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ORIGINAL ARTICLE

Macroprolactin screening in 464 patients with hyperprolactinaemia

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Abstract

Introduction: Macroprolactinaemia is usually detected by polyethylene glycol (PEG) precipitation in clinical laboratories. Laboratory data on prolactin and macroprolactin screening by PEG precipitation in a tertiary hospital were reviewed in order to revise the local policy for reflex screening and reporting of macroprolactin in patients with hyperprolactinaemia. *Materials and Methods*: Paired prolactin results from 464 patients before and after PEG precipitation, either requested by a clinician or performed as a reflex test, were retrieved and reviewed. *Results*: Recovery of prolactin after PEG treatment was highly variable (3.7 to 97.7%). The distribution of prolactin recovery percentages after PEG precipitation in patients with true hyperprolactinaemia was markedly different from that in patients without true hyperprolactinaemia. The proportion of patients with true hyperprolactinaemia increased gradually with increasing pre-PEG prolactin concentrations; the reverse was true with macroprolactinaemia. Five patients (1.1%) were found to have co-existing macroprolactinaemia and true hyperprolactinaemia. *Conclusion*: Results from this retrospective study indicate that macroprolactinaemia is common and can be present even in patients with very high serum prolactin concentrations. There is no cut-off limit for pre-PEG serum prolactin concentration that can totally exclude macroprolactinaemia. Moreover, co-existence of true hyperprolactinaemia and macroprolactinaemia in the same patient is not a rare phenomenon. Post-PEG prolactin concentration and percentage recovery should be reported together to guide the interpretation and management of hyperprolactinaemia.

Keywords: chemical precipitation, hyperprolactinemia, polyethylene glycols, prolactin

INTRODUCTION

Prolactin is an anterior pituitary hormone that has physiological roles in inducing and sustaining lactation. Common causes of hyperprolactinaemia include prolactin-secreting pituitary adenoma, medications such as antipsychotics and dopamine antagonists, pregnancy and severe primary hypothyroidism. Biochemical confirmation of an elevated serum prolactin concentration is essential for the diagnosis of hyperprolactinaemia.

Prolactin in circulation exists in three major forms: monomeric prolactin, big prolactin and macroprolactin.[1,2] Monomeric prolactin is the biologically active form and has a molecular weight of approximately 23 kDa. Big prolactin molecules, which are aggregates of monomers, have molecular weights between 50 and 60 kDa. Macroprolactin (also known as big big prolactin; molecular weight more than 150 kDa) is a complex consisting of monomeric prolactin and immunoglobulin(s). In healthy individuals, total prolactin in circulation comprises 60-90% of monomeric prolactin, 15-30% of big prolactin and <10% of macroprolactin.[1,2] Unlike monomeric prolactin, big prolactin and macroprolactin are considered to exhibit very little biological activity.[3-5] Macroprolactin molecules, which have longer renal clearance due to their large size, can accumulate in blood and contribute significantly to prolactin concentrations.[5,6] Given that currently available prolactin immunoassays are immunoreactive to macroprolactin to varying degrees,[5,7] serum prolactin results in patients with considerable macroprolactin may potentially lead to a misdiagnosis of true hyperprolactinaemia (defined as elevated concentrations of monomeric

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prolactin in blood).[3,8,9] Differentiation of patients with hyperprolactinaemia secondary to macroprolactinaemia from those with true hyperprolactinaemia is clinically important because the former condition is considered benign and generally requires no further investigation or treatment.[4,10,11]

