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Excessive Weight Loss in a Neonate - Novel Mutation Causing Primary Hypoaldosteronism

Excess weight loss in a term neonate is a worrying symptom. We report a full-term male neonate who presented with jaundice and was noted to have progressive weight loss. This prompted us to evaluate further, uncovering an underlying endocrine disorder.

A 9-day-old male baby, born at 39 weeks, presented to the outpatient department with jaundice. As serum bilirubin was at treatment threshold (17.7 mg/dL), the neonate was admitted for phototherapy. The neonate had excess weight loss (admission weight- 3.45 kg, birth weight- 3.82 kg, weight loss- 9.7%). With phototherapy, the jaundice subsided in next 36 hours, but the child continued to lose weight over next two days (3.37 kg by day 11). The baby was born to a 30-year-old third gravida mother, with one previous first trimester abortion and a healthy male child. Antenatal scans showed mild left hydronephrosis. Her blood sugars were deranged at 36 weeks and late onset polyhydramnios was noted at 38 weeks (amniotic fluid index-17.5). It was a vaginal birth with smooth perinatal transition. There were no evident physical anomalies/dysmorphism. Baby had jaundice on day 2 of life, for which phototherapy was given for 24 hours and discharged on day 4 of life. At discharge, the child weighed 3.52 kg, breast feeding was well established, and there was adequate urine output. At home, the mother had adequate lactation with signs of good attachment and milk output. Since the continued weight loss was worrisome, the child was evaluated with serum electrolytes, venous blood gas, urine specific gravity, urine culture and sepsis screen. Hyponatremia (124 mEq/L) and hyperkalemia (6.9 mEq/L) were uncovered. C-reactive protein, white blood cell count, blood gas and urine examination were normal. Urine culture revealed growth of *Escherichia coli*. Genitalia, skin pigmentation, blood pressure, urine output and blood sugar were normal. The possibilities considered were salt wasting congenital adrenal hyperplasia, adrenal hypoplasia/hemorrhage, and type 4 renal tubular acidosis.

The child was initiated on liberal fluids, sodium supplements and anti-hyperkalemic measures. However, serial investigations revealed persistence of hyponatremia, worsening of hyperkalemia, new onset normal anion gap metabolic acidosis, and natriuresis (fractional excretion of sodium- 5.8%), fitting into the picture of type IV renal tubular acidosis. On further evaluation, ultrasound of adrenals, expanded newborn screening, 17-hydroxy progesterone, testosterone, dehydroepiandrosterone and cortisol levels were normal, and an appropriate response was noted with ACTH stimulation test, ruling out the possibility of congenital adrenal hyperplasia (CAH) and other structural adrenal pathologies. Trans-tubular potassium gradient was low (0.5) and urinary pH was elevated (6.5) suggesting decreased aldosterone activity. Aldosterone level was low (4.05 ng/dL; normal: 5-90 ng/dL) and plasma renin activity was high (>120 ng/mL/h; normal range: 2-35 ng/mL/h), indicating a possibility of primary hypoaldosteronism. The child was continued on sodium and bicarbonate supplements, and fludrocortisone was initiated. Following this, the child started gaining weight, with normalization of electrolytes and was discharged on day 28 of life.

Whole exome sequencing revealed a novel heterozygous contiguous deletion of 3 kb involving exons 5-9 of *CYP11B2* (ENST00000323110.2) gene at chr8: g.(142913452_142914263)_(142917844_142910557), that results in corticosterone methyl oxidase type I (Type 1) and II (Type 2) deficiency, conclusive of aldosterone synthase deficiency (ASD) (primary hypoaldosteronism). 18-hydroxycorticosterone levels would have differentiated these subtypes, but they were unavailable. Parents were counseled regarding risk of recurrence and the need for antenatal diagnosis in future. At last follow-up, at 3½ months of age, child was on fludrocortisone and sodium supplements, with good weight gain (5.4 kg), and normal serum electrolytes (Na-131 mEq/L and K-5.1 mEq/L).

