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ORIGINAL ARTICLE

Hyperprolactinemia diagnostics – dilemmas over optimal selection of prolactinemia time points

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Abstract

Introduction. Laboratory discrimination of pathologic hyperprolactinemia is an important step in the diagnosis of pathology influencing overall health and fertility. A major issue is the choice of time and circumstances for obtaining a blood sample for prolactin assay that would be representative for mean daily plasma concentration of a subject.

Objectives. The aim of the study was a comparison of reliability of single prolactin assessment on various time-points in a day with circadian prolactinemia profile in order to find the easiest, the least expensive, and the most reliable method of hyperprolactinemia diagnosis.

Materials and method. The study was a retrospective analysis of 138 women, hospitalized in the Department of Endocrinology and Metabolic Diseases, Polish Mother`s Memorial Hospital – Research Institute, Lodz, Poland, in whom the circadian profile of prolactin (including assays at 8.00 am, 11.00 am, 2.00 pm, 5.00 pm, 8.00 pm, 11.00 pm, 2.00 am, 5.00 am and repeatedly at 8.00 am) had been assessed.

Results. On the basis of AUC (area under the curve) of prolactin concentrations, hyperprolactinemia was diagnosed in 34 subjects (24.6 % of the entire group). The attempts to diagnose hyperprolactinemia based on a single prolactin assay failed due to a high percentage of false negative and false positive results. Only significant hyperprolactinemia with mean prolactin concentration of about 100 µg/l or more appeared easy to diagnose. Combinations of several time points also appeared not reliable enough.

Conclusion. The nine-point daily profile of prolactinemia in any patient with clinical suspicion of hyperprolactinemia seems the best mode for estimating mean circadian prolactin concentration.

Key words

hyperprolactinemia, diagnosis, circadian profile

INTRODUCTION

Hyperprolactinemia is a state of an increased concentration of prolactin in the circulation. Thus, it seems to be easy to recognize – simply by finding the laboratory result above the reference value. Unfortunately, reliable diagnosis of hyperprolactinemia can be quite complicated. Current guidelines of The Endocrine Society [1] recommend basing the diagnosis on a single measurement of serum prolactin, as long as the serum sample is obtained without excessive venipuncture stress. This recommendation is highly controversial as a great number of well-known physiological and pathological factors influence prolactin secretion. Formerly, repeated prolactin assessment (at least two separate serum prolactin levels) and daily prolactin profiles were indicated [2]. Current guidelines do not recommend dynamic testing, such as the metoclopramide test, as they are not superior to a single random prolactin measurement [1].

Hyperprolactinemia is a quite common clinical finding, especially in young women with secondary amenorrhea. In such a group, its prevalence varies from 5.5% – 13.8%, depending on age and manifestation [3].

As mentioned above, plenty of factors and conditions can significantly increase prolactin secretion. Thus, a problematic matter is the interpretation of laboratory findings as well as the choice of time and circumstances for obtaining the blood sample for prolactin assay. The assayed prolactin concentration should be representative for mean plasma concentration of a subject. Problems in the diagnosis of pathological hyperprolactinemia can arise from pulsatile circadian rhythm of prolactin secretion, and from the fact that there are several physiological conditions that cause increased prolactin secretion. A sample obtained at the time of increased prolactin secretion due to some physiological stimulus would not be representative for mean prolactin concentrations. Among the most obvious physiological reasons of hyperprolactinemia are pregnancy and breast feeding. Transient prolactinemia elevation can be caused by breast stimulation, stress, physical exercise and sexual intercourse [4]. False positive results are possible because of the physiologic increase of prolactinemia. Several medical agents are known to cause increased prolactin secretion, the best known being anti-emetic (metoclopramid) and anti-psychotic drugs, anti-depressants, and anti-convulsants, as well as other frequently used drugs, such as verapamil or estrogens. Administration of any of them could also lead to false positive laboratory results [5]. Several pathologic conditions, such as hypothyroidism, chronic renal failure or cirrhosis may also cause hyperprolactinemia.

