

MACROPROLACTINAEMIA IN A 33-YEAR OLD PREMENOPAUSAL NIGERIAN WOMAN: A CASE REPORT

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ABSTRACT

BACKGROUND: Macroprolactin is a 150-170kDa heteropolymeric complex of monomeric prolactin and immunoglobulin G (IgG) that contributes less than 1% of circulating prolactin concentration in plasma. It exerts little or no biological action in vivo. Its elevated plasma concentration (macroprolactinaemia) is a notable cause of frequent misdiagnosis, unnecessary investigation, and inappropriate treatment in patients with biochemical hyperprolactinaemia.

OBJECTIVE: To highlight the need for macroprolactin screening in premenopausal women with biochemical hyperprolactinaemia.

METHOD: We report an investigated case of macroprolactinaemia in a 33-year old premenopausal nulliparous woman with sustained hyperprolactinaemia, normoovulatory and regular menstrual cycles, and no radiological evidence of pituitary tumour (prolactinoma).

RESULT: The patient had persistent hyperprolactinaemia even after treatment with bromocriptine for 1 month. The menstrual cycle remained regular with clinical and biochemical presumptive evidence of ovulation.

CONCLUSION: Macroprolactinaemia is a potential cause of (pseudo) hyperprolactinaemia in women of childbearing age. Its occurrence should be suspected and investigated especially in patients with hyperprolactinaemia and regular normoovulatory cycles. The polyethyleneglycol (PEG) precipitation test is a simple and cost-effective screening test for macroprolactinaemia.

KEYWORDS: Prolactin, hyperprolactinaemia, macroprolactin, macroprolactinaemia.

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INTRODUCTION

Usually, prolactin circulates in three major molecular forms in blood, viz: monomeric prolactin (little prolactin), dimeric prolactin (big-prolactin), and polymeric prolactin (big-big prolactin or macroprolactin).^{1,2} The molecular weights of these circulating forms of prolactin are 23kDa, 48-56kDa and 150-170kDa respectively.³ In health, monomeric prolactin is the major circulating form and constitutes 80 to 90% of circulating prolactin while big-prolactin and macroprolactin constitute 20% and less than 1% respectively.³ Hyperprolactinaemia is a fairly common endocrine abnormality among women of child-bearing age.⁴ Most cases of hyperprolactinaemia are due mainly to elevated plasma concentrations of monomeric prolactin. However, some cases of

hyperprolactinaemia occur as a result of increased plasma levels of macroprolactin. This has been referred to as macroprolactinaemia.⁵ Macroprolactin mostly consists of a heteropolymeric complex of monomeric prolactin and immunoglobulin G (IgG).⁶ It exerts little or no biological action of monomeric prolactin in vivo.⁷ Consequently, premenopausal female patients with macroprolactinaemia may or may not present with clinical features of hyperprolactinaemic syndrome. Hence, macroprolactinaemia was suggested as a cause of pseudohyperprolactinaemia.⁸ Macroprolactinaemia has been reported as a cause of frequent misdiagnosis, unnecessary investigation, and inappropriate treatment of hyperprolactinaemia especially in women of child-bearing age.⁹ In the routine clinical laboratory setting, the presence of macroprolactinaemia is commonly screened using the polyethyleneglycol precipitation method.^{10,11}

In this report, we present a case of 33-year old nullipara who presented with constant frontal headache and severe hyperprolactinaemia but had regular menstrual

cycles and no galactorrhea. Serial laboratory and radiological investigations excluded tumours of the hypothalamic-pituitary axis. Laboratory screening for macroprolactin revealed serum prolactin recovery of 40% which strongly suggested macroprolactinaemia.

