

Autoimmunity as the Most Frequent Cause of Idiopathic Secondary Adrenal Insufficiency: Report of 111 Cases

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(Submitted 21 November 2002; Accepted with revisions 3 February 2003)

The origin of the isolated secondary adrenal insufficiency is unknown in most cases. An observation of a group of over 100 patients with secondary adrenal insufficiency and coexisting autoimmune abnormalities suggests that autoimmunity could be a frequent cause of idiopathic secondary failure, similarly as in Addison's disease. We studied 176 patients with idiopathic isolated secondary adrenal insufficiency. The methods included clinical examination and measurements of pituitary, adrenal, thyroid and gonadal hormones in all the cases. Since thyroid autoimmunity has been the most frequent finding in Addison's disease we have also chosen thyroid autoantibodies as markers of an autoimmune process in our material. Anti-peroxidase, anti-microsomal and anti-thyroglobulin autoantibodies were determined in 151 patients. In 111 out of 151 patients (73%) coexisting autoimmune diseases and/or presence of thyroid autoantibodies were detected. The most frequent autoimmune diseases associated with secondary adrenal insufficiency were primary hypothyroidism, hyperthyroidism (mainly in the past) and premature ovarian failure. Thyroid autoantibodies, especially antiperoxidase autoantibodies, were present in 106 patients. Thus, coexistence of isolated secondary adrenal insufficiency with some autoimmune disorders in 73% of the patients under study suggests that autoimmunity is the most frequent cause of the idiopathic form of this disease.

Keywords: Secondary adrenal insufficiency; Autoimmunity; Thyroid autoantibodies; ACTH

INTRODUCTION

Autoimmune origin of a majority of cases of Addison's disease has been established in clinical and experimental studies.^[1–4] Adrenal specific enzymes in the steroid biosynthetic pathway were characterised as adrenal cortex auto-antigens in early nineties.^[5,6] In 2000 a new auto-antigen of enzymatic origin was described.^[7] An important immunological study on adrenal-cortex autoantibodies and steroid-producing cells autoantibodies in a significant number, 165, patients with Addison's disease was published in 1999.^[8] A recent review by Betterle *et al.*^[9] summarises the actual knowledge on the autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes, associated with Addison's disease, including minor autoimmune diseases. In our study including 180 patients with Addison's disease, 125 patients (69%) were believed to have adrenal insufficiency of autoimmune aetiology. In 20 patients multiple autoimmune disorders were found.^[10]

The general opinion is that the aetiology of isolated secondary adrenal insufficiency is uncertain,^[11,12] however, some authors suggested autoimmune origin of the disease.^[13–15] Our study aimed at demonstrating the association of isolated secondary adrenal insufficiency with some other autoimmune disorders to evidence that autoimmunity is the most frequent cause of this disease. This study is a continuation of the investigations initiated in early seventies. The search for autoimmunity in isolated secondary adrenal insufficiency was prompted by a case of a young patient with such a disorder associated with diabetes mellitus, primary hypothyroidism with high titre of antithyroglobulin autoantibodies, vitiligo and autoimmune thrombocytopenia.^[16] A considerable part of our material collected since that time has been re-investigated in the last few years. As thyroid autoimmunity is a frequent finding in idiopathic Addison's disease^[10,17] we decided to search for thyroid autoantibodies, especially for antiperoxidase autoantibodies (aTPO)^[18] as markers of autoimmunity in isolated secondary adrenal insufficiency. In 1998, we published our preliminary observations

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concerning 25 patients with isolated secondary adrenal insufficiency of probable autoimmune origin.^[19] In 23 of them some autoimmune diseases were found, and hypothyroidism being the most frequent finding. During the interval of time between the first and the last investigation, in a significant number of the patients under study some new additional autoimmune disorders were detected.

