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Original Article

Clinical and Laboratory Characteristics of Hyperprolactinemia in Children and Adolescents: National Survey

Short title: Hyperprolactinemia in children and adolescent

Erdal Eren, MD, Uludag University, Medical Faculty, Bursa, Turkey; ORCID 0000-0002-1684-1053
Ayca Torel Ergur, Professor, Kirikkale University, Faculty of Medicine, Kirikkale, Turkey; ORCID 0000-0002-7792-1727
Sukriye Pinar Isguven, MD, Sakarya University, Faculty of Medicine, Sakarya, Turkey; ORCID 0000-0002-6003-6908
Eda Celebi Bitkin, MD, On Dokuz Mayis University, Faculty of Medicine, Samsun, Turkey, ORCID 0000-0002-6586-7305
Merih Berberoglu, Professor, Ankara University, Faculty of Medicine, Ankara, Turkey, ORCID 0000-0003-3102-0242
Zeynep Siklar, Professor, Ankara University, Faculty of Medicine, Ankara, Turkey ORCID 0000-0003-0921-2694
Firdevs Bas, MD, Istanbul University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0001-9689-4464
Servet Yel, MD, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey, ORCID 0000-0001-6889-4504
Serpil Bas, MD, Marmara University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0001-6210-4807
Elif Sobu, MD, Uludag University, Faculty of Medicine, Bursa, Turkey; ORCID 0000-0002-2037-7046
Abdullah Bereket, Professor, Marmara University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0002-6584-9043
Serap Turan, Professor, Marmara University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0002-5172-5402
Halil Saglam, MD, Uludag University Medical Faculty, Bursa, Turkey ORCID 0000-0003-0710-5422
Zeynep Atay, Assoc Professor, Marmara University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0002-1044-6888
Oya Ercan, Professor, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey ORCID 0000-0001-7397-2837
Tulay Guran, Professor, Marmara University, Faculty of Medicine, Istanbul, Turkey ORCID 0000-0003-2658-6866
Mehmet Emre Atabek, Professor, Necmettin Erbakan Univ., Faculty of Medicine, Konya, Turkey ORCID 0000-0002-2242-9401
Huseyin Anil Korkmaz, MD, Balikesir Atatürk State Hospital, Balikesir, Turkey ORCID 0000-0001-5800-9014
Aylin Kilinc Ugurlu, MD, Gazi University, Faculty of Medicine, Ankara, Turkey ORCID 0000-0003-1265-4952
Aysehan Akinci, Professor, Inonu University Medical Faculty, Malatya, Turkey ORCID 0000-0001-7267-9444
Esra Doger, MD, Gazi University, Faculty of Medicine, Ankara, Turkey ORCID 0000- 0003-0802-3955
Enver Simsek, Professor, Osmangazi University, Faculty of Medicine, Eskisehir, Turkey ORCID 0000-0003-0120-9976
Emine Demet Akbas, MD, Gazi University, Faculty of Medicine, Ankara, Turkey 0000-0002-5746-6835
Ayhan Abaci, MD, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey ORCID 0000-0002-1812-0321
Ulku Gul, MD, Erciyes University, Faculty of Medicine, Kayseri, Turkey ORCID 0000-0001-7708-3498
Sezer Acar, MD, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey ORCID 0000-0002-0768-835X
Eda Mengen Ucakturk, MD, Cukurova University, Faculty of Medicine, Adana, Turkey ORCID 0000-0003-1597-8418
Melek Yildiz, MD, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey ORCID 0000-0002-6603-2983
Edip Unal, MD, Dicle University, Faculty of Medicine, Diyarbakir, Turkey ORCID 0000-0002-9807-0977
Omer Tarim, Professor, Uludag University, Faculty of Medicine, Bursa, Turkey ORCID 0000-0002-5322-5508

Corresponding author: Assoc. Prof. Erdal EREN, MD,
Uludag University, Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, TURKEY
Phone: +90 505 7686947
e-mail: erderen@yahoo.com

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What is already known on this topic?

