ORGAN-SPECIFIC ANTIBODIES IN IDIOPATHIC PANHYPOPIGITURITISM,
PRIMARY THYROID AND ADRENAL INSUFFICIENCY

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Abstract. Two hundred and forty-eight sera from patients with idiopathic panhypopituitarism, primary myxedema, idiopathic Addison's disease as well as matched controls have been investigated for the presence of circulating organ-specific antibodies.

Antibody against the secretory cells of the anterior pituitary could not be demonstrated by means of the technique used. In only one patient with pituitary failure was circulating antibody against thyroglobulin found, and neither microsomal thyroid antibody nor adrenal antibody could be detected in any case.

Based on these findings and a survey of the literature it is concluded that, in contrast to the findings in primary failure of the thyroid and the adrenals, the functional and anatomical alterations in these endocrine glands in hypopituitarism do not cause the formation of circulating organ antibodies.

Idiopathic panhypopituitarism (i.p.), i.e. pituitary insufficiency in which no cause can be demonstrated, and so-called Sheehan's syndrome may closely imitate primary myxedema and, although less frequently, Addison's disease.

Circulating antibodies against elements of the thyroid gland can be demonstrated in most sera from patients with primary myxedema (14, 15, 27, 28), and it has been suggested that primary myxedema is identical with or a variant of Hashimoto's thyroiditis (4, 8, 10). The occurrence of thyroid antibodies in various diseases of the thyroid gland has been studied by several investigators (10, 14, 15, 17, 20, 22, 25, 28). However, only one study comparing the occurrence of thyroid antibodies in primary and secondary myxedema has been published (31).

A number of papers on the occurrence of circulating antibody against the cytoplasm of adrenocortical cells in sera from patients with different types of primary adrenal insufficiency have appeared (1, 2, 6, 7, 23, 24), but no information on the possible occurrence of adrenal antibodies in secondary adrenal insufficiency is available.

Recently the theory has been advanced that i. p. may be an autoimmune disorder (12, 19) and in 18% of a group of women in the post-partum period and in one case of so-called Sheehan's syndrome Engelberth and Ježková demonstrated organ-specific-like activity against the adrenohypophysis (9). However Goudie (13), in a preliminary study, has so far been unable to confirm the existence of antibodies against the secretory cells of the anterior pituitary.

The purpose of this paper is to present the results of an investigation on the problem of whether or not the functional and anatomical changes in the thyroid and adrenal glands as seen in pituitary insufficiency may be correlated to the existence of organ antibodies. An attempt was made to demonstrate circulating antibodies against the secretory cells of the anterior pituitary in sera from patients with i. p. using an indirect immunofluorescence technique.

MATERIAL

Sera from a total of 248 individuals were examined. In 16 a diagnosis of i. p. was considered certain, since no cause of the disorder could be demonstrated. Five out of nine female patients were diagnosed as having Sheehan's syndrome.

All patients presented the classical symptoms and signs of pituitary insufficiency. In all of them the excretion of pituitary gonadotropins and corticosteroids (17-KGS) were low, as was the level of se-PBI (except in one case in whom iodine contamination was obviously present). In most patients the diagnosis was supported by additional investigations such as stimulation tests with thyrotropic and adrenocorticotropic hormones, and measurement of plasma cortisol concentration.

In addition sera from 60 patients with primary myxedema and 48 patients with idiopathic Addison's disease were examined.
Table I. Occurrence of antibodies against thyroid, adrenal, parietal cell, salivary gland and anti-nuclear factor in sera from patients with idiopathic panhypopituitarism and their respective control group (control group 1).

Cyto = Microsomal thyroid antibody demonstrated by the immunofluorescence technique. Trc = Tanned red cell test for antithyroglobulin. Ca₂ = Antibody against a colloid antigen different from thyroglobulin, demonstrated by the immunofluorescence technique. Par = Parietal-cell antibody demonstrated by the immunofluorescence technique. Sal = Salivary gland antibody demonstrated by the immunofluorescence technique.

