

17-hydroxylase/17,20-lyase deficiency due to a R96Q mutation causing hypertension and poor breast development

Asma Deeb, Hana Al Suwaidi, Salima Attia and Ahlam Al Ameri

Paediatric Endocrinology Department, Mafraq Hospital, Abu Dhabi, UAE

Correspondence
should be addressed
to A Deeb
Email
Adeeb@mafraqhospital.ae

Summary

Combined 17 α -hydroxylase/17,20-lyase deficiency is a rare cause of congenital adrenal hyperplasia and hypogonadism. Hypertension and hypokalemia are essential presenting features. We report an Arab family with four affected XX siblings. The eldest presented with abdominal pain and was diagnosed with a retroperitoneal malignant mixed germ cell tumour. She was hypertensive and hypogonadal. One sibling presented with headache due to hypertension while the other two siblings were diagnosed with hypertension on a routine school check. A homozygous R96Q missense mutation in P450c17 was detected in the index case who had primary amenorrhea and lack of secondary sexual characters at 17 years. The middle two siblings were identical twins and had no secondary sexual characters at the age of 14. All siblings had hypokalemia, very low level of adrenal androgens, high ACTH and high levels of aldosterone substrates. Treatment was commenced with steroid replacement and puberty induction with estradiol. The index case had surgical tumor resection and chemotherapy. All siblings required antihypertensive treatment and the oldest remained on two antihypertensive medications 12 years after diagnosis. Her breast development remained poor despite adequate hormonal replacement. Combined 17 α -hydroxylase/17,20-lyase deficiency is a rare condition but might be underdiagnosed. It should be considered in young patients presenting with hypertension, particularly if there is a family history of consanguinity and with more than one affected sibling. Antihypertensive medication might continue to be required despite adequate steroid replacement. Breast development may remain poor in mutations causing complete form of the disease.

Learning points:

- Endocrine hypertension due to rarer forms of CAH should be considered in children and adolescents, particularly if more than one sibling is affected and in the presence of consanguinity.
- 17 α -hydroxylase/17,20-lyase deficiency is a rare form of CAH but might be underdiagnosed.
- Blood pressure measurement should be carried out in all females presenting with hypogonadism.
- Anti-hypertensive medications might be required despite adequate steroid replacement.
- Initial presenting features might vary within affected members of the same family.
- Adverse breast development might be seen in the complete enzyme deficiency forms of the disease.

Background

Combined 17 α -hydroxylase/17,20-lyase deficiency is a rare autosomal recessive condition that accounts for 1%

of congenital adrenal hyperplasia (1). It is inherited in an autosomal recessive pattern and is caused by loss-of-function mutations in P450c17. It was first described by

Biglieri in 1966 (2) when he reported a patient presenting with features of hypogonadism, hypocortisolism and hypertension.

The gene encoding P450c17 (10q24.3) was cloned in 1987. It encodes eight exons over 6.4 kbDNA (3). Mutation in the gene was first reported in 1988 (4). Since then, various mutations have been described, including single amino acid changes (5). A multicentre study group from Brazil reported seven novel mutations in 19 Brazilian kindred with 17 hydroxylase deficiency. Point mutations were the most common form of genetic defect in this cohort (6). Genotype phenotype correlation was variable amongst different ethnic groups. In a Japanese cohort, the correlation was also well-established as it was in the Chinese population (7). Initial presentation can be variable based on the gene defect. Dhir *et al.* reported two 46 XY patients presenting with hypertension and short stature and another 46,XX patient in whom primary amenorrhea was the initial presenting feature (8).

Data on this rare condition from the Arab world is sparse despite the high consanguinity rate in the region. This might be due to the condition being underdiagnosed, in addition to being rare. The first case described in the region was a 22-year-old Omani patient who was confirmed to have c.287G>A p.Arg96Gln P450c17-homozygous mutation resulting in the complete absence of 17 α -hydroxylase/17/20-lyase activity (9). We describe a family of four affected siblings from the United Arab Emirates in whom age at presentation and presenting features were variable.

