Clinical Endocrinology (2000) **53,** 13–19

Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease

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(Received 4 June 1999; returned for revision 16 August 1999; finally revised 9 February 2000; accepted 17 March 2000)

Summary

BACKGROUND Cushing's disease is characterized by abnormalities of immune function.

OBJECTIVE To evaluate the prevalence of autoimmune thyroid diseases in patients with Cushing's disease (CD), after successful treatment and the possible association between previous nodular goitre or positive thyroid autoantibodies during the active phase of CD and the subsequent development of autoimmune thyroid diseases after cure.

SUBJECTS AND METHODS Twenty patients with CD and 40 sex- and age-matched healthy controls were considered for the study. In CD patients, thyroid ultrasonography and measurement of circulating free thyroxine (fT_4), free triiodothyronine (fT_3), thyroid stimulating hormone (TSH), antithyroglobulin (anti-Tg) and antithyroperoxidase (anti-TPO) antibodies were performed at diagnosis and 6 months after disease cure while in controls they were performed only at study entry.

RESULTS Serum fT_3, and fT_4 levels were similar in patients, either during the active phase or after cure of the disease, and controls. Conversely, in the patients, serum TSH levels were significantly lower during active disease ($0{\cdot}4 \pm 0{\cdot}05$ mU/l, $P = 0{\cdot}001$) and significantly higher after disease cure ($4{\cdot}7 \pm 0{\cdot}1$ mU/l, $P < 0{\cdot}001$) than in controls ($2{\cdot}3 \pm 0{\cdot}4$ mU/l). Four patients (20%) and 11 controls (27·5%) had positive anti-Tg and/or anti-TPO titre at study entry, while eight patients (40%) developed positive anti-Tg and/or anti-TPO titre after disease cure. The prevalence of positive antithyroid antibodies titre in cured CD patients was significantly higher than that observed in the same patients during the active disease ($P = 0{\cdot}008$) and in controls ($P = 0{\cdot}031$). A significantly higher prevalence of autoimmune thyroiditis was found in patients cured from CD (35%) than in patients with active CD (0%) ($P = 0{\cdot}016$) and in controls (10%) ($P = 0{\cdot}031$). A significant association was found between the presence of autoimmune thyroiditis after CD cure and the presence of a previous nodular goitre ($P = 0{\cdot}017$) or positive thyroid autoantibodies titre ($P = 0{\cdot}007$) during the active phase of the disease.

CONCLUSION Patients successfully treated for Cushing's disease have an increased prevalence of thyroid autoimmunity and autoimmune thyroiditis as compared to a control population. Therefore, patients with hypercortisolism need an accurate evaluation of thyroid function after remission of the disease in order to prevent the eventual onset of subclinical or overt post-thyroiditis hypothyroidism.

Hypercortisolism is known to exert an inhibitory action on immune function in humans (Dougherty, 1952). In fact, patients with endogenous hypercortisolism have involution of lymphoid tissue mass and lymphopenia and present with an increased susceptibility to infections (Bateman *et al*., 1989). In addition, development or exacerbation of autoimmune diseases were reported to occur in patients with hypercortisolism after cure (McGregor, 1990). Particularly, exacerbation of coeliac disease (Candrina & Di Stefano, 1993) and development of sarcoidosis (Steuer *et al*., 1995) or lupus erythematosus (Naguchi *et al*., 1998) were reported in two different patients after correction of hypercortisolism due either to an ACTH-secreting pituitary adenoma or to a glucocorticoid-secreting adrenocortical adenoma, respectively. The onset of autoimmune thyroid disease was also reported in three patients with hypercortisolism of different aetiology after successful cure of the disease (Takasu *et al*., 1990; Takasu *et al*., 1993). On the other hand, both endogenous and exogenous hypercortisolism, are known to be associated to several abnormalities of thyroid function (Ingbar, 1953; Gamsted *et al*., Jarnerotm, 1981; Cavalieri *et al*., Castle, 1984; Rubello *et al*., 1992) and Cushing's disease (CD), was recently found to be associated with an increased prevalence of nodular thyroid disease (Invitti *et al*., 1995).

