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Death in pediatric Cushing syndrome is uncommon but still occurs

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Abstract

Cushing syndrome (CS) in children is rare. Delayed diagnosis and treatment of CS may be associated with increased morbidity and, unfortunately, mortality. We performed a retrospective review of all patients with CS under the age of 18 referred to the NIH from 1998 to 2013 in order to describe deceased patients among cases of pediatric CS referred to the National Institutes of Health (NIH).

The deaths of 4 children (3 females and 1 male), aged 7.5–15.5 years (mean age 11.2 years) with length of disease 2–4 years were recorded among 160 (2.5%) children seen at, or referred to the NIH over the last 15 years. All died at different institutions, prior to coming to the NIH (two of them) or after leaving NIH (two of them). Presenting symptoms included increasing weight and decreasing height gain, facial plethora, dorsocervical fat pad (webbed neck), striae, headache, vision disturbances and depression and other mood or behavior changes; there were no differences between how these patients presented and the others in our cohort. The causes of CS in the deceased patients were also not different, in fact, they spanned the entire spectrum of CS: pituitary disease (one of them), ectopic corticotropin production (one of them), and primary adrenal hyperplasia (1). In one patient, the cause of CS could not be verified. Three died of sepsis and one due to residual disease and complications of the primary tumor.

Conclusions—Despite advances in early diagnosis and treatment of pediatric CS, a 2.5% mortality rate was identified in a large cohort of patients with this condition referred to an experienced, tertiary care referral center (although these deaths occurred elsewhere). Pediatricians need to recognize the possibility of death, primarily due to sepsis, in a patient with pediatric CS and act accordingly.

Keywords

Cushing syndrome; Cushing disease; mortality; pediatric endocrinology

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CONFLICT OF INTEREST

All the authors have nothing to disclose.

INTRODUCTION

Few studies have reported mortality among children with Cushing syndrome (CS) [13,16,28,14]. CS is a rare disease in children and adolescents and this has contributed both to the lack of data and the fact that children with CS still occasionally die: timely diagnosis is challenging and may be missed due to the nonspecific signs and symptoms that can mislead pediatricians and even endocrinologists [29]. Mortality rates vary depending on the type of tumor, age, sex, years of hypercortisolism and co-morbidities that stem from it (Table 2). The incidence of CS in children is less than 2 to 3 cases per million per year [19,30]; in addition, the average length of time for recorded symptoms prior to diagnosis of the condition exceeds 2 years [11,31]. Although it has been suggested repeatedly that children with CS should receive treatment in a specialized center, it is still the case that a number of these patients are cared for in medical centers with no experience in the disease or even community hospitals [2,31].

In the present investigation, we report all the deaths that occurred among patients under the age of 18 years (yr) that were referred to the National Institutes of Health (NIH) in the last 15 years; the review of these cases that were identified retrospectively has important lessons to teach us for the management of children with CS.

CLINICAL PROTOCOL & METHODS

The charts of one hundred sixty children seen at or referred to the NIH with the diagnosis of CS the years 1998 to 2013 were reviewed. All studies were conducted under clinical protocols 97CH0076, 00CH0160, and 95CH0059, all approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. Informed consent from the patients' parents (and assent from older children) was obtained for all patients. Diagnosis of CS was confirmed, as previously described [2,31].

