Macroprolactin—a cause of pseudohyperprolactinaemia

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Introduction

Hyperprolactinaemia is a relatively common endocrine problem. There are many differential diagnoses for hyperprolactinaemia, but one benign condition, macroprolactinaemia, is often overlooked. There are three major molecular forms of prolactin in the circulation: monomeric prolactin (little prolactin, 23 kDa), dimeric prolactin (big prolactin, 45-50 kDa), and macroprolactin (big-big prolactin, 150-170 kDa).1 Macroprolactin is a complex of immunoglobulin G and monomeric prolactin. The plasma half-life is prolonged because of delayed renal clearance. Although biological activity has been demonstrated in vitro, it is generally believed that macroprolactin lacks biological activity in vivo because it cannot cross the endothelial lining and reach the cell surface receptors.2,3 The degree of reactivity is assay-dependent. As a result, measured prolactin levels may be spuriously high and results measured by different assays cannot be compared. A polyethylene glycol (PEG) precipitation method can be used to screen for this condition.4,5 In this report, three patients with pseudohyperprolactinaemia secondary to macroprolactinaemia are presented and the potential adverse consequences if this condition is not recognised are discussed.

Reference:
1. Macroprolactin is a complex of immunoglobulin G and monomeric prolactin with little biological activity in vivo. Macroprolactin cross-reacts in modern commercial prolactin assays, however, leading to pseudohyperprolactinaemia. This report is of three patients with macroprolactinaemia and the untoward consequences if this benign condition is misdiagnosed as genuine hyperprolactinaemia are discussed. One adult and one child without symptoms of hyperprolactinaemia were incidentally found to have elevated serum prolactin levels, one of whom had a pituitary incidentaloma. Repeat prolactin measurement after polyethylene glycol precipitation showed that the majority of circulating prolactin was macroprolactin. The third patient had galactorrhoea and pituitary microadenoma. Polyethylene glycol study showed that macroprolactinaemia exists simultaneously with genuine hyperprolactinaemia leading to falsely high serum prolactin levels. The recognition of this relatively common and benign condition is important in order to avoid misdiagnosis and unnecessary investigations and treatment. Particular attention must be paid to patients in whom the clinical and radiological findings are incompatible.

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**Case reports**

**Case 1**
A 39-year-old woman was referred to a Hospital Authority hospital with suspected hyperprolactinaemia. Her prolactin level, measured by a private laboratory, was 51.8 ng/mL (reference range, 1-25 ng/mL). Her prolactin levels were normal to only marginally elevated (26.5 to 40.4 ng/mL) when repeatedly measured in the hospital laboratory (Beckman Coulter Access; Beckman Coulter, California, US; reference level, <30.7 ng/mL). The patient had no signs or symptoms of hyperprolactinaemia. Other pituitary hormone axes were intact. Magnetic resonance imaging (MRI) of the brain revealed a 3-mm mass in the pituitary gland. The attending physician noted the discrepant clinical picture and consulted the laboratory. One of the serum samples was sent to other laboratories for prolactin measurement by different immunoassays, the results were grossly different (Table). Using Roche Elecsys prolactin assay (Roche Diagnostics GmbH, Mannheim, Germany; reference level, <24.1 ng/mL) and a validated PEG precipitation protocol, the pre-PEG and post-PEG treatment prolactin levels were 173.5 ng/mL and 24.4 ng/mL, respectively. The recovery was 14.1% (macroprolactinaemia level, <40%; reference level, >50%). Pseudohyperprolactinaemia secondary to macroprolactinaemia was confirmed.

**Case 2**
An 11-year-old girl with premature adrenarche was incidentally found to have hyperprolactinaemia. Her levels of prolactin fluctuated from 73.5 to 153.2 ng/mL (Roche Elecsys; reference level, <31.6 ng/mL) during a 3-year follow-up period. With no diagnosis to explain the elevated prolactin level, MRI scan of the brain was performed, but this did not show any abnormality. Polyethylene glycol precipitation confirmed that the diagnosis of hyperprolactinaemia was spurious.

**Case 3**
A 43-year-old woman was referred to a Hospital Authority hospital with suspected hyperprolactinaemia. Her serum prolactin levels increased again, however, to 103.2 ng/mL. A repeat MRI scan did not show any pituitary lesion. The pre-PEG and post-PEG prolactin levels were 103.2 ng/mL and 62.0 ng/mL (Beckman Coulter Access), respectively, indicating that genuine hyperprolactinaemia coexisted with macroprolactinaemia in this patient.

**Discussion**
Hyperprolactinaemia is a common endocrine problem with diverse aetiologies (Box). Macroprolactinaemia is one aetiology that is considered benign. Failing to diagnose this condition could lead to unnecessary and costly investigations, inappropriate intervention, and needless apprehension. The estimated prevalence of macroprolactinaemia among patients with hyperprolactinaemia ranges from 9% to 42%, although its prevalence in healthy people is less than 1%. A 1-year study in a local regional hospital revealed that the prevalence of macroprolactinaemia among patients with hyperprolactinaemia in the hospital population was 16.5% (unpublished data.) Hence, this condition is sufficiently frequent to warrant greater attention. Macroprolactinaemia is known to occur in patients presenting with clinical features suggestive of hyperprolactinaemia, although the prevalence of macroprolactinaemia in other conditions is unknown.

