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Clinical Profile and Changing Etiological Spectrum of Hyperprolactinemia at a Tertiary Care Endocrine Facility

Üçüncü Basamak Bir Endokrin Kuruluşunda Hiperprolaktineminin Klinik Profili ve Değişen Etiyolojik Spektrumu

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Abstract

Objective: Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary axis. It is most commonly caused by a pituitary adenoma. Due to the recent easy availability of over-the-counter medication, many drugs, including herbals have commonly been related to this disorder. Our purpose was to study the clinical presentation and etiology of hyperprolactinemia and to address any changing trend in the etiological profile of this disorder. **Material and Methods:** This study was a cross-sectional observational study on the etiologic spectrum and clinical profile of hyperprolactinemia. A total of 100 consecutive non-pregnant and non-lactating patients attending or referred to the out-patient department of Endocrinology at SKIMS, Srinagar were included. Hyperprolactinemia was confirmed by a serum prolactin level of >25 ng/mL (normal range=1-20 ng/mL). Patients with suspicion of drug-related hyperprolactinemia were advised to stop drug consumption for a minimum of three days (if medically feasible) and retest for prolactin levels as per the Institutional protocol. Hyperprolactinemia in patients whose prolactin levels normalized after stopping drug consumption was labeled as drug-induced hyperprolactinemia. Young patients with pituitary adenoma were evaluated for multiple endocrine neoplasia syndrome (MEN 1). The results were compared with those of a study conducted two decades ago at the same center. **Results:** Galactorrhea was the most common presenting symptom occurring in 64% of subjects (all females), followed by oligomenorrhea or amenorrhea in 60 patients. Both menstrual abnormalities and galactorrhea were seen in 35 patients. Drug-induced hyperprolactinemia was the most common cause seen in 59 patients, followed by pituitary adenoma seen in 31 patients and idiopathic cause seen in only 4% of cases. However, in the study done two decades ago at the same center, microprolactinoma was the most common cause (35.8%), followed by idiopathic hyperprolactinemia (27.8%), with drugs being responsible in only 5% of the cases. Domperidone and levosulpride constituted about 88% of drug-induced hyperprolactinemia. Microprolactinoma was demonstrated in 15 patients, macroadenoma in 16 patients, hypothyroidism in 4% cases, and only one patient had the polycystic ovarian disease. In four patients, no apparent cause could be determined. **Conclusion:** In our study, drug-induced hyperprolactinemia was the most frequent identifiable etiology, with prokinetics being the most common cause; contrary to previous studies, where pituitary adenoma followed by neuroleptic drugs was found to be the most common. Discontinuation of the offending drug resolved HP in all the patients.

Keywords: Hyperprolactinemia; galactorrhea; domperidone; drug-induced hyperprolactinemia

Özet

Amaç: Hiperprolaktinemi, hipotalamus-hipofiz aksının en sık görülen bozukluğudur. En yaygın nedeni ise hipofiz adenomudur. Son zamanlarda reçetesiz satılan ilaçların kolay bulunabilirliği nedeniyle, bitkiler de dahil olmak üzere birçok ilaç bu bozuklukla ilişkilendirilmiştir. Burada, hiperprolaktineminin klinik prezentasyonunun ve etiyolojisinin incelenmesi ve bu bozukluğun etiyolojik profilindeki değişen eğilimlerin ele alınması amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışma, hiperprolaktineminin etiyolojik spektrumu ve klinik profili üzerine kesitsel, gözlemsel bir çalışmadır. Srinagar'daki SKIMS endokrinoloji polikliniğine gelen veya bu polikliniğe sevk edilen, gebe olmayan ve emzirmeyen toplam 100 hasta çalışmaya dahil edilmiştir. Hiperprolaktinemi, serum prolaktin seviyesinin >25 ng/mL olması ile doğrulanmıştır (normal aralık=1–20 ng/mL). İlaçla ilişkili hiperprolaktinemi şüphesi olan hastalara, en az üç gün süreyle ilaç kullanmayı bırakmaları (tıbbi olarak uygunsa) ve kurum protokolüne göre prolaktin seviyelerini yeniden test ettirmeleri tavsiye edilmiştir. İlaç kullanmayı bıraktıktan sonra prolaktin seviyeleri normale dönen hastalardaki hiperprolaktinemi, ilaca-bağlı hiperprolaktinemi olarak etiketlenmiştir. Hipofiz adenomlu genç hastalar multipl endokrin neoplazi sendromu (MEN 1) açısından değerlendirilmiştir. Elde edilen sonuçlar, aynı merkezde yirmi yıl önce yapılan bir araştırmanın sonuçlarıyla karşılaştırılmıştır. **Bulgular:** Galaktore, katılımcıların %64'ünde (tümü kadın) gözlenen en yaygın başvuru semptomuydu. Bunu oligomenore veya amenore izliyordu (60 hasta). 35 hastada hem menstrual anomaliler hem de galaktore görüldü. İlaca bağlı hiperprolaktinemi en sık neden iken (59 hasta), bunu hipofiz adenomu (31 hasta) ve idiyopatik neden (vakaların sadece %4'ü) izlemekteydi. Oysaki, 20 yıl önce aynı merkezde yapılan çalışmada mikroprolaktinoma en sık nedendi (%35,8), bunu idiyopatik hiperprolaktinemi (%27,8) izliyordu ve vakaların sadece %5'inden ilaçlar sorumluydu. Domperidon ve levosulpirid, ilaca bağlı hiperprolaktineminin yaklaşık %88'ini oluşturmaktaydı. 15 hastada mikroprolaktinoma, 16 hastada makroadenom, vakaların %4'ünde hipotiroidizm ve sadece bir hastada polikistik over hastalığı tespit edildi. 4 hastada belirgin bir neden saptanamadı. **Sonuç:** Çalışmamızda, ilaca bağlı hiperprolaktinemi en sık saptanabilir etiyolojiydi ve prokinetikler en sık nedendi. Daha önceki çalışmalarda ise hipofiz adenomu ve onun ardından nöroleptik ilaçlar en yaygın nedenler olarak bulunmuştu. Sorumlu olan ilacın kesilmesiyle tüm hastalarda hiperprolaktinemi ortadan kalktı.

