Hypokalaemic hypertension and 17-alpha-hydroxylase/17,20-lyase deficiency in a young girl: a case report

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Case presentation

A young girl aged 9 years 6 months was admitted to hospital in July 2022 with coronavirus disease 2019 infection and found to have refractory hypokalaemia. She reported good past health and denied taking any supplements or medications. Her nonconsanguineous parents and 4-year-old younger brother were healthy and family history was unremarkable.

Her body weight and height were 35.8 kg at the 75th to 95th percentile and 140 cm at the 75th percentile, respectively. Her body mass index was 18.3 kg/m² at the 75th percentile. Blood pressure was noted to be persistently high up to 152/117 mm Hg (112/73 mm Hg being the 90th percentile for her gender, age and height according to the American Academy of Pediatrics1). Cardiovascular and abdominal examinations were unremarkable. There was no hyperpigmentation or sign of virilisation. She was prepubertal, with normal female external genitalia.

Ambulatory blood pressure monitoring confirmed stage 2 hypertension. Electrolytes and hormone profile are summarised in the Table. Her bone age was 8 years 10 months according to the Greulich and Pyle method of assessment. A standard-dose Synacthen test did not stimulate a rise in 17-hydroxyprogesterone or cortisol level. Ultrasound of the pelvis revealed prepubertal uterus and bilateral ovaries. Her karyotype was 46,XX. Urine steroid profile showed a characteristic pattern compatible with 17-alpha-hydroxylase/17,20-lyase deficiency (17OHD), with a lack of androgen metabolites and an excess of progesterone, pregnenolone, and corticosterone metabolites (online supplementary Appendix).

Oral hydrocortisone was commenced at 7.6 mg/m²/day. Blood pressure improved to 119/81 mm Hg after 2 weeks. Spironolactone was added for better control.

Genetic analysis revealed compound heterozygous pathogenic variants in the CYP17A1 gene: c.297+2T>C in intron 1 and c.849delC p.(Ser284Glnfs*13) in exon 5, which confirmed the diagnosis of 17OHD. Parental testing confirmed that the two CYP17A1 variants were in trans, and the younger brother was a carrier.

Discussion

17-alpha-hydroxylase/17,20-lyase deficiency is a rare type of congenital adrenal hyperplasia that accounts for 1% of cases with an estimated incidence of 1 in 50,000 to 100,000.2 17-alpha-hydroxylase and 17,20-lyase enzyme defects result in cortisol and sex hormone deficiency, with compensatory rise in adrenocorticotropic hormone that drives excessive production of 11-deoxycorticosterone and corticosterone (Fig).3 Unlike the pathophysiology of the more common types of congenital adrenal hyperplasia such as 21-hydroxylase deficiency and 11-beta-hydroxylase deficiency, 17OHD does not cause excessive testosterone production with consequent virilisation in affected 46,XX females or precocious puberty in both sexes.3 Instead, due to the lack of sex steroid hormone production, it results in undervirilisation in 46,XY males and sexual infantilism in 46,XX females.3 The excessive accumulation of deoxycorticosterone and corticosterone exerts potent mineralocorticoid effects, resulting in sodium and fluid retention, hence suppression of renin with hypokalaemic hypertension,2 as in our patient. A high concentration of corticosterone provides sufficient glucocorticoid effect to prevent adrenal crisis.3 The classic presentation of 17OHD is a phenotypic female with delayed puberty, primary amenorrhoea, and hypokalaemic hypertension with diagnosis often made in young adulthood.3,4,5 Cases of retained partial enzyme activity resulting in ambiguous genitalia in 46,XY males have been reported.3,4 Delayed diagnosis of 17OHD is not uncommon.
due to its subtle and late presentation. Hypokalaemic hypertension should prompt a clinician to search for secondary causes of hypertension. Plasma renin activity is an important investigation to differentiate the causes, and would be suppressed in 17OHD by the potent mineralocorticoid activity, and is high in renovascular disease. On the contrary, aldosterone level could be suppressed, normal or raised in 17OHD. Low aldosterone level arises as a result of a suppressed renin angiotensin system while high level might be related to more severe enzyme defects resulting in greater production of end
product from aldosterone precursors. As 17OHD has a characteristic pattern of metabolite excretion and metabolite ratios on urine steroid profiling, this profiling is an important investigation when diagnosing the condition.

There is no consensus guideline on the management of 17OHD. The mainstay of treatment is glucocorticoid and sex hormone replacement. The use of glucocorticoid would decrease the adrenocorticotropic hormone drive and production of deoxycorticosterone and corticosterone, which would facilitate improved blood pressure control and electrolyte balance. Different forms and dosages of glucocorticoid replacement have been described in the literature, ranging from dexamethasone 0.25 mg to 1 mg daily, or equivalent. In some cases, an antihypertensive agent with a mineralocorticoid antagonist effect such as spironolactone or eplerenone may be required for blood pressure control. Patients may develop end organ damage such as hypertensive retinopathy if blood pressure control is suboptimal. Deoxycorticosterone and corticosterone levels might not be normalised despite treatment. Blood pressure control, electrolyte balance, and renin level are more important markers of disease control.

Our patient was phenotypically female, in line with her genotypic sex. Her hormone blood test revealed hypergonadotropic hypogonadism due to lack of sex hormone production. Oestrogen and progestin replacement should be commenced at an appropriate time during adolescence, or upon diagnosis in adulthood, to induce secondary sexual characteristics and cyclic uterine bleeding. Sex steroid replacement therapy may improve bone mineral density in 17OHD patients and prevent osteoporosis. For genotypic males, psychological assessment should determine gender preference prior to initiation of sex hormone replacement, and intraabdominal tests should be removed to prevent malignant change. A multidisciplinary team approach involving an endocrinologist, surgeon, psychiatrist, psychologist and social worker is essential and can help in parental counselling, achieving family consensus for gender assignment, and formulation of an individualised plan for each patient.

Genetic test on CYP17A1 is important to make the diagnosis of 17OHD. To date, the Human Gene Mutation Database has reported >100 different types of mutations on the CYP17A1 gene. Genetic analysis showed compound heterozygous pathogenic variants in the CYP17A1 gene (reference transcript: NM_000102.4): c.297+2T>C in intron 1 and c.849delC p.(Ser284GlnfsX13) in exon 5. c.297+2T>C is a splice site variant that has been previously described in patients with 17OHD (ClinVar accession No.: VCV000431980), while c.849delC is a truncating variant that creates a premature termination codon. It is expected to result in an absent or disrupted protein product (ClinVar accession No.: VCV00147343). This variant has an extremely low minor allele frequency in the general population and has not been reported in patients with CYP17A1-related disease.

17-alcohol hydroxylase/17,20-lyase deficiency is associated with infertility due to premature follicular arrest and poor endometrial development for implantation. Women with 17OHD have difficulty conceiving, even with the help of assisted reproductive technology. Though not promising, fertility had been possible for patients with partial 17OHD. Patients should be counselled about potential fertility difficulties and referred to an assisted reproductive service when appropriate.

To conclude, 17OHD should be considered in a young hypertensive individual with hypokalaemia. Timely management with glucocorticoid and sex hormone replacement can ameliorate the morbidity of hypertension and hypogonadism. Multidisciplinary collaboration is advised, especially for patients with gender identification or infertility issues.

Author contributions
All authors contributed to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. 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.

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Ethics approval
The patient was treated in accordance with the Declaration of Helsinki. The parents of the patient provided written consent for publication of this case report.

Supplementary material
The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine or the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2210635).
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