An infantile case of pseudohypoaldosteronism type 1 (PHA1) caused by a novel mutation of NR3C2

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Introduction

Pseudohypoaldosteronism type 1 (PHA1: OMIM # 177735) is an inherited salt wasting disorder, characterized by hyponatremia and hyperkalemia as a result of renal tubular insensitivity to aldosterone action during infancy (1). Cheek and Perry first reported an infant with PHA1 in 1958 (2). PHA1 has the two forms, namely renal PHA1 with autosomal dominant inheritance, and systemic PHA1 with an autosomal recessive inherited form. Renal PHA1 is caused by loss-of-function mutations in the human nuclear receptor subfamily 3 group C member 2 (NR3C2) gene (3).

Aldosterone plays an important role in regulating sodium reabsorption in the kidney and colon, exerting its action through the mineralocorticoid receptor (MR). Therefore, impairment of MR function leads to an inappropriate sodium loss. Riepe and colleagues have reported that mutations in NR3C2, the transcriptional gene for MR, are responsible for autosomal dominant PHA1 (4). MR functions impaired by NR3C2 mutations provoke salt wasting during early infancy. To the best of our knowledge, several NR3C2 gene mutations have been reported in individuals and families with PHA1, in Japan, as well as in other countries (3–11). Herein, we describe an infantile case of PHA1 due to a novel nonsense mutation.

Case Report

A 2-mo-old boy was referred to our hospital, presenting with unfavorable weight gain. He was born to non-consanguineous Japanese parents at 40 wk of gestational age, after an uneventful pregnancy and delivery. The birth weight was 3,850 g (+1.6 standard deviation (SD)). The newborn mass screening did not detect increased blood 17α-hydroxyprogesterone (data was not shown). Additionally, the child was breastfed. We observed no endocrinological or renal disorders in his family history (Fig. 1A). At referral, he weighed 5,400 g (–1.25 SD), with a height of 60.2 cm (–0.54 SD). He had normal genitalia, with no hyperpigmentation or abdominal mass. Blood examination revealed hyponatremia (serum sodium, 124 mEq/L), mild hyperkalemia (serum potassium, 5.4 mEq/L), and hypoosmosis (259.5 mOsm/kg H2O). Blood urea nitrogen and serum creatinine were 8.5 mg/dL and 0.25 mg/dL, respectively. Serum cortisol was 29.58 µg/dL, and the plasma ACTH level was 15.7 pg/mL. Plasma renin activity was markedly elevated (>20 ng/mL/h), and the plasma aldosterone level was 15,400 pg/mL. Urinalysis demonstrated no bacterial infection in the urinary tract. The fractional excretion of sodium (FENa) was 0.38%. Magnetic resonance imaging of the brain revealed no abnormalities. He was treated with oral sodium administration (sodium chloride (NaCl), 2.5 mEq/kg/day) to alleviate salt wasting. NaCl replacement was increased to 6.1 mEq/kg/, the maximum dose at 11 mo
of age. Subsequently, NaCl administration was tapered with no deterioration in the clinical course. Replacement therapy was discontinued at 25 mo of age.

Regarding developmental milestones, he presented with physical and behavioral developmental delays, capable of lifting and controlling his head at 6 mo. He was able to sit without support at 15 mo, using meaningful words to communicate at 20 mo.

**Mutation Analysis**

We performed genetic analysis on the proband, his parents, and older siblings aged 6 (sister) and 4 (brother) after obtaining written informed consent.Except for the proband, the family members were asymptomatic in terms of PHA1; however, we had no opportunity to perform blood and urine biochemical investigations in the family members. All procedures were reviewed and approved by the Institutional Review Board of Kobe University School of Medicine and were performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. Genomic DNA was isolated from peripheral blood leukocytes of the patient, his parents, and siblings. The inherited PHA1-responsible genes, including \( NR3C2 \), \( SCNN1A \), \( SCNN1B \), and \( SCNN1G \), were screened using next-generation sequencing (NGS) analysis with targeting sequencing. NGS samples were prepared using a HaloPlex Target Enrichment System Kit (Agilent Technologies, Santa Clara, USA) to capture the targeted genes according to the manufacturer’s instructions. Amplified target libraries were sequenced utilizing MiSeq (Illumina, San Diego, USA) and analyzed with SureCall (v.3.0; Agilent Technologies). The detected variant was confirmed by Sanger sequencing. NGS capture and Sanger sequencing confirmed the heterozygous nonsense mutation (c.1633C>T, p.Gln545*) in \( NR3C2 \). We used the Genebank transcript ID (NM_000901 or NM_001166104) as references to evaluate the pathological significance of the mutation.

