Autonomous secretion of prolactin (PRL) by a pituitary prolactinoma is a relatively common endocrine disorder characterized by increased serum concentrations of PRL and symptoms of menstrual irregularity, infertility, and galactorrhea in women and impotence and lack of libido in men (1). These clinical symptoms are common, and measurement of serum PRL is a key investigation used to identify the minority of patients who have hyperprolactinemia and warrant further investigation and who may benefit from treatment with dopamine agonists. Unfortunately, the laboratory finding of hyperprolactinemia is not specific because increased serum immunoreactive PRL may be caused by the presence of a high-molecular-mass complex of PRL (macroprolactin), which has been found in asymptomatic patients (2) and therefore appears to lack the biological activity associated with the normal, monomeric 23-kDa form of PRL. This problem is compounded by the limited sensitivity and specificity of pituitary imaging techniques in the confirmation of prolactinoma (1).

The report by Suliman et al. (3) in this issue carries two messages of considerable importance for clinical chemists: (a) hyperprolactinemia attributable to macroprolactin is a frequent cause of misdiagnosis and mismanagement of patients; and (b) this problem could be avoided if laboratories applied a screening test to all samples with increased total serum PRL to detect the presence of macroprolactin and reported a measure of the bioactive, monomeric PRL concentration.

Using gel-filtration chromatography (GFC), Suh and Frantz (4) demonstrated nearly 30 years ago that minor proportions of the total serum immunoreactive PRL circulate as high-molecular-mass forms, which are referred to as big PRL (40–60 kDa) and big-big or macroprolactin (150–170 kDa). Hyperprolactinemia attributable to a predominance of the fraction with the highest molecular mass was observed by Andersen et al. (5) in a patient complaining of infertility who subsequently conceived spontaneously. Andersen et al. (5) demonstrated the bioactivity of the macroprolactin component in vitro and suggested that the absence of bioactivity in vivo might be a result of the high molecular mass of the complex preventing passage through the capillary endothelium to reach target receptors. In the same year (1982), Soong et al. (6) reported a study of the size heterogeneity of serum PRL in a series of patients with hyperprolactinemia and identified a group in which this was attributable to macroprolactin. Soong et al. (6) observed that the patients in this group did not have the classic symptoms of the hyperprolactinemic syndrome and were unlikely to respond to treatment with bromocriptine; noting that this treatment was not without side effects, they recommended that such patients be identified in clinical practice.

Because the clinical confusion that can be caused by hyperprolactinemia attributable to macroprolactin has been recognized for some considerable time, it may seem surprising that testing for hyperprolactinemia attributable to macroprolactin is not commonplace in clinical laboratories. Some progress with methodology has been made based on increasing knowledge of macroprolactin, but testing is not common outside the United Kingdom and Ireland (7). This may be because clinical chemists are unsure of the best policy to adopt when there is continuing debate about the in vivo bioactivity of macroprolactin and its clinical importance (8). The controversy is largely a result of the finding of substantial numbers of patients with hyperprolactinemia attributable to macroprolactin and symptoms of the hyperprolactinemic syndrome (9). Suliman et al. (3) argue that the symptoms and hyperprolactinemia attributable to macroprolactin in these cases are coincidental, whereas Olukoga (8) suggests that the macroprolactin complex may dissociate in vivo in some cases, releasing bioactive, monomeric PRL that causes the symptoms. The issue of the in vivo bioactivity of macroprolactin is fundamental to the conclusions of Suliman et al. (3) and the testing policy they advocate and the relevant evidence therefore merits further consideration.

There is good evidence that macroprolactin does not affect the control of pituitary PRL secretion via the short loop feedback mechanism or the secretion of gonadotropins as does monomeric PRL in cases of prolactinoma. In cases of hyperprolactinemia attributable to macroprolactin, the responses of pituitary secretion of monomeric PRL and thyroid-stimulating hormone to dopamine antagonists (10, 11) are normal and the frequency distribution of the concentration of serum monomeric PRL is similar to that of total PRL in the whole population (12). In the series tested by Suliman et al. (3), serum estradiol and luteinizing hormone were significantly higher in the group with hyperprolactinemia attributable to macroprolactin than in the group with increased monomeric PRL. Furthermore, as also noted by Soong et al. (6), suppression of the hyperprolactinemia with dopamine agonists had little effect on the symptoms of menstrual irregularity in the group with hyperprolactinemia attributable to macroprolactin but led to a substantial improvement in the group with increased monomeric PRL.

