Pseudohypoaldosteronism Type II Caused by CUL3 Mutation Presented with Visual Impairment

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To the Editor: Pseudohypoaldosteronism Type II (PHAII), also known as Gordon syndrome, is a rare autosomal disease, caused by mutations in WNK1, WNK4, CUL3, or KLHL3 genes. Hitherto, about 200 individuals and families have been reported with PHAII; of these, 26 were caused by CUL3 mutation.\(^1\(^,\(^2\)\) In pediatrics, hyperkalemia-complicated hypertension is rare, and PHAII should be considered in this condition.

A Chinese boy of unremarkable history presented with ocular lesions and slightly short stature at the age of 5 years. Routine blood and urine tests were normal; however, persistent hyperkalemia was noticed. His parents were healthy and nonconsanguineous, and his younger sister was also healthy. His older brother died of intracranial hemorrhage at the age of 12 years. At the time of referral, the boy’s weight and height were at the 3rd percentile of normal. Furthermore, the blood pressure was normal. Sight test showed hypoplasia with uncorrected visual acuity (UCVA) of 0.4/0.5. Fundus examination showed temporal optic atrophy, and pattern visual-evoked response (PVER) test showed interference in bilateral optic nerve conduction. Imaging investigations displayed negative results of brain, adrenal, kidney, liver, spleen, ureter, and bladder.

During the hospital stay, blood biochemical examination showed normal liver and renal functions but significant hyperkalemia, hyperchloremia, and metabolic acidosis [Table 1]. Moreover, the potassium level was not reduced by hyperhydration and alkalinizing. Before acquiring the data of aldosterone, primary aldosterone deficiency should be excluded as persistent hyperkalemia of the patient. The oral 9α-fluorohydrocortisone (0.2 mg/d) was used in the trial. Although hyperkalemia was inhibited rapidly, the blood pressure of the boy was increased to 140/90 mmHg. Then, we reduced the level of 9α-fluorohydrocortisone (0.1 mg/d), and the blood pressure reduced to 120–130/70–90 mmHg; however, hyperkalemia recurred. The blood pressure and serum potassium could not be normalized synchronously. The seesaw-like relationship between blood pressure and potassium level suggested a potential accumulation of sodium. Moreover, 9α-fluorohydrocortisone facilitated the accumulation of sodium and promoted the blood pressure, which led to the suspected diagnosis of PHAII.

The elevated level of plasma aldosterone (221 pg/ml) further supported our speculation. Subsequently, a panel of genes (WNK4, WNK1, KLHL3, and CUL3) was analyzed, and heterozygous c.1377+1G>T of CUL3, a reported variant, was identified in the patient but not in the parents and sister.

As the inheritance of CUL3 mutation led to a predominant PHAII, penetrance is not clear, and hence, the complicated function of the mutation is verified. Next, we also amplified the 1058-bp segment containing exons 5–10 of CUL3 cDNA; the reverse transcription using mRNA confirmed that exon 9 was skipped, which proved the pathogenicity of the mutation. Thus, PAHII was diagnosed and c.1377+1G>T of CUL3 was the disease-causing mutation in this patient [Figure 1].

After diagnosis, hydrochlorothiazide (0.25 mg kg\(^{-1}\)d\(^{-1}\)) was prescribed, and 9α-fluorohydrocortisone was ceased. The patient did not administer hydrochlorothiazide for a prolonged period due to poor compliance. The level of serum potassium ranged from 5 to 7 mmol/L, and the blood pressure was 110–140/70–90 mmHg. After 2 years, he was rehospitalized for hyperkalemia, metabolic acidosis, and occasional migraine. In addition, the vision was not improved, hyperkalemia was also remarkable, and blood pressure was 130/90 mmHg. Oral hydrochlorothiazide (2 mg kg\(^{-1}\)d\(^{-1}\)) and intravenous sodium bicarbonate were administered immediately. After 4 days of treatment, all abnormal behaviors were inhibited. Then, regular oral hydrochlorothiazide (0.25 mg kg\(^{-1}\)d\(^{-1}\)) was prescribed. The patient is currently 9 years old and has been regularly administering oral hydrochlorothiazide for 2 years. His growth was similar to the other normal children at the same age, while the weight was at the 50th percentile of normal and height was at the 25th percentile of normal. Blood pressure and other laboratory examinations showed normal. His migraine almost disappeared, and vision improved gradually. The latest vision test showed UCVA of 0.6/0.3. Fundus did not show any apparent optic atrophy, while PVER showed left optic nerve block. The clinical characteristics and laboratory data of the patient are summarized in Table 1.

