Pituitary autoimmunity: a review

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The occurrence of autoimmune disease affecting several endocrine glands in the same patient has been studied clinically and immunologically for some years. Cases with clinical polyendocrinopathies are not common but patients with two endocrine disorders starting together or sequentially are seen quite often and in such cases it is sometimes possible to detect circulating antibodies or cell-mediated reactions to all the endocrine organs, including the pancreas and pituitary. Lymphocytic hypophysitis was described histologically in four previous publications (see Doniach 1977) and an autoimmune pathogenesis was postulated in 2 of the 4 cases owing to the association with thyroiditis, gastritis or adrenalitis.

Systematic examination by immunofluorescence on all endocrine glands of sera from Addisonian and hypoparathyroid cases led to the first description of the islet-cell antibodies (Bottazzo et al. 1974, MacCuish et al. 1974) which have proved of clinical significance for the separation and prediction of different types of diabetes mellitus (Lendrum et al. 1976, Irvine et al. 1977). When the same series of stored polyendocrine sera were applied to normal human pituitary glands obtained at hypophysectomy for alleviation of carcinoma of the breast, 19 out of 287 cases could be shown to have antibodies reacting specifically with the prolactin-secreting (PRL) cells of anterior pituitary (Bottazzo et al. 1975). Identification of the cells which showed a finely granular fluorescence over the entire cytoplasm was achieved by using a double fluorochrome four-layer technique (Figures 1&2).

In this, the patient’s serum was applied first and counterstained with goat-anti human immunoglobulin (Ig) conjugated with fluorescein. Then antisera to each of the six pituitary hormones raised in rabbits were applied in turn and counterstained with goat-anti rabbit Ig conjugated with rhodamine. When the patient and the rabbit react with the same cells, these are stained both red and green and the two colours can be seen on the same cells by changing the filters in the ultraviolet microscope. When a double exposure photograph is taken, the cells look yellow. If the patient’s serum reacts with different cells from those stained by the rabbit anti-hormone then the red and green fluorescence will be seen on separate cells with two filters and the double photo shows red and green cells with no yellow cells. The double technique is feasible because the patient’s antibodies are directed against the intracellular membranes belonging to the protein-synthesizing machinery of the cell whereas the rabbit sera react with the actual hormones produced in different cells. Unlike the pancreas where the islet-cell antibodies (ICA) of diabetes react with all the different endocrine cells, due to a common antigen, in the pituitary, no serum has ever been found to stain all the cells.

We did not find any pituitary antibodies in cases of panhypopituitarism but, since our first study, PRL-cell antibodies were detected in two cases showing mild or partial pituitary

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deficiencies. It may be that these antibodies are weak and disappear from the blood in the advanced stage of pituitary atrophy. Of the 19 cases in the initial study (Table I) 10 had more than one endocrine disease but no evidence of pituitary defect. TRH tests gave flat PRL responses in 2/8 cases tested; the others gave normal responses. A striking clinical correlation was with hypoparathyroidism: of the 19 positive patients 4 had this disease. The recent finding that prolactin stimulates the synthesis of a renal enzyme α-hydroxylase involved in vitamin D activation to the steroid hormone 1, 25(OH)2D3 may imply that prolactin deficiency could be involved in the final expression of parathyroid failure, though the main lesion is probably atrophy of the parathyroid gland itself in this disease. Hypoparathyroidism is associated with T-lymphocyte defects as shown by the chronic moniliasis seen in these patients and the high incidence of polyendocrine deficiencies in the families.

The second specific pituitary antibody to be identified was against the growth hormone (HGH) secreting cells. These antibodies were found in a young girl who showed retarded growth from age 6 years, and whose mother suffered from Addison's disease and thyroiditis (Bottazzo et al., in preparation). In addition there are several sera under study where the antibodies react neither with lactotrophs or somatotrophs and which do not stain the same cells as anti-TSH. Some of these may be against LH or FSH secreting cells. Thus it is likely that antibodies to each of the anterior pituitary cells will finally be identified.

There is another interesting phenomenon which is unrelated to autoimmunity. In the course of this work it was found that all normal human sera bind by the Fc or backbone end of the immunoglobulin molecules to adrenocorticotropic (ACTH) cells in the pituitary (Pouplard et al. 1976). This may represent a physiological mechanism connected with initiation of the stress...
Figure 2. Same pituitary as Figure 1 treated with serum from a patient with autoimmune polyendocrine disease. Some cells show finely granular cytoplasmic fluorescence. By the double IFL technique, using rabbit anti-hormone counterstained with rhodamine conjugate on the same section it was possible to demonstrate that the patient's serum reacted with lactotrophs. × 410

Table 1. Immunofluorescence on human pituitary

<table>
<thead>
<tr>
<th>Antibodies to prolactin-secreting cells</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panhypopituitarism</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Idiopathic hypoparathyroidism</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Idiopathic Addison's disease</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Thyroid/pernicious anaemia</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Polyendocrinopathies</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>Other diseases</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
<td><strong>268</strong></td>
</tr>
</tbody>
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reaction. Similar Fc receptors for IgE and some IgG heavy chains are known to lead to release of histamine and heparin from mast cells when the free Fab terminals of the Ig react with the appropriate allergen. Stimulation of ACTH release is thought to be mediated by more than one pathway in view of the lack of correlation between diurnal rhythm and stress reactions (Redgate 1976). An accessory release-mechanism mediated via immunoglobulin Fc attachment is therefore a valid possibility.

Addendum

Since this paper was submitted another possible case of autoimmune hypophysitis has been reported (Gleason et al. 1978). This concerned a 59-year-old woman with attacks of hypoglycaemia and unexplained arthralgias who at post-mortem showed an enlarged pituitary gland with the features of an autoimmune lesion, i.e. lymphoid follicles, interstitial round cell infiltrates, fibrosis and focal collections of pituitary cells. The condition was not diagnosed during life and pituitary antibodies were not tested for.

References

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Gleason T H, Stebbing P C & Shanahan M F (1978) Archives of Pathology and Laboratory Medicine 102, 46
Redgate E S (1976) Life Science 19, 137