CASE RECORDS OF DECEASED PATIENTS

Patient 1 was a 9.5 yr old female who initially presented to her pediatrician with weight gain and decreasing growth velocity during the previous 2 years. Physical examination revealed central obesity, facial plethora and hepatosplenomegaly. Her first pediatric endocrinologist diagnosed congenital deficiency of growth hormone (GH) but the patient's height remained unchanged even after GH replacement treatment for one year. Another endocrinologist noted adrenocorticotrophic hormone (ACTH)-independent hypercortisolism but because of an unremarkable adrenal computerized tomography (CT) she was referred to the NIH. Hypercortisolism was confirmed, due to an adrenal source (Table 1). Pituitary magnetic resonance imaging (MRI) was unremarkable (Table 1). She underwent bilateral adrenalectomy and the pathology was consistent with bilateral, isolated micronodular adrenocortical disease (iMAD). She was identified to have the 171delTfs41X inactivating *PDE11A* mutation (case CAR36.03) [12]. Postoperatively, she developed a pancreatic fistula, which was drained. The patient was treated with systemic antibiotics and discharged in stable condition after 3 weeks at the NIH. After a week, she was admitted to a regional hospital with intractable vomiting and fever. She expired a few days later due to

complications of gastroenteritis which led to necrotizing pancreatitis extensive fat necrosis and peritonitis with perisplenic abscess formation. Autopsy report also noted acute kidney tubular necrosis as well as pulmonary thromboemboli with pulmonary congestion

Patient 2 was a 13-yr-old male who initially presented to his pediatrician with weight gain and decrease in growth velocity during the preceding 2 years. Other symptoms included increased appetite, facial fullness, depression, fatigue, headaches and increased pigmentation of the back of his neck, knuckles and knees. He was referred to a pediatric endocrinologist who diagnosed him with hypertension (150/110 mmHg) and hypercortisolism (Table 1). An adrenal ultrasound and pituitary MRI were unremarkable. He was started on antihypertensive therapy and was referred to the NIH. CS was confirmed along with an elevated plasma ACTH (Table 1); an ovine cortisol releasing hormone test (oCRH test) and an 8 mg dexamethasone suppression test (8 mg DST) were consistent with an ectopic source of ACTH (Table 1). His pituitary MRI was unremarkable and an adrenal CT showed enlarged adrenals. A chest CT showed a thymic mass encasing numerous vessels and extending to nodes into neck and axillae with no evidence of distant metastasis. Surgery revealed a thymic carcinoid and significant tumor infiltration into cervical, peritracheal, and paraesophageal lymph nodes [24]. Clinical screening and genetic testing for multiple endocrine neoplasia (MEN1) were negative. Due to continuing hypercortisolism, severe hypertension, hypokalemia, and hypercoagulability he was transferred from the NIH to a chronic care facility where he died a few months later due to complications of his primary disease (i.e. airway obstruction). He passed away 3 years after the appearance of the first signs of CS.

Patient 3 was a 15.5-yr-old female who initially presented to her pediatrician with complaints of increased weight gain during the last 4 years and significant changes in her facial features, presence of dorsocervical fat and abdominal striae for one year. Other symptoms included increased appetite, hirsutism, headache, fatigue, polyuria, and difficulty in breathing. She was then referred to a tertiary medical center where the laboratory findings proved hypercortisolism (Table 1). She was suspected of having CS since she had high serum ACTH and she did not suppress her serum cortisol levels after a 1 mg DST (Table 1). Pituitary MRI was unremarkable which prompted referral to the NIH. CS was confirmed and the results of the 8 mg DST and the oCRH test were consistent with pituitary disease (Table 1). The patient was scheduled for transsphenoidal surgery (TSS), sent home, and due to come back for the procedure. The patient died three weeks prior to TSS at a regional hospital due to sepsis, although the origin of the infection remains unclear. She passed away 4 years after the appearance of the first signs of CS.

Patient 4 was a 7.5-yr-old female who initially presented to her pediatrician with increasing weight and decrease in growth velocity during the last 2.5 years. Other symptoms included facial plethora and flushing, obesity, dorsocervical fat pad, increased appetite, polyuria, headache, diplopia, depression, insomnia, and adult body odor. She was then referred to a pediatric endocrinologist, for further evaluation. Her laboratory findings showed hypercortisolism (Table 1) but after the 1 mg DST, serum cortisol levels were suppressed (Table 1). The adrenal CT and the pituitary MRI were unremarkable. Her endocrinologist suggested cyclical CS due to high 24h-UFC and referred her to the NIH. However, she died

from complications of bronchopneumonia before admission to the NIH-CRC. The cause of CS was never identified and she passed away 3 years after the appearance of the first signs of CS.

