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Case Report

Pseudo hypoaldosteronism type 1B due to novel deletion mutation in SCNN1A gene

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ABSTRACT

Pseudo hypoaldosteronism type 1B (PHA1B) is a systemic form of salt wasting. Children present after the first week of life with typical symptoms of an adrenal crisis. PHA1B is caused by autosomal recessive homozygous mutations in genes encoding epithelial sodium channels (ENaC) subunits α, β and γ. ENaC are widespread and present in renal tubules, airways, colon, sweat and salivary glands. Electrolyte imbalance is significant with severe hyponatremia, hyperkalemia and metabolic acidosis. In early life until approximately one year of age electrolytes remain unstable despite active management but then gradually improve. The mainstay of treatment is high dose salt replacement, sodium bicarbonate and sodium polystyrene therapy. The adequate treatment and monitoring can result in normal physical and psychomotor development. We present a case of PHA1B with severe intractable electrolyte imbalances in neonatal period. The genetic sequence revealed a novel homozygous deletion mutation in exon 4 of the SCNN1A gene (c.942delC, p.N315Tfs*16).

Keywords: Epithelial sodium channels, Hyperkalemia, Hyponatremia, Metabolic acidosis**,** Pseudo hypoaldosteronism type 1B, SCNN1A gene

INTRODUCTION

Pseudo hypoaldosteronism type 1 (PHA1) is a rare disease presents in the early neonatal period with severe electrolyte imbalance and failure to thrive. Children present with vomiting and weight loss; life threatening hyponatremia, hyperkalemia and metabolic acidosis. The most common consideration is congenital adrenal hyperplasia. Serum aldosterone and renin levels are significantly high in these patients and they do not respond to mineralocorticoid treatment. Cheek and Perry described the first case of PHA1 in 1958.[1]

There are two clinical forms of Pseudo hypoaldosteronism type 1; the renal form (PHA1A) and systemic form (PHA1B). Renal form (OMIM # 177735) is caused by an autosomal dominant mutation in the NR3C2 gene encoding the mineralocorticoid receptor (MR) PHA1A manifests as end organ resistance for mineralocorticoid in renal tubules causing urinary sodium losses.[2] The clinical picture is mild and they respond to sodium supplementation which maintains a normal sodium and potassium. Sodium supplementation is not required after three years of age in the majority of cases as mature renal tubules compensate for renal losses. The systemic form of pseudo hypoaldosteronism (OMIM # 264350) is the most severe type, presents in early neonatal life with intractable electrolyte imbalance and requires lifelong sodium supplementation. PHA1B is caused by an autosomal recessive mutation in one of the

genes encoding the epithelial sodium channel (ENaC) subunits. ENaC has three subunits α, β and γ encoded by SCNN1A, SCNN1B and SCNN1G genes respectively. Sodium losses in PHA1B are not limited to the renal tubules but also from sweat glands, salivary glands and colon. There are cutaneous and pulmonary phenotypes associated with PHA1B.[3]

The children with PHA1B are difficult to manage, especially during the early presentation. They are at risk of neurological and cardiac complications due to severe electrolyte imbalances. Hyponatremia requires high dose salt intake either orally or by intravenous fluids. The hyperkalemia is treated by correcting the metabolic acidosis, ion exchange resins, glucose-insulin infusion or occasionally peritoneal dialysis. They require meticulous monitoring of electrolytes and often have prolonged hospital stays to avoid clinical complications.[4] Authors present a case of pseudo hypoaldosteronism type 1B with a novel homozygous deletion mutation in exon 4 of the SCNN1A gene (c.942delC, p.N315Tfs*16). The management for electrolyte imbalance was very challenging in the neonatal period. The purpose of writing this case is to report the novel mutation of SCNN1A gene and highlight several important pitfalls of clinical management.

CASE REPORT

An eight-day old female baby was brought to the emergency department with vomiting and dehydration. She was born at full term following normal vaginal delivery. Her birth weight was 3.1 kilograms (38thpercentile; -0.3 SDS). Her parents are first degree cousins and she have one healthy female sibling. She was severely dehydrated at presentation with a weight of 2.62 kilograms. She had normal external genitalia. Initial blood tests showed sodium123 mmol/L (135-147); potassium 11 mmol/L (3.5-5.0) and bicarbonate12 mmol/L (22-31). She was given a high dose of intravenous hydrocortisone as the diagnosis of congenital adrenal hyperplasia was suspected. The hyperkalemia was aggressively treated with intravenous normal saline, sodium bicarbonate, calcium gluconate, salbutamol nebulizers, dextrose-insulin infusion and rectal sodium polystyrene.

Investigations

The biochemical profile showed Cortisol 1115 nmol/L (sample drawn before hydrocortisone dose); 17-hydroxyprogesterone 3.6 nmol/L(< 19.1); ACTH 7ng/L (5-60); and aldosterone 527 ng/dl (6.5-86); serum renin activity 25.6 ng/ml/hr (0.1-3.1). Abdominal ultrasound showed normal adrenal glands.

