Pituitary autoantibodies in patients with hypopituitarism and their relatives

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Abstract

Autoantibodies to human pituitary cytosol proteins were determined by immunoblotting in sera from patients with hypopituitarism and their relatives. Reactivity to an M_r 49 000 protein was significantly more frequent in patients (6/21 (28%) $P<0.05$) as well as in relatives (10/35 (28%) $P<0.02$) compared with controls (3/44 (6.8%)). Autoantibodies to this particular protein have previously been detected in sera from 70% of patients with biopsy-proven lymphocytic hypophysitis. Unlike patients with biopsy-proven lymphocytic hypophysitis, none of the patients in

this study presented with a suspected pituitary adenoma or showed an enlarged sella turcica. Cisternal herniation was seen in 6/21 patients and this may very well represent the end stage of lymphocytic hypophysitis. Since organ specific autoantibodies are frequent in patients with autoimmune endocrine disease as well as in their unaffected relatives, autoantibodies to this M_r 49 000 pituitary cytosolic protein may represent markers for an immunological process affecting the pituitary gland.

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Introduction

Hypopituitarism is most commonly explained by pituitary adenomas or by causes such as cranial irradiation, head trauma, infarction due to pituitary apoplexy or sarcoidosis. However, in some patients other causes of pituitary dysfunction must be considered. As in other endocrine organs, it is reported that the pituitary may also be the target for an autoimmune process (Goudie & Pinkerton 1962, Hume & Roberts 1967, Asa *et al.* 1981). This condition is usually referred to as lymphocytic hypophysitis, and is characterised by chronic inflammation and destruction of the anterior pituitary. Approximately 100 patients have been reported since the first description of the disorder in 1962 (Goudie & Pinkerton 1962). The classical presentation is peripartum hypopituitarism, often with pituitary mass and visual failure (Feigenbaum *et al.* 1991, Thodou *et al.* 1995). The diagnosis has been based on histological samples of pituitary biopsies or post-mortem tissue. Because of the risks associated with the neurosurgical procedure, biopsies are only indicated in patients whose pituitary pathology is unclear by computed tomography (CT) or magnetic resonance imaging (MRI). The radiological images of lymphocytic hypophysitis vary depending on time duration of the pathological process (Cosman *et al.* 1989). However, both CT and MRI may indicate a completely normal sella turcica (Mau *et al.* 1994). Therefore, a number of patients with hypo-

pituitarism of unknown origin may have undiagnosed autoimmune pituitary disease. It is most important to diagnose this condition since autoimmune pituitary disorder may be fatal if secondary adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH) insufficiency are not identified (Richtsmeier *et al.* 1980, Gal *et al.* 1986).

Autoimmunity of endocrine organs is characterised by the development of autoantibodies to specific autoantigens in the target organ. The presence of pituitary autoantibodies in sera from patients with hypopituitarism is therefore thought to be a marker for autoimmune pituitary disease. Pituitary autoantibodies have been detected in sera from patients with hypopituitarism or other endocrine diseases (Bottazzo *et al.* 1975, Mirakian *et al.* 1982, Sugiura *et al.* 1986, Kobayashi *et al.* 1988, Komatsu *et al.* 1988). Methodological problems have, however, hampered the characterisation of pituitary autoantigens. Recently, immunoblotting with human pituitary proteins (Crock *et al.* 1993) allowed detection and characterisation of pituitary autoantibodies in sera from patients with biopsy-proven lymphocytic hypophysitis (Crock 1998).

In this study we describe a group of patients with verified hypopituitarism. All other major causes of their hypopituitarism had been excluded and pituitary autoimmunity was therefore suspected. The presence of pituitary autoantibodies in these patients and their relatives

was investigated using the above described immunoblotting method. The clinical features of our patients with hypopituitarism were compared with the clinical data recorded in the literature on patients with lymphocytic hypophysitis.

