DOI: 10.4274/jcrpe.galenos.2021.2021.0174

Case report

Rare Coexistence of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency and Turner Syndrome: A Case Report and Brief Literature Review

Inácio I et al. Congenital Adrenal Hyperplasia and Turner Syndrome

Isabel Inácio[1], Joana Serra-Caetano[2], Rita Cardoso[2], Isabel Dinis[2], Alice Mirante[2]
[1]Endocrinology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal
[2]Department of Paediatric Endocrinology, Diabetes and Growth, Hospital Pediátrico de Coimbra, Coimbra, Portugal

What is already known on this topic?
The combination of Turner Syndrome and Congenital Adrenal Hyperplasia is rarely reported in literature.

What this study adds?
We report a new case of the coexistence of mosaic Turner Syndrome and non-classical form of Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency, associated with a *de novo* mutation in CYP21A2 gene. This case did not present short stature.

Abstract
Coexistence of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency and Turner Syndrome (TS) is rare. We report a 6-year-old Portuguese girl with mosaic TS [45,XO(39)/47,XXX(21)] presented with premature pubarche at the age of 5 years. Laboratory findings showed elevated 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, androstenedione and total testosterone, and sex-determining region Y (SRY) was negative. *CYP21A2* gene analysis revealed two mutations (c.[844G>T]; [*CYP21A2*del]), consistent with the non-classical form of CAH. Complete deletion of *CYP21A2* allele occurred *de novo*. At 6 years and 4 months, she presented accelerated growth velocity and hydrocortisone at the dose of 5 mg/m^2/day was initiated. This case highlights the need to perform global examinations looking for virilization signs in TS patients follow-up. It also supports the reported genetic combination of TS and CAH. Therefore, CAH should be kept in mind in TS patients with SRY negative and virilization signs, even in the absence of short stature.
Keywords: Adrenal hyperplasia, congenital, Turner syndrome, virilism, karyotyping

Isabel Inácio MD, Endocrinology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal
+351 234 378 300
isabelmrinacio@gmail.com
https://orcid.org/0000-0001-7882-1130
18.06.2021
28.07.2021

Published: 6 August 2021

Introduction
Turner syndrome (TS) is a common genetic disorder among young females and is characterized by infertility, premature ovarian deficiency, short stature and other abnormalities [1]. Some patients have the classical monosomy X (45,X) and others have various 45,X mosaicism, including mosaic monosomy X with a Y-bearing cell line. Virilization occurring in TS patients should prompt search for the Y chromosome-bearing cell line, as they are at risk of developing malignant gonadal tumours and they can present with ambiguous genitalia as with Congenital Adrenal Hyperplasia (CAH) [2, 3].
CAH secondary to 21-hydroxylase (21-OH) deficiency is one of the most common causes for virilization in females. There are three forms: the classic salt-wasting and simple virilising and the non-classical or late-onset, the latter being the most prevalent type [4].
CAH and TS are not very rare diseases, but their combination is rare and may be confounding [4, 5]. We report a case of TS with coexisting 21-OH deficiency. The second condition was only recognized during follow-up with the evaluation of puberty signs.
Written informed consent was obtained from the mother.

Case Report
The patient, known to be a mosaic for TS [45,XO(39)/47,XXX(21)] diagnosed in amniocentesis and confirmed with a postnatal karyotype, was referred to the Pediatric Endocrinology Department at 20 months of age. She was born at term from the second gestation of a 35-year-old mother. Birth weight was 2565 g, length 45 cm and head circumference 32.5 cm. The parents were nonconsanguineous. On physical examination, she presented good general

appearance, low posterior hairline, micrognathia, Tanner stage I. During follow-up, she had recurrent otitis media. Echocardiography, performed as part of routine investigations in TS patients, revealed no pathology. At 5 years and 8 months, she presented premature pubarche with three dark thick pubic hair on the labia majora (Tanner stage II pubic hair and Tanner stage I breasts). Her height was 109.2 cm [-0.62 standard deviation (SD)] and weight was 19.4 kg (0.09 SD). Initial laboratory findings showed 17-hydroxyprogesterone (17-OHP) 18 (0.03-0.9) ng/ml, dehydroepiandrosterone sulfate 2.76 (<0.05-0.57) ug/ml, androstenedione 1.4 (0.08-0.5) ng/ml, total testosterone 0.3 (<0.03-0.1) ng/ml, LH <0.1 (0.02-0.3) mUI/mL and FSH 2.6 (1.0-4.2) mUI/ml (Table 1). Repeated laboratory work-up confirmed the results (Table 1). Renal and pelvic ultrasonography demonstrated normal kidneys without renal anomalies, and a uterus with diameters of 2.3x0.7x1.1 cm. Both ovaries were 1.2x0.6 cm. Analysis of sex-determining region Y (SRY) gene was negative. Analysis of *CYP21A2* gene revealed the presence of the mild variant c.844G>T [p.(Val282Leuc)] in hemizygote associated with enzymatic activity of 21-OH of 50%, and the presence of non-functional allele, complete deletion of the *CYP21A2* (*CYP21A2d*el), associated with null enzymatic activity of 21-OH. These results were consistent with a partial deficiency of 21-OH compatible with the non-classical form of CAH.