<table>
<thead>
<tr>
<th>Idiopathic panhypopituitarism</th>
<th>Control group 1</th>
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<tbody>
<tr>
<td>Thyroid</td>
<td>Thyroid</td>
</tr>
<tr>
<td>No.</td>
<td>Sex</td>
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<td>1</td>
<td>♀</td>
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<td>2</td>
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<td>14</td>
<td>♀</td>
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<td>15</td>
<td>♀</td>
</tr>
<tr>
<td>16</td>
<td>♀</td>
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</table>

Finally an identical number of control persons, matched according to sex and age to each of the groups mentioned, was included in the study (control group I: 16 persons; control group II: 60 persons; control group III: 48 persons).

The results of the studies on the patients with primary myxedema and adrenal insufficiency have been published previously (14, 24).

METHODS

Microsomal thyroid antibody was demonstrated by an immunofluorescence technique as described by Holborow et al. (18). Thyroglobulin antibody was measured by means of thyroglobulin-sensitized sheep red cells from Burroughs Welcome & Co. Ca₂ antibody was demonstrated according to Balfour et al. (3) using the immunofluorescence technique on methanol-fixed thyroid sections.

Antibodies against parietal cells, adrenal cortex and salivary gland were demonstrated by immunofluorescence techniques using unfixed sections of human gastric mucosa, salivary gland, and adrenals from guenon and man as previously described by Irvine (21), Bertram and Halse (5) and Blizzard et al. (6).

Only sera in which thyroglobulin antibody was not present at all, or present in very low titres (<250), were examined for the presence of the Ca₂ antibody, because the thyroglobulin antibody may prevent the demonstration of the Ca₂ antibody.

An attempt to demonstrate antibodies against the secretory cells of the anterior pituitary was made by means of an indirect immunofluorescence technique in the following way: normal pituitaries from rabbit, monkey and man were used as antigens. The human glands were surgically removed from patients with cancer of the breast (Prof. N. Riskar). After removal, the pituitaries were immediately frozen and kept at -20°C until used. 6 µ cryostate sections were incubated with sera for varying intervals (30-60 min) at varying temperatures (4-37°C). The slides were washed with barbiturate buffer (pH 7.0) (3) for a varying length of time (10-30 min) in an excess of buffer at varying temperatures (room temperature - 37°C). This procedure was followed by incubation with 10 µl fluorescein-labelled antihuman globulin (horse origin, Progressive Lab., Maryland, USA) for 30 min at room temperature. After an additional washing in buffered saline the sections were mounted in a drop of glycerine buffer and immediately studied under the fluorescence microscope (Reichert "Zetopan").

RESULTS

Attempts to demonstrate circulating antibody against elements of the anterior hypophysis by means of the technique described were unsuccessful.

The presence of other organ antibodies is listed in Tables I, II and III. Table I shows that thyroid antibodies very infrequently could be demonstrated in sera from patients with i.p. Serum from only one patient contained thyroglobulin antibody in a low titre. In the corresponding control group
Table II. Occurrence of thyroid antibodies in sera from patients with idiopathic panhypopituitarism, primary myxedema and the corresponding control groups

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Cyto</th>
<th>Trc</th>
<th>Ca-2</th>
<th>One or more antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic panhypopituitarism</td>
<td>16</td>
<td>0</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Control group I</td>
<td>16</td>
<td>2 (12%)</td>
<td>3 (18%)</td>
<td>1 (6%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Primary myxedema</td>
<td>60</td>
<td>39 (65%)</td>
<td>46 (79%)</td>
<td>17/35 (48%)</td>
<td>57 (95%)</td>
</tr>
<tr>
<td>Control group II</td>
<td>60</td>
<td>6 (10%)</td>
<td>9 (15%)</td>
<td>4/35 (11%)</td>
<td>20 (33%)</td>
</tr>
</tbody>
</table>

one or more thyroid antibodies could be demonstrated in sera from five persons. The results indicate that thyroid antibodies occur less frequently in sera from patients with secondary myxedema than in control sera (chi²-test with Yates’s correction: 0.01 < p < 0.02).

Adrenal antibody could be demonstrated neither in sera from patients with i. p. nor in sera from control persons (control group I), while antibodies against parietal cells and salivary glands as well as antinuclear factor were found with the same frequency in both groups.