Gel filtration chromatography (GFC) is considered the gold standard method for differentiating the above-mentioned prolactin forms from one another. However, the GFC method is costly, labour-intensive and not routinely available in most clinical laboratories. Polyethylene glycol (PEG) precipitation is widely used as an alternative for the screening of macroprolactin in view of its technical simplicity and relatively low cost to perform in routine clinical laboratories. The PEG method has been validated against GFC in a number of studies and recovery of prolactin below 30-40% after PEG precipitation has generally been accepted to indicate the presence of significant macroprolactin.[8,12-14] However, the PEG method is not without its limitations. Using the traditional approach of reporting post-PEG prolactin recovery, there exists a recovery range in which results are considered indeterminate and require further investigations (such as by GFC) before a definitive diagnosis can be given.[12,13] In addition, co-precipitation of monomeric prolactin by PEG can lead to considerable under-recovery.[15,16] Over-recovery after PEG precipitation has also been reported in some assays.[16]

At present, our laboratory practises reflex testing for macroprolactin by PEG precipitation when the initial serum prolactin concentrations are ≥80 μg/L (≥1680 mIU/L; conversion formula: concentration in μg/L x 21 = concentration in mIU/L). For samples with prolactin concentrations below 80 μg/L, clinicians can request PEG precipitation and post-PEG prolactin measurement if they suspect macroprolactinaemia on clinical grounds. The results are reported as absolute post-PEG prolactin concentrations, together with locally-established reference intervals for post-PEG prolactin. An interpretative comment on the post-PEG prolactin concentration and macroprolactinaemia is also appended to all post-PEG prolactin results. In this retrospective study, we reviewed laboratory data over a period of 42 months in a tertiary hospital for women and children and sought to revise our policy for the reflex screening and reporting of macroprolactin in patients with hyperprolactinaemia.

MATERIALS AND METHODS

Serum prolactin results before and after PEG precipitation between November 2015 and April 2019 were extracted from the laboratory information system. This study included only results from patients whose initial serum prolactin concentrations were above the upper limits of the laboratory's reference intervals for pre-PEG prolactin (23.0 μg/L in patients aged 1-16 years; 32.9 μg/L and 24.8 μg/L in females and males above 16 years of age respectively). For patients from 1 to 16 years old, our hospital adopted the reference interval established by Konforte *et al*. (2013) from the CALIPER study cohort.[17] The reference intervals for both genders aged >16 years and post-PEG reference intervals were locally established. In those patients with more than one pair of pre-PEG and post-PEG prolactin results during the study period, only the first pair of results was included. In total, 464 patients' pre- and post-PEG prolactin results were reviewed. This study was conducted as a service evaluation for the improvement of routine laboratory practice and utilised only de-identified and anonymised data not traceable to any individual patient. In accordance with our institution's ethics compliance policy, institutional review board approval was thus not required.

Serum prolactin concentrations were measured on an Abbott Architect i2000 analyser (Abbott Laboratories, Abbott Park, IL, USA) by using a chemiluminescent microparticle immunoassay method according to the manufacturer's protocol. Within-laboratory coefficients of variation (CV) of the prolactin assay were 3.9%, 3.0% and 2.3% at mean prolactin concentrations of 3.9 μg/L, 13.7 μg/L and 43.0 μg/L respectively. Polyethylene glycol (PEG) precipitation was performed when it was requested by a clinician (the clinician request group) or as a reflex screening test for macroprolactin in those samples with initial prolactin concentrations at 80 μg/L or above (the reflex testing group). After the initial measurement of serum prolactin concentrations, samples were treated with PEG solution according to the following PEG precipitation protocol. PEG solution was prepared by dissolving 1.25 g of PEG 6000 (Sigma-Aldrich, St Louis, Missouri, USA) in 5 mL phosphate buffered saline. 250 μL of serum and 250 μL of PEG solution were mixed and incubated at room temperature for 10 minutes before centrifugation at 14,000 x g for 10 minutes. Post-PEG

prolactin concentrations were then measured in the supernatant. Results of post-PEG prolactin concentrations were corrected by a factor of two to account for the dilution factor. Recovery percentage for each sample was calculated by dividing the post-PEG prolactin concentration by the initial pre-PEG prolactin concentration and multiplied by 100. Performance of the PEG precipitation procedure was monitored by running in-house controls prepared from residual samples with or without macroprolactin.