CASE REPORT

The patient is a 33-year old nullipara who presented with history of dysmenorrhea and monthly cyclic headache that was mostly frontal in location. While the symptoms prevailed, her menstrual cycle remained regular with normal flow. There was no associated history of spontaneous or expressible galactorrhea. The patient was not on any routine drug that can increase plasma prolactin concentration. For the symptoms, patient was referred to the gynaecology clinic of University of Calabar Teaching Hospital for further investigation and management. The patient was clinically evaluated and some laboratory investigations were carried out. A baseline 21-day fertility hormone profile testing was performed and the following results were obtained: luteinizing hormone (LH) = 7.5µIU/ml (5 - 20); follicle stimulating hormone (FSH) = 5.0µIU/ml (<20); progesterone (PROG) = 11.0ng/ml (2.5 - 32); estradiol (E2) = 66.0ng/ml (60 - 150); prolactin (PRL) = 80.0ng/ml (8.39 - 20.15). The laboratory test result revealed hyperprolactinaemia despite normal levels of gonadotropins and gonadal hormones. In addition, serum TSH estimation carried out concomitantly with the fertility hormone profile revealed euthyroidism. The patient is a nun and there were no history of exercise, sexual activity or breast stimulation prior to blood specimen collection.

A repeat serum PRL estimation two weeks after the

first testing gave a serum prolactin value of 76.2ng/ml (8.39- 20.15). Despite the persistent hyperprolactinaemia the patient continuously had regular menstrual cycles and she admitted to experiencing the presumptive symptoms of ovulation. To rule out structural and functional disorders of the hypothalamic-pituitary endocrine axis, patient had a brain CT scanning. The tomographic technique comprised a scanogram followed by 3mm pre- and post-intravenous contrast helical sections with coronal and sagittal reformations. The findings were as follows: normal cerebral and cerebellar hemispheres; normal sulci and gyri; normal grey-white matter interphase; no intraxial or extraaxial mass lesions or collection seen; and normal ventricular systems. The radiological diagnosis was a normal brain CT scan.

Subsequently, the patient was treated with oral bromocriptine 2.5mg twice daily for 1 month. Following the completion of the bromocriptine treatment, a follow-up serum prolactin estimation revealed a value of 60ng/ml (2 - 29). Consequent upon the above laboratory and radiological findings, a provisional diagnosis of hyperprolactinaemia secondary to macroprolactinaemia was suggested. Based on this a serum sample was collected from the patient for macroprolactin screening using the polyethyleneglycol precipitation test. The test revealed a recovery (%) of less than 40% for monomeric prolactin. This was strongly suggestive of macroprolactinaemia and when combined with lack of features of hypogonadotrophic hypogonadism in the presence of severe hyperprolactinaemia, a diagnosis of macroprolactinaemia was made.

Table 1: Patient's day-21 fertility hormone profile

Hormone	Serum concentration	Reference interval
	7.5	
FSH (µIU/mL)	5.0	<20
PROG (ng/mL)	11.0	2.5 – 32.0
Estradiol (pg/mL)	66.0	60.0 – 150.0
PRL (ng/mL)	80.0	8.39 – 20.15
TSH (mIU/L)	2.6	0.2 – 5.0

Table 2: Patient's serial serum prolactin concentrations and percent monomeric PRL recovery

Date	25/09/10	09/10/10	3/4/11
Serum PRL (ng/mL)	80.0	76.2	60.0
% monomeric PRL Recovery (%R)	$\%R = \frac{\text{Serum PRL in supernatant}}{\text{Serum PRL before PEG precipitation}} \times 100\%$ $= \frac{16.9}{60.0} \times 100\%$ $= 28.2\%$		

NB: Macroprolactinaemia is conventionally defined by % monomeric PRL recovery =40%^{10,11}.

DISCUSSION

The case report has further highlighted macroprolactinaemia as an important but seldom recognized cause of biochemical hyperprolactinaemia among women of childbearing age. Macroprolactinaemia causes raised serum prolactin concentration without, in most cases, accompanying symptoms of the hyperprolactinaemic syndrome.³ The presence of high levels of macroprolactin in blood can cause a diagnostic and management confusion with regards to hyperprolactinaemia.^{5,8,9}

Prolactin is a 199-aminoacid protein hormone that is synthesized and secreted by the lactotrophic cells of the anterior pituitary gland.¹ It circulates in plasma in three molecular forms viz: monomeric PRL, big PRL and macro PRL.²⁷ Prolactin seems to play a permissive role in the regulation of reproduction. Normal levels of serum prolactin is a necessity for normal reproductive function in premenopausal females.¹² Commonly, increased circulating level of prolactin (hyperprolactinaemia) is associated with inhibition of synthesis and release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus.¹³ Thus, hyperprolactinaemia is a notable cause of hypogonadotrophic hypogonadism which is often characterized by oligomenorrhea/ amenorrhea; oligoovulation/anovulation and infertility among women of child-bearing age.¹⁴

