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Case Report

Macroprolactinemia – frequent cause of misdiagnosis and mistreatment- A Case Report

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Abstract

Objectives: Macroprolactinemia has often been neglected in the differential diagnosis of hyperprolactinemia, mainly due to the lack of adequate diagnostic methods and awareness among clinicians. This has led to subjecting the patients to a myriad of unnecessary investigations and therapies. Technical difficulties in identification of this molecule have hindered the accurate determination of its frequency and extent of interference. Differentiation between macroprolactinemia and true hyperprolactinemia is a promising concept that will effectively guide the therapy protocol while treating patients.
A 25 year old female, investigated for irregular cycles and secondary infertility and was started with cabergoline regime inappropriately without determination of true prolactin levels which was discontinued after few months.
Methods: Thyroid and fertility hormone profile (FSH, LH, Prolactin, Testosterone, DHEAS, Estradiol, Free T3, Free T4, and TSH) estimation was done in the institutional clinical chemistry laboratory using enhanced chemiluminescence immunoassay on Vitros-Eci platform (Orthoclinical Diagnostics, USA). Polyethylene glycol precipitation test was used to assess the presence of macroprolactin in patient's serum.
Results: Biochemical findings were suggestive of mild elevation in TSH (5.45 mIU/mL) and elevated prolactin levels (51.3ng/ml). A high LH: FSH ratio along with mild hyperandrogenemia was suggestive of PCOS. True prolactin was estimated using PEG precipitation method and the result obtained was 4.7ng/mL.
Conclusion: The patient had a normal conception after 3 months of therapeutic dose adjustments of thyroxine, regardless of higher total prolactin levels. The finding suggests that determination of true prolactin levels precludes the need of further examinations and medications if the concentrations after precipitating macroprolactin with PEG are normal.
Keywords: Macroprolactin, true prolactin, Polyethylene Glycol, Chemiluminescence

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1. Introduction

Macroprolactinemia has time and again been neglected in the differential diagnosis of hyperprolactinemia, mainly due to the lack of adequate diagnostic methods and lack of awareness among specialists. Consequently, patients have often been subjected to unnecessary diagnostic investigations, treatment and follow-ups. The need to differentiate between macroprolactinemia and true hyperprolactinemia, which requires therapy, is a promising concept.

2. Case Study

A 25 year old female was investigated by the clinician for irregular cycles and secondary infertility. She was a known case of hypothyroidism on medication since past four years. Evaluation for the cause of secondary infertility revealed bilateral polycystic ovarian disease (PCOD) with high prolactin levels observed on multiple occasions three months apart. The patient presented in the Department of Endocrinology in the tertiary care hospital in

December 2018 as a follow up case of secondary infertility. She had been on thyroxine 100 µg for the past 5 years. She had been euthyroid with TSH levels ranging from 0.5 to 3.6 m IU/ml. However prolactin levels remained high at around 50 ng/ml inspite of euthyroidism. She was also taking metformin 250 mg BD for PCOS. She had received cabergoline 0.5 mg for few months in the past which she had discontinued. Repeat investigations for thyroid and patient's fertility profile (Day 2 sample) were performed in the institutional clinical chemistry laboratory by using enhanced chemiluminescence immunoassay on the platform Vitros-Eci (Orthoclinical Diagnostics, USA).

2. Materials and Methods

This case report is a retrospective review of the clinical findings and medical records of the patient and due informed consent was solicited from the patient for the same.

Thyroid and fertility hormone profile (FSH, LH, Prolactin, Testosterone, DHEAS, Estradiol, Free T3, Free T4, and TSH) estimation was done in the institutional clinical chemistry laboratory using enhanced chemiluminescence immunoassay on Vitros-Eci platform (Orthoclinical Diagnostics, USA).

Table 1: Thyroid and Fertility Profile of the patient

Parameter	Result	Units	Reference Range
FSH	8.49	mIU/Ll	1.3-23.4 (fertile females)
LH	15.4	mIU/mL	0.8-15.5 (fertile females)
Prolactin	51.3	ng/mL	3-18.6
Testosterone	1.53	nmol/L	0.198-2.67 (females)
DHEAS	1.2	µg/mL	0.48-2.75 (females)
Estradiol	113.5	pmol/L	97.5-592 (follicular phase)
Free T3	1.12	pg/mL	2-4.4
Free T4	0.1	ng/dL	0.6-1.2
TSH	5.45	mIU/mL	0.5-5

