Hyperprolactinemia due to spontaneous intracranial hypotension

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OBJECT Spontaneous intracranial hypotension is an increasingly recognized cause of headaches. Pituitary enlargement and brain sagging are common findings on MRI in patients with this disorder. The authors therefore investigated pituitary function in patients with spontaneous intracranial hypotension.

METHODS Pituitary hormones were measured in a group of 42 consecutive patients with spontaneous intracranial hypotension. For patients with hyperprolactinemia, prolactin levels also were measured following treatment. Magnetic resonance imaging was performed prior to and following treatment.

RESULTS The study group consisted of 27 women and 15 men with a mean age at onset of symptoms of 52.2 ± 10.7 years (mean ± SD; range 17–72 years). Hyperprolactinemia was detected in 10 patients (24%), ranging from 16 ng/ml to 96.6 ng/ml in men (normal range 3–14.7 ng/ml) and from 31.3 ng/ml to 102.5 ng/ml in women (normal range 3.8–23.2 ng/ml). In a multivariate analysis, only brain sagging on MRI was associated with hyperprolactinemia. Brain sagging was present in 60% of patients with hyperprolactinemia and in 19% of patients with normal prolactin levels (p = 0.02). Following successful treatment of the spontaneous intracranial hypotension, hyperprolactinemia resolved, along with normalization of brain MRI findings in all 10 patients.

CONCLUSIONS Spontaneous intracranial hypotension is a previously undescribed cause of hyperprolactinemia. Brain sagging causing distortion of the pituitary stalk (stalk effect) may be responsible for the hyperprolactinemia.

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KEY WORDS headache; low-pressure syndrome; cerebrospinal fluid; intracranial hypotension; prolactin; diagnostic and operative techniques

S}pontaneous intracranial hypotension is an important cause of new, daily, persistent headaches that usually afflicts young to middle-aged adults, with a female predominance and a peak incidence in the 5th decade of life.16 The headache is typically orthostatic and is often accompanied by nausea, neck pain, and hearing abnormalities. Spontaneous intracranial hypotension is uncommon, with an estimated incidence of approximately 5 per 100,000 per year. The cause of spontaneous intracranial hypotension is almost always a spontaneous spinal CSF leak, and a systemic connective tissue disorder affecting the spinal dura mater is often suspected.14 In spontaneous intracranial hypotension, pituitary enlargement is one of the 5 main imaging features that can be found on brain MRI (Sagging of the brain, Enhancement of the pachymeninges, Engorgement of venous structures, Pituitary enlargement, and Subdural fluid collections [SEEPS]).16 Pituitary enlargement in spontaneous intracranial hypotension has now been well documented and can resemble a pituitary tumor.2,9,11,13,18 Moreover, sagging of the brain often is associated with distortion of the pituitary stalk. However, a systematic evaluation of pituitary function has not been reported in patients with spontaneous intracranial hypotension. Therefore, we investigated pituitary hormones in patients with this disorder.

Methods

This study was approved by the Cedars-Sinai Medical Center Institutional Review Board. Blood was drawn by
venipuncture to measure pituitary hormones in a group of 42 consecutive patients with symptomatic spontaneous intracranial hypotension. Spontaneous intracranial hypotension was diagnosed using previously established criteria. Pregnant and postpartum patients were excluded. Some patients received narcotics and antidepressants for the management of spontaneous intracranial hypotension, but none of the patients with hyperprolactinemia were taking drugs known to be associated with that disorder, such as tranquilizers, antipsychotic medications, metoclopramide, cisapride, alpha-methyldopa, reserpine, and ralmetone. Other causes of hyperprolactinemia (e.g., chronic renal failure, hypothyroidism, bronchogenic carcinoma, sarcoidosis, and polycystic ovary syndrome), also were excluded. For patients who were found to have hyperprolactinemia, prolactin levels also were measured following treatment of their spontaneous intracranial hypotension.

Results of brain MRI studies were scored by a board-certified neuroradiologist (M.M.M.) who was blinded to the results of pituitary hormone measurements. One or more of the following imaging findings were considered as brain sagging: downward displacement and distortion of midbrain and pons, flattening of the ventral surface of pons, inferior displacement of the mammillary bodies, downward sloping of the optic chiasm, and inferior extension of the cerebellar tonsils. In addition, serial prolactin levels were measured in 1 patient during a several-day course of intrathecal saline infusion correcting low CSF volume.

Differences in patient characteristics and MRI findings according to hyperprolactinemia status were assessed with the Fisher exact test and the Wilcoxon-Mann-Whitney test for categorical and continuous variables. Multivariate logistic regression was used to determine factors associated with hyperprolactinemia while adjusting for patient confounders. A p value < 0.05 was considered to be statistically significant. All analyses were performed with SAS software (version 9.2; SAS Inc.).

Results

The study group consisted of 27 women and 15 men with a mean age at onset of symptoms of 52.2 years (SD 10.7 years; range 17–72 years). All of the patients had a history of orthostatic headaches, although the headaches had resolved at the time of treatment in 2 patients (1 of these patients had persistent dizziness and 1 patient had developed a cervical myelopathy). None of the patients reported galactorrhea or menstrual disturbances. Typical brain MRI findings were present in 32 (76%) of the 42 patients. The following hormones were measured in all 42 patients: prolactin, thyroxine, thyroid-stimulating hormone, 3,5,3'-triiodothyronine uptake, luteinizing hormone, and follicle-stimulating hormone. Adrenocorticotropic hormone and cortisol were measured in 40 patients, growth hormone in 37 patients, insulin-like growth factor in 30 patients, and testosterone in 13 of the male patients. Except for elevated prolactin levels, hormone abnormalities were not detected in more than a single patient.

Hyperprolactinemia was detected in 10 patients (24%), ranging from 16 ng/ml to 96.6 ng/ml in men (normal range 3–14.7 ng/ml) and from 31.3 ng/ml to 102.5 ng/ml in women (normal range 3.8–23.2 ng/ml) (Table 1). Hyperprolactinemia was associated with sagging of the brain. This MRI finding was present in 60% of patients with hyperprolactinemia and in 19% of patients with normal prolactin levels (p = 0.02). Of note, pituitary enlargement was present in 30% of patients with hyperprolactinemia and in 28% of patients with normal prolactin levels (p = 1.0). There was a trend toward hyperprolactinemia being more common among men and being associated with a shorter duration of symptoms, but this did not reach statistical significance.

Following successful treatment of the spontaneous intracranial hypotension, hyperprolactinemia resolved in all 10 patients. This usually occurred within a few days (Fig. 1). Treatment consisted of epidural blood patching in 5 patients, surgical repair of the underlying spinal CSF leak in 3 patients, percutaneous fibrin glue injections in 1 patient, and intrathecal saline infusion in 1 patient. The brain MRI findings of spontaneous intracranial hypotension resolved along with the hyperprolactinemia in all 8 patients who had both (Fig. 2).

In 1 patient with spontaneous intracranial hypotension, serial prolactin levels were measured prior to and during a course of intrathecal saline infusion at increasing rates from 2.5 to 12.5 ml per hour, with resolution of hyperprolactinemia at the highest rate, along with resolution of headache (Fig. 3).

Discussion

In this study, we found that approximately one-fourth of patients with spontaneous intracranial hypotension had hyperprolactinemia. This is a previously unreported association. Although study participants were consecutive and unselected, our practice is biased toward more complex cases of spontaneous intracranial hypotension often requiring surgical intervention, making our results not necessarily generalizable to the general population of patients with this disorder. The degree of elevation of prolactin levels was mild to moderate, and it was similar to that seen in patients with “stalk effect.”

The etiology of hyperprolactinemia in spontaneous intracranial hypotension is speculative. Hypothalamic dopamine secretion inhibits prolactin secretion from the pituitary lactotrophs. Dopamine reaches the anterior pituitary gland via the dopaminergic neurons of the pituitary stalk. Physiological prolactin secretion therefore requires disinhibition of the pituitary lactotrophs. This process is unique among anterior pituitary hormones in 2 ways: 1) prolactin release is inhibited by its hypothalamic factor, dopamine, whereas other pituitary hormones are stimulated by releasing hypothalamic factors; and 2) dopamine is transmitted to the anterior pituitary via direct neuronal transmission, whereas the other factors are released in the hypothalamus and travel to the pituitary via a portal venous system. Thus, mechanical factors that impact on neuronal activity, such as stretch or compression, may impact dopamine release (and subsequent prolactin release), but not other hypothalamic factors.

The well-described pituitary stalk effect refers to a mild...
to moderate elevation in serum prolactin levels in the presence of a pituitary tumor that is not prolactin secreting. Hyperprolactinemia due to stalk effect typically results in serum prolactin levels in the range of 20–85 ng/ml, and they very rarely exceed 100 ng/ml, whereas more than 95% of prolactin-secreting pituitary tumors will produce a serum prolactin level greater than 85 ng/ml. Classically, the stalk effect has been attributed to compression of the pituitary stalk by a mass within or near the pituitary gland that inhibits or blocks delivery of hypothalamic dopamine to the pituitary lactotrophs, resulting in impaired dopamine delivery to the pituitary and, consequently, disinhibition of the lactotrophs. Interestingly, studies have demonstrated that the extent of the stalk effect is not related to tumor size, tumor volume, degree of suprasellar extension, or extent of distortion of the pituitary stalk[^19], leading several people to hypothesize an alternate mechanism of action, although very little proof exists to support these theories.

The exact mechanism by which intracranial hypotension leads to hyperprolactinemia has yet to be established. In this series, brain sagging was the only radiological feature associated with hyperprolactinemia, whereas pituitary engorgement, subdural hematoma, and meningeal enhancement were not associated. Based on this observation, the most likely hypothesis for hyperprolactinemia would be that brain sagging results in stretching of the pituitary stalk and/or hypothalamic region, with subsequent diminishment in dopamine transmission to the anterior pituitary, and increased prolactin levels. Laboratory investigations into the effect of mechanical stretch on neurons suggest that it can result in increased synaptic vesicle accumulation at the synaptic junction, and that this effect is reversible once the mechanical stretch is removed.[^1]

One could hypothesize that brain sagging results in stretching of hypothalamic dopamine neurons, with subsequent increased accumulation of dopamine in the anterior pituitary. Subsequent feedback regulation from the lactotrophs to the hypothalamus (a standard mechanism of hormonal regulation), along with potential downregulation of the number of dopamine receptors on the lactotrophs, would then result in an overall increase in prolactin release, which would rapidly return to normal after correction of spontaneous intracranial hypotension and resolution of the brain sagging. Of note, this effect would not occur for other hormonal axes, which depend on hypothalamic releasing factors delivered via the portal system.[^3]

### Table 1. Characteristics of 42 patients with spontaneous intracranial hypotension

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>Hyperprolactinemia</th>
<th>No Hyperprolactinemia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>42</td>
<td>10</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, yrs</td>
<td>52.2 ± 10.7</td>
<td>49.7 ± 13.5</td>
<td>53.0 ± 9.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>54 (46–57)</td>
<td>50 (45–58)</td>
<td>55 (51–57)</td>
<td></td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>27 (64.3)</td>
<td>4 (40.0)</td>
<td>23 (71.9)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (35.7)</td>
<td>6 (60.0)</td>
<td>9 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms, mos</td>
<td>41.9 ± 51.2</td>
<td>20.1 ± 20.1</td>
<td>48.7 ± 56.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>21 (8–57)</td>
<td>16 (2–34)</td>
<td>22 (10–65)</td>
<td></td>
</tr>
<tr>
<td>Pituitary size, mm</td>
<td>6.2 ± 1.8</td>
<td>6.2 ± 2.4</td>
<td>6.2 ± 1.7</td>
<td>0.94</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6.3 (5.0–7.3)</td>
<td>6.4 (4.9–7.6)</td>
<td>6.3 (5.1–7.3)</td>
<td></td>
</tr>
<tr>
<td>Abnormal MRI findings, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S = subdural fluid collections</td>
<td>23 (54.8)</td>
<td>7 (70.0)</td>
<td>16 (50.0)</td>
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</tr>
<tr>
<td>E = enhancement of pachymeninges</td>
<td>30 (71.4)</td>
<td>8 (80.0)</td>
<td>22 (68.8)</td>
<td>0.70</td>
</tr>
<tr>
<td>E = engorgement of venous structures</td>
<td>5 (11.9)</td>
<td>2 (20.0)</td>
<td>3 (8.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>P = pituitary hyperemia</td>
<td>12 (28.6)</td>
<td>3 (30.0)</td>
<td>9 (28.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>S = sagging of the brain</td>
<td>12 (28.6)</td>
<td>6 (60.0)</td>
<td>6 (18.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>No. (%) of abnormal MRI findings; SEEPS*</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>0</td>
<td>10 (23.8)</td>
<td>2 (20.0)</td>
<td>8 (25.0)</td>
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<tr>
<td>1</td>
<td>9 (21.4)</td>
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<td>4 (9.5)</td>
<td>1 (10.0)</td>
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<tr>
<td>3</td>
<td>14 (33.3)</td>
<td>3 (30.0)</td>
<td>11 (34.4)</td>
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<td>1 (10.0)</td>
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</tr>
<tr>
<td>5</td>
<td>3 (7.1)</td>
<td>2 (20.0)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range.

* 0 = normal MRI findings for all SEEPS assessments; 5 = abnormal MRI findings for all SEEPS assessments.
Similar mechanical effects such as increased vascular endothelial growth factor expression and neurite sprouting have all been observed following mechanical stretching of neurons, suggesting that brain sag could have a variety of effects on dopaminergic neurons that result in increased prolactin production in the pituitary lactotrophs.

It seems unlikely that the hyperprolactinemia we observed was simply due to low CSF volumes, because other radiographic changes such as pituitary gland enlargement, subdural hematoma, or dural enhancement were not associated with elevated prolactinemia, whereas each of these is associated with spontaneous intracranial hypotension. Furthermore, the fact that the stalk effect is commonly observed in cases not associated with spontaneous intracranial hypotension argues for a mechanism specific to dopamine neurons and/or mechanical distortion.

Because patients who had more substantial brain sag were more likely to have hyperprolactinemia, the source of this endocrine issue may be primarily at the hypothalamic level and not at the pituitary level. Hypothalamic sagging may lead to an alteration in the production of thyrotropin-releasing hormone (TRH) which in turn stimulates the secretion of prolactin by the pituitary gland.

FIG. 1. Graph showing pre- and posttreatment prolactin levels (ng/ml) in 10 patients with spontaneous intracranial hypotension and hyperprolactinemia.

FIG. 2. Pretreatment (left) and posttreatment (right) sagittal T1-weighted MR images showing resolution of brain sagging in a patient who underwent surgical repair of a thoracic CSF leak. The patient’s prolactin level decreased from 97 ng/ml before surgery to 11 ng/ml after surgery.

FIG. 3. Graph showing serial prolactin levels (ng/ml) in a patient with spontaneous intracranial hypotension undergoing intrathecal saline infusion at increasing rates. At the highest infusion rate (12.5 ml/hr) her headache resolved.
releasing hormone, a known inhibitor of prolactin release, resulting in an elevation of prolactin levels. Similarly, both the hypothalamus and brainstem contain neurons that secrete prolactin-releasing peptide, an RF-amide peptide that can cause prolactin release along with a variety of other functions.\(^2\) The RF-amide peptides are a broad class of neuropeptides that are believed to modulate stress responses, energy metabolism, and analgesia. Due to the low receptor affinity of these peptides there are probably significant cross-interactions, and it is possible that the headache pain experienced by patients with spontaneous intracranial hypotension is significant enough to affect the release of RF-amides that cross-react with prolactin-releasing peptide and cause prolactin release in the pituitary. Similar effects may explain elevation of prolactin caused by depression and other psychologically stressful situations.

Along similar lines, could prolonged brain sag lead to an alteration in orexin production? Orexin is a hypothalamic neuropeptide that has some yet-undefined effect on prolactin secretion (probably inhibitory, based on animal model studies). Orexin modulates trigeminal nucleus caudalis activity; orexin A has antinoceptive effects, whereas orexin B is pronociceptive.\(^9,10\) Thus, orexin can play a role in the pain process of spontaneous intracranial hypotension. One can then hypothesize that alterations in orexin in activity occurring as a component of the pain response in spontaneous intracranial hypotension will simultaneously promote prolactin secretion. Seen in this way, various neuropeptides can play a role in the observed hyperprolactinemia. Clearly these hypotheses would need to be verified, and at present represent little more than conjecture. Nonetheless, as a greater appreciation is gained about the complex role of these neuropeptides in the regulation of pituitary prolactin release, it may shed light on the true cause of hyperprolactinemia in cases of spontaneous intracranial hypotension associated with brain sag.

Pituitary enlargement was not demonstrated to be associated with hyperprolactinemia in our study. Pituitary enlargement was demonstrated in 29% of patients in our study, compared with 8%—100% in other studies.\(^7,5,7,18\) The hyperprolactinemia was asymptomatic in our patient population. Galactorrhoea, however, has been reported previously in a patient with spontaneous intracranial hypotension. This patient did not have hyperprolactinemia, but an abnormal response of prolactin was elicited by thyrotropin-releasing hormone.\(^20\)

Many of the findings on brain MRI studies seen in patients with spontaneous intracranial hypotension can be explained by the Monro-Kellie hypothesis.\(^5,12\) Because of the intact skull, the sum of the volumes of brain, blood, and CSF must remain constant. Loss of CSF volume thus results in an increase of intracranial blood volume, explaining the findings of pachymeningeal enhancement due to dilation of veins in the subdural zone, engorgement of dural venous sinuses, and pituitary enlargement due to hyperemia. Sagging of the brain, however, which in our study was the only MRI finding associated with hyperprolactinemia, is not explained by the Monro-Kellie hypothesis but rather by the loss of CSF buoyancy. The finding of hyperprolactinemia in a patient with pituitary enlargement due to spontaneous intracranial hypotension may further a misdiagnosis of pituitary adenoma, and thus it is important to recognize this association.

**Conclusions**

In this study, hyperprolactinemia resolved soon after treatment of the spontaneous intracranial hypotension, often within 24 hours, along with resolution of symptoms and brain MRI findings. This suggests that in some patients with spontaneous intracranial hypotension, prolactin levels may be a possible marker for disease severity. The recurrence rate of spontaneous intracranial hypotension is not negligible, but we have not had the opportunity yet to measure prolactin levels in patients with recurrent symptoms.

**References**


Author Contributions
Author contributions to the study and manuscript preparation include the following. Conception and design: Schievink. Acquisition of data: Schievink, Maya, Mamelak, Carmichael. Analysis and interpretation of data: all authors. Drafting the article: Schievink. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Schievink. Statistical analysis: Schievink, Nuño, Bonert.

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