

# Macroprolactinemia Associated with Anti-Prolactin Antibodies: A Case Report

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Macromolecular form of prolactin is generally associated with asymptomatic hyperprolactinemia. Increases in molecular size may result from self-aggregation or binding with antiprolactin antibodies. Such a benign clinically insignificant laboratory abnormality could be documented by gel filtration chromatography, polyethylene glycol precipitation methods or directly detecting antiprolactin autoantibody itself.

Here we report a case of asymptomatic hyperprolactinemia due to macroprolactinemia associated with prolactin autoantibodies to notice the importance of clinically insignificant isolated laboratory abnormalities.

**Key words:** Macroprolactinemia, antiprolactin autoantibody, hyperprolactinemia

## Introduction

Prolactin has several forms of different molecular sizes, including "little", "big" and "big-big" prolactin in circulation (1). The 23-kD monomeric little prolactin is the predominant form in the general population (1).

Rare forms with unknown prevalences are ~50-kD possibly dimeric big prolactin and a larger one of >100-kD big-big prolactin (macroprolactin) (1-3).

Macromolecular form of prolactin is characterized as a complex of hormone itself with an IgG antibody (known as prolactin autoantibody) or aggregates of little prolactin (4-5). It has been suggested that due to its larger size, macroprolactin has reduced bioactivity with low receptor activity *in vivo* and slower clearance from circulation, leading to hyperprolactinemic measures with some commercial immunoassays in asymptomatic individuals (1,4,6).

Although it has been assumed to be a benign condition not requiring neither treatment nor further evaluation, exceptionally some patients with macroprolactinemia have been reported to have clinical manifestations of hyperprolactinemia and evidence of adenoma (7-9).

Macroprolactin can be detected by gel filtration chromatography or by a simpler method of polyethylene glycol precipitation test regardless of antibody-bound or aggregated form, and also by directly showing presence of prolactin autoantibodies (2,10).

## Materials and Methods

A 38-year-old asymptomatic female was referred to our endocrinology department in September 1998 for hyperprolactinemia that had been detected during an incidental laboratory over-evaluation of unknown indication from a primary care center. She had no complaints of either amenorrhea/oligomenorrhea or galactorrhea. The patient's past medical history was unremarkable. The physical examination was completely normal. Her prolactin level was 92 ng/ml (reference interval: 1.7-27 ng/ml). The other laboratory evaluations including anterior pituitary hormone

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profile were all in normal ranges. Autoantibodies, including anti-glutamate decarboxylase, anti-insulin, anti-TSH receptor, anti-thyroid peroxidase, anti-thyroglobulin, antinuclear and anti-DNA antibodies were all negative. After a pituitary MRI which also revealed normal radiological findings, idiopathic hyperprolactinemia was diagnosed. Without any medication or surgical intervention, during the follow-up period between September 1998 and October 2001 she stayed asymptomatic and hyperprolactinemic with subsequent prolactin levels of; 96.4 ng/ml, 90.1 ng/ml, 87 ng/ml, 221 ng/ml, 152 ng/ml, 227 ng/ml. With that clinical course, the diagnosis of macroprolactinemia was suspected, and a serum sample was sent to a laboratory in USA to search for prolactin autoantibodies in October 2001, sponsored by our own personal contacts. Presence of antiprolactin IgG-antibodies in high titers was documented, explaining the laboratory abnormality of our otherwise healthy patient.

### Discussion

Recent developments in laboratory techniques offer physicians opportunity to solve clinical problems more accurately, but on the other hand the same opportunity simultaneously carry the risk of *de novo* creations of new laboratory problems of its own -not of real clinical problems- in healthy subjects, as in the case we report here. Endocrinologists are exposed to such clinically insignificant, laboratory abnormalities very often, especially due to inappropriate TSH screening test results. Although a further work-up of an isolated laboratory abnormality in a patient who is otherwise well is absolutely wasteful and unproductive, such incidental and inappropriate experiences sometimes enables us to discover new horizons on pioneer signals of diseases (e.g. subclinical hypothyroidism and subclinical hyperthyroidism.) or at least variations of normal physiology (e.g. macroamylasemia).

Here we report a case of asymptomatic hyperprolactinemia due to macroprolactinemia associated with prolactin autoantibodies which points out the importance of such clinically insignificant isolated laboratory abnormalities.

Existence of macroprolactinemia has been known for a long time. The incidence of macroprolactinemia in the general population has been estimated to be around 0.1-0.2 % (2). Its prevalence among

hyperprolactinemic patients has been reported to be ranging from 15.4% to 42%, with a large variation resulting from the different reactions of available commercial immunassays to macromolecular forms (1,4,9).

Although it has been commonly accepted as a benign condition without any clinical significance, macroprolactinemia still remains as a current subject of laboratory research owing to its unnecessarily further evaluations. It means financial burden in routine clinical practices.

Pascoe-Lira et al (9) reported that the frequency of macroprolactinemia was 3.8% among healthy pregnant women, which was caused by anti-prolactin autoantibodies in 62.5% of cases. Interestingly, they demonstrated a positive correlation between titers of prolactin autoantibodies and serum prolactin levels, suggesting that anti-prolactin autoantibodies bound-prolactin causes an alteration in feedback action on hypothalamic-pituitary axis, which in turn may cause an increase in prolactin secretion (9). Accurate significance of such an effect of macroprolactinemia on hypothalamic-pituitary axis in long term, definitely requires further research.

Recently, Gilson *et al* (4) showed that prolactin assays from different manufacturers give highly variable prolactin results for samples containing macroprolactin, and in conclusion underscored the necessity of a systematic screening strategy for macroprolactin in all samples with increased prolactin. Macroprolactinemia is quite frequent in patients with hyperprolactinemia, but is hardly ever considered in work-ups or differential diagnosis, a fact which has problematic consequences such as inappropriate treatment, unnecessary diagnostic procedures and aftercare investigations. Our case demonstrates once more that without any clinical implication, all isolated laboratory abnormalities surely requires some explanation, but never needs any medical intervention alone.

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