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# Macroprolactin — a cause of pseudohyperprolactinaemia

## 大催乳素——導致偽高催乳素血症的因素

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 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.

大催乳素是免疫球蛋白G和單節催乳素的複合物，在體內的活性很低。然而，在商用催乳素分析中，大催乳素的交叉反應能導致偽高催乳素血症。本報告報導了三名大催乳素血症者，並討論若這良性情況被誤診為真正的高催乳素血症所帶來的後果。患者中的一名成人及一名小童，其中一人患有垂體偶發瘤，兩人均無高催乳素血症的徵狀，但在偶然的情況下，被發現血清催乳素水平升高。經聚乙二醇沉澱後重複進行的催乳素測量顯示，其中大部分循環中的催乳素是大催乳素。第三名病人患有溢乳和垂體微腺瘤。聚乙二醇研究顯示，這名病人同時患有大催乳素血症及真正的高催乳素血症，以致呈現血清催乳素過高的假象。識別這種甚為普遍和良性的情況可避免誤診和不必要的檢查與治療。尤其對於那些臨床和放射診斷結果呈現矛盾的患者，必須加以注意。

### Key words:

Hyperprolactinemia;  
 Immunoassay;  
 Polyethylene glycol;  
 Prolactin

### 關鍵詞：

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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).<sup>1</sup> 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.<sup>2,3</sup> Macroprolactin is a significant source of analytical error affecting most, if not all, of the prolactin assays in current use.<sup>4,5</sup> 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.<sup>6,7</sup> In this report, three patients with pseudohyperprolactinaemia secondary to macroprolactin are presented and the potential adverse consequences if this condition is not recognised are discussed.

## 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,<sup>8</sup> 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 presented with galactorrhoea and was found to have a prolactin level of 124.5 ng/mL (Beckman Coulter Access). Magnetic resonance imaging of the brain revealed a microadenoma on the left side of the pituitary gland. There were no other hyperprolactinaemic symptoms and the remaining pituitary functions were intact. Treatment with bromocriptine was instituted, which decreased the prolactin level to less than 9.4 ng/mL and halted the galactorrhoea. Treatment was stopped after 18 months. The patient remained asymptomatic for the following 3 years.

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.<sup>9</sup> Failing to diagnose this condition could lead to unnecessary and costly investigations, inappropriate intervention, and needless apprehension. The estimated prevalence of macroprolactin among patients with hyperprolactinaemia ranges from 9% to 42%,<sup>6,7,10-12</sup> although its prevalence in healthy people is less than 1%.<sup>10</sup> 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.<sup>4,5</sup>

#### 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**

Analyser	Serum prolactin (ng/mL)	Post-polyethylene glycol serum prolactin (recovery %)*	Reference level (ng/mL)
Beckman Coulter Access	40.4	-	<30.7
Bayer Centaur	49.6	-	<29.2
Bayer ACS:180	64.6	-	<30.7
Roche Elecsys 2010	173.5	24.4 (14.1)	<24.1

\* 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.<sup>8,10</sup>

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,<sup>8,11-13</sup> PEG may interfere in some assays.<sup>4,5</sup> 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.<sup>14-17</sup> In addition, macroprolactinaemia may be misdiagnosed as prolactinoma because of the relatively common occurrence of pituitary incidentaloma on imaging studies.<sup>14,17-19</sup> It has been suggested that this might account for part of the failure of pituitary microsurgery for prolactinoma.<sup>14</sup> In case 2, hyperprolactinaemia was an incidental finding. Although most of the reports are of adults, macroprolactinaemia has been found in children.<sup>16</sup> 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.<sup>11</sup> 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.<sup>2,12,14</sup> It has also been demonstrated that dopamine agonists substantially decrease the macroprolactin level, which is accompanied by partial or complete resolution of hyperprolactinaemic symptoms.<sup>12</sup> However, the majority of the reported macroprolactinaemia cases were asymptomatic.<sup>3,8,16,19</sup> A recent study of 55 patients with macroprolactinaemia showed that the classical symptoms of hyperprolactinaemic syndrome were uncommon.<sup>9</sup> 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.

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