Macroprolactin interferes with the common commercial assays in markedly different degrees. As illustrated by case 1, the same serum sample yielded a slightly elevated prolactin level (40.4 ng/mL) in one assay and a very high level (173.5 ng/mL) in another. Recent surveys studying the reactivities of macroprolactin in commonly used prolactin immunoassays have divided the assays into low-reactivity, medium-reactivity, and high-reactivity groups. 

**Common causes of hyperprolactinaemia**

(1) Physiological
- Pregnancy, lactation

(2) Hypothalamic disorders
- Tumours (craniopharyngioma, germinoma), infiltrative diseases (sarcoidosis), pseudotumour cerebri, cranial irradiation

(3) Pituitary disorders
- Prolactinoma, acromegaly, Cushing's disease, pituitary stalk section, empty-sella syndrome, infiltrative disease (sarcoidosis)

(4) Drugs
- Neuroleptic agents, antidepressant agents, antihypertensive agents, oestrogens, opioids, calcium-channel blockers

(5) Neurogenic
- Chest wall or spinal cord lesion, breast stimulation

(6) Others
- Primary hypothyroidism, chronic renal failure, cirrhosis

(7) Idiopathic

**Table. Prolactin results of case 1 analysed by different commercial assays**

<table>
<thead>
<tr>
<th>Analyser</th>
<th>Serum prolactin (ng/mL)</th>
<th>Post-polyethylene glycol serum prolactin (recovery %)*</th>
<th>Reference level (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman Coulter Access</td>
<td>40.4</td>
<td>-</td>
<td>&lt;30.7</td>
</tr>
<tr>
<td>Bayer Centaur</td>
<td>49.6</td>
<td>-</td>
<td>&lt;29.2</td>
</tr>
<tr>
<td>Bayer ACS:180</td>
<td>64.6</td>
<td>-</td>
<td>&lt;30.7</td>
</tr>
<tr>
<td>Roche Elecsys 2010</td>
<td>173.5</td>
<td>24.4 (14.1)</td>
<td>&lt;24.1</td>
</tr>
</tbody>
</table>

* Recovery percentage is calculated by dividing the post-polyethylene glycol prolactin level by the pre-polyethylene glycol prolactin level, expressed in percentage. For Roche Elecsys prolactin assay, a value of <40% is indicative of macroprolactinaemia and a level of >50% makes this condition unlikely.8,10
It is advisable for clinicians to have some knowledge of the assay properties used by their laboratories. For all patients found to have hyperprolactinaemia, it is prudent to exclude macroprolactinaemia. One of the commonly used methods to screen for macroprolactinaemia is PEG-precipitation. Although this method has been validated in a number of commercial prolactin immunoassays, PEG may interfere in some assays. The cut-off level is also assay-dependent. Therefore, a careful evaluation is necessary before the adoption of this method into routine use in laboratories.

Case 1 had isolated hyperprolactinaemia without related signs and symptoms. Biologically inactive macroprolactinaemia was demonstrated to be the major prolactin fraction. The tiny pituitary mass revealed by MRI scan is likely to be an incidentaloma of little clinical significance. Indeed a significant proportion ‘idiopathic’ hyperprolactinaemia could be due to macroprolactin. The presence of macroprolactinaemia leading to unnecessary investigations and treatment has been reported in the literature. In addition, macroprolactinaemia may be misdiagnosed as prolactinoma because of the relatively common occurrence of pituitary incidentaloma on imaging studies. It has been suggested that this might account for part of the failure of pituitary microsurgery for prolactinoma. In case 2, hyperprolactinaemia was an incidental finding. Although most of the reports are of adults, macroprolactinaemia has been found in children. In case 3, the prolactin level remained elevated (>55.5 ng/mL) after PEG treatment, that is, both the biologically active monomeric prolactin and macroprolactin were elevated. The prolactin levels were suppressed to a low level when the patient was taking bromocriptine and there was a rebound hyperprolactinaemia after withdrawal of the medication. This agreed with the observations in a previous study that increases in monomeric prolactin and macroprolactin can occur simultaneously. Knowing the level of monomeric prolactin is desirable for patient management since this is the biologically active form. Therefore, for patients with macroprolactinaemia and genuine hyperprolactinaemic syndrome, the post-PEG prolactin level should be used for monitoring disease progress and response to therapy.

There is still some debate about the true clinical implications of macroprolactinaemia. A proportion of patients with macroprolactinaemia have one or more symptoms of hyperprolactinaemic syndrome. It has also been demonstrated that dopamine agonists substantially decrease the hyperprolactinaemic syndrome. It has also been demonstrated that dopamine agonists substantially decrease the hyperprolactinaemic syndrome. It has also been demonstrated that dopamine agonists substantially decrease the hyperprolactinaemic syndrome. However, the majority of the reported macroprolactinaemia cases were asymptomatic. A recent study of 55 patients with macroprolactinaemia showed that the classical symptoms of hyperprolactinaemia syndrome were uncommon. The authors concluded that macroprolactinaemia was a relatively benign condition and referral and intensive investigations of these patients might not be necessary. In summary, macroprolactin is a prevalent benign condition that may be confused with other causes of hyperprolactinaemia. To avoid unnecessary investigations, treatment, and creation of patient anxiety, macroprolactin should be considered in the differential diagnosis of hyperprolactinaemia, particularly for those patients without clinical signs and symptoms of hyperprolactinaemic syndrome.

References