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Incidence of Autoimmune and Related Disorders After Resolution of Endogenous Cushing Syndrome in Children

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Abstract

Glucocorticoids are widely used for immunosuppression in autoimmune diseases. After the resolution of hypercortisolemia, the immune system recovers allowing for autoimmune diseases to manifest. Here we investigated the presence of autoimmune and related diseases that developed after cure of endogenous Cushing syndrome (CS) in children. We identified 129 children who were diagnosed and successfully treated for endogenous CS at the National Institutes of Health from 1997 until 2017, and who were followed for at least 6 months after treatment. We performed a retrospective chart review analysis to identify the presence of autoimmune or related diseases after cure. Ten children were diagnosed with a new autoimmune or related disorder after resolution of hypercortisolemia. This results in a frequency of 7.8% of our pediatric CS population. The identified patients had a shorter duration of hypercortisolemia prior to diagnosis, but did not otherwise differ from the remaining patients. The various identified diseases were: celiac disease (n = 1), psoriasis (n = 1), Hashimoto thyroiditis (n = 1), Graves disease (n = 1), optic neuritis (n = 2), skin hypopigmented lesions/vitiligo (n = 2), allergic rhinitis/asthma (n = 1), and neuropathy responding to glucocorticoid treatment (n = 1). The reported time between the treatment of CS and diagnosis of autoimmune disorder ranged from 6 to 19 months. The presence of autoimmune or related diseases might be masked by the hypercortisolemic state in endogenous CS. After resolution of hypercortisolemia, the presentation of new autoimmune diseases or recurrence of previously known autoimmune conditions should be considered when concerning symptoms arise.

Keywords

hypercortisolemia; immune system; thyroiditis; children

Introduction

Pharmacologic doses of glucocorticoids (GCs) are widely used for their immunosuppressive effects in autoimmune and atopic diseases [1–3]. Endogenous Cushing syndrome (CS), which represents a state of endogenous hypercortisolemia, results also in suppression of the

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Conflict of Interest

The authors declare that they have no conflict of interest.

immune system [4]. As a consequence, during the period of hypercortisolemia, patients with endogenous CS are expected to have lower risk for autoimmune and related diseases.

The immunosuppressive effects of hypercortisolemia usually reverse after its resolution; thus, recurrences of autoimmunity may occur after discontinuation of GC treatment [5]. Previous studies have reported an increased incidence of new onset or exacerbation of previously diagnosed autoimmune diseases in adult patients after cure of endogenous CS [6, 7]. However, similar studies in children have not been performed with the exception of an earlier report from our group on resurgence of autoimmune thyroid disease following cure for CS in pediatric patients [8]. In addition, a few cases of pseudotumor cerebri in children cured by their CS after the removal of an ACTH-producing tumor were speculated to be linked to possible autoimmunity [9].

In the present work, we studied our entire recent pediatric cohort of children with CS and asked the question whether resolution of endogenous hypercortisolemia led to the presentation of an autoimmune or related disease. Since children with pseudotumor cerebri were reported previously, we did not study these children here [9]. On the other hand, thyroid disease was recorded, as the previous report was from a different (and much older) cohort limited to children with pituitary tumors only [8].

Subjects and Methods

Subjects

We screened 197 patients who were seen for CS at the National Institutes of Health from 1997 until 2017 with an age of onset < 18 years old. Patients who were not cured or had a recurrence of CS at their follow up visits, or who were followed up for < 6 months after cure, were excluded from the analysis. We identified 127 children who fulfilled the above criteria. The patients were evaluated at the Clinical Center of the National Institutes Health (NIH) under the protocols 97-CH-0076, 95-CH-0059 and 00-CH-0160. Our research was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Institutional Review Board. Written informed consent was obtained from the parents of the minor patients, and assent from the minor patients.

Data collection

Demographic, clinical, and biochemical data were collected from the electronic medical record system. The diagnosis of CS and the classification of the various etiologies were based on previously described criteria: elevated urinary free cortisol (UFC), abnormal diurnal cortisol secretion and/or lack of suppression to low dose dexamethasone [10]. The diagnosis was confirmed histologically after surgery for all patients that underwent surgical resection. Resolution of CS was documented based on normal or suppressed (in the case of posttreatment suppression of the hypothalamic-pituitary-adrenal [HPA] axis) diurnal rhythm of cortisol secretion.