Molecular studies

After obtaining an Institutional Review Board approval and informed consent, genomic DNA from peripheral blood leucocytes was isolated using the Gentra Blood Kit (Qiagen Corp, Valencia, CA, USA) according to the manufacturer's instructions. The Twelve coding exons and the exon-intron boundaries of the SCNN1A gene were amplified by polymerase chain reaction (PCR) using primers and PCR conditions as previously described.[5] Successful amplification was confirmed on a 2% agarose gel. Each successfully amplified amplicons were directly sequenced in forward and reverse directions using a Big-Dye Terminator V3Æ1 Cycle Sequencing kit (Applied Biosystems, Lincoln, CA, USA). The sequence revealed a novel homozygous deletion mutation in exon 4 of the SCNN1A gene (c.942delC, p.N315Tfs*16). This mutation results from deletion of Cytosine at nucleotide 942 (reference sequence NM_001038.5) leading change of the codon from CAA to AAC with frameshift and subsequent change of the amino acid sequence and creation of stop codon and truncation 16 amino acids downstream of the mutation codon (Figure 1).

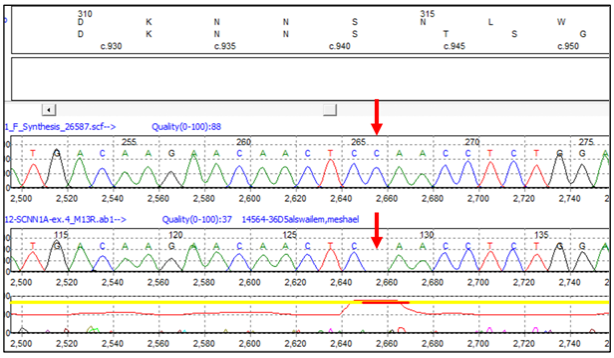

Figure 1: A chromatogram of exon 4 of the SCNN1A gene showing a deletion at nucleotide 942 (c.del942C). The upper panel shows normal reference sequence and the lower panel shows the site of deletion (arrows). This deletion leads to frameshift with subsequent change in the sequence and truncation 16 amino acids downstream of the mutation site (p.N315Tfs*16).

Management

The clinical course in the hospital was turbulent with extreme variations in electrolytes and difficult to achieve balance. Electrolytes were monitored 2-4 times per day. Despite severe hyponatremia and hyperkalemia she did not have any cardiac or neurological event. The electrocardiogram did not show any abnormalities associated with hyperkalemia even when serum potassium was 11 mmol/L. The sodium was replaced by adding salt supplements to her feeds (up to 3 grams per 100 ml) and NaCl 20 mmol four times a day. Hyperkalemia was treated with sodium bicarbonate (to treat metabolic acidosis) and rectal sodium polystyrene up to 5 gram /kg/day in 4-6 doses per day. Large doses of sodium polystyrene caused hypernatremia (up to165 mmol/L). Gradually she was switched to oral sodium polystyrene 2 gram/kg/day in three divided doses. She

was discharged home on oral salt supplements, sodium polystyrene and sodium bicarbonate.

She did not show any dermatological or pulmonary manifestations. She had few admissions in first year of life with electrolytes imbalance but after one year of age her clinical picture became more stable. Currently she is two years old and thriving with normal psychomotor development.

DISCUSSION

Pseudo hypoaldosteronism type 1B is an autosomal recessive condition presenting with an acute adrenal crisis in early neonatal life. Congenital adrenal hyperplasia is the commonest cause of adrenal crisis in this age group but can be excluded by the presence of high cortisol and aldosterone levels and insensitivity to fludrocortisone therapy. The typical clinical manifestations of hyponatremia such as seizures and cardiac arrest secondary to hyperkalemia are not usually seen in these cases. Patients have an insidious and prolonged disturbance in electrolytes and the myocardium tolerates much higher than physiological levels of potassium.[6] Our patient did not have any seizures despite severe hyponatremia and no cardiac events even when the potassium was 11 mmol/L. Some case reports documented cardiac arrest when the potassium was above10 mmol/L; suggesting that the managing medical team should be prepared for any acute event.[4,7]

Systemic PHA1B caused by mutations in ENaC gene also exhibit cutaneous and pulmonary symptoms. The high salt concentration in sweat causes flare up of pustules in the dependent parts of the body before and during salt wasting crisis. Cutaneous lesions signal the impending salt wasting crisis. Eccrine ducts develop inflammation secondary to high salt concentration in sweat presenting with seborrheic dermatitis, folliculitis and miliaria rubra-like lesions.[8]

The amiloride-sensitive epithelial sodium channel (ENaC) is a heterotrimer consisting of three subunits α, β and γ. All subunits have a three-dimensional structure; two transmembrane segments with intracellular N and C-termini and a large extracellular loop.[9] The subunit α is mandatory for channel activity, β and γ subunits are critical for channel expression and cell surface activity. [10] These subunits are encoded by the SCNN1A gene on chromosome 12p13.31, the SCNN1B gene on 16p12.1 and the SCNN1G on chromosome 16p12.1.[5] Mutations in all these genes result in truncated non-functional proteins. Mice with β and γ subunit gene mutation die secondary to severe dehydration and hyperkaliemia and α subunit knockout mice die of respiratory symptoms.[11] The majority of reported mutations are in the SCNN1A gene. Autosomal recessive mutations of the ENaC gene is most severe forms of systemic salt wasting as ENaC are widespread in renal tubules, airway, colon, salivary and sweat glands.

The genetic sequence in this case revealed a novel homozygous deletion mutation in exon 4 of the SCNN1A gene (c.942delC, p.N315Tfs*16). The active management of electrolyte imbalance resulted in normal psychomotor development at the age of 2 years.

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