Macroprolactin has not been found in pituitary tissue (13), the culture medium of pituitary tissue (9), or in the extravascular space (cerebrospinal fluid) (13) of cases of hyperprolactinemia attributable to macroprolactin. After pituitary stimulation or suppression with dopamine antagonists or agonists, the increase or decrease in serum monomeric PRL is followed by slower, similar changes in macroprolactin concentration (11, 14). Macroprolactin thus appears to be formed in and confined to the vascular compartment, as envisaged by Andersen et al. (5). In the clearance of macroprolactin, it is not known whether the whole complex is removed from circulation or it first dissociates to release monomeric PRL, as suggested by
Olukoga (8). However, the macroprolactin complex is stable in vitro and does not readily dissociate, e.g., during GFC or in the presence of the high-affinity anti-PRL antibodies used in some assay systems that show minimal reactivity with most forms of macroprolactin. If dissociation does occur in vivo, it seems unlikely to be a process that would cause the symptoms of the hyperprolactinemic syndrome.

Data on the detection of macroprolactin as a substantial component of the total PRL in different populations are also relevant to the debate. In a population of 955 patients whose symptoms prompted a request for measurement of serum PRL, increased results (>700 mIU/L) were found in 71 (7.4%), and the hyperprolactinemia was found to be attributable to macroprolactin in 14 (20%) of the 69 cases investigated further (15). The data presented in this way emphasize that macroprolactin is a common cause of hyperprolactinemia but obscure the fact that the prevalence of hyperprolactinemia attributable to macroprolactin in this population as a whole was ~1.5% (14 of 955).

Macroprolactin has been detected with similar prevalences as a major component of the total PRL in populations with hyperprolactinemia ascribed to other causes, e.g., pregnancy (2.7%) (16), drugs (4.8%) (17), and prolactinoma (2.7%) (17), and in populations without hyperprolactinemia (1.3%) (17).

To summarize, there is a substantial body of evidence indicating that macroprolactin is a random phenomenon found in many populations in which it may cause or contribute to hyperprolactinemia, but it is not bioactive in vivo and is not related to symptoms of the hyperprolactinemic syndrome.

The clinical importance of macroprolactin is that it may cause hyperprolactinemia, leading to clinical confusion and inappropriate management as described by Suliman et al. (3), and it is therefore important to identify such cases. Measurement of the recovery of serum PRL after precipitation with polyethylene glycol (PEG) has been most extensively used for the detection of macroprolactin in cases with hyperprolactinemia, but it has become clear that macroprolactin may be present in substantial quantities in conjunction with increased monomeric PRL from a prolactinoma or other cause; it is therefore necessary not only to detect the presence of macroprolactin but also to determine the concentration of the monomeric PRL component (3, 7). It has been suggested that because recovery of PRL after PEG precipitation correlates with the quantity of macroprolactin present, an estimate of monomeric PRL may be obtained by determining recovery after PEG precipitation and interpolation from the correlation (7). Suliman et al. (3) advocate an attractively simple, alternative approach using PRL after PEG precipitation as a measure of the monomeric PRL and comparison with values obtained by treating serum from healthy individuals with PEG. The group of individuals studied by Suliman et al. (3) and defined as having hyperprolactinemia attributable to macroprolactin by their approach appear to be rather clear-cut cases; they were selected on the basis of relatively high total PRL (>1000 mIU/L) and had clearly low recovery of PRL after PEG precipitation, indicating that macroprolactin was present as a major component of the total serum PRL. GFC was not used to provide independent confirmation of the presence of macroprolactin or determination of the monomeric PRL component but would probably not have led to a different interpretation in these cases. However, as Suliman et al. (3) point out, PEG precipitation and GFC give different estimates of monomeric PRL because some monomeric PRL is coprecipitated with serum proteins by PEG. It is likely that PEG also precipitates big PRL to some extent. The in vivo bioactivity of big PRL is not known, and it is usually a minor component of the total PRL; in cases of modest hyperprolactinemia, however, macroprolactin may be a minor component and big PRL a relatively major fraction. It would be valuable to extend the clinical study of Suliman et al. (3) to such cases and compare definitions of hyperprolactinemia attributable to macroprolactin determined by PEG precipitation with those determined by GFC. Further work is also required to validate PEG precipitation as a measure of the monomeric PRL with PRL assays that react less strongly with most forms of macroprolactin than the DELFIA assay used by Suliman et al. (3) and to investigate the technique with PRL assays in which PEG interferes and a different analytical approach may still be required (7).

The essential message of Suliman et al. (3) should not become obscured by discussion of details; currently available information indicates that clinical chemists could contribute to improving patient care and the best use of health service resources by introducing testing protocols to detect hyperprolactinemia attributable to macroprolactin.

References


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