

## Case report

### Macroprolactinemia and Empty Sella Syndrome



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#### Abstract

Macroprolactinemia is a polymeric form of prolactin-release, causing mildly symptomatic clinical pictures. The former can be isolated or associated with other causes of hyperprolactinemia. The association with an empty sella syndrome is rare. We report a case of a female patient discovered with this association. It's about a female patient 47 years old, followed up since the age of 31 years for bilateral galactorrhea and a spaniomenorrhoea. There has been no associated drug intake. Her exploration has showed a serum prolactin level of 635 mIU/L. Thyroid test results were normal T4 = 10,2ng/L and TSH = 1.76 mIU/L. A brain scan has showed an empty sella turcica. Despite the unchanged levels of prolactinemia, the evolution under dopaminergic 5 mg /D has been marked by the occurrence of a pregnancy with persistent moderate hyperprolactinemia in the postpartum. Chromatography has showed a predominance of the macroprolactin form with: Prolactin monomer at 4.8%, Big Prolactin at 5% and Big Big Prolactin at 83%, thus stopping bromocriptine. Our observation suggests that macroprolactinemia can be associated with conventional etiologies of moderate hyperprolactinemia as the empty sella syndrome. Its detection would prevent the use of dopaminergic therapy which seems not useful.

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## Introduction

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Prolactin (PRL) exists in the blood under many forms: monomeric (60 to 85%), polymeric and PRL-protein complexes of higher molecular weight [1]. Macroprolactinemia is a polymeric form of prolactin-release, causing mildly symptomatic clinical pictures [2]. The former can be isolated or associated with other causes of hyperprolactinemia [3]. We report the case of a macroprolactinemia being discovered in a patient with an empty sella Syndrome.

## Patient and observation

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It consists in a 47 years old female patient, who has been followed up since the age of 31 years for bilateral galactorrhea and a spaniomenorrhoea. There has been no associated drug intake. Her exploration has showed a serum prolactin level of 635 mIU /L. Thyroid test results were normal T4 = 10,2ng/L and TSH = 1.76 mIU/L. A brain scan has showed an empty sella turcica. Despite the unchanged levels of prolactinemia, the evolution under dopaminergic 5 mg /D has been marked by the occurrence of a pregnancy with persistent moderate hyperprolactinemia in the postpartum. The patient has had menopause at the age of 47, with elevated gonadotrophins FSH = 78 mIU/mL, LH = 33 mIU/mL and estradiol: 35 pg/mL. Chromatography has showed a predominance of the macroprolactin form with: Prolactin monomer at 4.8%, Big Prolactin at 5% and Big Big Prolactin at 83%. After the discovery of the macroprolactinemia, we decided to stop bromocriptin treatment. The clinical evolution of the patient is favorable without drugs intake.

**Abbreviations:** PRL: Prolactin; FSH: Follicle-stimulating Hormone; LH: luteinizing hormone.

## Discussion

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We report a case of a patient with an association of empty sella Syndrome and macroprolactinemia. Macroprolactin is a non-bioactive prolactin isoform usually composed of a prolactin monomer and an IgG molecule having a prolonged clearance rate similar to that of immunoglobulins. The clinical picture may be completely asymptomatic [2] or mildly symptomatic in 22-46% of

cases as in our observation. [3]. The big big prolactin isoform, is considered idiopathic and poorly symptomatic. Furthermore, the macroprolactinemia has been raised in our perception ahead of the non-functional character of hyperprolactinemia evidenced by the occurrence of pregnancy and after the menopause, although hyperprolactinemia has persisted which seems insensitive to bromocriptine [4], suggesting its non-functional character. Anderson AN and Al have as well evoked a case of a female patient, in whom a pregnancy occurred [5], with macroprolactinemia. The frequency of macroprolactinemia in pregnancy has been assessed by Hattori N. et al; over 109 pregnant women, 3 (2.9%) of them have had a macroprolactinemia [6]. Several dosing methods serve to diagnose macroprolactinemia [7]. Its detection with most of the available immunoassays in the same way as the monomeric form of PRL may result in a false diagnosis of hyperprolactinemia. In our case, the diagnosis has been confirmed by Gel permeation chromatography, which remains the method of choice for its detection [7, 8]. The high molecular-weight forms are predominant, despite their reduced biological activity, so they lead to overestimation of prolactinemia measured by classical immunoassays.