Generally, the causes of hyperprolactinaemia may be physiological, pathological or idiopathic.⁴ Physiological hyperprolactinaemia occurs in pregnancy and lactation. Pathological hyperprolactinaemia can be caused by pituitary tumours, drugs, polycystic ovary syndrome, and hypothyroidism.⁴ Recently, macroprolactinaemia was recognized as a fairly common cause of biochemical hyperprolactinaemia.^{5,8} Macroprolactin has been shown to have little or no biological activity in *in vitro* bioassay studies.¹⁵ Thus, women with biochemical hyperprolactinaemia due to macroprolactinaemia may present with just few or no clinical features of the hyperprolactinaemic syndrome.^{3,7} Several reasons have been suggested on the relative biological inactivity of macroprolactin *in vivo*. The most plausible is the high-molecular weight nature of macroprolactin which prevents its interaction with cell-surface prolactin receptors.^{6,7} Macroprolactin mostly consists of a heteropolymeric complex of monomeric prolactin with IgG.^{7,16} It is also possible that the IgG that is avidly bound to prolactin are circulating anti-prolactin autoantibodies which are predominantly inhibitory in action.¹⁷

For our reported case, the patient persistently had

regular ovulatory menstrual cycles in the presence of severe hyperprolactinaemia. Expectedly, at this level of hyperprolactinaemia the symptoms of hyperprolactinaemia such as amenorrhea and galactorrhea would be present in the patient. However, the patient only had dysmenorrhea with cyclic frontal headache, which prompted the clinical, laboratory, and radiological evaluations. To further consolidate the diagnosis of macroprolactinaemia in this patient, brain CT scan result was normal, suggesting the absence of pituitary adenoma.

Macroprolactinaemia has been recognized as a frequent cause of misleading diagnosis, unnecessary investigation, and wrong treatment of affected patients.⁹ Our reported case was subjected to series of not-so-cheap investigations and treatment and yet the hyperprolactinaemia persisted. It has been emphasized that clinicians should be aware of the macroprolactin problem.³ Normal ovulatory cycles in the presence of sustained hyperprolactinaemia among premenopausal women should raise a suspicion of macroprolactinaemia.¹⁸ The ability to recognize this will save the patient the burden of unnecessary investigations and treatment which may not be cost-effective after all. Usually, a high-index of suspicion should be entertained. This should be followed by screening for macroprolactinaemia using the polyethyleneglycol precipitation method. This screening test has been extensively validated and adapted by most clinical laboratories in developed countries.^{10,11} It is also inexpensive, easy to carry out and amenable to routine laboratory application. Where available, the presence of macroprolactin should be confirmed using gel-filtration chromatographic (GFC) method for macroprolactin detection. The GFC method is the gold-standard and confirmatory test for macroprolactin detection.¹⁹ For our reported case, we were not able to carry out the GFC test due to unavailability and cost of the test procedure.

In most studies, macroprolactin screening were carried out for patients with persistent serum prolactin concentration that was above 700mIU/L (or 20ng/ml).^{3,9,10} Notwithstanding, screening for macroprolactinaemia has been recommended for all cases of biochemical hyperprolactinaemia with or without the presence of symptoms and signs of the hyperprolactinaemic syndrome.^{3,7,9}

CONCLUSION

This report has shown that macroprolactinaemia is a potential cause of hyperprolactinaemia in premenopausal Nigerian women. Macroprolactin is a heteropolymeric complex of monomeric PRL and IgG with little or no biological activity. Its presence should be suspected and investigated in premenopausal

women with sustained biochemical hyperprolactinaemia in the presence of normal regular ovulatory cycles. The timely detection of macroprolactin and diagnosis of macroprolactinaemia will avert diagnostic confusion and save affected patients from misleading diagnosis, inappropriate investigations, and unnecessary treatment.

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