RESULTS

We retrospectively reviewed 160 pediatric patients with CS, referred to the NIH between 1998 and 2013 (Figure 1). Female-to-male predominance (86 females:74 males) was similar to the adult population (Fig. 1) [19]. Of these children, 122 children had CD (76.25%), 31 (19.37%) had adrenal tumors, 6 (3.75%) had ectopic production of ACTH and one had CS from an unknown etiology (0.625%). We identified four children (2.5%) [(3 females, 1 male), aged 7.5–15.5 yr (mean age 11.2 yr) with length of disease 2–4 yr], whose death was attributed to the complications of CS. One of these four children was diagnosed with a pituitary adenoma, another with adrenal hyperplasia (iMAD), one with ectopic production of ACTH and one had CS from an unknown etiology. Thus, in this study, mortality rates in the four main diagnostic categories of CS in children were 0.81% (1:122) for pituitary adenoma, 3.22% (1:31) for adrenal tumors, and 16.7% (1:6) for ectopic ACTH-producing tumors.

There was nothing unusual about these patients in terms of the severity of their disease when they were first detected of having CS or at their presentation at the NIH-CRC when compared to all other 156 patients. One patient even had cyclical, periodic CS which is typically mild. These children were referred to a specialized center and the diagnosis and treatment were made according to pediatric-specific protocols [2,19,29,31]. They all shared increasing weight gain accompanied and a slowing growth velocity, as we have reported before for children with CS [2,31]. Other symptoms varied and included facial plethora and flushing, dorsocervical fat pads, striae, polyuria, hypertension, headache, vision disturbances, depression and insomnia as has already been reported in pediatric patients [30]. Their cortisol levels and responses to tests (Table 1) were like any other patient with CS that we have seen in these last 15 years. The cause of death was related to sepsis in 3 of the 4 cases, whereas in one case it was due to the primary tumor.

DISCUSSION

Few reports of pediatric mortality due to CS exist (Table 2) [13,16,28,14]. Our study found a small but not negligible mortality rate among a large series of children with CS: 2.5%. A number of studies on mortality in CS in adults are available [25,35,1,26,33,4,18,17,9,30,6,22,7]. The exact cause of death is not clearly stated in most cases, and data are not always standardized (size of the cohort, follow up period, definition of remission of disease) [25]. The epidemiology of CS, the morbidity and the mortality of CS in children and in adults are quite different [1,31,25]. Moreover the mortality rate in CS might be attributed either to the main disease/tumor or to co-morbidities that stem from sustained hypercortisolism. In agreement with previous studies, the mortality in our patients was mainly attributed either to infection/sepsis due to sustained hypercortisolism or to residual disease/progression of disease [25,7,35,13]. The mortality rate according to type of disease/tumor in children is almost the same with adults (Figure 1) [18,9]; mortality is lower

for CD, it is quite higher for adrenal tumors and it is dramatically higher for ectopic ACTH-producing tumors (Table 2).

Since these children were not different from any others in our cohort, what led to death in these 4 cases and what lessons can we derive from them? If one sets aside the child with the thymic carcinoid who died of complications of his primary tumor, the other 3 died of an infection that led to sepsis: in two the cause was identified as gastroenteritis (one of them) and pneumonia (one of them); in the third, the primary infection is unknown. Although detailed immune work up is not available for any of the 4 children, we have to assume that sepsis developed in 3 of the 4 due to immunosuppression as a result of CS.

