Original Article

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Biochemistry Section

Prevalence of Macroprolactinaemia in Women with Hyperprolactinaemia: A Retrospective Study

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ABSTRACT

Introduction: Macroprolactinaemia causes asymptomatic hyperprolactinaemia in many patients which leads to misdiagnosis, inappropriate investigation and needless treatment in these patients. Though immunoassays for prolactin are sturdy and reliable, they are prone to interference from macroprolactin. Polyethylene Glycol (PEG) precipitation is used as a screening test for macroprolactinaemia.

Aim: To find out the prevalence of macroprolactin in women with hyperprolactinaemia, this will help in evaluation and treatment of such patients.

Materials and Methods: This retrospective study was conducted at a Global Reference Laboratory in Mumbai over a period of three and a half years from January 2018 to May 2021. Total available data of 1,15,149 women with age above 18 years were included in the study. Prolactin concentrations were measured before and after PEG precipitation. Macroprolactinaemia was characterised by percentage recovery and post PEG prolactin concentrations. Continuous variables were expressed as Mean±Standard Deviation (SD), range and categorical variables as number and percentage. The differences in categorical variables were assessed with Chi-square test or Fisher's-exact test.

Results: Out of total 1,15,149 women, 36,247 (31.48%) women were observed to have hyperprolactinaemia. Prevalence of macroprolactinaemia using recovery criteria of ≤50% was 7.88%. Amongst the women diagnosed with hyperprolactinaemia maximum women were between 18-30 years age group i.e., 22,639 (62.46%). Macroprolactin and age were found to be statistically significant ($p<0.05$). Infertility, Oligomenorrhoea/amenorrhoea, and thyroid disorders was seen more frequently in hyperprolactinaemia than in macroprolactinaemia. Twelve women with prolactin values above 100 ng/mL were found to have macroprolactinaemia.

Conclusion: Macroprolactin determination with the PEG precipitation method might prevent unnecessary tests and treatments during the diagnosis process and follow-up of patients.

Keywords: Infertility, Monomeric prolactin, Polyethylene glycol precipitation, Prolactin, Screening

INTRODUCTION

Prolactin is a 198-amino acid protein {23- kilodalton (kDa)} produced in the lactotroph cells of the anterior pituitary gland. Prolactin is an important hormonal test used for female and, male reproductive health. Prolactin stimulates breast growth development during pregnancy for the production of breast milk [1]. The primary control of prolactin is inhibitory instead of stimulatory and the principle prolactin inhibitory factor is dopamine that regulates prolactin secretion [2]. Low levels of prolactin are usually not a concern in women or men. However, very high levels of prolactin, known as hyperprolactinaemia, can indicate a deeper issue [2].

Human prolactin exists in multiple forms: monomeric prolactin having a molecular weight of 23 kDa, dimeric prolactin or big prolactin with a molecular weight of 50-60 kDa and polymeric form big-big prolactin (Macroprolactin) having a molecular weight of 150-170 kDa [3]. Monomeric prolactin is the biologically and immunologically active form of prolactin accounting for 80-95% of the total prolactin in cases with normoprolactinaemia and true hyperprolactinaemia. Dimeric prolactin makes <10% and macroprolactin is 1% of the total prolactin [4].

Macroprolactin is a complex of monomeric prolactin with an Immunoglobulin G (IgG) antibody with a prolonged half-life leading to hyperprolactinaemia which is suspected in asymptomatic individuals or in patients without symptoms. Many women with macroprolactinaemia are asymptomatic with normal menstrual cycle but however have clinical symptoms of hyperprolactinaemia due to the rise in the levels of monomeric prolactin [1,5]. The prolactin-IgG complex has limited bioavailability and bioactivity because it cannot cross the endothelial lining and reach target organs. Prevalence of macroprolactinaemia is reported to be 26% in patients with hyperprolactinaemia [6].