We documented the presence of a new autoimmune or related disorder after cure as these occurred and by retrospective review. Patients who were diagnosed with an autoimmune disorder prior to the diagnosis of CS were included in the analysis, but did not count as

positive subjects unless a second disorder presented after cure. The diagnosis of a new autoimmune or related disorder was verified by either biochemical confirmation (if available) or evaluation of the patient by the corresponding subspecialist.

Statistical analysis

The results are presented as frequencies and percentages, and mean ($\pm$ standard deviation, SD). Data were assessed for distributional normality, and non-parametric tests were used for non-normally distributed data. Continuous data were compared between groups using the two-sample t-test or Wilcoxon rank-sum test, as applicable. Categorical data between groups were compared by means of the χ^2 or Fisher's exact tests, as appropriate. Data were considered statistically significant if the resulting p-value was < 0.05 . Analyses were carried out using IBM SPSS (IBM Corporation, NY, USA).

Results

Characteristics of the patients of the study

The characteristics of the included patients are shown in ►Table 1. Their mean age of diagnosis was 12.5 years (± 3.5), with a mean duration of disease of 2.5 years prior to treatment. More patients were females ($n = 72$, 55.8%). The mean duration of follow up was 31.2 months (± 32.7 , range: 6–163 months). The etiology of CS was a pituitary corticotroph adenoma (Cushing disease, CD) in 77.5 % of the patients ($n = 100$), while 21.7 % ($n = 28$) had ACTH-independent CS and one patient was diagnosed with ectopic CS (0.8 %). The patients with a diagnosis of CD were treated with transsphenoidal surgery (TSS), while the patients with ACTH-independent CS underwent unilateral or bilateral adrenalectomy, depending on the cause of their disease. The patient with ectopic CS underwent resection of the ectopic source of ACTH (bronchial carcinoid). Of the 28 patients with ACTH-independent CS, 13 patients had clinical and genetic confirmation of Carney complex (CNC).

Characteristics of the patients identified with an autoimmune (or related) disorder

Ten children were diagnosed with a new autoimmune or related disorder after resolution of hypercortisolemia, which results in a frequency of 7.8 % in our pediatric CS population. The main characteristics of the identified patients are shown in ►Table 1. When comparing the patients who presented with an autoimmune or related disorder to those who did not, there was no significant difference in the age at diagnosis, gender, mean serum morning and midnight cortisol levels, and urinary free cortisol (UFC) level at diagnosis. The patients with a new autoimmune or related disorder had a statistically significantly shorter duration of symptomatic hypercortisolemia (1.4 years, ± 0.9) compared to the patients without such a diagnosis (2.5 years, ± 1.9 , $p = 0.048$). Regarding the etiology of CS, the relative frequency of CD and ACTH-independent CS did not differ between the two groups. The only patient with ectopic CS included in the study presented with a new autoimmune disorder after resolution of hypercortisolemia.

Types of autoimmune (or related) disorders

The various diseases that were seen are shown in ►Table 2. These include: celiac disease (n = 1), psoriasis (n = 1), Hashimoto thyroiditis (n = 1), Graves disease (n = 1), optic neuritis (n = 2), skin hypopigmentation/vitiligo (n = 2), allergic rhinitis/asthma (n = 1) and neuropathy of unknown origin responsive to GCs (n = 1). The reported time between the treatment of CS and diagnosis ranged from almost 1 month to 19.7 months with a mean time to diagnosis of 9.8 months (± 5.1). Most of the patients had a positive family history for other autoimmune or related disease (70 %). All patients were successfully treated medically and did not experience any serious complication. Although the size of our cohort did not allow for comparison of the frequency with the general population, it seems that there was a higher frequency of optic neuritis than expected.

Presentation of uncommon autoimmune disorders

Three of our patients presented with uncommon cases of autoimmune diseases: two with optic neuritis and one with neuropathy of unknown etiology that responded to GC therapy.

The patients who developed optic neuritis were diagnosed with CS at the age of 7 and 8 years old, being the younger patients of the group with autoimmune/atopic diseases. They were both diagnosed with a pituitary adenoma causing CD and successfully treated with TSS. They developed signs of optic neuritis within 7–10 months after the surgery. Optic neuritis presented with blurred vision and scotomas. They were both evaluated by a neuroophthalmologist who confirmed the abnormal disc edema and the diagnosis. They were treated with ophthalmic drops with subsequent improvement of their symptoms.

