Case Report

Novel co-occurrence of hypophosphatemic rickets with 46XY DSD (disorder of sex development) due to a CYP17A1 variant

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ABSTRACT

17-α-hydroxylase deficiency causes a rare type of congenital adrenal hyperplasia (CAH). X-linked hypophosphatemic rickets (XLH) is a rare disorder caused by inactivating mutations in the PHEX gene. We report a novel co-occurrence of XLH with 46XY disorder of sex development due to 17-α-hydroxylase deficiency. A young child reared as a girl, presented as a toddler with genu varus, low phosphorus, normal calcium, and parathormone, and was treated as hypophosphatemic rickets. In early childhood, due to short stature and hypertension, the child was investigated for Turner syndrome. Ultrasound revealed intra-abdominal gonads and an absent uterus. The karyotype was 46XY. Investigations revealed low serum cortisol, renin, normal 17-hydroxyprogesterone, and aldosterone. A year later, a bilateral orchidectomy was performed. Two years later, she was referred to us for further management. Adrenocorticotrophic hormone (ACTH), cortisol, renin, deoxycorticosterone, and clinical exome were advised. She was lost to follow-up for 3 years. On follow-up in early adolescence, she was pre-pubertal; biochemical findings of hypophosphatemic rickets, elevated ACTH, low cortisol, and low normal aldosterone were noted. Clinical exome revealed variants in the *CYP17A1* gene (homozygous) causing CAH (17-α-hydroxylase) and *PHEX* (hemizygous) gene causing XLH. Treatment with hydrocortisone, phosphate, cholecalciferol, and calcitriol was commenced. Hypertension is now well-controlled, but genu varus persists and may require surgical correction.

Key words: Congenital adrenal hyperplasia, CYP17A1, Disorder of sex development, Hypophosphatemic rickets, PHEX

17-α-hydroxylase deficiency, a rare type of congenital adrenal hyperplasia (CAH), accounts for only 1% of CAH cases and presents as delayed puberty and hypertension in phenotypic females. It is often missed during childhood in both sexes [1]. Affected males may often be raised as females owing to female external genital appearance and are diagnosed with 46XY karyotype and 17-α-hydroxylase deficiency only at puberty when they present with absent breast development. Less severe enzyme deficiency in males may present with varying degrees of under-virilization and disorders of sex development (DSD) (perineal hypospadias, bifid scrotum with or without palpable gonads, and blind vaginal pouch) [1]. X-linked hypophosphatemic rickets (XLH), caused by inactivating mutations in the PHEX gene, are characterized by disproportionate short stature, premature cranial sutural fusion, and dental abscesses [2].

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Objectives

We report a novel co-occurrence of XLH with 46XY DSD due to 17-α-hydroxylase deficiency.

CASE REPORT

A 10.6-year-old child, reared as a girl, born of non-consanguineous marriage, first presented as a toddler to an orthopedic surgeon with genu varus and disproportionate short stature (upper: lower segment ratio=1.5:1). She was referred to a pediatrician following poor response to treatment with cholecalciferol (60,000 IU weekly for 8 weeks). Investigations revealed low serum phosphorus, normal serum calcium, alkaline phosphatase, and parathormone (Table 1), with subtle radiological evidence of rickets (splaying, fraying, and thick cortices involving the radius and tibia). She was treated as hypophosphatemic rickets (Table 1) and visited multiple doctors thereafter.

