LYMPHOCYTIC HYPOPHYSESIS. THE CLINICAL SPECTRUM OF THE DISORDER AND EVIDENCE FOR AN AUTOIMMUNE PATHOGENESIS

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SUMMARY

Lymphocytic hypophysitis, a rare disease hitherto restricted to women, usually presents with symptoms of hypopituitarism in relationship to pregnancy. Two patients who developed pituitary insufficiency from lymphocytic hypophysitis are described. In the first, visual deterioration due to chiasmal compression from hypophysitis arising in ectopic pituitary tissue responded to bromocriptine and corticosteroids. In the second, an insidious onset of hypopituitarism occurred over 5 years in an elderly male. Combined HLA and complement typing confirmed that both patients shared MHC class I, II and III alleles. These class II and III alleles have been described in association with Hashimoto's thyroiditis and insulin-dependent diabetes mellitus (IDDM), both of which may be associated with antipituitary antibodies. The features of these two cases extend the known clinical and pathological spectrum of this disease and, through identifying a common immunogenetic background, provide a possible link between the previous associations of this disorder and autoimmune thyroid disease and IDDM.

Lymphocytic hypophysitis, considered a disease restricted to women, usually presents with symptoms of hypopituitarism in relationship to pregnancy. In the first description a 22-year-old woman died from adrenocortical insufficiency after 6 months of progressive hypopituitarism dating from the birth of her child (Goudie & Pinkerton, 1962). The lymphocytic infiltration was confined to the anterior pituitary in this and all subsequent reports (Table 1). Although the aetiology remains unknown considerable evidence exists for an autoimmune pathogenesis including an association with autoimmune thyroiditis (Goudie & Pinkerton, 1962; Richtsmeier et al., 1980; Jensen et al., 1986), pernicious anaemia (Hume & Roberts, 1967; Mazzone et al., 1983), organ-specific antibodies, including antipituitary antibodies (Mayfield et al., 1980), antimitochondrial (Asa et al., 1981), antiparietal (Mazzone et al., 1983) and antinuclear antibodies (Guay et al., 1987).

The diagnosis remains difficult as CT scanning shows only non-specific features of a contrast-enhancing pituitary mass, angiography shows only non-vascularity.

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(Hungerford et al., 1982), and the predictive value of pituitary cell antibodies is uncertain, given the presence of such antibodies in normal women in the post-partum period (Engelberth & Jezcova, 1965). The diagnosis has rested on histological examination of pituitary tissue, as established by post-mortem examination in nine of the 17 cases reported to date (Table 1). The two cases presented here extend the clinical spectrum of this disease, particularly the occurrence of the disease in a male with a gradual onset over 5 years.

**CASE 1**

A previously well 22-year-old Caucasian primigravida was referred at 28 weeks gestation for the complaint of nocturnal bitemporal headaches and a right-sided visual field defect. Examination showed a bitemporal hemianopia, but no evidence of hypopituitarism. Initial investigations included a normal haemoglobin, neutrophil leucocytosis (20.0 x 10^9/l,
N < 11 × 10⁹), and elevated serum prolactin of 5196 IU/ml (normal range in pregnancy 50–800). Serum FSH, LH and thyroid indices were normal. No source of sepsis was found. A CT scan with coronal views demonstrated the presence of a suprasellar mass. Immunological investigations including antinuclear (Hep 2), antismooth muscle, antimitochondrial, antithyroid microsomal, antithyroglobulin, antipancreatic islet cell, and antiadrenal antibodies were negative. Antipituitary antibodies were assayed by incubating normal post-mortem human pituitary tissue sections for 30 min with serial dilutions (1:2 and 1:20) of sera in phosphate buffered serum (PBS), washing with PBS and incubating with fluorescein isothiocyanate conjugated rabbit anti-human immunoglobulin for 30 min. The sections were washed, and visualized with a Leitz fluorescence microscope. The result was negative. Her HLA typing was A2 Aw68 B13 Bw58/4 DR4/7 DQw2/3 and complement allotyping C4A3 C4B1 BfI BfS.

Bromocriptine 2.5 mg b.d., prednisolone 15 mg b.d., and betamethasone 0·5 mg b.d. were commenced at 30 weeks gestation to treat a presumed prolactinoma, and promote fetal lung maturation. The visual defect improved significantly for 5 weeks but subsequently deteriorated, prompting surgical management. At admission she had a live fetus, with a fundal height consistent with 36 weeks of gestation. Visual acuity was reduced to 6/14 in each eye and a bitemporal hemianopia. Investigations showed normal serum urea and electrolytes but a persistent neutrophil leucocytosis. Again no source of sepsis was found. At transfrontal surgery a suprasellar mass was found arising from the pituitary stalk and associated with intense arachnoid fibrosis adhering to the optic chiasm and the superior hypophyseal arteries supplying the hypothalamus. The mass was removed down to the level of the sella turcica. Histological examination of the mass showed normal pituitary tissue infiltrated by lymphocytes and plasma cells with a smaller number of neutrophils and interspersing strands of fibrous tissue (Fig. 1). Immunoperoxidase staining with a panel of anterior pituitary hormones by the method of Sternberger (1974) identified the presence of normal anterior pituitary endocrine cells without apparent selective loss of any cell line. It was considered the mass derived from ectopic pituitary tissue. The patient's visual acuity deteriorated in the postoperative period, returning over the ensuing months to 6/9 in the right and 6/12 in the left eye with minimal temporal field defect. Postoperatively in the puerperium an insulin tolerance test was abnormal with a poor cortisol response to hypoglycaemia and prolactin levels were less than 50 IU/ml. Pituitary hormone replacement therapy was continued with DDAVP 50 μl twice daily, thyroxine 100 μg daily, cortisone acetate 37·5 mg daily, and ethinyl oestradiol 50 μg daily with medroxyprogesterone acetate 10 mg daily for 5 days each month.

