Importance of cascade family screening and precision medicine for patients with familial hyperkalaemia: a case report

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Case report

The patient was the only child of a non-consanguineous Chinese couple and was born at full term by normal vaginal delivery with a birth weight of 2.85 kg. She had good past health except for admission for a reflex-anoxic attack at age 7 months. Physical examination at that time was unremarkable with normal growth parameters and normal blood pressure for her age. Investigations showed normal anion gap metabolic acidosis and hyperkalaemia with a potassium of 7.1 mmol/L but normal serum sodium and renal function. In view of the biochemical findings, the provisional diagnosis was type IV renal tubular acidosis. Fludrocortisone was started with sodium bicarbonate and furosemide and a low potassium diet commenced. However, recurrent episodes of hyperkalaemia continued despite good compliance, requiring potassium binder and medication adjustment.

In December 2019, because of the suboptimal control of hyperkalaemia, with a fluctuating potassium level of 4.5 to 6.4 mmol/L, the patient was referred to our unit at age 10 years. Her blood pressure remained normal throughout. Blood test results revealed hyperreninaemic hyperaldosteronism with elevated supine renin at 5.59 ng/mL/hr (reference: 0.15-2.33 ng/mL/hr) and elevated aldosterone at 785 pmol/L (reference: 28-444 pmol/L). Pseudohypoaldosteronism type I was suspected initially.

Trio whole exome sequencing revealed a paternally inherited novel missense change in *WNK4*:NM_032387.5:c.1685A>G:p.(Glu562Gly), confirming a diagnosis of pseudohypoaldosteronism type IIB. This patient was coincidentally part of a larger whole exome sequencing cohort where the study was focused on cost-effectiveness of rapid whole exome sequencing.[1] The patient was treated with oral 25 mg hydrochlorothiazide once daily and remained stable with normal growth and development. The serum potassium and blood pressure were well controlled and there were no dental or renal complications on follow-up examination.

Family cascade screening revealed that her father, paternal grandmother, and paternal aunt had hyperkalaemia. All were subsequently confirmed to have the same mutation (Fig 1). Retrospectively, the father had provided a history of kidney stone, hyperkalaemia, hypercalciuria and hypertension since age 35 years. He was found to have a serum potassium level of 7 mmol/L during the cascade screening. Although asymptomatic, his electrocardiogram already showed hyperkalaemic changes with tented T waves and high blood pressure at 176/116 mmHg. He was started on hydrochlorothiazide with normalisation of both serum potassium and blood pressure a few days later. The paternal grandmother also had a history of hyperkalaemia and partially controlled hypertension. The paternal aunt was asymptomatic with good past health but was found to be hypertensive and hyperkalaemic on screening. They were also started on hydrochlorothiazide with good response.

Discussion

We report a Chinese family with the rare cause of hyperkalaemia and type IV renal tubular acidosis due to an autosomal dominant condition called Pseudohypoaldosteronism type II (PHAII). Whole exome sequencing established the diagnosis in our index patient, and subsequently, other affected family members were identified through cascade family screening.

Pseudohypoaldosteronism type II, also referred to as familial hyperkalaemic hypertension, or Gordon's syndrome, was first described in 1964.[2] By 2013, around 100 to 200 individuals and families with PHAII had been reported.[3] Hyperkalaemia with normal renal function is the main characteristic. Other common features include metabolic

acidosis, diminished renal potassium excretion, hypercalciuria, low plasma renin/aldosterone levels and hypertension. Short stature and dental abnormalities have also been reported.[4]

Mutation in the gene encoding with-no-lysine kinase 4 (*WNK4*), one of the novel proteins involved in the pathogenesis of PHAII, was identified in our patient. Other identified genes include *WNK1*, kelch-like 3 and cullin 3.[3] The *WNK4* is one of the *WNK* isoforms that regulates sodium-chloride co-transporter (NCC) in the distal convoluted tubule. Without the inhibitory effect of normal *WNK4*, sodium and chloride reabsorption are increased via the NCC, leading to volume expansion and consequent hypertension. The NCC is more proximal to the epithelial sodium channel at the distal convoluted tubule. Excessive sodium reabsorption at NCC results in reduced sodium delivery to epithelial sodium channels for potassium secretion at Na^+/K^+ exchange.[3] This theory explains why thiazide is effective in PHAII as it inhibits NCC. Increased intracellular sodium due to increased NCC activity will cause decreased basolateral Na^+/Ca^{2+} exchange that may result in hypercalciuria as in the father of our index patient. It has been suggested that mutant *WNK4* decreases the activity of renal outer medullary potassium channels more than wild-type *WNK4*. Another proposed mechanism of this Chloride Shunt Syndrome is increased chloride reabsorption through paracellular pathways due to the mutant *WNK4*, resulting in reduced negativity at the distal epithelial sodium channel.[3] These can all lead to reduced urinary potassium excretion (Fig 2) with consequent increase in serum potassium. With increased potassium retention, the excretion of hydrogen is impaired leading to metabolic acidosis. Hypertension tends to appear later in life, in men aged 30-40 years and in women aged 40-50 years,[5] but can also be absent in 20% of cases.[3]

In this patient, pseudohypoaldosteronism type I was initially suspected in view of the grossly elevated renin and aldosterone levels. However, the age of disease onset and normal sodium level were atypical. The elevated renin and aldosterone levels in our patient could be explained by the use of furosemide that could have resulted in hypovolaemia and thus activation of the renin-angiotensin-aldosterone-system. This made the interpretation of the biochemical picture challenging. In this regard, the use of genetic testing demonstrated superiority in guiding the diagnosis of these chronic conditions in which a classic clinical phenotype had already been modified by existing treatments.

