LETTER TO THE EDITOR

All the studies on hyperprolactinemia should not forget to consider the possible presence of macroprolactinemia

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Prolactin (PRL) in human serum has been classified into three main species on the basis of molecular mass: monomeric PRL, big PRL and big, big PRL (bb-PRL), called 'macroprolactin', with molecular masses of 23 kDa, 50–60 kDa and 150–170 kDa respectively (1). Although the nature of bb-PRL is heterogeneous, the most common form of macroprolactin is a complex of PRL and immunoglobulin G (2, 3). Most patients with macroprolactinemia do not show any clinical symptoms of hyperprolactinemia, such as amenorrhea, galactorrhea and infertility, despite high hyperprolactinemic levels and they do not need specific treatment (4–6).

Macroprolactin is recognized, in various degrees, by immunoassays for PRL (6, 7) and has a slower clearance from serum than PRL, causing diagnostic confusion in evaluating hyperprolactinemic conditions. The incidence of macroprolactinemia ranges from 15% up to 26% of all hyperprolactinemic sera (4, 5) and represents the main cause of interassay variability for PRL dosage (7).

Methods for big and bb-PRL detection are gel filtration chromatography, sensitive and specific but expensive (1), and polyethylene glycol (PEG) precipitation, a screening test for bb-PRL, not applicable to all immunometric assays (5, 6, 8).

In their interesting work 'Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia' (9), Colao *et al.* seem not to have evaluated the possibility of macroprolactinemia being a cause of hyperprolactinemia among their patients. Considering the very high PRL levels and the numerous clinical manifestations, macroprolactinemia is very unlikely in the 'macroprolactinoma' groups, but it cannot be excluded in either the 'microprolactinoma' or the 'non-tumoral' groups. Interestingly, 24% and 20% of the women included in the latter two groups, respectively, did not show menstrual disturbances (i.e. they were eumenorrhoeic) and this is very suggestive of macroprolactinemia.

In our recent study (10), we noted that macroprolactinemia is actually the main cause of persistent hyperprolactinemia in eumenorrhoeic women, being present

in 14 out of 15 cases. All these patients had normal (monomeric) PRL concentrations after macroprolactin precipitation with PEG. Although macroprolactinemia has been considered to be a cause of apparent resistance to antiprolactinemic drugs (4, 11), neither PRL normalization on dopaminergic treatment nor the presence of a pituitary mass can exclude macroprolactinemia, the former varying from 100% (12) to 46% (13). As for the latter, macroprolactinemia has been quite often associated with pituitary adenomas, probably not prolactinomas (3, 10, 11).

Colao and coworkers (9) report a decrease in PRL levels from 144 ± 62 to 14.4 ± 21.5 $\mu\text{g/l}$ in microprolactinomas with cabergoline treatment (9). However, the graphics in their Fig. 2 show that some patients with basal PRL close to 100 $\mu\text{g/l}$ have similar values after 6 months of therapy. It would be interesting to check whether these patients overlap the eumenorrhoeic women classified in the 'microprolactinoma' group. If so, the presence of macroprolactinemia would be highly probable.

Finally, we consider that every study concerning hyperprolactinemia should look carefully for the presence of macroprolactin, its amount and hence the monomeric PRL concentrations. Otherwise, patients who are not 'pathologically' hyperprolactinemic may be classified as such, causing an important bias.

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