

CASE REPORT

Cushing's syndrome as a rare manifestation of adrenal tumours in infants – case report

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ABSTRACT

We report a case of a six-week-old male infant with a congenital tumour of the left suprarenal gland. The tumour was diagnosed by ultrasound examination (USG) as a neonatal suprarenal mass. By the third month of life, the patient had typical signs of Cushing's syndrome. Based on the results of hormonal tests and imaging studies (USG and MRI), an adrenocortical tumour was suspected. The patient could only be cured by surgery. Histopathological examination confirmed clinical diagnosis of an adrenocortical tumour. We concluded that Cushing's syndrome may be a rare clinical manifestation of adrenal tumour in neonates. Only careful observation allows for proper diagnosis and appropriate treatment. Correct diagnosis is essential for optimal postnatal treatment.

KEY WORDS:

Cushing's syndrome, infant, suprarenal tumour.

INTRODUCTION

The incidence of neonatal suprarenal masses has increased in the last decade due to the expanded use of pre- and postnatal ultrasonography. Differential diagnoses of these masses included benign and malignant diseases such as neonatal adrenal haemorrhage/haematoma (NAH), neuroblastomas (NBLs), cysts, subdiaphragmatic extralobar pulmonary sequestration, and adrenocortical tumours (ACTs) [1, 2].

Among such diseases, NAH is the most common, with an incidence estimated between 1 : 400 to 3 : 100,000 live-born newborns [2, 3]. Primary malignant tumours

of the adrenal gland in children includes NBLs and ACTs [1, 2, 4–6]. The most common malignant tumours of suprarenal glands in neonates and infants are NBLs [1, 7].

In clinical practice, differential diagnosis of adrenal gland masses in newborns is limited to isolating the newborns with NBLs from the large group of newborns with NAH. Initially, other less frequent pathological changes in adrenal glands are not considered [4].

ACTs are rare among children. They occur with a frequency of 0.2% of all tumour types in patients below 18 years of age [8]. The incidence depends on latitude and varies across geographic regions, with a worldwide incidence of 0.3 per million, ranging from 0.1 in Hong-

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Kong and Bombay to a remarkably high 3.4–4.2 per million in southern Brazil, which is due to the high incidence of specific germline or somatic *TP53* mutations [8, 9]. Most children diagnosed with ACTs come from southern Brazil (79.5%), 13% are from the USA, and the remaining 7.5% live in other regions of the world [8–10]. The estimated incidence of ACTs is 0.4 per million during the first four years of life, and it decreases to 0.1 per million during the subsequent 10 years [8]. Most patients are under five years of age and 14% are patients over 14 years old. During the first four years of life ACTs arise from the foetal adrenal gland [11].

Approximately 90% of children with ACTs have clinical evidence of an endocrine syndrome. Due to their ability to produce hormones, adrenocortical tumours are often clinically manifested by virilisation (80%) and very rarely by Cushing's syndrome (5.5%), hyperoestrogenism (feminisation), or aldosteronism (Conn syndrome) [9, 11].

Due to the relatively low incidence, most paediatricians and paediatric oncologists see only a few or no cases of this disease. This presents considerable difficulties and diagnostic doubts, especially in the early stages of the child's life.

We report a case of six-week-old male infant with a congenital adrenocortical tumour of the left suprarenal gland and Cushing's syndrome. We present difficulties with proper diagnosis, and we emphasise differences in proceedings depending on the suprarenal gland tumour nature. We also provide an overview of the available literature.

CASE REPORT

On the day of admission to the hospital, patient was a six-week-old male infant, born on time in good general condition (Apgar 10). Due to umbilical cord compression during delivery, an abdominal ultrasound (US) was performed during the first days of life. The US revealed a hyperechogenic mass size 29 mm × 21 mm × 26 mm in the left adrenal gland without visible vascularisation. In the follow-up ultrasound, taken a few days later, the mass was slightly greater and was similar to an evolving haematoma. The child was observed, and a further follow-up ultrasound was recommended. During a follow-up examination after a month, the mass was still present with dimensions of 27 mm × 25 mm × 23 mm, and it then presented with flow under the CD option. Based on suspicion of NBL, the patient was sent to our department for further diagnostic examinations.