Case presentation

The affected patients are four sisters born to first degree related parents (Fig. 1). The index case (patient 1) is an XX female who presented with a malignant mixed germ cell tumour with yolk sac elements. At the age of 17, she had no secondary sexual characters and had primary

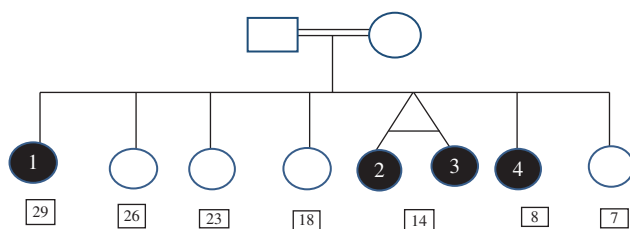


Figure 1
Family tree showing the index case (1) and three affected siblings. Boxes underneath indicate age in years.

amenorrhea. She had palmer pigmentation and her initial blood pressure was 170/96 (5).

Patient 2 is a 14 year old (twin 1) who was referred from school after a routine health check when she was found to have a high blood pressure of 163/117. Clinically, she had no secondary sexual characteristics and normal external female genitalia. Both her height and weight were at the 3rd percentile.

Patient 3 is twin 2 (identical). She presented with a headache for 6 months prior to hospital referral. Her blood pressure on presentation was 155/110. Clinically, she was pre-pubertal with normal growth parameters.

Patient 4 is an 8-year-old girl who was referred from school following a routine health check. Her blood pressure was 153/85 (above 97th percentile for age) but she was asymptomatic. Clinically, she was pre-pubertal and had normal female external genitalia. Her height and weight were at the 50th percentile.

Patients 2, 3 and 4 were diagnosed eight and nine years following the diagnosis of the index case respectively. At the time of the index case diagnosis, no siblings were screened for the genetic mutation, neither were they followed up for blood pressure monitoring. The older siblings, 23 and 26 years, have given birth to children. The 18-year-old sibling entered puberty at 12 and currently has a regular period and the youngest 7 year old is growing normally and has a normal blood pressure.

Investigation

Index case: She was hypokalemic with a serum potassium of 2.5 mmol (NR 4.0 to 4.8) and high gonadotropin levels. Serum aldosterone was high at 643 pmol/l (NR 55 to 250) and plasma renin was undetectable as were her serum dehydroepiandrosterone sulphate, 17 hydroxy progesterone and testosterone. Serum cortisol was decreased at 15 nmol/l at 0900 h with a concurrent ACTH level of 21 mcg/l (NR 3 to 11). Serum α fetoprotein was elevated at 12 714 mU/l. Retroperitoneal mass was diagnosed on computerized axial tomography scanning. Histopathology showed malignant mixed germ cell tumor with yolk sac components. The gonads had the macroscopical appearance of ovaries but were not biopsied. Adrenal ultrasonography showed bilateral adrenal hyperplasia. Mutation analysis revealed a homozygous R96Q missense mutation in P450c17.

Patient 2: Biochemical investigations showed an ACTH of 55.7 mcg/l and potassium of 3.8 mmol. Her testosterone, DHEAS and androstendion were undetectable and her 17 hydroxy progesterone was 1.8 mmol/l

(NR 1.9 to 3.4). Her gonadotropin levels were high for her pubertal status and her karyotype was 46,XX.

Patient 3: Her ACTH was 35 mcg/l and potassium 3.3 mmol/l. Her testosterone, DHEAS, androstenedione and 17 hydroxyprogesterone were undetectable. Karyotype was 46,XX.

Patient 4: ACTH on presentation was 198, potassium 3.3. Her 11 deoxycorticosterone was grossly elevated at 7983 pmol/l (NR 60 to 340) and corticosterone was high at 130 mg/ml (NR 1.4 to 14). Testosterone, DHEAS, Androstenedione and 17 hydroxyprogesterone were undetectable. No response was seen for cortisol or androgens to ACTH stimulation test. Her karyotype was 46,XX. She had a normal kidney ultrasound scan and normal renal artery Doppler.

Clinical presentation and initial investigations for the four siblings are summarized in Table 1.

Treatment

Index case: She had tumor resection and six cycles of bleomycin, etoposide, cisplatin chemotherapy. Remission was achieved and serum fetoprotein reduced from 12 714 to 5 mU/l. She was commenced on prednisolone treatment (2 mg am, 4 mg pm). Puberty was induced with 5 µg ethinyl estradiol daily and increased gradually to 20 µg over 18 months after which Levonorgestrel was added.

Patients 2 and 3: Both girls required antihypertensive medications on presentation in the form of spironolactone at 25 mg orally daily. Hydrocortisone was commenced orally at 12–15 mg/m² per day in three divided doses. Puberty was induced by 5 mcg of ethinylestradiol with a plan to follow the same regime as for the index case.

Patient 4 was started on hydrocortisone replacement at 15 mg/m² per day in three divided doses and Spironolactone 25 mg once daily.