PATIENTS AND METHODS

Patients

In 176 patients (165 women and 11 men) aged 17–78 years, referred to the Department of Endocrinology in Warsaw with a suggestion of idiopathic secondary adrenal insufficiency the diagnosis was confirmed on the basis of clinical characteristics and hormonal investigations (as described later). The most important clinical features included weakness and fatigability, postural dizziness, orthostatic hypotension and depigmentation of the aureoles of mammary glands. In some old women the episodes of vomiting and diarrhoea followed by severe hyponatraemia were observed. Some other female patients were referred to our department because of attacks of sudden loss of energy, which were diagnosed as reactive hypoglycaemia.

Since the initial immunological examinations could be done only in 151 patients, further, more precise studies were performed only in this group, which included 145 women and 6 men, 17–78 years old (mean, 46.8) at the time of first admission. Conventional X-ray studies revealed sellar enlargement in five cases and no abnormalities in the remaining group of patients.

Hormonal Investigations

Determination of serum levels of cortisol at 08.00 and 22.00 h, prolactin (Prl), luteinising hormone (LH) and follicle stimulating hormone (FSH), thyroxine (T₄) and/or free thyroxine (fT₄) was made by radioimmunoassay and thyrotropin (TSH) by a radioimmunometric method (Spectria, Finland). Normal basal values were: cortisol, 193–690 nmol/l at 08.00 h and 110–386 nmol/l at 22.00 h; Prl, 91–697 mU/l; LH, women 1.0–12.6 U/l, menopause 9.0–75.0 U/l, men, 1.0–5.8 U/l; FSH, women 1.0–9.3 U/l, menopause 31–134 U/l, men 1.0–10.5 U/l; thyroxine, 54–150 nmol/l, free thyroxine, 10–23 pmol/l; TSH, 0.35–5.0 IU/l. Plasma ACTH levels were measured by a radioimmunometric method,^[20] normal values at 08.00 h: 4.5–13.6 pmol/l (20–60 ng/l), at 22.00 h: 2.2–6.4 pmol/l (10–28 ng/l). In 15 women a test with metoclopramide (10 mg orally) was performed, with Prl determinations at 0, 60 and 120 min. Twenty-four hour urinary excretion of 17-hydroxycorticosteroids (17-OHCS) was determined by the Silber and Porter method in basal conditions (normal range: 6.1–19.3 μ mol/24 h), and during two days of

ACTH administration (Synacthen Depot, 0.5 mg intramuscularly, every 12 h).

Immunological Investigations

Serum antithyroglobulin (aTg) and antimicrosomal (aM) autoantibodies were examined by a haemagglutination test (Thymune T and Thymune M, respectively, Murex, UK) (normal values: up to 1/120). Autoantibodies against thyroid peroxidase (aTPO) were determined as described previously^[17] (abnormal values equal or over 1/1000).

Imaging Studies

Magnetic resonance imaging (MRI) of the pituitary was performed in 27 patients, the images being acquired in sagittal and coronal planes.

Informed consent for the studies was obtained from all the patients.

RESULTS

Clinical Studies

On the basis of the above mentioned methods we selected a group of 111 patients with idiopathic secondary adrenal insufficiency (out of 151 patients under study) associated with some autoimmune diseases and/or the presence of antithyroid autoantibodies. In this group there were 108 women and 3 men, aged 17–78 years (mean 48.3) at the time of diagnosis, ten women below 25 years old and 32 patients over 60 years old. The coexisting autoimmune diseases are listed in Table I; 31 patients with the presence of antithyroid autoantibodies as the sole marker of autoimmunity were not included in the table. In 18 patients more than one autoimmune disorder was associated with secondary adrenal insufficiency. Primary hypothyroidism was the most frequent autoimmune disease in this group of patients. Subclinical hypothyroidism was diagnosed in the patients with Hashimoto's disease with normal fT₄ values and moderately elevated