The patient with the new onset neuropathy had been diagnosed with bronchial carcinoid and ectopic CS at the age of 13 years old. She was treated with two surgical resections of the right lower lobe tumor with confirmed resolution of CS afterwards. Soon after the second surgery she presented with a motor and sensation disorder, including muscle weakness, tingling sensation and spasms of her extremities. Her workup, including voltage gated potassium channel (VGKC) antibodies, anti-acetylcholine receptor (AChR) antibodies, muscle-specific kinase (MuSK) antibodies and paraneoplastic autoantibody panel, was inconclusive for any of the known disorders, but the patient responded to pharmacologic doses of GCs with improvement of her neurologic symptoms. She remains under the care of a neurologist who follows her progress.

Discussion

We present a comprehensive study of new onset autoimmune or related diseases after the resolution of CS in children. We found that 7.8 % of the children developed such a disorder, with a mean time of diagnosis of 9.8 months after treatment. The patients who developed a new autoimmune or related disorder had a shorter duration of CS, but otherwise did not differ significantly from the remaining patients. The various identified diseases included both common disorders, such as autoimmune thyroiditis and celiac disease, as well as less frequently encountered diseases, such as optic neuritis and neuropathy of unclear etiology.

A previous study in the adult population by de Mota et al., reported that 8 out of 78 adult patients with CS (10.3 %) presented with a new autoimmune or allergic disease after treatment for endogenous CS [7]. Older studies have focused on specific autoimmune disorders, such as thyroid disease, while few additional case reports have described the exacerbation or manifestation of autoimmunity, leading to diseases such as rheumatoid arthritis, celiac disease and systemic lupus erythematosus, after cure of CS [6, 11–13]. We previously reported thyroid autoimmunity in a few children with CD after their cure, as well as pseudotumor cerebri in a small number of patients from the same cohort. [8]

The reason for the presence of autoimmune diseases after resolution of hypercortisolemia remains unclear. GCs induce many changes in the immune system, affecting both the number and function of WBC lineages, leading to leukocytosis, neutrophilia, lymphopenia, as well decrease of the inflammatory proteins [14–16]. Changes of the B cells (mainly thought to derive by the effects of altered T cell function) result in alterations of the humoral immune system that is involved in the pathogenesis of autoimmune and atopic diseases [14]. These effects occur soon after the administration of GCs and resolve after discontinuation, which may allow for recurrence or manifestation of autoimmunity [17]. But would autoimmunity be there if CS had not occurred? And is the detected autoimmunity a transient phenomenon in these patients? There remain questions that cannot be answered from the current investigation. Previous studies have reported that there is an increased incidence of thyroid disease in adult patients after treatment of CS, suggesting that previous hypercortisolemia may lead to an aberrant rebound response of the immune system [6, 18]. Such an increased incidence, however, has not been clearly documented in other studies [19]. Further investigation is needed to elucidate this phenomenon, since the presence of autoimmunity is associated with additional complications, such as papillary thyroid microcarcinoma in the case of Hashimoto thyroiditis especially in young patients [20, 21].

Additional factors that may contribute to the emergence of autoimmunity may include the duration of hypercortisolemia, since it seems that patients with shorter duration of disease had a higher chance to develop an autoimmune or related disorder. This could be due to lower suppression of the immune system or longer duration of follow up of the patients (although not statistically different). Previous studies have shown that the recovery of the WBC counts after short exposure to exogenous GCs occurs within 24 h [22]. However, there are no studies on the timing of recovery of the immune system in patients with endogenous CS. One could hypothesize that the longer exposure to hypercortisolemia, the more changes, both numeric and functional, occur in the cells of the immune system, that require longer time to recover or reactivate, or even cause a more long term suppression.

The discontinuation of the GC treatment in patients with a disorder of the immune system may result in exacerbation of the underlying disease, which is routinely monitored by the primary physician. This, however, may not be the case in the pediatric population with CS, where the presence of new symptoms might be initially linked to CS and delay the diagnosis of a new unrelated disorder. This study emphasizes that this population is at risk for autoimmune and atopic disorders during the postoperative period, which should be in the differential diagnosis of the caring physician when new findings present.

One of the main strengths of this study is the large number of patients, which is to our knowledge the largest cohort of children with CS, since our institution serves as an international referral center. We also have long follow up for most of our patients after the treatment and documentation of their clinical and biochemical progress, for a mean time of 31 months. A limitation of the study is its retrospective nature. Thus, we were not able to measure markers of autoimmunity (such as the thyroid antibodies) in all our patients, but rather only those with related symptoms. We also did not record baseline autoantibody titers for the patients prior to treatment, nor obtained historic titers, if available prior to the presumed development of CS. This could potentially assist in distinguishing those with already positive antibodies, who already had a predisposition to later developing autoimmune disease especially in the setting of positive family history, such as in patient case 5 (► Table 2). We were also not able to document the changes in the severity of previously diagnosed autoimmune or related diseases. For example, some of our patients have been diagnosed with asthma prior to the diagnosis of CS, but there was no documentation of the asthma severity before, during and after their disease.