CASE 2

A 61-year-old Caucasian male was admitted to hospital with symptoms of severe postural hypotension. For 5 years he had noted an insidious and progressive increase in tiredness, loss of concentration and decreased libido and potency. He had also noted the onset of Raynaud's phenomenon. Multiple neurofibromas and lipomas had been removed over the previous 6 years. There was no family history of diabetes or thyroid disease.

On examination he was apathetic, with dry skin and reduced chest and pubic hair. Blood pressure was 130/80 mmHg supine and 95/70 erect with a pulse of 60 beats per minute. Reflexes were markedly slowed in their relaxation phase. Testicular volume was reduced and the consistency was soft. The remaining examination was normal. Full blood
Fig. 1. Photomicrograph of H & E stained tissue from patient 1 showing lymphocytic infiltration of ectopic pituitary tissue. Arrows indicate residual pituitary cells. Bar, 200 μm.
Fig. 2. Photomicrograph of H & E stained tissue from patient 2 shows a dense lymphocytic infiltration of anterior pituitary tissue. Arrows indicate residual pituitary cells. Bar, 200 μm.
count, ESR, urea, creatinine, electrolytes, calcium, phosphate, liver function tests and blood glucose were normal. The serum free T4 was 5 pmol/l (N 13–32 pmol/l), TSH 0.4 mU/l (N 0.2–3.0), serum testosterone 0.2 nmol/l (N 10–35), prolactin 72 IU/ml (N < 540), FSH < 11 IU/l (N 1–7), LH 1 IU/l (N 2–16). A CT scan with coronal views showed diffuse enlargement of the pituitary gland with minimal suprasellar extension but some lateral displacement of the cavernous sinus. There was no discrete mass or contrast enhancement within the pituitary gland. Antithyroid, antimuclear, antimitochondrial and antipituitary antibodies were negative but antiparietal cell antibodies were positive in a titre of 1:40. Serum B12 was normal and C3, C4 and CH50 were normal. His HLA typing was A2/28 B60 Bw62/6 DR4/13 DRw52/53 DQw1/3 and complement allotyping C4A3 C4B1 BF1 BFS.

He was commenced on cortisone acetate 25 mg b.d. and then stabilized on 37.5 mg daily, thyroxine 50 µg daily increasing to 150 µg over the next 3 months, and testosterone enanthate 250 mg monthly with good clinical response. Three months later he underwent transphenoidal surgery for resection of a presumed pituitary adenoma. The sella turcica was filled by grey, tough, rubbery tissue. There was no definite cleavage plane or any normal-looking pituitary tissue and resection was limited to a pituitary biopsy. The postoperative course was uncomplicated. The histological appearance was of areas of dense connective tissue containing bands of anterior pituitary cells and a patchy infiltration of small round cells resembling small cleaved lymphocytes accompanied by scattered histiocytes (Fig. 2). Immunoperoxidase staining with the panel of anterior pituitary hormones confirmed the presence of residual anterior pituitary cells without any apparent evidence of selective loss of any specific cell type. Subsequent investigations including a CT scan of the abdomen and chest, and bone marrow trephine showed no evidence of lymphoma. A CT scan of the pituitary performed 3 months after surgery showed a very small amount of residual tissue, disproportionately small for the size of the initial biopsy taken. The patient remains well on full replacement therapy with a gradual resolution of his Raynaud's phenomenon.

DISCUSSION

Classically, as with the first case, lymphocytic hypophysitis presents in females in relationship to pregnancy and is often associated with a mild elevation of prolactin (Asu et al., 1981; Mazzone et al., 1983; Jensen et al., 1986; Guay et al., 1987) attributed to either the disruption of the hypophyseal transport of prolactin inhibitory factor by a large mass compressing the pituitary stalk, or a direct effect of the inflammatory process on the prolactin cells, or a lactotroph-stimulating antibody arising as a consequence of the inflammatory process (Portocarero et al., 1981).