Outcome and follow-up

Index case: She had no recurrence of the tumor for 17 years post-surgery and chemotherapy. Her hypertension remained difficult to control and she needed combined antihypertensive treatment of spironolactone 50 mg and amlodipine 5 mg daily. She has regular withdrawal bleeds on cyclical combined pills and remained compliant of prednisolone. Her breast development is poor and is currently considering breast augmentation.

Patients 2 and 3: Both girls remained on antihypertensive medication (spironolactone 25 mg daily) to

Table 1 Summary of initial clinical and biochemical findings in the four siblings.

Index case	Presenting feature	Age at presentation (years)	Karyotype	Initial blood pressure	Initial potassium level (mmol/l) (NR 4.0–4.8)	Initial ACTH level (mcg/l) (NR 3–11)	Testosterone level	DHEAS level	17 OHP level (nmol/l) (NR 0.9–8.8)
Patient (1)	Abdominal pain (retroperitoneal germ cell tumor)	17	46 XX	170/96	2.5	21	Undetectable	Undetectable	Undetectable
Patient (2)	Hypertension on routine check	14	46 XX	163/117	3.8	55.7	Undetectable	Undetectable	1.8
Patient (3)	Headache Hypertension	14	46 XX	155/110	3.3	35	Undetectable	Undetectable	Undetectable
Patient (4)	Hypertension on routine check	8	46 XX	153/85	3.3	198	Undetectable	Undetectable	Undetectable

control blood pressure for over a year after diagnosis. No secondary sexual characters were seen after starting hydrocortisone replacement and estradiol despite the reassured compliance by mother.

Patient 4: She remained on steroid replacement and 25 mg spironolactone to control her blood pressure.

The compliance issue was strictly monitored on the 4 siblings through steroid medications refill monitoring and was confirmed biochemically by normalization of the ACTH in all of the siblings.

Discussion

Hypertension and hypokalemia are essential features in combined 17 α -hydroxylase/17,20-lyase deficiency. However, it is noted that the age at the onset of hypertension and the degree of hypokalemia vary even within the same mutation (1). In addition, the presentation of the condition varies with 15% of patients being normokalemic and normotensive at diagnosis (1). Our four patients were hypertensive at diagnosis, although in the index case hypertension was not the presenting feature of the disease. Only one sibling presented with symptomatic hypertension. The other two were found to be hypertensive on routine school check while the index case was diagnosed with hypertension during her work up for the presenting germ cell tumor. The youngest was 8 years old when she presented with symptomatic hypertension. To the best of our knowledge, she is the youngest patient reported in the literature to present with hypertension due to this mutation. Mula-Abdel reported a case of 17 α -hydroxylase/17,20-lyase deficiency who presented at 10 years old with hypertension and was treated with antihypertension medication until the age of 22 when the diagnosis was confirmed (9). This highlights the importance of considering this disease in the differential diagnoses of hypertension in children and adolescents which might be underdiagnosed.

The index case presented with a mixed germ cell tumor. This is likely to be a chance association with the P450c17 mutation. A gonadoblastoma has been reported in a 17-year-old 46,XX Brazilian patient with combined 17 α -hydroxylase/17,20-lyase deficiency (6).

The R96Q mutation in this family resulted in a complete absence of 17 α -hydroxylase/17,20-lyase activity (5). Our index case was reported in 2006 when the mutation (R96Q) was novel. In 2013, Athanasoulia reported the same mutation in another patient who showed breast tissue unresponsiveness despite estradiol treatment (10). This phenomenon was attributed to the

high progesterone levels pre-diagnosis having an irreversible effect on breast tissue. This feature was observed in our eldest patient who remained at breast stage II-III, despite adequate estradiol replacement and is currently considering breast augmentation surgery. Compliance with steroid replacement is crucial for correction of hypokalemia and treatment of the hypertension. Adherence to appropriate oestradiol regime ensures progression to puberty. In this family, compliance in the four siblings has been monitored carefully and is believed to be good on the basis of uptake of medication in each case and normalisation of ACTH on therapy. Accordingly, we speculate that this particular mutation has a specific adverse effect on puberty progression particularly on breast development.

Endocrine causes for hypertension should be considered in children and adolescents presenting with high blood pressure. Thorough history and clinical exam is essential to make the diagnosis of this rare condition. In addition, hypertension is an important sign in patients with primary amenorrhea as it should point attention to adrenal disorder.