TABLE I Autoimmune diseases co-existing with secondary adrenal insufficiency in the group of the patients under study

| Disease | Number of patients |
|----------------------------|--------------------|
| Hypothyroidism | 40 |
| Subclinical hypothyroidism | 9 |
| Hyperthyroidism | 14 |
| Vitiligo | 10 |
| Premature ovarian failure | 9 |
| Pernicious anaemia | 3 |
| IDDM | 2 |
| Thrombocytopenia | 2 |
| Lymphoma | 2 |
| Celiac disease | 2 |
| Alopecia areata | 2 |
| Chronic active hepatitis | 1 |
| Hypoparathyroidism | 1 |
| Addison's disease | 1 |

TSH levels (up to 10.0 mU/l), without evident clinical signs of thyroxine deficiency. Hyperthyroidism, including Graves' disease and the Hashi-toxicosis syndrome, was noted in the past history of 12 patients and only in two other patients thyrotoxicosis was present at the time of diagnosis of adrenal insufficiency. In most cases vitiligo preceded the diagnosis of adrenal insufficiency. Premature ovarian failure was diagnosed when it appeared before the patients were 35 years old. Atrophic gastritis was found in three patients suffering from pernicious anaemia. Insulin-dependent diabetes was present in two patients with polyglandular syndromes (primary hypothyroidism, vitiligo and thrombocytopenia in one patient and premature ovarian failure and recurrent Hashi-toxicosis in the other). Autoimmune thrombocytopenia developed in two young women, and was the main cause of death in one of them, as a result of a cerebral haemorrhage. In contrast, lymphoma developed in two old women with Hashimoto's disease and hypothyroidism; in a 76 years old patient it appeared four years after the establishment of adrenal insufficiency diagnosis and in a 78 years old one—it was found simultaneously with diagnosing of adrenal hypofunction. Idiopathic hypoparathyroidism was under observation for over 15 years in a female patient with Hashimoto's disease and secondary adrenal insufficiency diagnosed at the age of 32 years. The diagnosis was confirmed by a low parathormone level of 0.3 pmol/l, normal, 2–6 pmol/l. Hyperpigmentation in the patient with Addison's disease disappeared after 18 years of observation and the ACTH concentration decreased from 74 to 2.2 pmol/l. She also suffered from primary hypothyroidism (with antiperoxidase autoantibodies in a high titre, up to 1/256000), diagnosed in the second year of Addison's disease. In a 35 years old patient, with celiac disease diagnosed simultaneously with secondary adrenal insufficiency and Hashimoto's disease, but existing probably for many years in a benign form, high titre, 1/51200, of antitransglutaminase autoantibodies were found.

Hormonal Examinations

Serum cortisol levels at 08.00 h ranged from undetectable values to 230 pmol/l and at 22.00 h, from undetectable concentration to 68 pmol/l. Urinary 17-OHCS excretion in basal conditions was decreased below 6.0 μ mol/24 h. In 86 patients tested with synthetic ACTH the 17-OHCS excretion increased gradually, reaching maximal values on the second day of the test. In many cases ACTH provoked a 20–50 times rise in 17-OHCS excretion. In the patient previously observed for Addison's disease this test was not performed. Plasma ACTH levels ranged from 0.66 to 4.4 pmol/l at 08.00 h and from undetectable values to 2.2 pmol/l at 22.00 h (the evening determinations were performed in about 60% of the patients).

Basal Prl levels were found to be within normal limits. The stimulation test with metoclopramide in five patients revealed a hyperactive response, with Prl levels up to 5307 mU/l, lack of response in a patient with an empty

sella syndrome and normal response in the remaining patients under study.

Serum LH and FSH concentrations remained within normal limits in all women before menopause and they were increased in the post-menopausal patients. An exception was a 60 year old woman with Hashimoto's disease and hypothyroidism, in which low gonadotrophins levels were found (7 years after the last menstrual bleeding).