The unique aspects of our first case include improvement of both visual fields and acuity with bromocriptine, prednisolone and betamethasone therapy, the site of origin from the infundibular stalk of one of the tumours, and the nature of the acute inflammatory infiltrate. Betamethasone was introduced here to reduce the potential risks of premature labour through stimulating fetal lung maturation. In the absence of subsequent histological evidence of a prolactinoma, it seems reasonable to propose that the improvement in visual symptoms was due to a direct effect of steroid on the inflammatory mass. It is possible that bromocriptine also contributed to the improved visual symptoms through an inhibitory effect on the pregnancy-induced lactotroph
hyperplasia. The second unique feature of this patient was the origin of this tumour from the infundibular stalk with no extension below the diaphragm sellae. Classically, the inflammatory process involves only the anterior pituitary, sparing the stalk and the posterior pituitary. The site of the present lesion in the stalk may explain the mild elevation of prolactin. A third unusual feature was the systemic neutrophil leucocytosis associated with the neutrophil infiltration of the pituitary, in addition to the characteristic picture of infiltration by small lymphocytes, plasma cells, giant cells and fibrosis. This systemic neutrophilia and pituitary neutrophil infiltration may have been observed because our patient presented at an earlier stage of the inflammatory process due to the suprasellar site of the mass causing compression of the optic chiasm.

At the time of the diagnosis in our second case, lymphocytic hypophysitis had not been described in males. Furthermore, the insidious onset of symptoms distinguishes him from previous reports (Table 1). Extensive investigations, including CT scan of the abdomen and chest, bone marrow aspiration and biopsy, and prolonged observation over 44 months appear to exclude an unusual manifestation of lymphoma. Raynaud's phenomenon, which occurs with other autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus and mixed connective tissue disease (Morris, 1983) began with his initial symptoms, continued for 5 years, and then gradually resolved. Investigations excluded the presence of known associated disorders. The time course of his Raynaud's phenomena in conjunction with the report of vasculitis with the anterior pituitary in lymphocytic hypophysitis (Egloff et al., 1969), suggests the two disorders may be causally related. In addition, although pituitary-adrenal failure has been described as a common and early mode of presentation in seven previous reports, this was not the case in our patient. Immuno-peroxidase staining did not demonstrate the selective loss of ACTH staining cells as previously described (Mayfield et al., 1980; Richtsmeier et al., 1980; Jensen et al., 1986). This suggests that his presenting symptoms may have arisen from an array of endocrine insufficiencies.

In both patients, antipituitary antibodies were negative at the time of surgery. These antibodies may have disappeared from the sera by this time. Transient anti-islet cell antibodies have been described in insulin-dependent diabetes mellitus (IDDM) (Cudworth & Woodrow, 1975) and transient anti-thyroid antibodies in thyroid disease (Hawkins et al., 1979, 1980). Interestingly, Hashimoto's thyroiditis has been reported in association with lymphocytic hypophysitis (Goudie & Pinkerton 1962) and Kobayashi and co-workers (1985) in a preliminary report, found a high prevalence of antipituitary antibodies in patients with Hashimoto's thyroiditis. However, they employed an assay system with rat pituitary tissue as substrate which may detect heterophil antibody not associated with pituitary diseases. Nevertheless, antipituitary antibodies have been detected in 16% of islet cell antibody positive insulin-dependent diabetic (IDDM) subjects at the onset of their disease and in 36% of high-risk first-degree relatives of IDDM subjects with positive islet cell antibody (Mirakian et al., 1982). Therefore in view of this possible autoimmune association with lymphocytic hypophysitis, we performed both HLA and complement typing in our patients to examine whether a particular immunogenetic background predisposed to the development of these apparently diverse endocrine disorders. Previous HLA typing in lymphocytic hypophysitis in two black females demonstrated A28 and Bw35 (Asa et al., 1981; Mayfield et al., 1980). Both are associated with IDDM but not in Caucasians (Srikanta & Mehra 1981). The principle of 'supratyping' (Dawkins et al., 1988) views the MHC as a gene cluster in which alleles at a
given locus mark specific alleles at other loci. Thus, the combined use of HLA and complement allotyping enables recognition of sets of alleles or supratypes. It was of interest therefore that, given the known HLA associations of Hashimoto's thyroiditis with HLA class II alleles DRw53/52, DQw3 and DR4 (Farid & Balazs, 1988) and HLA DR4 in Hashimoto's thyroiditis with complements C4A3 C4B1 BfS (Skanes et al., 1986), that both our patients shared all these alleles. Furthermore, since susceptibility to IDDM is marked by three supra types (Kelly et al., 1985), the presence of one of these (the rare supratype B60 C4A3 C4B1 BfS DR4 DQw3 found normally in only 1.8% of Caucasians) (Kelly et al., 1985) in our second patient was also noteworthy. Thus, because the alleles A2 C4A3 C4B1 BfF1 BfS DR4 DRw53 DQw3 were shared by our two patients, it is suggested that the presence of these alleles may predispose Caucasians to the development of thyroiditis, IDDM and less commonly antipituitary antibodies, and rarely the emergence of lymphocytic hypophysitis. In conclusion, although lymphocytic hypophysitis usually occurs in young women in relationship to pregnancy, the disorder may occur in males. It is suggested that an association between this disease and certain immunogenetic markers of other endocrinological conditions may be important in the genesis of this disorder.

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