ORIGINAL RESEARCH PAPER

Paediatrics

KEY WORDS:

ZELLWEGER SYNDROME WITH WILSONS DISEASE- A CASE REPORT

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ABSTRACT

A 1-year-old child who presented with jaundice and abdominal distention from early infancy. The child underwent medical evaluation, and various differential diagnoses were considered, including inborn errors of metabolism- storage disorders, Wilson's disease, and malignancy. To confirm the diagnosis, molecular genetic studies were conducted, and the results were used to counsel the parents about the inheritance pattern of the disease. This case emphasizes the value of using molecular genetic testing for definitive diagnosis in patients with suspected inherited diseases.

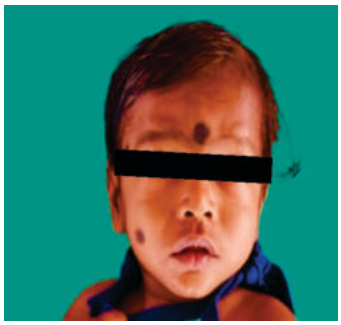
BACKGROUND

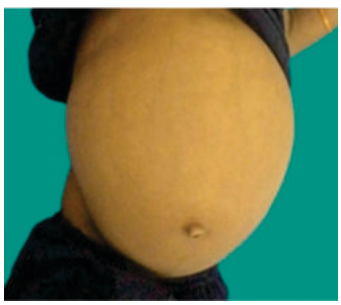
Zellweger syndrome (ZWS) (MIM #214100) (1) also known as cerebrohepatorenal syndrome, is the prototype of peroxisome biosynthesis disorders, and is the most common peroxisomal disorder to present in early infancy. The incidence is 1 in 50,000 to 100,000 live births(2) are caused due to defect in peroxisomes -They are caused by mutations in at least 12 different genes (3) . The majority of infants with these conditions have mutations in either the PEX1 or PEX6 genes that encode ATPases needed to import protein from the cytosol into peroxisomes.

CASE DESCRIPTION

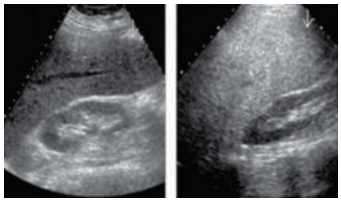
A 1 year old child born to 3rd degree consanguineous married couple , with no significant antenatal and natal history , presented with yellowish discoloration of eye and skin since 3 days of life , with abdominal distention since 3 months of age , and increased frequency of stools since 5 months of age , around 7-8 times /day ,semi -solid consistency , not associated with blood in stools, pale yellowish colour, with normal developmental history , with documented failure to thrive since early infancy, and normal vision and hearing .

On examination child had yellowish discoloration of skin and eyes , doll like facies , with normal size and shape of face , reduced muscle tone , abdomen appears to be distended with gross hepatosplenomegaly and B/L testis were descended.





Child was evaluated further , complete blood count showed low Haemoglobin with Peripheral smear showing Microcytic hypochromic anaemia with moderate degree of leukocytosis. Liver profile was deranged showing elevated direct bilirubin , Serum Glutamic Oxaloacetic Transaminase Serum Glutamic Pyruvic Transaminase, LDH , Coagulation profile and hypoalbunemia . VBG showed metabolic acidosis with elevated lactates. Ophthalmological evaluation showed normal fundus. Serum Ammonia , USG of abdomen – showed hepatomegaly with liver 10.5 cms , distendend GB wall with sludge , distended urinary bladder , splenomegaly + .



2 D ECHO , Liver biopsy, serum ceruloplasmin were not done due to financial constraints. Need of genetic evaluation was counselled and whole exome sequencing was done which showed pathogenic variant - c.373C>T (p.Arg125Ter) , with autosomal recessive inheritance caused by substitution in exon 4 of PEX 2 gene , which confirmed the diagnosis of Peroxisome biogenesis disorder 5A (Zellweger syndrome) (OMIM#614866) , the genetic study also revealed likely pathogenic variant (-) c.3007G>A , (p.Ala1003Thr ENST00000242839.1 0) , with autosomal recessive inheritance caused by mutation in ATP7B gene , which confirmed the diagnosis of Wilson disease (OMIM#277900).

Variant Description

A homozygous non sense mutation in PEX 2 gene in chromosome 8q21.13 , in locus/gene number 170993 was detected first in Japan Shimozawa et al. (1992) (4). In 3 patients with Zellweger syndrome, Gootjes et al. (2004) identified homozygous mutations in the PEX2 gene.

DISCUSSION

Zellweger spectrum disorders (ZSDs) (MIM #214100) – are caused due to defect in peroxisomes -They are caused by mutations in at least 12 different genes .The majority of infants with these conditions have mutations in either the PEX1 or PEX6 genes that encode ATPases needed to import protein from the cytosol into peroxisomes.

Peroxisomes are subcellular organelles of 0.05 to 0.5 micron in diameter, found in almost all cells except mature red blood cells. They are most concentrated in the liver and kidney. Peroxisomes catalyze numerous catabolic and anabolic functions in cellular metabolism. Catalytic functions include

beta-oxidation of very long-chain fatty acids (VLCFA); oxidation of pipecolic, phytanic, pristanic, and many dicarboxylic acids; and degradation of hydrogen peroxide by catalase . Anabolic functions include synthesis of bile acids and plasmalogens, which are important components of cell membranes and myelin.Peroxisomal disorders are a group of inherited metabolic disorders that affect peroxisome function, leading to neurological dysfunction in most cases. These disorders are diverse, and the severity and symptoms vary depending on the specific disorder.

ZSD 's encompass a range of clinical manifestations that can vary from mild to severe. The symptoms of mild ZSD can become evident early in life and commonly include developmental delay, vision loss, hearing loss, ataxia, and polyneuropathy. In some cases, ZSD can affect the liver, leading to a range of presentations such as hepatomegaly, cholestasis, elevated transaminases fibrosis, cirrhosis, and hepatocellular carcinoma.

Zellweger Syndrome is a condition that usually presents itself within the first few hours or days of a newborn's life. Symptoms include poor muscle tone, seizures, difficulties with feeding, liver dysfunction, vision loss, hearing loss, and distinct facial characteristics such as a flattened face, broad nasal bridge, high forehead, upslanting palpebral fissures, and epicanthal folds. Additional symptoms may include abnormal head size, a protruding tongue, neck skin folds, cataracts, glaucoma, and/or nystagmus. Skeletal abnormalities, such as chondrodysplasia punctata, may also be present.

Wilson disease is an autosomal recessive disorder caused by mutation in the ATP7B gene, which causes impairment of biliary excretion of copper, characterized by accumulation of intracellular hepatic copper with subsequent hepatic and neurologic abnormalities.

CONCLUSION

Zellweger syndrome is a rare congenital disorder , and currently no effective treatment is available for ZWS , but with next generation sequencing-based testing, the exact mutations could be identified, which helped in confirmation of the diagnosis of the proband, in providing accurate genetic counselling to the family and in offering prenatal diagnosis for their next planned pregnancy.

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