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Macroprolactin and macroprolactinaemia: A narrative review

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Abstract

Background: Macroprolactin is a heteropolymeric complex of monomeric prolactin and immunoglobulin G (IgG) with little or no biological activity in vivo. Macroprolactinaemia is a notable cause of misdiagnosis and unnecessary treatment of patients with biochemical hyperprolactinaemia. Hence, it needs to be excluded in all patients with laboratory-established increase in serum prolactin levels. The polyethylene-glycol (PEG) precipitation method is commonly used for the routine laboratory screening for macroprolactinaemia.

Objective: To review the concept of macroprolactinaemia and its impact on the clinical manifestations, biochemical features, laboratory and radiological evaluations, and management of patients with hyperprolactinaemia.

Method: Review of available literature and selected references on macroprolactinaemia and its contribution to the aetiology of biochemical hyperprolactinaemia.

Conclusion: Macroprolactinaemia is diagnostically and clinically important in reproductive endocrinology practice. Routine laboratory screening of macroprolactinaemia using the PEG-precipitation method is highly recommended for all cases of hyperprolactinaemia.

Keywords: Hyperprolactinaemia; Macroprolactin; Macroprolactinaemia; PEG-precipitation method

1. Introduction

Prolactin is a polypeptide hormone synthesized and secreted by the acidophilic lactotrophic cells of the anterior pituitary gland[1]. It is one of the hormones that are commonly measured for the evaluation of amenorrhea and infertility in females or erectile dysfunction and infertility in males. It is also analyzed during biochemical assessment of patients with suspected hypothalamic or pituitary tumours. Increased plasma concentration of prolactin (hyperprolactinaemia) is a common endocrine abnormality that is frequently observed among women and men with disorders of fertility and reproduction [2,3].

Prolactin has been reported to circulate in plasma in three different molecular forms viz: monomeric prolactin (little prolactin), dimeric prolactin (big prolactin), and polymeric prolactin (big-big prolactin or macroprolactin)[4,5]. Monomeric prolactin has a molecular weight of approximately 23kilodaltons and consists of 199 amino acid residues with three inter-molecular disulphide linkages[6]. Dimeric prolactin or big prolactin has a molecular weight of 50 to 60kilodaltons while polymeric prolactin or macroprolactin has a molecular weight of 150 to 170kilodaltons[5]. Monomeric prolactin is known to be the most predominant form of prolactin in the blood circulation of healthy

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individuals as well as in most patients with hyperprolactinaemia. Big prolactin or macroprolactin may predominate only in a few patients with biochemical hyperprolactinaemia[7]. Hyperprolactinaemia secondary to elevated plasma concentration of macroprolactin has been referred to as macroprolactinaemia [8].

Macroprolactin has been shown to exhibit little or no biological activity *in vivo*[9]. Also, women with biochemical hyperprolactinaemia that is predominantly due to increased plasma levels of macroprolactin (macroprolactinaemia) have been reported to conceive with or without treatment of the hyperprolactinaemic condition[10,11]. Based on this, macroprolactinaemia is believed to represent a form of "pseudo-hyperprolactinaemia[12]. Macroprolactinaemia has been reported as a cause of frequent misdiagnosis and unnecessary treatment of women with biochemical hyperprolactinaemia [13,14].

Aim for review

The aim of this review is to highlight the concept of macroprolactin/ macroprolactinaemia and the need for clinical practitioners to be informed on the importance of excluding macroprolactinaemia as a possible cause of spurious and benign hyperprolactinaemia so as to avoid misdiagnosis and unnecessary treatment of affected patients.

1.1. Search methods and selection of literature

We selected articles published in English on the following key words: prolactin, hyperprolactinaemia, macroprolactin and macroprolactinaemia. The relevant articles on the above key words were searched for using Medline, Google Scholar, and Pubmed databases. Each selected publication was critically reviewed.

