The Anterior Pituitary Lobe in Patients with Cystic Craniopharyngiomas: Three Cases of Associated Lymphocytic Hypophysitis*

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Summary
Specimens of the anterior pituitary lobe were investigated histologically in 28 craniopharyngioma patients operated on trans-sphenoidally. The pituitary glands in 3 patients revealed lymphocytic invasion giving a histological appearance typical of lymphocytic hypophysitis (incidence: 11%). At follow-up examination all three patients with associated lymphocytic hypophysitis had complete pituitary insufficiency, whereas only 36% of the craniopharyngioma patients without associated lymphocytic hypophysitis were in this poor postoperative endocrine state.

The phenomenon of associated lymphocytic hypophysitis in craniopharyngioma patients has not been reported so far. This might be due to the fact that investigators have failed to systematically examine the anterior pituitary lobe in craniopharyngioma patients. The 60 cases of lymphocytic hypophysitis reported in the literature occurred, for the most part, in women during late pregnancy or shortly after delivery. An auto-immune origin is assumed in this type of inflammation. In contrast to this pathophysiological mechanism, we assume a local induction of inflammation resulting from the craniopharyngioma cyst in our 3 patients.

Keywords: Hypophysitis; craniopharyngioma; hypopituitarism.

Introduction
Partial or complete endocrine insufficiency of the pituitary gland is a symptom found in about 90% of patients with craniopharyngiomas located primarily intrasellarly3,4,13–16,21,35. From the pathophysiological point of view, this hypopituitarism is due to the compression exerted by the tumour on the pituitary gland and/or on the pituitary stalk. Corresponding to this compression, the structure of the anterior pituitary lobe is altered from alveolar to trabecular39. However, only one systematic investigation of the anterior pituitary lobe in craniopharyngioma patients has been described in the past38. This report appeared in the Soviet literature in 1987. As far as we know, an invasion of the pituitary tissue by inflammatory cells, which leads to a histological appearance typical of lymphocytic hypophysitis, has not been described previously in craniopharyngioma patients.

Methods
Patients and Operative Procedure
Between 1982 and 1992 40 patients with craniopharyngiomas were operated upon trans-sphenoidally. Because of the primarily intrasellar tumour localization with an enlarged sella turcica, a direct transnasal-submucosal-trans-sphenoidal and not a transcranial approach to the tumour was chosen in all these patients14. After opening the sella floor and clearing the sella capsule, the anterior pituitary lobe was relatively thick and showed a frontobasal localization relative to the tumour in 28 of these 40 patients. Therefore, a vertical paramedian incision of the anterior pituitary lobe was chosen by the surgeon (D.K.L.) to enable access to the tumour. Due to this approach, some small trauma to the anterior pituitary lobe was unavoidable. To clearly discriminate between the anterior pituitary lobe and the tumour capsule, small biopsies of the anterior pituitary lobe were taken. The reason for the small size of the biopsies was to avoid postoperative pituitary insufficiency resulting from the biopsies themselves.

Morphological Methods
Frozen sections of both tumour tissue and tissue of the anterior pituitary lobe were made intra-operatively. For the purpose of definitive histological examination, tumour tissue and tissue of the anterior pituitary lobe were fixed in 4% buffered formaldehyde and embedded in paraffin. The sections were stained with haematoxylin-eosin (HE) and periodic acid-Schiff (PAS)-reaction. The slices yielding pituitary tissue were processed for immunohistochemistry using the avidin-biotin-peroxidase method and antibodies to the pituitary hormones (Dakopatts, Hamburg, Germany). Histological diagnosis and stag-
Follow-up Examination

In all 28 craniohypophysial patients who had undergone histological examination of the anterior pituitary lobe, the pre-operative symptoms and signs, and both the pre-operative and postoperative endocrine functions of the anterior pituitary lobe were investigated retrospectively. In the 3 patients with associated lymphocytic hypophysitis, a detailed follow-up examination including ophthalmological examination, endocrinological examination, and MRI-scan was performed. Information about actual endocrine states and required hormonal substitution treatment of the 25 patients without associated lymphocytic hypophysitis was obtained from various physicians, who carried out the follow-up examinations at regular intervals.

In all patients the evaluation of the pre-operative and postoperative endocrine functions was based on basal plasma levels of all hormones of the anterior pituitary lobe. Different functional endocrinological tests of the anterior pituitary lobe were performed by various referring endocrinologists and paediatricians before operation and at follow-up. For purposes of simplifying the evaluation of the different groups of craniohypophysial patients, the extent of pituitary insufficiency was staged according to the following scheme. Lowered GH plasma levels were seen as an indicator of pituitary insufficiency only in adolescents, but not in adults. Diabetes insipidus was diagnosed when clinical symptoms and signs presented.

Intact pituitary function: all hormones of the anterior pituitary lobe within the normal range.

Partial pituitary insufficiency: 1 or 2 hormones of the anterior pituitary lobe below the normal range.

Complete pituitary insufficiency: more than 2 hormones of the anterior pituitary lobe below the normal range.

