Practice points

- Cabergoline is more efficacious and better tolerated than bromocriptine and generally should be considered as first-line therapy for patients with hyperprolactinemia
- The cost of cabergoline is usually higher than that of bromocriptine, which can influence the choice of therapy
- Both drugs appear to be safe for use in the early part of pregnancy, although the safety database for bromocriptine is 10-fold larger than that for cabergoline
- In patients who require greater than standard doses, cabergoline may pose a small risk for cardiac valvular abnormalities, and surveillance echocardiographic monitoring may be indicated

Nunes *et al.* and clinical experience all point to cabergoline as being more efficacious and better tolerated than bromocriptine in the treatment of patients with prolactinomas. Only three areas of concern remain. First, when larger than standard doses are used, the risk of potential cardiac valvular abnormalities is probably higher with cabergoline than bromocriptine. Second, for women who wish to conceive, both drugs appear to be safe, but the safety database is 10-fold larger for bromocriptine than for cabergoline. Finally, the cost of cabergoline remains higher than that of bromocriptine. In the US, generic bromocriptine costs US$124 for 60 tablets of 2.5 mg, whereas generic cabergoline costs $266 for 8 tablets of 0.5 mg, although some would argue that most patients can be treated with just one tablet per week of cabergoline, thus reducing the cost to only $133 per month.

What does this all mean to the clinician? What should I advise my colleague who is still prescribing bromocriptine? My conclusion and recommendation is that cabergoline should be the initial dopamine agonist prescribed. I generally use one tablet of 0.5 mg per week of cabergoline as a starting dose, which is usually successful. If a larger dose is necessary, then an increased dose of bromocriptine would potentially also have been necessary, or bromocriptine might not have been effective, and the patient would be switched to cabergoline anyway. I only perform surveillance echocardiograms if the dose of cabergoline is higher than 2 mg per week, a dose required in less than 10% of my patients but up to 18% of those treated by Ono *et al.*[5] In other words, the meta-analysis of Dos Santos Nunes *et al.* simply confirms what I have been doing for many years.

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Competing interests
The author declares no competing interests.

1. Dos Santos Nunes, V., El Dib, R., Boguszewski, C. L. & Nogueira, C. R. Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis. *Pituitary* doi:10.1007/s11102-010-0290-z.
2. Gillam, M. P., Molitch, M. E., Lombardi, G. & Colao, A. Advances in the treatment of prolactinomas. *Endocr. Rev.* **27**, 485–534 (2006).
3. Colao, A. *et al.* Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. *J. Clin. Endocrinol. Metab.* **82**, 876–883 (1997).
4. Iyer, P. & Molitch, M. E. Positive prolactin response to bromocriptine in two patients with cabergoline resistant prolactinomas. *Endocr. Pract.* doi:10.4158/EP10369.CR
5. Ono, M. *et al.* Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J. Clin. Endocrinol. Metab.* **93**, 4721–4727 (2008).
6. Molitch, M. E. The cabergoline-resistant prolactinoma patient: new challenges. *J. Clin. Endocrinol. Metab.* **93**, 4643–4645 (2008).
7. Dekkers, O. M. *et al.* Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **95**, 43–51 (2010).
8. Molitch, M. E. Prolactinomas and pregnancy. *Clin. Endocrinol. (Oxf.)* **73**, 147–148 (2010).
9. Smith, G. C. & Pell, J. P. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* **327**, 1459–1461 (2003).
10. Lewiecki, E. M. & Binkley, N. Evidence-based medicine, clinical practice guidelines, and common sense in the management of osteoporosis. *Endocr. Pract.* **15**, 573–579 (2009).

AUTOIMMUNITY

Acquired versus inherited pituitary deficiency—same difference?

Jacques Drouin and Shinobu Takayasu

Mutations in genes encoding transcription factors that control pituitary development cause early-onset pituitary hormone deficiencies. Now, circulating antibodies against one such factor, PIT1, have been identified as being responsible for hormone deficits and pituitary cell loss similar to those caused by mutations of its gene *POU1F1* but with a late onset.

Drouin, J. & Takayasu, S. *Nat. Rev. Endocrinol.* **7**, 255–256 (2011); published online 22 March 2011; doi:10.1038/nrendo.2011.53

In contrast to early-onset conditions—predominantly inherited forms of either isolated or combined pituitary hormone deficiencies (CPHD)—the etiology of late-onset pituitary hormone deficiency remains poorly defined.[1] Acquired pituitary deficiencies have been broadly associated with autoimmune hypophysitis, sometimes within the context of the autoimmune polyglandular syndromes (APS).[2] The recent characterization[3] of three patients with antibodies against the pituitary-specific positive transcription factor 1 (PIT1) and the association of this antibody with pituitary cell loss and hormone deficiency provides a molecular basis for specific pituitary hormone disorders. Furthermore, these patients constitute a late-life model of similar deficiencies observed in young carriers of mutations in *POU1F1*, the gene that encodes PIT1.

Consistent with the role of the pituitary as the master gland of the endocrine system, pituitary hormone deficiencies have dire consequences on multiple organ systems. Over the past two decades, the discovery of critical regulators of pituitary function has also led to the implication of the genes encoding these factors in inherited forms of pituitary hormone deficiencies. Indeed, genetic forms of isolated hormone deficiencies, as well as of CPHD, have been associated with mutations in genes that encode transcription factors involved in pituitary organogenesis, cell differentiation and/or cell-specific functions.[1] Inherited pituitary hormone deficiencies typically present with early onset, often owing to the loss of corresponding pituitary cells. For example, isolated adrenocorticotropic hormone (ACTH) deficiency, which is caused by mutations in the gene encoding

the corticotroph-restricted T-box transcription factor TPIT, typically leads to neonatal death if untreated.[4,5] By contrast, growth hormone (GH) deficiency, whether isolated or associated with CPHD, will manifest itself as reduced growth during childhood.