Subjects and Methods

Subjects

Patients with hypopituitarism A total of 11 men and 10 women treated for hypopituitarism of unknown origin at the Department of Endocrinology and Diabetology, Karolinska Hospital participated in this study (Table 1). The age range was 24–87 years. Their medical histories were evaluated and blood samples collected for analysis of pituitary autoantibodies.

Family members Blood samples were collected from 35 family members (first degree relatives and husband or wife) for pituitary autoantibody analysis. There were 15 men and 20 women, the age range being 22–80 years.

Positive control Serum from a patient with biopsy-proven lymphocytic hypophysitis and pituitary autoantibodies by immunoblotting was used as a positive control.

Normal controls Sera from 44 healthy subjects from the Stockholm area were used as controls in the pituitary autoantibody analysis. There were 28 men and 16 women, age range 21–60 years. Exclusion criteria were major illness or autoimmune disease.

The study was approved by the Ethics Committee of the Karolinska Hospital. All subjects gave informed consent.

Methods

Detection of pituitary autoantibodies by immunoblotting Normal human pituitary tissue was obtained at autopsy, 4–8 h post mortem and frozen at -70°C . A total of ten pituitaries was homogenised in phosphate-buffered saline (PBS) with protease inhibitors. The homogenate was centrifuged to give a cytosolic fraction. The cytosolic fraction was depleted of immunoglobulin G (IgG) using protein A Sepharose (Pharmacia, Uppsala, Sweden) and stored in aliquots at -70°C . Pituitary samples were boiled for two min in the presence of 1,4-dithiothreitol. The cytosol preparations were subjected to 10×10.5 cm sodium dodecylsulphate (SDS)-polyacrylamide gels (10% running gel, 4% stacking gel) by electrophoresis. A total amount of 50 μg protein was loaded in each well. Molecular weight markers (Bio-Rad, Hercules, CA, USA) were included in each experiment. After electro-

phoresis, the proteins were transferred to polyvinylidene difluoride (PVDF; Bio-Rad) transfer membranes. After blocking for 1 h in 5% fat-free skimmed milk (BLOTTO)/PBS, membranes were divided into ten lanes using a Deca-Probe Incubation Manifold (Hoefer, San Francisco, CA, USA). Lanes were incubated with patient, relative or control serum diluted 1:50 in 1% BLOTTO/PBS on a shaker at 4°C overnight. Control lanes were incubated with 1% BLOTTO/PBS only. Following incubation the membranes were washed with PBS-0.05% Tween 20 and incubated with alkaline phosphatase-conjugated goat anti-human IgG antiserum (Sigma-Aldrich; Sigma, St Louis, MO, USA) diluted 1:2500 in 1% BLOTTO/PBS for 1 h at room temperature on a shaker. After final washing, membranes were incubated with 5-bromo-4 chloro-3 indolyl phosphate and nitroblue tetrazolium until colour development was optimal. Results of the immunoblotting assay experiments were reported independently by two observers who were blinded to the status of the serum samples. For further technical information see Crock *et al.* (1993).

Statistical analyses

Reactivity to cytosolic proteins by immunoblotting was compared between groups using Fisher's exact test.

Results

Clinical findings

Among the patients (Table 1), three women and three men had panhypopituitarism (patients 1–6). One of the women (patient 1) also had vasopressin deficiency for which she received treatment. The duration of symptoms for these six patients varied. Two of the men had already had symptoms in childhood (patients 5 and 6). None of the six patients had any other suspected autoimmune disease. One woman in our study only exhibited prolactin (PRL) secretion (patient 7). She received her diagnosis rather late in life, after a short duration of symptoms. One man exhibited only growth hormone (GH) secretion (patient 8). Four patients had selective ACTH deficiency (patients 9–12). They were all women who were diagnosed after the age of 30 years. Their duration of symptoms varied from one week up to one year. Two of these patients had other suspected autoimmune diseases showing antibodies towards parietal cells and cardiolipin (patients 11 and 12). One male (patient 13) with multiple endocrinopathies, diabetes mellitus, thyroiditis, vitiligo and pernicious anaemia, was evaluated because of a clinical history and symptoms pointing to hypopituitarism. Lymphocytic hypophysitis was suspected, but at the time of laboratory evaluation, signs and symptoms had disappeared and only isolated prolactin deficiency could be proven. Three

