Association of Addison's disease with autoimmune disorders – a long-term observation of 180 patients

A.A. Kasperlik-Zaluska¹, B. Migdalska¹, B. Czarnocka², J. Drac-Kaniewska¹, E. Niegowska and W. Czech

Departments of ¹Endocrinology and ²Biochemistry, Centre of Postgraduate Medical Education, 01-809 Warsaw, Ceglowska 80, Poland.

Summary: This study aimed at evaluating the frequency of autoimmune disorders in Addison's disease. We have observed 180 patients (113 females, 67 males, aged 9–74 years) for 1 to 26 years. Tuberculosis was noted in 54 patients. Autoimmune disorders were found in 80 patients (44%); however, 125 (69%) patients were believed to have an autoimmune origin of adrenocortical insufficiency. In 20 patients two or more autoimmune disorders were found to coexist with Addison's disease.

Introduction

Between 1960 and 1990, 180 patients with Addison's disease were observed in the Department of Endocrinology in Warsaw. In this long-term study we investigated the occurrence of autoimmune disorders accompanying the disease.

Subjects and methods

In 180 patients (113 females) aged 9–74 years (44 ± 14 , mean $\pm$ s.d.) primary adrenocortical insufficiency was diagnosed on the basis of clinical characteristics and stimulation test with the use of ACTH. Every patient had evaluation of other endocrine functions and investigations into non-endocrine autoimmune disorders. The follow-up observation was continued for 1 to 26 years (mean 10 ± 8). The investigations were repeated at about 6–12 month intervals.

Investigations

Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH),¹ thyroid stimulating hormone (TSH),² thyroxine (T4) and triiodothyronine (T3) levels³ were determined by radioimmunoassay. Serum adrenal antibodies were sought by means of an indirect immunofluorescent technique⁴ in 52 cases. Antibodies to thyroglobulin were detected and titrated by a haemagglutination test (Thymune-T, Wellcome kits) and by a quantitative

haemagglutination test (Sera-Tek, Ames kits), examinations being carried out in 151 cases. Thyroid microsomal antibodies were assayed by a haemagglutination test (Thymune-M, Wellcome kits) in 45 patients and antithyroid peroxidase antibodies by ELISA method⁵ in 50 patients. The antibodies to the intrinsic factor were sought in 41 patients. The absorption of labelled vitamin B₁₂ from the digestive tract, the serum level of this vitamin and unsaturated binding capacity of ⁵⁷Co-labelled vitamin B₁₂ in the serum⁶ were determined in the same group in 41 patients. All patients had chest and abdominal X-rays. Age and sex distribution, as well as the age at the beginning of the adrenal insufficiency, were compared in these groups. Statistical significance was evaluated by an unpaired Student's *t*-test.

Results

On the basis of the above mentioned methods we divided the patients into two groups: A – comprising 52 patients with a history of tuberculosis or radiological evidence of this disease and three patients with other processes destroying the adrenals, metastases from a bronchogenic carcinoma, infiltration by a retroperitoneal lymphoma, and amyloidosis. In 50 patients tuberculous infection was diagnosed 5 to 13 years (mean 8) and in two patients 2 years prior to the onset of adrenocortical insufficiency; B – the other 125 patients. Two of the patients had pulmonary tuberculosis diagnosed 2 years earlier, but as adrenal antibodies were detected they are included in group B.

The comparison of the groups is shown in Table

I. The evidence of autoimmune disease in group B is shown in Table II. Table III lists patients with more than one associated autoimmune disorder.

In hypothyroidism, serum T4 levels ranged from 16 to 36 nmol/l (normal range: 51–150 nmol/l) and TSH 18–230 mU/l (normal range: 0.45–6.5 mU/l). In one patient transient spontaneous remission of hypothyroidism was observed. Additionally, six patients with slightly elevated TSH concentrations (8.0–24.0 mU/l) and normal T4 levels, without clinical features of thyroxine deficiency, were classified as subclinical hypothyroidism (Table II). In hyperthyroidism serum T3 levels varied from 3.4 to 4.0 nmol/l (normal range: 1.3–2.9 nmol/l) and T4 levels from 171 to 297 nmol/l. Two euthyroid women had nodular goitres.

The titre of antimicrosomal antibodies ranged

from 1:80 to 1:3240 and antithyroid peroxidase antibodies from 1:2000 to 1:256000. Six patients developed hypothyroidism within 1 to 3 years and one became hypothyroid within 1 year of the initial investigations.⁷

Thyrotoxicosis aggravated the course of Addison's disease as previously reported.⁸ In the women presenting features of premature ovarian failure (secondary amenorrhoea at the age of ≤ 35 years) LH levels ranged from 38–82 mU/ml (normal; 5–25 mU/ml) and serum FSH levels, 42–86 mU/ml (normal; 4–25 mU/ml). In the youngest patient with alopecia areata a spontaneous remission appeared after 5 years' duration, in the second year of replacement therapy with hydrocortisone.