**Discussion**

In the present case, we detected a novel pathogenic mutation (p.Gln545*) on the \( NR3C2 \) gene. The current mutation has not been documented in open databases, including ClinVar, dbSNP (the latest version, Aug 8, 2019), the genome aggregation database (gnomADv2.1.1), and the Human Gene Mutation Database (HGMD professional 2019.4 released). The \( NR3C2 \) gene is located on chromosome 4p31.1 and composed of 10 exons encoding 984 amino acids of the MR protein. The MR protein structure consists of three distinct domains: the N-terminal transcriptional activation domain, the central DNA-binding domain (DBD), and the C-terminal ligand-binding domain (LBD) (4). In the MR protein, the p.Gln545* position of the amino acid sequence is located in the N-terminal domain. The p.Gln545* mutation predicts a truncated MR protein, indicating a loss-of-
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We postulate that the p.Gln545* mutation of NR3C2 was related to a milder phenotype. In the present case, hyponatremia and hyperkalemia were substantially non-life-threatening to further worsen consciousness and lead to hypovolemic shock. Regarding the severity of the clinical course, the genotype-phenotype correlation in patients with renal PHA1 and the NR3C2 mutation has been not established, although an accumulation of clinical cases is expected with genetic analysis. Interestingly, Hubert et al. (10) have previously reported that a renal PHA1 patient demonstrated life-threatening hyperkalemia instead of NR3C2 mutations, with the disease inherited in a recessive inherited manner; the patient was as an extremely severe case, treated with high-dose NaCl treatment through a nasogastric tube or percutaneous endoscopic gastrostomy. Bowden et al. (11) have described a case with a large NR3C2 deletion (a 130 kb loss, including the range from exon 3 to exon 5) manifesting a severe clinical course, as well as the case reported by Hubert and colleagues. Accordingly, the genotype-phenotype correlation remains controversial in renal PHA1 with NR3C2 mutation.

Notably, the index patient’s mother and sibling, presenting the p.Gln545* mutation, had never experienced any illness regarding PHA1. Additionally, we noted the expressivity of the genetic carriers of the p.Gln545* mutation in the current family. The cause of intrafamilial phenotypic diversity remains unknown. Infection, intercurrent events, and living circumstances could influence disease worsening. However, developmental milestones of the proband were delayed. In patients with PHA1, a long-term prognosis regarding neurological development should be established by including cases with the NR3C2 mutation. Moreover, the previous case reported by Huber et al. demonstrated growth retardation and psychomotor delay (10).

Compared with patients with systemic PHA1, patients with renal PHA1 present a milder phenotype (12). Patients with renal PHA1 require NaCl replacement during early infancy. Generally, salt replacement therapy ceases between 1 to 3 yr of age, demonstrating a good prognosis in renal PHA1 (2, 4). However, PHA1, which results from mutations in the three genes encoding the subunits of the epithelial sodium channel ENaC (SCNN1A, SCNN1B, and SCNN1G), is a clinically severe form with no remission (5, 12, 13). Patients with systemic PHA1 need a larger amount of salt replacement than that required in patients with renal PHA1 (12, 13). Our experience shows that genetic analysis is useful to reach a differential diagnosis between renal PHA1 and systemic PHA1. Moreover, genetic diagnosis is recommended to distinguish treatment and duration of treatment in infants with PHA1.

Conflict of interest: The authors declare that they have no conflict of interest.

References


