

Case series of testicular adrenal rest tumours in boys with congenital adrenal hyperplasia: A single centre experience

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SUMMARY

Testicular adrenal rest tumours (TART) are aberrant adrenal tissue within the testes (1). Although benign, they can lead to obstruction of the seminiferous tubules and infertility in patients with congenital adrenal hyperplasia (CAH). We report six boys who developed TART, a complication of CAH. Diagnosis was confirmed by ultrasound and testicular vein sampling of elevated 17-hydroxyprogesterone (17-OHP) levels. Glucocorticoids dosages were increased 1½-2 folds to suppress size of the aberrant adrenal tissues. Despite reductions in 17-OHP, the lesions remained unchanged. Three patients had testis-sparing surgery to excise the TART and to preserve normal testicular tissues.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is caused by enzymatic defects in the pathway of cortisol biosynthesis in the adrenal cortex. 21-hydroxylase deficiency is the commonest cause of CAH (found predominantly in adrenal cortex). It converts 17-OHP to 11-deoxycortisol and cortisol. 21-hydroxylase deficiency causes inadequate production of cortisol which in turn leads to excessive ACTH production. Excessive ACTH hyper-stimulates the adrenals causing bilateral hyperplasia and accumulation of steroid precursors prior to the enzymatic block. In 21-hydroxylase deficiency, there is excessive accumulation of 17-OHP which is diverted to form androgens. Treatment aims are to replace glucocorticoid and suppress ACTH using supraphysiological doses of hydrocortisone.

Testicular adrenal rest tumour (TART) was first reported in 1940 and thought to be aberrant adrenal tissue within the testes that became hyperplastic due to chronic ACTH stimulation.¹ These tumours produce excessive 17-OHP and androgens.¹ Although benign, they can lead to obstruction of the seminiferous tubules, azoospermia and gonadal dysfunction and is an important cause of infertility.¹

CASE REPORT

We report a case series of six boys with salt wasting CAH due to 21-hydroxylase deficiency under follow up in the Paediatric Endocrine Clinic in UKMMC who were diagnosed to have TART. All patients were of Malay ethnicity. Diagnosis was based on their clinical phenotype and biochemical profile of markedly elevated 17-OHP and testosterone and salt loss at presentation. Their age of diagnosis of CAH ranged from two weeks to two months old. They were

diagnosed to have TART between 3 years 5 months and 24 years 4 months. All were poorly controlled CAH. This was demonstrated clinically by hyperpigmentation of the skin, rapid growth and advanced bone ages. Apart from these features, Patient-1 had features of androgen excess; sexual precocity with elongation of penile length and development of pubic hair. Biochemically, they had elevated 17-OHP and testosterone levels. The diagnosis of TART was suspected when their CAH control was difficult with persistently elevated 17-OHP and/or testosterone despite vigilant medical supervision to ensure adherence to medication. On digital palpation of their testes, only two out of the six boys had palpable nodules. However, ultrasound examination showed presence of testicular nodules in all patients. The diagnosis of TART in these patients was supported by venous blood sampling (Figure 1) showing a significant step-up in 17-OHP level in the testicular vein compared to the inferior vena cava (IVC) (Table I). The step-up was exaggerated after administration of intravenous synacthen (Table I). All the patients except patients 2 and 5, had higher 17-OHP levels in the testicular vein than IVC (pre-synacthen) suggesting presence of adrenal tissues in the testes which secrete 17-OHP. Post-synacthen, this difference (17-OHP in testicular vein/17-OHP in IVC) was exaggerated in all the patients except patient-2 where blood samples were missing. Nevertheless, patient-2's 17-OHP level in the testicular vein post-synacthen was markedly elevated (Table I). All patients were started on supraphysiological doses of glucocorticoid ranging from 20-33mg/m²/day for three months to suppress ACTH and regress the TART. Post-treatment evaluation showed a reduction in 17-OHP levels. However, ultrasound showed persistent testicular nodules, unchanged in their numbers and sizes. The doses of glucocorticoids were subsequently reverted to previous maintenance doses ranging from 18-22.¹ mg/m²/day. The patients were referred for surgical resection of the nodules. Three boys had surgical removal of TART. Follow up ultrasound showed no recurrence of TART.

DISCUSSION

TART is an important complication of CAH with a reported prevalence of 24% in a group of 34 CAH children between 2 to 18 years old.² This suggests TART is common even during childhood.