The immune-endocrine interactions are complex. They are likely mediated by hormonal pathways and neuropeptides, as well as cytokines and chemokines [20]. Hypercortisolemia from an endogenous or an exogenous source induces immune suppression and predisposes to opportunistic infections affecting mainly the cell-mediated immunity [27]. Some patients with CS may present with mucocutaneous fungal infections, postoperative wound infections, opportunistic bacterial infections (eg. *Pneumocystis carinii*), or reactivation of latent tuberculosis [8] and other diseases. Notably the duration and the degree of hypercortisolism correlate positively with the induced immune deficiency and the frequency and the severity of infection. Interestingly even if CD is more common in children than adrenal tumors and ectopic ACTH syndrome, the opportunistic infections usually occur to the last two since they are characterized by higher serum cortisol levels [8,15,34,20,32,27].

One could speculate on the basis of these data that any child with CS, even in the absence of any other predisposing factors or co-morbidities, has a certain risk of sudden death, primarily due to uncontrolled complications of a primary infection. Therefore hypercortisolism may mask the signs and symptoms of infection due to its potent anti-inflammatory actions explaining the high risk of sepsis in CS [8,6,35]. The assessment of immunodeficiency by means of the complete blood count or by the measurements of body temperature is not reliable in patients with CS. Moreover these indices did not correlate with the levels of cortisol, UFC or urinary 17-OH-steroids. Some clinicians suggested to start antibiotic prophylaxis in patients with severe hypercortisolism [27]. These are important to consider given that, due to its nonspecific initial signs and symptoms, in our experience, CS is diagnosed by referring endocrinologists at least two years from when pictures and growth chart data date the beginning of the disease [11,31].

The present data suggest that recognition of early signs and symptoms of CS is extraordinarily important; once the disease is diagnosed early treatment is essential. And finally, even after curative surgery, patients should be followed carefully as the risk of sepsis remains for some time [6]. Detailed investigation of the immune system recovery in patients with CS is lacking at this time, but one should have a low threshold for treating infections aggressively the first few months after cure of CS. Referral to an experienced medical center for the treatment of CS and its complications has been mentioned before as an essential factor in providing state-of-the-art care to these patients [10].

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ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
ACC	Adrenocortical carcinomas
ACT	Adrenocortical tumors
CD	Cushing disease
CS	Cushing syndrome
CT	Computerized tomography
GH	Growth hormone
iMAD	Isolated micronodular adrenocortical disease
IPSS	Inferior petrosal sinus sampling
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
oCRH test	Ovine cortisol releasing hormone test
PPNAD	Primary pigmented nodular adrenal dysplasia
RR	Reference range
TSS	Transsphenoidal surgery
yr	Year
24 h UFC	24 hour urine free cortisol
1 mg DST	Low dose (1mg) dexamethasone suppression test
8 mg DST	High-dose (8 mg) dexamethasone suppression test or Liddle's test

REFERENCES

1. Ammini A, Tandon N, Gupta N, Bhalla A, Devasenaspathy K, Kumar G, Sahoo J, Chittawar S, Philip J, Baruah M, Dwarakanath C, Tripathi S. Etiology and clinical profile of patients with Cushing's syndrome: A single center experience. *Indian J Endocrinol Metab.* 2014; 18(1):99–105. [PubMed: 24701438]
2. Batista DL, Riar J, Keil M, Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. *Pediatrics.* 2007; 120(3):575–586.
3. Bhansali A, Walia R, Rana S, Dutta P, Radotra B, Khandelwal N, Bhadada S. Ectopic Cushing's syndrome: experience from a tertiary care centre. *Indian J Med Res.* 2009; 129(1):33–41. [PubMed: 19287055]
4. Clayton R. Mortality in Cushing's disease. *Neuroendocrinology.* 2010; 92(1):71–76. [PubMed: 20829622]