The presence of prolactin-secreting pituitary tumour is usually easy to diagnose because of significantly elevated prolactin levels and lack of circadian secretion rhythm. Prolactinomas should be diagnosed as early as possible to

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avoid pituitary damage with all its consequences. These tumours respond well to pharmacotherapy which should be introduced immediately. Non-prolactin-secreting pituitary tumours, or other parasellar masses, also lead to hyperprolactinemia because a disruption or compression of the pituitary stalk results in lack of prolactin secretion inhibition by hypothalamic dopamine. The lack of circadian rhythm is characteristic for pituitary or parasellar tumours and seems to be an important finding in the course of diagnosis. Moreover, the circadian prolactin rhythm assessment is proved to have high repeatability [6], while poor repeatability seems to be the most important weak point of a single prolactin assessment. Problems connected to the proper diagnosis of hyperprolactinemia can also result from the laboratory inequality. The so called 'hook effect' is a well-known phenomenon which occurs when apparently low prolactin concentration results from antibody saturation, by exceptionally high serum prolactin, during immunochemistry or immunoradiometric assay [7]. The hook effect is the cause of false negative results and serial dilution of serum samples is recommended to eliminate this artefact [1]. Obviously, a simple laboratory mistake is also possible.

Hyperprolactinemia should not be considered as a distinct disease but a condition and laboratory sign related to several pathologies. Consequently, a major problem is to find the reason for hyperprolactinemia.

OBJECTIVES

The aim of the presented analysis was a comparison of reliability of a single prolactin assessment on various time-points in a day with circadian prolactinemia profile, in order to find the easiest, the least expensive, and the most reliable method of hyperprolactinemia diagnosis. The diagnostic value of abridged – few points AUC (area under the curve) of prolactin concentration was also assessed.

MATERIAL AND METHODS

The study was a retrospective analysis of patients hospitalized in the Department of Endocrinology and Metabolic Diseases, Polish Mother`s Memorial Hospital – Research Institute, Lodz, Poland. The medical reports of female patients hospitalized for various reasons were researched. 138 women in whom the circadian profile of prolactin had been assessed were enrolled.

The predominant indications for circadian prolactin secretion assessment in the analysed group of patients were: menstrual disorders – occurring in 95 women (69% of the entire group); menstrual disorders associated with hirsutism – in 21 patients (15%); hirsutism as the main problem, which occurred in 12 women (9%), infertility – in 11 women (8%) [7 of them (5%) were menstruating regularly], and – in 21 cases – other conditions, including galactorrhoea, complex endocrine disorders or osteoporosis.

The routine procedure for prolactin profile assessment in our Department included nine prolactin concentration assessments every three hours: at 8.00 am, 11.00 am, 2.00 pm, 5.00 pm, 8.00 pm, 11.00 pm, 2.00 am, 5.00 am and repeatedly at 8.00 am. The blood samples were obtained from the cubital vein using previously inserted cannula.

The prolactin was assayed by the electrochemiluminescence immunoassay method using commercial 'ECLIA' kit on a Cobas immunoassay analyzer. The upper normal limit of prolactinemia assayed by this method in our laboratory was 29 μg/l.

The area under the curve (AUC) of prolactin concentrations was calculated to assess mean daily prolactin secretion. The upper limit of AUC was assumed to be equal to 696. This value was calculated by substitution of 29 in the formula for AUC calculation, and corresponded to the mean circadian prolactin concentration of 29 μg/l.

Diagnosis of hyperprolactinemia on the basis of AUC was considered the point of reference. Diagnostic value of a single assessments of prolactinemia at various hours of the day (8.00 am, 11.00 am, 2.00 pm, 5.00 pm) and of AUC containing less points (8.00 am, 11.00 am, 2.00 pm, 5.00 pm; 8.00 am, 11.00 am, 2.00 pm; 8.00 am, 5.00 pm, 2.00 am, 8.00 am; 8.00 am, 5.00 pm, 2.00 am, and double 8.00 am) was assessed by finding the number of false positive and false negative diagnoses.

RESULTS

The daily profile of prolactinemia comprised 9 time-points. Mean prolactin concentrations in the study group at every time-point are presented in Table 1. The highest mean prolactinemia in the entire study group was observed at 2.00 am (Fig. 1).

Table 1. Mean prolactin concentrations at nine time points of daily prolactinemia profile in 138 women

Time	Prolactin concentration [μg/l]			
	Minimum	*Maximum*	*Mean ±SD*	*Median*
8.00 am	2.76	323.4	35.31±43.16	23.97
11.00 am	2.06	309.4	23.33±37.64	12.75
2.00 pm	1.73	262.8	23.17±33.41	13.12
5.00 pm	2.09	276.9	25.87±34.05	15.3
8.00 pm	2.84	288.9	28.45±34.31	18.26
11.00 pm	3.52	268.0	28.12±33.14	19.35
2.00 am	1.86	283.2	43.28±35.43	33
5.00 am	3.47	291.8	39.90±34.92	30.38
8.00 am second day	4.21	336.2	36.09±39.37	26.84

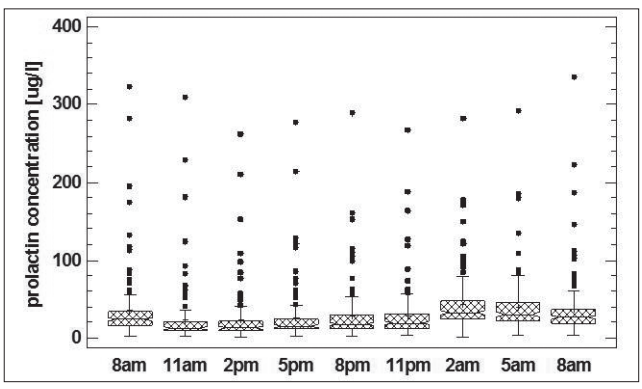

Figure 1. Prolactinemia during 24 hours in all 138 studied patients

The only time point that was assayed twice was 8.00 am. The difference between two 8.00 am assays for each individual patient was highly variable, from -59.0 – 212.2; mean -0.781295±21.6848; median – 1.7. It should be stressed, however, that this variability results mostly from a single outlier with a value of 212.28. Figure 2 illustrates the frequency of various differences. The individual circadian changes of prolactin concentration varied widely (Fig. 3).

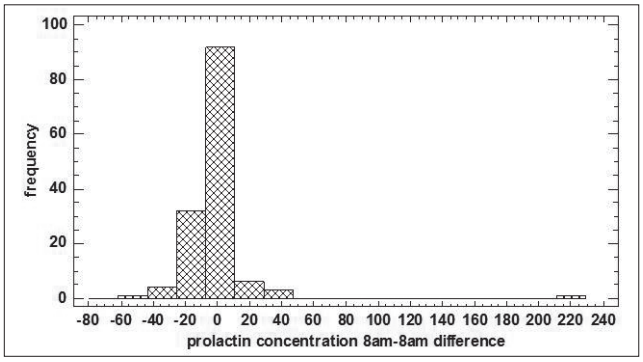

Figure 2. Variance of 8am prolactin concentration on following two (2) days in individual cases

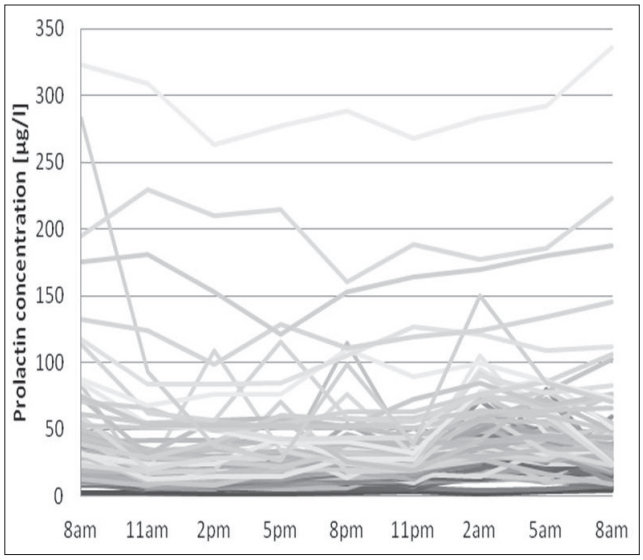

Figure 3. Variable individual circadian changes of prolactin concentrations

The mean AUC of circadian prolactin concentrations in the entire group was 743.48±810.93, median 538.35. The mean daily prolactin concentration in the entire group was 30.98±33.79 µg/l; median 22.43 µg/l. According to the AUC, hyperprolactinemia was diagnosed in 34 subjects (24.6% of the entire group). The AUC in the hyperprolactinemic subgroup was 1587.12±1313.19; median 1118.42. The mean daily prolactinemia in the hyperprolactinemic group varied from 29.21 µg/l – 288.85 µg/l; mean 66.13±54.7163 µg/l; median 46.60 µg/l. In the hyperprolactinemic group, 18 subjects (53%) had mean daily prolactinemia below 50 µg/dl, in 8 women (24%) mean daily prolactinemia was between 50 µg/l – 75 µg/l, 3 subjects (8%) had prolactinemia between 75 µg/l – 100 µg/l and in 5 patients (15%) prolactinemia was above 100 µg/l.

The attempt to diagnose prolactinemia on the basis of single prolactin concentration assessment appeared highly inconsistent. The number of hypothetically diagnosed hyperprolactinemia cases according to a single prolactinemia assessment on different time-points in reference to hyperprolactinemia diagnosed according to the AUC and mean daily prolactin concentration is illustrated in Table 2.

In 15 subjects, all 9 assayed prolactin concentrations were above 29 µg/l. The mean prolactinemia in these 15 subjects was 99.36±68.53 µg/dl, median 63.97 µg/l. Among these 15, only one subject's mean daily prolactinemia was below 50 µg/l, in 7 subjects mean daily prolactinemia varied between 50 µg/l – 75 µg/l, in 2 cases it was between 75 µg/l – 100 µg/dl, and in five subjects it was above 100 µg/l.

In attempt to find a more simple way to diagnose hyperprolactinemia, several combinations of two, three and four time-points were assessed. The AUC and mean prolactinemia were calculated for two 8.00 am assays, two three-point curves including: 8.00 am, 11.00 am, 2.00 pm and 8.00 am, 5.00 pm, 2.00 am and two four-point curves including: 8.00 am, 11.00 am, 2.00 pm, 5.00 pm and 8.00 am, 5.00 pm, 2.00 am, 8.00 am. The detailed data are contained in Table 3.

Assessment of the circadian prolactin profile appeared to be the most reliable tool for hyperprolactinemia diagnosis as none of the alternative models appeared reliable as a tool for this diagnosis. Wach of them appeared less reliable than circadian AUC and mean daily prolactin concentration. The number of false results for every alternative curve is presented in Table 4.

Table 2. Number of misdiagnosed cases of hyperprolactinemia on the basis of a single assessment in different time-points

Time point	No. of subjects with prolactinemia >29 µg/l)	Percent (%) of hyperprolactinemia cases in the entire group	No. of false positive	Percent (%) of false positive	No. of false negative	Percent (%) of false negative
8.00 am	47	34%	17	36%	4	12%
11.00 am	22	16%	1	5%	13	38%
2.00 pm	24	17%	1	4%	11	32%
5.00 pm	28	20%	4	14%	10	29%
8.00 pm	36	26%	8	22%	6	18%
11.00 pm	42	30%	16	38%	8	24%
2.00 am	89	64%	56	63%	1	3%
5.00 am	76	55%	45	59%	1	3%
8.00 am	56	40%	29	52	7	21%

Table 3. Alternative combinations of two (2) to four (4) time-point means

Time points included in AUC	Minimum		Maximum		Mean±SD		Median	
	AUC	*mean prolactin [µg/l]*	*AUC*	*mean prolactin [µg/l]*	*AUC*	*mean prolactin [µg/l]*	*AUC*	*mean prolactin [µg/l]*
8.00 am 11.00 am 2.00 pm	14.54	2.42	1807.5	301.25	157.71±220.59	26.28± 36.76	95.1	15.85
8.00 am 11.00 am 2.00 pm 5.00 pm	20.27	2.25	2617.05	290.78	231.27±317.49	25.69± 3528	136.65	15.18
8.00 am 5.00 pm 2.00 am	39.6	2.2	5221.8	290.1	586.49±622.93	32.58± 34.61	422.82	23.49
8.00 am 5.00 pm 2.00 am 8.00 am	57.81	2.41	7080	295	824.61±834.81	34.36± 34.78	606.9	25.29
8.00 am 8.00 am	83.64	3.49	7915.2	329.8	856.70±956.61	35.69± 39.86	588	24.5

Table 4. Number of misdiagnosed hyperprolactinemia cases on the basis of various two to four point models

Time points	No. of prolactinemia cases above normal range	Percent (%) of hyperprolactinemia cases in the entire group	No. of false positive	Percent (%) of false positive	No. of false negative	Percent (%) of false negative
8.00 am 11.00 am 2.00 pm	27	20%	2	7%	15	44%
8.00 am 11.00 am 2.00 pm 5.00 pm	27	20%	0	0	8	24%
8.00 am 5.00 pm 2.00 am	40	29%	9	23%	3	9%
8.00 am 5.00 pm 2.00 am 8.00 am	46	33%	15	33%	3	9%
8.00 am 8.00 am	50	36%	21	42%	5	15%

DISCUSSION

The circadian AUC of prolactin concentration and mean daily prolactin derived from it were considered the reference in the presented analysis. This allowed avoiding a mistake originating from the circadian rhythm of prolactin secretion or temporary increase due to stress, and appeared the most reliable method.

The presented study demonstrates the superiority of the circadian prolactin profile over other schemes of prolactin assessment in adults. Other results from our department indicate that this method is also the best tool for making a reliable hyperprolactinemia diagnosis in children [Stawerska et al., unpublished observations]. Only a repetition of the profile on another day could be more precise. Hyperprolactinemia diagnosed according to the mean daily prolactinemia in the analyzed patient group appeared quite frequently, occurring in 24.6% of subjects. This is in concordance with the authors expectations, as it must be emphasized that the group consisted of women hospitalized for some endocrine disorders. Performing a nine-point daily profile would be impossible in outpatient modality. In patients without indications for hospital diagnostics the prevalence of hyperprolactinemia would probably be lower. In a study by Alpañés et al. [8], hyperprolactinemia was found in only 4.1% of healthy female blood donors.

Recent guidelines of The Endocrine Society recommend a single measurement of serum prolactin, stating that a level above the upper limit of reference value confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress. The Society does not recommend dynamic testing of prolactin secretion for the diagnosis of hyperprolactinemia [1]. The recommendations are reasoned by the opinion that a single determination is usually sufficient to establish the diagnosis. However, in case of doubt, the recommendations advise repeating the sampling on a different day at 15- to 20-min intervals to account for possible prolactin pulsatility [1].

Former methods of diagnosis of hyperprolactinemia, besides dynamic testing, like the metoclopramide test,

included repeated prolactinemia assays. It has been emphasized that the serum prolactin level should be checked on at least 2 separate occasions, as mild elevations could be caused by a variety of stress factors, such as exercise, sexual intercourse, meals and venipuncture [9]. In turn, Zgliczyński et al. [10] proposed performing the metoclopramide test in every case of prolactin concentration above the reference value found in a fasting sample. The metoclopramide test may be practically useful in further management of slightly elevated prolactinemia with lack of characteristic rhythm of concentration values in daily profile. No circadian rhythm of prolactin secretion concomitant with no response of prolactin to metoclopramide is suggestive of prolactinoma, despite a modestly elevated prolactin level.

Because of the fact that stress related prolactinemia can be found in about 30% of patients when randomly sampled in resting condition, obtaining three blood samples at 20 min intervals has been proposed [11].

When single prolactin assessment is indicated, the circumstances for obtaining the sample are extremely important; excessive venipuncture stress must be avoided and the sample should be obtained at least 1 hour after awakening or eating. When the levels appears slightly above the normal range, assessment should be repeated before the diagnosis of hyperprolactinemia [12]. Stress is an important factor influencing prolactin secretion, the nervousness about venipuncture is among the emotions that can stimulate prolactin secretion [9]. Prolactin does increase in response to psychosocial stress. The response, however, is individually variant in magnitude. The pattern of prolactin response does not appear to be different between males and females: women may have a higher magnitude of the increase than men. The magnitude of the prolactin responses, to some extent, is related to the magnitude of cardiovascular responses. In women, the magnitude of prolactin response also seems to be dependent on estradiol levels [13].

Among factors influencing prolactin secretion is sexual activity. It was found that sexual intercourse with orgasm induced not only the well-established immediate prolactin increase of 300%, but also an additional prolactin elevation around noon of the next day [14]. This implies the necessity to ask about recent sexual activity before sampling for prolactinemia.

Recently, much attention has been paid to familial hyperprolactinemia due to a heterozygous mutation in the prolactin receptor gene [15]. Familial hyperprolactinemia is usually symptomatic and should be taken into consideration in all women and men with no other clinical cause of elevated prolactin levels. Family history is of special regard in every patient in whom genetic factors are considered [15].

The adequacy of single prolactin assessment at several hours a day was evaluated in the current analysis. Unfortunately, none of the single assessments at different time-points appeared to be sufficiently reliable. The 8.00 am assay was characterized by high prevalence of false positive results. The lowest prevalence of false positive results occurred at 11.00 am and at 2.00 pm. In our previous observation a high incidence was found of false negative diagnosis of hyperprolactinemia at 8.00 am [16]. The highest prevalence of prolactin concentrations exceeding 29 μg/l was found during the night hours, at 2.00 am and 5.00 am. This was obvious and in accordance with the physiologic circadian rhythm of prolactin secretion. The occurrence of false positive results can be easily explained by the circadian rhythm and physiological increase of prolactin secretion in response to several stimuli.

The occurrence of false negative results appeared much more suprising. At 8.00 am, 4 cases of false negative normal prolactinemia were found. The highest incidence of false negative results was observed at 11.00 am. The possibility of false negative result at a single assessment appears an important clinical problem. Additional issue against single assay diagnosis of hyperprolactinemia is high variability of prolactin concentration at a selected time point, as checked by double assessment of prolactin at 8.00 am at the first and the following day.

In order to find a simpler and less expensive way to diagnose hyperprolactinemia, several combinations of a reduced number of time points of prolactin assessment were analysed. Unfortunately, none of them appeared sufficiently accurate, with a high incidence of false negative results when daytime hours were chosen. This can be partly dependent upon individual variances in daily prolactin secretion. It has been observed that gender, age, and BMI specify distinct prolactin dynamics [17]. Elevated plasma prolactin levels were observed in obese women and the level reduction was recorded after body weight loss [18].

In the analysed group, the least problematic was the diagnosis of hyperprolactinemia in subjects in whom the mean daily prolactinemia was about 100 μg/l, or more. In these patients, any single sample for prolactinemia allowed the proper diagnosis. Unfortunately, with lower prolactinemia, the diagnosis appeared problematic. This is a considerable problem, as even mild prolonged hyperprolactinemia exerts several deleterious health effects.

Clinical manifestation of hyperprolactinemia in women varies upon the levels of prolactin. Significant prolactin excess (>100 μg/l) is commonly associated with hypogonadism, galactorrhea and amenorrhea. The prolactinemia above 100 μg/l is generally considered a sign of prolactinomas [19], and pituitary tumour cannot be excluded in the presence of lower prolactinemia. Moderate prolactin excess (50–75 μg/l) is associated with oligomenorrhea. Mild prolactin excess (<50 μg/l) is associated with short luteal phase and decreased libido [20].

Prolonged hyperprolactinemia is associated with mineral bone loss. This seems to depend mainly on sexual hormones deficiency, but there are studies indicating that prolactin itself enhances the calcium mobilization from bones, even at sufficient calcium intakes. It is suggested that prolactin takes part in the regulation of calcium homeostasis in the organism [21]. Prolactin may also modulate lipoprotein metabolism and insulin sensitivity. Thus, even mild hyperprolactinemia should not be neglected.

Another clinically important problem is the possibility of the presence of a biologically- inactive form of prolactin. The assessment of biological activity of prolactin is an essential aspect in the proper diagnosis of hyperprolactinemia. Some hyperprolactinemic patients are characterized by macroprolactinemia which does not cause hormonal impairment or clinical symptoms [22]. The monomeric prolactin is biologically-active and is present in the majority of patients with hyperprolactinemia. In some patients, high molecular weight forms of prolactin are found. The predominance of high molecular mass complexes of prolactin and anti-prolactin immunoglobulins is called

macroprolactinemia [23]. Some authors suggest that biochemical hyperprolactinemia in the absence of clinical symptoms is characteristic for macroprolactinemia. Other authors observed that macroprolactinemia and monomeric hyperprolactinemia may co-exist in the same patient; in such cases, persistent hyperprolactinemia after polyethylene glycol precipitation of macroprolactin should always be carefully diagnosed for prolactinoma [24].

A shortcoming of this study was the selection of the study group among the subjects hospitalized in our Department for some pathology suspicion. Thus, the presented conclusion cannot be transferred the general, asymptomatic population. Moreover, the circadian profile was not compared with the assessment of prolactin at the 20 min intervals indicated in the guidelines.

CONCLUSIONS

Based on the analysis of the presented data and the review of literature, it must be concluded that the area of doubts indicated in recent guidelines is so wide that in most of the patients with any clinical suspicion of hyperprolactinemia, a single assessment of prolactin is definitely insufficient. The probability of false positive results is not a major problem as these are the subjects in whom further diagnostics are to be performed. The real problem lies in false negative results which could result in leaving a patient with a hormonal and metabolic problem without proper diagnosis and treatment. The authors are in favour of performing the nine-point daily profile of prolactinemia in any patient with a clinical suspicion of hyperprolactinemia, as we believe the cricadian profile to be the best mode for estimating the mean prolactin concentration. This will obviously include women with menstrual and fertility problems.

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