Pseudotumor cerebri and prolactin secreting pituitary adenoma

Association or coincidence?

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ABSTRACT

يعتبر الورم الدماغي الكاذب (PTC) و ارتفاع نسبة البرولكتين في الدم المرتبط بورم الغدة النخامية نادر الحدوث، كما أنه لم يتم معاينة العلاقة بين هذه الأمراض بصورة كافية بعد أشعة الرنين المغناطيسي MRI. يصف هذا التقرير مريضة مصابة بورم صغير في الغدة النخامية مفرز للبرولكتين مع الورم الدماغي الكاذب PTC. لم تثبت أشعة الرنين المغناطيسي وجود ضغط على التجويف الكهفي، أو أي من التجاويف الأخرى. استجابت المريضة في البداية للعلاج بالإسيتازولمايد، و الكابرجولين. لكن بعد 9 أشهر، انتكست أعراض الورم الدماغي الكاذب PTC على الرغم أن مستوى البرولكتين في الدم كان طبيعي، و أشارت الأدلة إلى صغر حجم ورم الغدة النخامية في أشعة الرنين المغناطيسي MRI، تحسنت المريضة بعد أن أجريت لها عملية تركيب أنبوب قطني برتيوني. نستنتج أن نتائج المرضى لا تدعم العلاقة بين الورم الدماغي الكاذب PTC، و زيادة نسبة البرولكتين في الدم، أو ورم الغدة النخامية المفرز للبرولكتين، لكن تدعم الحالة الحاجة إلى التفكير في تشخيص الورم الدماغي الكاذب PTC للمرضى الذين يعانون من ورم نخامي صغير و تظهر أعراض زيادة الضغط الدماغي.

The occurrence of pseudotumor cerebri (PTC) and hyperprolactinemia related to a prolactinoma are extremely rare, and the link between these pathologies has not been examined adequately in the post-MRI era. We report a patient with a small intrasellar prolactinoma who also developed PTC. Magnetic resonance venography did not show any evidence of compression of the cavernous or any other sinuses. She initially responded to treatment with acetazolamide and cabergoline. However 9 months later, her PTC symptoms recurred despite a normal serum prolactin level and a mild reduction of the pituitary tumor size on MRI. She improved after a lumboperitoneal shunt. We conclude that the findings in our patient do not support an association between PTC and hyperprolactinemia or prolactinoma. However, the case supports the need for clinicians to consider the diagnosis of PTC when patients with small pituitary lesions exhibit raised intracranial pressure features.

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Pseudotumor cerebri (PTC) is a syndrome of increased intracranial pressure (ICP) without hydrocephalus or a mass lesion with normal CSF composition. Prolactin secreting pituitary adenoma (prolactinoma) is a well-recognized lesion that usually presents with endocrine disturbance-related symptoms. A patient with a large prolactinoma may present with raised ICP and/or mass effect manifestations as a result of compression of the optic structures, pituitary gland, and cavernous sinus. On the other hand, a patient with a small prolactinoma is unlikely to present with symptoms and signs of raised ICP, and in the presence of such features other diagnoses including PTC should be considered. Pseudotumor cerebri has been linked to a number of drugs and diseases; an association that is well documented with some factors more than others. Hyperprolactinemia[1] and pituitary adenoma[2] are examples of the rare clinical entities that have been reported in patients with PTC, though the link has not been adequately examined. We report a female patient with a small prolactinoma who presented with headaches, visual deterioration, and papilledema related to PTC. The aim of this article is to

examine whether the occurrence of the pituitary tumor and hyperprolactinemia with PTC is an association or a coincidence. In addition, it is also hoped that the case will serve to remind clinicians of the need to consider PTC in patients with small pituitary tumors and raised ICP features.

