Primary empty sella syndrome in a series of 142 patients

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Object. The primary empty sella syndrome (ESS) represents a heterogeneous clinical picture characterized by endocrine disturbances and signs of intracranial hypertension. An increase in intracranial pressure (ICP) is proposed to be one of the involved pathogenetic factors.

Methods. The series included 142 patients who were observed during a period of 20 years. All patients underwent an ICP and cerebrospinal fluid (CSF) dynamics evaluation through the use of a lumbar constant-rate infusion test.

Impairment of ICP and CSF dynamics was observed in 109 patients (76.8%). In 35 of the 36 patients affected by severe intracranial hypertension without rhinorrhea, improvement in adverse neurological symptoms was achieved after implanting a CSF shunt. Visual function, already seriously compromised before surgery, remained severely altered in one patient. In the group of 34 patients affected by rhinorrhea, CSF leakage was controlled using different surgical treatments: CSF shunt placement in 16 cases, surgical repair of the sellar floor in three, and both procedures in the remaining 13. Two patients refused any surgical treatment.

Conclusions. The role of increased ICP in the pathogenesis and perpetuation of primary ESS has been confirmed.

Adverse neurological signs and a CSF leak are correlated with an actual increase in ICP and are relieved after CSF shunt insertion. Cerebrospinal fluid rhinorrhea is more common than generally thought. Its resolution can be achieved using a careful diagnostic protocol and sometimes may require different surgical procedures.

Key Words • empty sella • rhinorrhea • cerebrospinal fluid pressure • cerebrospinal fluid shunt

The term “empty sella” was first used by Busch in 1951 to indicate a peculiar anatomical condition, observed in human cadavers, particularly females, characterized by a sella turcica only partially filled by a pituitary gland severely flattened against the sellar floor. In 1968 Kaufman demonstrated that an empty sella was related to an extension of the subarachnoid space into the sella, which caused it to be enlarged, deepened, and reshaped; in these cases, an incomplete or incompetent sellar diaphragm was usually present. The term “primary empty sella” is used to refer to the condition when it is unrelated to previous surgical, pharmacological, or radiotherapeutic treatment of the sellar region. In some cases, particularly in young women, the condition is associated with endocrine disturbances, such as obesity, hypertrichosis, irregular menses, and galactorrhea, as well as with signs of intracranial hypertension, such as headache, visual disturbances, and papilledema. This anatomicoclinical picture is referred to as “primary ESS.” In 8 to 20.7% of patients, spontaneous CSF leakage is part of the clinical presentation.

A chronic or intermittent increase in ICP is thought to be one of the causative factors playing a role in the development and perpetuation of primary ESS. In a previous study of 58 female patients with primary ESS, we observed an impairment in ICP and/or CSF dynamics in 84% of the cases. Furthermore, we reported a correlation between elevated ICP and hypothalamic/hypophysial imbalance of prolactin secretion.

In the present paper we report the clinical findings obtained in 142 patients affected by primary ESS in whom clinical data, ICP, and CSF dynamics were studied. The indications for surgical treatment and the long-term results are also discussed.

Clinical Material and Methods

Patient Population

This series included 142 patients (125 females and 17 males), observed during a period of 20 years (1975–1995). The mean patient age was 43 years (range 13–64 years), and the mean duration of symptoms was 61 months (range 3 months–12 years). Neurological, endocrinological, and visual symptoms are reported in Table 1; each patient presented with at least one of these symptoms.

All patients underwent computerized tomography scanning and/or magnetic resonance imaging studies. An intrasellar arachnoidcele with normal or small ventricles was documented in all cases, without evidence of a sellar or an intracranial neoplasm. In a few patients among those with CSF rhinorrhea, we performed computerized tomography scanning with intrathecal contrast medium injection to confirm the site of CSF leakage.

All patients also underwent a lumbar infusion test at a constant rate of 1 ml/minute for 30 minutes, as described.
The basal ICP and CSF AR values were analyzed (normal values in our laboratory: basal ICP = 13 mm Hg and AR > 0.11 ml/min/mm Hg).