In this study, true hyperprolactinaemia was defined as hyperprolactinaemia identified in patients whose post-PEG prolactin concentrations remained above the post-PEG reference intervals,[8] while macroprolactinaemia was defined as <40% prolactin recovery after PEG precipitation.[12,14]

Statistical analyses were performed using the Microsoft Excel software. The Mann-Whitney U test was used to compare post-PEG prolactin recoveries in the two groups of patients described above.

RESULTS

The 464 patients included in this study (462 females and 2 males) were between 13 and 69 years of age (median, 33 years; interquartile range, 27-38 years) at the time of specimen collection; six patients were below the age of 16 years. Serum pre-PEG prolactin concentrations ranged from 33.0 to 1277.6 μg/L, and post-PEG prolactin concentrations were between 2.9 and 978.8 μg/L.

Recovery of prolactin after PEG treatment spanned a large range (3.7% to 97.7%). Figure 1 shows the frequency distribution of post-PEG prolactin recovery. Two distinct groups were observed, with peaks located at 10-15% and 75-80% recovery respectively. The median prolactin recovery after PEG precipitation in the clinician request group (70.1%; IQR, 30.1-77.3%; n=207) is slightly lower than that in the reflex testing group (75.5%; IQR, 69.7-80.3%; n=257) ($p < 0.001$).

Among patients with true hyperprolactinaemia (white bars in FIG. 1), the vast majority (95.1%) had >60% prolactin recovery after PEG precipitation, whereas only 3.4% and 1.5% of patients with true hyperprolactinaemia were found to have 40-60% and <40% prolactin recovery respectively. In comparison, among patients whose post-PEG prolactin concentrations were within the corresponding reference intervals (absence of true hyperprolactinaemia; grey bars in FIG. 1), 29.7% had >60% prolactin recovery, while 10.1% and 60.2% of them were found in the 40-60% and <40% recovery groups respectively. Taken together, these findings show that the distribution of prolactin recovery after PEG precipitation in patients with true hyperprolactinaemia is markedly different from that in patients without true hyperprolactinaemia.

The distributions of patients with true hyperprolactinaemia or macroprolactinaemia

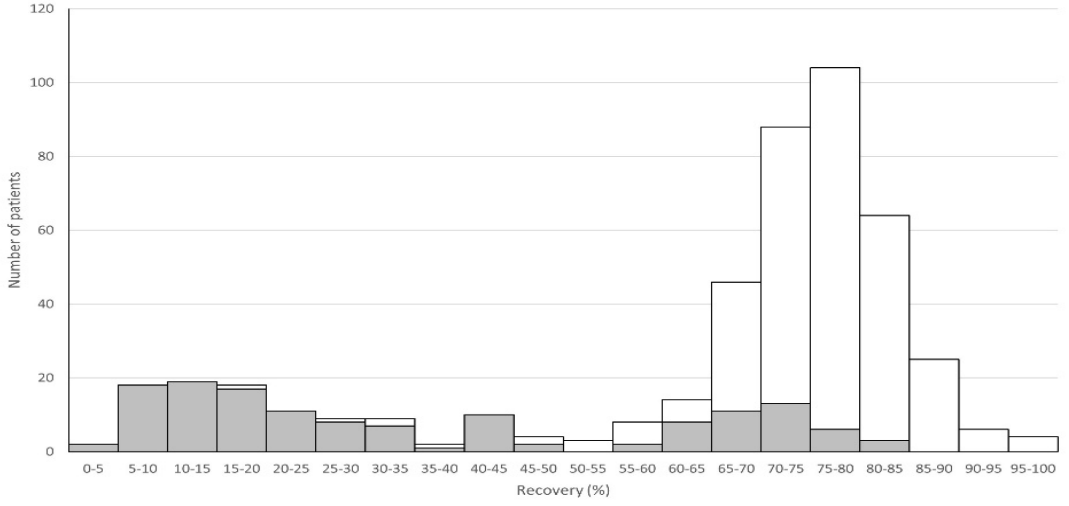

FIG. 1: Distribution of post-precipitation recovery (%). Gray bars represent patients who have absence of true hyperprolactinaemia (post-PEG prolactin concentrations within post-PEG reference interval). White bars represent patients who have true hyperprolactinaemia (post-PEG prolactin concentrations above post-PEG reference interval).