TABLE 1. The results of the hormonal tests

	Cortisol 8:00 (nmol/l)	Cortisol 20:00 (nmol/l)	Braking test (nmol/l)	ACTH (pg/ml)	DHEA-S (ug/dl)	Androstenedione (ng/ml)	Testosterone (nmol/l)
A	668	572	518	13.1	> 1000	28.2	10.13
B	386	–	–	10	15	0.3	0.32

A – before treatment, B – after treatment, ACTH – adrenocorticotropic hormone, DHEA-S – dehydroepiandrosterone sulfate

When the patient was admitted to the clinic, physical examination revealed general muscular hypotension and poor weight gain (birth weight [BW] 3350 g, at the age of six weeks 4200 g). The abdomen was soft and painless, with no perceptible pathological restraints. Apart from an elevated neuron-specific enolase (NSE) level (36.13 µg/l), the laboratory tests showed no changes. Catecholamine levels in urine did not deviate from normal levels. The MR of the abdomen showed a solid tumour, size of 27 mm × 16 mm × 23 mm in the location of the previously described lesion, which was undergoing moderate inhomogeneous enhancement of contrast. The entire clinical presentation suggested neuroblastoma. According to the Low and Intermediate Risk Treatment Protocol of the Neuroblastoma Societe Internationale d'Oncologie Pediatrique European Neuroblastoma (SIOPEN) Study, which considers the age of the child (< 1 year), the size of the tumour, and local advancement of the disease, the patient was admitted for observation.

One month later, during follow-up, the child presented classical symptoms of Cushing's syndrome: general muscular hypotension, poor weight gain (4650 g), dry skin composition, rash on face and shoulders, *facies lunata*, and buffalo neck (Fig. 1). Blood pressure was between the 90th and 95th percentile. In laboratory tests, NSE was lower than in previous tests (16.36 µg/l); other parameters showed no significant abnormalities. Based on physical examination and endocrine tests, the child was diagnosed with Cushing's syndrome (Table 1). In the MR, the tumour had enlarged to 36 mm × 26 mm × 28 mm (Fig. 2).

Mixed-cell ACT was suspected based on the MR imaging and the results of the hormonal tests, which revealed the following: hypercortisolaemia, no rhythm of



FIGURE 1. The typical features of Cushing's syndrome (*facies lunata*)



FIGURE 2. Magnetic resonance image with contrast

cortisol and adrenocorticotrophic hormone (ACTH) secretion, no cortisol secretion inhibition with dexamethasone inhibition test, and high hormone-active androgen levels (Table 1, column A). There were no clinical signs of premature puberty. The patient was treated surgically at the age of five months. Histopathological examination revealed an ACT with moderate malignancy potential – microscopically no radical excision. The tumour was partially encapsulated, built of cells with focal atypia, and without infiltration of the fibrous capsule. Tumour cells in the tumour area with no capsule were seen in the resection's margin. Due to no angioinvasion in histopathological examination and the absence of metastases, the disease was assessed as grade I. The patient received intravenous hydrocortisone on the day of surgery to prevent adrenal cortex insufficiency after tumour removal. Then, oral supplementation was given in gradually reducing doses.

A few weeks after surgery during the follow-up visit, a significant improvement in the child's general condition was seen: gradual weight gain, normalisation of muscle tone, and removal of other phenotypic features of Cushing's syndrome. The results of the hormonal tests five days after surgery in comparison to results before the procedure are presented in Table 1, column B. There was an increased level of cortisol after the procedure results from the oral supplementation, which was given to prevent adrenal cortex insufficiency.

DISCUSSION

In recent years, the frequency of recognising lesions in adrenal glands in neonates and infants has increased rapidly due to the improvement of neonatal and paediatric care as well as greater access to ultrasound examinations. If lesions are limited to the adrenal gland and are small (< 5 cm in diameter), they are often asymptomatic. In these cases, according to the rules of the European Low and Intermediate Risk Neuroblastoma Protocol: A SI-OPEN Study, the child should be observed until week 48

[5]. In this case study, we could observe a malignant tumour. In contrast to the distribution of NBL (1 case/7000 live births) [12], ACTs are rare (3 cases/1,000,000) [1]. Most of them (90%) are hormonally active and have a clear clinical manifestation, which is virilisation in girls and gonadotropin-independent precocious puberty in boys [11]. It presents with pubic hair, clitoral hypertrophy, hirsutism (55%), Cushing's syndrome (5.5%), and mixed hormonal disorders (29.2%), and the remainder of tumours are non-functional tumours (10.2%) [1, 11]. Much less frequently seen clinical signs are loss or lack of weight gain, a moon-like face, change of voice, and even convulsions [9]. Infants are more likely to show generalised obesity and muscle wasting [1].