Results

Histological Results

At histological examination of the 28 craniohypophysialomas comprising this study, 12 tumours were classified as spinocellular and 4 tumours as basocellular. The latter 4 tumours were subclassified as follows: 1 cylindromatous, 2 ameloblastomatous, and 1 paracarcinomatous. 12 craniohypophysialomas could not be further classified because of extensive regressive changes.

The histological examination of the 28 anterior pituitary gland specimens revealed a normal alveolar structure of the glandular parenchyma in 11 patients (Fig. 1). In 14 patients signs of chronic compression of the anterior pituitary gland by the intrasellar mass of the craniohypophysialoma could be seen. The compressed gland revealed loss of the alveolar structure and subsequent development of a trabecular structure (Fig. 2). In the case of three patients (no. 1 with basocellularparacarcinomatous craniohypophysialoma, nos. 2 and 3 with spinocellular craniohypophysialoma), the anterior pituitary gland was invaded by numerous inflammatory cells, mainly lymphocytes (Figs. 1-3). In all of these cases the lymphocytic inflammation of the anterior pituitary gland included the whole parenchyma within the obtained specimen (Figs. 1 and 2). The diagnosis of associated lymphocytic hypophysitis was made on the basis of these morphological characteristics. This led to an incidence of 11% associated lymphocytic hypophysitis among patients with partially intrasellarly localized craniohypophysialomas. The inflammation of

Fig. 1. The entire anterior pituitary lobe of patient no. 1 is invaded by numerous lymphocytes leading to the histological diagnosis of an associated lymphocytic hypophysitis. The alveolar structure of the anterior pituitary lobe is only partially preserved (arrow). Periodic acid-Schiff (PAS)-reaction, × 340

Fig. 2. The whole anterior pituitary lobe of patient no. 2 shows severe infiltration by lymphocytes. The alveolar structure of the anterior pituitary lobe has been partially altered to a trabecular structure (arrow), indicating chronic compression of the pituitary by the adjacent spinocellular craniohypophysialoma. Periodic acid-Schiff (PAS)-reaction, × 340
Fig. 3. Near the transition zone between the spinocellular craniopharyngioma (c) and the anterior pituitary lobe (p), the concentration of lymphocytes is pronounced, giving the impression of a local induction of inflammation (pat. no. 3). Periodic acid-Schiff (PAS)-reaction, × 340

the glandular parenchyma was most pronounced in the vicinity of the transition zone between the pituitary parenchyma and the cystic wall of the craniopharyngioma (Fig. 3). This gave the impression that the inflammation spread in continuity with the tumour to the pituitary gland. Immunohistochemical investigations showed results corresponding to the microscopic diagnosis of the pituitary glands in all cases. A pattern of different pituitary hormones was present.

**Clinical Results**

The clinical and endocrinological data of the three patients with craniopharyngioma and associated lymphocytic hypophysitis are shown in Table 1.

The MRI-scan showed an intrasellar cystic tumour as the cause of the enlarged sella turcica in all 3 patients. In patients no. 2 (Fig. 4) and no. 3 the suprasellar extension reached the optic chiasma and explained the visual symptoms and signs. At follow-up examination all 3 patients had complete pituitary insufficiency and required full hormonal replacement therapy.

The 25 craniopharyngioma patients without associated hypophysitis (10 females and 15 males, mean age: 24 years) were diagnosed solely because of endocrinological symptoms and signs in 10 patients (40%), and because of both visual and endocrinological findings in 15 patients (60%). On the basis of the symptomatology at diagnosis and of the pre-operative endocrinological findings, the three craniopharyngioma patients with associated lymphocytic hypophysitis

Table 1. Clinical and Endocrinological Findings in 3 Patients with a Craniopharyngioma and Associated Lymphocytic Hypophysitis Before and After Transsphenoidal Operation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Symptoms leading to diagnosis</th>
<th>Duration of symptoms</th>
<th>Endocrine state pre-operative</th>
<th>Duration of follow-up</th>
<th>Endocrine state postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>42</td>
<td>m</td>
<td>failure of sexual development</td>
<td>25 years</td>
<td>complete pituitary insufficiency and hyperprolact. hypogonadotrophic hypogonadism</td>
<td>11 years</td>
<td>complete pituitary insufficiency</td>
</tr>
<tr>
<td>No. 2</td>
<td>52</td>
<td>f</td>
<td>loss of vision</td>
<td>2 months</td>
<td></td>
<td>2 years</td>
<td>complete pituitary insufficiency</td>
</tr>
<tr>
<td>No. 3</td>
<td>51</td>
<td>m</td>
<td>fatigue, impotence, loss of vision</td>
<td>9 months + 6 months + 2 months</td>
<td>complete pituitary insufficiency</td>
<td>6 months</td>
<td>complete pituitary insufficiency, diab. insp.</td>
</tr>
</tbody>
</table>
Table 2. Endocrinological Findings in 25 Patients with a Craniohypophysialoma but without Associated Lymphocytic Hyphopithitis Before and After Trans-sphenoidal Operation