General symptoms of excess prolactin in premenopausal women are oligomenorrhoea, amenorrhoea and galactorrhoea. Other symptoms in women with hyperprolactinaemia are menstrual irregularities, decreased libido, anovulation, infertility, chronic hyperandrogenism, prolonged hypoestrogenism, decreased bone mass and osteopenia [5]. The causes of hyperprolactinaemia can be either physiological or pathological like- pregnancy, stress, hypothyroidism, pituitary tumours, nipple stimulation, certain foods, medicines given for depression and high blood pressure [2]. Since the prevalence of oligomenorrhoea and galactorrhoea is 57% and 29% in macroprolactinaemia, most often patients are misdiagnosed as hyperprolactinaemia leading to unnecessary treatment and mismanagement [1,6,7].

In Indian subcontinent small and medium sized laboratories do not perform macroprolactin test in cases of hyperprolactinaemia. Hence misdiagnosed cases are started on unnecessary treatment. Presently there is only one Indian study on hyperprolactinaemia by Turankar S et al., done on 30 women [8]. As not many such studies are done in Indian Subcontinent on a larger sample size, this study would help laboratory as well as clinicians to take the right clinical decision which will help in evaluation and treatment of such patients. Hence, this study was designed to understand the exact prevalence of macroprolactinaemia to create awareness on laboratory testing for macroprolactin.

MATERIALS AND METHODS

This retrospective study was conducted at a Global Reference Laboratory in Mumbai over a period of three and a half years from January 2018 to May 2021. Data was collected and analysed in July 2021. The study was conducted retrospectively from the data available in Laboratory Information System (LIS) of the laboratory.

Approval on usage of Laboratory Information Management System (LIMS) and survey based patient data for scientific research and publication was obtained from Conscience Independent Ethics Committee (ECR/233/Indt/GJ/2015/RR-21) wide approval reference (02062021/09:44).

Inclusion criteria: Total available data of 1,15,149 female patients aged more than 18 years were included in the study irrespective of clinical history.

Exclusion criteria: All male patients and females below 18 years were excluded from the study.

Sample size: During the period from January 2018 to May 2021 there were a total of 1,15,149 females for prolactin requests, all were included.

Information about the patient's age, gender, clinical history details was taken from the Test Requisition Form (TRF). Clinical history of only 839 patients was available. The patients were divided into two groups, group A with values within normal reference interval for prolactin and group B with values above reference interval for prolactin (group A ≤23.3 ng/mL, group B >23.3 ng/mL).

Laboratory Method

1. Prolactin was analysed by Electrochemiluminescence Immunoassay (ECLIA) method.
2. PEG precipitation method is used to detect the presence of macroprolactin in the sera of patients with hyperprolactinaemia as it precipitates the IgG and therefore the macroprolactin as well. After addition of 25% PEG to the serum specimen the sample is spun down. The supernatant is taken off and re-assayed for prolactin. If a significant difference is observed from the original result, then macroprolactin is to be suspected. [2].
3. Presence of macroprolactinaemia is expressed as prolactin recovery (% Recovery) and prolactin concentration after PEG treatment (post PEG prolactin ng/mL). Pseudohyperprolactinaemia is defined with post PEG prolactin within post PEG reference intervals and true hyperprolactinaemia above the upper limit of the post PEG reference interval. [9].
4. Samples with a prolactin value of >50 ng/mL were subjected to the PEG precipitation test [10,11] [Table/Fig-1].

Serum prolactin levels	Interpretation	Remark
4.79-23.3 ng/mL	Normal	Biological reference interval
23.4-50 ng/mL	Mild prolactin excess	Often seen with physiological conditions like physical/emotional stress, exercise, pregnancy, lactation, etc. This may not be associated with clinical hyperprolactinaemia and needs review after a month.
51-75 ng/mL	Moderate prolactin excess	Often associated with clinical hyperprolactinaemia (short luteal phase, oligomenorrhoea), hypothyroidism (often subclinical), macroprolactinaemia.
76-100 ng/mL	Marked prolactin excess	Often associated with clinical hyperprolactinaemia- hypogonadism, amenorrhoea, galactorrhoea, hypothyroidism (often subclinical), macroprolactinaemia.
Above 100 ng/mL	Marked prolactin excess	Often associated with pituitary adenoma requiring further workup. High levels may be repeated with tri pooled sample.

[Table/Fig-1]: Interpretation of hyperprolactinaemia in females.

