Editorial: The Macroprolactin Problem

Human prolactin (PRL) is synthesized as a prehormone with a molecular weight of 26,000 kDa. When the preprolactin is cleaved, the resulting polypeptide has a molecular weight of 23,000 kDa, and this monomeric form accounts for the majority of total PRL. Serum also contains a 50,000-kDa form that is termed big PRL and another species with a molecular weight of greater than 100,000 kDa, which is termed big big PRL. In general, big big PRL consists of an antigen antibody complex of monomeric PRL and IgG (1). When the serum of a patient with hyperprolactinemia contains mostly big big PRL the condition is termed macroprolactinemia. Macroprolactinemia has been recognized for many years and is suspected when a patient with hyperprolactinemia lacks typical symptoms and/or has no radiographic evidence of a pituitary tumor (2, 3).

Macroprolactinemia is seen in both sexes and in children, and increases in big big PRL occur during pregnancy due to binding of PRL to specific autoantibodies. The incidence of macroprolactinemia in patients with hyperprolactinemia ranges from 18-42% when samples from reference laboratories are assayed (4-6). In contrast, the incidence of macroprolactinemia in patients from an endocrinology practice is closer to 10% (7). Because reference laboratories routinely analyze samples for confirmation of unexpectedly high PRL levels, it is not surprising that macroprolactinemia is more frequent in that situation. Whereas the incidence of macroprolactinemia is not known precisely, the condition is more common than previously recognized.

Whether macroprolactin is biologically active is controversial. The earliest studies showed no activity in the NB2 lymphoma cell bioassay, but more recent studies have demonstrated normal bioactivity of big big PRL in the NB2 assay. If big big PRL is biologically active, the effects may be blunted because of decreased bioavailability. The large PRL-Ig complex may fail to reach receptors because of limited capacity to cross-vascular endothelium. Although many patients with macroprolactinemia lack typical symptoms of an elevated PRL, in addition to the monomeric form. In these cases, gel filtration chromatography would be necessary to confirm the presence of macroprolactinemia.

Equipment manufacturers and clinical laboratories need to clearly characterize their assays with respect to macroprolactin and provide a procedure for detection of big big PRL. Whereas PEG precipitation is simple and could be widely used, not all instrumented assays may be compatible with serum treated in this fashion. It is also vital that laboratories publicize their assay characteristics and that clinicians understand the limitations and variability of the assays.

Abbreviations: PEG, Polyethylene glycol; PRL, prolactin.

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tient with no clinical suspicion of hyperprolactinemia could obviate the need for a pituitary magnetic resonance imaging or other testing.

Smith et al. (10) also noted that some patients with macroprolactinemia have elevated levels of monomeric PRL and suggest that the diagnosis of macroprolactin be used only when a PRL level falls to a level seen in sera from normoprolactinemic subjects treated with PEG. Although this would help ascertain whether an excess of monomeric PRL is present along with macroprolactin, it would require establishment of new reference ranges for all PRL assays.

Macroprolactinemia is a common cause of hyperprolactinemia, the recognition of which could obviate the need for extensive diagnostic testing in some patients. Commercial and hospital laboratories must develop techniques to detect and report the presence of macroprolactin.

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