2. Hyperprolactinaemia

Hyperprolactinaemia has been observed as the most common disorder of the hypothalamic pituitary axis in clinical endocrinology practice[15,16]. It may be caused by physiological and pathological conditions that are associated with hypersecretion of prolactin by lactotrophs of the anterior pituitary gland[17]. Physiological causes of hyperprolactinaemia include: pregnancy and lactation[15,18]. Pathological hyperprolactinaemia may result from pituitary (lactotroph) adenoma or from several conditions that may interfere with normal dopamine inhibition of prolactin release such as: stress, hypothalamic or pituitary tumours, D_2-dopamine receptor blockers and hypothyroidism[19-22]. Hyperprolactinaemia has also been reported in patients with polycystic ovary syndrome and end-stage renal disease[23,24].

In a good number of patients with biochemical hyperprolactinaemia, no cause could be found despite application of extensive clinical, endocrinological, and neuroradiological work-up. In this category of individuals, hyperprolactinaemia was noted to persist for several years with or without the institution of dopaminergic therapy. These groups of patients were characterized as having a condition referred to as "idiopathic hyperprolactinaemia"[25]. A small percentage of patients with idiopathic hyperprolactinaemia was found to have extremely small prolactin-secreting microadenomas that defied available imaging techniques[26]. Again, some of the idiopathic hyperprolactinaemic patients were found to have macroprolactinaemia[27]. Hyperprolactinaemia seen especially in infertile women may suggest the presence of increased plasma concentration of macroprolactin (macroprolactinaemia)[28].

3. Nature of macroprolactin

Studies have revealed that macroprolactin, in most cases, consists of a heterpolymeric complex of monomeric prolactin and immunologlobin G (IgG)[29]. In addition, other less common forms of macroprolactin have been described especially in patients with prolactinomas. These forms are often composed of covalent or non-covalent homopolymers of monomeric prolactin with molecular weights that are up to 500kilodaltons[30,31]. Cavaco et al in their study confirmed that macroproalctin is in part, a complex of 23kilodalton prolactin with immunologlobulin G (IgG) and not an autoantibody that mimicked the action of prolactin as has been demonstrated for some isoforms of growth hormone[31].

Hattori and co-workers reported the presence of autoantibodies to prolactin in patients with macroprolactinaemia[32]. Their study was able to demonstrate that the IgG in their study subjects was complexed with monomeric prolactin. In summary, macroprolactin predominantly consists of a heteropolymeric complex of monomeric prolactin and IgG in plasma[31,33].

3.1. Definition of macroprolactinaemia

Macroprolactinaemia has been defined in various ways by different research groups. Generally, macroprolactinaemia is characterized by elevated serum macroprolactin concentration in the presence of serum monomeric prolactin level

that falls within normal reference limits[13,34]. Essentially macroprolactinaemia is a condition characterized by serum macroprolactin levels that are elevated while the monomeric prolactin concentrations remain within reference values[35]. Most laboratories that carry out routine screening for macroprolactinaemia base their definition of macrprolactinaemia on prolactin recoveries of less than 40% after treatment of sera with polyethylene-glycol (PEG) precipitation technique so as to distinguish between true hyperprolactinaemia and macroprolactinaemia[36-38]. The 40% cut-off routinely used for diagnosis of macroprolactinaemia is arbitrarily defined with little scientific basis. It has been observed that in some cases, recoveries of less than 40% may still be obtained in the presence of elevated monomeric prolactin concentration (true hyperprolactinaemia). The use of absolute cut-off to distinguish between true hyperprolactinaemia and macroprolactinaemia has been queried. Thus, it has been suggested that PEG recoveries that fall between 30% to 65% should be classified as intermediate with samples further subjected to gel filtration chromatography (GFC) for a definitive diagnosis[38,39].