Hyperprolactinemia affects gonadal function in the adolescent. Cabergoline is a useful treatment model for pituitary adenomas. Pituitary surgery for macroadenomas may need in some patients. Some drugs increase the prolactin level. Macroprolactinemia is one of the causes of hyperprolactinemia.

What this study adds?

Cabergoline is an effective treatment in the adolescent. There is no difference in term of age between the micro- and macroadenomas. Physicians should review surgical indications for macroadenomas. Macroprolactinemia is a neglected cause of hyperprolactinemia in cases with unexplained etiology.

Abstract

Objective: We aimed to study the characteristics on admission, diagnosis, treatment, and follow-up of hyperprolactinemic cases in a large multicenter study.

Methods: We reviewed 233 hyperprolactinemic patients under 18 years of age who were followed by different centers. The patients were divided as having microadenomas, macroadenomas, drug-induced hyperprolactinemia, and idiopathic hyperprolactinemia. Complaints of the patients and their treatment (medication and/or surgery) responses were evaluated in detail.

Results: The mean age of the patients with hyperprolactinemia was 14.5 years, and 88.4% were female. In terms of etiology, microadenomas were observed in 32.6%, macroadenomas in 27%, idiopathic hyperprolactinemia in 22.7%, and drug-induced hyperprolactinemia in 6.4%. Common complaints in females (n = 206) were sorted into menstrual irregularities, headaches, galactorrhea, primary or secondary amenorrhea, and weight gain, whereas a headache, gynecomastia, short stature, and blurred vision were common in males (n = 27). Median prolactin levels were 93.15 ng/ml, 241.8 ng/ml, 74.5 ng/ml, 93.2 ng/ml, and 69 ng/ml for microadenomas, macroadenomas, idiopathic hyperprolactinemia, drug-induced hyperprolactinemia, and other causes of hyperprolactinemia, respectively. Of 172 patients with hyperprolactinemia, 77.3% was treated with cabergoline and 13.4% with bromocriptine. 20.1% of the patients with pituitary adenomas underwent pituitary surgery.

Conclusions: We present the largest cohort of children and adolescents with hyperprolactinemia in the literature thus far. Hyperprolactinemia is more common in females, and cabergoline is highly effective and practical to use in adolescents due to its biweekly dosing. Surgery indication should be revised in childhood.

Keywords: Pituitary, prolactin, children, microadenomas, macroadenomas, cabergoline, surgery

Introduction

Prolactin (PRL) is a luteotropic and pleitropic hormone involved in many physiological functions, such as angiogenesis, immune response, osmoregulation, reproductive behavior, and lactogenesis. It is needed for the regulation of gonadal luteinizing hormone receptors in both genders, and it is necessary for lactation in females (1,2). Elevated PRL levels causes various problems. Stress, using drugs affecting the dopaminergic system, and macroprolactinemia increase PRL to moderate levels, but pituitary adenomas increase PRL levels significantly (3,4,5). Signs and symptoms related to increased PRL are more common in women during adolescence. Menstrual irregularity is the most common reason for referral, and males tend to experience

intracranial pressure symptoms due to tumor growth. Medical treatment with dopamine agonist is the first line treatment option for prolactinoma, and surgical intervention is considered in some cases (6).

Hyperprolactinemia is a common problem in adults and the etiology is different in adults and children. Hyperprolactinemia is less frequently diagnosed in children and the literature is more scarce accordingly. We aimed to investigate the differences in children and adults in terms of etiology, treatment modality, and response to treatment in this large national cohort.

