Congenital Glucose-Galactose Malabsorption in a Child

Congenital glucose-galactose malabsorption (cGGM) is a rare autosomal recessive disorder [1] resulting from defective transport of glucose and galactose across intestinal epithelium due to mutations of *SLC5A1* gene encoding the intestinal sodium-dependent glucose transporter (SGLT1). It presents in newborns with severe osmotic diarrhea, hypernatremic dehydration, medullary nephrocalcinosis and distal renal tubular acidosis. If treated early with elimination of oral glucose and galactose containing diet, patients recover and develop normally [2, 3]. We report a novel mutation of *SLC5A1* gene in a child with cGGM for the first time from India.

A 6-month-old boy, product of 3rd degree consanguineous marriage with birth weight of 2.8kg presented with history of recurrent episodes of explosive watery diarrhea with perianal excoriation from 1st week of life. Repeated episodes of diarrhea with severe dehydration would warrant frequent hospitalizations. There was no history of blood or mucous with stools, vomiting, abdominal distension, rash or fever. Baby was exclusively breastfed for first 6 weeks. Thereafter, in view of persistent diarrhea breastfeeding was stopped and child was given soy milk formula.

On examination, child was severely dehydrated and malnourished [weight 3.1 kg (<-3SD), length 55cm (<-3SD) and weight for length < -3SD as per WHO charts], with glossitis and cheilitis. Polyuria was present (6.5 mL/kg/h) despite dehydration. Blood investigations showed severe metabolic acidosis (pH 7.04, HCO3 7.8 mEq/L, anion gap 10), severe hypokalemia (1.4 mEq/L), hypernatremia (155 mEq/L), with anemia (hemoglobin 6.8 g/dL). Total leucocyte count (10.8×10^3/µL), platelet count: (280×10^3/µL) and serum creatinine (0.2 mg/d) were normal. There was no clinical evidence of fat malabsorption. There was laboratory evidence of protein gut losses evidenced by hypoproteinemia (4.7 g/dL) and hypoalbuminemia (2.6 g/dL). Child was stabilized with intravenous fluids and potassium supplementation. Stool pH was 5 and was positive for reducing substances depicting osmotic diarrhea. During hospitalization, diarrhea would improve with fasting and worsen with introduction of WHO ORS. Therefore soy feeds were stopped and child started on amino acid formulation (*Neocate; Nutricia*) but had no improvement. Baseline workup for immunodeficiency disorders were unremarkable. Computerized tomography (CT) enterography showed normal bowel and pancreas. However, CT showed bilateral medullary nephrocalcinosis. Esophagogastroduodenoscopy was done with neonatal endoscope for obtaining biopsies from second part of duodenum as a work up for intractable diarrhea, which were both normal. In view of repeated episodes of severe dehydration requiring repeated hospitalizations high-lighted the possibility of osmotic with a component of secretary diarrhea. Normal anion gap metabolic acidosis, hypokalemia and bilateral nephrocalcinosis suggested possibility of distal renal tubular acidosis (RTA).

In view of early neonatal onset diarrhea that would worsen with ORS, acidic stool with stool positive for reducing substance (glucose), evidence of medullary nephrocalcinosis and distal RTA a diagnosis of cGGM was considered. Empirically glucose and galactose free diet was started. Since, there is no commercial formula specific to this disorder available in India, a carbohydrate-free formula designed for carbohydrate metabolic disorder (Metanutrition CMD by *Pristine organics, India*) was supplemented with fructose powder. Three grams of carbohydrate-free formula and 6g of fructose were mixed in 50 mL of water and the mixture was fed orally every 3 hours. The volume of the formula was tailored according to the weight. Child showed dramatic response with cessation of loose stools. Clinical exome sequencing of the child showed novel homozygous missense variation in exon 13 of the *SLC5A1* gene (c.1601T>C; p. Phe534Ser; ENST00000266088.4) classified as variant of uncertain significance as per ACMG guidelines [4]. Mutation was further confirmed by Sanger sequencing, confirming the diagnosis of cGGM. The human genome reference assembly used in this analysis was GRCh37/hg19. This variant has not been previously reported in the genome databases 1000 genomes, gnom-AD, Genome Asia 100k and dbSNP and described to be damaging by in-silico analysis. Parents were found to be heterozygous carriers of the same mutation and have been advised prenatal testing for future pregnancies.

After 3 months of exclusive formula feeding, child was supplemented with fruits (apple, mango, and banana), vegetables (beans, carrot) and pulses (green gram) in a graded manner. On follow-up, the child is asymptomatic and continues to have good weight gain (12 kg, 50th percentile) at 21 months of age.

Intractable diarrhea of early neonatal onset can be due to congenital enteropathies and structural gut abnormalities (malrotation, congenital short -gut) [5]. Structural abnormalities were ruled out with CT enterography, while normal villous/crypt architecture on histology excluded microvillus inclusion disease and other disorders of epithelial trafficking and polarity. As the diarrhea persisted even after lactose exclusion, congenital lactase deficiency was ruled out. In the absence of clinical steatorrhea, congenital bile acid synthesis defect and pancreatic insufficiency were unlikely.

Treating these rare diseases is challenging in resource poor settings. However, trial of combination of two different preparations was found to be affordable and effective. A previous literature review on cGGM reported 61 out of 107 cases from Middle East countries [1], and this is the first case reported from India.

