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Congenital Adrenal Hyperplasia Case Attending With Hypertension Diagnosed With 21OH Deficiency

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Case Report

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Abstract

Background

Congenital adrenal hyperplasia (CAH) is a group of disorders with autosomal recessive inheritance, characterized by diverse pathological gene variations in enzymes regulating steroid synthesis in the adrenal glands. Deficiency of 21-hydroxylase (21OHD) comprises nearly 95% of all CAH cases. This is followed by 11-*β*-hydroxylase deficiency (11OHD). In this case, we present a 24-year old male with initial presentation of hypertension who was considered to have biochemical and hormonal 11OHD and 21OHD combined CAH and was genetically diagnosed with 21OHD deficiency-linked CAH.

Case presentation

This case describes a 24-year old male patient who frequently attended the emergency service due to hypertension and was referred to the endocrinology clinic for differential diagnosis of secondary hypertension. Blood pressure was 180/100 mmHg, height 178 cm, weight 84 kg, body mass index 26.5 m2. He was consistent with Tanner stage adult male. Apart from hypertension, physical examination was normal. Precocious puberty was not described. As a result of testing requested due to high dehydroepiandrosterone sulfate in serum, hormonal and biochemical combined CAH was considered when 17-OHP and 11-DOC were high. On the CYP21A gene, v281L homozygote mutation was identified. Blood pressure control was ensured with spironolactone treatment.

Conclusion

This case is a combined CAH case linked to 21OHD and 11OHD. The cause of the combined CAH error is not clear. This case showed that hypertension may be a rare but critical reason for attendance for 21OHD-linked CAH. In 21OHD, high androgen precursors in the adrenal gland may locally suppress 11*β*-OH activity and it is thought the accumulated steroids may cause hypertension through the vasoconstrictor effect. In young adults, CAH should definitely be recalled during secondary hypertension differential diagnosis.

Background

Congenital adrenal hyperplasia (CAH) is a group of disorders with autosomal recessive heredity characterized by a variety of pathological gene changes in enzymes regulating steroid synthesis in the adrenal gland. It has a broad clinical and biochemical phenotype with defects in secreting glucocorticoids and/or mineralocorticoids and sex steroids.

It may cause a life-threatening adrenal crisis and varying degrees of anomalies in the external sexual organs of both sexes. Deficiency of 21-hydroxylase (21OHD) comprises nearly 95% of all CAH cases.

This is followed by 11-β-hydroxylase deficiency (11OHD).(1) In a series of 223 cases studied by Ertörer et al., rates were 81% OHD and 12% 11OHD.(2)

The classic type of 21OHD emerges in the neonatal period with symptoms like genital virilization, hyponatremia, hyperkalemia and adrenal failure or crisis. Non-classic congenital adrenal hyperplasia (NCAH) is a situation that is more common and frequently missed. It generally emerges in the childhood, adolescent or adult periods and is characterized by early puberty, irregular menstruation, excessive hair growth and acne. A less common cause of CAH is 11OHD. It causes symptoms like hypertension, hypokalemia and excessive androgen. For all forms of CAH, the severity of the clinical tableau is inversely proportional to the amount of remaining activity in the mutated enzyme. The more severe the mutation, the less remaining enzymatic activity there is; hence, the clinical tableau is more severe.(1, 3)

As serum 17-hydroxyprogesterone (17-OHP) level is clearly high with 21OHD, it is accepted as a diagnostic marker for this disease. Deficiency in a later stage of cortisol biosynthesis comprises 11OHD. In 11OHD, the direct precursor steroids of 11-deoxycortisol (11-DOC) and 11-deoxycorticosterone accumulate, in addition to the accumulation of 17-OHP. As a result, the clinical tableau emerging in 11OHD is similar to the one for 21OHD, apart from whether there is hypertension and hypokalemia linked to excess 11-DOC or not. Deficiency of both enzymes comprises a similar androgen elevation tableau.(4)

In rare situations, it is possible for an individual to have both 21OHD and 11OHD. These cases are rare in the literature. Clinical symptoms have not been explained in detail. In this case, we present a rare case of a 24-year old male with initial presentation of hypertension considered to have biochemical and hormonal combined CAH linked to 11OHD and 21OHD, but later identified to only have homozygote V281L mutation on the CYP21A1 gene.