Table 1 Some data on patients with hypopituitarism

Patient no.	Age at diagnosis (years)		Age at evaluation (years)	Duration of symptoms (years)	Pituitary hormone secretion					CT/MRI	M _r 49 000 reactivity	Other M _r reactivity ($\times 10^3$)	Other suspected autoimmune disease/autoantibodies
	Sex				TSH	LH	FSH	GH	PRL	ACTH			
1	F	69	75	40	—	—	—	—	—	—	+	39, 91	
2	F	42	64	3	—	—	—	—	—	—	—	36	
3	F	34	37	5	—	—	—	—	—	—	—	34, 39, 103	
4	M	68	72	8 weeks	—	—	—	—	—	—	—	57, 83, 91	
5	M	7	26	Since childhood	—	—	—	—	—	—	—	33, 100	
6	M	10	24	Since childhood	—	—	—	—	—	—	+	—	
7	F	73	87	0.5	—	—	—	—	N	—	—	38	Thyroid-ab
8	M	50	53	4 months	—	—	—	N	—	—	—	40	
9	F	65	78	0.5	N	N	N	N	N	—	—	50, 57	
10	F	50	53	1	N	N	N	N	N	—	—	—	
11	F	41	49	1	N	N	N	N	N	—	—	—	
12	F	31	32	1 week	N	N	N	N	N	—	—	—	
13	M	67	69	1	N	N	N	N	—	N	—	43	Parietal Cell-ab
											+	37, 80	Nuclear antigen-ab
												—	Cardiolipin-ab
												—	IDDM
												—	Vitiligo
												—	Pernicious anaemia
												—	Thyroid-ab
14	F	59	60	20	N	N	—	—	N	N	+	—	
15	F	57	60	Since puberty	N	N	—	—	N	N	—	—	
16	M	11	58	Since childhood	N	N	—	—	N	N	—	—	
												—	Thyroid-ab
17	M	69	71	0	N	—	—	N	N	N	+	35, 55	Rheumatoid arthritis
												—	Thyroid-ab
												—	IDDM
												—	
18	M	69	71	15	N	—	—	N	N	N	—	42	Vitiligo
19	M	62	63	2	N	—	—	N	N	N	—	36, 57, 73, 78	
20	M	56	57	0.5	N	—	—	N	N	N	—	—	IDDM
21	M	32	36	3	N	—	—	N	N	N	+	36, 39	

F, female; M, male; LH, luteinising hormone; FSH, follicle-stimulating hormone; N, normal hormonal secretion/radiology; —, hormonal insufficiency; +, patients with autoantibodies to the M_r 49 000 pituitary cytosolic protein.

Cisternal herniation is described as a herniation >50% of sellar volume. Pituitary autoantibodies are presented together with other suspected autoimmune disease/autoantibodies (ab).

patients had isolated GH insufficiency (patients 14–16). Other autoimmune diseases were known in two of these patients. Finally, five patients suffered from isolated gonadotrophin deficiency (patients 17–21). Duration of symptoms varied between 0.5 and 15 years. Two of these patients had other known autoimmunity (patients 18 and 20).

Clinical evaluation showed that fatigue was the most common symptom (seen in 12/21 patients). Decreased libido (5/21) and impotence (5/21) were also frequent, while eye symptoms were not noticed in any of the patients. One patient (no. 17) was asymptomatic at the time of diagnosis. His gonadotrophin deficiency was revealed at a routine health check-up.

Radiological examinations

Eight patients exhibited normal findings, while ten patients had pathological findings by CT or MRI (Table 1). Six patients showed cisternal herniation of varying degree with none or little visible pituitary tissue left. Two patients had pituitary cysts. One patient had a balloon-shaped sella turcica of normal size, one patient showed pathological pituitary stalk deviation and another a pathologically thick pituitary stalk with intense contrast loading. No patient had an enlarged sella turcica and suspected pituitary tumour could not be seen in any patient. CT and MRI were not performed in three cases.

