Does Pituitary Stalk Compression Cause Hyperprolactinemia?

Accepted thinking has been that all adenohypophyseal hormones are under stimulatory control of hypothalamic-releasing factors except for prolactin, which is believed to be controlled by an inhibitory factor, dopamine. If the hypothalamic factors are denied access through interruption of the portal circulation, which occurs when the stalk is damaged, prolactin secretion increases and that of the other pituitary hormones falls (7,14). The hyperprolactinemia found in association with pituitary tumors that do not secrete prolactin or with other space-occupying lesions such as craniopharyngiomas, metastases, and the like is believed to be due to pressure on the pituitary stalk, which then deprives the normal prolactin-secreting cells of adequate inhibition (3,6,9,11). How tenable is this supposition?

First of all, do tumors pressing on the stalk interrupt the portal circulation? As the adenohypophysis relies for its blood supply on the portal circulation (8), experimental stalk section leads to extensive infarction (2). Slowly growing tumors may be associated with neovascular channels, which might explain the rarity of infarction. The "stalk-related" hyperprolactinemia is not necessarily paralleled by hyposecretion of other pituitary hormones nor is it associated with evidence of diabetes insipidus. Furthermore, it is very likely that reverse flow of prolactin along the portal vessels is at least partially responsible for its suppressive effect on gonadotropin-releasing hormone.

It has been suggested that raised intrasellar pressure due to pituitary tumors or other space-occupying lesions might compress the long portal vessels and cause interruption of blood flow (8). Although there may be a two- to threefold rise in intrasellar pressure, there is no correlation with serum prolactin levels; nevertheless, two-thirds of the patients studied showed mild hyperprolactinemia.

Recently, compelling evidence has been presented for the presence of prolactin-releasing factors that could be responsible, at least in part, for the hyperprolactinemia found in this group of patients. Thyrotropin-releasing hormone (TRH) causes prolactin release, but its physiological role is unclear: Prolactin release is not impaired in hyperthyroidism in which TRH is probably suppressed, but the hyperprolactinemia found in association with primary hypothyroidism is most probably related to TRH excess, although hypothalamic dopamine depletion may also play a role. Vasoactive intestinal polypeptide (VIP) is a 28–amino acid peptide that is synthesized in the paraventricular region of the hypothalamus and that has a marked prolactin-releasing effect. It is secreted as a prohormone, which also contains a 27–amino acid peptide, called peptide histidine methionine (PHM 27) (13). PHM, like VIP, is a member of the secretin-glucagon group of peptides and has a wide distribution in various tissues including the hypothalamus and pituitary stalk, paralleling that of VIP. It too has potent prolactin-releasing activity. The physiological role of these two closely related peptides is still unclear. In animal experiments, destruction of the VIP-secreting cells causes decreased prolactin cell responsiveness to various stimuli such as 5-hydroxytryptophan, which is a serotonin precursor (12). The prolactin rise in response to stress, related to adrenergic effects, is also blocked. VIP (and probably PHM 27) is also secreted by the pituitary. Addition of blocking antibodies inhibits prolactin release in tissue culture (12). Its function is probably a paracrine one, modulating prolactin release.

Beta-endorphin too has a potent prolactin-releasing effect. It is present in pituitary corticotrophs and may exert a paracrine stimulatory effect on lactotrophs to account for the hyperprolactinemia frequently found in association with Cushing's disease (4), although it may also cause hypothalamic dopamine depletion. Posterior pituitary beta-endorphin rises after stalk section and appears

to be inhibited by dopamine (5). Its role in prolactin secretion is unclear, especially as the prolactin-releasing activity of posterior pituitary extracts following stalk section diminishes by up to 90% (5). Another small peptide with potent prolactin-releasing properties was found in the posterior pituitary, but its structure has not yet been elucidated (5). Arginine vasopressin, oxytocin, and neurotensin cause prolactin release provided only that the hypothalamus-pituitary flow is intact. Recently, galanin has been found to inhibit hypothalamic dopamine, causing prolactin release, but it can also act as a direct prolactin releaser after intraventricular injection, as demonstrated in rats (15). In this species, estrogens may stimulate galanin gene expression in both hyperplastic lactotrophs and prolactin-secreting adenomas and may therefore have a role in the induction and maintenance of the "stalk pressure effect."

Growth factors may also play an important part in prolactin secretion. Epidermal growth factor (EGF) increases prolactin gene expression, reduces growth hormone (GH) synthesis in GH_3 and GH_4 cells, and is produced by some pituitary tumors (15). However EGF receptors are absent in prolactin- and GH-secreting and nonsecreting pituitary tumors (1).

Lastly, suckling induces a prompt sustained prolactin release that appears to be under posterior pituitary control, presumably by a fraction of the propressorphysin prohormone (12).

From the clinical point of view, the correlation between size and secretory activity is a useful guideline (10). Prolactin values greater than approximately 150–200 μg/L are almost always associated with prolactin-secreting tumors. The larger the tumor and the more invasive, the higher is the serum prolactin level (2,3). Some of the immunoreactive prolactin secreted, however, may be biologically inert, and so the clinical picture may be that of a nonfunctioning tumor.

What of those patients having serum prolactin levels below 150–200 μg/L? Those with large tumors probably do not have a prolactin-secreting adenoma; however, prompt tumor shrinkage in response to a dopamine agonist would make the diagnosis likely. No provocative tests thus far have distinguished prolactin-secreting tumors from hyperprolactinemic states not caused by this tumor type.

The precise role of the various prolactin-modulating factors still needs to be elucidated and is likely to clarify the mechanism of the frequent prolactin elevations not associated with radiological lesions as well as those associated with non-prolactin-secreting tumors. It is unlikely that stalk pressure alone is the mechanism explaining the serum prolactin elevations found in association with non-prolactin-secreting pituitary tumors.

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