

Early Onset Hepatocellular Disease in an Infant with Zellweger Syndrome

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Received: 25 Jan. 2014; Accepted: 28 Jun. 2014

Abstract- Zellweger syndrome (ZS) is a peroxisomal disorder with a multiple congenital anomalies, characterized by stereotypical facies, profound hypotonia, organ involvement including cerebral, retinal, hepatic, and renal. Herein, a 3-month-old female with ZS is presented who was referred because of increased liver enzymes (subclinical hepatitis), which was detected in work-up of her neck cyst, severe hypotonia, and abnormal facies. An increased concentration of very long chain fatty acid in lipid profile was detected. ZS should be considered in the list of differential diagnosis in infants with stereotypical phenotype, neurodevelopmental delay, and severe hypotonia in association with liver and other organs involvement.

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Acta Med Iran 2015;53(10):656-658.

Keywords: Zellweger syndrome; Peroxisomal disorder; Micorecluplication

Introduction

Zellweger syndrome (ZS), also named as cerebro-hepato-renal syndrome, is a peroxisomal disorder, characterized by abnormal facial appearance, profound hypotonia and absent neonatal reflexes during infancy (1). The patients with ZS usually have a high forehead with widely open metopic palpebral fissures, underdeveloped supraorbital ridges, triangular mouth, and low-set shaped ears.

Hyperbilirubinemia, hypertransaminemia, coagulopathy, and hepatomegaly (2,3), glomerulocytic kidney disease (4), abnormal calcification of the patella and chondrodysplasia punctata (5), cerebral dysgenesis (6,7), pigmentary retinopathy (8), are some characteristics features of the ZS. Central nervous system could also be involved due to defective neuronal migration, in addition to abnormal qualitative myelin synthesis (9-12). Thus, seizures are also one of the most clinical presentations of cerebral disease, and the neurodevelopmental delay is also a common finding in patients with ZS (1).

Although several organs can be involved in ZS, it is quite an unusual detecting hepatocellular disorder during the first three months of life, in those survive the neonatal period (2,3). However, severe liver disorder is almost universal in ZS (13,14). Aberrant metabolism in peroxisome-deficient liver could lead to an increased level of compounds such as hydrogen peroxide and saturated very long-chain fatty acids (VLCFAs) (1).

Herein, an infant with ZS is presented who manifested with early onset liver involvement.

Case Report

A 3-month-old female was referred to the Children's Medical Center Hospital, the Pediatrics Center of Excellence in Tehran Iran, with elevated liver enzymes, which was detected during laboratory workup for her neck cyst.

She was the second child of healthy non-consanguine parents. Their first child of the family is healthy. Birth body weight was 3,300 g and head circumference was 34 cm.

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The patient suffered from a profound hypotonia, head lag and decreasing of grasp reflex, but normal fixing. Hepatomegaly (2 cm below costal merge) and a 2×3 cm mass in the anterior aspect of her neck were detected. Body weight was 5,400 gr (50 percentile for age), and head circumference was 41 cm (50 percentile for age).

Complete blood count (CBC) revealed normocytic anemia: Hemoglobin (Hb): 9.7 gr/dl; MCV: 80.7 fl; MCH: 28.8 pg; MHC: 34.4 gr/dl; RBC: 3.75×10⁶/ml. Liver function tests (LFTs) revealed elevated liver enzymes: AST: 272, ALT: 129; while other indices of LFTs (alkaline phosphates, bilirubin, prothrombin time) were normal. Other chemical laboratory test results (blood sugar, blood urea nitrogen, creatinine, sodium, potassium, phosphorus, calcium, triglyceride, cholesterol, and lactic dehydrogenase) were all within normal range. Arterial blood gas (ABG), serum lactate and pyruvate, serum and urine amino acids chromatography, urine sugar chromatography, urine reducing substances, thyroid function tests (TFTs), creatine phosphokinase (CPK), TORCH study and mass spectrometry were also normal.

ABR was non-reactive, and her slit lamp examination showed retinal dystrophy and salt-pepper appearance. Kidney ultrasound showed fullness in right kidney and micro lithiasis in both lower and upper poles of the right kidney; also, there was thickening of right uroepithelium.

Ultrasound of brain did not show intracranial hemorrhage, intraventricular hemorrhage, hydrocephalus and mass effect. Soft tissue ultrasound of neck revealed a hypoechoic mass, suggesting normal thymus (normal variant). Because of suspicious peroxisomal disorders, VLCFA was measured, which showed an elevated concentration of pythanic and pristanic acid, suggesting a typical pattern for ZS. Genetic analysis for common microdeletion/microduplication syndrome by multiplex ligation-dependent probe amplification (MLPA) was done, which was inconclusive.

Discussion

ZS was primarily explained in 1967, as a multiple congenital anomaly syndrome by Passarge and MC Adams (15), which termed cerebo- hepato-renal syndrome. Later, comprehensive studies were done on the pathology of ZS and its associated biochemical abnormalities (16,17). It should be noted that three syndromes have already been classified as a peroxisomal disorder, including ZS, Infantile refsume disease, and

Neonatal adrenoleukodystrophy¹. All of them have mutations in 12 different PEX genes, affecting PTS1 mediated assembly and enzyme import system (18-21). ZS has a distinct phenotype with abnormal facies, which is sometimes reminiscent of Down syndrome (1). Although the main limitation of the report is not sequencing of the gene to make the definite diagnosis of the syndrome, the clinical and biochemical findings are typical for the syndrome.

Liver disease is usually less apparent during the three first mouths, but may be evident as direct hyperbilirubinemia, hypertrasaminasia, coagulopathy or hepatomegaly alone, while severe liver disease is a common phenotype of the patients with ZS (2). Biochemical abnormalities, including increased level of VLCFAs (phytanic acids and pristanic acids, etc.) in tissues, plasma and urine, serum transaminasia, bilirubin, serum iron, etc as well as decreased level of cholesterol, prothrombin are usually seen in ZS22.

Liver histology may show some combination of lobular disarray, focal hepatocytic necrosis, portal fibrosis or cirrhosis, intracellular and Intra canalicular cholestasis and increased iron storage by electronic microscopy and histochemistry (for the marker enzyme catalase) peroxisome have been undetectable in the liver of almost all patients with classic ZS (13,14).

The presented patient was referred with hypertransaminasia early in infancy; she had also retinal dystrophy in eye examination while renal involvement detected by ultrasound. Other manifestations of the patella were not seen. Considering abnormal facies and cerebro-hepato-renal involvement, peroxisomal disorders especially ZS is considered for the patient; so, VLCFA was measured, which showed an increased concentration of phytanic acids and pristanic acids.

ZS should be considered in infants with stereotypical phenotypic and neurodevelopmental delay when there is an evidence of liver and other organs involvement (1). Subsequently, VLCFAs should be measured in patients with suspicious of abnormal peroxisomal metabolism (22).

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