Her mother did not present any of the genetic alterations and her father is a carrier of the mild variant c.844G>T. Her 13-year-old sister had recurrent otitis media and premature pubarche since the age of six. Her genetic testing identified also mild variant c.844G> T, associated with the enzymatic activity of the 50% 21-hydroxylase, in heterozygosity, in the *CYP21A2* gene, although not sufficient for the diagnosis of CAH. The sister's current laboratory evaluation showed sodium 137 (136-146) mmol/L, potassium 4.6 (3.5-5.1) mmol/L, 17-OHP 4.19 (0.18-2.3) ng/ml, androstenedione 3.4 (0.77-2.25) ng/ml, total testosterone 0.3 (0.13-0.32) ng/ml, LH 5.0 (<12.0) mUI/mL and FSH 4.1 (<9.6) mUI/mL.

At 6 years and 4 months, weight of the patient was 24.3 kg (0.98 SD) and height was 119.8 cm (0.54 SD), with accelerated growth velocity (10.6 cm in 10 months). Hydrocortisone treatment at the dose of 5 mg/m^2/day was initiated. During the last visit at 6 years and 7 months, her weight was 25.3 kg (1.03 SD) and height 1**21.3 cm (0.51** SD). Laboratory work-up (table 1) was performed, under hydrocortisone at the dose of 5 mg/m^2/day although with irregular compliance. The need for treatment was reinforced to avoid complications.

Discussion

We described a new case of CAH due to 21-OH deficiency in a 6-year-old Portuguese girl with a mosaic form of Turner karyotype.

The first sign of virilization in our patient was premature pubarche at the age of 5 years. She was known to have a mosaicism TS, but have only a few TS stigmas and did not present short stature. Laboratory investigation revealed elevated levels of 17-OHP and androgens, with normal sodium, potassium, FSH, LH, IGF1, cortisol, adrenocorticotropic hormone, active renin and aldosterone levels. As is strongly recommended, the SRY gene analysis was performed and was negative. Continuing the investigation, the rare occurrence of coexisting CAH was looked for [2]. Her elevated basal 17-OHP level and the *CYP21A2* gene analysis (*CYP21A2* genotype: c.[844G>T]; [*CYP21A2*del]) established diagnosis of the non-classical form of 21-OH deficiency. As her mother did not present any of the genetic alterations, it is possible to infer that the complete deletion of *CYP21A2* allele occurs *de novo*. The occurrence rate of *de novo* mutations in *CYP21A2* alleles in affected patients with 21-OH deficiency has been assessed at 1-2%. Her sister genetic testing did not confirm a non-classical CAH, although did not allow it to be ruled out completely.

This rare combination of TS and CAH was first described by del Arbol et al. in 1983 [6]. So far, ten cases with both TS and CAH due to 21-OH deficiency have been previously reported in the literature [1-3, 5-11]. Unlike most of the previously reported cases that were diagnosed as TS during the investigation of ambiguous genitalia or presented concomitant diagnosis [2, 3, 6-10], in our case the diagnosis of TS was made first. Only three cases known to have TS were later diagnosed as CAH [1, 5, 11].

As in our patient, most of the previous cases had different degrees of virilism [2]. Only one case of a 28-year-old woman who had decreased endometrial receptivity during IVF did not show virilism [1]. Likewise, all cases described until now, except one had a mosaic Turner karyotype [2, 8].

The diagnosis of coexisting CAH, particularly the non-classical type, is difficult in patients with TS, as typical signs such as short stature, amenorrhea and hirsutism may be present in both diseases [2, 11]. Furthermore, at an early age like our case, it is even more difficult to detect coexisting CAH, because some of these signs of both diseases including short stature have not yet manifested. Therefore, it is important to include genital examinations for virilization signs in routine visits in patients with TS [4], and measure 17-OHP levels, especially in the presence of moderate-to-severe virilization [2].

