

Case report

Recurrent haematuria; a rare presentation of 46XX congenital adrenal hyperplasia presenting late and reared as males – two cases

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Journal of the Ceylon College of Physicians, 2018, **49**, 30-34

Key words: congenital adrenal hyperplasia, gender assignment, recurrent haematuria, 21-hydroxylase, 11-beta hydroxylase

Introduction

Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive disorders characterized by a defect in enzymes involved in biosynthesis of cortisol, aldosterone or both¹. The commonest type is 21-hydroxylase (21-OH) deficiency accounting for 90 to 95%. The second commonest type is 11-beta hydroxylase deficiency (6-8%)². In CAH loss of negative feedback from cortisol results in ACTH hypersecretion, and adrenocortical hyperplasia³. Accumulation of steroid precursors above the enzyme deficiency shunted into androgen synthesis pathway will result in androgen excess (Figure 1). The clinical presentation depends on severity of mutation and this varies from neonatal salt wasting, virilisation to non-classic CAH in adulthood. The degree of virilisation in a female CAH (46XX) also vary from nearly female looking external genitalia to completely male looking ones with Prader stages 2-5. In these cases, if the diagnosis is made early during infancy, gender assignment as female is not debatable. When presented later and already reared as males and presenting late gender re-assignment and management is highly challenging.

The following describes two adults with 2 different forms of CAH presenting very late with recurrent haematuria and the challenges posed on managing them.

Case 1

A 36-year-old man presented to the surgical clinic with intermittent painless hematuria for last 2 years.

He was referred to endocrinology unit for short stature and gynaecomastia. His childhood and family history was unavailable. Until this admission, no expert medical help had been sought for his short stature. He was single and working as a manual labourer. His height was 137.5cm and weighed 46kg with body mass index of 26 kg/m². He had bilateral breast enlargement with no male pattern body hair. Genital examination showed Tanner 3 staging for pubic hair and hypospadias with meatus at mid shaft of phallus. Testes were not palpable in the under-developed scrotal sac (Figure 1). His blood pressure was 120/80 mmHg and rest of the examinations were unremarkable. His karyotype was 46XX. He had elevated 17 hydroxyprogesterone (17 OHP) with slightly elevated testosterone. Although his basal cortisol was normal, the level after ACTH stimulation was suboptimal. Laboratory tests were described in table 1. Imaging with CT showed enlarged left adrenal gland (3.2x3.3cm), uterus and ovaries.

The diagnosis of CAH (21 hydroxylase deficiency) was made and consequences of the pathology that could have on the patient's life were explained. He decided to keep his sex allocation as male. He underwent surgical removal of the uterus, ovaries, upper third of the vagina and fallopian tubes under steroid cover. Bilateral mastectomy was planned and the possibility of staged male genitoplasty comprising of chordee correction, male urethroplasty and insertion of artificial testicular prosthesis in the labioscrotal sac was discussed with the patient. He was advised on the need for steroid cover during severe illness and surgery and steroid alert card was given. Monthly testosterone replacement was started.

Patient informed consent and permission to use these views was granted in accordance with recognised guidelines on the ethics of such photography.

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Figure 1. Patient with congenital adrenal hyperplasia showing short stature, breast enlargement and ambiguous genitalia.

Case 2

A 23-year-old man was transferred from a local hospital with the history of abdominal pain, haematuria and high blood pressure. He was the third child of non-consanguineous parents from a very low socio economic background. He had been admitted to the local hospital at the age of fifteen with headache and haematuria. At that time he was treated for hypertension and followed up for few months. Three years ago he was re admitted with painful genitalia and haematuria associated with clots especially at the end of the micturition. This time he was transferred to National Hospital of Sri Lanka for further evaluation for short stature and haematuria. While investigating he dropped out from follow-up. He had 4 healthy siblings. He was average in school performance and had studied up-to grade 9. But he dropped out from school due to bullying related to his short stature. At admission to local hospital he was hypertensive with a blood pressure of 240/120mmHg. He was very short with a height of 130cm and weighed 36.2kg (body mass index of 21.42kg/m²). There was no cutaneous hyperpigmentation. He had male pattern facial and body hair. His genitals were Tanner staging 4 for pubic hair, with phallus length of 4cm. He had distal hypospadias with subcoronal meatus. Scrotum was not well formed and

testes were not palpable (Figure 2). He had hypertensive retinopathy changes with silver wiring.

Karyotype was 46XX and was negative for *SRY* gene. Biochemistry and endocrine investigations shown in table 1. He had elevated 17 OHP and testosterone levels. His basal as well as ACTH stimulated cortisol levels were very low indicating adrenal insufficiency. Imaging with ultrasound scan showed rudimentary uterus and MRI showed enlarged adrenals with cystic areas, uterus with bilateral small ovaries.

The diagnosis of CAH (11 beta hydroxylase deficiency) was made based on available clinical and biochemical findings. The levels of 11-deoxycortisol and ACTH were not measured due to availability problems in the region. Similar to previous patient, he also decided to keep his sex allocation as male. Surgical removal of the uterus, ovaries, upper third of the vagina and fallopian tubes and bilateral mastectomy was planned and the possibility of staged male genitoplasty comprising of chordee correction, male urethroplasty and insertion of artificial testicular prosthesis in the labioscrotal sac was discussed with the patient. He was advised on the need for long term therapy with steroid and steroid alert card was given. Monthly testosterone replacement was started along with hydrocortisone and anti-hypertensives.