The risk of developing TART is increased in poorly controlled CAH. However, studies have shown development of TART even in cases of controlled CAH.¹ In 2001, it was reported that 11 out of 12 CAH patients that were treated adequately or

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Table I: 17-OHP levels for all the study patients pre and post synacthen of 250 mcg taken from the IVC and testicular vein

Patient no	Pre-synacthen 17-OHP (ng/ml)		Post-synacthen 17-OHP (ng/ml)	
	IVC	testicular vein	IVC	testicular vein
1	2.04	8.79	10.67	206.68
2	39.8	-	-	106.28
3	4.23	37.26	17.58	193.71
4	19.69	66.67	17.46	92
5	53.7	52.5	54.1	70.1
6	31.6	49.3	33.7	95.4

17-OHP 17-hydroxyprogesterone, IVC inferior vena cava

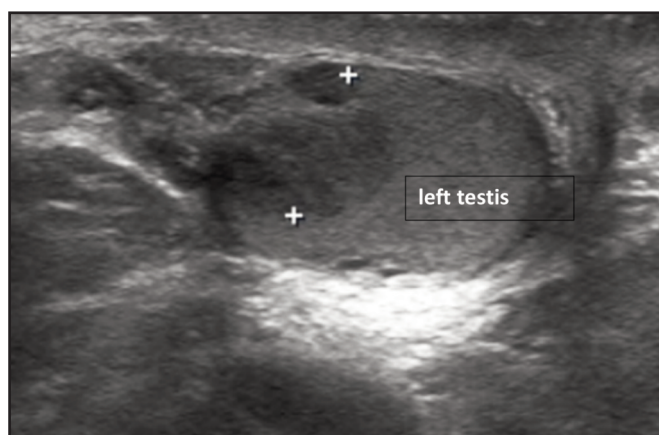


Fig. 1: Hypoechoic lesions (indicated by + symbol) in the left testis representing testicular adrenal rest tumour (TART).

over-treated had TART on ultrasonography.³ Hence it is important to screen for TART in all CAH patients.

TART are described to be located within the rete testis and are usually bilateral. Only lesions that are larger than 2cm on imaging may be detected clinically by digital palpation.¹ As digital palpation is insensitive, we should consider using ultrasound to detect these lesions. However, as ultrasound is unable to differentiate a malignant and benign lesion, confirmation of the diagnosis of TART can only be made by testicular vein sampling demonstrating a significant step-up in 17-OHP levels in the testicular veins.

The pathogenesis of the tumour growth is unclear. ACTH may be an important stimulator of tumour growth as ACTH receptors are present on the tumour tissue.¹ Therefore, intensifying glucocorticoid therapy may lead to a reduction or disappearance of the tumour through suppression of ACTH from the pituitary gland via the negative feedback mechanism.¹

TART although benign could enlarge and lead to obstruction of the seminiferous tubules, azoospermia and fibrosis.² Once diagnosed, it is extremely important to commence suprphysiological doses of glucocorticoids early to try suppress ACTH levels and thus preventing further enlargement of these lesions and a reduction and subsequent resolution of these lesions.

If medical therapy fails (due to non-compliance or resistant lesions) referral for surgical excision should be done to remove the lesions and to salvage the remaining viable testicular tissue.⁴ Long-term follow up to assess gonadal function and fertility would be important.⁴

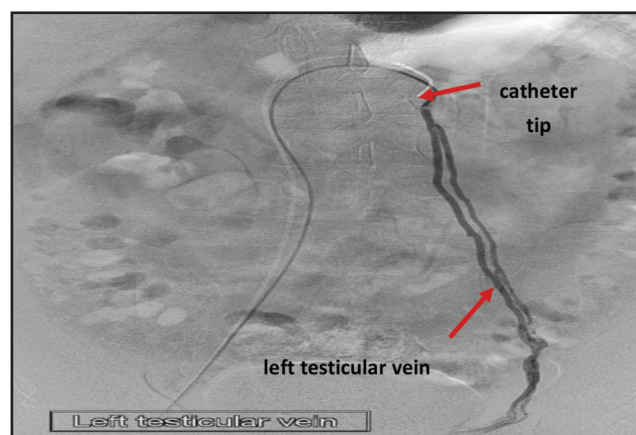


Fig. 2: left testicular vein sampling of 17-OHP.

A catheter is inserted into the left testicular vein (indicated by the arrows) and another is inserted into the IVC (not shown in the figure). Blood samples are taken via the catheters placed at the left testicular vein and inferior vena cava (IVC) before and 30 minutes after intravenous synacthen 250 mcg (synthetic ACTH) 17-OHP 17-hydroxyprogesterone, IVC inferior vena cava

CONCLUSION

From our study, we recommend regular ultrasound as an important tool to screen for TART in CAH children. This is especially important in boys with poorly controlled CAH, sexual precocity or advancing bone age as they are at high risk of developing TART. All our patients with TART had poor control of their disease. We emphasize the importance of optimal control of CAH to minimise the development of TART and its subsequent damages. Early surgical referral and testis sparing surgery should also be considered if medical therapy fails to salvage testicular tissue and to preserve fertility in these boys.

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