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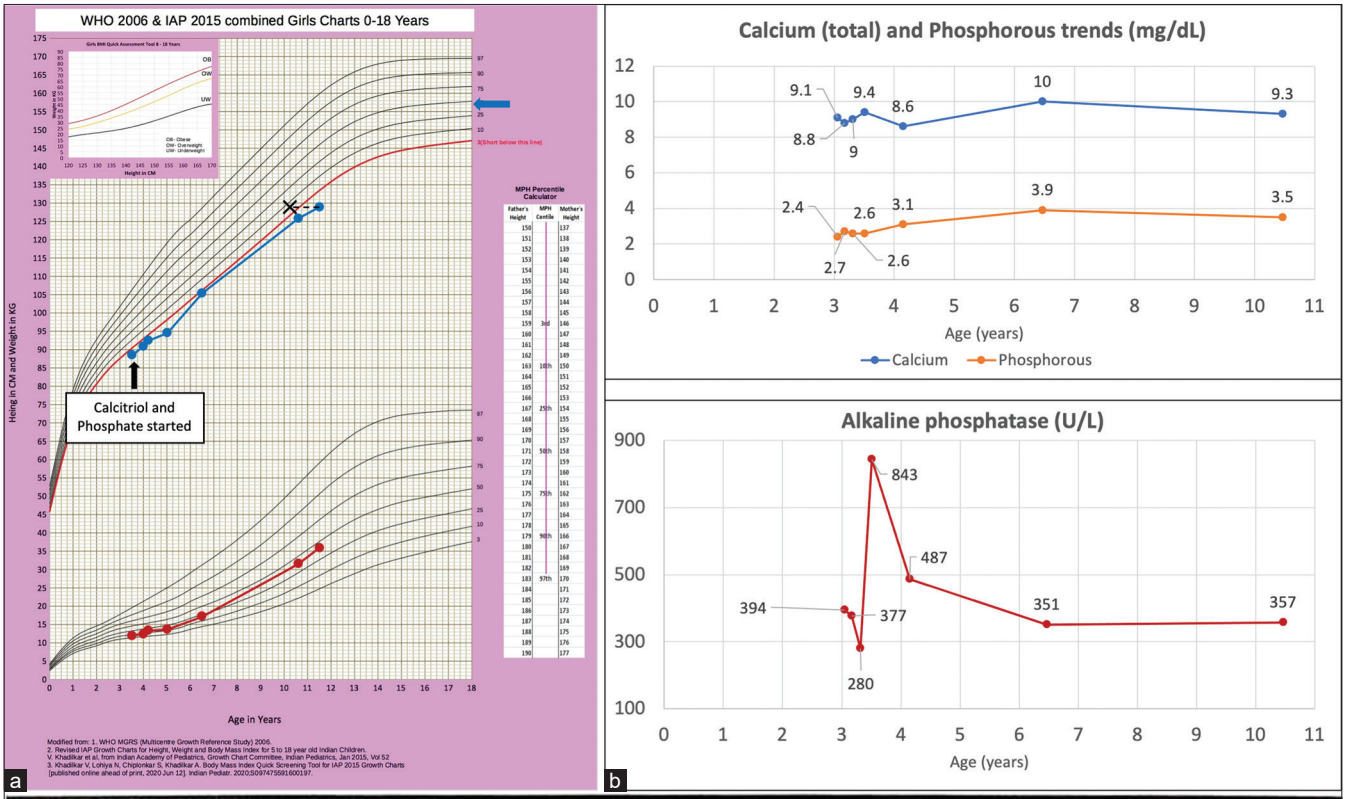
Table 1: Serial anthropometric, biochemical, and treatment details