ACTs are more common in girls (F : M = 1.6 : 1 to 3 : 1) and may be associated with other genetic disorders such as Beckwith-Wiedemann syndrome and hemihypertrophy. A medical history can provide information on the prevalence of adrenal tumours or others in the family, such as hepatocellular carcinoma. However, it is believed that most often these tumours occur sporadically [1, 9, 11]. These facts from history and physical examinations can be helpful in determining the diagnosis.

The rarity of ACTs in children can cause difficulties with diagnosis. Most of the available scientific papers describe individual cases observed for only a few years (Table 2) [8, 13–15].

On the other hand, the authors emphasise that ACTs are the most common cause of adrenal-dependent Cushing's syndrome in neonates and infants [8, 16].

Cushing's syndrome in children very rarely may be caused by ACTH ectopic excretion of tumours located in organs other than suprarenal gland. There are case reports of Cushing's syndrome in children due to a sacrococcygeal teratoma and neuroblastoma [17–19]. Adrenal NBL may be responsible for paraneoplastic Cushing's syndrome [18].

In most cases, ACT diagnosis is delayed. The median period from onset of first symptoms to time of diagnosis in infants is, on average, five months. Isolated Cushing's syndrome occurs more often in the older age group (median 12.6 years) [11].

At the time of diagnosis, in 2/3 of cases, the disease is limited to the adrenal gland (stage I or II) [9].

The basic treatment for ACTs is surgery. However, because of the tumour's tissue fragility, bursting of the capsule and outpouring of tumour contents is relatively frequent [9]. Patients with no possibility of radical resection undergo systemic treatment with mitotane monotherapy, multidrug chemotherapy, and radiotherapy [8–10, 20].

The presented case report shows that diagnosing adrenal gland lesions during the neonatal period can cause difficulties. In our patient, the adrenal gland mass was initially assessed as NAH and later as NBL. Only at a later age, when the patient demonstrated signs of Cushing's syndrome, did it lead to the correct diagnosis.

TABLE 2. The references from recent years regarding Cushing's syndrome in infants [13–15]

Authors	Age (months)	Sex	Family history	Gestation week	Birth weight (g)	Disease history time (months)	Physical examination	Laboratory tests	MRI/CT results	Treatment	Histopathology	Follow
Dutta <i>et al.</i> [13]	23	F	No malignancy	39	3544	2	Moon face, buffalo hump, facial and back hirsutism, facial acne, greasy hair, no palpable mass, BP 140/100 mm Hg, Tanner stage 2	Midnight cortisol 796 nmol/l, ACTH < 5 ng/l, mean cortisol 728 nmol/l, loss of circadian rhythm, raised serum androgens, no suppression of cortisol in overnight dexamethasone suppression test	Right-side mixed solid/cystic suprarenal mass 6,8 mm × 6,5 mm, no vascular, hepatic or renal invasion, no metastases	Laparoscopic surgery, metyrapone preoperatively, complete removal of tumour with no spillage, maintenance hydrocortisol	Adrenal cortical carcinoma with complete resection.	Gradual improvement in height and weight; no evidence of tumour in US
Fudge <i>et al.</i> [14]	6	F	Non-contributory	At term	3060	3	Moon face, facial acne, irritability, arrested linear growth, increased weight, BP 110/70 mm Hg, poor muscle tone, no virilization signs	Serum cortisol 240 mcg/dl, total testosterone 1185 ng/dl, DHEA-S 401 mcg/dl, serum ACTH < 5 pg/ml	Right-side adrenal heterogeneous mass 36 mm × 54 mm × 38 mm; tumour thrombus into the inferior vena cava, no metastases	Preoperatively ketoconazole, surgical resection of tumour and thrombus; hydrocortisone during and after surgery	Adrenocortical carcinoma with no capsular and vascular invasion, 5–10% necrosis, spotty calcification	Normalization of hormonal markers postoperatively
Vieira and Brain [15]	4	F	Maternal pregnancy-induced hypertension	At term	2800	3	Moon face, chubby, protruding abdomen, increase weight, normal BP	Cortisol 41 mcg/dl	Homogenous left adrenal mass 53 mm × 48 mm × 37 mm with distinct borders	Preoperatively ketoconazole, laparotomy with excision of the mass; postoperatively hydrocortisone and fludrocortisone	Adrenal adenoma without vascular capsular invasion	

ACTH – adrenocorticotrophic hormone, DHEA-S – dehydroepiandrosterone sulfate

CONCLUSIONS

In diagnosing adrenal lesions, not only NAH and NBL should be considered as possibilities but also very rarely occurring ACTs. Only performing a very thorough physical examination of the child and noticing abnormalities can lead to proper diagnosis.

DISCLOSURE

The authors declare no conflict of interest.

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