The macroprolactin in the serum sample was detected by (Polyethylene Glycol) PEG-6000 precipitation test. Precipitation with PEG was carried out by adding 200 µl of serum to 200 µl of 25g/L (25%) of PEG-6000 (Sigma Aldrich). 25% solution of PEG-6000 was prepared by dissolving 25 gm of PEG-6000 powder in 100 ml of phosphate buffered saline (PBS) pH 7.4. After thorough mixing and vortexing the mixture was centrifuged at 1500g for 30 minutes at 4°C in refrigerated centrifuge. The supernatant was removed for prolactin estimation. Recovery of PRL after precipitation with PEG was determined by comparison with a dilution of 200 µl of serum in 200 µl of 10 mmol/L PBS (pH 7.4). Prolactin in the supernatant after precipitation of serum with PEG and in the diluted serum was measured as for untreated serum using the manufacturer's guidelines. Ratio of the PRL in the supernatant to total PRL in diluted serum was calculated and presented as percentage recovery of Prolactin. Based on recovery percentage, samples were classified into truly hyperprolactinemic (recovery >60%), probably/borderline hyperprolactinemic (recovery 40-60%), and macroprolactinemic sera (recovery <40%).

3. Results

Biochemical findings were suggestive of mild elevation in TSH and elevated prolactin levels. Serum LH and FSH levels were evaluated on Day-2 of menstrual cycle. A high LH: FSH ratio along with mild hyperandrogenemia was suggestive of PCOS. Macroprolactin is a frequent cause of misdiagnosis and mismanagement of hyperprolactinemic patients. Consequently screening for macroprolactin is done as a routine practice in our laboratory to preclude the same. Polyethylene glycol precipitation test (25% PEG solution, pH-7.4) was used to assess the presence of macroprolactin in patients' serum and considerable variation was observed. Total prolactin was 51.3 mg/ml while true prolactin levels obtained were 4.7ng/ml. The percentage ratio Prolactin $_{PEG}$/Prolactin $_{TOTAL}$ was calculated and percentage recovery 9.16% was obtained. This was in accordance with most literature data that suggested a result equal to or below 40% was due to the presence of macroprolactin in the serum sample of the patient.[1-3] Radiological evaluation of pituitary imaging by magnetic resonance scanning was not suggestive of any abnormality. All these findings were highly suggestive of presence of macroprolactin in the patient's serum.

Based on the laboratory findings, necessary adjustments were made in the patient's pharmacotherapy. Thyroxine dose was increased to 125 µg OD while metformin was continued at the same dosage.

The patient was advised OPD visits at regular intervals for timely follow up. Repeat TSH was normal at 1.17 m IU/ ml after increasing the thyroxine dose. Repeat total prolactin estimation was done after a month and was found to be 48.8 ng/ml, which was higher than the reference range. She nonetheless had a normal conception after 3 months of therapeutic dose adjustments regardless of higher total prolactin levels.

4. Discussion

Macroprolactinemia is not known to require any definite treatment [3, 4] and no response to the antiprolactinemic therapy has been discovered in the studies carried out for this purpose [4, 5]. Failure of laboratories to systematically screen all hyperprolactinemic patients for the presence of macroprolactin, has led to diagnostic confusion and unnecessary interventions [6, 7].

The study laboratory has adopted the routine practice of estimating macroprolactin in all patients with therapeutic range hyperprolactinemia i.e. 25ng/ml. Diagnosis of macroprolactinemia has been based on the finding that 40% [8, 9] was recovered after treatment of the serum with 25% polyethylene glycol (PEG).

In the existing case, the patient was started with cabergoline regime in the past inappropriately without determination of true prolactin levels. The accurate practice of reporting true prolactin levels collectively with a guide to interpretation enabled the discontinuation of the needless cabergoline therapy.

The patient conceived spontaneously despite high levels of total prolactin which was primarily due to macroprolactinemia. The biological activity of macroprolactin is low and pregnancy is possible without any treatment for hyperprolactinemia.

5. Conclusion

Macroprolactinemia can be one of the significant causes which can be considered as a differential diagnosis of hyperprolactinemia.

Recommendations

Macroprolactinemia is a heterogeneous condition with varied etiologies and further studies are required to determine the reference range of true prolactin. The current requisite for all diagnostic laboratories is to determine true prolactin in all serum samples with raised prolactin for the differential diagnosis as it is one of the key cause of hyperprolactinemia. This precludes the need of further examinations and medications if true prolactin concentrations after precipitating macroprolactin with PEG are normal.

Limitations

The patient findings should be confirmed by the diagnostic methodology like Gel filtration chromatography or by ultrafiltration. Due to unavailability of the said resources, we could not confirm the macroprolactinemia by diagnostic method.

Conflicts of Interest - The authors report no conflict of interest

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