Macroorchidism: Consequence of Untreated Congenital Adrenal Hyperplasia

ASHU RASTOGI, RAMA WALIA, *UMA NAHAR SAIKIA AND ANIL BHANSALI
*From the Departments of Endocrinology and *Pathology, PGIMER, Chandigarh 160 012, India.*

Correspondence to:
Dr Anil Bhansali, Professor and Head, Department of Endocrinology, PGIMER, Chandigarh 160 012, India.
anilbhansali_endocrine@rediffmail.com
Received: May 05, 2011;
Initial review: June 06, 2011;
Accepted: December 28, 2011.

Testicular adrenal rest tumors (TART) are consequences of delayed diagnosis and/or undertreatment in patients with congenital adrenal hyperplasia (CAH). We describe a case of CAH with TART who presented with bilateral macroorchidism. He was managed with glucocorticoids which led to decrease in testicular size without restoration of spermatogenesis.

Key words: *Congenital adrenal hyperplasia, Macroorchidism, Testicular adrenal rest tumors.*

Children with classical common variants of congenital adrenal hyperplasia (CAH) usually present with genital ambiguity in girls and sexual precocity in boys with or without salt losing crisis (rarer types like 17 α-hydroxylase and 3 β–hydroxysteroid dehydrogenase deficiencies cause undervirilization in the male). The consequences of delayed diagnosis and/or undertreatment in patients with CAH are short stature, sexual precocity, menstrual disturbances, infertility, adrenal myelolipoma, and not uncommonly, testicular adrenal rest tumors.

Testicular adrenal rest tumors (TART) are the ectopic adrenal rest cells which show functional features of ACTH dependent adrenocortical tissue [1]. The prevalence of TART ranges between 0 and 94% depending upon the modality of tumor detection [2,3]. Ectopic adrenal rests have also been described in spermatic cords, ovaries and rarely even in celiac plexus, spinal cords and liver in normal individuals [4]. We report a case of CAH with TART who presented with bilateral macroorchidism and responded well to treatment with dexamethasone.

CASE REPORT

A 14-year-old boy, product of non-consanguineous marriage presented with short stature, bilaterally enlarged testes and acneiform lesions over the trunk. The parents noticed enlargement of testes at the age of 3 years along with appearance of facial and body hair. He also experienced rapid height gain in early childhood. He had no history of hypoglycemic episodes, dehydration, failure to thrive, jaundice or seizures in neonatal period. Developmental milestones were normal. He had no complaints of headache, gelastic episodes,visual abnormalities, constipation, delayed eruption of teeth or abdominal pain. No history of sibling death was present.

On examination, his weight was 41 kg, height 144 cm, upper to lower segment ratio of 1.18:1 (78cm:66cm), target height of 172 cm, predicted adult height of 159 cm, height age of 11.1 years and bone age of 16 years (Greulich and Pyle's charts). His blood pressure was 166/120 mm Hg in supine position (>99 percentile). Tanner's sexual maturity rating was genitalia stage V, pubic hair stage V, axillary hair were present. Both testes measured greater than 25 mL and stretched penile length was 9 cm. He had no gynecomastia. No facial dysmorphism or any skeletal defects were apparent. Rest of the systemic examination was normal.

On investigations, hemoglobin was 9.8 g/dL, total leukocyte count 6600/mm^3 with normal differential and platelet counts. Biochemistry revealed serum sodium 144 mEq/L, potassium 3.1 mEq/L, creatinine 1.22 mg/dL and urea 53.1 mg/dL. Arterial blood pH was 7.36 and HCO_3, 20.9 mmol/L. The hormonal work-up showed serum LH <0.1 mIU/L (1.7-8.6), FSH 0.3 mIU/L (1.5-12.4), testosterone 17.4 nmol/L (9.9-27.8), estradiol 26.8pg/mL (7.6-42.6), ACTH 244.2 pg/mL (5-60), cortisol 223.2nmol/L (171-536), prolactin 17.4ng/mL (4-19), T_3 0.8 ng/mL (0.8-2.0), T_4 5.2 µg/dL (4.8-12.7), free T_4 1.3ng/dL (0.7-1.7 ng/dL) and TSH 3.0 mIU/mL (0.3-4.2 mIU/mL). Basal 17 OH-progesterone was 20.5 ng/mL and 60 minutes after 250 µg cosyntropin, it did not increase further (21.6 ng/mL).

Ultrasonography of the testes revealed diffusely enlarged bilateral testes, [right testes measured 4.2×

7.9×4.5 cms (volume 105 cc) and left 5.1× 2.8× 7.9 cms (volume 80 cc)], heteroechoic with thickened epididymis. MRI testes confirmed these observations. CT Scan showed normal right adrenal but bulky medial limb of left adrenal, and normal kidneys. MRI sella was normal.