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This study evaluated the prevalence of autoimmune thyroid disease or thyroid autoantibodies after the successful cure of CD in 20 patients and compared this prevalence to that of the same patients at the time of CD diagnosis as well as to that of a control population. The possibility that thyroid autoimmunity, developed after CD cure, could be related to pre-existent nodular goitre or positive thyroid autoantibodies was also evaluated.

Patients and methods

Patients

In this study were considered all the patients admitted to our Department in the last 7 years for hypercortisolism, and diagnosed as CD, who achieved a successful cure for at least 6 months. Among 30 patients, undergoing a complete thyroid screening, including thyroid hormone and autoantibody assays and thyroid ultrasonography, complete records either during the active disease or after disease cure were obtained in 20 patients (four males, 16 females; 13–38 years old). The data from these 20 CD patients were included in this study. Forty healthy subjects (eight males, 32 females; 13–38 years old), coming from the same geographical area as the patients were used as control group. Controls were unselected apart from the exclusion criteria of those genetically related to the patients and those with documented endogenous or exogenous hypercortisolism. The controls were enrolled for the study during the last 3 years.

The diagnosis of CD was based on the following criteria: (1) increased excretion of daily urinary cortisol with inappropriately high plasma ACTH concentrations; (2) increased serum cortisol concentrations with lack of physiological circadian rhythm; (3) failure of urinary and serum cortisol suppression after low dose but a greater than 50% decrease after high dose dexamethasone test. A pituitary adenoma was documented in all patients by computed tomography, magnetic resonance imaging or inferior petrosal sinus sampling, performed as previously described (Oldfield *et al*., 1991; Colao *et al*., 1996; Colao *et al*., 1998). Cure of CD was established on the basis of the following criteria: (1) plasma ACTH concentrations and daily urinary cortisol excretion below or within the normal range; (2) serum cortisol concentrations below or within the normal range with restoration of circadian rhythm; (3) suppression of urinary and serum cortisol concentrations after low-dose dexamethasone test (Colao *et al*., 1999b).

All patients were submitted to surgical selective resection of the ACTH-secreting pituitary adenoma by transsphenoidal approach. The results of histology and immunohistochemistry on the surgically removed pituitary adenoma confirmed in all patients the diagnosis of CD. After surgery, 14 patients had remission of the disease whereas the remaining six had persistent disease and underwent pituitary radiotherapy, which induced remission of the disease in five patients after 1–3 years. The remaining patient was subjected to bilateral adrenalectomy. This patient and three others who had developed postsurgical or postradiation hypocortisolism received replacement therapy with cortisone acetate at standard doses (12·5–37·5 mg/day). No residual anterior pituitary deficiencies were recorded after treatment in the 20 patients except one woman who developed hypogonadism and diabetes insipidus, treated with oestrogen and progesterone at standard doses and desmopressin at the dose of 15 μg/day. The adequacy of replacement therapy was periodically monitored during follow-up measuring blood pressure, serum electrolyte levels, daily water balance and regularity of menses. All patients also underwent an arginine plus GH-releasing hormone test and/or insulin tolerance test after CD cure to evaluate residual GH secretion (Colao *et al*., 1999a). GH deficiency was recorded in four patients, who were given human recombinant GH at the dose of 0·0125 U/kg/day. All patients had been followed-up at least twice yearly after CD cure to verify the complete and persistent control of cortisol secretion and to assess the development of pituitary insufficiencies. Patients' profile at diagnosis of CD is shown in Table 1.

Protocol of the study

In all patients, thyroid ultrasonography (USG) and measurement of circulating free thyroxine (fT_4), free triiodothyronine (fT_3), thyroid stimulating hormone (TSH), antithyroglobulin (anti-Tg) and antithyroperoxidase (anti-TPO) antibodies, were performed at diagnosis and 6 months after the cure of the disease while in controls they were performed only at study entry.

Assays

Serum fT_4, fT_3, TSH, anti-Tg and anti-TPO levels had been measured by immunoassay using commercial kits. The normal ranges were: fT_4: 9·1–23·8 pmol/L; fT_3: 2·5–5·2 pmol/L; TSH: 0·5–4·7 mU/l; anti-Tg and anti-TPO: 0–100 U/ml. anti-Tg and anti-TPO titres 3 standard deviations above the mean were considered as positive.