Excess weight loss with abnormal electrolytes in neonatal period heralds the presence of an underlying life-threatening disorder. Diagnostic approach primarily rests on ruling out congenital adrenal hyperplasia due to 21-hydroxylase deficiency; while X-linked adrenal hypoplasia congenita, ASD and aldosterone resistance (pseudohypoaldosteronism, PHA) are the other less common causes [1,2]. A normal 17-hydroxy progesterone rules out 21-hydroxylase deficiency and normal cortisol and response to ACTH stimulation rules out adrenal hypoplasia. Normoglycemia, stable hemodynamics, and abnormality in electrolytes, acid-base balance, and weight points

to an exclusive aldosterone pathway defect. Disorders of aldosterone pathway, namely, ASD and PHA can be differentiated by aldosterone levels [3]. A decreased/ inappropriately low levels of aldosterone clinches the diagnosis of ASD [4]. The presence of low/near normal aldosterone levels favors the diagnosis of ASD type 2 [5,6]. While most common mutations are missense and nonsense, we noted a deletion in the index case. This mutation was not noted in about 1,670 variants described MGeND database and 942 variants described in gnomAD database. ASD type 2 is an autosomal recessive condition and this is the first report of a heterozygous mutation resulting in ASD type 2. The child requires lifelong mineralocorticoid replacement and continued monitoring of electrolytes and growth.

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Expanding the Neuroradiological Phenotype of 18q Deletion Syndrome

Central nervous system (CNS) abnormalities characterize several rare genetic diseases and syndromes. Case reports on rare conditions, and their uncommon findings can help to delineate their clinical phenotypes. Deletions of the long arm of chromosome 18 (18q-) (MIM 601808), occur in 1/40,000 liveborn infants [1]. The phenotype is variable, characterized by facial dysmorphisms, short stature, foot and hands deformities, congenital aural atresia (CAA), variable intellectual disability (ID), microcephaly and cerebral white matter (WM) abnormalities [1,2]. Kidney malformations, bone dysplasia, congenital heart disease, and IgA deficiency are less common [1]. Autoimmune diseases have been associated to 18q- [1].

We report a 10-years-old girl carrying an 18q22'!qter heterozygous deletion and showing dysmorphic features, juvenile idiopathic arthritis (JIA), autoimmune thyroiditis and IgA deficiency. She also developed hydrocephalus due to stenosis of aqueduct of Silvius, suggesting this might represent an expansion of the spectrum of the CNS abnormalities in 18q-syndrome.

The patient was born at term, with normal weight and length. She received percutaneous pulmonary valvuloplasty at one year for a pulmonic stenosis and has also got an interventricular septum defect.

She came to our observation at 10 years, for unsteady gait. Her height, weight and cranial circumference were normal (138.3 cm, -0.14 SD; 38 kg, +0.97 SD; 52.5 cm, +0.5 SD, respectively). Physical examination revealed: heart murmur, arthritis of the left knee, horizontal nystagmus, dysmetria at the finger-to-nose test, hyporeflexia, and unstable gait. Romberg test was negative. Psychomotor and cognitive development were normal. No data on previous cranial circumference measurements were available. Patient's parents reported unsteady gait from the very first steps. Nystagmus has always been complained as well.

Blood tests revealed increase in C-reactive protein and erythrocyte sedimentation rate, antinuclear antibody was positive with a titer of 1:640. IgA deficiency and increased thyroglobulin antibody levels, with normal thyroid hormones were also detected. JIA, autoimmune thyroiditis and IgA deficiency were diagnosed [2]. Ophthalmological evaluation revealed neither uveitis, nor coloboma. Dysmorphic features, hands and feet abnormalities were noted (**Web Fig. 1 J-O**), array CGH analysis was performed (ISCAv2 8x60K, Agilent Technologies) revealing a *de novo* heterozygous 18q22'!qter deletion of about 13.3 Mb (**Web Fig. 1P**). The brain magnetic resonance imaging (MRI) showed supra and infratentorial dismyelination of white matter, and a segmental stenosis at the third distal part of the aqueduct of Sylvius with secondary enlargement of the third and lateral ventricles (**Web Fig. 1A-H**). Follow-up brain MRI showed worsening of ventriculomegaly and subependymal transudation (**Web Fig. 1I**), so she received a successful endoscopic ventriculocisternostomy at 11 years.

Monosomy 18q is a well-recognized chromosomal abnormality comprising deletions ranging from 18q21.2, 18q21.3 to 18q22.2'!qter, that can be associated with autoimmune disease and neuroradiological findings [1,2]. We report a 18q22.2'!qter deletion in a patient presenting with rheumatological and neurosurgical issues.

Feenstra, et al. [3] defined the critical regions for