Surgical Indication and Treatment

In all patients with increased ICP or altered CSF dynamics who had presented with adverse neurological signs (papilledema, severe headache, and visual defects) or rhinorrhea, surgery consisted of CSF shunt placement. We have used different types of shunt devices: LP (at the beginning of the study, 16 cases), VP (30 cases), and ventriculoatrial (22 cases) at high opening pressure.

In patients with CSF rhinorrhea without altered CSF dynamics (three cases) or in whom a CSF shunt was insufficient to resolve the fistula (13 cases), transsphenoidal surgical repair of the sellar defect was realized. Direct surgical repair was achieved using biological glue and freeze-dried dura mater arranged in a tilelike fashion.

Results

In this series most of the patients were female (88%) and more than 80% of them became symptomatic during the fourth or fifth decade of life, as previously described in the literature. The basal ICP and CSF AR values were analyzed (normal values in our laboratory: basal ICP = 13 mm Hg and AR > 0.11 ml/min/mm Hg).

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TABLE 1

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neurological</td>
<td>142 (100)</td>
</tr>
<tr>
<td>severe headache</td>
<td>124 (88)</td>
</tr>
<tr>
<td>nausea</td>
<td>24 (17)</td>
</tr>
<tr>
<td>vomiting</td>
<td>21 (15)</td>
</tr>
<tr>
<td>papilledema</td>
<td>35 (25)</td>
</tr>
<tr>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>blurred vision</td>
<td>41 (29)</td>
</tr>
<tr>
<td>visual field reduction</td>
<td>19 (13)</td>
</tr>
<tr>
<td>amaurosis</td>
<td>4 (2)</td>
</tr>
<tr>
<td>diencephalic &amp;/or pituitary endocrine dysfunction</td>
<td></td>
</tr>
<tr>
<td>females</td>
<td>125 (88)</td>
</tr>
<tr>
<td>obesity</td>
<td>65 (52)</td>
</tr>
<tr>
<td>irregular menses</td>
<td>50 (40)</td>
</tr>
<tr>
<td>galactorrhea</td>
<td>33 (26)</td>
</tr>
<tr>
<td>hypertrichosis</td>
<td>23 (18)</td>
</tr>
<tr>
<td>males</td>
<td>17 (12)</td>
</tr>
<tr>
<td>sexual disturbance</td>
<td>9 (53)</td>
</tr>
<tr>
<td>hypogonadism</td>
<td>2 (12)</td>
</tr>
<tr>
<td>gynecomastia</td>
<td>2 (12)</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td>34 (24)</td>
</tr>
</tbody>
</table>

Fig. 1. A sagittal T1-weighted magnetic resonance image demonstrating a typical empty sella turcica.

Fig. 2. Bar graph of patients with CSF pressure and/or dynamics alteration (109 cases) demonstrating the correlation between basal ICP values (measured in millimeters of mercury) and papilledema. 1 = patients with papilledema (35 patients, mean ICP value 18.43 ± 7.53 mm Hg); 2 = patients without papilledema (74 patients, mean ICP value 13.06 ± 5.37 mm Hg; p < 0.005).
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TABLE 2
Cerebrospinal fluid dynamics and surgical procedures in 34 patients with primary ESS and rhinorrhea

<table>
<thead>
<tr>
<th>CSF Dynamics &amp; Ops</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>11</td>
</tr>
<tr>
<td>TS surgical repair</td>
<td>3</td>
</tr>
<tr>
<td>TS surgical repair + CSF shunt</td>
<td>87</td>
</tr>
<tr>
<td>pathological</td>
<td>23</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>16</td>
</tr>
<tr>
<td>CSF shunt + TS surgical repair</td>
<td>5</td>
</tr>
<tr>
<td>refusal of surgery</td>
<td>2</td>
</tr>
</tbody>
</table>

* TS = transsphenoidal.
† Patients featured in Table 3.

TABLE 3
Cerebrospinal fluid dynamics in eight patients with rhinorrhea before and after surgical sella repair

<table>
<thead>
<tr>
<th>Case</th>
<th>ICP (mm Hg)</th>
<th>AR (ml/min/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop*</td>
<td>Postop</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>23.2</td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
<td>16.4</td>
</tr>
<tr>
<td>3</td>
<td>3.6</td>
<td>17.5</td>
</tr>
<tr>
<td>4</td>
<td>6.4</td>
<td>15.8</td>
</tr>
<tr>
<td>5</td>
<td>9.3</td>
<td>17.9</td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
<td>14.7</td>
</tr>
<tr>
<td>7</td>
<td>7.7</td>
<td>15.3</td>
</tr>
<tr>
<td>8</td>
<td>13.3</td>
<td>16.9</td>
</tr>
</tbody>
</table>

* Basal condition.

Discussion

Primary ESS presents a heterogeneous clinical picture in which pathogenesis is not definitively clarified and treatment is still controversial. Incompetence of the sellar diaphragm is considered important in the formation of primary empty sella. In a series of 266 patients subjected to transsphenoidal hypophysectomy for metastatic breast cancer or diabetic retinopathy, Hardy and Maira observed an incompetent or completely absent sellar diaphragm in 76 patients (28.5%). Sellar arachnoidal diverticulum was found in 41 patients (15.4%) and was always associated with a large or absent sellar diaphragm. In contrast, an absent diaphragm or a large orifice could not be associated with an empty sella, as these authors discovered in 35 patients. Incompetence of the sellar diaphragm in humans has been demonstrated in 22 to 77% of cases. Most of these defects do not result in herniation of the subarachnoid space, however. These data confirm that the anomaly of the sellar diaphragm is essential for the development of the empty sella, although other factors seem to be relevant as well.

The role of intracranial hypertension in the formation of the primary empty sella has been proposed by many au-
Various intracranial conditions that elevate CSF pressure have been associated with ESS, including hydrocephalus, brain tumors, and Arnold–Chiari malformations. Primary ESS shares many features with pseudotumor cerebri, which is characterized by a severe increase in ICP. Brismar and Bergstrand have found impaired CSF circulation in the majority of patients with primary ESS. Foley and Posner found elevated basal CSF pressure in 65% of patients affected by primary ESS.

In accordance with our previous work, results in the present study confirm the pathogenetic role of ICP and/or altered CSF dynamics in patients affected by primary ESS. We observed ICP or CSF dynamics alterations in 109 (76.8%) of the 142 patients studied. In particular, a higher-than-normal ICP level was found in 88 (77.3%) of the 142 patients studied. The increased ICP ranged from 14 to 24 mm Hg, values insufficient to provoke a clear instance of intracranial hypertension but sufficient to maintain the neurological symptomatology of primary ESS (that is, headache and visual disturbances). Our results indicate that the same neurological picture may be sustained by normal ICP values when coupled with an alteration in CSF AR, as found in 21 of 109 cases. Therefore, the finding of a normal ICP during waking periods is insufficient to rule out an alteration in CSF dynamics, which can be demonstrated by the lumbar constant-rate infusion test. When papilledema or visual field deficits occurred in patients with primary ESS, intracranial hypertension was always documented.

In patients with CSF leakage, the elevation of ICP combined with pulsation of the intrasellar arachnoidocoele is considered to be the cause of progressive sellar erosion and leakage. In our series, despite spontaneous opening of the intracranial system related to the fistula, 23 (68%) of 34 patients with rhinorrhea presented with an alteration in ICP and CSF dynamics. In eight (23.5%) of 34 patients, the fistula acted as a safety valve hiding the alteration in CSF dynamics, which became evident after transsphenoidal closure of the sellar opening. Only three cases without evidence of CSF alterations were definitively cured via transsphenoidal closure of the skull defect. We may suppose that in these last cases, a previous transitory CSF alteration provoked the empty sella and sellar erosion and that the CSF fistula was thereafter maintained by a persistent large anatomical defect.

A careful evaluation must be performed in selecting patients for surgery. Surgical treatment is mandatory in patients with rhinorrhea, papilledema, debilitating headache, and progressive or severe visual alterations and in whom clear impairment of CSF pressure or dynamics has been verified. In our series, 65 (59.6%) of 109 patients with ICP or CSF dynamics alterations underwent CSF shunt insertion. An improvement in neurological symptoms was observed in all patients and excellent results were obtained in patients suffering from rhinorrhea or visual alterations. In some cases slight or moderate symptoms due to orthostatic overdrainage became evident but disappeared after a few weeks.