Pituitary autoantibodies

Six of the 21 (28%) patients with hypopituitarism showed reactivity to an M_r 49 000 pituitary cytosolic protein (Table 1). Sera from 10/35 (28%) family members also reacted with this protein (Table 2). Of the control sera, 3/44 (6.8%) showed M_r 49 000 reactivity. Statistical analysis proved that patients as well as relatives showed M_r 49 000 reactivity in significantly higher frequencies than controls ($P<0.05$ and $P<0.02$ respectively). Figure 1 shows this M_r 49 000 reactivity in some sera. A number of other pituitary cytosolic proteins were detected by individual sera, but there were no significant patterns or differences between patients, relatives and controls (Table 1).

Discussion

This study shows that patients with hypopituitarism of unknown cause have a significantly higher prevalence of autoantibodies to an M_r 49 000 pituitary cytosolic protein compared with control subjects. The role of autoantibodies in the development of autoimmune disease is unclear but they are believed to be markers for these diseases. Auto-antibodies to this M_r 49 000 pituitary protein have been detected in 7/10 (70%) sera samples from patients

Table 2 Tabulation of relatives with M_r 49 000 reactivity. Their relationships to patients with hypopituitarism as well as additional M_r reactivity are shown. Details of the patients are taken from Table 1. Patients 5, 7 and 9 exhibited other M_r reactivity, whereas patients 14 and 21 as well as the 10 relatives were M_r 49 000 positive

		M_r 49 000 reactivity	Other M_r reactivity ($\times 10^3$)
Patient no.	Relative		
5		—	33, 100
	Mother	+	38
7		—	38
	Daughter	+	—
9		—	50, 57
	Sister	+	—
	Brother	+	33, 62
	Husband	+	—
	Daughter	+	—
14		+	—
	Daughter	+	—
	Daughter	+	—
21		+	36, 39
	Mother	+	64
	Brother	+	—

Figure 1 One immunoblotting experiment with human pituitary cytosol (50 µg protein/well) as antigen, showing the reactivity in different sera. M_r , molecular mass markers ($\times 10^3$). Lane 1, sera from the positive control patient with biopsy-proven lymphocytic hypophysitis, showing reactivity to an M_r 49 000 protein. Lanes 2 and 4, sera from patients 21 and 14 showing reactivity to an M_r 49 000 protein. Lane 3, sera from a normal control subject showing no reactivity to pituitary proteins. Lanes 5 and 6, sera from two daughters of patient 14, both showing reactivity to an M_r 49 000 protein.

with biopsy-proven lymphocytic hypophysitis (Crock 1998). Therefore, we suggest that some of our patients with hypopituitarism of unknown cause may also have

autoimmune pituitary disease which, for ethical reasons, cannot be confirmed by biopsy.

Relatives of patients with hypopituitarism of unknown cause also showed a significantly higher prevalence of autoantibodies to this M_r 49 000 pituitary cytosolic protein. None of these relatives showed any signs of pituitary insufficiency themselves; however, extensive pituitary function tests were not performed. Pituitary autoantibodies have not been analysed in relatives of patients with biopsy-proven lymphocytic hypophysitis. Autoantibodies to non-characterised rat pituitary cytosolic proteins have been described in a few family members of two patients with Sheehan's syndrome and one patient with partial hypopituitarism (Kajita *et al.* 1991). However, autoantibodies are often present among relatives of patients with organ-specific autoimmune diseases. In insulin-dependent diabetes mellitus (IDDM) for example, glutamic acid decarboxylase (GAD) autoantibodies are shown to be early and sensitive markers for later development of this autoimmune endocrine disease (Baekkeskov *et al.* 1987). In addition, relatives of GAD-positive patients are more likely to have GAD antibodies than control subjects, but they do not necessarily become diabetic. A combination of different autoantibodies and genetic markers seems to be crucial for development of IDDM (Hagopian *et al.* 1995). This might also be the case for pituitary autoimmune disease and may explain the absence of hypopituitarism in our autoantibody-positive relatives.