3.2. Prevalence of macroprolactinaemia

Macroprolactionaemia as a cause of hyperprolactinaemia is often an overlooked diagnosis whose actual frequency is certainly underestimated[40]. It has been observed that macroprolactinaemia is somewhat common and a known cause of misdiagnosis, unnecessary investigation and inappropriate treatment for patients with biochemical hyperprolactinaemia[12-14]. The prevalence of macroprolactinaemia has been reported to be between 0.1% and 0.2% in the general population[41]. Macroprolactinaemia has also been reported to account for approximately 26% of all cases of hyperprolactinaemia[36]. Some clinical laboratories that carryout routine screening of macroprolactin have reported about 20% to 30% prevalence of macroprolactinaemia among hyperprolactinaemic samples[9,42-46]. Studies have shown that prevalence of macroprolactinaemia depends on the method of macroprolactin detection. Gibney et al in their retrospective study, reported a 22% prevalence rate of macroprolactinaemia among all hyperprolactinaemic samples identified in their laboratory over a 5year period using the PEG precipitation method[47].

With regard to gender and age of occurrence, macroprolactinaemia has been observed in both sexes and in children[48,49]. However, about 90% of reported cases of macroprolactinaemia occur in females[28]. In women, macroprolactinaemia has been found to be seldom associated with menstrual disorders, infertility and galactorrhea[9-11]. In men, it has been noted that gonadotropin function is usually preserved despite alleged association of macroprolactinaemia with erectile dysfunction[48].

3.3. Biological activity of macroprolactin

Macroprolactin has been shown to exhibit varying degrees of biological activity *in-vitro*[10]. However, because of its high molecular weight, macroprolactin tends to be confined intravascularly *in-vivo,* hence it is unable to traverse cellular membranes and as such is physiologically not bioavailable and inactive[12, 29]. Again, a delayed metabolic clearance of macroprolactin has been suggested[32]. Owing to the little or no biological activity of macroprolactin, a good proportion of patients with macroproalctinaemia seldom present with the classical symptoms of the hyperprolactinaemic syndrome[8-10]. Notwithstanding, a small percentage of women with established diagnosis of macroprolactinaemia may present with typical features whereas others may present with varying degrees of oligomenorrhea, amenorrhea, galactorrhea or infertility[9,47]. Several studies have reported that some cases of macroprolactinaemia presented with clinical symptoms of hyperprolactinaemia. However, in approximately 81% of the cases, fertility is maintained[11,12]. Macroprolactinaemia has also been reported in men with sexual dysfunction[48]. However, the functional activities of the gonadotropins are preserved in these male subjects.

Hyperprolactinaemia due to elevation of plasma concentrations of the biologically active monomeric prolactin is usually associated with suppression of gonadotropins' secretion and gonadal dysfunction[10,15,16]. In contrast, macroprolactinaemic patients are known to have little or no abnormal gonadotropin and gonadal functions. Nevertheless, as stated above, some common and non-specific symptoms of true hyperprolactinaemia may occasionally be observed in patients with macroprolactinaemia[9,10]. Olukoga tried to explain this phenomenon by suggesting that; the macroprolactin complex may dissociate *in vivo* in some of the affected individuals[50]. This will release the bioactive monomeric prolactin that causes symptoms of hyperprolactinaemia. Macroprolactinaemia does not affect the regulation of anterior pituitary secretion of monomeric prolactin. In addition, in cases of macroprolactinaemia, the response of pituitary secretion of monomeric prolactin to dopamine antagonists remains normal[7,8].

3.4. Biochemical and clinical features of macroprolactinaemia

In healthy individuals and most patients with true hyperprolactinaemia, macroprolactin makes little or no contribution to the total plasma prolactin concentration. Usually, monomeric prolactin constitutes about 85% to 95% while macroprolactin constitutes approximately less than 1% of total serum prolactin levels in healthy adults[34,41,47]. Plasma

levels of leutenizing hormone (LH) and estradiol have been found to be higher in macroprolactinaemic patients when compared with true hyperprolactinaemic patients[13,47]. This finding is in keeping with the reduced ability of macroprolactin to suppress the hypothalamic-pituitary-gonadal axis. It may also explain the limited bioactivity of macroprolactin *in vivo.* Notwithstanding, a significant overlap between the biochemical and clinical features of macroprolactinaemia and true hyperprolactinaemia has been observed[9,10].

Gibney et al observed that clinically, macroprolactinaemic subjects could not be distinguished from true hyperprolactinaemic patients except by screening for macroprolactin[47]. From their study, they reported that oligomenorrhea and galactorrhea occurred less frequently in patients with macroprolactinaemia. Vallette-Kasic and coworkers reported that a significant proportion of patients with macroprolactinaemia appeared to have common symptoms of the hyperprolactinaemic syndrome such as: menstrual irregularities, infertility and galactorrhea[41]. They observed that circumstances that have prompted the suspicion and diagnosis of macroprolactinaemia included: infertility (29%), menstrual disorders (36%), and galactonhea (46%). Despite the occurrence of some of the symptoms of the hyperprolactinaemic syndrome in macroprolactinaemia, fertility is maintained in about 81% of women with macroprolactinaemia[8,10,12,47].

Plasma prolactin concentration is usually moderately elevated in conditions of macroprolactinaemia. However, it may be markedly elevated to the level of 3,600mlU/L[41]. Serum prolactin levels have been observed to remain stable overtime in subjects with macroprolactinaemia with or without treatment of the coexisting symptoms[51,52]. In a few number of cases, macroprolactinaemia has been reported in patients with pituitary lesions such as prolactinoma[53].

3.5. Detection and measurement of macroprolactin

Various methods have been used to isolate and subsequently detect the presence of macroproalctin in hyperprolactinaemic sera. Majority of the methods involve the pretreatment of the hyperprolactinaemic sera with substances that precipitate macroprolactin out of biological solutions. Examples of these precipitants include: polyethyleneglycol (PEG), protein A (pA) protein G (PG), anti-human immunoglobulin G (anti-hlgG), and ultra-filtration (UA)[54-59]. Gel-filtration chromatography (GFC) is regarded as the "gold standard" for separation of bioactive monomeric prolactin from sera containing both monomeric prolactin and macroprolactin[54,55]. The GFC method is comparatively more expensive than the above-mentioned pretreatment methods. It is also labour-intensive and requires the measurement of prolactin in multiple fractions. For these reasons, the pretreatment methods (especially the PEG precipitation method) are commonly used in the routine clinical laboratory[57].

For the pretreatment methods, each serum sample requires 2 estimates of prolactin concentration, the first to establish the presence of biochemical hyperprolactinaemia and secondly to measure the residual prolactin concentration after pretreatment of the serum sample with the pretreatment method. The PEG-precipitation method has been found to be cost-effective and as such is widely used in most clinical laboratories to screen for macroprolactinaemia[54-57]. It is simple and amenable to use in the routine clinical laboratory. It is commonly regarded as the method of choice for simultaneous removal of both macroprolactin and big-prolactin from hyperprolactinaemic sera[57]. It provides the best correlation with the GFC method, achieves acceptable precision, and is the least expensive. It has been extensively evaluated and validated against the GFC method with acceptable outcomes[36,55,57,60].

3.6. Screening for macroprolactinaemia

Macroprolactinaemia has long been recognized as an established cause of biochemical hyperprolactinaemia in clinical endocrinology practice[14,27]. Despite the diagnostic and clinical implications of macroprolactinaemia, it is surprising that screening for macroprolactinaemia in women with hyperprolactinaemia is not routinely carried out in most clinical laboratories especially in developing countries like Nigeria. Globally, it has been observed that testing for macroprolactin is not common outside the United Kingdom, USA, and Ireland[46]. This may have resulted from the uncertainty that surrounded the nature, *in vivo* bioactivity, and clinical significance of macroprolactin/ macroprolactinaemia. Clinically, macroprolactinaemia as a cause of "pseudohyperprolactinaemia" can lead to wrong diagnosis, unnecessary laboratory and radiological investigations, and inappropriate treatment of affected patients[12,13]. For this reason, it is very pertinent to identify individuals with macroprolactinaemia. This, in effect, has informed the need for routine screening for macroprolactinaemia in patients with established diagnosis of biochemical hyperprlactinaemia.