Our results indicate that CSF shunt placement is the best way to treat primary ESS, even in patients in whom visual alterations are the most relevant clinical signs. Other surgical approaches aimed at reducing the stretching or compression of visual structures—transsphenoidal chias-

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mapexy, optic nerve sheath decompression, or sub-temporal decompression—have been advocated. None of these procedures is without risk; for example, permanent visual loss as a result of intraoperative axonal or vascular damage has been described. Headache, which is the most prevalent symptom of primary ESS, in many cases does not improve after surgery, and CSF shunt insertion may still be required.

Some authors have documented a clear relationship among intraabdominal, intrathoracic, and intracranial pressure in obese patients, and weight loss has been proposed as a valid therapeutic strategy in obese patients suffering from primary ESS, thus confirming the role of CSF hypertension caused by chronically increased intraabdominal pressure. In the present series, surgical diversion of CSF permitted complete resolution of headache and papilledema and the improvement of visual disturbances in all patients but one (a patient with seriously compromised sight and in whom the diagnosis of primary ESS was delayed).

Cerebrospinal fluid rhinorrhea is a clear indication for surgical intervention because of the risk for meningitis. According to the literature, closure of the fistula may be attempted using direct surgical methods, and, more recently, an endoscopic procedure. Many of these surgical procedures are invasive and risky. Moreover, despite improvements in diagnostic procedures, localization of the fistula remains difficult and even impossible in many cases. Favorable initial results have been reported using each type of approach. Note, however, that long-term follow-up data have demonstrated a recurrence rate as high as 41% together with the risk of meningitis and death. Cerebrospinal fluid leakage may continue after sellar floor repair, requiring repeated intervention and, finally, insertion of a CSF shunt. Treatment of CSF rhinorrhea therefore remains a challenge and requires a safe and effective therapeutic strategy. In principle, we have used two therapeutic approaches: surgical repair of the skull defect or CSF drainage. Direct surgical repair was performed in all cases with normal CSF pressure and dynamics. Although the possible presence of an extrasellar fistula has been reported in patients with primary ESS, in all cases in the present series, in which very accurate radiological investigations were performed, the fistula was always recognized at the sellar level.

Cerebrospinal fluid drainage was achieved in all cases in which CSF pressure and dynamics had been abnormal. No evidence in our series supported the notion that the drain could reverse the flow gradient and thus induce pneumocephalus or infection. Nevertheless, normalization of CSF pressure alone or simple closure of the fistula is insufficient to treat rhinorrhea. In 13 patients both of these procedures were required. In all cases our surgical strategy permitted the definitive arrest of rhinorrhea.

The relative simplicity of CSF deviation compared with other neurosurgical procedures is matched by the possible occurrence of complications that frequently require surgical revision. In addition, there are several controversies regarding the reliability and efficacy of the type of shunt used. Greenblatt and Wilson reported on two cases of spontaneous CSF rhinorrhea treated with LP shunt insertion. Davis and Kaye documented restoration of normal ICP in one patient in whom spontaneous rhinorrhea in the context of ESS was treated following the placement of an LP shunt.
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Among our cases, the types of CSF diversion included the following: VP, 30 patients; ventriculoatrial, 22 patients; and LP, 16 patients. The incidence of required revisions was greater in patients treated with an LP shunt (37%) compared with those treated using a VP (33%) or ventriculoatrial (8%) shunt. Obstruction, malposition, infection, and hyperdrainage were the most frequent causes of VP and LP shunt dysfunction. More than one third of all ventriculoatrial shunt revisions were necessitated by distal displacement. These differences were not statistically significant, however.

Conclusions

Primary ESS represents a complex and evolving syndrome in which ICP and CSF dynamics alterations together with an incompetent sellar diaphragm play a clear pathogenetic role. Cerebrospinal fluid rhinorrhea as a complication of primary ESS is a more common condition than is generally accepted and can be resolved using a careful diagnostic protocol and various surgical procedures. The role of the increased ICP in the pathogenesis and perpetuation of the primary ESS was confirmed in the present study. Clinical signs such as papilledema and CSF leakage correlate well with the finding of an actual increase in ICP and can be relieved after CSF shunt insertion.

As in the diverse syndromes collectively termed “benign intracranial hypertension,” the pathophysiology of increased ICP remains unexplained in the context of primary ESS.

References

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