Lymphocytic Hypophysitis

Endocrine glands are particularly likely to be affected by organ-specific autoimmune disease. Thyroid autoimmune disease, for instance, is well recognized and common. Autoimmune disease of the anterior pituitary, however, is little known and appears to be rare. Nevertheless, there is strong pathologic evidence of its existence; commencing with the report of Goudie and Pinkerton (1) in 1962 of lymphocytic hypophysitis seen at autopsy in a young woman with Hashimoto’s thyroiditis there are now several reported cases with histologic observations.

In this issue Asa and her colleagues (2) report two further cases, with ultrastructural evidence supporting an autoimmune basis for the disease. Because of the clinical findings in their patients and the evidence in the literature, these authors have concluded that lymphocytic hypophysitis is an autoimmune disease primarily of pregnancy and the puerperium. Apart from this conclusion, the report is also interesting in that the diagnosis was established during life and the presentation was that of pituitary tumor with some evidence failure, as reported previously by Mayfield and colleagues (3). The development during pregnancy of a sellar space-occupying lesion, with suprasellar extension in one of their patients causing visual field abnormality, led to the clinical suspicion of prolactinoma. Although serum prolactin levels were only moderately elevated in one case and unmeasured in the other, on surgical exploration no tumor was found. An extensive cellular infiltration, mainly of lymphocytes, was found.

The criteria of Wittebisky and colleagues (4) for autoimmune disease require the direct detection of circulating autoantibodies to a recognized specific antigen, an experimental model of the disease produced in an animal by the injection of antigen with pathologic changes broadly similar to those of the human disease, and the transfer of the experimental disease by serum or immune cells. Examining putative autoimmune pituitary disease as described in the literature with respect to these criteria, we find that in only two cases of lymphocytic hypophysitis has there been the opportunity to seek anterior pituitary antibodies, but antibodies have been detected in one (3). Bottazzo and his colleagues (5-8) have reported the finding of pituitary autoantibodies by an immunofluorescence technique in three main categories of patients: those with polyendocrinopathy, those with hypoparathyroidism, and those with mild pituitary dysfunction (8). They have not found autoantibodies in panhypopituitarism (5). Previous attempts to show immunofluorescent autoantibodies using postmortem pituitary tissue in the procedure had been unsuccessful (8). It was not until normal pituitary tissue obtained at hypophysectomy for treatment of breast cancer was used that autoantibodies were detectable. Using a double fluorochrome four-layer technique (5). Almost all these autoantibodies have been directed against the prolactin-secreting cell, using the double fluorochrome technique has shown that the antibodies so detected are directed against the cell and not the hormone. These workers have also found antisomatostatin antibody in an unusually short patient with Turner’s syndrome and a family history of autoimmune adrenal and thyroid diseases (7).

Pituitary autoantibodies have been reported in Sheehan’s syndrome (10), which could suggest that these antibodies might be secondary to pituitary damage by nonspecific mechanisms. The indirect method of detection in this report, however, using a serum “complement-consumption” index in response to pituitary antigen, and the absence of objective criteria of pituitary failure in the patients studied render this evidence of uncertain value. Interpreting pituitary autoantibodies as evidence of primary autoimmune disease is, therefore, reasonable.
An experimental model for pituitary autoimmunity was first reported by Triplett (11) who hypophysectomized tree frog embryos, maintained the pituitaries by transplant into other larvae, and reinplantated them into the mature frogs, which thereafter rejected the tissue. The interpretation of these elegant experiments is that adenohypophysial tissue was absent during the development of immune competence and self-tolerance, and hence it was perceived as foreign on autograft into the mature frog. A more conventional experimental model was subsequently developed by Levine (12) who produced an allergic adenohypophysitis by the injection of pituitary tissue and adjuvant into the footpads of adult rats. The affected pituitaries showed a dense lymphocytic and mononuclear infiltrate similar to that of human lymphocytic hypophysitis. Although passive transfer of the experimental disease has not been reported, these data overall, especially when taken with the common finding of other autoimmune diseases in those affected, provide strong evidence that human pituitary autoimmune disease exists and that lymphocytic hypophysitis is part of its spectrum.

A most interesting facet of the disease, highlighted by Asa and colleagues, is the strong association with pregnancy and the postpartum period. Of interest here is that Levine (12) mentioned preliminary results indicating that adenohypophysitis could be induced in pregnant rats and was increased in severity in postpartum. Pregnancy influences many autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis, and thyroiditis. A current view is that the fetus can act as a “suppressor-cell graft” (13), causing improvement of autoimmune disease in pregnancy with postpartum exacerbation. Although this theory is attractive and consistent with the observed general trend of changes of disease activity, it is not in accord with all the observed facts: Indeed, lymphocytic hypophysitis in the patients reported in this issue actually developed during pregnancy. Furthermore, although postpartum exacerbation of SLE was most strongly noted by Garsenstein and associates (14), they also found an increased risk of heighted disease activity in the first trimester of pregnancy. More recently one study of SLE and pregnancy (15) found both worsening and improvement of active disease during pregnancy but no postpartum flare, and another study (16), while finding no major effect on systemic or renal manifestations of SLE during pregnancy, did report postpartum flare in a substantial minority of patients. These findings indicate that the interactions of the pregnant state with the systems of immune self-tolerance are complex and still unclear. The association of lymphocytic hypophysitis with pregnancy and the puerperium, nevertheless, by analogy with other autoimmune disease, strengthens the case of an autoimmune basis of the disease.

How, then, should the diagnosis of this disease be made? Plainly, in hypopituitarism developing in pregnancy and the puerperium, autoimmune pituitary disease should be suspected in the absence of events typical of Sheehan’s syndrome, and it must be a differential diagnosis of pituitary tumor in pregnancy. Proper diagnostic procedure is, however, unclear, as only now has preoperative diagnosis been achieved (2, 3), by means of pituitary exploration and biopsy. Visual pathway compression may necessitate surgery, but obviously invasive procedures should be avoided if possible. Unfortunately the sensitivity of serologic diagnosis is not known, and the immunofluorescent pituitary autoantibody technique is not widely available. Although leucocyte migration inhibition testing as a measure of autoimmunity has been reported to be positive in nonnontumorous hypopituitarism (17), the exact relevance of this observation and worth of this technique for pituitary disease are not established. Lymphocytic transformation testing using tritiated thymidine uptake as a measure of sensitization to pituitary antigen is another possible avenue that should be explored.

In cases of apparent tumor, where surgery is not mandatory, the angiographic vascular pattern might differ in lymphocytic hypophysitis—that is, no “tumor blush” would be seen—but this has not been assessed. A trial of steroid therapy to attempt reduction of the “tumor” may be a reasonable course of action in these circumstances and if successful might suggest an inflammatory lesion.

Although pituitary autoimmune disease is likely to be quite rare, its true incidence will be established only by a wider application of immunologic techniques in the investigation of non-neoplastic pituitary disease. In this regard, and for the individual patient, methods for detecting immunofluorescent pituitary autoantibodies seem most likely to be helpful and should be established in more centers. (Duncan J. Topliss, M.B., B.S.; and Robert Volpe, M.D.; Endocrinology Research Laboratory, University of Toronto; Toronto, Ontario, Canada)

References