Ultrasonography study

The USG examination of the thyroid was carried out by a commercially available real-time instrument using a 7·5-MHz transducer. Goitre was diagnosed when the anteroposterior diameter in both lobes was $\geq$ 20 mm. The presence of a diffuse hypoechoic pattern with or without hyperechoic lines was considered suggestive of thyroiditis.

Table 1 Clinical profile of patients with Cushing's disease (CD)

Patient (sex/age)	Age of disease onset (years)	Disease duration (years)	Radiological findings	Treatment for CD	Treatments after disease remission	Urinary cortisol levels (nmol/24 h)	
						Before cure	*After cure*
1 (f/27)	16	6	mA	TS	C	579	364
2 (f/50)	36	8	mA	TS	AH	1490	141
3 (f/19)	13	5	N	TS	none	1597	359
4 (f/44)	37	2	mA	TS	none	1007	279
5 (f/36)	25	5	mA	TS	none	999	149
6 (f/41)	27	8	MA	TS, RT, AS	none	2759	306
7 (f/39)	30	4	mA	TS	none	690	345
8 (f/45)	25	15	mA	TS	AH	894	132
9 (f/50)	25	5	mA	TS	none	773	270
10 (f/50)	35	10	N	TS	AH, GL, C, hrGH	1004	339
11 (f/47)	30	12	mA	TS	none	773	270
12 (m/29)	19	4	mA	TS	AH	1479	309
13 (f/44)	38	1	mA	TS, RT	AH, GL	4304	331
14 (m/20)	12	3	mA	TS	none	1393	284
15 (m/27)	17	4	N	TS, RT, BA, AS	C	2759	359
16 (f/32)	25	6	mA	TS, RT, AS	hrGH	1269	315
17 (f/26)	13	8	mA	TS, RT	none	3060	370
18 (f/27)	15	4	N	TS, RT, AS	hrGH	2119	94
19 (m/40)	36	3	N	TS	hrGH	2456	372
20 (f/24)	15	4	MA	TS	C, EP, D	2119	121

mA, microadenoma; MA, macroadenoma; N, negative; TS, transsphenoidal surgery; RT, radiotherapy; AS, adrenosuppressor drugs; BA, bilateral adrenalectomy; C, cortisone acetate; EP, estroprogestinic; D, desmopressin; hrGH, human recombinant GH; AH, antihypertensive drugs; GL, glucose lowering drugs. Urinary cortisol levels normal range, 96·5–349 nmol/24 h.

Statistical analysis

Data were expressed as mean ± SEM. The statistical analysis was performed by SPSS for Windows version 8·0 (Cary, NC, USA). The comparison between the numerical data were performed by Student's *t*-test for unpaired or paired data. The *P*-values and 95% confidence intervals were given for these analysis. Comparisons between categorical data were performed by χ^2 test with the Yates correction, Fisher exact test or McNemar test as appropriate. The *P*-values were given for these analysis. Significance was set at 5%.

Results

Thyroid hormone profile in CD patients before and after the disease cure is shown in Table 2. Thyroid hormones and TSH levels in the control group were in the normal range in all cases. Serum fT_3 and fT_4 levels were similar in patients with CD, either before or after disease cure, and in controls (Table 3). Conversely, serum TSH levels in CD patients were significantly lower during active disease and higher after disease cure, than in controls (Table 3). Particularly, serum TSH levels were below the normal range in 12 active patients (60%) while they were above the normal range in five cured patients (25%) and in two controls (5%).

Serum anti-Tg and anti-TPO levels in cured patients were significantly increased compared to those observed in the same patients during active disease and in controls, whereas they were similar in the active CD patients and controls (Table 3). Particularly, four patients (20%) and 11 controls (27·5%) had positive anti-Tg and/or anti-TPO titre. After cure, eight patients (40%) developed positive anti-Tg and/or anti-TPO titre. As a whole, the prevalence of positive antithyroid antibodies was significantly higher after CD cure (60%) than during the active disease (25%)($P = 0{\cdot}031$) and in controls (27·5%)($P = 0{\cdot}008$).

