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Importance of macroprolactinemia in hyperprolactinemia

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ABSTRACT

Macroprolactin is an antigen–antibody complex of higher molecular mass than prolactin (>150 kDa), consisting of monomeric prolactin and immunoglobulin G. The term 'macroprolactinemia' is used when the concentration of macroprolactin exceeds 60% of the total serum prolactin concentration determined by polyethylene glycol precipitation. The gold standard technique for the diagnosis of macroprolactinemia is gel filtration chromatography. The prevalence of macroprolactinemia in hyperprolactinemic populations varies between 15% and 35%. Although the pathogenesis of these antibodies is not clear, it is possible that changes in the pituitary prolactin molecule represent increased antigenicity to the immune system, leading to the production of anti-prolactin antibodies. Mild hyperprolactinemia usually occurs because macroprolactin is not cleared readily from the circulation due to its higher molecular weight. Moreover, the hypothalamic negative feedback mechanism for autoantibody-bound prolactin is inactive because macroprolactin cannot access the hypothalamus, resulting in hyperprolactinemia. Reduced in-vivo bioactivity of macroprolactin may be the reason for the lack of hyperprolactinemic symptoms. It also seems that anti-prolactin autoantibodies may compete with prolactin molecules for receptor binding, resulting in low bioactivity. Additionally, the large molecular size of macroprolactin confined in the intravascular compartment prevents its passage through the capillary endothelium to the target cells, which may be the reason for the lack of symptoms.

Macroprolactinemia is considered to be a benign clinical condition in patients with normal concentrations of bioactive monomeric prolactin, with a lack, or low incidence, of hyperprolactinemic symptoms and negative pituitary imaging. In such cases with resistance to anti-prolactinaemic drugs, no pharmacological treatment, diagnostic investigations or prolonged follow-up are required. However, macroprolactinemia may also occur in patients with conventional symptoms of hyperprolactinemia who cannot be differentiated from patients with true hyperprolactinemia. These symptoms are mainly attributed to excess levels of monomeric prolactin, and this is of concern. The diagnosis of macroprolactinemia is misleading and inappropriate. A multitude of physiological, pharmacological and pathological causes, including stress, prolactinomas, hypothyroidism, renal and hepatic failure, intercostal nerve stimulation and polycystic ovary disease, can contribute to increased levels of monomeric prolactin. It is important for patients with elevated monomeric prolactin levels to undergo routine evaluation to identify the exact pathological state and introduce adequate treatment, regardless of the presence of macroprolactin. In addition, macroprolactinemia occasionally occurs due to macroprolactin associated with pituitary adenomas, with biological activity of macroprolactin comparable with that of monomeric prolactin. In cases when excess macroprolactin occurs with clinical manifestations of hyperprolactinemia, macroprolactinemia should be regarded as a pathological biochemical variant of hyperprolactinemia. An individualized approach to the management of such patients with macroprolactinemia may be necessary, and pituitary imaging, dopamine treatment and prolonged follow-up should be applied.

