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Short Communication

Prolactinomas and Macroprolactin: The Complexity of Interpreting Macroprolactin Data

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Abstract

Hyperprolactinemia is a condition that can present itself in many different contexts ranging from physiological during pregnancy, pharmacological (e.g., due to antidepressants or antipsychotics) or truly pathological. Pathological mechanisms of hyperprolactinemia include pituitary tumors, tumor metastases, autoimmune diseases and ectopic prolactin producing tumors. In addition, prolactin values may be elevated due to macroprolactin. Detection of macroprolactin through PEG-precipitation is performed under various conditions in different laboratories and reporting of post PEG-prolactin is performed through different approaches. Also, prolactin assays have distinct sensitivity towards macroprolactin. Therefore, the likelihood of the presence of true pathological hyperprolactinemia always needs to be assessed in the context of the assay used, the sensitivity of the assay to prolactin adducts, type of PEG polymer used and the manner in which prolactin adducts are reported by the laboratory.

Key words: hyperprolactinemia; macroprolactin; peg precipitation

Introduction

Hyperprolactinemia is a condition that can present itself in many different contexts ranging from physiological during pregnancy, pharmacological (e.g., due to antidepressants or antipsychotics) or truly pathological [1]. Pathological mechanisms of hyperprolactinemia include pituitary tumors, tumor metastases, autoimmune diseases and ectopic prolactin producing tumors [2-4]. A recent position paper of the Italian Association of Clinical Endocrinologists (AME) and International Chapter of Clinical Endocrinology (ICCE) [5], adds to the existing JCEM guidelines for the diagnosis and treatment of hyperprolactinemia [6] and advises to measure prolactin in all patients with clinical suspicion. In addition, it is advised to confirm a randomly elevated prolactin measurement after insertion of a catheter and 20 minutes of rest, unless prolactin is clearly elevated (>1.7 U/L). A detailed medical and pharmacological history needs to be taken in order to exclude physiological and iatrogenic causes of hyperprolactinemia. Screening for macroprolactin is indicated in asymptomatic patients, patients with an atypical clinical presentation, patients with conflicting prolactin results in diverse assays and patients with a lack of prolactin decline under therapy.

Current guidelines with respect to prolactin measurements

The JCEM guideline mentions that a prolactin value of >10.6 U/L is diagnostic for macroprolactinoma and >5.3 U/L is indicative for a prolactinoma [6]. Nonetheless, medications such as risperidone and metoclopramide are known to induce prolactin elevations above 4,2 U/L in patients without a pituitary adenoma. Psychoactive drugs, estrogen, disconnection hyperprolactinemia (a pituitary tumor that disrupts dopamine release by compressing the pituitary stalk), infiltrative disease, hypothyroidism, renal failure, idiopathic causes or microprolactinomas are known to induce prolactin levels between the upper reference limit (URL) and 2,0 U/L [7]. In addition, prolactin values might exceed the URL because of the presence of macroprolactin. Macroprolactin is a biologically inactive form of prolactin that arises as IgG antibodies form a complex with monomer prolactin resulting in reduced clearance rates and thus increased plasma values [8]. As stated above, there are various arguments to screen for macroprolactin in patients with hyperprolactinemia. This is especially important in order to not unnecessarily expose patients to therapy such as dopamine agonists or expensive investigations such as CT or MRI scans. To this extent, the existing JCEM guideline recommends to screen for macroprolactin in all asymptomatic patients with hyperprolactinemia. In practice, screening for macroprolactin in first- and second-line care laboratories is performed under various rules and is achieved by PEG precipitation. These rules encompass: screening for macroprolactin in all hyperprolactinemic samples, above a specific threshold or only upon request of the endocrinologist. This difference in screening rules might arguably be due to the lack of specific clinical symptoms related to hyperprolactinemia in patients in which prolactin measurements are performed under some circumstances.

Variation of macroprolactin prevalence is possibly attributed to differences in laboratory operating procedures, methods to establish prolactin adducts and assay sensitivity