At USG, nodular goitre was found in nine patients with active CD (45%) and six controls (20%) whereas a normal thyroid was detected in 11 patients (55%) and 34 controls (80%). A USG pattern suggestive of thyroiditis was detected in none of the active patients and in four controls (10%). In cured patients, USG confirmed the presence of nodular goitre in nine patients (45%), normal thyroid in six (30%), a thyroid with normal size but with a finely nonhomogeneous USG pattern in four (20%) and a USG pattern suggestive of thyroiditis in seven patients (35%). CD patients had an increased prevalence of nodular goitre compared to controls ($P = 0{\cdot}027$). Furthermore,

Table 2 Thyroid profile of patients with Cushing's disease (CD) before and after cure

	Serum fT3 (pmol/l)		Serum fT4 (pmol/l)		Serum TSH (mU/l)		anti-Tg titre (U/ml)		anti-TPO titre (U/ml)		Thyroid USG	
Patient	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure	Before cure	After cure
1.	3·7	3·5	12·1	15·4	0·6	7·2	250	790	300	685	NG	NG/T
2.	2·6	4·3	15·2	15·4	0·2	1·8	35	800	55	220	N	D
3.	3·7	4·4	15·4	12·9	0·5	2·0	26	250	38	44	NG	NG
4.	2·8	4·9	14·4	15·4	0·4	1·5	15	25	28	25	N	N
5.	5·2	2·1	16·1	8·2	0·2	9·8	190	956	215	798	NG	NG/T
6.	3·1	5·2	12·9	12·6	0·4	3·7	48	60	35	56	NG	NG
7.	4·9	3·2	8·0	9·1	0·1	1·0	12	40	18	65	NG	NG
8.	2·9	4·0	19·2	12·3	0·2	1·8	25	80	38	200	N	D
9.	4·0	3·8	19·6	16·9	0·5	1·5	55	325	71	415	N	D
10.	2·6	4·1	13·1	10·2	0·5	8·7	180	900	250	1050	NG	NG/T
11.	3·8	3·2	12·9	9·3	0·7	1·2	18	275	56	395	N	D
12.	4·6	3·5	14·8	14·0	0·4	0·5	13	27	12	35	N	N
13.	5·2	3·7	11·6	10·8	0·3	7·6	18	275	85	198	NG	NG/T
14.	3·5	3·8	14·9	19·4	0·1	1·5	28	56	47	81	N	N
15.	3·1	2·4	14·0	15·6	0·5	2·1	62	90	77	80	N	N
16.	3·4	3·8	11·2	15·7	0·6	5·9	188	350	190	544	NG	NG/T
17.	4·8	6·4	10·0	22·3	0·4	4·7	44	50	35	85	N	N
18.	4·9	2·0	22·3	8·1	0·7	20·8	26	650	15	2500	NG	NG/T
19.	3·4	3·8	17·4	15·4	0·4	8·4	65	1700	55	895	N	T
20.	3·7	3·1	14·3	12·5	0·1	3·1	25	35	18	44	N	N
Mean ± SEM	3·8 0·2	3·8 0·2	14·5 0·7	13·6 0·8	0·4 0·05	4·7 1·1*	66·0 16·2	386·7 99·7*	81·9 19·0	420·7 130·8*		

N, normal; NG, nodular goiter; T, thyroiditis; D, thyroid with normal size but finely nonhomogeneous pattern. Hormonal normal values, serum fT3, 2·5–5·2 pmol/L; serum fT4, 9·1–23·8 pmol/l; serum TSH, 0·5–4·7 mU/l; serum antiTg and antiTPO, 0–100 U/ml. *$P < 0·01$ compared to baseline evaluation.

cured patients had a prevalence of USG pattern suggestive of thyroiditis significantly higher than active patients ($P = 0·016$) and controls ($P = 0·031$).

A diagnosis of autoimmune thyroiditis was suspected on the basis of the presence of positive thyroid autoantibodies and ultrasonographic imaging suggestive of thyroiditis without any general or local physical symptom or sign of thyroid inflammation, in seven cured CD patients and in four controls. The diagnosis of autoimmune thyroiditis (chronic lymphocytic thyroiditis) was also confirmed by cytological examination of a

Table 3 Comparison of thyroid profile values between patients with Cushing's disease and controls