5. Clayton R, Raskauskiene D, Reulen R, Jones P. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metab.* 2011; 96(3):632–642. [PubMed: 21193542]
6. Dekkers O, Horváth-Puhó E, Jørgensen J, Cannegieter S, Ehrenstein V, Vandenbroucke J, Pereira A, Sørensen H. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab.* 2013; 98(6):2277–2284. [PubMed: 23533241]
7. Etxabe J, Vazquez J. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol (Oxf).* 1994; 40(4):479–484. [PubMed: 8187313]
8. Graham B, Tucker WJ. Opportunistic infections in endogenous Cushing's syndrome. *Ann Intern Med.* 1984; 101(3):334–338. [PubMed: 6331781]
9. Graversen D, Vestergaard P, Stochholm K, Gravholt C, Jørgensen J. Mortality in Cushing's syndrome: a systematic review and meta-analysis. *Eur J Intern Med.* 2012; 23(3):278–282. [PubMed: 22385888]
10. Guignat L, Bertherat J. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol.* 2010; 163(1):9–13. [PubMed: 20375177]
11. Gust D, Gordon T. Late diagnosis of Cushing's disease in a child: what lessons can be learned? *J Pediatr Endocrinol Metab.* 2013; 26(7–8):753–756. [PubMed: 23612592]
12. Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, Stein E, Levine E, Delimpasi G, Hsiao HP, Keil M, Heyerdahl S, Matyakhina L, Libe R, Fratticci A, Kirschner LS, Cramer K, Gaillard RC, Bertagna X, Carney JA, Bertherat J, Bossis I, Stratakis CA. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. *Nat Genet.* 2006; 38(7):794–800. [PubMed: 16767104]
13. Joshi SM, Hewitt RJ, Storr HL, Rezajooi K, Ellamushi H, Grossman AB, Savage MO, Afshar F. Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery.* 2005; 57(2):281–285. discussion 281–285. [PubMed: 16094156]
14. Kanter A, Diallo A, Jane JJ, Sheehan J, Asthagiri A, Oskouian R, Okonkwo D, Sansur C, Vance M, Rogol A, Laws EJ. Single-center experience with pediatric Cushing's disease. *J Neurosurg.* 2005; 103(5):413–420. [PubMed: 16302612]
15. Kronfol Z, Starkman M, Schteingart D, Singh V, Zhang Q, Hill E. Immune regulation in Cushing's syndrome: relationship to hypothalamic-pituitary-adrenal axis hormones. *Psychoneuroendocrinology.* 1996; 21(7):599–608. [PubMed: 9044443]
16. Kundel A, Thompson G, Richards M, Qiu LXC, Schwenk F, Lteif A, Pittock S, Kumar S, Tebben P, Hay I, Grant C. Pediatric endocrine surgery: a 20-year experience at the Mayo Clinic. *J Clin Endocrinol Metab.* 2014; 99(2):399–406. [PubMed: 24423286]
17. Lambert J, Goldberg L, Fayngold S, Kostadinov J, Post K, Geer E. Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *J Clin Endocrinol Metab.* 2013; 98(3):1022–1030. [PubMed: 23393167]
18. Lindholm J, Juul S, Jørgensen J, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jørgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metab.* 2001; 86(1):117–123. [PubMed: 11231987]
19. Magiakou M, Mastorakos G, Oldfield E, Gomez M, Doppman J, Cutler GJ, Nieman L, Chrousos G. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med.* 1994; 331(10):629–636. [PubMed: 8052272]
20. Melmed S. Series introduction. The immuno-neuroendocrine interface. *J Clin Invest.* 2001; 108(12):1563–1566. [PubMed: 11733548]
21. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda E, Caran E, Oliveira-Filho A, Marques R, Pianovski M, Lacerda L, Cristofani L, Jenkins J, Rodriguez-Galindo C, Ribeiro R. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. *J Clin Oncol.* 2004; 22(5):838–845. [PubMed: 14990639]