Prevalence of macroprolactin in patients with hyperprolactinemia is reported to be 4% to 46% [9]. This might be related to the population in which prolactin is measured. In some centers there is a much higher à priory chance to encounter serum samples with macroprolactin due to the fact that samples with a high suspicion of macroprolactin are sent there for analysis. Furthermore, there is a known inter-assay difference with respect to macroprolactin cross-reactivity [10]. In addition, there are other, more subtle, factors that might influence the reporting of the presence of macroprolactin. First of all, many laboratories uphold different macroprolactin screening criteria. These can range from measuring macroprolactin in all hyperprolactinemic samples (as is performed in our own laboratory) to only screening samples > 1 U/L [11]. Recent literature shows that by only screening samples > 1U/L, a relevant number of macroprolactinemic samples would be missed, rendering a false diagnosis of hyperprolactinemia [12]. Even though the clinical relevance of such mildly elevated prolactin should be properly investigated. Secondly, there is no consensus as to when a hyperprolactinemic serum sample should be regarded macroprolactinemic. Many have opted to define the presence of macroprolactin by a post-PEG prolactin measurement within the gender specific monomeric reference intervals [13, 14], whilst others opt to define the presence of macroprolactin by using a recovery threshold, which is often subjectively set between 40% and 60% [15, 16]. It is important to note that the type of PEG used (PEG6000 vs PEG8000) affects the monomeric reference intervals as some monomeric prolactin is also precipitated and that the monomeric reference intervals should be determined in the context of the assay used and population attributed to the laboratory [10, 17]. All these variables drastically impact the presumed presence of macroprolactin, as is illustrated by our own data.

Problem illustrated from a practical point of view

To illustrate the problem, we show the impact of switch from one prolactin measuring method (Siemens Immulite XPi) to another (Roche Cobas Pro®). Should gender specific prolactin monomeric reference values be used, on average approximately 25% of all hyperprolactinemic samples are deemed hyperprolactinemic measured by both methods (Table 1).

Assay	# measurements	# PEG precipitations	% PEG precipitations	% Samples with PEG precipitations which normalize after PEG precipitation*	% Samples with PEG precipitations which normalize after PEG precipitation* and show < 50% recovery**
Siemens Immulite	1127	184	16,3%	25,0%	10,8%
Immulite men	213	38	17,8%	36,8%	20,5%
Immulite women	914	146	14,9%	23,5%	8,1%
Roche Cobas pro	1679	473	28,2%	25,4%	2,3%
Cobas pro men	378	124	32,8%	29,8%	2,2%
Cobas pro women	1301	349	26,8%	23,8%	2,4%

**Normalization according to method-dependent post-PEG prolactin values, **50% recovery is based on recent literature. Percent recovery = (post-PEG prolactin ÷ pre-PEG prolactin) × 100; <50% Recovery means that more than 50% of the measured pre-PEG prolactin comprises of prolactin adducts (e.g., macroprolactin).*

When adding <50% recovery to the abovementioned rule of leveling within the monomeric reference intervals, a substantially smaller percentage of Siemens and Roche samples would be assumed to be macroprolactinemic with 10.8% and 2.3% respectively (Table 1). This would especially be impactful if no post-PEG prolactin value would be reported along with the %-recovery and exemplifies the importance of being acquainted with the rules a laboratory sets for the presence of macroprolactin, but also the assay the lab utilizes.

Limitation of guideline recommendation

Unfortunately, such technicalities can impossibly be captured in guidelines and might be unknown to the clinician even though they could potentially impact decision making (especially when the post-PEG prolactin value is not reported and laboratory reports only recovery value). Thus, in final reporting, it is very important to define laboratory specific monomeric reference intervals when the presence of macroprolactin is defined by normalizing within monomeric reference intervals. In addition, post-PEG prolactin values should be reported when utilizing recovery as a defining factor for the presence of macroprolactin in order to prevent misdiagnosis. Differences between both reporting strategies might be smaller or larger depending on the assay used and its sensitivity to macroprolactin. Monomeric reference intervals are more suitable in assays that are known to be relatively insensitive to macroprolactin. The relative sensitivity for macroprolactin in various assays is nicely described by Overgaard and colleagues [10], resulting in various inter-assay discrepancies in samples with hyperprolactinemia and macroprolactinemia. In a setting of hyperprolactinemia, assays relatively insensitive to macroprolactin tend to overestimate the true prolactin value upon PEG-precipitation. On the other hand, in macroprolactinemic samples, pre-PEG prolactin values will logically more closely resemble post-PEG prolactin values, resulting in a very large inter-assay variability between both the pre-and post-PEG prolactin values. This means that results between assays are absolutely not interchangeable, especially when a substantial amount of macroprolactin is concomitantly present with prolactin monomers.

Conclusion: when assessing the likelihood of the presence of pathological hyperprolactinemia based on routine prolactin measurements, it is of importance to keep in mind the assay utilized, its sensitivity to prolactin adducts, type of PEG-polymer used and the way of reporting prolactin adducts.

Conflicts of interest: All authors declare no conflicts of interest

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