Previous reports of lymphocytic hypophysitis indicate a female predominance with a female:male ratio of 8.5:1 (Thodou *et al.* 1995). We did not find a female predominance in the present study of 11 men and 10 women. Four out of six patients with autoantibodies to the M_r 49 000 pituitary cytosolic protein were men. This difference is difficult to interpret. One explanation may be the fact that our patients include men seeking medical attention for impotence and infertility problems due to gonadotrophin deficiency. This is of interest since these patients have not so far been thoroughly examined in respect to autoimmune pituitary disease.

A striking difference between our study of patients with hypopituitarism of unknown origin and biopsy-proven cases of lymphocytic hypophysitis is the outcome of the radiological examination. Patients with biopsy-proven lymphocytic hypophysitis almost exclusively have enlarged pituitaries causing hypopituitarism and many of them have visual disturbances (Powrie *et al.* 1995). None of our patients had an enlarged pituitary on MRI/CT examinations and a pituitary tumour was not suspected in any case. Nor did any of our patients complain of visual disturbances. Thus, pituitary biopsy was not indicated. Three of our M_r 49 000 antibody-positive patients showed cysternal herniation, and this was also the predominant pathological finding in the patient group, i.e. 6/10 patients with sellar pathology showed cysternal herniation. A combination of clinical symptoms, laboratory data, radio-

logical results and pituitary pathology data reveals that lymphocytic hypophysitis probably progresses through different stages (Cosman *et al.* 1989). In the acute phase of the disease, the pituitary gland is enlarged, but later the pituitary tissue may be more or less destroyed by the severe inflammation. Shrinkage and atrophy of the pituitary gland is seen as a common end stage of this process. The cysternal herniation seen in a number of our patients may very well represent the end stage of lymphocytic hypophysitis.

Most patients with biopsy-proven lymphocytic hypophysitis were described as having acute symptoms of pituitary insufficiency because of their severe pituitary inflammation. On the other hand, we believe that a gradual inflammatory process affecting the pituitary gland may cause a slowly developing pituitary insufficiency as noticed in many of our patients. The patients in our study presented with selective hormone deficiency as well as total panhypopituitarism. This is also known for patients with biopsy-proven lymphocytic hypophysitis (Jensen *et al.* 1986, Cosman *et al.* 1989).

Subclinical forms of endocrine autoimmune disease during pregnancy, i.e. thyroiditis may develop into overt disease after delivery (Amino *et al.* 1977). This also seems to be the case for lymphocytic hypophysitis, that often causes partial or total hypopituitarism in women ante, during or post partum. Our patient group contained two women (patients 3 and 12) who developed hypopituitarism in relation to pregnancy. Neither of these two patients showed reactivity to the M_r 49 000 pituitary cytosolic protein.

Coexistent autoimmune disease is reported in approximately thirty percent of patients with biopsy-proven lymphocytic hypophysitis. Overall we found a similar prevalence in our study. Interestingly, it was those patients with selective pituitary hormone deficiencies who were more likely to have another autoimmune condition. None of the patients with panhypopituitarism had an underlying autoimmune disease. Only one of our M_r 49 000-positive patients suffered from other known autoimmune disease (patient 13). The three M_r 49 000 autoantibody-positive controls did not show any signs of pituitary dysfunction or other endocrinopathies.

In conclusion, we have identified autoantibodies to an M_r 49 000 pituitary cytosolic protein by immunoblotting in significantly higher frequencies in sera from patients with partial or total hypopituitarism and also in sera from their relatives. The results are in agreement with knowledge about specific autoantibodies in other autoimmune endocrinopathies like IDDM. The possibility of an hereditary immunological pituitary process causing partial or panhypopituitarism in some patients cannot be excluded.

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