WOLCOTT RALLISON SYNDROME- A CASE REPORT

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Abstract: Wolcott–Rallison syndrome (WRS) is a rare autosomal recessive disease first described in 1972(1). A mutation in eukaryotic initiation factor 2 alpha kinase 3 (EIF2AK3) gene on chromosome 2p12 locus which codes translation initiation factor 2 alpha kinase has been identified with this syndrome(2). Here we report a girl who came to our hospital at 5 years of age with infantile onset diabetes mellitus, hypothyroidism, short stature, self-resolving hepatitis, and acute kidney injury. The diagnosis was confirmed by the presence of a homozygous mutation in the catalytic domain of EIF2AK3-PERK protein.

Keyword: wolcott rallison syndrome, EIF2AK3

INTRODUCTION:
Wolcott–Rallison syndrome is a rare autosomal recessive syndrome first reported in 1972 by Wolcott and Rallison who described three siblings with permanent diabetes mellitus of infancy and multiple epiphyseal dysplasia.(1) Idiopathic recurrent self limiting hepatitis, prerenal azotemia, developmental delay, central hypothyroidism, osteoporosis, fractures, short limb dwarfism, spondylo-epiphyseal dysplasia, grey blue sclera, high arched palate, tooth discoloration and dry skin constitute the spectrum of manifestations associated with this syndrome(3). In 1982, Stoss et al. described two siblings with neonatal diabetes, spondyloepiphyseal dysplasia, hepatosplenomegaly, renal insufficiency, short-trunk dwarfism and stiff joints(4). Other anomalies have also been noted, such as blue sclera, hypoplastic pancreas and cardiac and brain developmental defects.

CASE REPORT:
5 year old female, second child born to 2º consanguineous parents with previous spontaneous abortion presented with fever, non-bilious vomiting followed by jaundice of 2 weeks duration with passage of high colored urine and normal colored stools. She was diagnosed earlier at 8 months of age as diabetes mellitus, on regular insulin therapy and hypothyroidism on thyroxine supplementation. There was history of decreased urinary output, swelling of face and legs and abdominal distension. There was no history of bleeds, altered sensorium, breathlessness and seizures. There was a history of motor developmental delay. Her appetite had decreased and she was lethargic. She was not given any form of indigenous medicines.

On examination she was icteric, afebrile, had dry skin, abnormal gait with pes cavus deformity. Her weight was 10 kg (severe underweight), length was 82 cm (severe stunting) and head circumference was 43cm (microcephaly). No facial dysmorphism was noted. Examination of abdomen revealed an enlarged, smooth, firm liver 5 cm below the right costal margin. Examination of other systems was normal. Investigations showed Hb of 12.1 g/dl, leucocyte count of 8600-cells/cu. mm with lymphocyte predominance (65%). Her total serum bilirubin was 3.2 mg/dl with direct 2.9 mg/dl and indirect 0.3 mg/dl, SGOT 470.4 IU/L, SGPT 490.8 IU/L and SAP 1390 IU/L. Random blood sugar was 187mg/dl. Blood urea and serum creatinine were 110mg/dl and 2.2 mg/dl respectively. Thyroid function test, serum amylase, C-peptide (<0.5ng/ml) were within normal limits. Anti islet cell antibodies were negative. Ultrasound abdomen was reported as hepatosplenomegaly with homogenous echo texture. Urine examination did not reveal albuminuria, glycosuria or pyuria. There was no ascites. Chest X ray was normal. Echo cardiography was normal.

FIGURE- SKELETAL SURVEY SHOWED EVIDENCE OF SPONDYLO EPIPHYSEAL DYSPLASIA
Subsequently renal parameters were in decreasing trend with normal urine output, hence peritoneal dialysis was deferred. Child was managed conservatively with fluid and salt restriction, diuretics, insulin and supportive treatment. By two weeks, the anasarca, hepatomegaly regressed and serum aminotransferases, SGOT and SGPT decreased to 26 IU/L and 29 IU/L respectively. TORCH screening and viral markers for Hepatitis A, B, dengue and HIV were negative.

