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The Importance of Macroprolactin in the Diagnosis of Hyperprolactinemia

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Abstract

This article provides a brief review of macroprolactin (MPRL) – what, why, how, and when. Prolactin (PRL) secretion is uniquely controlled by tonic dopamine inhibition. Circulating PRL is a heterogeneous mixture of different sized proteins – monomer, dimer, and a large PRL-immunoglobulin aggregate also known as MPRL. Hyperprolactinemia (HPRL), which affects male sexual function and female reproduction, is a common endocrine disorder. Elevated PRL may be physiologic, pharmacologic, or pathologic. However, MPRL is quite common (ranging from 13–30%) and should be excluded before inappropriate investigations and therapy for HPRL are initiated. MPRL can be precipitated by mixing serum with polyethylene glycol (PEG) followed by centrifugation; monomeric PRL remains in the supernatant. MPRL is considered present if the PRL recovery is less than 40% or if the post-precipitation PRL concentration is low. The use of both measures for MPRL provides greater clarity. Different immunoassay platforms recognize MPRL differently necessitating assay-specific reference ranges. All HPRL samples should be screened for MPRL.

Keywords: hyperprolactinemia, macroprolactin, screening, polyethylene glycol

Abbreviations: MPRL: macroprolactin; PRL: prolactin; HPRL: hyperprolactinemia; PEG: polyethylene glycol; cAMP: cyclic-adenosine monophosphate

Introduction

Prolactin (PRL) is unique among hormones in endocrinology in that its secretion is constantly under tonic inhibition by dopamine from the hypothalamus. Dopamine interacts with pituitary lactotroph receptors to produce inhibitory G-proteins causing diminished adenyl cyclase levels, decreased cyclic-adenosine monophosphate (cAMP), and thus low

PRL. PRL levels rise when lactotrophs escape their inhibitory influences (*e.g.*, hypothalamic-pituitary disease) or when subjected to strong stimuli (*e.g.*, drug interference on pituitary dopaminergic inputs). PRL elevation also occurs in disease states - hypothyroidism (increased thyrotropin releasing hormone stimulates PRL release) and renal failure/liver dysfunction (decreased PRL clearance). Stimulation of intercostal nerves (chest wall lesions, herpes zoster) and nipples (suckling) reduces dopamine output through diminished tyrosine hydroxylase phosphorylation. More detailed PRL pathophysiology has been recently reviewed [1, 2].

Prolactin and Macroprolactin

Circulating PRL concentrations in normal men and women are 3–14 ug/L and 4–24 ug/L (PRL conversion units: 1 ug/L = 21.2 mU/L) [1]. In blood, PRL is a heterogeneous mixture of PRL of variable sizes: 65–85% monomeric PRL, 15–30% dimeric (40–60 kDa) "big" PRL, and < 10% >150 kDa macroprolactin (MPRL) [3–5]. MPRL is a complex formed by monomeric PRL and IgG anti-prolactin auto-antibodies although non-IgG variants do exist. Clinically, MPRL is inactive and without biological function. Most patients with anti-prolactin auto-antibodies/MPRL do not display the classic symptoms of hyperprolactinemia (HPRL) [2] and HPRL patients ≥40 years old with MPRL were less likely to display galactorrhoea [6]. Despite this, MPRL can persist for several years causing consistently raised PRL results [3, 7].

Macroprolactin and Hyperprolactinemia

HPRL is among the top few conditions seen in the endocrine laboratory. The prevalence of HPRL is about 10/100,000 in men and 30/100,000 in women. HPRL commonly causes amenorrhea/infertility in women [1, 8] while its effects in men are more subtle and insidious (sexual dysfunction). Causes of HPRL include physiological changes (*e.g.*, pregnancy, lactation), pharmacologic causes (*e.g.*, dopamine antagonists such as anti-psychotics and anti-depressants), pathologic states (*e.g.*, pituitary adenomas), and MPRL, a laboratory artefact. In the quest to exclude pituitary tumors in HPRL evaluation, it is important to remember MPRL lest unnecessary investigations and injudicious treatment are instituted. MPRL causing HPRL is deceptively common. One study estimates an MPRL incidence of 10% in their hospital [9]. In our laboratory, 12–18% of our HPRL results were due to MPRL [1]. In a large series (n = 1229) of HPRL from India, the prevalence of MPRL was 13.7% [10]. A recent meta-analysis estimated that the overall global prevalence of MPRL was 18.9% with geographic variation from 12.6% in the Western Pacific region to 30.3% in Africa [11]. In Croatia, HPRL is common (41%) in patients receiving antipsychotic drugs (n = 238), but MPRL was surprisingly detected in only 2 subjects [12]. This is in contrast to the 10.5% seen in Omani subjects receiving such medications [13].