Methods

Patient analysis

We reviewed 233 hyperprolactinemic patients under 18 years of age who were followed at 32 centers. Some of cases of the participant centers in this paper were previously published (7,8,9). Hyperprolactinemia was diagnosed when repeated PRL levels were above 20 ng/ml. The maximal diameter of the adenoma was evaluated using cranial magnetic resonance imaging (MRI), where a microadenoma was defined as a pituitary tumor of less than 1 cm in diameter and a macroadenoma was defined as a tumor above 1 cm in diameter. Drug-induced hyperprolactinemia was diagnosed if the patient had a history of medications such as antipsychotic, antidepressants, and antidopaminergic agents. In this group PRL levels decreased to normal when the drug was ceased. If there was no mass in a pituitary MRI, no drug exposure, and thyroid, kidney and liver dysfunction were excluded, it was called idiopathic hyperprolactinemia. Serum macroprolactin levels were questioned in the group with idiopathic hyperprolactinemia, and complaints of the patients and their treatment (medication and/or surgery) responses were evaluated in detail. The age, sex, and auxological evaluation results (height, weight, body mass index (BMI)), as well as the standard deviation score (SDS) of the patients were evaluated (10).

Data collection

This retrospective, multicenter, nationwide web-based study used an electronic recording form (ERF) designed by two physicians (EE, OT) experienced with PRL and ERF preparation. The ERF was used to collect the demographic data and clinical and laboratory findings of the patients with hyperprolactinemia. The ERF was uploaded to the CEDD Net Web Registry System website (www.cedd.saglik-network.org). Informed consent from the parents of the patients was provided. The study protocol was approved by the Uludag University Ethics Committee (number 2015-19/10).

Statistical analysis

Statistical analyses were performed using SPSS v.23 for Windows. Data are presented as mean ± SD for parametric data and median for non-parametric data. Normality test was performed by Shapiro-Wilk test. Student's t-test was used for parametric variables, and Mann-Whitney U test was used for non-parametric data. Chi-square tests were used to determine significant differences in proportions among categorical variables. Spearman rank test was used for analysis of correlation among parameters. A p value of less than 0.05 was considered statistically significant.

Results

The median age (min-max) of the patients with hyperprolactinemia was 15.3 (0.12-17.7) years, and 88.4% (n=203) were female. In terms of etiology, pituitary microadenoma was observed in 32.6% (n = 76), macroadenoma in 27% (n = 63), idiopathic hyperprolactinemia in 22.7% (n = 53), drug-induced hyperprolactinemia in 6.4% (n = 15), and other causes of hyperprolactinemia were defined in 11.3% (n = 26) (Table 1, Figure 1). Common complaints in females (n = 206) were sorted into menstrual irregularity, headache, galactorrhea, primary or secondary amenorrhea, and weight gain, whereas headache, gynecomastia, short stature, and blurred vision were common in males (n = 27) (Table 2). A family history of high PRL levels was detected in only seven cases and the mutation analysis of *MEN* or *AIR* gene was not analyzed in that group. The cases with idiopathic hyperprolactinemia (n = 53) complained of menstrual irregularity (49%), headache (22.6%), weight gain (22.6%), pubertal delay (20.7%), and galactorrhea (17%). Hyperprolactinemia was coincidentally detected in 13.2%. Other causes of hyperprolactinemia

were sorted into non-pituitary masses (n = 6), craniopharyngioma (n = 5), macroprolactinemia (n = 5), hypothyroidism (n = 3), polycystic ovary syndrome (PCOS; n = 2), pituitary stalk interruption syndrome (PSIS; n = 2), rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysfunction (ROHHAD) syndrome (n = 2), and tuberous sclerosis (n = 1). In the group with drug-induced hyperprolactinemia, risperidone was used in nine of 15 cases, and various antipsychotic or antidepressants were used in the other cases. Serum macroprolactin was measured in 48 cases with idiopathic hyperprolactinemia and detected in 5 (10.4%), with a median PRL level of 127 (63.5-200) ng/ml. The median prolactin levels were 93.15 ng/ml, 241.8 ng/ml, 74.5 ng/ml, 93.2 ng/ml, and 69 ng/ml for microadenomas, macroadenomas, idiopathic hyperprolactinemia, drug-induced hyperprolactinemia, and other causes of hyperprolactinemia, respectively (Table 1).

