Coexistence of Neonatal Bartter Syndrome and Congenital Cutis Laxa, in which a new mutation in SLC12A1 was identified

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ABSTRACT

Objective: Neonatal Bartter Syndrome (NBS) is an extremely rare congenital chronic renal tubular transport disorder characterized by preterm birth, polyhydramnios, polyuria, salt wasting, and severe dehydration. Congenital Cutis Laxa (CCL) is a rare disease characterized by the loss of skin flexibility, laxity, and an atypical facial appearance.

Case: A 1290-gram female baby born at 30+6 weeks of gestation was hospitalized due to premature birth and respiratory distress. During the physical examination, an atypical facial appearance, forehead wrinkles, skin laxity, philtrum, a small chin, and arachnodactyly in the fingers and toes were observed. The patient displayed metabolic alkalosis in her blood gases. Due to the patient’s atypical facial features and current symptoms, exome sequencing was conducted for genetic diagnosis. Genetic analysis revealed the presence of a homozygous NM_001184832.2:c.2485+5G>A (rs749269268) mutation in SLC12A1, leading to the diagnosis of NBS Type 1. Additionally, a novel heterozygous NM_000501.4:c.352G>T, p.Val118Phe (rs781922544) variant was detected in ELN, leading to the diagnosis of CCL syndrome with autosomal dominant inheritance.

Conclusions: The rare coexistence of NBS and CCL syndrome in our patient appears to be coincidental. Given that this is the first reported case in the literature, we believe it is important to present this case.

Keywords: Neonatal Bartter Syndrome, Congenital Cutis Laxa

INTRODUCTION

Bartter syndrome is an autosomal recessive condition characterized by normal blood pressure despite the presence of hypokalemia, metabolic alkalosis, and hyperreninemic hyperaldosteronism. Neonatal Bartter Syndrome (NBS) is an exceptionally rare congenital renal tubular transport disorder, typically associated with preterm birth, elevated amniotic fluid chloride levels, polyhydramnios, polyuria, salt wasting, and severe dehydration. Hypercalcuiuria and nephrocalcinosis may also manifest (1,2). On the other hand, Congenital Cutis Laxa (CCL) is a rare disorder marked by the loss of skin flexibility and laxity, hyperelastic joints, keratocnosis, inguinal hernia, and atypical facial characteristics. This condition presents in autosomal recessive, autosomal dominant, and X-linked recessive forms, with mutations in ELN, FBLN5, and ALDH18A1 seen in the autosomal dominant variety (3,4).
CASE

A 1290-gram female baby was delivered via cesarean section at 30+6 weeks of gestation. The mother, an 18-year-old in her second pregnancy, and the father, who were first-degree cousins, had a history of polyhydramnios during the prenatal period, but their first child was healthy. During the physical examination, the baby displayed an atypical facial appearance, forehead wrinkles, skin laxity, and a prominent philtrum. Additionally, the baby had a small chin and arachnodactyly in the fingers and toes (see Figure 1).

Clinical Presentation: The patient required mechanical ventilation and developed polyuria and dehydration during the second postnatal week. Despite maintaining normal blood pressure, the patient exhibited abnormal levels in her biochemical profile: magnesium (1.9 mg/dL), calcium (9.5 mg/dL), and phosphorus (6.1 mg/dL) were within normal limits, but serum potassium (2.6 mEq/L), sodium (125 mEq/L), and chloride (78 mEq/L) were notably low. Blood gas analysis revealed metabolic alkalosis (pH: 7.49, pCO2: 37 mmHg, HCO3: 28 mmol/L, BE: -1.3 mmol/L). Elevated levels of urea (66 mg/dL) and creatinine (1.6 mg/dL) were also observed. The patient received appropriate fluid and electrolyte management.

Abdominal ultrasonography did not reveal nephrocalcinosis, and eye examination results were unremarkable.

Laboratory Findings: The patient's aldosterone (2236 pg/mL) and renin (95 ng/mL/h) levels were elevated, consistent with Bartter syndrome.

Genetic Diagnosis: Due to the patient's atypical facial features and clinical presentation, exome sequencing was conducted for genetic diagnosis. The analysis identified a homozygous NM_001184832.2:c.2485+5G>A (rs749269268) mutation in SLC12A1, confirming a diagnosis of NBS Type 1.

Additionally, a novel heterozygous NM_000501.4:c.352G>T, p.Val118Phe (rs781922544) variant was found in ELN, leading to the diagnosis of CCL syndrome with autosomal dominant inheritance.

Outcome: Regrettably, the patient passed away at 18 days of age due to late neonatal sepsis. The family has since initiated genetic counseling and follow-up.
DISCUSSION

Bartter syndrome is the result of gene mutations occurring in the tubular epithelial cells within the ascending limb of the loop of Henle. Neonatal Bartter Syndrome (NBS) is primarily caused by impaired salt absorption due to mutations in the Na-K-2Cl cotransporter or potassium channels within the thick ascending arm of the loop of Henle. NBS is most commonly classified as type I or type II (associated with mutations in the SLC12A1 and KCNJ1 genes, respectively) (5). Volume loss due to salt and chloride depletion stimulates the renin-angiotensin-aldosterone (RAA) system. Consequently, elevated aldosterone levels cause serum sodium to rise while potassium levels drop. Hypokalemia prompts prostaglandin synthesis, reigniting the RAA axis. Surprisingly, despite elevated levels of renin, aldosterone, and prostaglandin, blood pressure often remains lower than expected. Nephrocalcinosis and growth retardation are common manifestations, although renal failure and tubulointerstitial nephritis are rare occurrences (6).

Our patient, displaying symptoms of hypokalemia, hyponatremia, metabolic alkalosis, and normal magnesium levels, underwent genetic investigation based on the suspicion of NBS. Sequencing analysis of the SLC12A1 gene revealed a previously unidentified mutation, leading to a diagnosis of Type I NBS.

Congenital Cutis Laxa is a rare disorder of elastic tissue, with potential complications such as heart valve insufficiency, hernias, and emphysema. It is characterized by skin laxity and thickening. Cutis laxa can also manifest in adulthood, often as a reaction to specific medications. It presents in autosomal recessive, dominant, and X-linked forms. Approximately 30% of patients with autosomal dominant inheritance exhibit de novo mutations without a family history. These cases typically present with skin-related symptoms from birth (7,8).

An investigation into elastic tissue dysfunction was conducted due to these findings. Exome sequencing analysis identified a unique heterozygous NM_000501.4:c.352G>T, p.Val118Phe (rs781922544) variation in the autosomal dominant ELN gene, leading to a diagnosis of CCL.

CONCLUSION

Infants presenting with polyhydramnios, a history of preterm birth, and hypokalemic hypochloremic metabolic alkalosis should be evaluated for the exceedingly rare NBS. If symptoms include skin laxity, loss of elasticity, and an atypical facial appearance, further testing for CCL syndrome is warranted. The co-occurrence of NBS and CCL syndrome in our patient is considered an unusual coincidence. Given that this is the first reported case in the literature, we find it important to present this case.

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Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.
REFERENCES


