births [18]. More accurate incidence data about Zellweger Spectrum Disorders will become available in the near future, since newborn screening for X-linked adrenoleukodystrophy (X-ALD) will be implemented in several countries [19, 20]. The screening method is based on C26:0-lysophosphatidylcholine (C26:0-lysoPC) measurement in dried bloodspots using LC-MS/MS technology, which will also identify ZSD patients [21].

Psychosocial intervention

The primary role of the psychosocial intervention was to maintain an acceptable level of positive mental health and acceptance of everything that happens to the sick child. In addition, the other main issue is to alleviate anxiety and family concern regarding their sick baby, and to provide psychosocial support to family members. This case considered one of the rare cases in terms of its recurrence, and there was an important role for psychosocial intervention for the mother and the family in general. Because the presence of a case type; puts the family in a real crisis, need special dealings with the sick child. Counseling sessions conducted with the family and information provided about the health status in terms of causes, symptoms and disease progression. In addition, that this case considered a dilemma for them. In order not to reject the child socially and to deal with satisfaction with his health. It was so important to listen from family to inquiries related to signs and symptoms of case; and how to deal with it in terms of health care, providing treatments and preventing complications as much as possible.

Prognosis:

Although a rough genotype-phenotype, correlation exists for several PEX genes, such as PEX1 and PEX26 the severity and progression of the disease is difficult to predict for individual patients. This will become more relevant as newborn screening implemented. Because of newborn screening for X-ALD by C26:0-lysoPC in several countries ZSD will also be diagnosed at birth. Children with the severe phenotype (neonatal-infantile presentation with severe clinical symptoms) have a poor prognosis and these patients usually die within the first year of life. Patients that present in childhood or adolescence usually have a better prognosis, but can develop progressive liver disease or leukodystrophy and deteriorate. If progressive liver disease or leukodystrophy occurs prognosis is poor. The remaining milder individuals can reach adulthood without progression or with long periods of stabilization. When progression occurs, it is mainly related to peripheral neuropathy and pyramidal signs, while cognition remains stable [23].

III. CONCLUSIONS

Because of the recently implemented newborn screening, more medical doctors in different specialties (e.g. pediatricians, clinical geneticist and neurologists) will encounter patients with a Zellweger Spectrum Disorders.

Zellweger Spectrum Disorders are clinically heterogeneous with high morbidity in almost all patient and mortality in some. Although treatment is currently only symptomatic, it is important to initiate proper supportive therapy to improve quality of life of these patients.

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