In 40 hypothyroid patients T_4 and/or fT_4 levels were below the lowest normal limit. Serum TSH concentrations, before thyroxine replacement therapy were increased up to 98 IU/l. In three patients, despite of Hashimoto's disease with hypothyroidism, TSH levels ranged between 0.22 and 3.3 IU/l before thyroxine supplementation. In nine patients with subclinical hypothyroidism the TSH values were slightly elevated, ranging from 6.0 to 10.2 IU/l. In the past history patients with thyrotoxicosis had high T_4 and low TSH levels (<0.3 mU/l) before the remission had been achieved. In the patients not affected with a thyroid function disorder, despite of the presence of thyroid autoantibodies, normal T_4 , fT_4 and TSH values were observed.

Immunological Investigations

The antiperoxidase autoantibodies (aTPO) were present in 106 patients, ranging from 1/1000 to 1/256000. The highest values were found in five patients with hypothyroidism and in one patient with Hashi-toxicosis. The significant titre values of antimicrosomal autoantibodies, ranging from 1/240 to 1/6840, were noted in 35 patients. In 71 patients the titre of antimicrosomal autoantibodies ranged from 1/80 to 1/120, which was qualified as negative, while the titre of aTPO autoantibodies was equal or exceeded 1/1000 (the test for aTPO autoantibodies determination is more specific). In the remaining 5 patients the aM autoantibodies ranged between 1/20 to 1/40. Antithyroglobulin autoantibodies exceeding 1/120 were observed in 45 patients, in the remaining patients they ranged from 1/20 to 1/120. In 31 patients high titre of the thyroid autoantibodies was the only characteristic of autoimmunity.

Imaging Studies

MRI revealed an empty sella in five patients with sellar enlargement on routine X-ray skull examination. Two patients with this finding had regular menstrual bleedings whereas, one patient presented a premature ovarian failure syndrome.

In 10 patients a partially empty sella was diagnosed. In four young patients, ranging in age from 19 to 30 years, a slightly to moderately enlarged pituitary gland was found. In the remaining eight patients no abnormalities in MR imaging were stated.

DISCUSSION

Secondary adrenal insufficiency is usually associated with other endocrine deficiencies due to hypopituitarism. Most frequently it is explained by pituitary adenomas, especially while treated by neurosurgery and/or cranial irradiation, or destructed by pituitary apoplexy, granulomatous infiltrations or parasellar tumours. A different example of a diffuse pituitary lesion is Sheehan's syndrome. Isolated deficiency of ACTH remained an enigmatic finding for many years.^[11,12] A process that selectively induces destruction of corticotroph cells^[21,22] could be of autoimmune origin and such opinions were expressed by some authors.^[14,15,23] The most frequent form described in the literature was lymphocytic hypophysitis, sometimes complicated by acute features of adrenal failure and by signs of a progressive intrasellar tumour.^[15,24–27] Probably more frequent is subclinical lymphocytic hypophysitis, slowly leading to an overt endocrine deficit. We suppose that such a mechanism played the main role in a majority of our patients. Since a reliable diagnosis of lymphocytic hypophysitis can be made only histologically, we believe that such cases should be rather called "autoimmune hypophysitis". It is difficult to explain why ACTH deficiency seems to be the most frequent sign of autoimmune pituitary destruction. In our previous report,^[19] we speculated that corticotrophs representing the most active functionally cells during severe stress related to lymphocytic autoimmune inflammation, become also the most vulnerable.

Low cortisol levels accompanied by low or low normal plasma ACTH concentration without decrease in all other parameters of pituitary function reveal isolated secondary adrenal insufficiency. Normal plasma ACTH concentrations in the presence of decreased cortisol levels indicate a fall in functional corticotroph cells reserve. In our study the morning cortisol and ACTH values were both low, however, the earliest sign of secondary adrenal insufficiency were decreased evening cortisol levels.