When the cases with a prolactinoma (n = 139) were divided into two groups as micro- and macroadenomas, there were no statistically significant differences in terms of age. In terms of gender distribution, 93.4% of microadenomas cases were female (71 female, 5 male) and 77.7% of macroadenoma cases were female (49 female, 14 male) ($p<0.05$). There was no significant difference in height, weight, height SDS, weight SDS, BMI, and BMI SDS between the two groups. However, BMI and BMI SDS were higher in the macroadenoma group (Table 3). The maximal diameter of the adenomas was 5.9 ± 2.1 mm in microadenomas and 17.3 ± 7.4 mm in macroadenomas, and there was a significant correlation between adenoma size and PRL level ($p <0.05$, $r=0.494$) (Figure 2).

Of 172 patients with hyperprolactinemia (micro/macroadenomas plus some patients with idiopathic hyperprolactinemia), 77.3% was treated with cabergoline and 13.4% with bromocriptine. The remaining 9.3% was switched from bromocriptine to cabergoline because of treatment failure. The median (min-max) an initial dose of cabergoline and bromocriptine was 0.5 (0.25-2.5) mg/week and 2.5 (0.5-7.5) mg/day, respectively, and the normalization period of PRL was 2 (0.5-47) months for cabergoline and 3 (1-17) months for bromocriptine, and statistical difference was found ($p<0.170$). There were no serious side effects for both drugs. In total, 20.1% (28/139) of the patients with pituitary adenomas underwent pituitary surgery. Surgical option was the choice of the neurosurgeon or the patient who was not seen by an endocrinologist before the surgeon. Transcranial surgery was performed in only two cases, while transsphenoidal surgery was performed in others. In addition, 86.2% of these cases required a dopamine agonist after the operation, and only four cases received radiotherapy.

Discussion

In this large retrospective multicenter cohort study, hyperprolactinemic children and adolescents were evaluated and prolactinoma was detected in 60% of them. While some of the cases (23%) were idiopathic, others were due to various medications or other causes of hyperprolactinemia. Pituitary adenomas, most common in adults, are rare in children, and few studies have been conducted on the clinical signs and treatment outcomes in children. To date and to our knowledge, this is the largest cohort of pediatric patients with hyperprolactinemia in the literature. Therefore, we believe it sheds light on all aspects of this disease with its differences from the adult population.

The ratio of macroadenoma seem very high in both girls and boys compared to adults who have a higher prevalence of macroadenomas seen in males (11,12). A similar disproportion has also been reported in other series of children (5,13). The mean age of two groups (micro-/macroadenomas) was not different significantly. This finding is contrary the assumption that neglect of symptoms for many years is reason for macroadenomas in men. Large tumors are predominated in men, it may be related with biologic behavior of prolactinomas.

Macroprolactinemia can be present in some cases with idiopathic PRL elevation. Macroprolactin is a big big-PRL, accounting for 1% of total PRL. In some cases, this ratio increases and leads to a false diagnosis of hyperprolactinemia. There is no need for treatment, and a diagnosis is made with chromotography or polyethylene glycol (PEG). Macroprolactinemia is detected in 15–46% of hyperprolactinemic cases (14,15). In our study, macroprolactinemia was checked in 48 cases and found in only five (10.5%). Some cases of idiopathic hyperprolactinemia are likely to have received unnecessary treatment because

macroprolactinemia is not excluded. Macroprolactinemia should be considered in cases having non-specific symptoms and no abnormal features in pituitary imaging. Another cause of idiopathic hyperprolactinemia may be a PRL receptor mutation. Familial hyperprolactinemia has been described in some of these cases (14,16,17). In familial cases, *AIP* and *MEN1* must be considered for genetic analysis. In a study, patients with macroprolactinoma were found to have *AIP* (9%) and *MEN* (5%), and dopamine agonist resistance was found in *MEN1* mutations (18). In our study, *MEN1* or *AIP* were not questioned.