Parameters	Observed findings					Reference range
Age (years)	3.3 years	4 years	7.5 years	10.6 years	11.5 years	
Height (cm) (Z score)	88.5 (−1.2)	91.0 (−1.7)	110.1 (−2.1)	125.9 (−2.3)	129.0 (−2.5)	-
Weight (kg) (Z score)	11.9 (−0.6)	12.3 (−1.1)	21.0 (−0.5)	31.5 (−0.4)	36.2 (−0.2)	-
Blood pressure (mmHg)	-	140/100	140/96	130/80	116/70	-
Calcium (mg/dL)	9.1	8.6	-	9.3	9.2	8.8–10.8 mg/dL
Phosphorous (mg/dL)	2.4	3.1	-	3.5	3.9	3.7–5.6 mg/dL
Alkaline phosphatase (U/L)	394	487	-	357	298	140–420 U/L
PTH (pg/mL)	39.9	-	-	40.3	-	15–65 pg/mL
25-Hydroxy cholecalciferol (ng/mL)	-	-	-	8.3	-	20–50 ng/mL
Cortisol (mcg/dL)	-	0.78	-	1.6	2.3	5–25 mcg/dL
17-Hydroxyprogesterone (ng/mL)	-	0.23	-	-	-	<2 ng/mL
ACTH (pg/mL)	-	-	-	284.3	72.3	7.2–63 pg/mL
Aldosterone (pg/mL)	-	148.6	-	35.8	-	12–340 pg/mL
Plasma renin activity (ng/mL/h)	-	0.39	-	-	-	1–5 ng/mL/h
Sodium/potassium (meq/L)	-	136/3.8	-	142/3.7	139/4.0	Sodium: 135–145 meq/L Potassium: 3.7–5.5 meq/L
Bone age (years)	-	-	-	-	10.3	-
Suspected clinical diagnosis	Hypophosphatemic rickets	Hypophosphatemic rickets with hypertension (due to renal artery stenosis), short stature, (Turner syndrome is to be ruled out)	Hypophosphatemic rickets with DSD and hypertension due to congenital adrenal hyperplasia (17-α-hydroxylase deficiency)	Hypophosphatemic rickets with DSD and hypertension due to congenital adrenal hyperplasia (17-α-hydroxylase deficiency)	Hypophosphatemic rickets with DSD and hypertension due to congenital adrenal hyperplasia (17-α-hydroxylase deficiency)	-
Treatment	Oral phosphate solution (50 mg/kg/day), calcitriol (0.02 ng/kg/day)	Spironolactone (2 mg/kg/day), amlodipine (0.4 mg/kg/day), clonidine (10 mcg/kg/day)	The patient did not follow up with reports for further treatment	Oral hydrocortisone (10 mg/m^2/day), cholecalciferol (60,000 IU monthly), calcitriol (0.02 ng/kg/day), phosphate (40 mg/kg/day), spironolactone (2 mg/kg/day), amlodipine (0.4 mg/kg/day), clonidine (10 mcg/kg/day)	Oral hydrocortisone (12 mg/m^2/day), cholecalciferol (60,000 IU monthly), calcitriol (0.02 ng/kg/day), phosphate (40 mg/kg/day), spironolactone (2 mg/kg/day), amlodipine (0.4 mg/kg/day)	-

ACTH: Adrenocorticotrophic hormone, DSD: Disorders of sex development

Evaluation elsewhere at 4 years of age revealed hypertension (140/100 mmHg, partially controlled with three antihypertensives, (Table 1) genu varus, normal female genitalia, and short stature (growth chart illustrated in Fig. 1a). Renal Doppler showed evidence of renal artery stenosis; however, CT renal angiogram was normal. A pelvic ultrasound performed with suspicion of Turner syndrome (owing to short stature and hypertension in a girl child), revealed absent Mullerian structures, with gonads simulating testes at deep inguinal rings. Karyotype depicted 46XY chromosomal status. Early-morning serum cortisol was low, with normal 17-hydroxyprogesterone, plasma aldosterone, and potassium concentrations, and suppressed plasma renin activity (PRA) (Table 1). As the child identified themself as female, she underwent a bilateral orchidectomy a year later. Histopathology



Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
CYP17A1 NM_000102.3	c.1283C>T (p.Pro428Leu)	Exon 8	Homozygous	Adrenal Hyperplasia, Congenital, Due to 17-Alpha-Hydroxylase Deficiency (202110)	Autosomal Recessive	Likely Pathogenic
PHEX NM_000444.5	c.2239C>T (p.Arg747Ter)	Exon 22	Hemizygous	Hypophosphatemic Rickets, X-Linked Dominant (307800)	X- Linked Dominant	Pathogenic

c

Figure 1: Longitudinal clinico-biochemical follow-up (a) Growth chart depicting short stature; (b) Trends in metabolic bone profile parameters, (c) Clinical exome analysis reporting the two genetic variants)

revealed Sertoli cells without Leydig cells/spermatogonia. Treatment for hypophosphatemic rickets was continued and growth and blood parameters were serially monitored as demonstrated in Fig. 1a and b. She was referred to our pediatric endocrinology unit for short stature and DSD at 7.5 years of age. Examination revealed hypertension (140/96 mmHg), clitoral length of 3.3 mm, two separate openings for the urethra and vagina. Plasma adrenocorticotrophic hormone (ACTH), cortisol, PRA, deoxycorticosterone (DOC), electrolytes, and clinical exome analysis were advised but not done due to financial constraints. She followed up subsequently at our institute at 10.6 years of age. Examination revealed the pre-pubertal tanner sexual maturity stage. Investigations assessed after stopping all antihypertensives except amlodipine revealed borderline low phosphorus, low 25-hydroxy vitamin D3, normal parathormone, elevated ACTH, low cortisol, low normal aldosterone, and normal potassium (Table 1). Clinical exome sequencing revealed a homozygous missense variant (c.1283C>T) in exon 8 of the *CYP17A1* gene resulting in amino acid substitution from proline to leucine at codon 428 (p.Pro428Leu, previously reported, classified as likely pathogenic as per American College of Medical Genetics and Genomics, i.e., ACMG guidelines) and a hemizygous non-sense variant (c.2239C>T) in exon 22 of the *PHEX* gene resulting in a stop codon and premature truncation of the protein at codon 747 (pArg747Ter, previously reported, classified as pathogenic as per ACMG guidelines), clinching the diagnosis of CAH due to 17-α-hydroxylase with 17, 20-Lyase deficiency and XLH, respectively (Fig. 1c). She was treated with oral hydrocortisone, cholecalciferol, calcitriol, and phosphate (Table 1) with a plan to taper antihypertensives subsequently. At the latest visit, she was 11.5 years old and seemed to have a milder phenotype of XLH as apart from genu varus (slated for surgical correction given persistence), she had no other complaints (bone pain, nephrocalcinosis, and dental abnormalities). Hypertension was well-controlled and clonidine could be tapered off successfully. Pubertal induction was deferred due to short stature and the family has been counseled about the need for estrogen replacement therapy and surrogacy in the future. They have also been undergoing psychological counseling; the child has no gender dysphoria and has always identified herself as female. The proband's younger sibling tested negative for both variants and there is no history of hypophosphatemic rickets in the mother or her siblings. During genetic counseling, the parents have been advised to undergo testing for the pathogenic variants in the proband, given the 25% risk of disease recurrence and 50% risk of carrier state for 17-α-hydroxylase CAH in future pregnancies,