22. Mishra A, Agarwal A, Gupta S, Agarwal G, Verma A, Mishra S. Outcome of adrenalectomy for Cushing's syndrome: experience from a tertiary care center. *World J Surg.* 2007; 31(7):1425–1432. [PubMed: 17534556]
23. Mittal R, Ramadan D, Khalifa N, Khalifa S, Mazidi Z, Zaki M. Adrenocortical tumors in children: a Kuwait experience. *Gulf J Oncolog.* 2012; 12:38–46. [PubMed: 22773214]
24. Neary NM, Lopez-Chavez A, Abel BS, Boyce AM, Schaub N, Kwong K, Stratakis CA, Moran CA, Giaccone G, Nieman LK. Neuroendocrine ACTH-Producing Tumor of the Thymus—Experience with 12 Patients over 25 Years. *The Journal of Clinical Endocrinology & Metabolism.* 2012; 97(7):2223–2230. [PubMed: 22508705]
25. Ntali G, Asimakopoulou A, Siamatras T, Komninos J, Vassiliadi D, Tzanela M, Tsagarakis S, Grossman A, Wass J, Karavitaki N. Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *Eur J Endocrinol.* 2013; 169(5):715–723. [PubMed: 23996696]
26. Pivonello R, De Martino M, De Leo M, Tauchmanová L, Faggiano A, Lombardi G, Colao A. Cushing's syndrome: aftermath of the cure. *Arq Bras Endocrinol Metabol.* 2007; 51(8):1381–1391. [PubMed: 18209877]
27. Sarlis N, Chanock S, Nieman L. Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. *J Clin Endocrinol Metab.* 2000; 85(1):42–47. [PubMed: 10634361]
28. Savage M, Lienhardt A, Lebrethon M, Johnston L, Huebner A, Grossman A, Afshar F, Plowman P, Besser G. Cushing's disease in childhood: presentation, investigation, treatment and long-term outcome. *Horm Res.* 2001; 55(1):24–30. [PubMed: 11408758]
29. Savage MO. Work-up and management of paediatric Cushing's syndrome. *Curr Opin Endocrinol Diabetes Obes.* 2008; 15(4):346–351. [PubMed: 18594275]
30. Steffensen C, Bak A, Rubeck K, Jørgensen J. Epidemiology of Cushing's syndrome. *Neuroendocrinology.* 2010; 92(1):1–5. [PubMed: 20829610]
31. Stratakis CA. Cushing syndrome in pediatrics. *Endocrinol Metab Clin North Am.* 2012; 41(4):793–803. [PubMed: 23099271]
32. Tuckermann J, Kleiman A, McPherson K, Reichardt H. Molecular mechanisms of glucocorticoids in the control of inflammation and lymphocyte apoptosis. *Critical Reviews in Clinical Laboratory Sciences.* 2005; 42(1):71–104. [PubMed: 15697171]
33. Valassi E, Crespo I, Santos A, Webb S. Clinical consequences of Cushing's syndrome. *Pituitary.* 2012; 15(3):319–329. [PubMed: 22527617]
34. Würzburger M, Prelevi G, Brki S, Vuckovi S, Pendi B. Cushing's syndrome-transitory immune deficiency state? *Postgrad Med J.* 1986; 62(729):657–659. [PubMed: 3748930]
35. Yaneva M, Kalinov K, Zacharieva S. Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. *Eur J Endocrinol.* 2013; 169(5):621–627. [PubMed: 23939921]

Figure 1.
Mortality rate in 160 pediatric patients with CS

Diagnostic tests and final diagnosis of the 4 children with Cushing's syndrome who died