according to initial pre-PEG serum prolactin concentrations are summarised in Table 1. The percentage of true hyperprolactinaemia increases gradually from 78.3% in patients with pre-PEG prolactin ≥ 40 μg/L to 95.0% in those with pre-PEG prolactin ≥120 μg/L. By contrast, the proportion of patients with macroprolactinaemia decreases from 19.5% in patients with pre-PEG prolactin ≥40 μg/L to only 7.6% in those with pre-PEG prolactin ≥120 μg/L (Table 1). The total number of patients on each row in Table 1 is not equal to the sum of the number of patients with true hyperprolactinaemia and those with macroprolactinaemia because the two biochemical entities are not mutually exclusive, and some patients had neither condition.

In this retrospective study, the prevalence of macroprolactinaemia in all patients with elevated serum prolactin concentrations during the study period could not be determined because not all hyperprolactinaemic samples had been screened for macroprolactin by PEG precipitation. However, as a result of our reflex testing protocol, all serum samples with initial prolactin concentrations ≥80 μg/L underwent PEG precipitation, and 11.3% of 257 patients were found to have macroprolactinaemia.

Five patients were found to have co-existing macroprolactinaemia and true hyperprolactinaemia by the definitions used in this study. Their initial pre-PEG prolactin concentrations were between 80.6 μg/L and 383.6 μg/L; the corresponding post-PEG prolactin concentrations ranged from 30.3 μg/L to 106.1 μg/L (18-38% prolactin recovery).

DISCUSSION

As the definition of 'hyperprolactinaemia' has been used with variations in the literature, we have chosen to define 'true hyperprolactinaemia' in this study as hyperprolactinaemia with post-PEG prolactin concentrations above the corresponding reference intervals for post-PEG prolactin, whereas 'macroprolactinaemia' is present when prolactin recovery after PEG precipitation is less than 40%.

Macroprolactinaemia and pre-PEG prolactin concentration

In this study, the proportion of patients with true hyperprolactinaemia gradually increased with increasing pre-PEG serum prolactin concentrations (Table 1). By contrast, the percentage of patients with macroprolactinaemia exhibited an inverse relationship with pre-PEG serum prolactin concentrations, indicating that macroprolactinaemia is less likely to be found in patients with markedly elevated pre-PEG prolactin concentrations. McCudden *et al*. suggested that clinicians should not be concerned with macroprolactinaemia when prolactin concentration was >85 μg/L.[6] However, our data shows that macroprolactinaemia can be found in samples with relatively high pre-PEG prolactin concentrations; three patients' very high pre-PEG prolactin concentrations (159, 161 and 219 μg/L respectively) were normalised by PEG precipitation (5%-9% prolactin recovery) to well within the post-PEG prolactin reference interval (9, 14 and 11 μg/L respectively). Another study

Table 1: Distribution of patients with true hyperprolactinaemia and macroprolactinaemia according to initial serum pre-PEG prolactin concentrations

Pre-PEG prolactin concentrations	Number of patients with true hyperprolactinaemia[a]	Number of patients with macroprolactinaemia[b]	Total number of patients
≥40 μg/L	318 (78.3%)	79 (19.5%)	406
≥50 μg/L	286 (86.1%)	49 (14.8%)	332
≥60 μg/L	262 (87.6%)	41 (13.7%)	299
≥70 μg/L	248 (90.2%)	32 (11.6%)	275
≥80 μg/L	233 (90.7%)	29 (11.3%)	257
≥90 μg/L	187 (91.2%)	22 (10.7%)	205
≥100 μg/L	152 (92.7%)	16 (9.8%)	164
≥110 μg/L	134 (93.1%)	14 (9.7%)	144
≥120 μg/L	113 (95.0%)	9 (7.6%)	119

[a] Patients are classified as having true hyperprolactinaemia if their post-PEG prolactin concentrations are above the reference intervals established for post-PEG prolactin concentrations.

