Antibodies to pituitary surface antigens during various pituitary disease states

Y M Keda, I V Krjukova¹, I A Ilovaiskaia², M S Morozova, O V Fofanova³, M B Babarina², E I Marova², Y A Pankov and V I Kandror¹

Laboratory of Molecular Endocrinology, Institute of Experimental Endocrinology, Research Centre for Endocrinology, Moscvorechje 1, 115478 Moscow, Russia
¹Laboratory of Pathologic Physiology of Endocrine System, Institute of Experimental Endocrinology, Research Centre for Endocrinology, Moscvorechje 1, 115428 Moscow, Russia
²Department of Neuroendocrinology, Institute of Clinical Endocrinology, Research Centre for Endocrinology, Dm. Uljanov 11, 117036 Moscow, Russia
³Department of Pediatric Endocrinology, Institute of Clinical Endocrinology, Research Centre for Endocrinology, Dm. Uljanov 11, 117036 Moscow, Russia

Requests for offprints should be addressed to Y M Keda; Email: bik181936@mtu-net.ru

Abstract

Autoantibodies to cell surface antigens of human somatotropinoma (ASAS), human prolactinoma (ASAP) and rat adenohypophysis (ASARA) were assayed in the serum of patients with pituitary diseases associated with GH deficiency (GHD), such as pituitary dwarfism and primary empty sella syndrome (ESS), and in the serum of patients with hyperprolactinaemia of different etiologies: idiopathic hyperprolactinaemia, prolactinoma and ESS. The investigation was carried out with a cellular variant of an ELISA. Among children with GHD, the highest percentage of antibody-positive patients was found in the group with idiopathic isolated GHD (89% of ASAS+ patients and 30% of ASARA+ patients vs 33·3% and 0% respectively in the group with idiopathic combined pituitary hormone deficiency, and 33·3% and 9% in patients with pituitary hypoplasia associated with isolated GHD or combined pituitary hormone deficiency). Among hyperprolactinaemic patients, the highest ASAP and ASARA frequency was observed in patients with idiopathic hyperprolactinaemia (67·7% and 41·9% respectively) where it was twice as high as in the group of patients with prolactinoma.

The proportion of ASAS+ and ASARA+ did not differ significantly between the groups of patients with ESS with or without GHD. Similarly, there was no significant difference between the number of ESS ASAP+ and ASARA+ patients with or without hyperprolactinaemia.

The data obtained suggested that autoimmune disorders may be primary, and responsible, at least in part, for pituitary dysfunction in the cases of idiopathic isolated GHD and idiopathic hyperprolactinaemia. At the same time, the autoimmune disorders in the patients with prolactinoma or ESS are probably secondary to the organic pituitary lesion and their significance in the development of the pituitary dysfunction is obscure.

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Introduction

The endocrine system is considered to be predisposed to autoimmune lesions. Autoimmune disturbances may lead to a number of endocrine diseases. Autoantibodies may appear long before clinical manifestation of the disease and may serve as markers of the beginning of the autoimmune attack against the gland which indicates groups at risk. Autoantibodies to the peripheral endocrine gland antigens are seen in cases of insulin-dependent diabetes, primary adrenal insufficiency, Graves’ disease, Hashimoto’s thyroiditis and other disorders.

Recently, a hypothetical role of the immune system in the development of a number of pituitary disorders has attracted increasing attention. Autoantibodies to adenohypophysial cell antigens were first revealed in women during the postpartum period, and antibodies persisting for 6–12 months after labour were associated with the development of pituitary insufficiency in 25% of cases compared with 4% in women who did not show these antibodies (Engleberth & Jezkova 1965). Antipituitary antibodies were later found in patients with different disorders: Turner’s syndrome (Bottazzo et al. 1980), primary empty sella syndrome (ESS), various kinds of pituitary deficiency, idiopathic panhypopituitarism, prolactinoma, inactive pituitary tumour (Komatsu et al. 1988, Sauter et al. 1990), Cushing’s disease (Sherbaum et al. 1987) and hypogonadism (Barkan et al. 1985).