Interpretation

1. The total prolactin reference ranges are 4.79-23.3 ng/mL for women [12].
2. A recovery of >50% is considered to be a negative screen for macroprolactin.
3. A recovery of ≤50% is a positive screen indicating possible macroprolactin interference. Macroprolactin may be present and further characterisation is required [Table/Fig-2] [2,3,6].
4. Serum prolactin (Monomeric post PEG) reference range is 3.5-17 ng/mL [6].

% Recovery	Monomeric/ Active prolactin	Suggested interpretation*
More than 50%	High or Normal	Macroprolactin absent. Other causes for hyperprolactinaemia should be considered.
Less than and equal to 50%	High	Macroprolactin present with co-existing increased monomeric/active form. Further workup, to identify cause for hyperprolactinaemia to be considered.
	Normal	Macroprolactin present. Current consensus opinion state that patients positive for macroprolactin and no clinical symptoms do not warrant further investigations or treatment intervention.

[Table/Fig-2]: Interpretation for macroprolactin.

STATISTICAL ANALYSIS

All statistical analysis was performed using "R Studio version 1.4.1103". A two-tailed p-value of <0.05 was considered as statistically significant. Continuous variables were expressed as Mean±SD, range and categorical variables as number and percentage. Shapiro-Wilks test was used to determine whether data sets differed from a normal distribution. The differences in categorical variables were assessed with Chi-square test or Fisher's-exact test. For continuous variable differences between two groups was examined using unpaired t-test.

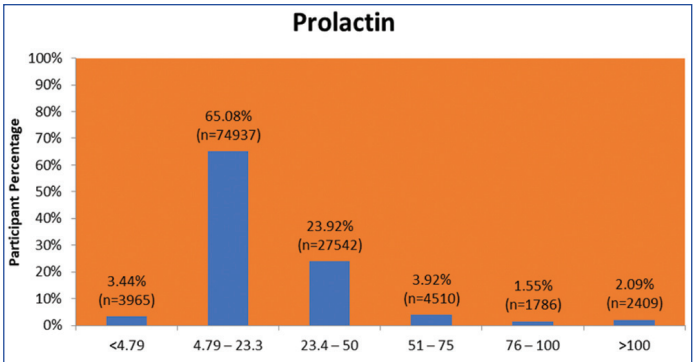
RESULTS

Distribution of total prolactin age wise: During the period from January 2018 to May 2021 there were a total of 1,15,149 female prolactin requests. The mean age was found to be 30.12 years and 68,337 patients (59.35%) were in range between 18-30 years age group [Table/Fig-3]. Out of total 68,337 patients, 22,639 (62.63%) patients having hyperprolactinaemia were between 18-30 years.

Age group (years)	Total	Prolactin				p-value
		Group A		Group B		
		n	%	n	%	
18-30	68337	45698	57.92	22639	62.46	<0.0001
31-40	35891	25165	31.89	10726	29.60	
41-50	8899	6459	8.19	2440	6.73	
51-60	1502	1188	1.50	314	0.86	
>60	520	392	0.5	128	0.35	
Total	115149	78902	100	36247	100	

[Table/Fig-3]: Age wise distribution of prolactin.
N: Number of participants; %: Percentage; p<0.05 considered statistically significant; Group A ≤23.3 ng/mL, Group B >23.3 ng/mL; Statistical test: Chi-square test

Prevalence of hyperprolactinaemia: Out of the total 1,15,149 patients, 36,247 women (31.48%) were observed to have hyperprolactinaemia with prolactin values above the reference range and 78,902 (68.52%) had prolactin with normal limits [Table/Fig-4].



[Table/Fig-4]: Percentage distribution of prolactin values showing prevalence of hyperprolactinaemia.

Prevalence of clinical symptoms: Among the 839 prolactin patients whose clinical history was available, thyroid disorders was

the most prevalent clinical history observed followed by patients on medicines in patients screened for prolactin. A total of 94 (33.22%) was thyroid disorders followed by 82 (28.98%) women on medication history in group B [Table/Fig-5].