[b] Macroprolactinaemia is defined as <40% prolactin recovery after PEG precipitation.

also reported only 2% of monomeric prolactin (confirmed by gel filtration chromatography) in a patient whose prolactin concentrations were between 350 and 400 μg/L over a three-year period, with no evidence of pituitary adenoma.[18] Taken together, the above findings indicate that macroprolactinaemia can be present in patients with very high serum prolactin concentrations, and that there is no cut-off limit for pre-PEG serum prolactin concentration that can totally exclude macroprolactinaemia.

Reporting of PEG precipitation results

In clinical practice, macroprolactinaemia is usually considered to be present when post-PEG recovery of prolactin is less than 40%, whereas recovery above 50% to 60% indicates the absence of macroprolactinaemia.[3,9,12,14,19] This conventional approach for the identification of macroprolactinaemia has two limitations. Firstly, macroprolactinaemia status in samples with post-PEG prolactin recovery of 40-50% or 40-60% is uncertain and often classified as indeterminate.[9,12,13] Additional investigations such as GFC are then required to classify these samples. Secondly, the approach of using prolactin recovery alone to identify macroprolactinaemia may oversimplify the relationship between macroprolactinaemia and true hyperprolactinaemia. In this approach, a sample with elevated serum prolactin concentration can be explained by either macroprolactinaemia or true hyperprolactinaemia, but not both. However, macroprolactinaemia and true hyperprolactinaemia are not mutually exclusive biochemical entities. The coexistence of macroprolactinaemia and true hyperprolactinaemia has been highlighted in a number of studies,[3,9,20,21] and was also observed in five patients in the present study. The potentially missed diagnosis of true hyperprolactinaemia, when macroprolactinaemia is also present in the same patient, supports the increasingly favoured approach of reporting post-PEG prolactin concentration with an appropriate post-PEG prolactin reference interval.[8,9,15,16,21] Nevertheless, this approach can lead to clinicians overlooking the presence of macroprolactinaemia in these patients. Given the persistent nature of macroprolactin,[11,22] a lack of awareness of macroprolactinaemia in patients with coexisting true hyperprolactinaemia and macroprolactinaemia may potentially confuse and mislead clinicians during the monitoring and management of these patients. Therefore, we propose that post-precipitation percentage recovery should be reported together with post-PEG prolactin concentration (with an appropriate post-PEG prolactin reference interval) to facilitate interpretation of PEG precipitation results. Appendage of interpretative comments that further enhance clarity could be considered by individual laboratories.

With this proposed diagnostic approach, one would identify a group of patients (11.9% of cases in our study) that have neither true hyperprolactinaemia nor macroprolactinaemia (ie post-PEG prolactin concentrations within the reference intervals and >40% recovery after PEG precipitation). As some monomeric prolactin can be lost during the PEG precipitation process, it is possible that samples with a borderline high initial prolactin concentration can return a post-PEG prolactin concentration within reference interval. In addition, the presence of small amounts of macroprolactin (at physiological levels) in these samples may have contributed to this picture. A repeat sample collection and PEG precipitation is therefore advisable for this group of patients to rule out any significant elevations of monomeric prolactin or macroprolactin, particularly for those patients who have both pre- and post-PEG prolactin concentrations close to the upper limits of their respective reference intervals.