Another cause of hyperprolactinemia is drug use. Many antipsychotic agents increase PRL by affecting the dopaminergic system (19,20). In total, 6% of our cases had increased PRL due to antipsychotic drugs, and the mean level of PRL was 100 ng/dl, with a maximum level of 200 ng/dl. The treatment for drug-induced hyperprolactinemia is a reduction of the drug dose or a transition to another drug. Pituitary imaging is needed in case of clinical signs. Other causes of hyperprolactinemia include craniopharyngioma that presses the pituitary gland, non-pituitary tumors, and PSIS that may affect the tuberoinfundibular pathway and increase PRL.

The problem is mostly observed after the onset of puberty and mostly in the female gender, and menstrual irregularity, galactorrhea, and gynecomastia can be seen commonly. In a study in which 27 pediatric cases were evaluated, 17 girls (63%) had a mean age of 15.6 years (3). In our study, the mean age of the participants was 14.49 years, and the mean age of the patients with a prolactinoma was 15 years. In the patients with macroprolactinoma, headache and visual problems are the first signs in males whereas primary or secondary amenorrhea is seen in all females (13). Oligomenorrhea and galactorrhea were the most common symptoms of macroadenoma in a study of 13 cases (10 female) (21). In another study, 80% of females with hyperprolactinemia presented with menstrual problems, galactorrhea, and headache, while males presented with headache, visual problems, and gynecomastia (18). In our study, 60% of girls had menstrual problems, 25% had headache, and 25% had galactorrhea, whereas half of boys complained of headaches. In summarize, half of the males had headache, while half of the females presented with menstrual problems. It is possible that a larger pituitary adenoma could cause headaches due to delayed diagnosis. Other complaints in men were not specific. Hyperprolactinemia should be considered in the differential diagnosis of women with menstrual problems during puberty, and cranial and pituitary imaging should be done to elucidate the etiology.

In our series, interestingly, about 10% of cases experienced weight gain and 30.9% (n = 72) of our cases were overweight or obese. The increase in BMI was found more in macroprolactinoma. However, there was no correlation between BMI and PRL levels. In a study, 11 cases (6 females, 5 males) with hyperprolactinemia presented with short stature or growth acceleration in four cases, weight gain in four cases, and pubertal problems in three cases (4). In another study, 23% of cases were referred to a physician with weight gain (18). In a study in which non-functional pituitary adenomas and prolactinoma were evaluated, it was emphasized that BMI is significantly higher in the prolactinom group. That group had also diminished GH and IGF-1 which may affect the lipid metabolism (22). It has been shown that the modulator effect of PRL may influence fat tissue, and PRL changes body weight and composition. In 44 patients with prolactinoma, waist and hip circumference increased significantly, while fasting insulin and triglyceride were found to be high and fasting glucose and HDL cholesterol were normal (23). The relationship between PRL and obesity is still speculative and unclear. The prolactin-releasing peptide (PrRP) was found to be secreted by the hypothalamus, and it increases the pituitary PRL. It has also been found that PrRP is associated with nutrient and energy balance and that PrRP reduces weight gain and has an anorexigenic effect (24). The discovery of the relationship between PrRP and PRL could help explain weight gain in hyperprolactinemic individuals.

Dopamin agonists are the first choice of drugs to treat prolactinoma, and cabergoline has been used for many years as a highly effective and tolerable treatment. It was first used as a treatment for a patient who developed bromocriptine resistance about 30 years ago (25,26). This agent, which shrinks tumor cells and performs best with weekly use. It has been shown to be effective even in pituitary adenomas with no function (27); and it has been used for years even in giant macroadenomas (28,29). In a study of 26 prolactinomas, bromocriptine was initiated in all cases, and conversion to quinagolide or cabergoline was made due to intolerance or resistance to bromocryptine had developed (13). In our study, most of the centers preferred cabergoline as

first line medication, and some had switched to cabergoline due to drug resistance. This study has shown that cabergoline can be used safely in children and adolescents with practical usage and effective treatment.