Figure 2.

Table 1. Laboratory investigations of the patients with congenital adrenal hyperplasia

Test	Case 1	Case 2	Reference value
Total testosterone (ng/ml)	1.87	3.8	0.3 - 1.2
17 OHP – basal	14	12.8	< 5
17 OHP, 60 min post synacthen (nmol/L)	93.06	93	< 30
DHEA-sulphate (µg/ml)	4.2	5.4	0.9-3.6
LH (mIU/L)	12.2	3.72	2-20
FSH (mIU/L)	9.72	5.4	2-20
Free T4 (ng/dl)	1	1.7	0.9-1.7
TSH (µIU/ml)	3.52	3.3	0.3-4.20
Cortisol (nmol/l) basal	252	60	123-626
Cortisol – 30 min post synacthen (nmol/l)	382	64.5	>550nmol/l
FBS (nmol/l)	4.6	4.3	3.9-5.5
Serum K ⁺ (mmol/l)	4	3	3.5-5.3
Serum Na ⁺ (mmol/l)	137	135	135-148
Serum creatinine (mg/dl)	0.87	0.9	0.6-1.2
Serum calcium (mmol/l)	2.21	2.18	2.1-2.55
Albumin (g/L)	4.2	3.7	3.5-5.5

Discussion

Gender identity is the sense of belonging that one feels for a particular sex psychologically and socially independent of one's biological sex. Gender assignment become very complex if the genitalia are highly virilised. Apart from karyotype, sociocultural influences and parental expectations play a significant role in this. There is scarcity of data on gender identity among females with CAH⁴. Some studies showed among 46XX CAH, only a minority developed gender dissatisfaction when reared as females, but there are also reports of successful male gender assignments^{5,6}.

These two patients have been raised as boys since birth and they are satisfied with their male gender identity. Although both of them were very short and had ambiguous genitalia, they did not seek medical attention until very late. Cyclical haematuria secondary to uterine bleeding was the main reason for them to seek medical advice. The reason for delayed presentation could be the family's desire for a male child in our sociocultural background or ignorance that early treatment is required. The diagnosis of CAH was made very late in these two patients when they have already had a firm male gender identity and the society and family has accepted them as males. Therefore we offered individualized treatment considering their medical, social and psychological wellbeing.

Management of classic form of CAH includes replacement of cortisol and aldosterone to control excess androgen symptoms. Treatment of adult patients with CAH remains controversial due to lack of randomized controlled trials comparing treatment regimens⁷. The Endocrine Society Guidelines recommend glucocorticoid treatment for adult CAH in only individuals with a significant degree of hyperandrogenism or those who desire fertility⁸. Hydrocortisone is the drug of choice in children, but in adults, long acting glucocorticoids such as prednisolone and dexamethasone can be used without concern about growth inhibition. Careful individualized therapy to optimize psychological, reproductive and sexual and bone health, avoiding steroid related side effects will benefit adults with CAH.

Although the fertility will not be possible as males in our patients, they could function as normal males with regard to marriage, relationship and occupation. There were few favourable points to these two patients; male gender identity and partial male external body habitus. Moreover they need not to face the legal issues of changes in name and sex on birth certificates and identity cards.

Sharma and Gupta⁶ have described seven children

with CAH presenting late with severe virilisation and reared as males. In this series patients underwent male genitoplasty and surgical removal of female adnexa. Over the mean follow-up duration of 9.2 years, majority were well adjusted and had good surgical and social outcome, but one had recurrent urinary tract infection and poor social adjustment.

Although CAH patients who presented late have different disease characteristics, the major sex reassignment surgical interventions in the female to male transsexual patients can be utilized for this patients. The main interventions are subcutaneous mastectomy combined with hysterectomy and oophorectomy and male genitoplasty. The interventions may differ for each patient depending on their degree of virilisation. Creation of a male chest by means of a subcutaneous mastectomy allows the patient to live more easily in the male role. Removal of the female adnexa; uterus, ovaries, fallopian tube and upper vagina will avoid other complications such as uterine bleeding presenting as haematuria like in our two patients. At a later stage, a testicular prostheses can be inserted⁹. They need hormonal treatment with testosterone replacement with monitoring of haematocrit and lipid profile.

Conclusion

Gender assignment in patients with ambiguous genitalia is a complex process especially if there is discordance between genetic and phenotypic characteristics. In patients with 46XX CAH, if the diagnosis is made in early infancy, the sex of rearing is female even if the genitalia is fully virilised. However this will be complicated in delayed patients with the concurrent development of masculine identity. Therefore early diagnosis by improving awareness among general physicians is important. In delayed or inadvertent late presentations, the management should be individualized. The quality of life will be improved by offering hormonal and surgical remedies without changing or reassigning the gender to females. These two patients were comfortable with the surgical outcome and were willing to undergo further planned surgical interventions.

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