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The ocular lesion was not reported in PAHII patients previously. Our patient had decreased vision and optic atrophy and the ocular symptoms improved after treatment; thus, we speculated a correlation between ocular lesions and PHAII, rendering it as a new symptom of the profile. The effect of Cullin 3 protein in nervous systems is yet unclear. However, the ubiquitin–proteasome system has been proved to play a crucial role in the various aspects of neuronal development, and Cullin 3-KLHL20-E3

Table 1: Clinical characteristics and laboratory data of PHAII patient in this study

| Items                      | First hospitalization (5-year-old) | Second hospitalization (7-year-old) | Thiazide treatment for 2 years (9-year-old) | Normal range |
|----------------------------|------------------------------------|------------------------------------|---------------------------------------------|--------------|
| Weight (kg)                | 15                                 | 20                                 | 31                                          |              |
| Height (cm)                | 104.5                              | 117.0                              | 131.0                                       |              |
| Blood pressure (mmHg)      | 110/70 (before treatment), 140/90   | 130/90                             | 100/65                                      |              |

Clinical symptoms
- Migraine: No, Yes, No
- Physical retardation: Yes, No, No
- Intellectual impairment: No, No, No
- Enamel hypoplasia: No, No, No
- Schizophrenia: No, No, No
- Muscular cramp or weakness: No, No, No
- Sight test: 0.4/0.5, 0.4/0.6, 0.3/0.6

Fundus examination
- Bilateral optic atrophy, Bilateral optic atrophy, No optic atrophy

Blood chemistry
- K (mmol/L): 7.12, 7.18, 3.85
- Na (mmol/L): 135.9, 139.0, 137.5
- Cl (mmol/L): 113.0, 116.0, 99.3
- Venous blood gas analysis:
  - pH: 7.33, 7.31, 7.35–7.45
  - pCO₂ (mmHg): 31, 34, 60–100
  - TCO₂ (mmol/L): 20.1, 18.1, 24.0–32.0
  - BE (mmol/L): –6.0, –9.2, –3.0–3.0

Endocrine test
- Aldosterone (pg/ml): 221.0, 143.0
- Rennin activity (ng·ml⁻¹·h⁻¹): 0.44, 0.45
- ACTH (pg/ml): 22.8, 24.4
- Cortisol (µg/dl): 17.4, 11.4
- Testosterone (µg/dl): 20.0
- 17-hydroxycorticosteroid (ng/ml): 1.97

PHAII: Pseudohypoaldosteronism type II; ACTH: Adrenocorticotropic hormone; BE: Base excess.

Figure 1: RT-PCR of CUL3 mRNA in this patient with pseudohypoaldosteronism Type II. (a) RT-PCR of CUL3 mRNA demonstrated two bands in gel image (1058 bp and 887 bp). (b and c) RT-PCR sequence of the two bands. The smaller band showed skipping of exon 9 and joining exon 8 to exon 10. RT-PCR: Reverse transcription polymerase chain reaction; PT: Patient; WT: Wild type.
ubiquitin ligase complex facilitated neurite outgrowth through a ubiquitin-dependent pathway.\(^3\) Moreover, the constitutive activation of thiazide-sensitive NaCl cotransporter (NCC) in the distal convoluted tubule was confirmed as the pathogenesis of PAHII that could affect the gamma-aminobutyric acid neurotransmitter conduction,\(^4\) which in turn could affect the excitability of neurons, leading to nervous system symptoms. All these studies suggested that PHAII was associated with the nervous system; however, further case accumulation was essential for conclusive findings.

Mostly, serendipitous hyperkalemia and/or hypertension is the primary complaint in PHAII patients.\(^{[1,2]}\) While hypertension is usually presented in adulthood, pediatric patients usually show only hyperkalemia. Early diagnosis is rather difficult in children. In our patient, persistent hyperkalemia was characterized initially. Hyperkalemia is usually induced by renal insufficiency, drugs, tumor cell necrosis, congenital adrenal insufficiency, and aldosterone deficiency. Our patient did not present these issues. Thus, the seesaw-like relationship between blood pressure and potassium level was under intensive focus, which indicated a potential accumulation of sodium in the patient’s body, and 9α-fluorohydrocortisone facilitated the accumulation and escalated the blood pressure. This prompted the diagnosis of PHAII, thereby providing a new diagnostic approach for distinguishing the varieties of hyperkalemia in pediatrics.

After clinical diagnosis of PHAII, \(CUL3\) c.1377+1G>T and reverse transcription confirmed the diagnosis. To date, 23 mutations of \(CUL3\) gene have been reported, of which 17 are responsible for PHAII. All the reported \(CUL3\) mutations causing PHAII are heterozygous and located in intron 8, exon 9, and intron 9. Furthermore, reverse-transcription polymerase chain reaction confirmed that all mutations causing PHAII resulted in skipping of exon 9 during transcription.\(^5\) Here, the mutation c.1377+1G>T is also identified influence splicing of exon 9.

Exon 9 encodes the amino acid fragment 403–459, and this region is related to bric-a-brac tramtrack broad complex and Really Interesting New Gene binding domains of the \(CUL3\) protein. The skipping of exon 9 causes unstable substrate binding, followed by decreased ubiquitination of WNK kinases, and finally overacts NCC, which forms the underlying pathogenesis of PHAII.\(^5\)

In addition, reported cases of \(CUL3\) mutation were likely to present more severe phenotype. They tended to have earlier development of hypertension, more severe hyperkalemia, and more likelihood of growth retardation, whereas the other three types of PHAII often showed hypertension after 18 years.\(^5\) Our patient showed significant hyperkalemia and hypertension at the early age of 5 years, consistent with previous reports.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient’s parents have given their consent for their child’s images and other clinical information to be reported in the journal. The patient’s parents understand that their child’s name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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