Case presentation

A 24-year old male attended our emergency service 3 times in 2 weeks due to a headache continuing for 2 weeks. Blood pressure was above 180/100 mmHg on each attendance, so he was referred to the endocrinology clinic for differential diagnosis of causes of endocrine hypertension. History had no features apart from citalopram use due to major depression. One week previously, the cardiology clinic had begun Zofenopril 30 mg/day for hypertension. Family history did not include genetic diseases. Physical examination found blood pressure was 160/100 mmHg. Respiratory, cardiovascular and abdominal examinations were normal. Tanner stage was consistent with adult. Height was 178 cm, weight 84 kg and body mass index 26.5 kg/m^2. Initial biochemical data are shown in Table-1. Tests performed for endocrine hypertension etiology are given in Table-2. Renal doppler USG did not identify renal artery stenosis. Electrocardiography was normal. Dihydroepiandrostene dion sulfate (DHEAS) was very high when examined 2 times. Surrenal MR was normal. Adrenocortical cancer was excluded. 11-DOC and 17-OHP basal values were high. Standard adrenocortical stimulation with 250 g intravenous Synacthen (an ACTH1-24 analogue) found 11-DOC and 17-OHP levels were high. The test results for intravenous stimulation with Synacthen are given in Table-3. These findings were assessed as combined

CAH. However, sequencing of the CYP21 gene in this patient detected homozygote V281L (c.844G > T /p. Val 282Leu) mutation on the exons investigated on the CYP21A2 gene. The patient was not found to have any mutation on the CY11B1 gene. Zofenopril was stopped. Spironolactone 50 mg/day was begin. Blood pressure control was ensured.

Table-1: Initial laboratory investigation

Test	Result	Reference range
Glucose (mg/dL)	86	74–106
Creatinine (mg/dl)	0.9	0.6–1.2
LDL	135	100–160
ALT (U/L)	29	0–50
Sodium (mmol/L)	139	136–146
Potassium (mmol/L)	4.1	3.5–5.1
TSH (mIU/ml)	1.59	0.38–5.33
S-T4 (ng/dL)	0.97	0.61–1.12
DHEAS	759–963	85–690
ACTH (pg/mL)	54.3	7.2–63.6
Total Testosterone (ng/mL)	5.6	1.75–7.81
FSH (mIU/ml)	4.6	1.27-19
LH (mIU/ml)	6.7	1.24–7.81

Table-2: Endocrine Hypertension Laboratory Tests

Test	Result	Reference range
24-hour urine (mcg/24 h)		
Metanephrine	118	44–261
Normetanephrine	213	103–390
Epinephrin	3.8	0–21
Norepinephrine	38.7	15–80
Dopamine	189	65–400
Plasma renin activity (PRA, ng/mL/ h)	10.9	
Plasma aldosterone (PAK, ng/dL)	50	
PAK/PRA	4.58	
Basal cortisol (µg/dL)	19.18	6.7–22.6
1 mg Dexamethasone suppression test (µg/dL)	0.6	< 1.8

Table-3: ACTH stimulation test

17-OHP(ng/ml) basal	**9.44**
17-OHP (ng/ml) 0 min	**9**
30th min	**> 50**
60th min	**> 50**
11-DOC (ng/ml) basal	**5.9**
11-DOC (ng/ml) 0 min	**8.7**
30th min	**11**
60th min	**12**

Discussion

21OHD is the most common cause of CAH and comprises more than 90% of all cases. Varying according to ethnic group, this is followed by 11OHD. Though the frequency of 11OHD cases is reported to be 3–5%, a series in Türkiye found 81% of cases had 21OHD, while 12% of cases had 11OHD.(2)

The clinical symptoms of 21OHD and 11OHD are the same, apart from the hypertension and hypokalemia that may be seen with 11OHD.(5) However, 35% of patients diagnosed with 11OHD were shown to be normotensive and normokalemic.(6)

A case report by Hurwitz et al. from 1985 defined combined CAH linked to 21OHD and 11OHD in 5 people from 3 different families. The cases had high levels of 17-OHP, 11-DOC and 21 deoxy cortisol (21-DF), a small side path from 17-OHP. The clinical spectrum ranged from severe virilization to only hirsutism and 1 patient had adrenal failure. In these 5 cases, 3 had hypertension identified. A 17-year old male patient from the first family had normal external genital organs and the only symptom was hypertension, similar to our case. These 5 cases were assessed as having combined CAH in hormonal and biochemical terms; however, none had genetic analysis performed.

All of these patients had high 11-DOC, as in our case. Simulation of the zona fasciculata by ACTH increases 11-DOC. The progesterone occurring with the increase in 11-DOC may contribute to the extrarenal conversion to 11-DOC and in both situations, this is thought to explain hypertension in patients.

