

## Macroprolactinemia: an unnoticeable factor

Hyperprolactinemia most commonly results from physiologic or pathologic conditions that cause hypersecretion of PRL by lactotroph cells. Physiologic causes include pregnancy and lactation while pathologic hyperprolactinemia may result from a lactotroph adenoma or from several readily identifiable causes that may interfere with normal dopamine inhibition of PRL secretion. However, in some patients whose serum PRL concentration may remain elevated for many years no cause can be found despite an extensive clinical, hormonal, and neuroradiological workup<sup>1</sup>. A subset of such patients may harbor microprolactinomas that are left undetected by current imaging techniques or may present another cause of hyperprolactinemia, described by Jackson et al.<sup>2,3</sup> as macroprolactinemia.

In human serum, three main species of PRL have been identified by gel filtration chromatography. These are monomeric PRL (molecular mass 23 kDa), big PRL (molecular mass 50-60 kDa), and big big PRL or macroprolactin (molecular mass 150-170 kDa)<sup>4</sup>. In most normal individuals and in the majority of patients with hyperprolactinemia, monomeric PRL is the major circulating form. However, it has been known for many years that in some patients with hyperprolactinemia, macroprolactin or big big PRL predominates. The structure of macroprolactin has yet to be fully defined with various molecular forms having been described. Earlier studies reported an oligomeric form of little PRL whereas more recent work described macroprolactin as a complex of monomeric PRL with an IgG antibody (antiprolactin autoantibody)<sup>5-8</sup>.

Whether macroprolactin is biologically active is still controversial. Recent studies have demonstrated normal bioactivity of big big PRL but its biological effect 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,

there are reports of patients with macroprolactinemia who present with amenorrhea, galactorrhea, and infertility<sup>9,11</sup>. The frequency and clinical consequences of macroprolactinemia have not been clearly established, mainly because of difficulty in identifying these patients. Laboratories do not differentiate routinely between the different forms of PRL because the use of gel filtration chromatography, a labor-intensive, expensive technique is required. Recently, a screening test using polyethylene glycol (PEG), to precipitate large molecular mass proteins, has been used to identify the presence of macroprolactin in serum.

The incidence of macroprolactinemia is not known precisely. The incidence of macroprolactinemia in every day clinical practice is around 10%<sup>9</sup>, significantly lower than its incidence (18-42%) in patients with hyperprolactinemia when samples are assayed from reference laboratories<sup>10-12</sup> for confirmation of unexpectedly high PRL levels. Macroprolactinemia is seen in both sexes and in children as well as during pregnancy<sup>13</sup>.

Macroprolactin, if present in serum, is precipitated by PEG leaving reduced levels in the supernatant<sup>11,14,15</sup>. A percentage recovery of 40% or less in the supernatant is very sensitive for detecting significant amounts of macroprolactin<sup>11,12</sup>. Values between 40% and 60% are ambiguous and, in these cases, gel filtration chromatography would be necessary to confirm the presence of macroprolactinemia. However, the significant variation of macroprolactin detection with commonly used PRL immunoassays<sup>16,17</sup> should be noted. Differences in cross-reactivity due to the nature of the macroprolactin-autoantibody complex, which may mask epitopes that are recognized by the antibodies of the assay, may explain this discrepancy. Immunoassays with minimal cross-reactivity with macroprolactin are advised but it is unlikely that all PRL determinations could be done using only those assays. It would be better for laboratories to develop the

method of PEG to screen all samples with elevated PRL for the presence of macroprolactin.

Of great interest is the possible association of macroprolactinemia with pituitary lesion. Vassilatou et al., in this issue of "Hormones" present a young man with macroprolactinemia and an MRI imaging suspicious for microadenoma. When macroprolactinemia coexists with an evidence of a pituitary microadenoma it is sometimes difficult to resolve whether the tumor is prolactin-secreting, contributing to raised serum prolactin, or nonfunctioning. This is especially important taking into account that approximately 10% of healthy subjects have radiographic evidence of a pituitary adenoma<sup>9</sup>. Macroprolactinemia has been described in cases of histologically confirmed pituitary adenomas<sup>9</sup> but most of the patients with macroprolactinemia have normal radiographic results. Furthermore, persistent hyperprolactinemia has been observed after a successful surgical removal of a pituitary microadenoma.

Hence, macroprolactinemia is a cause of hyperprolactinemia, which is usually overlooked, and causes diagnostic confusion. In cases of hyperprolactinemia without identifiable cause, or gonadal dysfunction, and in persisting hyperprolactinemia despite appropriate medical or surgical treatment, a search for macroprolactin constitutes a useful diagnostic step.

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