Our case also highlights the importance of cascade family screening. The three family members were identified to have potentially life-threatening hyperkalaemia and were treated promptly based on their genetic mutation. Affected patients will

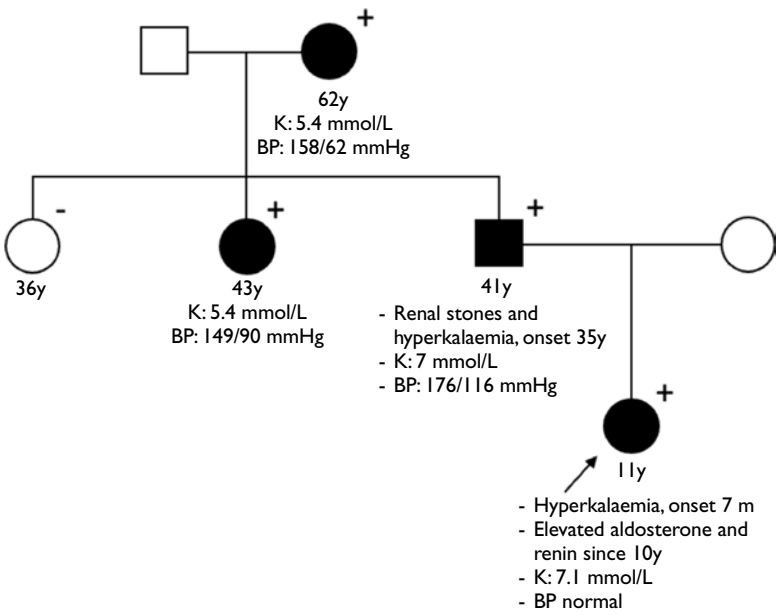

FIG 1. Pedigree of the family affected with Gordon's syndrome*

Abbreviations: +: *WNK4*:NM_032387.5:c.1685A>G:p.(Glu562Gly) was detected in the individual; -: *WNK4*:NM_032387.5:c.1685A>G:p.(Glu562Gly) was not detected in the individual; BP = baseline blood pressure; K: baseline serum potassium level; *WNK4* = with-no-lysine kinase 4

* K and BP were measured before initiation of hydrochlorothiazide

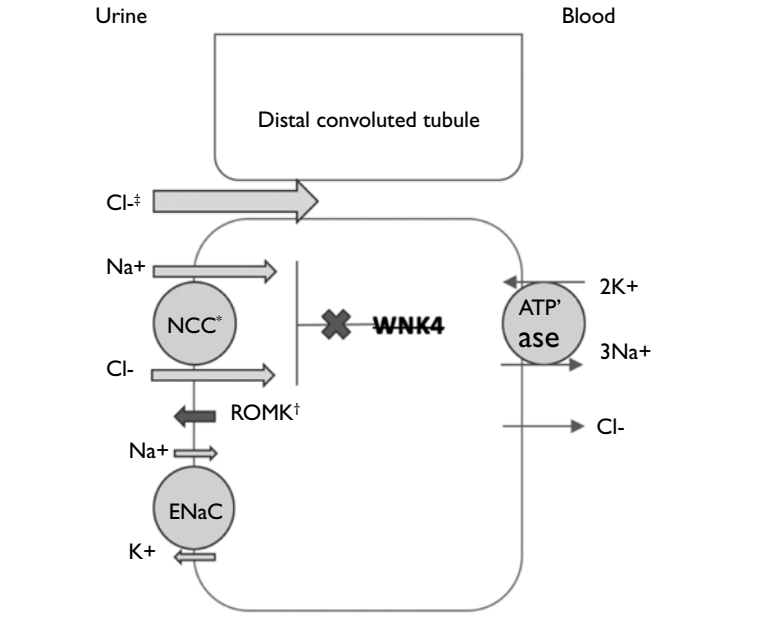

FIG 2. Proposed mechanisms of hyperkalaemia in pseudohypoaldosteronism type II

* Mutated with-no-lysine kinase 4 (*WNK4*) cannot exhibit normal inhibitory action on sodium-chloride co-transporter (NCC). Therefore, there would be increased sodium absorption via NCC. The NCC locates more proximal to epithelial sodium channel (ENaC). As a result, less sodium is delivered to ENaC for potassium secretion

† In addition, the decreased activity of renal outer medullary potassium contributes to hyperkalaemia due to reduced potassium excretion

‡ Also, there is increased chloride reabsorption via the paracellular pathway. Less negativity at ENaC will lead to less potassium excretion

continue regular follow-up with serum electrolyte and blood pressure monitoring. With specific treatment, the disease can be well-controlled. This case illustrates the importance of precision medicine, as well as its benefits of personalised and targeted interventions.

Author contributions

Concept or design: HY Lam, ALT Ma.
Acquisition of data: YH Chan, ALT Ma
Analysis or interpretation of data: All authors.
Drafting of the manuscript: HY Lam, EYH Chan.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The father of the patient consented verbally to publication of this case report.

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Answers to CME Programme
Hong Kong Medical Journal August 2022 issue

Hong Kong Med J 2022;28:285–93

I. Stillbirth rate in singleton pregnancies: a 20-year retrospective study from a public obstetric unit in Hong Kong

A	1. True	2. True	3. False	4. False	5. False
B	1. False	2. False	3. True	4. True	5. True

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II. Airway management in children with COVID-19

A	1. False	2. True	3. True	4. False	5. False
B	1. False	2. False	3. True	4. True	5. False