Table 2: Review of cases with CYP17A1 mutation reported from India

Author group	Age/sex of rearing/ karyotype	Salient clinical findings	Investigations
Maheshwari *et al*., 2022 [4]	17.9 years/ Female/46XY	Primary amenorrhea, hypertension, SMR – P1B1, female external genitalia, laparoscopic-gonadectomy done.	Ultrasound pelvis – Absent Mullerian structures, abdominal gonads. Elevated FSH, LH, ACTH, suppressed PRA, normal aldosterone, elevated progesterone, DOC, normal 17 OHP, and low cortisol. Hypoplastic Leydig cells on histopathology.
	5 years/ Male/46XY	Atypical genitalia – micropenis, penile hypospadias, and inguinal testes.	Low, low stimulated testosterone and androstenedione, elevated FSH, LH, ACTH, normal PRA and aldosterone, elevated DOC and progesterone, low 17 OHP.
	20 years/ Male/46XY	Gynecomastia, infertility, male external genitalia, and normotensive.	Normal AMH and inhibin B, semen analysis-azoospermia, elevated ACTH, suppressed PRA, normal aldosterone, elevated DOC, low normal stimulated cortisol, elevated progesterone, and elevated 17 OHP.
	19 years/ Male/46 XY	Gynecomastia, male external genitalia, and hypertensive.	Elevated FSH, LH, suppressed PRA, normal aldosterone, elevated DOC, low normal cortisol, elevated progesterone, and elevated 17 OHP.
Sarathi *et al*., 2018 [5]	19 years/ Female/46 XY	Primary amenorrhea, SMR – A1P1B5, female external genitalia, inguinal gonads palpable, normotensive, and laparoscopic gonadectomy done.	Ultrasound pelvis – absent Mullerian structures. Elevated FSH, LH, low testosterone, low DHEAS, elevated progesterone, elevated 17 OHP, normal basal cortisol, low stimulated cortisol, and normal PRA. Hyperplastic Leydig cells on histopathology.
Sukumar *et al*., 2017 [10]	14 years/ Female/46XY	Primary amenorrhea, SMR – A1P1B1, female external genitalia, normotensive, and laparoscopic gonadectomy done.	Ultrasound pelvis – absent Mullerian structures. Elevated FSH, LH, low testosterone, low androstenedione, low cortisol, elevated ACTH, elevated progesterone, low 17 OHP, normal aldosterone, and suppressed PRA.
Philip *et al*., 2004 [11]	43 years/ Female/46XX	Secondary amenorrhea at 17 years, menstruating only with oral contraceptive pills. At 43 years: Severe proximal myopathy, fatigue, carpopedal spasms, ventricular bigeminy (due to hypokalemia), hypertension, and SMR – P1B2.	Ultrasound pelvis – right adrenal mass. Hypokalemic metabolic alkalosis, low cortisol, elevated ACTH, FSH, LH, low estrogen, low DHEAS, and mildly elevated basal 17 OHP but low after stimulation, mildly elevated aldosterone, osteoporosis (lumbar spine T score of – 3.6 on Dual-energy X-ray Absorptiometry)

AMH: Anti Mullerian hormone, ACTH: Adrenocorticotrophic hormone, OHP: Hydroxyprogesterone, DOC: Deoxycorticosterone, PRA: Plasma renin activity, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone

and 100% risk of XLH in girls if the father carries an affected gene versus 50% chance of an affected daughter or son if the mother carries the pathogenic variant. However, the parents have deferred testing due to financial constraints and the completion of the family.

DISCUSSION

We report a case of CAH due to *CYP17A1* defect with XLH, in a genetic male, reared as a girl, who presented with short stature, genu varus, and hypertension.

The differential diagnoses of DSD with hypertension in a genetic male include 17-α-hydroxylase deficiency and gonadal dysgenesis with renal abnormalities namely, Denys-Drash, Frasier, and WAGR syndromes. Denys-Drash and Frasier syndromes, both caused by mutations in the *WT1* gene required for nephrogenesis and gonadogenesis, are characterized by ambiguous genitalia and predisposition to diffuse mesangial sclerosis nephropathy and Wilm's tumor in infants with Denys-Drash, and focal segmental glomerulosclerosis and gonadal tumors with Frasier [3]. WAGR syndrome encompasses a constellation of Wilm's tumor, aniridia, genital abnormalities, and mental retardation, and is caused due to contiguous gene deletion involving the *WT1* and *PAX6* genes [3]. Our patient neither had features of nephropathy nor syndromic associations and the clinical exome analysis covering WT1 did not yield any pathogenic variants.

Pathogenic variants in *CYP17A1* are a rare cause of CAH characterized by cortisol and sex steroid deficiency and mineralocorticoid excess [1]. It is usually diagnosed in adolescence due to delayed puberty, in both, genetic females and males, although the latter may present as ambiguous genitalia or males with infertility or gynecomastia depending upon the severity of enzyme deficiency [1,3-5].