In practice, all hyperprolactinaemic patients with associated discrepancy in their clinical biochemical or follow-up data are candidates for macroprolactin screening[61,62]. Screening for macroprolactinaemia is highly indicated among the following categories of individuals: (1) patients with hyperprolactinaemia in the presence of normal gonadal function; (2) patients diagnosed as having "idiopathic hyperprolactinaemia" after other identifiable causes of increased plasma,

prolactin concentrations are excluded; (3) hyperprolactinaemic patients that show lack of normalization of serum prolactin values despite appropriate medical or surgical treatment; (4) patients that exhibited marked discrepancy in serum prolactin results after using different immunoaasay methods.[33-35,41].

In several clinical laboratories the PEG-precipitation method has been adopted for routine screening of macroprolactinaemia in hyperprolactinaemic individuals. Review of available literature reveals that serum prolactin concentrations greater than and equal to 700mlU/L (20ng/ml) were subjected to macroprolactin screening[7,34-39]. However, it has been recommended that the cut-off value for serum prolactin that calls for macroprolactin testing should be determined by individual laboratories based on the prolactin immunoassay that is used routinely in the laboratory[58,63].

3.7. Management of patients with macroprolactinaemia

Before the introduction of routine laboratory screening for macroprolactin, patients with biochemical hyperprolactinaemia were managed according to the known pathology that underlies the hyperprolactinaemia[64]. Most macroprolactinaemic patients before the routine screening of macroprolactin had pituitary imaging with negative results and were treated with dopamine agonists such as bromocriptine[65].

Some of these patients were erroneously managed by surgical procedures such as transphenoidal exploration and adenomectomy.

Treatment of macroprolactinaemic patients with dopamine agonists has been noted to produce improvements of some of the symptoms of hyperprolactinaemic syndrome such as galactorrhea[41]. Improved galactorrhea after dopamine agonists treatment may be misleading in this category of patients. This is because dopamine agonists therapy has been discovered to also correct galactorrhea in normoprolactinaemic women. Valette Kasic et al reported that dopamine agonist therapy in macroprolactinaemic patients led to reduction and normalization of monomeric prolactin concentrations[41]. However, in some patients, macroprolactinaemia may produce a pseudo-resistance to dopamineigic therapy with associated failure of normalization of serum prolactin levels[12]. Furthermore, prolactin levels in patients with macroprolactinaemia have been reported to decrease after about five years follow-up with or without dopamine agonist therapy. Nevertheless, some study groups have reported that serum prolactin levels remain stable overtime in macroprolactinaemic individuals[51,52].

4. Conclusion

The review of available literature has shown that macroprolactin has gone from an emerging concept to an established phenomenon in the fields of clinical endocrinology and gynaecology. It is therefore, of much clinical importance for macroprolactinaemia to be ruled out as a cause of "pseudo-hyperprolactinaemia" so as to avoid the subjection of patients with biochemical hyperprolactinaemia to unwarranted investigations and therapeutic procedures. There is the need for concerned clinicians and gynaecologists to entertain a high index of suspicion with regard to macroprolactinaemia as a potential cause of biochemical hyperprolactinaemia. It would also be a welcome development for each clinical laboratory to evaluate and validate the available method(s) of macroprolactin screening in their local centres especially the strongly recommended PEG-precipitation method.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Authors' Contribution

IECO and OHC conceptualized the work. IECO, OHC, and IOU contributed to the literature review. OHC and IECO prepared the manuscript. IECO and IOU proofread the final manuscript before submission. All authors approved the submission of the manuscript for publication.

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