Parameters	Patients before cure (A)	95% confidence interval (p) A *vs.* C	Patients after cure (B)	95% confidence interval (p) B *vs.* A	Controls (C)	95% confidence interval (p) B *vs.* C
Serum fT3 (pmol/l)	3·8 ± 0·2	– 0·79; 0·18 (0·325)	3·8 ± 0·2	– 0·22; 0·70 (1·508)	4·1 ± 0·2	– 0·56; 0·18 (0·325)
Serum fT4 (pmol/l)	14·5 ± 0·7	– 0·61; 2·10 (0·652)	13·6 ± 0·8	– 2·62; 1·46 (0·525)	14·2 ± 0·4	– 2·2; 1·15 (0·696)
Serum TSH (mU/l)	0·4 ± 0·05	– 3·04; – 0·76 (0·001)	4·7 ± 1·1	2·13; 6·57 (0·001)	2·3 ± 0·4	0·48; 4·32 (0·015)
Anti-Tg titre (U/ml)	66·0 ± 16·2	– 63·83; 32·83 (0·523)	386·7 ± 99·7	126·19; 514·91 (0·003)	81·5 ± 15·0	158·95; 451·45 (0·000)
Anti-TPO titre (U/ml)	81·9 ± 19·0	– 61·13; 27·73 (0·455)	420·7 ± 130·8	72·69; 605·01 (0·015)	98·6 ± 12·5	135·16; 509·04 (0·001)

sample obtained after fine needle biopsy of the thyroid in all seven patients. Among these patients, five had serum TSH levels higher than the normal range together with serum fT_3 and fT_4 levels within normal range and without any clinical symptom or sign. The remaining two patients and the four controls had higher serum TSH levels and lower serum fT_3 and fT_4 levels and a clinical syndrome characterized by weight gain, skin dryness and somnolence. Subclinical hypothyroidism was diagnosed in the first group and clinical hypothyroidism in the second group of subjects. Two of these 11 subjects had a transient clinical syndrome suggestive of thyrotoxicosis during the previous 3 months. All seven patients were subsequently given replacement therapy with L-T_4 at the dose of 75–125 μg/day. Among the remaining five patients with elevated serum antithyroid antibodies levels followed-up for at least 3 years, three normalized while in the remaining two, antithyroid antibodies levels decreased but remained constantly above the normal range (data not shown). None of them developed thyroiditis. Cured patients had a prevalence of autoimmune thyroiditis significantly higher than that observed in patients with active CD ($P < 0{\cdot}016$) and controls ($P = 0{\cdot}031$). All the patients with CD in the current study have been followed up for 1–3 years after the disease cure and none of the patients who did not have an autoimmune thyroiditis during the first 6 months, developed it after this period.

A significant association was found between the presence of autoimmune thyroiditis in cured patients and the presence of a previous nodular goitre ($P = 0{\cdot}017$) or positive antithyroid antibodies titre ($P = 0{\cdot}007$) during the active phase of CD.

Discussion

Hypercortisolism is well known to induce immunosuppression in humans. However, no study has ever evaluated the consequences of the resolution of hypercortisolism on immune function with the exception of some case reports (Takasu *et al*., 1990; Candrina & Di Stefano, 1993; Takasu *et al*., 1993; Steuer *et al*., 1995) which described the onset or exacerbation of autoimmune diseases in patients cured of Cushing's syndrome. The current study was performed with the aim of evaluating the prevalence of autoimmune thyroid diseases in a series of patients with CD after at least 6 months of successful cure in comparison to an unselected control population and thus to investigate whether CD is a risk factor for the development of autoimmune thyroid disease. The results demonstrated that patients with a history of CD have an increased prevalence of thyroid autoimmunity as compared to controls, and frequently develop autoimmune thyroiditis during the first 6 months after the normalization of serum cortisol levels. The probability of developing an autoimmune thyroiditis was significantly associated to the presence of a previous nodular goitre or positive antithyroid antibodies titre during the active phase of the disease. Furthermore, CD patients had suppressed serum TSH levels during the active phase of the disease, probably related to the hypercortisolism itself as demonstrated by the normalization of hormone levels after the disease cure in all patients, except those who developed a post-thyroiditis hypothyroidism and had persistently elevated serum TSH levels.