In this child, all the hallmarks of Wolcott-rallison syndrome were present, including infantile onset type 1 diabetes, spondylo-epiphyseal dysplasia, hepatic dysfunction, acute kidney injury and growth retardation. Based on these findings, the diagnosis of WRS was made. The diagnosis was confirmed by the presence of homozygous novel mutation in EIF2AK3 -T658 S M/M. Screening of the sibling revealed homozygosity for same gene mutation. Subsequently he was developed diabetes mellitus at 4 months of age and is under regular follow-up. Both the parents are heterozygous for the novel mutation in EIF2AK3 -T658 S M/N and are asymptomatic until now. (M-Mutation, N-Normal)

DISCUSSION

WRS may be under diagnosed because of early death before diagnosis. Diabetes occurs early, generally before six months of age, is permanent and insulin-dependent from the onset. Neonatal diabetes mellitus (NDM) is defined as an insulin requiring hyperglycemia occurring within the first 3 months of life. Massa et al (5) suggested the term permanent diabetes mellitus of infancy (PDMI) instead of PNDM and included infants up to 6 months of age. Rarely PDMI may be due to pancreatic dysgenesis or early onset type I diabetes mellitus (6). Pancreatic dysgenesis is usually associated with exocrine pancreatic insufficiency, elevated serum amylase, lipase and fecal chymotrypsin levels.

Skeletal dysplasia generally manifests within the 1st or 2nd year of life, and is associated with short stature (dwarfism with short trunk). Deficient mineralization or dysplastic changes, affecting the long bones, pelvis and vertebrae, but usually not the skull, may be seen on radiography as early as diabetes onset. Hepatic dysfunction is the 3rd characteristic feature and the most life-threatening complication, and manifestations by elevated hepatic enzymes, liver enlargement and recurrent acute liver failure. The most common cause of death is acute hepatic failure. Other manifestations vary between patients in type and severity and include renal dysfunction, exocrine pancreatic insufficiency, intellectual deficit, hypothyroidism, neutropenia and recurrent infections.

WRS is caused by mutations in the EIF2AK3 gene encoding eukaryotic translation initiation factor-2-alpha kinase 3 (PKR-like endoplasmic reticulum kinase; PERK), which plays a key role in translation control during unfolded protein response. Eukaryotic initiation factor 2 kinase 3 (EIF2AK3, also called PERK or PEK) regulates protein synthesis during stress by phosphorylating the -subunit of the eukaryotic initiation factor 2 (eIF2). There are four protein kinases known to phosphorylate eIF2: GCN2, heme-regulated inhibitor (HRI), double-stranded RNA-activated protein kinase (PKR), and EIF2AK3/PERK. PERK, identified as the eIF2kinase enriched in pancreatic cells, is uniquely located to the endoplasmic reticulum (ER) (7) and is activated by the accumulation of unfolded proteins in the ER lumen (8). Activation of PERK results in phosphorylation of eIF2 that acts as a dominant inhibitor of the guanine nucleotide exchange factor eIF2B and prevents the recycling of eIF2 between successive rounds of protein synthesis. Through halting translation initiation and protein synthesis, PERK may relieve ER stress by reducing the number of unfolded proteins in the ER and prevent cell death. Loss of PERK kinase activity leads to human disease and confirms that PERK is necessary for normal islet-cell function and skeletal development in humans. Diagnosis should be suspected in any infant with permanent neonatal diabetes and acute liver failure and/or renal dysfunction, and family history of consanguinity and/or neonatal diabetes. Radiographs show early signs of multiple epiphyseal dysplasia and deficient mineralization. Molecular genetic testing confirms the diagnosis. Differential diagnosis of skeletal dysplasia includes other spondylo-epiphyseal dysplasias such as mucopolysaccharidoses where diabetes may occur independently at an older age.

Wolcott-Rallison syndrome is a very rare and challenging disease. The condition is typically fatal. Though there is no specific treatment apart from good control of diabetes mellitus, prenatal diagnosis (2) is possible and genetic counselling can be offered to the family. Quadruple organ transplant (transplantation of liver, pancreas and kidneys) as a newer treatment modality has been tried recently.

REFERENCES: