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Original Article

Low prevalence of macroprolactinaemia among patients with hyperprolactinaemia screened using polyethylene glycol 8000

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الملخص

أهداف البحث: فرط بروﻻكتين الدم الجسيم هو سبب حميد معروف لفرط بروﻻكتين الدم. التفريق بين فرط بروﻻكتين الدم الجسيم وفرط بروﻻكتين الدم الحقيقي مهم، لأن الأول لا تطلب أي علاج. تم إجراء هذه الدراسة لتحديد مدى انتشار فرط بروﻻكتين الدم الجسيم بين مرضى فرط بروﻻكتين الدم باستخدام البولي إيثيلين جلايكول ٨٠٠٠.

طرق البحث: أجريت دراسة مستعرضة على مرضى تم تشخيصهم بفرط بروﻻكتين الدم بمستشفى سينز ماليزيا الجامعي من عام ٢٠١١م إلى ٢٠١٣م. وقيس البروﻻكتين من مصل المرضى باستخدام كوباس إي ٤١١، وتم علاج نفس المصل باستخدام البولي إيثيلين جلايكول ٨٠٠٠، للتفريق بين فرط بروﻻكتين الدم الحقيقي وفرط بروﻻكتين الدم الجسيم. واستخدم شفاء البروﻻكتين لأقل من ٤٠٪ كمؤشر على وجود فرط بروﻻكتين الدم الجسيم.

النتائج: ضمت مجموعة الدراسة ١٣٣ مريضا بفرط بروﻻكتين الدم، منهم ١٢٠ (٩٠٪) إمرأة و١٣ (٩.٨٪) رجلا، أعمارهم ١٨-٦٨ عاما، ومعدل العمر لهم (الانحراف المعياري) ٣٤.٣٧ (١١.٧٥) عاما. وُجد فرط بروﻻكتين الدم الجسيم لدى تسع سيدات بمعدل انتشار ٦.٨ ٪ (٩٥٪ فترة ثقة: ٢.٤٪، ١١.١٪).

الاستنتاجات: معدل انتشار فرط بروﻻكتين الدم الجسيم الذي تم اكتشافه باستخدام البولي إيثيلين جلايكول ٨٠٠٠ بين المرضى الذين تم تشخيصهم بفرط بروﻻكتين الدم كان منخفضا. وأظهر فحص فرط بروﻻكتين الدم الجسيم باستخدام البولي إيثيلين جلايكول ٨٠٠٠ أن معظم المرضى الذين حضروا بفرط بروﻻكتين الدم في مستشفى سينز ماليزيا الجامعي كان فرط بروﻻكتين الدم الحقيقي.

الكلمات المفتاحية: فرط بروﻻكتين الدم؛ فرط بروﻻكتين الدم الجسيم؛ البولي إيثيلين جلايكول ٨٠٠٠

Abstract

Objectives: Macroprolactinaemia is a known benign cause of hyperprolactinaemia (hyperPRL). Differentiating macroprolactinaemia and hyperPRL is important, as macroprolactinaemia does not require treatment. This study was conducted to determine the prevalence of macroprolactinaemia among hyperPRL patients through the use of polyethylene glycol 8000.

Methods: From 2011 to 2013, a cross-sectional study was conducted on patients diagnosed with hyperPRL in Hospital Universiti Sains Malaysia (HUSM). Sera from these patients were measured for PRL using cobas e411 (Roche Diagnostics, Indianapolis, USA) (sandwich principle) and the same sera were treated with polyethylene glycol (PEG) 8000 to differentiate true hyperPRL from macroprolactinaemia. PRL recovery of less than 40% was used as an indicator of the presence of macroprolactin.

Results: A total of 133 hyperPRL patients, 120 (90%) women and 13 (9.8%) men, aged 18–68 years, with mean (standard deviation) age 34.37 (11.75) years comprised this study cohort. Nine female patients were found to have macroprolactinaemia with an estimated prevalence of 6.8% (95% CI: 2.4%, 11.1%).

Conclusions: The prevalence of macroprolactinaemia detected using PEG 8000 among patients diagnosed as hyperPRL was low. Screening for macroprolactin using

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PEG 8000 indicated that the majority of patients who presented with hyperPRL in HUSM were true hyperPRL.

Keywords: Hyperprolactinemia; Macroprolactin; Macroprolactinemia; PEG 8000

Introduction

Prolactin (PRL) is a polypeptide hormone, consisting of 199 amino acids that is synthesized in and secreted by lactotroph, which are specialized cells of the anterior pituitary gland. PRL is secreted episodically by the anterior pituitary and is primarily under tonic inhibitory control of the hypothalamus.[1]

PRL is synthesized as a prehormone with a molecular weight of 26 kDa.[2] When the prehormone is proteolytically cleaved, the resulting mature polypeptide has a molecular mass of 23 kDa, and this monomeric form accounts for the majority (85%) of total PRL in the serum of normal subjects.[1] In addition to monomeric PRL, other molecular mass variants of PRL can be demonstrated in serum. Big PRL has a molecular mass in the 50 kDa range and is thought to be a covalently bound dimer of PRL, accounting for approximately 10–15%. Big big PRL or macroprolactin, which has a molecular mass of more than 150 kDa, usually contributes a small, though variable amount to circulating levels.[2] Moreover, post-translational modification of pituitary PRL generates a variety of additional species, including glycosylated and phosphorylated variants, together with 14, 16 and 22 kDa proteolysed forms,[1] and has three intramolecular disulphide bonds.[3]

Physiological levels of PRL are higher during pregnancy and lactation than otherwise, and mean serum levels are higher in women than in men.[2] HyperPRL is a condition of excess monomeric PRL. The clinical syndromes of hyperPRL are galactorrhoea, oligomenorrhoea, amenorrhoea, and infertility in women; and reduced libido, oligospermia, impotence and galactorrhoea in men.[4] HyperPRL has an estimated prevalence of 15% in women with secondary amenorrhoea, a condition that affects at least 3% of women of reproductive age.[5]

In general, macroprolactin is a non-bioactive prolactin isoform, usually composed of a PRL monomer and an IgG molecule that has a prolonged clearance rate similar to that of immunoglobulins. This isoform is clinically non-reactive but interferes with immunological assays used for the detection of PRL.[6] When the serum of a patient with hyperPRL contains mostly big big PRL, the condition is termed macroprolactinaemia. Because certain laboratories fail to screen hyperprolactinaemic sera for macroprolactin, this may lead to misdiagnosis and unnecessary medical and surgical intervention[7] or delayed diagnosis and inappropriate treatment.[8,9]

Screening hyperprolactinaemic sera for the presence of misleading concentrations of macroprolactin is readily performed in biochemistry laboratories, although the procedures are not automated. The most widely employed method is to treat the hyperprolactinaemic serum with PEG, which precipitates out high-molecular weight constituents including immunoglobulins. Re-assay of the serum for PRL will then identify those sera, which yield values within the relevant normal range indicative of macroprolactinaemia, and not true hyperPRL.[10]

Materials and Methods

A cross-sectional study was conducted in 2013 involving patients aged ≥18 years old, in Kelantan, who were investigated for hyperPRL, and who attended Endocrine Clinic HUSM from 2010 to 2013. PRL levels which were above the reference range for our hospital for age and sex (female-non pregnant: 0.21–1.0 nmol/L, male: 0.17–0.65 nmol/L) were included in this study. These interval values were used, as hyperPRL was defined as a level of PRL above the upper limit of normal PRL level, in a single measurement, as described by Melmed et al. 2011.[11]

The number of serum samples required to determine the prevalence of patients with macroprolactinaemia was calculated using the one-sample proportion formula, and with the Type I error and study precision at 5%, the number of serum samples required was from 196 subjects.

Inclusion criteria in this study were: patient with PRL level of >0.65 nmol/L for male patients and >1.0 nmol/L for female patients. We excluded patients with inadequate or missing serum samples and patients with more than 30% missing data. After applying inclusion and exclusion criteria, only 133 serum samples were available. Since the calculated sample size was larger than the number of serum samples available, no sampling method was applied and all serum samples were included in the study. These serum samples were stored at −20° C until further analysis.

Data on presenting symptoms and medical history were extracted from hospital medical records. This study was approved by the Human Research Ethics Committee of USM (HREC) USMKK/PPP/JEPeM [263.4(1.4)]. All aspects of this study comply with the Declaration of Helsinki.

A volume of 250 μL of the patient's serum was treated with 250 μL of PEG 8000 (25% w/v) solution. The mixtures were mixed for approximately ten seconds in a rotating shaker and centrifuged between 1500 and 10,000 g for five minutes. The supernatant was measured for PRL and results were expressed as percentage of PRL recovery. The recovery of PRL post-PEG was calculated using the following formula: % Recovery post PEG precipitation = (PRL value post PEG precipitation/PRL value in pre PEG) × 2 × 100%.

Data were entered and analysed using SPSS version 21. Exploratory data analysis was conducted to determine the distribution of numerical data and frequency of categorical data. Numerical data with normal distribution are presented as the mean and standard deviation (SD), whereas for skewed data, data are presented as median and interquartile range (IQR). The prevalence of patients with macroprolactinaemia and 95% CI was calculated.

Table 1: Descriptive statistics for overall subjects (n = 133).

Variables	Mean (SD)	n (%)
Age	34.37 (11.75)	
Sex		
Female		120 (90.2)
Male		13 (9.8)
Race		
Malay		123 (92.5)
Chinese		5 (3.8)
Indian		1 (0.8)
Others		4 (3.0)
Pre PEG (μg/mL)	1.50 (1.30)[a]	
Post PEG (μg/mL)	11.91 (10.40)[a]	
PEG Recovery (%)	66.21 (18.14)	
Oligomenorrhoea		
No		105 (78.9)
Yes		28 (21.1)
Amenorrhoea		
No		109 (82.0)
Yes		24 (18.0)
Galactorrhoea		
No		105 (78.9)
Yes		28 (21.1)
Infertility		
No		74 (55.6)
Yes		59 (44.4)
Headache		
No		118 (88.7)
Yes		15 (11.3)
Eye symptoms		
No		117 (88.0)
Yes		16 (12.0)

[a] Median (IQR).

Results

In this study, 133 samples were analysed to screen for macroprolactinaemia. The majority of patients were Malay females (Table 1).

Nine samples [prevalence = 6.8% (95% CI = 2.4%, 11.1%)], had post-PEG recovery levels of <40%, and there were 20 samples (15.0%) with recovery between 40% and 60%. The remaining 104 (78.2%) samples had recovery >60%. All nine patients with recovery <40% were female and presented with: infertility problems (four patients), secondary amenorrhoea (one patient), investigation of temporal lobe epilepsy (one patient), complex partial seizure on antiepileptic (one patient), polycystic ovary syndrome (one patient), and eye symptoms-reduced vision (one patient). None of these patients had undergone any imaging study, such as CT scan or MRI of the brain or were being treated with dopamine agonist therapy. Demographic data and clinical history for patients with PEG recovery <40% are shown in Table 2.

Table 2: Demographic data and clinical history for patients with PEG recovery < 40%.

Patient no	Age (years)	Gender	Race	Clinical history
1	44	Female	Malay	Complex partial seizure on antiepileptic
2	60	Female	Malay	Eye symptom (reduced vision)
3	19	Female	Malay	Polycystic ovary syndrome (PCOS)
4	38	Female	Chinese	Primary infertility
5	37	Female	Malay	Secondary infertility
6	34	Female	Malay	Primary infertility
7	26	Female	Malay	Infertility, oophorectomy secondary to endometriosis
8	31	Female	Malay	Secondary amenorrhoea
9	18	Female	Malay	Investigation for temporal lobe epilepsy

Discussion

Macroprolactinaemia is a benign variant of HyperPRL.[12] Nevertheless, identification of macroprolactin in sera is important, as it has a clinical impact leading to diagnostic confusion. Failure to differentiate between true HyperPRL and macroprolactinaemia may lead to unnecessary investigation, inappropriate treatment and a delayed correct diagnosis.[10] Symptoms of hyperprolactinaemic syndrome are common and non-specific,[13] limiting the diagnostic value of clinical symptoms to differentiate between true hyperPRL and macroprolactinaemia.

In true hyperPRL, inhibition of hypothalamic gonadotrophin-releasing hormone by PRL leads to hypogonadotropic hypogonadism, which then causes oligomenorrhoea or amenorrhoea.[14] These conditions are characterized by low levels of oestradiol and low or inappropriate concentrations of FSH and LH, reflecting the hypothalamic origin of the disturbance.

Symptoms of hyperprolactinaemic syndrome are also commonly found in patients with macroprolactinaemia, and the exact mechanism of the clinical symptoms in these patients is not thoroughly understood. A study that investigated the relationship between clinical symptoms and macroprolactinaemia suggested that macroprolactin may be the reason the patient with macroprolactinaemia has symptoms.[15]

Several studies found that the association between the relatively common symptoms of galactorrhoea and oligomenorrhoea with the biochemical finding of macroprolactinaemia is coincidental.[7,16] In macroprolactinaemia, macroprolactin is confined to the vasculature and has limited bioactivity in vivo. This condition might explain why macroprolactinaemia patients are asymptomatic.[9] This finding was supported by Suliman et al. who found that compared with true hyperprolactinaemic subjects, plasma levels of oestradiol and LH were significantly higher in individuals with macroprolactinaemia, consistent with the limited bioactivity of macroprolactin.[8]

In this study, four out of the nine macroprolactinaemia patients presented with infertility problems, either primary or secondary, which accounted for 6.8% of the infertility patients. Some studies have showed that the prevalence of macroprolactinaemia among infertility patients is about ten to 12%.[17,18] Due to difficulties in differentiating true hyperprolactinaemia and macroprolactinaemia, screening is highly recommended because patients with macroprolactinaemia should be investigated for causes of infertility, as the management is different.

In this study, 90% of patients were female, and only 9.8% were male. Among these patients, nine were found to have

macroprolactinaemia and all were female. None of the male patients was found to have macroprolactinaemia. No significant association was found between gender and macroprolactinaemia in this study. This finding agrees with previous studies that also reported no significant association between gender and macroprolactinaemia.[19]

Previous studies have also reported a higher prevalence of macroprolactinaemia among females.[16,20,21] This could be due to, compared to men being investigated for sexual dysfunction, a higher number of female patients being investigated for infertility and menstrual disturbances.[22,23]

The prevalence of macroprolactinaemia among hyperPRL patients in this study is 6.8%, which is almost similar to previously reported prevalences.[24,25] However, compared to the current study,[26,27] other studies have reported a higher prevalence. The prevalence of macroprolactinaemia in hyperprolactinaemia, in other populations, found by other researchers, ranged from 15% to 46%. The difference in the prevalence of our study may possibly be due to patient selection, prolactin level and also the analyser that was used.

For the patients with recovery between 40% and 60%, further confirmation by GFC needs to be completed to confirm the presence of either monomeric prolactin or macroprolactin. However, GFC was not performed and is beyond the scope of this study.

In our lab, PRL measurement is performed by Elecsys II, which has been shown to have relatively low reactivity toward macroprolactin, similar to Advia Centaur and Access/Dxl (Beckman).[7,28] This may be a reason why our prevalence of macroprolactinaemia is very similar to Jamaluddin et al. and Jassam et al. who both used Advia Centaur.[24,25]

In this study, PEG 8000 was used in a similar method to other previously conducted studies.[8,29,30] However, other studies used PEG 6000 instead of PEG 8000[31–33]. Although it has been reported that there was no significant difference in PRL levels between post-PEG 6000 and post-PEG 8000, a significant constant bias has been observed in these two tests. Laboratories that use PEG 8000 should therefore exercise caution, when interpreting post-PEG PRL levels using reference values established with PEG 6000.[34]

The cut-off of <40% was used to indicate the presence of macroprolactin,[31,35] as a PEG recovery of <40% has been shown to be 100% sensitive for detecting macroprolactin. Most studies identify a grey area with recovery between 40% and 60%; at this level it has been shown that the sample may contain monomer PRL together with macroprolactin. Therefore, GFC is recommended to detect the presence of macroprolactin, and this finding is supported by previous research.[24]

The gold standard for the determination of macroprolactin is gel filtration chromatography (GFC), which allows quantitation of all forms of PRL and estimates its molecular mass. This method, however, is time consuming, expensive and generally not suitable for the routine clinical laboratory.[5] PEG is therefore considered the most recommended method for the detection of macroprolactin.[30]

There were several limitations in our study. Compared to the sample size calculations, the number of patients in our study was relatively small. It would be desirable to have a multicentre study, in order to see the true prevalence of macroprolactinaemia in our population. A larger number of male patients and infertility patients also may be needed to look for macroprolactin in these groups of patients.

As this is a cross-sectional study, the records cannot be reviewed for further evaluation of hormonal status and thus cannot be assessed. This study used a leftover sample; therefore, there was only a small amount of sera, and there was not enough for further analysis of other hormones and to study the association of hormonal changes in these patients. As in the records review, there were few missing records and data, which enables further detailed study of the patients. Further follow-up in these patients would be beneficial to study the nature of the symptoms: do symptoms persist or resolve, with or without treatment?

Conclusions

Screening for macroprolactin is necessary and has been highly recommended by several studies, but the decision for screening must be accordingly made by the attending physician. At present, this screening should not be routinely performed, due to laboratory costs. However, if cost is not a problem, screening is most beneficial to both patients and attending physicians. As the main clinical approach in hyperprolactinaemic patients is to determine the cause of hyperprolactinaemia, as the management differs according to primary cause, it is also important to identify which patients require further evaluation and treatment. Therefore, detecting macroprolactinaemia is very important. When the presence of macroprolactin is at a normal level of monomeric PRL, patients do not need further imaging study and do not require a dopamine agonist. Preferably, laboratories should establish the reference intervals, providing a measurement of bioactive PRL, which provides the most useful information for clinicians.

Authors' contributions

Dr. Noor Azlin Azraini Che Soh designed the study, conducted the research, and collected and organized the data. Dr. Julia Omar provided research materials. Dr. Najib Majdi Yaacob analysed and interpreted data. Wan Mohd Izani Wan Mohamed and Mohamed Rusli Abdullah provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript. All authors contributed equally to this work.

Conflict of interest

The authors have no conflict of interest to declare.

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