Testicular biopsy showed diffuse sheets and lobules of large, polygonal cells with abundant eosinophilic cytoplasm. The cells had ill defined borders separated by thick fibrous septa and and focally some cells contained brown lipofuschin pigment. Normal sertoli cells and Leydig cells were also seen. However, no germ cells, seminiferous tubules or Reinke crystals could be appreciated. There was no evidence of any infiltrative disorder. Based on these features a diagnosis of TART was considered.

The patient was advised oral potassium supplementation, dexamethasone 0.5 mg twice a day and ramipril 5 mg daily.

DISCUSSION

We describe a patient of CAH with testicular adrenal rest tumor based on isosexual precocious puberty, short stature, hypertension, hypokalemia, bilateral orchidomegaly and elevated 17 OH-progesterone. The possibility of 11 β–hydroxylase deficiency is most likely as patient had hypertension, hypokalemia without any genital ambiguity. The increase in 17OH-progesterone in patients with 11 β- hydroxylase deficiency is modest as this enzyme converts 11-deoxy cortisol to cortisol, while 17OH-progesterone is upstream in the steroid biosynthetic pathway.

TART have not been demonstrated in non classical 21α-hydroxylase or 11 β-hydroxylase deficient variant of CAH [6]. This can be possibly be explained because of milder enzyme deficiency in the non classical CAH while in 11 β-hydroxylase deficiency, 11 deoxy cortisol has cortisol like activity, thereby some degree of hypothalamo-pituitary-adrenal axis feedback is maintained resulting in modest rise in ACTH. The possible reason for having TART in the present case may be due to longstanding, untreated CAH. There are conflicting reports of functioning status of these tumors as some authors have described a steroid gradient between gonadal vein and peripheral vein sampling, while others could not demonstrate such findings [1-6].

Consequences of TART include discomfort due to massive orchidomegaly and infertility. Infertility is attributed to compression of the surrounding seminiferous tubules by the tumor tissue [6], ongoing ischemia and fibrosis and suppression of gonadotropins due to weaker adrenal androgens, consequently resulting in atrophy of the tubules [7,8]. The present case had absence of germ cells on testicular biopsy and azoospermia on semen analysis, suggesting irreversible damage to seminiferous tubules.

Glucocorticoid treatment in patients of CAH with TART results in regression of testicular size and restoration of fertility [9]. In the present case, steroid therapy led to decrease in the testicular size after a follow up visit at 6 months; however, spermatogenesis was not restored because of fibrotic changes in testes.

REFERENCES

1. Claahsen-van der Grinten HL, Otten BJ, Sweep FC, Span PN, Ross HA, Meuleman EJ, *et al*. Testicular tumours in patients with congenital adrenal hyperplasia due to 2l-hydroxylase deficiency show functional features of adrenocortical tissue. J Clin Endocrinol Metab. 2007; 92: 3674-80.
2. Avila NA, Premkumar A, Merke DP. Testicular adrenal rest tissue in congenital adrenal hyperplasia: comparison of MR imaging and sonographic findings. Am J Roentgenol. 1999;172:1003-6.
3. Claahsen-van der Grinten HL, Sweep FCGJ, Blickman JG, Hermus A RMM, Otten BJ. Prevalence of testicular adrenal rest tumors in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Eur J Endocrinol. 2007;157:339-44.
4. Souverijns G, Peene P, Keuleers H, Vanbockrijck M. Ectopic localization of adrenal cortex. Eur Radiol. 2000;10:1165-8.
5. Reisch N, Scherr M, Flade L, Bidlingmaier M, Schwarz HP, Müller-Lisse U, *et al*. Total adrenal volume but not testicular adrenal volume is associated with normal control in patients with 21-hydroxylase deficiency. J Clin Endocrinol Metabol. 2010;95:2065-72.
6. Claahsen-van der Grinten HL, Otten BJ, Stickelbroeck MML, Sweep FCGJ, Hermus ARMM. Testicular adrenal rest tumours in congenital adrenal hyperplasia. Best Pract Res Clin Endocrinol Metabol. 2009;23: 209-20.
7. Claahsen-van der Grinten HL, Otten BJ, Hermus AR, Sweep FC, Hulsbergen-van de Kaa CA. Testicular adrenal rest tumours in patients with congenital adrenal hyperplasia can cause severe testicular damage. Fertil Steril. 2008;89:597-601.
8. Bercovici JP, Fiet J, Gibault L,Volant A, Abalain JH, Floch HH, *et al.* Testicular adrenal rest tumours in salt wasting congenital adrenal hyperplasia (in vivo and in vitro studies). J Steroid Biochem Mol Biols. 2005;93:67-72.
9. White CP, Carter JN. Adrenal and testicular tumors and azoospermia in congenital adrenal hyperplasia. Aust New Zeal J Med. 1993;29:410.