High efficacy of dopamine agonists, surgery is needed rarely in prolactinomas. Surgical treatment in our series was 20%, and this rate is likely higher than that in the adult literature. Adult studies generally show outcomes of the cases who underwent surgery. Because of that, to compare adult and child data for surgery ratio is not practical. In a pediatric study, 7 of 27 patients (25.9%) were treated surgically, whereas 37.5% of adult patients with macroprolactinomas underwent surgery and 33% developed hypopituitarism (5,30). In another study evaluating nine surgically treated patients, transient complications, such as electrolyte disturbance, were observed postoperatively, and no long-term sequelae were observed (31). Surgically, the transsphenoidal procedure is not associated with mortality, and no serious complications are observed (32). It is unclear when the surgical treatment of prolactinoma should be considered in children. It has been stated that transsphenoidal surgery can be used in patients who developed dopaminergic agonist intolerance or resistance or side effects from a drug. In addition, large adenomas causing visual problems and CSF leakage due to pressure on the base of the skull are also candidates for surgery (33,34). In our cases, dopaminergic drugs had to be started or continued in 86.2% of the patients who underwent surgery. The surgical option should not be preferred in children with prolactinoma because of recurrence after surgery, the development of various complications including hypopituitarism, and the need for dopamine agonistic therapy again.

Limitations and Strength

Limitations of the study include various laboratory data in different centers that can use different methodology, and having different treatment models and different approaches. The study's strength lies in its large case series, including most pediatric endocrinology centers in the country, and having detailed data.

Conclusion

Hyperprolactinemia, which is more common in girls, is mostly caused by pituitary adenomas. Macroprolactinemia should be investigated in cases of unexplained hyperprolactinemia. Cabergoline is an effective treatment because of its weekly usage and the absence of significant side effects in children. The surgical option should not be considered in children even in giant adenomas, because dopaminergic agonistic therapy is highly effective. Surgical indications should be reviewed by physicians.

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Ethical standards

The study protocol was approved by the Uludag University Ethics Committee (number 2015-19/10).

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Age, gender distribution and serum prolactin level according to diagnosis

	Age (years)	n (M/F)	Prolactin (ng/ml) Median	min-max
Microadenomas	15.08 ± 1.97	76 (71/5)	93.15	31.5-929
Macroadenomas	14.77 ± 1.86	63 (49/14)	241.8	52.7-5097
İdiopathic	14.65 ± 3.03	53 (50/3)	74.5	27.2-288
Drug induced	13.72 ± 4.49	15 (14/1)	93.2	50.6-200
Others	12.27 ± 4.72	26 (22/4)	69.0	35-200
Total	**14.49 ± 2.93**	**233 (206/27)**	**99.2**	**27.2-5097**

Table 2. Common complaints and symptoms according to gender in the patient with hyperprolactinemia

Female	**N=206 (%)**	**Male**	**N=27 (%)**
Menstrual irregularities	83 (40.2)	Headache	13 (48.1)
Headache	58 (28.1)	Gynecomastia	4 (14.8)
Galactorrhea	54 (26.2)	Short stature	4 (14.8)
Secondary amenorrhea	27 (13.1)	Blurred vision	4 (14.8)
Weight gain	20 (9.7)	Convulsion	4 (14.8)
Randomly	18 (8.7)	Visual field defect	3 (11.1)
Primary amenorrhea	13 (6.3)	Weight gain	2 (7.4)
Blurred vision	10 (4.8)	Randomly	2 (7.4)
Hirsutism	6 (2.9)	Delayed puberty	2 (7.4)
Infantile spasm	6 (2.9)	Infantile spasm	1 (3.7)