The presence of adrenal antibodies was observed only in patients with the duration of Addison's

Table I The characteristics of 180 patients with Addison's disease with either a history of tuberculosis or infiltrating disease (Group A) or without (Group B)

	Group A	Group B
Number of patients	55	125
Female:Male	26:29	87:38
Female/Male ratio	0.9	2.3
Age at admission (years)	51.0 (23–74)	40.8 (9–68)*
Age at onset of AD	43.6 (13–67)	34.9 (2–60)**
Adrenal calcification	13/50†	0/118
Adrenal antibodies	0/6	19/46
Antithyroglobulin auto-antibodies	0/39	49/112
Thyroid antimicrosomal auto-antibodies	0/5	31/40
Thyroid antiperoxidase auto-antibodies	0/6	38/44
Antithyroid auto-antibodies (total)	0/41	66/120
Intrinsic factor auto-antibodies	0/7	2/34
Vitamin B ₁₂ malabsorption	0/7	9/33

Age expressed as mean and range: * $P < 0.002$; ** $P < 0.005$; †number of tests positive/number of tests performed; AD – Addison's disease.

Table II The frequency of autoimmune disorders in 180 patients with Addison's disease

	Group A total	Group B (%)	Sex		Mean age at onset (yr) (range) Addison's disease	Autoimmune disorder
			F	M		
Hypothyroidism	0 (0)	17 (14)	15	2	43.0 (27–60)	37.3 (26–58)
Subclinical hypothyroidism	0 (0)	6 (5)	6	0	41.2 (22–56)	36.1 (19–54)
Thyrotoxicosis	0 (0)	15 (12)	13	2	33.9 (17–51)	37.1 (22–54)
Hypogonadism	0 (0)	18 (14)	17	1	31.4 (20–35)	33.8 (19–56)
Diabetes mellitus (type 1)	0 (0)	7 (6)	4	3	44.9 (31–53)	42.9 (33–53)
Diabetes mellitus (type 2)	2 (4)	0 (0)	1	1	67, 57	40, 53
Hypoparathyroidism	0 (0)	3 (2)	1	2	10.3 (5–17)*	12.7 (7–19)
Vitiligo	0 (0)	17 (14)	15	2	34.6 (10–50)	36.8 (18–60)
Pernicious anaemia	0 (0)	4 (3)	4	0	44.7 (33–65)	37.8 (32–48)
Alopecia areata	0 (0)	3 (2)	0	3	19.0 (13–28)	21.0 (14–30)
Chronic active hepatitis	0 (0)	2 (2)	1	1	8, 36	1, 36

*In the youngest patient moniliasis was also found.

Table III Multiple autoimmune disorders associated with Addison's disease

Patient	Age	Sex	Hypo-thyroidism	Thyro-toxicosis	Hypo-gonadism	Diabetes mellitus	Hypopara-thyroidism	Vitiligo	Pernicious anaemia	Chronic active hepatitis	Lymphocytic hypophysitis
1	39	F		+	+	+			+		
2	40	F	+		+					+	+
3	22	F			+		+	+			
4	44	F		+	+			+			
5	34	F	+			+			+		
6	53	F		+		+					
7	49	F		+	+						
8	33	F		+	+						
9	34	F		+	+						
10	60	F	+		+						
11	51	M	+		+						
12	28	F	+		+				+		
13	50	M	+			+			+		
14	68	F	+						+		
15	49	F	+			+					
16	45	F	+					+	+		
17	35	F		+				+			
18	45	F			+				+		
19	33	F			+			+			
20	53	F			+			+			

+ confirmed at postmortem.

disease not exceeding 8 years. The titre of the antithyroglobulin antibodies ranged from 1:80 to 1:10000.

The total series included 63% of females and 37% of males. The female/male ratio was 1.7.

Discussion

Long-term observation of a series of patients with Addison's disease provides more information on the frequency of additional autoimmune disorders than a single assessment made at the time of the initial diagnosis. In this series of 180 patients, autoimmune disorders were found in 80 (44%); 53 patients (29%) had autoimmune diseases as shown in Table II, while the other 27 patients had adrenal and/or thyroid antibodies. The remaining patients in group B, without a history of past tuberculosis or other diseases known to destroy the adrenals, could be classified as having idiopathic Addison's disease. Thus the total number of patients with probable autoimmune aetiology of the adrenal insufficiency is 125 (69%). This percentage is similar to that (66%) in Nerup's series⁹ of 108 patients. Our series had a higher percentage of females than in that of Nerup,⁹ with a female/male ratio of 1.7 compared to 1.25. All our patients with previous tuberculous infection, as well as 4 with evidence of active infection, were treated for tuberculosis. Antituberculous drugs were also given for prophylaxis in 8 patients with idiopathic Addison's

disease.

Thyrotoxicosis was more frequent in our series than in others.^{10,11} Hypothyroidism with Addison's disease is sometimes reversible¹² as in one of our patients in whom a transient recovery of normal thyroid function of about 4 years duration appeared, followed by recurrent thyroid insufficiency.

