Functional Adrenocortical Tumour in Young

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Introduction

Adrenocortical tumours (ACTs) in children are extremely rare, accounting only for 0.3-0.4% of all neoplasms in this age [1]. Adrenocortical tumours mostly secrete hormones, resulting in Cushing's syndrome, virilisation, hyperaldosteronism or feminization, while the non-functioning ones are unusual. Two syndromes have a clear association with adrenocortical tumour : Li Fraumeni syndrome is associated with mutations of the p53 gene, and Beckwith Wiedemann syndrome which has mutations in the 11p15 region [2]. Here we are reporting a rare case of functional adrenocortical tumour in a three year old boy.

Case Report

A three year old boy was referred for obesity, which was noticed since ten months. There was no preceding history of any significant drug intake or associated illness. On examination, the patient was 87cm long (<5th centile) and weighed 19 Kg (>97th centile). His blood pressure (BP) was 140/110 mm of Hg (>95th centile). He had generalized obesity, moon facies, plethoric face, double chin, short neck and buffalo hump (Fig. 1). Signs of virilisation in the form of hirsutism and deepening of voice were present. No signs of precocious sexual maturation (testicular volume was 0.8 ml and stretched penile length was 5 cm), dysmorphism (e.g. café-au-lait spots, fibrous dysplasia) or systemic abnormalities were detected on clinical examination. Investigations revealed a raised midnight serum cortisol level of 1239.7 nmol/L (normal range 180-720 nmol/L), raised serum 17-hydroxyprogesterone level of 4.97 nmol/L (normal range 0.59-3.4 nmol/L) and raised serum dehydroepiandrosterone (DHEA) sulphate levels of 204 ng/dl (normal range 13-83 ng/dl). Serum cortisol after dexamethasone (low dose) suppression remained high at 1129.3 nmol/L (normal < 140 nmol/L). Urinary 17-ketosteroid levels were raised to 12 µmol/24 hour (normal < 7 µmol/24 hour). Bone age was corresponding to the chronological age. Fundus examination, electrocardiograph (ECG) and other investigations, including blood glucose (and glucose tolerance test), serum cholesterol, serum electrolytes

(potassium-3.7 mEq/L) and thyroid profile were normal. Computed tomography (CT) scan of abdomen showed the presence of a large right adrenal tumour measuring 4.5 × 3 × 2.5 cm with Hounsfield units (HU) value of 14 (Fig. 2). Left adrenal gland was hypoplastic.

On the basis of physical examination, endocrine and radiologic assessment, diagnosis of Cushing's syndrome due to functional adrenal tumour (right) was made. The child was treated with initial drug therapy (β blockers and acetyl choline esterase (ACE) inhibitor) for hypertension and adrenalectomy (approximately 125 g of tumour mass excised). There was good response after surgery with body weight gradually reducing to 14 kg over next 6-8 weeks, BP having normalized, Cushingoid features disappearing and serum cortisol levels dropping to below normal levels (0.44 µg/dl) within five days of surgery. Histopathology revealed it to be a benign tumour (adenoma). Postoperatively, the child was started on maintenance oral steroid on titrating dosage. The child is on regular follow up with weight and BP record, clinical monitoring for precocious puberty and virilisation, three monthly hormonal (cortisol and serum adrenal androgen levels) assay and scanning of abdomen for recurrence (since, in rare cases, adrenocortical adenoma may progress to carcinoma) for the next two years and subsequently every six monthly for another five years.

Discussion

ACTs are very rare in children with a worldwide annual incidence of 0.3 per million children below the age of 15 years [3]. Adrenocortical carcinoma comprises 0.2% of all childhood malignancies. There appears to be a 15 times higher frequency of ACT in southern Brazil, most of these children having a p53 germline mutation [1]. The incidence is higher in young girls with a female to male ratio of 2:1, whereas in adolescence the sex ratio is equal. Virilisation, with early onset of pubic hair, hypertrophy of the clitoris or penis, accelerated growth, gynaecomastia or acne, is the most common presentation of ACT [3]. The second most common manifestation is with hypercortisolism

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Fig. 1 : Typical moon facies, double chin and truncal obesity in a three year old boy with Cushing's syndrome.

(Cushing's syndrome), whilst presentation with a palpable abdominal mass is unusual (most functioning adrenal tumours with a palpable mass are carcinomas). Very few tumours are non-hormone secreting (20-40% of patients with adrenocortical carcinoma). Cushing's syndrome in children younger than seven years is usually caused by adrenocortical tumour (usually an adenoma, but rarely a carcinoma) and beyond seven years by pituitary adenoma [4]. Bilateral micronodular hyperplasia and macronodular hyperplasia of adrenal glands (e.g. Carney syndrome, McCune Albright syndrome) are rare causes of Cushing's syndrome.

