Staged Bilateral Laparoscopic Adrenalectomy for Infantile ACTH-independent Cushing's Syndrome (Bilateral Micronodular Non-pigmented Adrenal Hyperplasia): A Case Report

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Key words: Cushing's syndrome; laparoscopic adrenalectomy; infant.

ACTH-independent Cushing's syndrome is an uncommon disorder in children. While laparoscopic adrenalectomy is well-established in adults, it is rarely used in infants and is associated with some concerns. A seven-month infant was referred to our hospital due to progressive signs and symptoms of Cushing's syndrome. Laboratory data confirmed ACTH-independent hypercortisolism. No history of exogenous corticosteroid contact was observed. The patient underwent left transperitoneal laparoscopic adrenalectomy when she was 7 months old, nevertheless, complete response was not seen. The patient underwent right laparoscopic adrenalectomy (contra-lateral adrenal gland) when she was 20 months old. The signs and symptoms of Cushing's syndrome began to resolve and serum and urine cortisol levels became normal 3 months after the second surgery. laparoscopic adrenalectomy is safe and feasible in infants, and in this case, relieved patient of the symptoms and saved her life.

INTRODUCTION

Cushing's syndrome is a potentially life-threatening disorder which usually occurs in adults. Approximately 10% of Cushing's syndrome are observed in children (up to 18 years old), and it is a very rare disorder in the infancy period. Endogenous Cushing's syndrome is typically categorized to ACTH-dependent and ACTH-independent variants. More than 80 percent of Cushing's syndrome are due to pituitary adenomas and are ACTH-dependent (So called Cushing disease). ACTH-independent Cushing's syndrome is far uncommon and may be due to adrenal adenoma, hyperplasia or cortisol producing carcinoma[1].

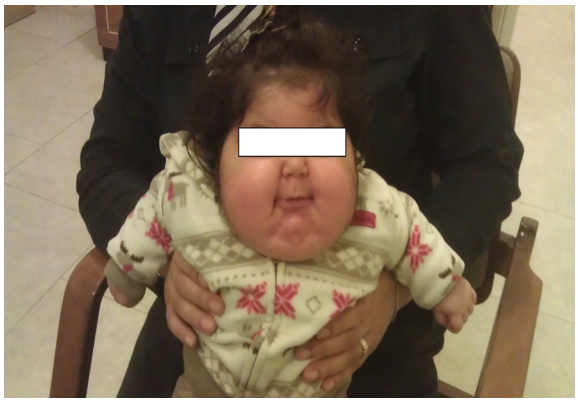

Figure 1. Patient appearance before the first surgery.

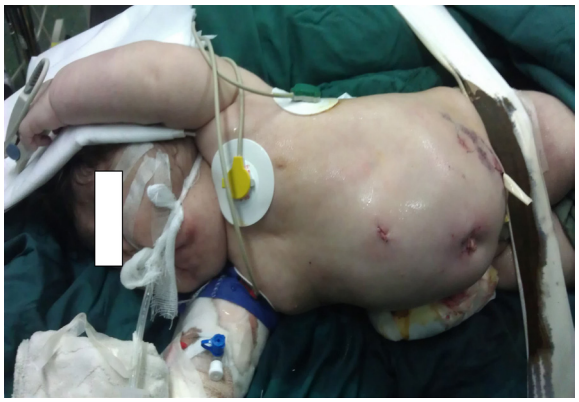

Figure 2. First laparoscopic adrenalectomy on the left side (image taken after completion of the operation).

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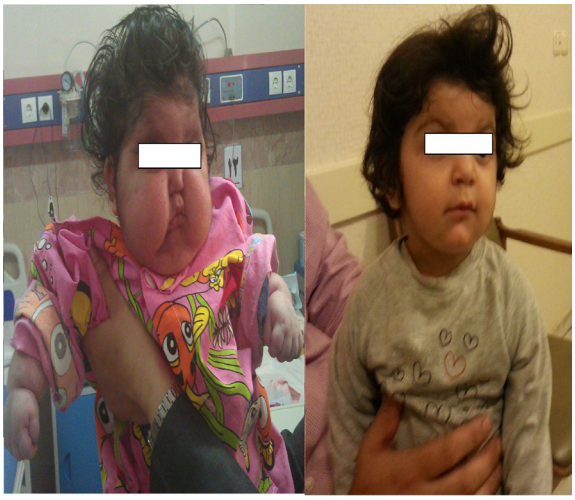

Figure 3. Patient appearance before the second surgery and after bilateral adrenalectomies.