The final heights of patients with concomitant TS and CAH tend to deteriorate due to both diseases. [3] Unopposed hyperandrogenism caused by CAH may lead to initial skeletal maturation. However, it can mask the growth disorder, because premature closure of growth plates leads to short final heights [2]. In addition, insufficient hormone replacement therapy or overtreatment of CAH also causes final short stature [7]. On the other hand, TS can cause short stature. However, the prevalence of short stature in rare 45,X/47,XXX mosaicism individuals is only 64.3%, that is, much less frequent than in pure 45,X monosomy (over 95%) [12]. Therefore, we think the patient's karyotype may lead to better growth. It has been speculated that this may be related to the presence of 47,XXX cell lines, because the triple-X syndrome often presents with taller stature [12]. Nevertheless, the final adult height is not guaranteed without growth hormone treatment [13].

While it is possible to achieve good results in CAH patients with regular follow-up and treatment, in TS, growth hormone (GH) treatment initiated at supraphysiological doses and at an early age (before age 4 years) can lead to a considerable height gain, despite the absence of GH deficiency in TS [7, 11]. In a previously case of a one-year-old patient with TS and CAH, in addition to treatment with appropriate doses of glucocorticoids and mineralocorticoids, GH treatment was initiated when a slowing in growth was later observed [7]. Our patient did not have short stature, probably due to accelerated skeletal maturation and some partial protection provided by her karyotype, as discussed previously. But, due to the coexistence of the two pathologies and irregular therapeutic compliance, the growth potential may be compromised. In our country, Portugal, GH treatment is approved for TS when there is a diagnosis confirmed by chromosomal analysis, chronological age >2 years, bone age <12 years, before puberty, height <-2 SD and z-score of the height velocity <10th percentile for 1 year. After improving the patient compliance and adequately controlling CAH, we can question whether our patient will benefit from GH treatment as early as possible, because the height may never be <-2 SD, but growth may end too soon.

In conclusion, we presented a patient with non-classical form of CAH due to 21 hydroxylase deficiency and mosaic TS, who presented with premature pubarche. To our knowledge, this is the first report of this rare combination in a Portuguese patient. A review of the literature showed that this is the fourth case which diagnosis of CAH was later than TS. If signs of virilism are detected in patients with TS, rare coexisting CAH should be suspected in absence of SRY.

Informed Consent: Written informed consent was obtained from the mother.

Author contributions: Surgical and Medical Practices: Joana Serra-Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante; Concept: Isabel Inácio, Joana Serra-Caetano, Alice Mirante, Design: Isabel Inácio, Joana Serra-Caetano, Rita Cardoso, Alice Mirante; Data Collection or Processing: Isabel Inácio, Joana Serra-Caetano, Rita Cardoso; Analysis or Interpretation: Isabel Inácio, Joana Serra-Caetano, Rita Cardoso; Literature Search: Isabel Inácio; Writing: Isabel Inácio, Joana Serra-Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante.