The common practice is to test antipituitary antibodies by indirect immunofluorescence on human pituitary sections to define the antibodies to cytoplasmic antigens (Bottazzo et al. 1975, 1980, Mirakian et al. 1982). For the
determination of antibodies to surface pituitary antigens some authors have used the growth hormone (GH)-producing rat GH3 cell line and the adrenocorticotrophin (ACTH)-producing mouse AtT20 cell line (Komatsu et al. 1988, Yabe et al. 1994). The aim of the present study was to detect markers of autoimmune attack against the pituitary using the cellular ELISA in patients with some of the pituitary diseases associated with GH deficiency (GHD), such as pituitary dwarfism and ESS, and with hyperprolactinaemia (idiopathic hyperprolactinaemia, prolactinoma and ESS).

Materials and Methods

Patients

GHD Serum from 42 children (26 boys and 16 girls) with complete GHD was studied. The diagnosis was confirmed using the insulin (0·1 U/kg weight, i.v.) and clonidine (0·15 mg/m² of body surface) tests. The maximum GH response to stimulation did not exceed 5 ng/ml, averaging 0·68 ± 0·18 ng/ml (0·1–4·5 ng/ml) in the insulin test and 1·44 ± 0·29 ng/ml (0·1–6·0 ng/ml) in the clonidine test. The average chronological age of the patients was 11·39 ± 0·55 years (3·8–17·4 years) and the average bone age was 6·1 ± 0·5 years (0·8–12 years). The growth deficiency in SDS growth parameters for chronological age and sex was −4·34 ± 0·23 (from −9·23 to −2·50). Thirty-one patients had not received GH previously and 11 patients had received irregular short-term courses of treatment with pituitary-derived human somatotrophin (Kaunas Endocrine Plant, Kaunas, Lithuania) in the past (not less than 2 years before their arrival in our centre). At the beginning of the investigation all patients were examined for the presence of anti-GH antibodies. Twenty children had idiopathic isolated GHD (group I), 11 children had idiopathic GHD combined with thyrotrophin (TSH), prolactin, ACTH or a gonadotrophin deficiency (group II), and group III consisted of 11 patients with pituitary hypoplasia established by magnetic-resonance imaging (MRI) (BNT-1000; Bruker, Erlanden, Germany): seven of the children had isolated GHD and four of them had GHD combined with prolactin, TSH and gonadotrophin deficiency.

Antipituitary antibodies were also studied in the serum of 37 parents (24 mothers and 13 fathers) of the patients with GHD. At the time of investigation the average age of the mothers was 35·5 ± 1·1 years (25–45 years) and that of the fathers was 35·4 ± 1·5 years (31–39 years). The SDS growth values were −0·33 ± 0·19 for the mothers and −0·34 ± 0·4 for the fathers.

ESS Serum from 48 patients (6 men and 42 women), average age 42·2 ± 12·4 years (15–61 years) with ESS established by MRI of the brain was studied. ESS was diagnosed in the cases where the pituitary lay flat along the base of the sella turcica and its vertical size did not exceed 1–2 mm. Twenty-six patients had GHD of various degrees. Their average GH basal level was 0·54 ± 0·54 ng/ml and they gave a low response to the insulin test (the stimulated GH level did not exceed 5 ng/ml). Seven of these 26 patients did not respond at all to stimulation tests (the response was no higher than 0·98 ng/ml). These 26 patients were attributed to the group with GHD. Twenty-five of them were of normal height and one patient was of short stature. In 13 patients, hyperprolactinaemia with an average basal prolactin level of 1420 ± 943·2 mU/l was observed, four patients had both hyperprolactinaemia and GHD. ESS was accompanied by primary hypothyroidism in eight patients and two patients had secondary hypothyroidism.

Prolactinoma and idiopathic hyperprolactinaemia Serum from 31 women with idiopathic hyperprolactinaemia and 44 women with prolactinoma (19–46 years) was investigated. Their main clinical features consisted of menstrual disorders, oligomenorrhoea or amenorrhoea, galactorrhea, infertility and headache. The state of the sella turcica was evaluated using computer tomography (CT) and/or MRI. In patients with prolactinoma, the tumour size varied from 8 to 14 mm. Prolactin levels in serum were 7500 ± 1250 MU/ml in the group of patients with prolactinoma and 1240 ± 300 MU/ml in the group with idiopathic hyperprolactinaemia.