Macroprolactinemia is a common cause of hyperprolactinemia [9], but its research is not systematic [4]. According to two studies on 1225 [3] and 2089 [10] blood samples, macroprolactinemia frequencies have been estimated by 26% and 22% respectively. In another study realized by Alfonso A. and al on 40 patients with hyperprolactinemia, 18 (45%) have had macroprolactinemia [11]. The big-big prolactin was considered for a long time as a rather rare form of hyperprolactinemia. Nevertheless it seems to be much more present than it was initially studied. Macroprolactinemia is usually isolated [12], constituting the diagnosis of exclusion after a negative etiological investigation [2, 9]. The etiological research requires clinical, biological and radiological investigations including MRI [13], which objectified the empty sella in our patient. Although macroprolactin is commonly found in patients with hyperprolactinemia, neither symptoms nor MRI findings are useful in predicting its presence. The particularity of our case is that, it is associated with a common cause of hyperprolactinemia which is the empty sella syndrome [14]. This association has not been described; however associations with a prolactinoma are possible. Mounier et al have conducted a study on patients with macroprolactinemia, with whom we have discovered a micro-pituitary adenoma associated [15].

Macroprolactinemia reported during the Prolactinoma can reach up to 76% of the secreted prolactin. It is in fact composed of the complex monomer prolactin and circulating immunoglobulin G [16]. This fixation suggests that big big PRL has a lower receptor affinity due to the interference of the immunoglobulin and may account for the lack of clinical and biological effect upon the patient. Its high molecular weight may also reduce its access to target organs and be part to explain the poor clinical symptoms. The discovery of a macroprolactinemia may have an important clinical and therapeutic impact [1, 17], formerly neglected [9], avoiding the dopaminergic treatment led on our patient without interest for many years, as cited Vaishya and al. [4]. Several studies recommend systematic prolactin test [4, 9, 12, 18]. As these hyperprolactinemias are not pathological, a simple detection test using polyethylene glycol has been validated to avoid unnecessary investigations. Even if the clinical significance of macro-prolactinemia remains uncertain, the long-term assessment without treatment seems favorable [19]. There is a need to explore the diagnosis and pathophysiology of macroprolactinemia for improving patient care. A valid diagnostic method must be available in African centers to avoid unnecessary hormonal or radiological investigations and excessive treatments, exposing patients to several side effects.

## Conclusion

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Our observation suggests that macroprolactinemia can be associated with conventional etiologies of moderate hyperprolactinemia as the empty sella syndrome. Its detection would prevent the use of dopaminergic therapy and excessive investigations.

## Competing interests

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The authors declare no competing interest.

## Authors' contributions

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Dr Ach Taieb wrote the manuscript. All the co-authors are the member staff of the Endocrinology and Diabetes Department-University Hospital Farhat Hached Sousse. They collaborated in the

treatment process of the patient and in writing of the manuscript. All authors have read and agreed to the final version of this manuscript.