References

1. Cohen MA, Sauer MV, Lindheim SR. 21-hydroxylase deficiency and Turner's syndrome: a reason for diminished endometrial receptivity. Fertil Steril. 1999;72:937-9.
2. Lee KF, Chan AO, Fok JM, Mak MW, Yu KC, Lee KM, et al. Late presentation of simple virilising 21-hydroxylase deficiency in a Chinese woman with Turner's syndrome. Hong Kong Med J. 2013;19:268-71.
3. Maciel-Guerra AT, Guerra G, Jr., Marini SH, Matias Baptista MT, Marques-de-Faria AP. Female pseudohermaphroditism due to classical 21-hydroxylase deficiency in a girl with Turner syndrome. Clin Genet. 1997;51:351-3.
4. Onder A, Aycan Z, Cetinkaya S, Kendirci HN, Bas VN, Agladioglu SY. Assessment of the 21-hydroxylase deficiency and the adrenal functions in young females with Turner syndrome. J Pediatr Endocrinol Metab. 2012;25:681-5.
5. Ságová I, Stančík M, Pavai D, Kantárová D, Vaňuga A, Vaňuga P. [Rare combination of Turner syndrome and congenital adrenal hyperplasia with 21-hydroxylase deficiency: case report]. VnitrLek. 2018;64:432-6.
6. del Arbol JL, Soto Más JA, Fernández-Abril JA, Raya Muñoz J, Martínez Tormo F, Gómez Rodríguez J, et al. Turner syndrome caused by deletion of the long arm of the X chromosome associated with adrenogenital syndrome caused by partial deficiency of 21-hydroxylase. Rev Clin Esp. 1983;171:67-71.
7. Kendirci HNP, Aycan Z, Çetinkaya S, Bas VN, Ağladıoğlu SY, Önder A. A Rare Combination: Congenital Adrenal Hyperplasia Due To 21 Hydroxylase Deficiency and Turner Syndrome. J Clin Res Pediatr Endocrinol. 2012;4:213-5.
8. Larizza D MM, Cascone E, Daielle P, Cuccian M. A genetic and hormonal investigation of 21-hydroxylase deficiency in Turner's syndrome. In: Pintor C, Muller EE, Loche S, New MI, editors Advances in paediatric endocrinology Berlin and Heidelberg: Pythagora Press, Milano & Springer-Verlag. 1992:189-94.
9. Montemayor-Jauregui MC, Ulloa-Gregori AO, Flores-Briseño GA. Associated adrenogenital and Turner's syndrome mosaicism. Plast Reconstr Surg. 1985;75:877-81.
10. Rabbani B, Mahdieh N, Sayarifar F, Ashtiani MT, New M, Parsa A, et al. A girl with 45,X/46,XX Turner syndrome and salt wasting form of congenital adrenal hyperplasia due to regulatory changes. Clin Lab. 2012;58:1063-6.
11. Atabek ME, Kurtoğlu S, Keskin M. Female pseudohermaphroditism due to classical 21-hydroxylase deficiency and insulin resistance in a girl with Turner syndrome. Turk J Pediatr. 2005;47:176-9.
12. Tang R, Lin L, Guo Z, Hou H, Yu Q. Ovarian reserve evaluation in a woman with 45,X/47,XXX mosaicism: A case report and a review of literature. Mol Genet Genomic Med 2019;7(7):e00732. (In eng). DOI: 10.1002/mgg3.732.
13. Yoo SH, Ahn MB, Kim SH, et al. A case of 45,X/47,XXX mosaic Turner syndrome: Clinical manifestations and effect of growth hormone treatment. J Genet Med 2020;17(1):47-50. (In eng). DOI: 10.5734/JGM.2020.17.1.47.

Table 1: Laboratory analysis of the patient.			
Age	5 years and 8 months	5 years and 10 months	6 years and 7 months
Sodium, mmol/L	139 (136-146)		141 (136-146)
Potassium, mmol/L	4.9 (3.5-5.1)		4.3 (3.5-5.1)
ACTH, pg/mL		22 (10-60)	20 (10-60)
Cortisol, ug/dL		10 (3-21)	7.1 (3-21)
Glucose, mg/dL	82 (60-100)		89 (60-100)
Creatinine, mg/dL	0.56 (0.44-0.64)		
FSH, mUI/mL	2.6 (1.0-4.2)	2.7 (1.0-4.2)	
LH, mUI/mL	<0.1 (0.02-0.3)	0.1 (0.02-0.3)	
Estradiol, pg/mL	<13 (5-20)	<13 (5-20)	
AMH, ng/mL		0.28	
17-OH progesterone, ng/mL	18 (0.03-0.9)	17 (0.03-0.9)	19 (0.03-0.9)
Total Testosterone, ng/ml	0.3 (<0.03-0.1)	0.2 (<0.03-0.1)	
Androstenedione, ng/mL	1.4 (0.08- 0.5)	1.4 (0.08- 0.5)	
DHEA-SO4, ug/mL	2.76 (<0.05-0.57)	3.72 (<0.05-0.57)	3.30 (<0.05-0.57)
IGF1, ng/ml	150 (35-232)	142 (35-232)	
TSH, uUI/mL		2.7 (0.70-4.17)	
FT4, ng/dL		0.90 (0.89-1.37)	
Aldosterone, pg/mL		185 (30 – 350)	155.0 (30 – 350)
Active Renin, uU/mL		55 (7 - 76)	84 (7 - 76)
17-OH, 17-hydroxy; ACTH, adrenocorticotropic hormone; AMH, Anti-Mullerian Hormone; DHEA-SO4, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; FT4, free thyroxine; IGF1, insulin like growth factor 1; LH, luteinizing hormone; TSH, thyroid stimulating hormone.			