Wolcott-Rallison Syndrome-Endocrinopathy with Recurrent Acute Liver Failure

A 2-yr-old child with early onset diabetes and hypothyroidism, and diagnosed as Wolcott-Rallison Syndrome, developed two episodes of acute liver failure and recovered, but he remains at high risk of developing another episode of acute liver failure. Autoimmune, metabolic or genetic disorders should be evaluated in children with recurrent acute liver failure and genetic tests needs to be considered.

Keywords: *Diabetes* mellitus, Genetic *disorder, Metabolic disease, Recurrent acute liver failure, Skeletal dysplasia*.

Wolcott-Rallison syndrome is an autosomal recessive disease characterized by neonatal/ early-onset diabetes mellitus (DM), skeletal dysplasia and growth retardation [1]. Acute hepatitis or recurrent acute liver failure (ALF) can occur in up to 85% of patients [2]. We report a child with Wolcott-Rallison syndrome who developed recurrent ALF and recovered.

A two-year-old boy presented with history of fever, jaundice and altered sensorium for last 5 days. He was diagnosed with DM at the age of 4.5 months with ketoacidosis and hyponatremic seizures. He was also diagnosed with hypothyroidism that was treated with thyroxine. DNA extraction and Sanger sequencing of the *EIF2AK3* gene showed a pathogenic homozygous nonsense mutation *c.1080T>A* in exon 6 (resulting in premature termination, *p.Tyr360Ter*) confirming the diagnosis of Wolcott-Rallison syndrome. There were no mutations in *KCNJ11, Insulin,* and *ABCC8* genes. Parents were heterozygous carriers of *EIF2AK3* nonsense mutation. Examination showed low weight and height (7200 g and 70 cm, respectively, both <3rd centile). Child was icteric and had hepatomegaly and encephalopathy (grade I-II). Baseline laboratory values were: total bilirubin 7 mg/dL (normal 0.3-1.2), aspartate aminotransferase 2898 U/L (normal <40), alanine aminotransferase 4690 U/L (normal <40), albumin 3.8 g/dL (normal 4-5.5), international normalized ratio (INR) 2.3, ammonia 128 mmol/L (normal <35), and blood glucose level 282 mg/dL. Serology for viral hepatitis (A,B,C,E), and polymerase chain reaction for Ebstein Barr Virus and Cytomegalovirus was negative. Autoimmune markers (anti-nuclear, anti-smooth muscle, anti-liver-kidney muscle-1, anti-liver-cytosol-1 antibody) were negative. He improved over one week with supportive care with antibiotics, ammonia lowering measures and fluid therapy. His liver function had normalized after one month. Detailed developmental assessment showed global delay with predominant lag in fine motor and language milestones. He presented after one year with features of ALF, which began with fever followed by jaundice and altered sensorium. Child was dehydrated, and laboratory work-up revealed total bilirubin 10 mg/dL, aspartate aminotransferase 1569 U/L, alanine aminotransferase 3560 U/L, albumin 4 g/dL, INR 2.2 and ammonia 112 mmol/L. Hepatotropic viral serology and autoimmune markers were again negative. He improved with supportive care over the next 10 days. Parents were counselled on the possibility of further recurrence of ALF and the need for early hospitalization and treatment with each febrile episode. Child is on long-acting insulin and his blood glucose levels are within target range.

Wolcott-Rallison Syndrome is caused by mutations in the gene encoding eukaryotic translation initiation factor 2a kinase 3 (*EIF2AK3*), which leads to abnormal sensing of cellular stress causing endoplasmic reticulum dysfunction, affecting lipid and glucose metabolism in liver [1]. Children present in early infancy with DM which is permanent and insulin-dependent, multiple epiphyseo-metaphyseal dysplasia and short stature [1,2]. Other variable clinical manifestations include hypothyroidism, exocrine pancreatic deficiency, renal failure, intellectual deficits, neutropenia and recurrent infections [1]. Recurrent ALF triggered by mild intercurrent infections is the characteristic feature of Wolcott-Rallison syndrome [1,2]. In a cohort of 28 patients with Wolcott-Rallison syndrome, liver disease was the commonest (90%) extra-pancreatic feature, with 60% mortality [2]. Patients are at risk of developing acute multi-organ failure during episodes of intercurrent illness [1,2]. The Pediatric Acute Liver Failure Study Group data showed that 54% of ALF were of indeterminate etiology in children <3 years of age [3]. ALF may be falsely attributed to known etiologies (*e.g.* paracetamol poisoning) due a temporal association between events in undiagnosed or underdiagnosed autoimmune, metabolic or genetic disorders [3,4]. Wolcott-Rallison syndrome represents one such etiology where ALF can present any time from neonatal period, can rarely occur before or at the onset of DM, and patient may die before genetic confirmation [1,2]. Liver

transplantation can prevent the recurrence of ALF [2] and should be offered in presence of INR >4 and total bilirubin >17.6 mg/dL, irrespective of hepatic encephalopathy [5]. Many metabolic/genetic disorders are associated with recurrent ALF in pediatric age group [4,6]. Recurrent ALF associated with mild infections or febrile episodes is extremely rare and can occur in mitochondrial defects, neuroblastoma amplification sequence deficiency and Wolcott-Rallison syndrome [4]. It is recommended that any child of consanguineous parents presenting with diabetes within the first 6 months of life should be tested for *EIF2AK3* mutations [1,2]. Patients should be carefully managed during every febrile episode and early referral to a liver transplant centre should be done, if liver function deteriorates. Recurrent ALF in pediatric age group should raise the possibility of autoimmune, metabolic or genetic diseases even if other obvious etiologies are present.

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Primary Segmental Intestinal Volvulus in a Neonate

Primary segmental intestinal volvulus is a rare disease with an aggressive clinical course. Early diagnosis and prompt management prevents life-threatening necrosis and perforation. A 1-day-old newborn girl with this disorder is reported to emphasize the presentation, imaging findings and management.

Keywords: *Necrosis, Perforation, Surgical emergency*.

Primary segmental intestinal volvulus (PSIV) is a rare disease with an aggressive clinical course. To prevent necrosis and perforation, early diagnosis and prompt management is paramount. A 1-day-old newborn girl with PSIV whose clinical features and radiologic findings appeared to be intestinal atresia is presented.

A 1-day-old female weighing 2110 g at 35 weeks gestation was born *via* caeserean section to a 34-year-old mother (para 2). The patient was admitted to our department with abdominal distention, bilious emesis and failure to pass meconium. Plain abdominal radiograph was suggestive of neonatal intestinal obstruction. Initial management included restoration of adequate body temperature, hydration and electrolyte balance. The neonate underwent an urgent exploratory laparotomy. Mid-ileal volvulus was encountered with ischemic changes of the 15 cm of the involved ileum. There was no evidence of obvious pathologies responsible for volvulus like malrotation, intestinal atresia or congenital bands. The involved ileal segment was resected and end-to-end ileoileal anastomosis was performed. Histopathologic examination revealed an ischemic infarct of resected ileal segment. The postoperative course was uneventful. The baby is gaining weight and doing well and is under our follow-up.

Anomalies of the gut development including a narrow intestinal mesenteric root has long be considered as the major cause of volvulus with catastrophic end result like intestinal necrosis [1]. If whole intestine is involved, massive intesinal necrosis leading to short bowel disease may occur. Of the intestinal volvulus, 80% of cases present during the first year of life and of these 60% are