We conclude that diagnosis of such a rare disease of cGGM is possible with appropriate clinical and investigative approach. Dietary modifications results in good outcome.

BS PRASAD, SURENDER KUMAR YACHHA*
Department of Pediatric Gastroenterology, Pediatric Hepatology & Liver Transplantation, Sakra World Hospital, Bangalore, Karnataka.
skyachha@yahoo.co.in

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Delayed Rise of Serum Thyroid Stimulating Hormone in a Micro-preemie With Congenital Hypothyroidism

Preterm neonates are at higher risk for deranged thyroid function test (TFT). Repeated thyroid screening tests by measuring thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels are recommended in preterm and very low birth weight (VLBW) neonates [1]. Delayed TSH elevation, either alone or in association with low thyroxine level are more common in preterms as compared to term babies. We managed a preterm micro-preemie with congenital hypothyroidism (CH) diagnosed at 10 weeks of age.

A third order preterm (28+4 weeks) girl with birth weight of 630 g (IUGR), was delivered by caesarean section for abnormal doppler with fetal distress. Product of non-consanguineous marriage, was a spontaneous conception with antenatal history of two previous first trimester abortions and no drug or radiation exposure. Mother was diagnosed with hypothyroidism during second trimester, remained euthyroid on oral thyroxine 25 µg/day. Anticipating preterm delivery, antenatal steroids were given. Baby was limp at birth requiring intubation in delivery room with APGAR 4/10 and 5/10 at 1 min. and 5 min, respectively. Baby had respiratory distress syndrome (RDS), sepsis with shock (received dopamine infusion for initial 3 postnatal days), hemo-dynamically significant PDA, neonatal jaundice and was managed conservatively as per NICU protocol. Screening cranial ultra-sound revealed Grade I intraventricular hemorrhage. Baby was weaned off to nasal CPAP on day 13 and to room air on day 37 of life. Trophic feeding was started on day 2 along with total parenteral nutrition (TPN), on increasing feeds baby developed feed intolerance with NEC like features on day 6 and therefore, was continued on TPN only. Feeding was restarted on day 13, gradually increased to reach full feeds (120 mL/kg/day) by day 20. Baby received four units of packed red blood cell (PRBC) transfusions during hospital stay. Pale stool with high coloured urine and yellowish discoloration of body was noticed in third week of life and liver function test suggested neonatal cholestasis. Sepsis evaluation including urine culture, metabolic screening, TFT, TORCH profile, urine CMV PCR and eye examination were done for cholestasis evaluation. She was managed conservatively for TPN induced cholestasis and it improved gradually over next ten weeks. She had fully vascularized retina and normal cranial ultrasound at 40 weeks corrected gestational age (CGA). Initial thyroid profile on day 5 of life showed FT4 - 1.1 ng/dL, TSH - 4.6 µIU/mL; on day 27 FT4 - 1.6ng/dL, TSH 9.58 µIU/mL and on day 48 FT4 - 1.2 ng/dL, TSH - 14.8 µIU/mL. Considering rising trend of TSH and multiple prematurity related illness, repeat TFT was done at 10 weeks showing FT4 - 0.2 ng/dL and TSH >100 µIU/mL. Neck ultrasound showed normal sized thyroid gland with isthmus and *X* ray bilateral knee had presence of femoral and tibial epiphyses. A diagnosis of atypical CH was made at 2 months CGA and baby was started with oral levothyroxine at 15 µg/kg and dose adjusted as per serial TFT [2]. Currently baby weighs 7.75 kg at corrected age of 9 months, in euthyroid state on levothyroxine at a dose of 16 µg/day and planned to be followed up every three monthly till three years of age.

The thyroid profile on day 5 of our baby was not absolutely normal (low FT4 and normal TSH), which could be attributed to sick euthyroid syndrome, prematurity or dopamine infusion. Subsequent rising TSH with normal FT4 at 4 and 7 weeks is suggestive of either improvement from sick euthyroid syndrome or progressive maturity of hypothalamic pituitary adrenal (HPA) axis. In sick euthyroid syndrome, neonates may have lower T3/FT3, normal or low T4/FT4 with normal TSH during stress (RDS, IUGR) and usually manifest with rising trends of TSH during recovery [3]. Few ELBW neonates develop hypothy-roxinemia with delayed TSH rise during recovery from sick euthyroid syndrome labelled as atypical CH [4]. This should be distinguished from delayed rise of TSH, which warrants starting lower dose of levothyroxine (8µg/kg/day). The dose of levothy-roxine supplementation for maintenance of normal TFT with advancing age may help to differentiate transient CH from permanent CH. In this neonate as need of levothyroxine dose is declining with age it might be a case of transient CH. So brief trial of stoppage of medication may be considered after 3 years of age.

The incidence of delayed TSH elevation is inversely related to gestational age and birth weight; neonates born at gestational age 23-24 weeks or birth weight <800 gm are at higher risk [5]. In a cohort of preterm neonates caesarean section, mechanical ventilation, PDA, pneumothorax, PRBC transfusion and some specific medications (antibiotics, dopamine, postnatal steroids) found to be risk factors of delayed TSH elevation [6]. Therefore, this case