In our patient, 46XY karyotype was an incidental finding amidst the investigation for Turner syndrome. Short stature could be attributed to hypophosphatemic rickets. However, other features of XLH (skull shape distortion and dental abscesses) were absent. *CYP17A1* defect should be suspected in a child with 46XY DSD and hypertension. However, multiple confounders were present in our patient. Hypertension due to *CYP17A1* defect was initially attributed to renal artery stenosis. There were no features of hypokalemia (muscle weakness and paralytic ileus), cortisol deficiency (hypoglycemia, fatigue, and weight loss), or hyperpigmentation. A review of literature by Maheshwari

et al. have reported hypokalemic muscle paresis in 6 out of 144 probands [4]. Most studies have not reported hyperpigmentation, or overt cortisol deficiency [4,5]. The absence of overt cortisol deficiency could be attributed to glucocorticoid activity of excess corticosterone, the same mechanism being postulated for mild elevation of ACTH (absence of hyperpigmentation) [1]. Although unlikely in our case, more severe 17, 20-lyase deficiency than 17-α-hydroxylase deficiency with subsequent less severe involvement of the cortisol axis has also been postulated [4].

CYP17A1 deficiency is typically characterized by suppressed PRA and aldosterone owing to excess DOC [1]. Similar to our patient, a case series of four Indian patients reported normal aldosterone, whereas others have reported elevated concentrations [4,5]. This variability could be explained by assay-related interference (normal on radioimmunoassay, but subsequently low normal using chemiluminescence immunoassay/ high-performance liquid chromatography), which was observed in our patient and a previously reported case [6], though the severity of enzyme deficiency could also be a contributory factor (not in our case).

As observed from previous studies, chances of malignancy in non-dysgenetic gonads, particularly with androgen biosynthetic defects, are rare. However, the risk may be higher in 46XY intra-abdominal gonads [1]. A recent study has reported testicular malignancy among two late-diagnosed individuals with 17-α-Hydroxylase deficiency [7]. Gonadectomy in childhood may have been justified in our patient, as the sex of rearing was female; however, etiology (CAIS/CAH/5-α-reductase) should have been confirmed by the treating physician with testosterone, dihydrotestosterone, androstenedione, cortisol, DOC levels, and preferably next-generation sequencing, with hydrocortisone initiation before surgery. Our patient had no gender dysphoria and identified self as female. This may be explained by a lack of fetal brain androgen imprinting, akin to that observed in complete androgen insensitivity [4,8].

Leydig cell hyperplasia is classically seen in testosterone biosynthetic defects. However, our patient demonstrated Leydig cell hypoplasia, possibly explained by the autocrine role of androgens in progenitor cell differentiation into adult Leydig cells [9].

In our patient, the presence of hypertension, DSD, and low cortisol were early pointers to the diagnosis of CYP17A1 involvement. However, multiple confounders and poor follow-ups led to delayed diagnosis. To the best of our knowledge, this is the first reported case of *CYP17A1* with *PHEX* gene mutation in the world. The inability to perform parental genetic analysis is a limitation of our assessment. Contrary to most Indian reports (Table 2), our patient was diagnosed in childhood, despite being 46XY DSD with normal female genitalia.

CONCLUSION

Although by chance, the co-occurrence of an X-linked dominant and an autosomal recessive endocrine disorder, despite non-consanguineous origin, with different genetic loci is intriguing and indeed challenging to manage. Contrary to most other Indian case reports wherein the diagnosis of 46XY DSD with normal female genitalia was in late adolescence (Table 2), our patient was diagnosed in childhood. This diagnosis could be proved due to clinical exome analysis, thus, highlighting the importance of genetic testing in DSD.

CONSENT

Informed consent was obtained from the patient's father.

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