Additionally, while hypertension is observed in spite of suppressed renin level and reduced aldosterone production with excess 11-DOC, renin levels were not suppressed in our case. Hypertension was not linked to volume, but is thought to be linked to the vasoconstrictor effect of accumulating steroids.(7)

Tonetto et al. retrospectively re-evaluated 133 patients with 21OHD. In all cases, 21-DF, 17-OHP and 11-DOC levels were measured. Of the 133 patients with 21OHD diagnosis, 1 was identified to be diagnosed with 11OHD and not 2OHD and was identified to have Q365X mutation on the CYP11B1 gene. Combined CAH linked to 21OHD and 11OHD was evaluated for 1 patient with high 17-OHP, 21-DF and 11-DOC. As in our case, this patient was not identified to have any mutation on the CY11B1 gene, but had heterozygote V281L point mutation on the CYP21A gene.(4)

In a case presented by Gill et al., a 46XX infant girl with 11OHD diagnosis attended with adrenal crisis. In DNA, homozygote splice mutation of CYP21A2 was identified with no mutation of CYP11B1.(8)

Tonetta et al. did not identify mutations apart from CYP21A2 in a 6-year old case with ambiguous genitalia and adrenal failure considered to have combined CAH. During 6-year follow-up, 11-DOC returned to normal levels. They interpreted that 11 beta hydroxylase inhibition resolved when the androgen burden reduced with treatment.(9)

Additionally, androgens were shown to suppress 11 β-OH activity in both in vitro and in vivo environments in animals.(10, 11, 12) Similarly, 11β-OH deficiency was reported in patients with hyperandrogenemic polycystic ovarian (PCO) syndrome.(13)

In the combined CAH cases presented by Gills et al. and Tonetta et al., and in our case, CYP11B1 mutation was negative. In this situation, we think the increased adrenal androgen secretion due to 21OHD may occur linked to suppression of 11β-OH enzyme activity. Another mechanism is that 17-OHP accumulation exceeds the capacity of the CYP11B1 enzyme and slows the 11β-OH cycle. This moves to the 21-DF side path and this situation may bring non-adrenal environmental conversion paths into play.

A 30-year old female case with hirsutism and menstrual irregularity complaints, attending without hypertension, was presented by Fontera et al. After 17-OPH elevation was noted, genetic analysis identified heterozygote pathogenic CYP21A2 variant and a heterozygote CYP11B1 variant with unknown significance. In this patient 11-DOC was not examined.

In our case, in spite of 11-DOC elevation and hypertension, we did not identify mutation of the CYP11B1 gene. Though we did not identify a pathogenic variant in our routine genetic analyses, promoter region mutations were not evaluated, which limits complete exclusion of a possible genetic etiology.(14)

A study of 270 asymptomatic women aged 18–45 years by Polat et al. found the frequency of 21OHD-linked CAH carriers was 12.6%, while the frequency of 11OHD-linked carriers was 15.2%. In this study, they emphasized the importance of examining promoter mutations when performing full genotyping in individuals with NCAH suspicion without genetic mutations due to high heterozygote incidence.(15)

Dall'Asta et al. performed the ACTH stimulation test on 48 nonfunctioning incidentaloma and 10 subclinical Cushing cases and observed both high 17-OHP and 11-DOC elevation in both groups. They reported that in 7 of 8 operated patients, this pathological response was normalized postoperatively. These findings may be explained by local enzyme inhibition in adrenal tumors. Again, as considered in our case, the high intra-adrenal androgen concentration resulting from the initial enzymatic deficiency observed in combined CAH may be considered to obstruct other enzymatic activity.(16)

Conclusion

This case is a case of combined CAH linked to 21OHD and 11OHD. The cause of the combined CAH error is not clear. This case shows that hypertension may be a rare but critical reason for attendance in 21OHD-linked CAH. High androgen precursors in the adrenal gland in 21OHD may locally suppress 11β-OH activity and it is considered that the accumulating steroids may cause hypertension with their vasoconstrictor effect. Genetic analysis along with biochemical and hormonal findings play key roles in determining the definite diagnosis and correct treatment strategy. Due to the high heterozygote rate in CAH, promoter mutations should be examined along with routine genetic analyses. CAH should definitely be remembered for differential diagnosis of secondary hypertension in young adults.

Declarations

Ethics approval and consent to participate: Not needed.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report**.**

Clinical trial number: Not applicable

Availability of data and material: The data supporting the findings of this case report are included within the article. No publicly available datasets were generated. Raw genetic data are not publicly available

due to patient confidentiality and privacy considerations

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Author Contributions: Concept – E.T.; Design – E.T.; Supervision – E.T.; Materials – E.T; Data Collection and Processing – E.T.; Analysis and Interpretation – E.T.; Literature Review – E.T., .; Author – E.T.; Critical Review – E.T.

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