The frequency of autoimmune disorders found in our material = of 73% was higher than 25% described by Thodou,^[15] 30% reported by Cosman^[25] and 50% noted by Crock.^[28] Our observation is similar to the frequency of autoimmunity related to the aetiology of Addison's disease.^[3,10] It is worth of mention that in a group of 31 patients an occult Hashimoto's disease was detected, characterised only by the presence of thyroid autoantibodies as the unique sign of autoimmunity, without any abnormalities of thyroid function. The detection of the aTPO autoantibodies was a more frequent finding than the detection of the antimicrobial autoantibodies because that latter test is less sensitive.

In many reports a relationship between autoimmunity development and pregnancy has been observed.^[15,28] The majority of our patients were pregnant 5 to more than 40 years prior to the study, however, in this group there were also nine young women who had never been pregnant; there were also three men. It is of interest that in

three young patients, clinical and hormonal signs of secondary adrenal insufficiency developed within a few weeks following parturition, without any symptoms of an intrasellar mass. In one of them Hashimoto's disease with hypothyroidism also developed. We suppose that such a mechanism could concern more numerous group of women with deterioration of their well being in the post-parturition period.

According to our observations thyroid diseases (57% of cases, and with occult Hashimoto's disease—85%) have been the most frequent disorder, like in other series of patients.^[15] A high frequency of the thyroid autoantibodies was partially provoked by the method of our investigations using these antibodies as a standard marker of an autoimmune mechanism. Only in a small number of patients antiparietal, antinuclear and antimitochondrial autoantibodies were determined (all results were positive). Since pituitary autoantibodies are a hallmark of pituitary autoimmunity a new technique of their determination (by immunoblotting) was introduced.^[23,28] The assays of pituitary autoantibodies will be the next step in our study. Interestingly, vitiligo (9% of cases) and premature ovarian failure (8%), traditionally related with Addison's disease of autoimmune origin, have been next on the list of frequency. Similarly as in Addison's disease, idiopathic hypoparathyroidism developed in a young girl, proceeding by more than 15 years secondary adrenal failure manifestation. Haematological disorders of autoimmune aetiology, thrombocytopenia and lymphoma accompanying secondary adrenal insufficiency seem to be the first such observations in the literature, whereas, pernicious anaemia has been recently described.^[28]

In majority of our patients isolated ACTH deficiency was diagnosed. However, among these patients, there was a woman with decreased FSH and LH values, and three patients presenting primary hypothyroidism with low TSH concentrations. These cases prove that concomitant autoimmune destruction of other lines of pituitary cells could be present.

Imaging studies, performed nearly in about 25% of the patients, revealed in some of them intrasellar changes characteristic of different stages of autoimmune hypophysitis. In the early stage in young patients, enlargement of the pituitary was seen. A gradually progressing destruction of the pituitary gland resulted in partially empty sella in most cases. Empty sella, found in five patients, was a sign of advanced pituitary lesion. The descriptions of MRI findings in lymphocytic hypophysitis were rather rare.^[15,23,29]

Generally, clinical symptoms of Addison's disease progress promptly to a dramatic stage, when replacement therapy appears to be inevitable, while secondary adrenal insufficiency may remain occult for a long time. In an early stage of observation this is rather a problem of life discomfort than of a life-threatening syndrome. However, even in this early period of the disease, a sudden adrenal crisis may develop in stressful situations. We believe that the diagnosis of subclinical isolated secondary adrenal

insufficiency is underestimated and more attention is necessary in suspected cases. It concerns especially old women with complaints of distinct fatigue and a tendency to hyponatraemia and reactive hypoglycaemia, more frequent than in general population. With special interest should be also treated patients presenting an exaggerated fatigability and postural hypotension following the parturition. Insufficient corticotroph cells function due to an autoimmune process during pregnancy (probably transient in some cases) could be responsible for this feeling of discomfort.

In summary, in our material of secondary adrenal insufficiency, autoimmunity was found in 73% of cases, similarly as it has been observed in Addison's disease. Thus autoimmune hypophysitis seems to be the most frequent cause of idiopathic secondary adrenal insufficiency.

Acknowledgements

This work was supported by 501-2-2-07-66/99 and 501-2-2-07-30/02 CMKP grants.

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