ACTH-independent bilateral adrenal lesions are very rare in children and have occasionally been reported. Some of these cases have been related to familial syndromes. Primary pigmented nodular adrenal disorder (in relationship with Carney complex disease) and bilateral macronodular adrenal hyperplasia (as part of Mc-Cune-Albright syndrome) are some instances[2, 3]. Laparoscopic adrenalectomy is seldom done in younger children with Cushing's syndrome owing to extreme obesity, abundant perinephric fat and a high incidence of pre- and postoperative complications. Here, we present our experience with a case of non-pigmented non-familial bilateral adrenal hyperplasia in an infant which resulted in ACTH-independent Cushing's syndrome; and was successfully treated with staged bilateral laparoscopic adrenalectomy.

CASE PRESENTATION

A 7-month-old infant was referred due to the symptoms and signs of Cushing's syndrome (**Figure 1**). The patient was the first daughter of a non-consanguineous marriage and was born after an uncomplicated gestation and vaginal delivery. Her birth weight was 3.170 Kg and she did not have any problems up to three months of age. The early manifestations were moon face, facial plethora, progressive central obesity, hypertrichosis which were noted by her parents. No history of exogenous contact with corticosteroid containing products was reported.

Table 1 indicates the level of 8 AM serum cortisol, urine free cortisol and ACTH, before and after low dose dexamethasone suppression test. Very high levels of cortisol in serum and urine, plus suppressed serum levels of ACTH (<1 pg/mL) confirmed a case of ACTH-independent hypercortisolism. Further assessment of adrenal region was performed using abdomino-pelvic computed tomography (CT) without and with contrast medium. The only abnormal finding was mild enlargement of left adrenal gland (11*8 mm vs. 8*5 mm for right adrenal gland) without any clear tumor.

The patient underwent left laparoscopic adrenalectomy

Table 1. Laboratory investigations of the patient.

Hormonal Tests	Patient's values	Reference range
Basal		
Cortisol 08:00 A.M µg/dL	68	4.5 - 22
24h urine free cortisol		
µg/24h	110	Up to 75.2
ACTH pg/mL	< 1	7.2 - 64
After single dose overnight dexamethasone suppression test		
Cortisol 08:00 A.M (µg/dL)	> 50.7	4.5 - 22
Post high dose dexamethasone Suppression test		
Cortisol 08:00 A.Mr (µg/dL)	85	< 2
24h urine free cortisol (µg/24h)	239	< 5
ACTH pg/mL		< 1
DHEA-S (µg/dL)	564	5-85*
Testosterone (ng/mL)	1.26	0.01 – 0.05**
Androstenedione (ng/mL)	3.0	0.08 – 2.5***
PTH (pg/mL)	< 4	4.5 - 58
PTH related peptide (pmol/L	< 0.1	< 0.4
Biochemical tests at 6 months before operation		
Blood sugar (mg/dL)	128	< 126
Blood urea nitrogen (mg/dL)	10	6 - 23
Serum creatinine (Cr) (mg/dL)	0.6	0.6 – 1.2
Serum sodium (meq/L)	136	135 - 145
Serum potassium (mmol/L)	3.2	3.8 – 5.0
Serum calcium (Ca) (mg/dL)	12.4	8.9 – 10.5
Serum phosphorus (P) 4.0	4.5 – 6.5	
24 hr Urine Ca (mg/kg)	7.6	< 4
Urine ca/cr ratio 1	0.8	
Fraction excretion of P	17%	< 15%
25 (OH) D (ng/mL)	48	30 - 100
1,25(OH)2 D (ng/L) `	50	20 - 135
After operation		
Serum Ca~ (mg/dL)	9.6	8.9 – 10.4
Serum P~ (mg/dL0	5	4.5 – 6.5

Abbreviations: P, Phosphorus; Ca, Calcium; dL, deciliter; DHEA-S, dehydroepiandrosterone sulphate; *, normal range (NR) < 9 years; **, NR for sex and age; ***, NR for child

when she was 7 months old (**Figure 2**). The specimen reported to be micronodular adrenal hyperplasia. She was followed for resolution of clinical and laboratory abnormalities. Although there was a mild reduction in symptoms and signs of Cushing's syndrome, complete response was not observed. Laboratory data 10 months after surgery (when the child was 17 months old) indicated that the patient had hypercortisolism state. Urine free cortisol was 95 µg/dL (normal range up to 75) and serum cortisol was 26.5 µg/dL (normal range up to 22). Plasma ACTH level was again suppressed (1.2 pg/mL), indicating ACTH-independent hypercortisolism. The patient underwent right laparoscopic adrenalectomy roughly one year after the first surgery (contra-lateral adrenal gland), when she was 20 months old. The pathology report was micronodular adrenal hyperplasia, as well. The patient was given hormonal replacement therapy and soon, the signs and symptoms of Cushing's syndrome began to resolve and serum and urine cortisol levels became normal 3 months after surgery. **Figure 3** shows patient's appearance before the second stage of adrenalectomy and 1 year after, respectively. After two years follow up, no recurrence was occurred.