## References

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1. Marteil AM, Sapin R, Jean Didier N. La macroprolactine: implications biologiques et cliniques. *Immuno-analyse & Biologie Spécialisée*. 01 November 2000; 15(6): 396-401. **Google Scholar**
2. Whittaker PG, Wilcox T, Lind T. Maintained fertility in a patient with hyperprolactinemia due to big, big prolactin. *J Clin Endocrinol Metab*. 1981 Oct; 53(4): 863-6. **PubMed | Google Scholar**
3. Leslie H, Courtney CH, Bell PM, Hadden DR, McCance DR, Ellis PK et al. Laboratory and clinical experience in 55 patients with macroprolactinemia identified by a simple polyethylene glycol precipitation method. *J Clin Endocrinol Metab*. 2001 Jun; 86(6): 2743-6. **PubMed | Google Scholar**
4. Richa V, Rahul G, Sarika A. Macroprolactin; a frequent cause of misdiagnosed hyperprolactinemia in clinical practice. *J Reprod Infertil*. 2010 Oct-Dec; 11(3): 161–167. **PubMed | Google Scholar**
5. Andersen AN, Pedersen H, Djursing H, Andersen BN, Friesen HG. Bioactivity of prolactin in a woman with an excess of large molecular size prolactin, persistent hyperprolactinemia and spontaneous conception. *Fertility and sterility*. 1982 Nov; 38(5): 625-8. **Google Scholar**
6. Hattori N. The frequency of macroprolactinemia in pregnant women and the heterogeneity of its etiologies. *J Clin Endocrinol Metab*. 1996 Feb; 81(2): 586-90. **PubMed | Google Scholar**
7. Coussieu C. Le dosage de la prolactine aujourd'hui. *Immunoanal Biol Spéc*. 2000; 15: 186-90. **Google Scholar**

8. Gilson G, Schmit P, Thix J, Hoffman JP, Humbel RL. Prolactin results for samples containing macroprolactin are method and sample dependent. *Clin Chem*. 2001 Feb; 47(2): 331-3. **PubMed | Google Scholar**
9. Cortet-Rudelli C, Sapin R, Bonneville JF, Brue T. Etiological diagnosis of hyperprolactinemia. *Ann Endocrinol (Paris)*. 2007 Jun; 68(2-3): 98-105. **PubMed | Google Scholar**
10. Gibney J, Smith TP, McKenna TJ. The impact on clinical practice of routine screening for macroprolactin. *J Clin Endocrinol Metab*. 2005 Jul; 90(7): 3927-32. **PubMed | Google Scholar**
11. Alfonso A, Rieniets KI, Vigersky RA. Incidence and clinical significance of elevated macroprolactin levels in patients with hyperprolactinemia. *Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. 2006 May-Jun;12(3): 275-80. **Google Scholar**
12. Suliman AM, Smith TP, Gibney J, McKenna TJ. Frequent misdiagnosis and mismanagement of hyperprolactinemic patients before the introduction of macroprolactin screening: application of a new strict laboratory definition of macroprolactinemia. *Clin Chem*. 2003 Sep; 49(9): 1504-9. **PubMed | Google Scholar**
13. Donadio F, Barbieri A, Angioni R, Mantovani G, Beck-Peccoz P, Spada A et al. Patients with macroprolactinaemia: clinical and radiological features. *Eur J Clin Invest*. 2007 Jul; 37(7): 552-7. **PubMed | Google Scholar**
14. Fahie-Wilson M, Smith TP. Determination of prolactin: The macroprolactin problem. *Best Pract Res Clin Endocrinol Metab*. 2013 Oct; 27(5): 725-42. **PubMed | Google Scholar**
15. Mounier C, Trouillas J, Claustrat B, Duthel R, Estour B. Macroprolactinaemia associated with prolactin adenoma. *Hum Reprod*. 2003 Apr; 18(4): 853-7. **PubMed | Google Scholar**
16. Cavaco B, Leite V, Santos MA, Arranhado E, Sobrinho LG. Some forms of big big prolactin behave as a complex of monomeric prolactin with an immunoglobulin G in patients with macroprolactinemia or prolactinoma. *J Clin Endocrinol Metab*. 1995 Aug; 80(8): 2342-6. **PubMed | Google Scholar**
17. Olukoga AO. Macroprolactinemia is clinically important. *J Clin Endocrinol Metab*. 2002 Oct; 87(10): 4833-4; author reply 4834. **PubMed | Google Scholar**
18. Sapin R, Schlienger JL. Macroprolactinémie. *Immunoanalyse & Biologie Spécialisée*. 2005; 419(5): 265-342. **Google Scholar**
19. Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange S, Enjalbert A et al. Macroprolactinemia revisited: a study on 106 patients. *J Clin Endocrinol Metab*. 2002 Feb; 87(2): 581-8. **PubMed | Google Scholar**