Strategies for macroprolactin screening

At present, there are three main clinical and laboratory strategies for the detection of macroprolactin by using PEG precipitation. In the first strategy, macroprolactin screening is performed in asymptomatic patients with hyperprolactinaemia, and this approach is recommended by guidelines published by the Pituitary Society (2006) and Endocrine Society (2011).[23,24] However, such an approach has been challenged on the grounds that, on the one hand, the distinction between true hyperprolactinaemia and macroprolactinaemia by clinical assessment alone may not be sufficiently clear and, on the other hand, patients who present with symptoms of hyperprolactinaemia but have hyperprolactinaemia secondary to macroprolactinaemia, may potentially undergo unnecessary further investigations and treatment.[3,4,8,11,25]

Another strategy for macroprolactin detection requires that all hyperprolactinaemic samples be screened for macroprolactin.[4,8,10,21,25-27] While routine screening of macroprolactin in all

hyperprolactinaemic samples will inevitably lead to increased costs for the laboratory, it is thought that savings from the reduction in unnecessary clinical investigations and/or treatment will offset the increased laboratory costs, making it a cost-effective approach.[10,25,26] In the third strategy for macroprolactin detection, instead of screening all hyperprolactinaemic samples, the laboratory sets a cut-off prolactin concentration value for macroprolactin screening, above which all samples undergo PEG precipitation. In comparison with the second strategy, this approach can help to reduce the workload and cost of PEG precipitation. However, there is no standardised cut-off value above which PEG precipitation should be performed.[21] If the cut-off value is set too high, a considerable number of samples with macroprolactinaemia may be missed. A recent study showed that an increase in cut-off value from the upper limits of normal (15.2 μg/L in men and 23.3 μg/L in women) to 32.9 μg/L resulted in half of all macroprolactinaemic patients being missed.[21] Individuals laboratories will need to identify an appropriate cut-off value that is acceptable to its clinicians when adopting this approach.

Having reviewed the above study data and implications on diagnostic workflow, we have decided to continue with our current protocol for reflex macroprolactin screening, which has been agreed with endocrinologist colleagues.

CONCLUSION

In conclusion, the results from this retrospective study highlight the remarkably variable recovery of prolactin after PEG treatment (3.7 to 97.7%). Macroprolactinaemia can be present even in patients with very high serum prolactin concentrations, and there is no cut-off limit for pre-PEG serum prolactin concentration that can totally exclude macroprolactinaemia. Moreover, co-existence of true hyperprolactinaemia and macroprolactinaemia in the same patient is not a rare phenomenon. There are limitations associated with the approach whereby percentage recovery alone is utilised to identify macroprolactinaemia; we recommend that post-PEG prolactin concentrations (with assay-specific post-PEG prolactin reference intervals) be reported together with percentage recovery to guide the interpretation and management of hyperprolactinaemia.

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Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Fahie-Wilson MN, John R, Ellis AR. Macroprolactin: high molecular mass forms of circulating prolactin. Ann Clin Biochem. 2005; 42(Pt3): 175-92.
2. Hattori N, Aisaka K, Shimatsu A. A possible cause of the variable detectability of macroprolactin by different immunoassay systems. Clin Chem Lab Med. 2016; 54(4): 603-8.
3. Samson SL, Hamrahian AH, Ezzat S. American Association of Clinical Endocrinologists, American College of Endocrinology Disease State Clinical Review: Clinical Relevance of Macroprolactin in the Absence or Presence of True Hyperprolactinemia. Endocr Pract. 2015; 21(12): 1427-35.
4. Gibney J, Smith TP, McKenna TJ. Clinical relevance of macroprolactin. Clin Endocrinol (Oxf). 2005; 62(6): 633-43.
5. Smith TP, Suliman AM, Fahie-Wilson MN, Mckenna TJ. Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. J Clin Endocrinol Metab. 2002; 87(12): 5410-5.
6. McCudden CR, Sharpless JL, Grenache DG. Comparison of multiple methods for identification of hyperprolactinemia in the presence of macroprolactin. Clin Chim Acta. 2010; 411(3-4): 155-60.
7. Fahie-Wilson M, Bieglmayer C, Kratzsch J, *et al*. Roche Elecsys Prolactin II assay: reactivity with macroprolactin compared with eight commercial assays for prolactin and determination of monomeric prolactin by precipitation with polyethylene glycol. Clin Lab. 2007; 53(7-8): 485-92.
8. 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; 49(9): 1504-9.
9. Whitehead SJ, Cornes MP, Ford C, Gama R. Reference ranges for serum total and monomeric prolactin for the current generation Abbott Architect assay. Ann Clin Biochem. 2015; 52(Pt 1): 61-6.
10. Fahie-Wilson M, Smith TP. Determination of prolactin: the macroprolactin problem. Best Pract Res Clin Endocrinol Metab. 2013; 27(5): 725-42.