Conclusion

P450c17 mutation is rare but an important cause of hypertension. Rare forms of congenital adrenal hyperplasia should be considered in presence of hypertension, particularly if more than one sibling is affected. Anti-hypertensive medications might be required along with appropriate steroid replacement.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

Written informed consent has been obtained from patients' mother to publish the article.

Author contribution statement

Dr Asma Deeb is the named physician for the three younger siblings. Dr H Al Suwaidi, Dr S Attia and Dr A Al Ameri participated in data collection and reviewed the manuscript.

Acknowledgements

We acknowledge Dr JP Monson, who reported the index case, for provision of clinical details on the index case. We also acknowledge Dr H Dastoor, senior nephrologist, for his help in the hypertension treatment.

References

- 1 Yanase T, Simpson ER & Waterman MR 1991 17 α -hydroxylase/17, 20-lyase deficiency: from clinical investigation to molecular definition. *Endocrinology Reviews* **12** 91–108. (doi:10.1210/edrv-12-1-91)
- 2 Biglieri EG, Herron MA & Brust N 1966 17 hydroxylation in man. *Journal of Clinical Investigation* **45** 1946–1195. (doi:10.1172/JCI105499)
- 3 Chung BC, Picado-Leonard J, Haniu M, Bienkowski M, Hall PF, Shively JE & Miller WL 1987 Cytochrome P450c17 (steroid 17 hydroxylase/17, 20 lyase): cloning of the human adrenal and testis cDNAs indicates the same gene is expressed in both tissue. *PNAS* **84** 407–411. (doi:10.1073/pnas.84.2.407)
- 4 Kagimoto M, Winter JS, Kaagimoto K, Simpson ER & Waterman MR 1988 Structural characterization of normal and mutant human steroid 17 α hydroxylase gene: molecular basis of one example of combined 17 α hydroxylase/17, 20- lyase deficiency. *Molecular Endocrinology* **2** 564–570. (doi:10.1210/mend-2-6-564)
- 5 Brooke AM, Taylor NF, Shepherd JH, Gore ME, Ahmad T, Lin L, Rumsby G, Papari-Zareei M, Auchus RJ, Achermann JC & Monson JP 2006 A novel point mutation in P450c17 (CYP17) causing combined 17 α -hydroxylase/17, 20-lyase deficiency. *Journal of Endocrinology and Metabolism* **6** 2428–2431. (doi:10.1210/jc.2005-2653)
- 6 Costa-Santos M, Kater CE & Auchus RJ 2004 Brazilian congenital adrenal hyperplasia multicenter study group. Two prevalent CYP17 mutations and genotype-phenotype correlations in 24 Brazilian patients with 17-hydroxylase deficiency. *Journal of Endocrinology and Metabolism* **89** 49–60. (doi:10.1210/jc.2003-031021)
- 7 Zhang M, Sun S, Zhang H, Jiao Y, Wang W & Li X 2015 New, recurrent, and prevalent mutations: Clinical and molecular characterization of 26 Chinese patients with 17 α -hydroxylase/17, 20-lyase deficiency. *Journal of Steroid Biochemistry and Molecular Biology* **150** 11–16. (doi:10.1016/j.jsbmb.2015.02.007)
- 8 Dhir V, Reisch N, Bleicken CM, Lebl J, Kamrath C, Schwarz HP, Grotzinger J, Sippell WG, Riepe FG, Arlt W & Krone N 2009 Steroid 17 α -Hydroxylase Deficiency: Functional Characterization of Four Mutations (A174E, V178D, R440C, L465P) in the CYP17A1 Gene. *Journal of Endocrinology and Metabolism* **94** 3058–3064. (doi:10.1210/jc.2009-0172)
- 9 Mula-Abed WA, Pambinezhuth FB, Al-Kindi MK, Al-Busaidi NB, Al-Muslahi HN & Al-Lamki MA 2014 Congenital Adrenal Hyperplasia due to 17- α -hydroxylase/17, 20-lyase Deficiency Presenting with Hypertension and Pseudohermaphroditism: First Case Report from Oman. *Oman Medical Journal* **1** 55–59. (doi:10.5001/omj.2014.12)
- 10 Athanasoulia AP, Auer M, Riepe FG & Stalla GK 2013 Rare missense P450c17 (CYP17A1) mutation in exon 1 as a cause of 46 XY disorder of sexual development: implications of breast tissue 'unresponsiveness' despite adequate estradiol substitution. *Sexual Development* **4** 212–215. (doi:10.1159/000348301)

Received in final form 18 September 2015

Accepted 5 October 2015