How to Assess for Macroprolactin

It is difficult to differentiate MPRL from true HPRL based on clinical features alone. The gold standard for detecting MPRL is size exclusion gel filtration chromatography. However, this procedure is time-consuming, laborious, and impractical for routine MPRL screening. The use of polyethylene glycol (PEG) to precipitate MPRL is popular as it is rapid and inexpensive. Typically, PEG precipitation involves adding a 25% PEG solution to the sample, followed by centrifugation; monomeric PRL remains in the supernatant. PRL recovery is then calculated thus: supernatant PRL divided by total PRL. MPRL is present if recovery is < 40% and absent if recovery is > 60%; values between 40–60% are indeterminate. However, the PEG precipitation technique is not without pitfalls. Several different protocols for MPRL-PEG precipitation exist [14, 15], with some even designed for use on fully automated immunoassay analyzers [16]. PEG exists in 2 molecular forms - one with a molecular weight of 6000 (PEG6000) and the other of 8000 (PEG8000). Significant constant bias has been reported when different PEGs are used for MPRL precipitation - post-PEG6000 PRL > post-PEG8000 PRL by 8.2% [17]. Moreover, up to 20% of monomeric PRL can be co-precipitated with MPRL [18]. In addition, elevated GGT levels can cause false-positive MPRL [4], while non-IgG MPRL may cause false-negative results [18]. However, PEG precipitates all non-monomeric PRL - "big, big PRL" (or MPRL)

and dimeric PRL ("big PRL") which is strictly not MPRL. Thus, PEG-derived MPRL is over-estimated. In addition, the reported cut-offs based on percentage recovery are arbitrary and vary greatly between centers.

Some studies report post-PEG-PRL values with appropriate reference ranges, rather than percentage recovery [19]. Post-PEG-PRL reference ranges may also be able to detect true HPRL coexisting with MPRL. In one study, 2 patients with significant MPRL (recovery rate < 60%) were both categorized as true HPRL using post-PEG-PRL reference intervals [12]. In another study, when post-PEG PRL values were used instead of percentage recovery, 13.4% (13/97) of MPRL would be considered true HPRL while 2.3% (6/263) of true HPRL would be classified as MPRL [20]. However, due to variation between assays and PEG precipitation protocols (*e.g.*, PEG type, PEG reconstitution methods, sample incubation, and centrifugation), post-PEG-PRL reference intervals would need to be assay- and protocol-specific [17]. Different PRL immunoassays yield different amounts of MPRL [21, 22] necessitating different post-PEG-PRL reference intervals [9, 23]. Furthermore, the molecular structure of MPRL is heterogeneous [5] resulting in different measurement biases on different analytical platforms. Indeed, some MPRL may not aggregate with IgG antibodies, and instead, form complexes with other antibodies [21]. All these factors render the generation of post-PEG-PRL reference intervals a daunting undertaking. Studies have also shown that in patients with HPRL, a percentage recovery of ≤60% can yield a fairly similar detection rate as post-PEG-PRL reference intervals (8.7% *vs.* 8.8% detection rate) [24].

When to Screen for Macroprolactin

HPRL can present insidiously [3] in men (*e.g.*, erectile dysfunction and decreased libido) and in women (*e.g.*, galactorrhea, amenorrhea, oligomenorrhea, decreased libido, and infertility). Thus, PRL should be measured in these patients. When HPRL is detected, we should screen for MPRL. Previous Endocrine Society guidelines recommend screening for MPRL in asymptomatic HPRL only [8]. However, an increasing number of studies [4, 24, 25] suggest that all samples with a PRL concentration above the upper limit of the manufacturer's reference interval be screened for MPRL with PEG. In our own practice, we adopt this reflex testing approach as it saves time, costs, and inconvenience for the patient [1]. We also favor the use of both percent recovery and post-PEG PRL concentrations. Laboratories should consider screening all samples with HPRL for MPRL.

Conclusion

MPRL is commonly encountered in the evaluation of HPRL and both can co-exist in the same sample. PEG precipitation needs to be performed to rule out MPRL in all cases of HPRL, with final results reported as percentage recovery, or actual PRL levels post-PEG compared to assay-specific post-PEG-PRL reference intervals.

Conflicts of Interest

Authors declare no conflicts of interest.

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