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Introduction

Prolactin (PRL) is a single globular polypeptide hormone, synthesized and secreted by pituitary lactotroph cells. It exists in heterogeneous sizes in serum, with three major variants: monomeric, dimeric and polymeric isoforms. PRL is synthesized as a prehormone (molecular weight 26 kDa), and after cleavage, the resulting hormone is a monomeric isoform of PRL (molecular weight 23 kDa). Monomeric PRL is the major form in the blood of subjects with normoprolactinaemia and true hyperprolactinemia, accounting for 80–95% of the total PRL. It is known to be both biologically and immunologically active in vivo with a half-life of 26–47 min. The other forms of PRL include the dimeric (molecular weight 48–56 kDa) and polymeric (molecular weight >150 Da) isoforms and macroprolactin. In normal sera, the dimeric isoform accounts for <10% of total PRL, and the polymeric isoform accounts for a small (<1%) but variable percentage of total PRL; these two forms are known to have lower biological activity than monomeric PRL. The term 'macroprolactinemia' is characterized by the predominance of macroprolactin, and it is mainly suspected in asymptomatic subjects or those without typical hyperprolactinemia-related symptoms. In addition to prolactinomas and neuroleptics/anti-psychotic agents, macroprolactinemia is one of the three most common causes of hyperproplactinaemia [1]. The nature of macroprolactin is heterogenous, and it is generally identified as an antigen–antibody complex of high stability consisting primarily of monomeric PRL and immunoglobulin (Ig) G. However, non-IgG-bound forms of macroprolactin (complexes with IgA or IgM, highly glycosylated monomeric PRL, covalent or non-covalent aggregates of monomeric PRL) are occasionally detected, mainly in sera with marginally elevated levels. In spite of low in-vitro bioactivity, the complex appears to lack in-vivo bioactivity, although macroprolactin retains its immunoreactivity properties. Due to its high molecular weight, macroprolactin is confined to the vascular system; this may reduce its access to the PRL receptors of target organs in the periphery, as well as centrally, resulting in asymptomatic hyperprolactinemia [2,3]. Typical symptoms of hyperprolactinemia (oligomenorrhoea, amenorrhoea, galactorrhoea, infertility etc.) and abnormal imaging changes in the pituitary gland are not common in patients in whom macroprolactin is the predominant form of PRL. These IgG-type autoantibodies have low affinity and high capacity, and long-term follow-up has revealed that macroprolactinemia may be a long-lasting condition [3,4]. In patients with macroprolactinemia and normal concentrations of monomeric PRL, a low incidence of hyperprolactinemia-related symptoms was reported during prolonged follow-up. It has been suggested that macroprolactinemia should be considered as a benign variant with mildly elevated PRL levels, and a cause of evident resistance to anti-prolactinaemic drugs. Moreover, such patients can be reassured because no pituitary imaging investigations, dopamine agonist treatments or prolonged follow-up are necessary [5]. In addition, routine screening of all hyperprolactinemic sera for macroprolactin may be recommended, because reduced use of imaging and dopamine agonist treatment in patients with macroprolactinemia would result in net cost savings [6].

However, not all patients with macroprolactinemia lack clinical symptoms. There have been a number of reports regarding overlapping of the main hyperprolactinemic symptoms due to increased levels of monomeric PRL in subjects with true hyperprolactinemia and subjects with macroprolactinemia [7–11]. Moreover, no laboratory features in addition to clinical features were able to differentiate reliably between patients with macroprolactinemia and patients with monomeric hyperprolactinemia [8]. Comparison of multiple methods for the identification of hyperprolactinemia in the presence of macroprolactin revealed no difference in the prevalence of abnormal menses, galactorrhoea or abnormal pituitary imaging between patients with and without macroprolactin [9]. Although oligomenorrhoea and galactorrhoea occurred more frequently in patients with true hyperprolactinemia, they also occurred in 57% and 29%, respectively, of patients with macroprolactinemia, and these differences were not sufficient to distinguish between the two groups on the basis of clinical symptoms alone. Moreover, hyperprolactinemia due to macroprolactin led to diagnostic confusion, unnecessary investigations and unsuitable treatment before the introduction of macroprolactin screening by application of a reference interval to polyethylene glycol (PEG)-treated hyperprolactinemic sera [10]. Therefore, it is important that laboratories introduce screening programs to examine samples with elevated total immunoreactive PRL for the presence of macroprolactin, and to determine the monomeric PRL component that is responsible for bioactivity in vivo [11]. In a recent study, a few cases of macroprolactinemia of pituitary origin associated with prolactinoma experienced similar clinical manifestations comparable with monomeric hyperprolactinemia, and their disappearance after treatment with dopamine agonists suggested bioactivity of macroprolactin. Therefore, in spite of the fact that macroprolactinemia is considered to be a benign condition, pituitary imaging and conservative treatment with dopamine agonists and prolonged follow-up should be applied in these rare cases, as well as in patients with macroprolactinemia with elevated monomeric hyperprolactinemia [12]. This review will report various clinical features of macroprolactinemia explained through pathophysiological mechanisms, suggesting different approaches that could improve identification and adequate management of such patients.

Prevalence

The rate of macroprolactinemia in the general population has previously been reported at 0.2% in women and 0.02% in men [13]. However, macroprolactinemia may be more common, with a recently reported prevalence of 3.7% and no difference in prevalence between genders [14]. As the reported proportion of macroprolactinemia in hyperprolactinemic populations is much higher in most studies, and varies between 15% and 35% (mean prevalence 25%), macroprolactinemia is considered to be a

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