Of the autoimmune glandular insufficiencies, premature ovarian failure was found to be most frequent, as in the cases reported by Nerup.¹¹ Our observations differ from other reports as to the frequency of insulin dependent diabetes mellitus, which was found in only 5% of the patients. In four series of idiopathic Addison's disease reviewed by Nerup¹¹ the prevalence of diabetes mellitus was 14%. We found a high prevalence of vitiligo in 14% of the patients with nontuberculous Addison's disease. Autoantibodies to melanin-producing cells are found in vitiligo,¹³ which is a clinical marker of an autoimmune process.

When characterizing Addison's disease associated with different autoimmune disorders, Neufeld *et al.*¹⁴ distinguished two types: type I, including hypoparathyroidism and moniliasis, and type II comprising other autoimmune polyglandular syndromes. According to this classification, the majority of our patients represented type II of the polyglandular autoimmune syndrome. Only three type I patients were noted in group B. Irvine and Barnes¹⁵ reported the frequent coexistence of idiopathic hypoparathyroidism and idiopathic Addison's disease, especially in young patients but our obser-

vations have not confirmed this. An association of multiple autoimmune disorders occurs as in cases 1–5 (Table III). Lymphocytic hypophysitis has been found rarely.^{16,17}

Primary adrenocortical insufficiency seems to be a disease most frequently associated with other autoimmune disorders.¹⁸ One cannot exclude the possibility that cortisol deficiency is an important

factor disturbing humoral and cell-mediated immunity and thus facilitating more pronounced autoimmunization.

Acknowledgements

This work was supported by Grant MZ X/9.

References

1. Midgley, A.R. Radioimmunoassay: a method for human chorionic gonadotropin and human luteinizing hormone. *Endocrinology* 1966, **79**: 10–18.
2. Utiger, R.D. Radioimmunoassay of human plasma thyrotropin. *J Clin Invest* 1965, **44**: 1277–1286.
3. Jeske, W., Niewiadomska, A. & Czerwińska, A. The radioimmunoassay of total serum thyroxine and triiodothyronine. *Endokrynol Pol* 1977, **28**: 109–115.
4. Jeske, W., Gajl-Peczalska, K. & Kasperlik-Zaluska, A. Adrenal antibodies in Addison's disease and Cushing's disease. *Pol Arch Med Wew* 1971, **47**: 485–491.
5. Czarnocka, B., Ruf, J., Ferrand, M., Carayan, P. & Lissitzky, S. Purification of the human thyroid peroxidase and its identification as the microsomal antigen involved in autoimmune thyroid diseases. *FEBS Lett* 1985, **190**: 147–152.
6. Pawelski, S., Hartwig, W., Rechowicz, K., Konopka, L. & Kasperlik-Zaluska, A. Vitamin B₁₂ metabolism in adrenocortical insufficiency. *Haematologia* 1970, **4**: 287–293.
7. Kasperlik-Zaluska, A., Górowski, T., Jeske, W., Kaniewski, M. & Bardadin, K. Clinical significance of antithyroid antibodies in Addison's disease. *Poly Tyg Lek* 1978, **33**: 671–673.
8. Kasperlik-Zaluska, A., Drac-Kaniewska, J., Górowski, T. & Czech, W. Association of Addison's disease and hyperthyroidism. *Endokrynol Pol* 1986, **37**: 231–236.
9. Nerup, J. Addison's disease – clinical studies. A report of 108 cases. *Acta Endocrinol* 1974, **76**: 127–141.
10. Gastineau, C.F., Meyers, W.R., Arnold, J.W. & McConaheny, W.H. Thyroid disorders in Addison's disease. 2. Graves' disease. *Proc Mayo Clin* 1964, **39**: 939–945.
11. Nerup, J. Addison's disease – a review of some clinical, pathological and immunological features. *Dan Med Bull* 1974, **21**: 201–217.
12. Burrows, A.W. Reversible hypothyroidism after steroid replacement for Addison's disease. *Postgrad Med J* 1981, **57**: 806–814.
13. Betterle, C., Peserico, A. & Bersani, G. Vitiligo and autoimmune polyendocrine deficiencies with autoantibodies to melanin producing cells. *Arch Dermatol* 1979, **115**: 364–365.
14. Neufeld, M., MacLaren, M.K. & Blizzard, R.M. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine* 1981, **60**: 355–362.
15. Irvine, W.J. & Barnes, E.W. Addison's disease, ovarian failure and hypoparathyroidism. *Clin Endocrinol Metab* 1975, **4**: 379–434.
16. Goudie, R.B. & Pinkerton, P.H. Anterior hypophysitis and Hashimoto's disease in young woman. *J Pathol Bacteriol* 1962, **83**: 584–585.
17. Pestell, R.G., Best, J.D. & Alford, F.P. Lymphocytic hypophysitis. The clinical spectrum of the disorder and evidence for an autoimmune pathogenesis. *Clin Endocrinol* 1990, **33**: 457–466.
18. Meyerson, J., Lechuga-Gomez, E.E., Bigazzi, P.E. & Walfish, P.G. Polyglandular autoimmune syndrome: current concepts. *Can Med Assoc J* 1988, **138**: 605–612.