History	Total	Prolactin				p-value
		Group A		Group B		
		N	%	N	%	
Infertility	166	109	19.6	57	20.14	
Irregular menses	134	90	16.19	44	15.55	
On medication	249	167	30.04	82	28.98	
Thyroid	263	169	30.4	94	33.22	0.7783
Pregnancy	20	15	2.7	5	1.76	
Tumour	7	6	1.07	1	0.35	
Total	839	556	100	283	100	

[Table/Fig-5]: Prevalence of clinical symptoms in hyperprolactinaemia.
N: Number of participants; %: Percentage; p<0.05 considered statistically significant; Group A ≤23.3 ng/mL; Group B >23.3 ng/mL; Statistical test: Chi-square test

Incidence of macroprolactinaemia in women with hyperprolactinaemia: During the study period, 1,15,149 prolactin requests were received out of which 8,705 (7.56%) had prolactin >50 ng/mL and were advised for macroprolactin. Out of these 5,763 were tested for macroprolactin as this retrospective study was conducted in a reference laboratory and patients did not gave consent for the test. There were 454 (7.88%) samples with post PEG recovery of ≤50% and these were defined as containing macroprolactin. A recovery >50% was present in most of the patients (92.12%), indicating that the predominant form was little Prolactin (PRL) which cannot be precipitated with PEG [Table/Fig-6].

Macroprolactin	N	%
≤50%	454	7.88
>50%	5309	92.12
Total	5763	100

[Table/Fig-6]: Prevalence of macroprolactinaemia.
N: Number of participants; %: Percentage

Characteristics and PRL levels of patients with macroprolactinaemia (recovery ≤50% and recovery >50%): After PEG precipitation prolactin values reduced from 71.94-10.45 ng/mL in patients with macroprolactinaemia and from 70.85-30.10 in patients with monomeric prolactin predominance.

No significant difference was found for age but statistically significant difference was found for prolactin values between samples with recovery >50% and ≤50%. About 167 (93.30%) of the patients with monomeric prolactin predominance had prolactin values above 100 ng/mL in >50% recovery and 12 (6.7%) of the hyperprolactinaemic patients with PRL levels above 100 ng/mL had macroprolactinaemia in ≤50% recovery [Table/Fig-7].

Variables	Macroprolactin		p-value
	Recovery ≤50%	Recovery >50%	
Age (years)	29.2854±7.3781	29.9182±7.9123	0.091045
PRL ng/mL	71.9490±18.3539	70.8565±26.2620	0.000362
PRL 51-75 ng/mL	286 (7.18%)	3697 (92.82%)	0.0048
PRL 76-100 ng/mL	156 (9.74%)	1445 (90.26%)	
PRL >100 ng/mL	12 (6.70%)	167 (93.30%)	
Post PEG monomeric PRL ng/mL	10.4589±5.1344	30.1074±16.3499	<0.0001

[Table/Fig-7]: Characteristics and prolactin levels of patients with macroprolactinaemia.
Statistical test: Unpaired t-test; p-value <0.05 considered significant

Association of macroprolactin with age: Significant difference was observed between macroprolactin and age [Table/Fig-8].

Age group (years)	Macro prolactin				p-value
	Recovery >50%		Recovery ≤50%		
	n	%	n	%	
18-30	3155	91.21	304	8.79	0.0267
31-40	1656	93.56	114	6.44	
41-50	416	93.27	30	6.73	
51-60	50	90.91	5	9.09	
>60	32	96.97	1	3.03	

[Table/Fig-8]: Association of macroprolactin age wise.
N: Number of participants; %: Percentage; p<0.05 considered statistically significant
Statistical test: Chi-Square test

Incidence of pseudohyperprolactinaemia: In present study, 454 patients (7.88%) patients were found to have macroprolactin leading to pseudohyperprolactinaemia. Recovery criterion of ≤50% defined these patients as Macroprolactinaemic.

A total of 52 (11.45%) of them had PRL-monomeric above the upper limit of the post PEG reference interval (true hyperprolactinaemia) and macroprolactin was also present. A total of 83 (1.56%) women had post PEG prolactin monomeric within the reference interval and macroprolactin was absent. However, 402 (88.55%) women had post PEG monomeric within normal reference interval but macroprolactin was present. As macroprolactin is present with increased monomeric form and further workup has to be done to identify causes of hyperprolactinaemia. A total of 5226 women had post PEG prolactin monomeric above the upper limit of the reference limit and macroprolactin was absent. If no clinical symptoms are seen no further investigation is required [Table/Fig-9].