Table 1

1	Patient 1	Patient 2	Patient 3	Patient 4
2	Age (yrs) The start of the symptoms	7.5	10	11.5
3	Sex	F	M	F
4	Pre NIH			
5	24h UFC (mcg/24 hr)	138**	336 (RR: 4–56)	201 (RR: 4–56)
6	AVG 8:00am morning Cortisol* (mcg/dL)	23**	-	29**
7	AVG 23:30 late-night Cortisol* (mcg/dL)	19**	-	-
8	Cortisol*, post 1 mg DST (mcg/dl)	28**	25.5**	19.7**
9	Salivary Cortisol (mcg/dl)	N/A	N/A	8:00am: 0.2, 8:00pm: 0.3**
10	ACTH (pg/ml)	<5**	-	137**
11	Adrenal CT	No lesion	-	No lesion
12	Adrenal US	No lesion	No lesion	-
13	Adrenal MRI	No lesion	-	No lesion
14	Pituitary MRI	No lesion	No lesion	No lesion
15	At NIH			
16	Age (yrs)	9.5	13.5	15.5
17	AVG 24 UFC (mcg/24hr)	215 (RR: 24–108)	740 (RR: 4–56)	228.35 (RR: 4–56)
18	8:00am Cortisol* (mcg/dl)	19.8 (RR: 5–25)	32 (RR: 5–25)	23.5 (RR: 5–25)
19	23:30 Cortisol* (mcg/dl)	20.55 (RR: 5–25)	24 (RR: 5–25)	27 (RR: 5–25)
20	8:00am ACTH* (pg/ml)	< 4 (N/A)	250 (RR: 0–46)	49.5 (RR: 0–46)
21	23:30 ACTH* (pg/ml)	-	241.5 (RR: 0–46)	59.6 (RR: 0–46)
22	8mg DST (% cortisol* suppression)	-	16%**	77.5%**
23	oCRH test	-	Ectopic source of ACTH	CD
24	Adrenal CT	BAH	BAH	Thickened adrenals
25	Pituitary MRI	No lesion	No lesion	Microadenoma (5×5×5mm)
26	Bone age	8 yrs 10 m	13 yrs 6 m	16 yrs

1	Patient 1	Patient 2	Patient 3	Patient 4
27	2D Echo	Left atrial myxoma	Left ventricular function (50%)	Normal
28	Surgery	Bilateral adrenalectomy	Thymectomy	Not done
29	Pathology	PPNAD	Thymic carcinoid (ACTH producing)	N/A
30	Final diagnosis	PPNAD	Thymic carcinoid (ACTH producing)	CD
31	Immunosuppression	+	+	+
32	Reason of death	Necrotizing pancreatitis, CID	Residual disease Thymic carcinoid	Peritonitis, sepsis, CID
33	Genetics	171delTfs41X inactivating <i>PDE11A</i> mutation	-	-
34	Length of disease (yrs)	2	3	4

* Serum cortisol, plasma ACTH,

** RR: N/A,

Abbreviations: CD= Cushing disease, CS= Cushing syndrome, yrs= years, m= months, hr= hours, AVG= average, f= female, m= male, Post 1 mg DST= 1 mg Dexamethasone suppression test, PPNAD= primary pigmented nodular adrenal dysplasia, CID= disseminated intravascular coagulation, Post 8 mg DST= 8 mg Dexamethasone suppression test, N/A= not available, BAH= Bilateral adrenal hyperplasia, 24h UFC = 24 hours Urine Free Cortisol, oCRH test= Ovine cortisol releasing hormone test

Table 2

Review of literature regarding pediatric mortality due to Cushing syndrome.

Study	No. of patients	Age	Patients disorder (CD,CS,EAS,ACCs,ACT)	Mortality	Causes of mortality
Mittal R et al.[23]	6	15 m-12 yrs	CS, ACCs	83%	Progressive disease
Bhansali A et al.[3]	12	13 yrs-48 yrs	CS, EAS	83.3%	Progressive disease
Michalkiewicz E et al.[21]	254	< 20 yrs	CS, ACTs	38.2%	Progressive disease
Joshi S.M et al.[13]	25	6.6 –17 yrs	CD	0%	N/A
Savage M.O et al.[28]	17	6.8 –18.8 yrs	CD	0%	N/A
Kanter S.A. et al.[14]	33	5 – 19 yrs	CD	0%	N/A

Abbreviations: No=number, CD= Cushing disease, CS=Cushing syndrome, EAS=Ectopic ACTH syndrome, ACCs= Adrenocortical carcinomas,, ACT= Adrenocortical Tumors, OSR= Overall survival rate, N/A=not available