Physiological hyperprolactinaemia Twelve healthy pregnant women (19–31 years, 20–22 weeks of pregnancy) with an average prolactin level of 4537 ± 839 MU/ml were included in this group.

Control groups Sixty-five randomised adult donors without endocrine or allergic disorders of an average age of 35 ± 10·2 years (20–65 years) and 19 healthy children with an average age of 7·2 ± 4·5 (5·5–16 years) were used as controls. The serum from adult donors was from the Moscow Blood Transfusion Station. The children’s serum was obtained during medical examinations at the Research Centre for Endocrinology (Russia).

Methods

Serum levels of ACTH, human GH, luteinizing hormone, follicle-stimulating hormone and prolactin were determined by radioimmunoassay using commercial kits from CIS Bio-International (Gif-Sur-Ivette, France).

The antibodies to GH were determined in serum by the radioimmunological method based on the ability of serum immunoglobulin fractions to bind highly purified
Detection of antibodies to surface antigens of rat adenohypophysial cells (ASARA) and tumour cells of human pituitary somatotropinoma (ASAS) and prolactinoma (ASAP) Serum autoantibodies were detected by a cellular variant of an ELISA. The primary suspensions of rat adenohypophysial cells or human prolactinoma and somatotropinoma cells (surgical material) were obtained by the trypsin method (Keda et al. 1994). The tissue was cut up with scissors in Versen solution (produced in the Institute of Poliomyelitis and Viral Encephalitis; RAMS, Moscow, Russia) to obtain a homogeneous mass, then 10 ml 0·25% Trypsin solution (Serva, Heidelberg, Germany) was added, and the mixture was digested by stirring for 30 min at 37 °C. After digestion, cells were washed three times with Hanks’ solution and counted in a Goriaev chamber (Krasnogvardeets, St Petersburg, Russia) using a binocular microscope. Cells (50,000 cells/well) were immobilised in flat-bottomed 96-well plates (Nunc, Roskilde, Denmark) pretreated with 0·01% lysine solution (Merck, Darmstadt, Germany). The cells were precipitated by centrifugation at 800 r.p.m. for 2 min, fixed by 0·05% glutaraldehyde (Fluka, Buchs, Switzerland) in Na-phosphate-buffered solution (PBS) for 20 min and treated with 0·5% glycine (Serva) in PBS for 30 min. The non-specific binding was blocked by 2% BSA (Serva) in PBS within 22 h. All operations were conducted at 4 °C. The analysis was performed by routine ELISA. Serum samples (100 µl) at a dilution of 1:100 with PBS containing 1% BSA and 0·15 M NaCl were placed in the wells and incubated for 90 min at 37 °C. After removal of the serum, the wells were washed three times with PBS containing 0·05% Tween 20 (Serva), incubated with rabbit monoclonal anti-human IgG conjugated with horseradish peroxidase (Sorbent Service, Moscow, Russia) for 90 min at 37 °C and, after washing, incubated with α-phenylenediamine (Fluka) in citrate buffer for 10 min at room temperature. The reaction was stopped by 1 M H2SO4, and the value of the optical density (OD492) was measured with a photometer (Ephos, Moscow, Russia). Ten control negative serum samples (laboratory standard) were added to each plate. The serum tested was considered to be positive if its optical density exceeded the average OD492 of control serum samples by 3 · Y M KEDA and others

Table 1.

