Genotypic Sex and Severity of the Disease Determine the Time of Clinical Presentation in Steroid 17α-hydroxylase/17,20-lyase Deficiency

Erdal Kurnaz1, Emin Karay 2, Ayberk Türkylıez, Öğuzhan Yarali, Zehra Yavaş Ablalı, Serap Turan, Abdullah Bereket, Atila Çayır, Tulay Guran

1Department of Pediatric Endocrinology and Diabetology, Erzurum Regional Research and Training Hospital, Erzurum, Turkey
2Department of Internal Medicine, Division of Endocrinology and Metabolism, Erzurum Regional Research and Training Hospital, Erzurum, Turkey
3Department of Medical Genetics, Erzurum Regional Research and Training Hospital, Erzurum, Turkey
4Department of Paediatric Endocrinology and Diabetes, Marmara University, School of Medicine, Istanbul, Turkey

INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to steroid 17α-hydroxylase deficiency (17OHD) (MM # 203110) is a rare autosomal recessive disorder. The enzyme, cytochrome P450c17 catalyzes the 17α-hydroxylase and 17,20-lyase activities, which are involved in the biosynthesis of cortisol in the adrenal zona fasciculata and the generation of androgens, steroids and estrogens in the adrenal zona reticularis and in genital. Various severities of molecular defects in the CYP17A1 gene, which encodes P450c17 enzyme, are associated with the complete or partial 17OHD.

The metabolic signature of 17OHD includes low concentrations of cortisol, 11-deoxycortisol, dehydroepiandrosterone sulphate (DHEAS) and 17-hydroxyprogesterone together with elevated adrenocorticotropic hormone (ACTH), corticosterone, 11-deoxycorticosterone (DOC) and progesterone. The absence of secondary sexual characteristics or amenorrhea are the most common presenting symptoms of 17OHD due to deficiency of adrenal and gonadal sex steroids. The clinical manifestations of cortisol deficiency are not apparent due to the glucocorticoid effect of high corticosterone concentrations. Therefore, most of the previously reported cases have come to clinical attention at late pubertal ages.

RESULTS

Median age of diagnosis was 13.9 (range:0.04-29.5) years. All patients had consanguineous parents. Ten of 12 patients had 46,XY karyotype. The age range of the patients at the time of diagnosis was between 15 days and 25.9 years (median:13.96 years). Except one boy with partial 17OHD, all patients had female external genitalia hence raised as females. The clinical presentation of 17OHD was earlier (median age:7 years) in patients, who presented with severe hypotension, atypical genitalia or positive family history (n=6, 50%) than those without (median age:15.3 years; p=0.006). The latter group presented with amenorrhea (n=6, 50%). Sarin gonadotropin concentrations were elevated in patients <12 years (n=7), normal in pre-adolescents (n=4) and low in a patient who had a digenic inheritance of homozygous CYP17A1 and KS31R mutations. The clinical characteristics and biochemical results of the patients at the time of diagnosis are presented in Table 1 and Table 2. Clinical data of patients with 17OHD at the last evaluation is presented in Table 3.

AIM

Herein, we have evaluated the comprehensive clinical, hormonal and molecular characteristics of 12 patients with 17OHD to search the conditions related to early and late clinical presentation. Diagnostic challenges, follow-up characteristics, and treatment outcomes were discussed.

METHOD

Clinical data, steroid profiles by liquid chromatography-tandem mass spectrometry and flanger sequencing of CYP17A1 gene was evaluated in 12 patients with 17OHD diagnosed between 2004-2020.

DISCUSSION

Evaluation of our cohort with 17OHD revealed that, the diagnosis of 17OHD is mostly established at pubertal ages (14 years) unless the affected patients have severe hypertension or ambiguous genitalia. Although more than half of our patients were hypertensive at presentation, most common complaints of clinical presentation were absent puberty and amenorrhea. Nonetheless, the severe symptomatic hypertension and ambiguous genitalia due to partial 17OHD in 46,XY emerged as the factors for early clinical presentation of the condition. This relatively large series of 17OHD demonstrated that early diagnosis is associated with particular clinical manifestations including severe hypertension in both 46,XX and 46,XY and inadequate virilization of external genitalia in 46,XY patients. Family screening provide early diagnosis and management of 17OHD in yet asymptomatic 46,XY and 46,XX cases. Surveillance of adrenal functions and 17OHD is warranted in all cases with absent puberty and/or amenorrhea especially in 46,XX cases. Finally, the reported cases herein contribute to molecular and phenotypic repertoire of 17OHD.