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact pituitary function</td>
<td>n = 0 (0%)</td>
<td>n = 8 (32%)</td>
</tr>
<tr>
<td>Partial pituitary insufficiency</td>
<td>n = 11 (44%)</td>
<td>n = 8 (32%)</td>
</tr>
<tr>
<td>Complete pituitary insufficiency</td>
<td>n = 14 (56%)</td>
<td>n = 9 (36%)</td>
</tr>
<tr>
<td>Additional diabetes insipidus</td>
<td>n = 7 (25%)</td>
<td>n = 6 (21%)</td>
</tr>
</tbody>
</table>

(Table 1) showed no difference when compared to the 25 craniohypophysialoma patients without associated lymphocytic hyphopithitis (Table 2). However, both groups had different mean ages (48 years versus 24 years) and postoperative endocrine states. In the group of 25 patients without associated hyphopithitis, the trans-sphenoidal operation improved the endocrine state in 12 patients (48%). There was no change in the other 12 patients (48%). A deterioration was noted in only one patient (4%). Although a statistical analysis is not possible due to the low number of patients, the much poorer endocrine state in the group of patients with associated lymphocytic hyphopithitis (Table 1) when compared to the group of patients without associated lymphocytic hyphopithitis (Table 2) is remarkable. This might be indicative of additional damage to the anterior pituitary gland caused by the histologically confirmed inflammation.

Discussion

Minor inflammatory reactions within the pituitary gland were found in 7% of a large autopsy series14. Extensive infiltration of the anterior pituitary lobe by numerous lymphocytes, leading to the diagnosis of lymphocytic hyphopithitis, was found in only 2 of these cases (0.02%). However, clinical relevance of these inflammatory reactions (e.g. pituitary insufficiency) could not be established retrospectively.

The type and the intensity of inflammation in the anterior pituitary lobe found in 3 of our craniohypophysialoma patients exceeded the histological appearance of only a minor inflammatory reaction and was identical to the histological appearance of lymphocytic hyphopithitis.

The disease “lymphocytic hyphopithitis” is a very rare entity. Since the first description by Goudie and Pinkerton in 196210, 60 cases have been described to date (55 cases reviewed by Parent24,25 and 5 additional cases5,11,28,29,36). It typically affects women during pregnancy or shortly after delivery2,5,6,9,10,17,28,29 and only exceptionally affects males11,22,27,37. An association with other inflammatory diseases of the autoimmune type was found in 30% of cases9,10. Patients can present symptoms of both pituitary insufficiency and visual disturbances. Radiologically, lymphocytic hyphopithitis usually appears as a solid intrasellar mass. Histologically, it is characterized by an excessive number of lymphocytes within the adenohypophysis, occasionally accompanied by plasma cells, histiocytes and lymphoid follicles with germinal centers. Well-formed granulomas and giant cells are not seen8. The pathophysiological mechanism is assumed to be an auto-immune disorder7,19,27.

There has been only one report on the occurrence of lymphocytic hyphopithitis in a patient with Rathke's cleft cyst25. The occurrence of lymphocytic hyphopithitis in patients with craniohypophysialoma has not been described in the past. With this in mind, and in consideration of the extremely low incidence of lymphocytic hyphopithitis, the relatively high incidence (11%) of this pituitary inflammation found among our trans-sphenoidally operated craniohypophysialoma patients is remarkable. We explain this phenomenon by the fact, excluding the above-mentioned exception38, that no systematic investigation of the anterior pituitary lobe in craniohypophysialoma patients has been performed, either in operative1,4,13–16,18,21,32,35,37,39 or in autopsy series.

In contrast to the cases of “auto-immune” lymphocytic hyphopithitis described above, we assume that the inflammation in our 3 patients was “locally induced” by the cystic fluid of the craniohypophysialoma. The potential of craniohypophysialoma cyst fluids to induce inflammatory reactions is well documented in cases of meningitis20,26,34 and in cases of intrasellar abscesses without hyphopithitis23 due to an extravasation of this fluid. According to these cases and to Schenke et al.23 we assume a local induction of the lymphocytic hyphopithysis by rupture of the cystic wall of the craniohypophysialoma and consecutive extravasation of the cyst fluid into the parenchyma of the anterior pituitary lobe.

The clinical relevance of associated lymphocytic hyphopithitis is difficult to evaluate at the moment due to the small number of cases. However, the additional damage of the anterior pituitary gland by the inflammation may explain the reason why the endocrine state of all craniohypophysialoma patients with associated lymphocytic hyphopithitis did not improve after the trans-sphenoidal operation. It even worsened in one patient.
All these three patients retained complete pituitary insufficiency and required full hormonal substitution. On the contrary, a clear improvement in pituitary endocrine function could be seen postoperatively in 48% of these patients without associated lymphocytic hypophysitis. A deterioration was noted in only 4%.

Considering this relatively good postoperative endocrine state in the craniohypophyseal patients without associated hypophysitis, the trans-sphenoidal approach seems to be justified in patients with an enlarged sellar turcica 4,13-16,21,35. More radical procedures and other routes are indicated in other craniohypophyseal localizations and/or extensions 4,18,32,37,39. The latter may allow better localization of the pituitary stalk, although the rate of trauma to both pituitary stalk and anterior pituitary lobe is higher.

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References


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