Case Report. A 17-year-old female patient presented to our hospital with 3-year history of oligomenorrhea and galactorrhea, and one year's history of frontal headache, which was worse in the morning and on bending. Over the last month, her headache had worsened and was associated with blurring of vision and diplopia on looking to both sides. On examination, she was alert and oriented. She had bilateral papilledema with visual acuity reduced to finger counting and bilateral partial abducent nerve paresis. There was evidence of an enlarged blind spot with no temporal field loss. Her height was 157 cm, and her weight was 105 kg. Otherwise, she had no other clinical findings and no significant medical or family history. In addition, she denied using any medications apart from paracetamol. Blood investigations revealed an elevated serum prolactin level at 200 ug/L (normal 1.20-29.93 ug/L). Random cortisol, free triiodothyronine, and thyroxine, luteinizing hormone, follicle-stimulating hormone, growth hormone, and insulin-like growth factor-I were all within normal limits. An MRI (**Figure 1**) showed a 1.5 x 1.2 cm cystic pituitary lesion with heterogeneous signal intensity on T2 weighted images, and relative bright and heterogeneous signal on T1 weighted images, most likely reflecting either high protein content or previous hemorrhagic episode. The residual gland was in the periphery and pushed superiorly. The upper aspects of the tumor appeared to reach the optic chiasm, but not significantly compressing it. The pituitary stalk was pushed to the right side and there was no evidence of invasion of the cavernous sinus. Evaluation of the cavernous and dural sinuses by magnetic resonance venography (MRV) (**Figure 2**) was normal. The high serum prolactin and the MRI findings were diagnostic of a prolactinoma for which she was prescribed cabergoline 0.5 mg twice weekly. In addition, the chronic headaches, papilledema, enlarged blind spot, reduced visual acuity, and the bilateral abducent nerve palsies in the absence of an intracranial space occupying lesion that has a mass effect were supportive of the diagnosis of PTC. In view of her reduced visual acuity, and as the lumbar puncture (LP) and CSF pressure measurement could not be carried out straight away, treatment with acetazolamide 500 mg twice daily was started. Two weeks later the LP was performed. It revealed a CSF opening pressure of 27 mm Hg that was reduced to 10 mm Hg after draining 20 ml of normal CSF. She was maintained on acetazolamide

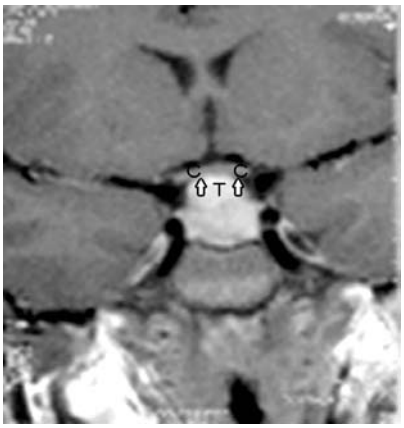

Figure 1 - Patient MRI at presentation, coronal T1 images with contrast showing a 1.5 x 1.2 cm cystic pituitary tumor with bright and heterogeneous signal, most likely reflecting either high protein content or previous hemorrhagic episode. The tumor (T, 2 arrows) appears to be touching the chiasm (C) but not significantly compressing it.

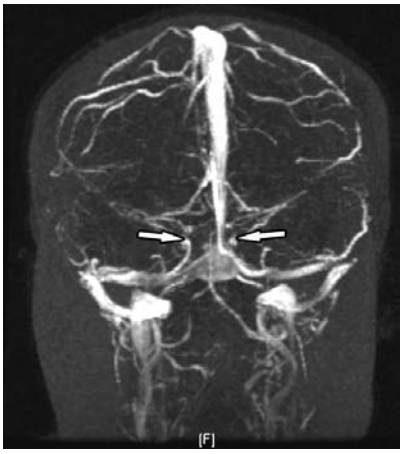

Figure 2 - The MR venography at presentation showing normal dural sinuses including the cavernous sinus (arrows).

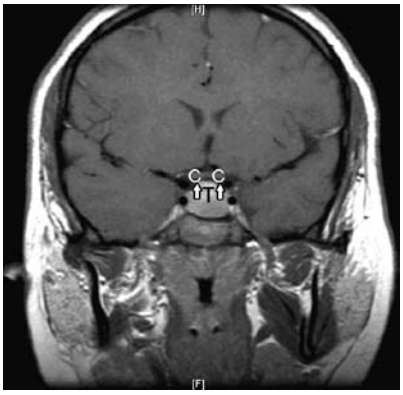

Figure 3 - Follow up MRI (coronal T1 images with contrast) after treatment with cabergoline, showing a slight reduction in the size of the pituitary adenoma. The tumour (T, 2 arrows) does not appear to reach the chiasm (C).