Table 3. Age, gender, BMI, BMI SDS, and pituitary adenoma diameter according to pituitary microadenomas and macroadenomas

	Microadenomas	Macroadenomas	p
Age (years)	15.08 ± 1.97	14.77 ± 1.86	0.348*
n (F/M)	76 (71/5)	63 (49/14)	0.023**
BMI	23.11 ± 4.57	24.30 ± 4.73	0.133*
BMI SDS	0.65 ± 1.40	0.98 ± 1.34	0.164*
Prolactin (ng/ml) (median (min-max))	93.15 (31.5-929)	241.8 (52.7-5097)	<0.001***
Maximal diameter of the adenoma (mm)	6 (1.3-10)	14 (10-35)	0.000***

* Student's t-test, **Chi-Square test, *** Mann-Whitney U test

Figure 1. Diagnostic distribution of the patient with hyperprolactinemia

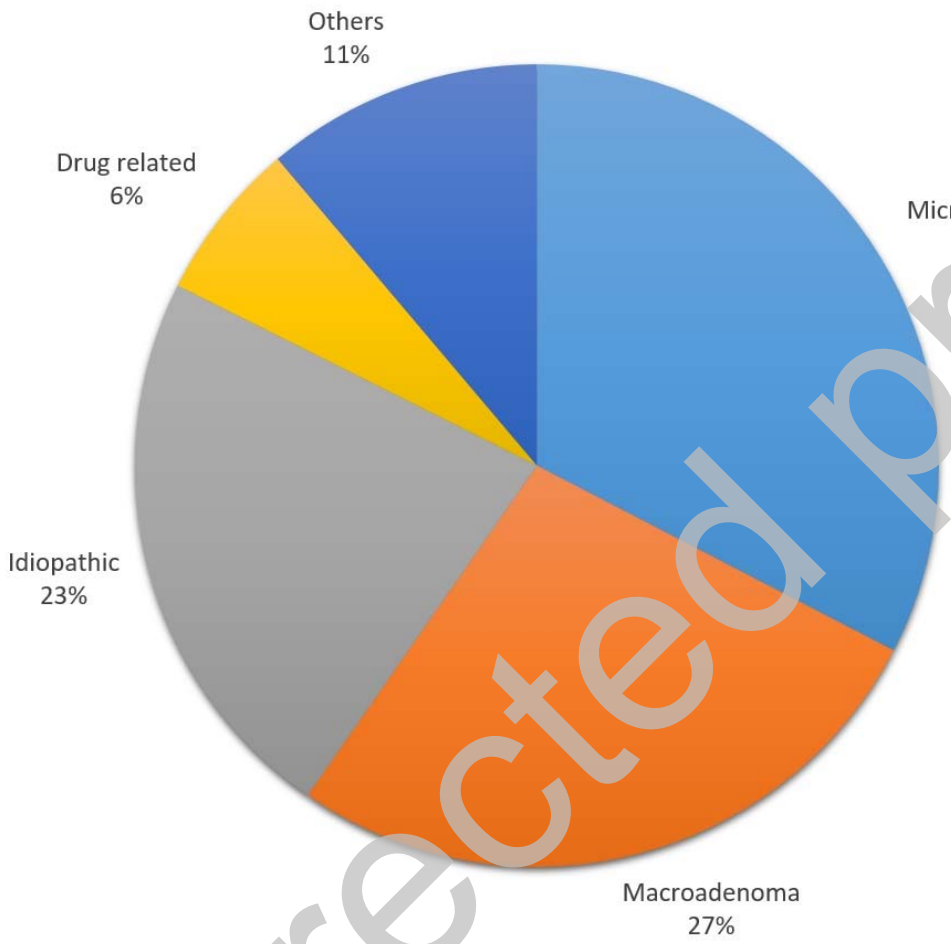

Figure 2. The correlation between serum prolactin levels and pituitary mass longitudinal diameter