ASARA prevalence in patients with different pituitary disorders determined by ELISA with rat adenohypophyseal cells as antigenic material

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of ASARA+ patients</th>
<th>% of ASARA+ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with GHD*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>20</td>
<td>6*</td>
</tr>
<tr>
<td>Group II</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Group III</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Primary ESS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With GHD</td>
<td>26</td>
<td>16*</td>
</tr>
<tr>
<td>Without GHD</td>
<td>22</td>
<td>9*</td>
</tr>
<tr>
<td>With hyperprolactinaemia</td>
<td>13</td>
<td>7*</td>
</tr>
<tr>
<td>Without hyperprolactinaemia</td>
<td>16</td>
<td>7*</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>44</td>
<td>8*</td>
</tr>
<tr>
<td>Idiopathic hyperprolactinaemia</td>
<td>31</td>
<td>13*&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physiologic hyperprolactinaemia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>Children</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Group I, patients with idiopathic isolated GHD; group II, patients with idiopathic deficiency of several pituitary hormones; group III, patients with isolated GHD or GH/prolactin/TSH/gonadotrophin deficiency associated with pituitary hypoplasia.</td>
<td></td>
<td></td>
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</tbody>
</table>
| <sup>a</sup>p<0·05 compared with corresponding normal adult or children group;  
| <sup>b</sup>p<0·05 compared with group with prolactinoma. |

*Statistical analysis*

Differences between groups were evaluated by χ2 criteria. Statistical analysis was performed with a software package (Glantz 1998). P<0·05 was considered as statistically significant.

**Results**

**GHD**

During the preliminary investigation, ASARA were revealed in some patients of the first group (the idiopathic isolated GHD) and were virtually absent from the other two groups (Table 1). When tested on somatotropinoma cells (Table 2 and Fig. 1), the prevalence of patients with
ASAS in group I appeared much greater: eight out of nine serum samples (four ASARA+ and five ASARA−/p1) were positive. In the group of children with idiopathic combined pituitary hormone deficiency, who were all ASARA−/p1, three serum samples were ASAS+. At the same time, the ASAS frequency in group II remained much lower than in group I (P < 0.05). The only ASARA + patient with pituitary hypoplasia (group III) appeared to be negative by ELISA using somatotropinoma cells, but the serum of the other three patients from this group (one with isolated GHD and two with GH/prolactin/TSH/gonadotrophin deficiency), who had been ASARA−, changed to ASAS+.

Anti-GH antibodies were revealed in three patients of group III, but their presence did not coincide with the presence of ASARA or ASAS; these children had not received pituitary-derived GH in the past.

The serum from parents of children with GHD were tested with ELISA using rat cells only. ASARA frequency made up 24.3% which was significantly higher than in the randomised healthy adult population (P < 0.001). ASARA frequency was somewhat higher in mothers (7/24, 28%) than in fathers (2/13, 14.3%). However, there was no correlation between the presence of antipituitary antibodies in children and in their parents, and ASARA were discovered in parents of ASARA− and/or ASAS− children as well as in the parents of children without both antibody types.

ESS ASARA were found in more than half of the patients with primary ESS and somewhat more often in patients with GHD, although the difference was not reliable (Table 1). When tested on somatotropinoma cells (Table 2 and Fig. 1), the number of ASAS+ patients appeared to be equal in both groups (with or without GHD) and significantly lower than the number of ASARA+ patients (P < 0.05).

Antibodies to GH were found in two patients with GHD and in three patients with normal GH secretion, but their presence, as well as in the case of children with dwarfism, did not correlate with the presence of antipituitary antibodies.

The number of ASARA+ patients with ESS was equal in groups with hyper- and normoprolactinaemia (Table 1). There was no significant difference between the numbers of patients with antibodies to ASAP in these two groups either (P > 0.05) (Table 3 and Fig. 2).

Among four patients with both hyperprolactinaemia and GHD, one had all three antibody types, one was ASARA+ and ASAS+ but ASAP−/p1, and two patients had no antibodies.

Prolactinoma and idiopathic hyperprolactinaemia

Serum from all patients with prolactinoma and idiopathic hyperprolactinaemia was tested by ELISA on rat adenohypophysial and human prolactinoma cells (Tables 1 and 3 and Fig. 2). The prevalence of patients with antipituitary antibodies was twice as high in the case of idiopathic hyperprolactinaemia than in patients with prolactinoma (P < 0.05) in both ELISA variants. In both groups, disclosure of antibodies were shown to be higher when prolactinoma cells were used as antigenic material.