while her symptoms were slowly improving. Follow up MRI 2 months after starting cabergoline, showed a slight reduction in the size of the pituitary adenoma as the upper surface of tumor did not reach the level of the chiasm (**Figure 3**). At that time her serum prolactin level dropped to 36.4 ug/L and she reported regular periods and no galactorrhea. Her headaches, diplopia, and visual deterioration recurred 9 months later while she was taking acetazolamide and cabergoline. At that time she had a low serum prolactin level with no increase in the size of the prolactinoma on MRI. A CSF diversion in the form of a lumbo-peritoneal shunt was performed with good postoperative improvement. At 3 months follow up she remains well with no headaches or diplopia, and visual acuity of 6/18 bilaterally, and her fundoscopy shows improvement in the papilledema changes. She remains under follow up.

Discussion. Pseudotumor cerebri is an idiopathic disorder defined by the modified Dandy criteria[3] as: 1) Signs and symptoms of raised ICP (headache, nausea, vomiting, transient obscuration of vision, and papilledema. 2) Normal neurological examination, except for a sixth nerve palsy. 3) Elevated CSF pressure (>250 mm H_2O) with normal constituents. 4) Modern neuroimaging, CT with and without contrast, or MRI demonstrating normal to small symmetrical ventricles and excluding a mass lesion or other cause of raised ICP. Our patient's presenting symptoms and signs, CSF pressure measurements, response to acetazolamide, and later to lumbo-peritoneal shunting were all supportive of the diagnosis of PTC despite the presence of a small intrasellar pituitary tumor. Hence, our case demonstrates that the diagnosis of PTC should be considered in patients with small pituitary lesions and raised ICP features.

The mechanisms leading to PTC are likely to be decreased CSF absorption or elevated intracranial venous pressure. Some authors believe that elevated venous pressure is the universal mechanism even in patients without demonstrable venous outflow obstruction.[4] Other authors believe that the decrease in CSF absorption by the arachnoid villi is a secondary phenomenon that results from compression of the arachnoid villi by elevated ICP from any cause.[4] Our patient's MRV did not show any evidence of cavernous sinus compression by the pituitary tumor, and the PTC symptoms recurred despite a mild reduction in the size of the tumor. Such findings do not support an association between pituitary tumor and PTC, and it contradicts the suggestion made by Bjerre et al[2] in 1982 that PTC in patients with a pituitary tumor may be caused by bilateral compression of the cavernous sinuses. It is true that this assumption was made a long time ago, however, the improved diagnostic imaging of pituitary tumors using MRI, and the lack of reports that examined the link between PTC and prolactinoma in the post-MRI era justifies reporting this case.

The literature contains numerous drugs and diseases that are associated with PTC and are considered etiological factors. These include: the female gender and obesity, pregnancy, menstrual irregularities, oral progestational drugs, antibiotic therapy such as tetracycline and its synthetic relative minocycline, cryofibrinogenemia, hypervitaminosis A, and dural sinus thrombosis.[4] Pseudotumor cerebri is also reported to be associated with a number of endocrine disorders such as Addison's disease, hypoparathyroidism, hypothyroidism,[5] and hyperprolactinemia.[1] In addition, PTC is reported following the withdrawal of corticosteroids and the removal of an adrenocorticotropic hormone secreting pituitary adenoma,[6] withdrawal of non-ergot dopamine agonist,[7] and treatment with recombinant human growth hormone.[8]

It is not surprising that a number of the etiological factors associated with PTC may be viewed skeptically as they do not satisfy the modified Dandy criteria. The observation in our patient that the PTC symptoms recurred despite a normal serum prolactin level does not support an association between hyperprolactinemia and PTC. This seems a fair conclusion since for a drug to be truly associated, the patient must improve after removal of the drug and symptoms must recur if the drug were retaken. In addition, the pituitary function tests of our patient, apart from the presenting hyperprolactinemia, were normal. This is in agreement with the current understanding that PTC does not lead to long-term hypothalamic pituitary damage.