Frequent clinical findings include weight gain, truncal obesity, moon facies, facial plethora, double chin, supraclavicular fat pads, purple striae, hypertension, premature sexual development, glucose intolerance and infections. Progressive obesity is often the first symptom, as was seen in our patient. Growth retardation is a common manifestation in children. Hypertension may be seen in up to 43% cases [5]. The following staging criteria can be adopted for ACT [6]:

Stage I : Tumour totally excised, tumour volume $<200 \text{ cm}^3$, absence of metastasis, normal hormone levels after surgery.

Stage II : Microscopic residual tumour, tumour >200

Fig. 2 : CT scan of abdomen showing the right adrenal tumour.

cm^3 , tumour spillage during surgery or persistence of abnormal hormone levels after surgery.

Stage III : Gross residual or inoperable tumour

Stage IV : Distant metastasis

Laboratory evaluation for patients suspected of having ACT includes measurement of urinary 17-ketosteroids (17-KS), 17-hydroxycorticosteroids (17-OHCS) and free cortisol as well as plasma cortisol, DHEA sulfate, testosterone, androstenedione, 17-hydroxyprogesterone, aldosterone, plasma rennin activity, deoxycorticosterone and other 17-deoxysteroid precursors [7]. This comprehensive panel of tests not only contributes to the diagnosis, but also provides useful markers for the detection of tumour recurrence. Urinary 17-KS frequently provide the pivotal clue to a diagnosis of ACT. Plasma DHEA sulfate levels are abnormal in 90% of cases of ACT and serve as a second sensitive tumour marker. Urinary 17-OHCS levels are elevated in all cases with clinical signs of excessive glucocorticoids. Several different imaging modalities like CT, ultrasonography (USG) and magnetic resonance imaging (MRI) are used to establish the diagnosis of ACT. Tumours larger than six cm are highly suspicious for malignancy and tumours between three and six cm represent diagnostic challenge for differentiation between benign and malignant ACT [8]. Measurement of Hounsfield units (HU) in unenhanced CT is of great value in differentiating malignant from benign adrenal lesions. ACT with an attenuation value of more than 10 HU in unenhanced CT or an enhancement washout of less than 50% and a delayed attenuation of more than 35 HU (on 10 to 15-minute delayed enhanced CT) are suspicious for malignancy [8]. To avoid misclassification of a small ACT as benign neoplasia, follow-up imaging is mandatory to detect early tumour growth and should be performed initially every 3-12 months. MRI with dynamic gadolinium enhanced- and chemical shift technique is

equally effective as CT in distinguishing malignant from benign lesions. Histopathology is crucial for the diagnosis of malignancy and may also provide important prognostic information. Differentiation between benign and malignant adrenal lesions is based on macroscopic features (tumour weight, haemorrhage and breached or intact tumour capsule) and a microscopic diagnostic score with the Weiss's score, the most widely used tool [9]. Nuclear atypia, atypical and frequent mitoses (more than five of 50 high-power fields), vascular and capsular invasion and necroses are suggestive of malignancy.

The diagnosis of Cushing's syndrome due to endogenous over production of cortisol requires the demonstration of inappropriately high serum or urine cortisol levels. Four methods are accepted for the diagnosis of Cushing's syndrome: urinary free cortisol level, low-dose and overnight dexamethasone suppression test, evening serum and salivary cortisol level, and dexamethasone corticotropin-releasing hormone (CRH) test. The dexamethasone-CRH test is intended to distinguish patients with Cushing's syndrome due to pituitary or adrenal cause (cortisol increase of >20% from the baseline has a high sensitivity for pituitary cause in children) [10]. Serum adrenocorticotrophic hormone (ACTH) levels can also be used to differentiate between pituitary and non-pituitary cause.

The treatment of choice for ACT is surgical resection of the causative tumour [2]. Agents that inhibit steroidogenesis, such as mitotane, ketoconazole, metyrapone, aminoglutethimide, trilostane and etomidate have been used rarely to cause medical adrenalectomy. Poor prognostic markers (i.e. indicators of malignancy) are age greater than or equal to 3.5 years at diagnosis, interval of greater than or equal to six months between first symptoms and diagnosis, tumour weight greater than 100 g, tumour size greater than 200 cm³ and high levels of urinary 17-KS and 17-OHCS. Ambulatory follow-up

should occur every month for the first two years. Scanning of the local area in the abdomen or pelvis and of sites of metastatic disease should continue every three months for the first two years, every four months for the next two years and every six months during the fifth year [5,8]. Along with scanning, patients should be monitored for the reappearance of adrenocortical hormone hyperactivity.

Conflicts of Interest

None identified

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