Technique of Surgery

After general anesthesia and in lateral decubitus position, a 5 mm port was inserted at the umbilicus using open access approach. Then three other 5 mm trocars (sub xiphoid, para rectal region parallel to umbilicus and medial of anterior superior iliac spine) were inserted under direct vision. Laparoscopic surgery was done via a transperitoneal approach by developing pneumoperitoneum via four ports. After medicalization of colon, adrenal gland was identified and released from its bindings. In the left adrenal approach at first we determined the left renal vein and then ligated the adrenal vein by cautery and released the adrenal gland. In the right side, at first we released the adrenal from the surrounded tissues and IVC by cautery. Adrenal gland was delivered using an endobag (**Figure 2**). A penrose drain was inserted and left at place at the end of the surgery. The operation times were 135 and 95 minutes in the first and second surgeries, respectively.

Urinary catheter was removed one day after the surgery, and enteral diet was introduced whenever bowel movements were assured. In each of the operations, patient was discharged after four days with no peri-operative complications. Penrose drain was removed at the time of discharge. Long-term follow up showed minimal surgical scar, which is a benefit of laparoscopic surgery.

DISCUSSION

Most cases of pediatric Cushing's syndrome are due to pituitary adenomas, which are ACTH-dependent and primarily treated with trans-sphenoidal surgery. ACTH-independent variant comprises a minority of patients with Cushing's syndrome (approximately 10%). Autonomous and non-controlled secretion of cortisol from adrenal cortex is the main event that leads to subsequent symptoms and signs. The primary lesion in adrenal gland may be unilateral or bilateral, macro-adenoma or hyperplasia and sporadic or familial (such as part of Mc-Cune Albright syndrome or Carney complex disease)[1].

Medical therapy with steroidogenesis inhibitors (such as metyrapone and ketoconazole) can reduce plasma cortisol levels; however surgical resection of the diseased adrenal is highly and rapidly effective in eliminating the source and thus it has been globally accepted as the standard treatment of ACTH-independent Cushing's syndrome. Laparoscopic adrenalectomy is considered as the standard treatment for benign adrenal masses in adults. Nevertheless, pediatric laparoscopic adrenalectomy is less well defined due to the infrequency of pediatric adrenal masses[4].

Pampaloni and their colleagues in 2004 reviewed the initial case series of laparoscopic adrenalectomy in children. 83 cases were reported till that time, of which the majorities were due to pheochromocytoma and neuroblastoma. The age range was from 1 month to 16 years old. They concluded that laparoscopic adrenalectomy in the pediatric group is safe and feasible[5]. Laje and Mattei in 2009 reported their experience with 8 cases of laparoscopic adrenalectomy in children aged 2 to 18 years old. The majority of cases were adrenal cortical adenomas[6].

Due to the very rare incidence of ACTH-independent Cushing's syndrome in children, its treatment is generally based upon data from adult type disease. The cases of pediatric ACTH-independent in children are infrequent, especially in infants. Care must be given to differentiate between endogenous and exogenous Cushing's syndrome in infants (which may be due to topical corticosteroids occasionally used for diaper rash)[7].

The case we reported herein was associated with special features. First, infantile ACTH-independent Cushing's syndrome is very rare and usually reported as part of Mc-Cune Albright or Carney complex disease in the literature. Mc-Cune Albright syndrome is usually associated with large adrenal glands resulting from macro-nodular hyperplasia. Carney complex disease leads to pigmented nodular hyperplasia of adrenal glands. Our case was a sporadic form of bilateral non-pigmented micronodular hyperplasia. Second, although laparoscopic adrenalectomy is widely accepted in adults and young adolescents, there may be still some concern in infants due to less experience and special features of infants. In contrast to open surgery, laparoscopic adrenalectomy may be associated with clearly less surgical scar, shorter convalescent period and minimal peri-operative complications (8). Third, in this case of bilateral hyperplasia, resection of the greater adrenal gland (i.e. Left adrenal) did not result in complete response, and the patient needed to undergo sequential contra-lateral adrenalectomy. This suggests that in cases of bilateral hyperplasia, pre-operative imaging findings like adrenal enlargement may not predict the response to unilateral adrenalectomy. However, the second laparoscopic operation was also feasible and performed without any side effects one year later.

In conclusion, we reported a rare case of sporadic infantile bilateral micro-nodular adrenal hyperplasia, which resulted in sever signs and symptoms of ACTH-independent Cushing's syndrome. The patient was successfully treated with sequential bilateral laparoscopic adrenalectomy, showing dramatic response without any important side effects.

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