Table II shows the occurrence of thyroid antibodies in primary and secondary myxedema. These antibodies were found in only one patient with pituitary myxedema. On the other hand one or more thyroid antibodies could be demonstrated in sera from 95% of the patients with primary myxedema. The fact that thyroid antibodies were found with the same frequency in the two control groups (control group II and III) indicates that the difference between the findings in primary and secondary myxedema is a real one and not merely an expression of a different composition of the two materials as regards sex and age.

Table III shows that adrenal antibody could be demonstrated in 66% of the patients with primary adrenal insufficiency—i.e. patients with idiopathic Addison’s disease.

Table III. Occurrence of adrenal antibody in sera from patients with idiopathic panhypopituitarism, idiopathic Addison’s disease and the corresponding control groups

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Adrenal antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic panhypopituitarism</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Control group I</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic Addison’s disease</td>
<td>48</td>
<td>31 (66%)</td>
</tr>
<tr>
<td>Control group III</td>
<td>48</td>
<td>0</td>
</tr>
</tbody>
</table>

DISCUSSION

Since it is questionable whether small necroses of the adenohypophysis resulting from post-partum hemorrhage may be solely responsible for the development of panhypopituitarism, cases of so-called Sheehan’s syndrome are included in this study.

Patho-anatomical changes in the anterior lobe of the pituitary justifying the term chronic, lymphocytic hypophysitis have been reported in very few cases (12, 19, 29, 33). Only in the two cases reported by Goudie and Pinkerton (12) and Hume and Roberts (19) are the changes so severe and extensive that a pathogenetic importance of the lesions may reasonably be suspected and an autoimmune mechanism be suggested. No such cases were included in the big series reported by Sheehan and Summer (30), and they may possibly be quite exceptional occurrences. Lymphocytic infiltration in the pituitary is not a characteristic finding in healed post-partum lesions. The round cell infiltration seen in pituitaries adjacent to giant cell granulomas is of an entirely different type (26, 30).

The failure to demonstrate pituitary antibodies in this study may be explained either by an insufficient technique or by the fact that the disorder in which the occurrence of an antihypophyseal antibody may be anticipated—i.e. chronic, lymphocytic hypophysitis—is so exceptional that it may not be included in the material presented.

The infrequent demonstration of thyroid antibodies in sera from patients with i. p. is in agreement with the study of Valloton et al. on patients with secondary hypothyroidism (31). It seems justified to postulate that, unlike primary myxedema, the anatomical and functional changes of the thyroid in pituitary insufficiency do not cause the appearance of circulating antibodies. This point deserves considerable interest as it may

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prove helpful in the, often difficult, differential diagnosis between primary and secondary myxedema.

When post-mortem examinations were carried out, changes in the thyroid gland essentially indistinguishable from those present in Hashimoto's thyroiditis and primary myxedema were found in 57% of the cases described by Sheehan and Summer (30), a figure which is in accordance with the frequency with which asymptomatic thyroiditis is found in elderly women in larger autopsy materials (11, 16, 32). Furthermore, it is well established that one or more circulating thyroid antibodies may be found in about 30% of apparently healthy persons above the age of 50. The findings in i.p. may serve as an example of thyroiditis without concomitant occurrence of antibodies. Whether the inactivity atrophy of the thyroid causes quantitative and/or qualitative changes of the thyroid antigens so as to make the formation of thyroid antibodies impossible remains to be elucidated.

The adrenal cortex in i.p. shows considerable atrophy, whereas scattered round cell infiltration has been reported only in one case (30). Consequently the failure to demonstrate adrenal antibody might be anticipated.

The functional and anatomical changes of the adrenals in secondary hypoadrenalism do not give rise to the formation of adrenal antibodies.

CONCLUSION
On the basis of these findings the following conclusions seem justified:

With the technique employed no antibodies against the anterior lobe of the hypophysis can be demonstrated in sera from patients with idiopathic panhypopituitarism.

Contrary to the findings in primary myxedema and idiopathic Addison's disease the functional and anatomical alterations of the thyroid and the adrenals in pituitary failure do not cause the formation of circulating thyroid or adrenal antibodies. This finding is of importance in the differential diagnosis between primary and secondary failure of the thyroid and the adrenals.

REFERENCES