11. Wallace IR, Satti N, Courtney CH, *et al*. Ten-year clinical follow-up of a cohort of 51 patients with macroprolactinemia establishes it as a benign variant. J Clin Endocrinol Metab. 2010; 95(7): 3268-71.
12. Olukoga AO, Kane JW. Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. Clin Endocrinol (Oxf). 1999; 51(1): 119-26.
13. Vieira JG, Tachibana TT, Obara LH, Maciel RMB. Extensive experience and validation of polyethylene glycol precipitation as a screening method for macroprolactinemia. Clin Chem. 1998; 44(8 Pt 1): 1758-9.
14. Fahie-Wilson MN, Soule SG. Macroprolactinaemia: contribution to hyperprolactinaemia in a district general hospital and evaluation of a screening test based on precipitation with polyethylene glycol. Ann Clin Biochem. 1997; 34(Pt 3): 252-8.
15. Kavanagh L, McKenna TJ, Fahie-Wilson MN, Gibney J, Smith TP. Specificity and clinical utility of methods for the detection of macroprolactin. Clin Chem. 2006; 52(7): 1366-72.
16. Beltran L, Fahie-Wilson MN, McKenna TJ, Kavanagh L, Smtih TP. Serum total prolactin and monomeric prolactin reference intervals determined by precipitation with polyethylene glycol: evaluation and validation on common immunoassay platforms. Clin Chem. 2008; 54(10): 1673-81.
17. Konforte D, Shea JL, Kyriakopoulou L, *et al*. Complex biological pattern of fertility hormones in children and adolescents: a study of healthy children from the CALIPER cohort and establishment of pediatric reference intervals. Clin Chem. 2013; 59(8): 1215-27.
18. Jackson RD, Wortsman J, Malarkey WB. Macroprolactinemia presenting like a pituitary tumor. Am J Med. 1985; 78(2): 346-50.
19. Leslie H, Courtney CH, Bell PM, *et al*. Laboratory and clinical experience in 55 patients with macroprolactinemia identified by a simple polyethylene glycol precipitation method. J Clin Endocrinol Metab. 2001; 86(6): 2743-6.
20. Jamaluddin FA, Sthaneshwar P, Hussein Z, Othman N, Chan SP. Importance of screening for macroprolactin in all hyperprolactinaemic sera. Malays J Pathol. 2013; 35(1): 59-63.
21. Sostaric M, Bokulic A, Marijancevic D, Zec I. Optimizing laboratory defined macroprolactin algorithm. Biochem Med (Zagreb). 2019; 29(2): 020706.
22. Hattori N, Adachi T, Ishihara T, Shimatsu A. The natural history of macroprolactinaemia. Eur J Endocrinol. 2012; 166(4): 625-9.
23. Casanueva FF, Molitch ME, Schlechte JA, *et al*. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006; 65(2): 265-73.
24. Melmed S, Casanueva FF, Hoffman AR, *et al*. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(2): 273-88.
25. Gibney J, Smith TP, McKenna TJ. The impact on clinical practice of routine screening for macroprolactin. J Clin Endocrinol Metab. 2005; 90(7): 3927-32.
26. McKenna TJ. Should macroprolactin be measured in all hyperprolactinaemic sera? Clin Endocrinol (Oxf). 2009; 71(4): 466-9.
27. Shimatsu A, Hattori N. Macroprolactinemia: diagnostic, clinical, and pathogenic significance. Clin Dev Immunol. 2012; 2012: 167132.