Prolactin (Monomeric active)	Macroprolactin				p-value
	Recovery ≤50%		Recovery >50%		
	n	%	n	%	
Abnormal	52	11.45	5226	98.44	<0.0001
Normal	402	88.55	83	1.56	
Total	454	100	5309	100	

[Table/Fig-9]: Incidence of pseudohyperprolactinaemia.
N: Number of participants; %: Percentage; p<0.05 considered statistically significant, Abnormal=Outside reference range, Normal=Within reference range.
Statistical test: Chi-square test

DISCUSSION

In present retrospective study, 7.88% of the patients with hyperprolactinaemia had the prevalence of macroprolactenaemia. This was similar to the findings by Barth JH et al., who reported macroprolactin incidence of 5% and also similar to recent studies by Sánchez-Eixerés MR et al., where the prevalence of hyperprolactinaemia was found to be 9% [13,14].

Macroprolactinaemia should be considered as differential diagnosis of hyperprolactinaemia. It can avoid unnecessary and costly diagnostic investigations, inappropriate treatments. Although patients with macroprolactinaemia are usually asymptomatic there are a number of women with macroprolactinaemia presenting hyperprolactinaemic clinical symptoms due to the rise in the levels of monomeric prolactin, that cannot be differentiated from the patients with true hyperprolactinaemia [1,15]. Macroprolactin can interfere with all commercial prolactin immunoassays leading to falsely elevated prolactin levels in terms of macroprolactinaemia. Therefore, PEG induced precipitation of macroprolactin is used as a screening technique for hyperprolactinaemic sera [16].

According to a study done in the United Kingdom by Olukoga AO and Kane JW [17], the prevalence of macroprolactin was 15% and this was lower than the prevalence of 25% reported in another study by Fahie-Wilson MN and Soule SG., 1997) [3]. As per studies done in Turkey by Muhtaroglu S et al., the prevalence of macroprolactinaemia is approximately 4% of the general population

and the frequency of macroprolactinaemia in other countries is detected in 4-46% of patients with hyperprolactinaemia depending on the immunoassay method platforms and population tested [18]. In present study, the finding of low prolactin recovery after PEG is indicative of the presence of macroprolactin, which has been accurately validated by Fahie-Wilson MN and Soule SG [3].

Out of the total available 1,15,149 data of female patients in present study 68,337 (59.35%) were between 18-30 years age group. The mean age for prolactin was found to be 30.12 years and prevalence of hyperprolactinaemia was highest 22,639 (62.46%) among this age group. A recent study by Pałubska S et al., also concluded that hyperprolactinaemia mostly affects women in the reproductive age between 25-34 years [19].

Hyperprolactinaemia, the presence of abnormally high levels of prolactin in the blood and hypothyroidism are found to be closely interrelated. As per study by Turankar S et al., some of the women with high prolactin levels have been diagnosed with hypothyroidism [8]. Similarly in present study, thyroid disorders (33.22%) have been found to be the most prevalent clinical characteristic in hyperprolactinaemic women. Clinical symptoms of infertility, irregular menses and thyroid disorders occurred more frequently in hyperprolactinaemia as compared to macroprolactinaemia in present study. This was in accordance with a study published by Toldy E et al., [20].

Therefore, present study helped to differentiate such cases based on macroprolactin estimation. Also, in present study the correlation between monomeric prolactin and macroprolactinaemia was 11.45% therefore, the presence of macroprolactinaemia may include pituitary pathology when post PEG prolactin is above reference range [1,16].

Limitation(s)

This was a retrospective data analysis based study so lack of detailed history for the subjects was limited. So, further investigation towards the causative classification of macroprolactinaemia is required.

CONCLUSION(S)

The present retrospective study demonstrates that 7.88% of the patients with hyperprolactinaemia have macroprolactinaemia. This in house study provides an assessment of macroprolactin as a cause of hyperprolactinaemia. This finding supports the inclusion of macroprolactinaemia screening in the differential diagnosis of hyperprolactinaemia to avoid unnecessary expensive examination. Detecting macroprolactinaemia favours a definitive diagnosis to be made in many cases that would otherwise be labelled idiopathic hyperprolactinaemia.

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