In conclusion, the presence of autoimmune or related diseases might be masked by the hypercortisolemic state in endogenous CS. After resolution of hypercortisolemia, the presentation of new autoimmune diseases or recurrence of previously known autoimmune conditions should be considered when concerning symptoms arise; this observation may also be applicable to children with iatrogenic CS.

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Table 1
Clinical and biochemical characteristics of the pediatric patients with CS included in the study.

	Characteristic	All patients (n = 129)	Patients with new autoimmune or related disorder (n = 10)	Patients without autoimmune or related disorder post treatment (n = 119)	p-value
	Mean age at diagnosis, years ($\pm$ SD)	12.5 ($\pm$ 3.5)	11.9 ($\pm$ 2.6)	12.5 ($\pm$ 3.5)	0.556
	Mean duration of disease, years ($\pm$ SD)	2.5 ($\pm$ 1.8)	1.4 ($\pm$ 0.9)	2.5 ($\pm$ 1.9)	0.048*
	Mean duration of follow up, months ($\pm$ SD)	31.2 ($\pm$ 32.7)	48.2 ($\pm$ 44.8)	29.7 ($\pm$ 31.4)	0.154
Gender	Male (%)	57 (44.2)	3 (30)	54 (45.4)	0.339
	Female (%)	72 (55.8)	7 (70)	65 (54.6)	0.339
At diagnosis	Mean morning Cortisol level (mcg/dl)($\pm$ SD)	21.1 ($\pm$ 15.7)	18.4 ($\pm$ 8.2)	21.3 ($\pm$ 16.1)	0.954
	Mean midnight Cortisol level (mcg/dl)($\pm$ SD)	19.3 ($\pm$ 15.2)	16 ($\pm$ 6.7)	19.5 ($\pm$ 15.6)	0.629
	UFC (mcg/24 H)($\pm$ SD)	437.9 ($\pm$ 1765.1)	284.2 ($\pm$ 295.1)	449.5 ($\pm$ 1829)	0.688
Etiology of CS	Cushing disease (%)	100 (77.5)	7 (70)	93 (78.2)	0.979 (when excluding the ectopic CS case)
	Ectopic ACTH production (%)	1 (0.8)	1 (10)	0 (0)	
	ACTH-independent CS (%)	28 (21.7)	2 (20)	26 (21.8)	

* After excluding the ectopic CS case. CS: Cushing syndrome; UFC: Urinary free cortisol.

Table 2

Summary of the identified autoimmune or related disorders.

Case	Autoimmune or related disorder identified	Gender	Etiology of CS	Age at diagnosis of CS (years)	Age at diagnosis of autoimmune or related disease (years)	Time of presentation after treatment (months)	Family history of autoimmune or related disorders	Frequency of the disorder in our cohort (%)	Frequency of the disorder in general pediatric population (%)
1	Celiac disease	Female	CD	12.2	13.9	20	No	0.78	0.76 [23]
2	Allergic rhinitis/Asthma	Female	ACTH-independent CS	12.0	13.0	12	Yes	0.78	8.5–14.5 [24]/8–13 [25]
3	Psoriasis	Male	CD	15.8	16.7	11	Yes	0.78	0.71 [26]
4	Skin hypopigmentation/vitiligo	Female	CD	11.2	12.2	12	No	1.55	0.1–4 [27]
5	Hashimoto thyroiditis	Female	ACTH-independent CS	11.5	12.2	9	Yes	0.78	1–2 [28]
6	Optic neuritis	Female	CD	7.5	8.0	7	Yes	1.55	0.0032 [29]
7	Neuropathy including tremors and paresthesia responding to glucocorticoids	Female	Ectopic CS	13.6	13.7	1	Yes	0.78	Unknown
8	Skin hypopigmentation/vitiligo	Male	CD	11.0	11.4	5	No	1.55	0.1–4 [27]
9	Optic neuritis	Male	CD	8.6	9.4	9	Yes	1.55	0.0032 [29]
10	Graves disease	Female	CD	15.5	24.6	12	Yes	0.78	0.01 [28]