The mechanism underlying the development of thyroid autoimmunity in CD patients after their cure is still unknown. On the other hand, the effect of glucocorticoids on the immune system is well known (Dougherty, 1952; Bateman *et al*., 1989; McGregor, 1990). The original clinical observations on the reduction in lymphoid-tissue mass and lymphopenia in Cushing's syndrome and the contrasting increase in lymphoid-tissue mass and lymphocytosis in adrenal insufficiency have been supplemented by considerable insight into the role of glucocorticoids in modulating the immune system (McGregor, 1990). The effect of glucocorticoids on lymphocyte function is predominantly directed on T cell proliferation, through the inhibition of the process of interleukin-1 generation by antigen-presenting macrophage cells and the process of interleukin-2 production by activated T cells (McGregor, 1990). The effects on B cells seem to be less relevant. Although glucocorticoids reduce the levels of circulating immunoglobulins, their influence on B cell function is probably related to their effect on T cell proliferation (Dougherty, 1952; Bateman *et al*., 1989; McGregor, 1990). These pieces of evidence demonstrate that glucocorticoids strongly influence the immune system, as hypercortisolism inhibits and hypocortisolism activates the immune function. Therefore, the observation of three hypercortisolaemic patients who developed autoimmune thyroiditis after resolution of hypercortisolism, lead to the hypothesis that this phenomenon may be related to a rebound in immune activity after its suppression during glucocorticoid excess (Takasu *et al*., 1990; Takasu *et al*., 1993).

The current study included a series of patients with pituitary-dependent hypercortisolism and confirmed that CD patients have an increased risk of developing thyroid autoimmunity after the resolution of hypercortisolism. The increased antithyroid antibody levels are transient in several cases. It induced true chronic lymphocytic thyroiditis and subsequent hypothyroidism especially in those cases with nodular goitre or positive antithyroid antibodies titre at the time of the active disease. A similar rebound in the immune response has been observed in a physiological condition, such as in the postpartum period. In fact, pregnancy is well known to be associated to a reduction of lymphocyte function and improvement of various autoimmune disease, as in active Cushing's syndrome, whereas the postpartum period is associated to a transient rebound of lymphocyte function and exacerbation of autoimmune diseases,

as in cured Cushing's syndrome (Amino, 1983; Jansson & Karlsson, 1986). Moreover, autoimmune thyroiditis was reported to occur frequently in the postpartum period especially in those patients with a previous diagnosis of thyroid disease and/or autoimmunity (Amino, 1983; Jansson & Karlsson, 1986). The causes of the suppression, during pregnancy, and the rebound, during the postpartum period, in the immune response as well as the onset and/or development of a postpartum autoimmune thyroiditis are not completely understood. However, pregnancy and postpartum represent a physiological example of environmental modulation of immune function and induction of autoimmune diseases. Similarly, CD may represent an example of pathological environmental modulation of immune function and autoimmune diseases. On the other hand, it may be argued that thyroid autoimmunity has, anyway, a multifactorial origin, with both genetic and environmental elements contributing to its development (De Groot & Quintans, 1989). On this basis, the fall in serum cortisol levels occurring in patients cured from CD is likely to induce an aberrant autoimmune resp onse only in those patients genetically predisposed to autoimmunity. Finally, since depression was described to be associated to increased circulating levels of thyroid autoantibodies (Pop *et al*., 1998) and it represents one of the most frequent features of Cushing's disease, the possibility that the described increased risk of autoimmune thyroid disorders might be related to the depression in these patients cannot be ruled out. Finally, as the patients in the current study underwent surgery and, in some cases, also radiotherapy, the possibility that either surgery or radiotherapy could have in some part influenced the autoantibody titre in our patients cannot be completely ruled out.

In conclusion, the results of this study demonstrated that patients cured from hypercortisolism have an increased prevalence of thyroid autoimmune disorders. Thus, Cushing's disease patients need an accurate evaluation of thyroid function after normalization of serum cortisol levels in order to prevent the possible onset of subclinical/overt post-thyroiditis hypothyroidism. The study of thyroid hormone profile and ultrasonography is recommended during the 6 months after the clinical and biochemical cure of Cushing's disease in those patients previously having positive antithyroid antibodies and/or a nodular goitre. Finally, the results of the current study suggested that the patients who receive treatment with corticosteroids for nonendocrine disease may also have an increased risk of developing autoimmune thyroid disorders after discontinuation of corticosteroid therapy.

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