None of the patients with prolactinoma had antibodies to prolactin (prolactin-binding did not exceed 8%).
Table 3 ASAP prevalence in patients with prolactinoma, idiopathic hyperprolactinaemia and ESS determined by ELISA with human prolactinoma cells as antigenic material

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of ASAP* patients</th>
<th>% of ASAP* patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
<td>44</td>
<td>15(^a)</td>
</tr>
<tr>
<td>Idiopathic hyperprolactinaemia</td>
<td>31</td>
<td>21(^a,b)</td>
</tr>
<tr>
<td>ESS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hyperprolactinaemia</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Without hyperprolactinaemia</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Physiologic hyperprolactinaemia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)P<0·05 compared with group with physiologic hyperprolactinaemia;
\(^b\)P<0·001 compared with groups with prolactinoma and physiologic hyperprolactinaemia.

women with idiopathic hyperprolactinaemia (seven ASARA\(^+\) and ASAP\(^+\) and four negative for both types of antibodies) serum prolactin-binding was 11–12% in three patients, and the simultaneous presence of both antipituitary antibodies and increased prolactin-binding was observed in one patient only.

Discussion

Antipituitary antibodies are of interest to researchers because of their possible role as markers of lymphocytic hypophysitis (LPH). In LPH, the pituitary is infiltrated with lymphocytes that can result in its dysfunction, leading to hypopituitarism. Hyperprolactinaemia is observed in about half of the patients with LPH (Okamoto et al. 1986). Originally, LPH was only found in women at a late stage of pregnancy or in the postpartum period but it is now acknowledged that it may occur in women without any connection with pregnancy and labour, as well as in men (Josse 1990, Thodou et al. 1995). Until recently, antipituitary antibodies have only been detected in a few cases of precisely diagnosed LPH (Cosman et al. 1989, Mayfield et al. 1980, Ozawa & Shishiba 1993) but there is no evidence as to their nature. In 1998, Crock showed that 70% of patients with biopsy-proven LPH had antibodies to 49 kDa pituitary cytosolic protein and 50% of them had antibodies to 40 kDa cytosolic protein (data from immunoblotting). Both these antigens were also present in rat pituitary. Antibodies to 49 kDa protein were also shown in 28% of patients with hypopituitarism and in their relatives (Strömberg et al. 1998).

For most of the pituitary diseases discussed in the present paper the frequency of antipituitary antibodies considerably exceeded that of the population in general. Isolated idiopathic GHD is of special interest, since ASAS were found in most of the patients. According to CT and/or MRI data, these children do not exhibit hypothalamic and pituitary changes. The appearance of autoantibodies as secondary to traumatic damage during labour is also excluded, as in none of the cases were such external factors as vacuum extraction, application of forceps or Caesarean section capable of evoking traumatic or ischaemic damage of the hypothalamus. We did not find any correlation between the presence of ASAS and previous treatment with GH since ASAS were detected in both treated and untreated patients and none of the patients of this group had anti-GH antibodies. The data obtained suggested that autoimmune disorders may be classed as primary in the group of patients with isolated idiopathic GHD and may underlie the disease, in at least some cases.

Molecular analysis, performed parallel with the present study, revealed some abnormalities in the GH gene in group III patients with GHD. Mutation in the GH1 gene (mutation of splicing) was found in one ASAS\(^+\) boy with isolated GHD (Fofanova et al. 2000a) and mutation in the PRO1 gene was detected in two ASAS\(^+\) siblings and two ASAS\(^-\) children with GH/prolactin/TSH/gonadotrophin deficiency (Fofanova et al. 1998a,b). Magnetic resonance imaging in all cases of patients with PRO1 mutation corresponded to anterior pituitary hypoplasia of various degrees, mostly to ESS (Fofanova et al. 2000b). Thus, mutations in the main candidate genes, not autoimmune damage of the anterior pituitary cells were responsible for pituitary disorders in these patients.