It has been shown that flattening of the posterior aspect of the globe is the only sign on cross-sectional imaging that, if present, strongly suggests the diagnosis of PTC.[9] It is still not clear whether the narrowing of the transverse and sigmoid dural sinuses that may be seen on MRV is a primary vascular venous disorder causing the PTC or rather the secondary effect of raised ICP on the cerebral veins.[9] Other reported radiographic findings in PTC include empty sella,[2] dilatation of the optic nerve sheaths, and slit-like ventricles.[10] The empty sella is thought to result from the chronically elevated ICP in association with a congenitally incompetent diaphragma sella. Its appearance can reverse after successful treatment of raised ICP in PTC.[10]

Treatment of patients with PTC aims to alleviate the symptoms and preserve the visual function. Our patient was started on acetazolamide, a carbohydrase inhibitor with proven ability to decrease CSF production. Her

symptoms appeared to be initially controlled with medical therapy. However, once the visual function began to deteriorate a lumbo-peritoneal shunt was performed. The patient is currently stable; however, other surgical options that can be considered if her vision worsens include optic nerve sheath fenestration. The normal MRV of our patient would imply that she was not a candidate for venous sinus stenting, which is reported to be of benefit to some PTC patients.[4] The management of the prolactinoma in our patient has been with the dopamine agonist cabergoline, with normalization of prolactin level and improvement in the hyperprolactinemia-related symptoms. In the circumstances, even with limited shrinkage of tumor size on MRI, trans-sphenoidal surgical excision has not been considered necessary and the patient is being followed up.

In conclusion, the association of PTC with so many conditions indicates that the mechanisms causing PTC may be multiple and may include genetic susceptibility. The observations that the PTC in our patient occurred in the absence of evidence of cavernous sinus compression by the pituitary tumor indicate that the occurrence of the PTC with the pituitary tumor in our case was probably coincidental rather than an association. The observations that the PTC recurred despite a normal prolactin level indicate that the occurrence of the PTC with the hyperprolactinemia in our case was probably coincidental rather than an association. In addition, our case also supports existing practices in recommending that PTC should be considered in patients with papilledema and visual deterioration in the presence of a small sellar pituitary tumor.

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References

1. Goldman M, Rabin A. Case report: hyperprolactinemia in a patient with pseudotumour cerebri. ***J Med Soc N J*** 1984; 81: 501-502.
2. Bjerre P, Lindholm J, Gyldensted C. Pseudotumour cerebri. A theory on etiology and pathogenesis. ***Acta Neurol Scand*** 1982; 66: 472-481.
3. Dandy WE. Intracranial pressure without brain tumour: Diagonosis and treatment. ***Ann Surg*** 1937; 106: 492-513.
4. Owler BK, Parker G, Halmagyi GM, Dunne VG, Grinnell V, McDowell D, et al. Pseudotumour cerebri syndrome: venous sinus obstruction and its treatment with stent placement. ***J Neurosurg*** 2003; 98: 1045-1055.
5. Azar ST, Sandid MS, Assi MA, Zantout MS. Improved pituitary function after V-P shunt insertion in pseudotumour cerebri. ***Endocr Res*** 2001; 27: 303-307.
6. Parfitt VJ, Dearlove JC, Savage D, Griffith HB, Hartog M. Benign intracranial hypertension after pituitary for Cushing's disease. ***Postgrad Med J*** 1994; 70: 115-117.
7. Atkin SL, Masson EA, Blumhardt LD, While MC. Benign intracranial hypertension associated with withdrawal of a non-ergot dopamine agonist. ***J Neurol Neurosurg Psychiatry*** 1994; 57: 371-372.
8. Francois I, Casteels I, Silberstein J, Casaer P, de Zegher F. Empty sella, growth hormone deficiency and pseudotumour cerebri: effect of initiation, withdrawal and resumption of growth hormone therapy. ***Eur J Pediatr*** 1997; 156: 69-70.
9. Agid R, Farb RI. Neuroimaging in the diagnosis of idiopathic intracranial hypertension. ***Minerva Med*** 2006; 97: 365-370.
10. Zagardo MT, Cail WS, Kelman SE, Rothman MI. Reversible empty sella in idiopathic intracranial hypertension: an indicator of successful therapy. ***AJNR Am J Neuroradiol*** 1996; 17: 1953-1956.

CASE REPORTS

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.