The inherited forms of CPHD have been linked to mutations in genes involved in pituitary organogenesis (such as the *LHX3*, *LHX4* and *PROP1* genes) and/or genes that encode factors involved in the differentiation of a subset of pituitary cell lineages, for example, the PIT1 transcription factor that is required for differentiation of cells that secrete GH, prolactin or TSH. Of these affected genes, mutations in *PROP1* are most often associated with CPHD, and in patients with these mutations, hormone deficiencies may become more severe with age.

> “...re-evaluation of patients with CPHD for autoimmune antibodies might be warranted...”

Similar to *POU1F1* mutations, which cause GH, prolactin and TSH deficiency early in life, *PROP1* mutations typically affect differentiation of the same cell lineages and hormones; however, *PROP1* mutations are also associated with progressive loss of other hormones. As indicated by its name ‘prophet of Pit1’, PROP1 activates *POU1F1* gene expression, the loss of which perturbs pituitary differentiation of PIT1-dependent lineages (prolactin, GH, TSH).[6] PROP1 mutations also affect pituitary organogenesis; progression of PROP1-dependent CPHD is thus variable and also involves loss of gonadotropins and, later in life, of ACTH.[7] Only a fraction of cases of CPHD have so far been ascribed to mutations in known genes. Hence, in many instances the cause of CPHD remains unknown.

Late-onset CPHD is not usually associated with mutations in the genes known to cause congenital CPHD, and its etiology remains largely to be elucidated. The recent investigation by Yamamoto *et al.* of three adult patients with late-onset CPHD, which affected GH, prolactin and TSH levels, revealed a different cause for this triple pituitary deficiency that resembles the CPHD associated with mutations in the *POU1F1* gene. Mutations previously associated with CPHD were excluded in these patients, who otherwise exhibited relatively normal ACTH and gonadotropin function. Moreover, all three patients showed normal growth and had no sign of pituitary deficiencies earlier in life.

All three patients were found to have serum antibodies against the PIT1 protein. Although the patients presented with other signs of autoimmune disease, the PIT1 antibodies were the most abundant against pituitary epitopes. Immunohistochemical analysis of the pituitary gland from one patient who died accidentally revealed an absence of cells stained positive for PIT1, GH, prolactin or TSH, with normal distribution of cells positive for ACTH, luteinizing hormone and follicle-stimulating hormone. Apparently, the serum PIT1 antibodies led to the loss of PIT1-expressing cells, a finding corroborated by the presence of pituitary lymphocytic infiltrations. Whether the anti-PIT1 antibodies were the primary cause of pituitary cell destruction or whether this phenomenon occurred secondary to another autoimmune reaction that could not be detected in the present study is unclear at this point. Be that as it may, the consequence of this autoimmune reaction was a form of CPHD that resembles the loss of GH, prolactin and TSH caused by mutations of the *POU1F1* gene.

Pituitary antibodies are detected in a number of autoimmune conditions, including hypophysitis; however, the three patients in the study by Yamamoto *et al.* appear to be unique in having serum anti-PIT1 antibodies. The three patients showed other clear evidence of autoimmune disease and symptoms, such as various autoantibodies, adrenalitis or gastritis, that are compatible with APS.[2] Nonetheless, at present, why these specific patients developed anti-PIT1 antibodies remains unanswered. The investigators identified a new cause of cell-restricted pituitary hormone deficiencies that is very similar to PIT1-dependent congenital CPHD. The striking specificity of the pituitary cell death observed in one patient suggests that a re-evaluation of patients with CPHD for autoimmune antibodies might be warranted for those without detectable mutations. Research into autoimmune reactions against PIT1 and other cell-restricted pituitary proteins or transcription factors such as PROP1 or TPIT will certainly be stimulated by the recent discovery of anti-PIT1 antibodies. The mechanism responsible for cell loss in the presence of circulating antibodies against nuclear transcription factors remains undeciphered and demands further investigation.

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Competing interests
The authors declare no competing interests.

1. Kelberman, D., Rizzoti, K., Lovell-Badge, R., Robinson, I. C. & Dattani, M. T. Genetic regulation of pituitary gland development in human and mouse. *Endocr. Rev.* **30**, 790–829 (2009).
2. Michels, A. W. & Gottlieb, P. A. Autoimmune polyglandular syndromes. *Nat. Rev. Endocrinol.* **6**, 270–277 (2010).
3. Yamamoto, M. *et al.* Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans. *J. Clin. Invest.* **121**, 113–119 (2011).
4. Pulichino, A. M. *et al.* Human and mouse TPIT gene mutations cause early onset pituitary ACTH deficiency. *Genes Dev.* **17**, 711–716 (2003).
5. Vallette-Kasic, S. *et al.* Congenital isolated adrenocorticotropin deficiency: an underestimated cause of neonatal death, explained by TPIT gene mutations. *J. Clin. Endocrinol. Metab.* **90**, 1323–1331 (2005).
6. Sornson, M. W. *et al.* Pituitary lineage determination by the Prophet of Pit-1 homeodomain factor defective in Ames dwarfism. *Nature* **384**, 327–333 (1996).
7. Vallette-Kasic, S. *et al.* PROP1 gene screening in patients with multiple pituitary hormone deficiency reveals two sites of hypermutability and a high incidence of corticotroph deficiency. *J. Clin. Endocrinol. Metab.* **86**, 4529–4535 (2001).