The prevalence of ASARA revealed in parents of children with GHD (28%) agrees with the data on the prevalence of antibodies to cytoplasmic pituitary antigens

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**Figure 2** Determination of ASAP in the serum of patients with idiopathic hyperprolactinaemia, prolactinoma and ESS by ELISA. The tested serum was considered to be positive if its optical density (OD\(_{492}\)) had exceeded the average OD\(_{492}\) value of ten control serum samples (the laboratory control) by 3\(^b\) (above line A). All serum samples below line A were considered to be negative. Patient groups: I, healthy pregnant women; II, idiopathic hyperprolactinaemia; III, prolactinoma; IV, ESS with hyperprolactinaemia; V, ESS without hyperprolactinaemia.
of 49 kDa (28%) (Strömberg et al. 1998) and to surface antigens of rodent tumour cells (25%) (Kajita et al. 1991) in members of families of probands with hypopituitarism. However, the lack of correlation between the presence of antibodies in probands and their parents makes it difficult to interpret these data and does not suggest a hereditary nature of pituitary autoimmune disorders.

ASARA and ASAP were revealed to some extent in all groups of hyperprolactinaemic patients, except that of healthy pregnant women with physiological hyperprolactinaemia. The highest number of ASAP patients was detected in the group with idiopathic hyperprolactinaemia. As in the cases of patients with idiopathic isolated GHD, none of these patients had obvious organic hypothalamic–hypophysial lesions, and the simultaneous presence of ASARA/ASAP and antibodies to prolactin was observed in only one patient. These data suggest that autoimmune disorders may be responsible for idiopathic hyperprolactinaemia. As mentioned above, increased prolactin secretion is observed quite often in LPH, although its mechanism remains obscure. It may be a consequence of the pressure of the swollen pituitary (Jensen et al. 1986), or it may be provoked by stimulating antibodies or disturbance of the interaction of prolactin-inhibiting factor with its cell receptor caused by the autoimmune process, or by some other, at present unknown, causes (Portocarrero et al. 1981, Josse 1990).

It is noteworthy that the overwhelming majority of ASARA+ patients with hypopituitarism (86%) and with idiopathic hyperprolactinaemia or prolactinoma (95%) appeared to be ASAS+ or ASAP+ respectively. At the same time, the number of ASAS- and ASAP- patients in these groups was much higher than the number of ASARA+ patients. This fact is apparently due to species specificity of surface antigens of human and rat pituitary cells and indicates that rat cells may be used only for preliminary investigations.

Contrary to the results discussed above, the prevalence of ASARA+ patients proved to be significantly higher than the number of ASAS+/ASAP+ patients in cases of ESS (P<0.05). The frequency of ASARA in these patients confirms the data reported by Komatsu et al. (1988) obtained by indirect immunofluorescence on rodent tumour cell lines GH3 and AtT20 (47 and 75% respectively). The much lower detection of ASAS and ASAP in comparison with ASARA is obviously explained by the fact that the appearance of autoantibodies in this case may be secondary to organic lesion of the pituitary; autoantibodies may be directed against surface antigens of different pituitary cells, and rat adenohypophysis containing the spectrum of all cells allows more complete indication of antipituitary antibodies. An equal ASAS frequency in subgroups with or without GHD and lack of a detectable difference between ASAP frequency in subgroups with or without hyperprolactinaemia cast doubt on the role of autoimmune processes in these disorders in patients with ESS. However, one cannot rule out the possibility that ASAS+ or ASAP+ patients who were without GHD or hyperprolactinaemia respectively at the time of investigation may develop corresponding disorders later.

Thus, the present study showed that (1) autoantibodies to surface antigens of prolactin-secreting cells are revealed significantly more frequently in patients with idiopathic hyperprolactinaemia than in cases of hyperprolactinaemia due to other causes and (2) autoantibodies to surface antigens of GH-secreting cells are revealed significantly more frequently in patients with idiopathic isolated hypopituitarism than in patients with other forms of GHD. The data obtained suggest the involvement of autoimmune mechanisms in the development of idiopathic isolated GHD in children and idiopathic hyperprolactinaemia in women. It might be assumed that pathogenesis of these diseases includes autoimmune attack against pituitary cells (LPH). In cases of ESS and prolactinoma, the organic pituitary lesion is primary; however, a possible participation of secondary autoantibodies in the subsequent disturbance of the pituitary function cannot be excluded.

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