Anahtar kelimeler: Hiperprolaktinemi; galaktore; domperidon; ilaca-bağlı hiperprolaktinemi

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Introduction

Hyperprolactinemia (HP) is a common endocrine disorder. Apart from hypothalamo-pituitary disease, it occurs secondary to the use of drugs and chronic diseases like hypothyroidism, chronic hepatic and renal disease, stress, and neurogenic disorders. In the absence of the above-said causes, an increase in serum prolactin (PRL) is known as an idiopathic HP. It affects the gonadal axis, which results in alterations in sexual or reproductive function and can be a major treatable cause of infertility (1-3). The presence of galactorrhea is the single most important clinical sign of HP, the frequency of which varies from 30-90% in hyperprolactinemic women (4). With the advancement in imaging, microprolactinomas of the size of 3 mm are easily visualized nowadays (5). Medical management of HP provides excellent results, and most of the patients do well (6). Pituitary adenoma has been mentioned in the literature to be the most common cause of HP (7). Recent studies have found drugs to be commonly associated with HP, which contrasts with our previous study (8,9). With the easy availability of over-the-counter drugs as well as the use of herbal medication in this part of the world and easy availability of the tests for prolactin estimation, we intended to study the impact on the etiology of hyperprolactinemia. In the present study, we describe the clinical presentation and etiological profile of our HP patients and also any changing trend in the etiology of hyperprolactinemia.

Material and Methods

This was a cross-sectional observational study on the etiologic spectrum and clinical profile of HP. A total of 100 consecutive non-pregnant and non-lactating patients attending or referred to the out-patient department of Endocrinology at SKIMS, Srinagar with symptoms & signs of HP or evaluation, and treatment of HP. Hyperprolactinemia was confirmed by a serum prolactin level of >25 ng/mL (10).
Galactorrhea was defined as spontaneous/expressive flow of milk from the breast in the absence of pregnancy and nursing. Oligomenorrhea was defined as a cycle length >35 days or less than 10 cycles per year. Institutional Ethics Committee exempted the study from the ethical clearance, as the study involved the collection of anonymous data of HP patients. After taking consent from all patients, age, marital status, symptoms along with their duration, and history of drug intake were noted. Patients with a suspicion of drug-related HP were advised to stop drug consumption for a minimum of three days (if medically feasible) and repeat for prolactin levels, which is the Institutional protocol. HP of patients whose prolactin levels normalized after stopping drug was labeled as drug-induced HP. A detailed clinical examination was done in all the patients including looking for galactorrhea and gonadal function. Investigations performed included tests for serum prolactin, thyroid function, and serum gonadotropins in addition to routine complete blood count and liver and kidney function tests as per the protocol followed for hyperprolactinemia patients. Serum prolactin levels were measured by using DXI 800 Beckman Coulter Chemiluminescence random access analyzer and following the manufacturer's protocol. The reference range for prolactin is 1-25 ng/mL. The intra-assay coefficient of variation is less than 5%, and the inter-assay coefficient of variation is less than 10%.
If the above test results were normal, MRI of the pituitary gland with dynamic contrast scan was performed to look for pituitary hypothalamic lesions. If no cause was identified, then the HP was labeled as idiopathic HP.

Statistical Analysis

SPSS 20 (Statistical Package for Social Sciences) program was used for statistical analysis. Numeric variables are presented as mean ±standard deviation. Descriptive statistics were performed for all variables.

Results

Over a period of one year, a total of 100 patients had biochemically documented HP of which, 93 participants were females, and 53 were married. The average age of patients was 30.71±10.35 years, with the mean age of females being lower (29.87 ±9.24 years) than that of males (41.85±17.5 years; p=0.003). Three-fourth of the patients (73%) were in the 3rd to 4th decade of life.

The presence of symptoms, along with their frequency, is presented in Table 1. Galactorrhea was the most common symptom (64%), followed by menstrual disturbances (60%). Thirty-eight females had amenorrhea, with most having secondary-type except one who presented at the age of 16 years with primary amenorrhea. Six of the seven males with HP had a history of erectile dysfunction. Many of the subjects presented with multiple symptoms. Table 2 gives the etiology of HP. Drug-induced HP (59%) was the most common, followed by a pituitary adenoma (31%). Domperidone was the most commonly involved drug, followed by levosulpiride; both drugs were used in combination with proton pump inhibitors for a probable diagnosis of acid peptic disease. Domperidone and levosulpiride, either alone or in combination with other drugs, constituted about 88% of drug-induced causes. Other drugs included amitriptyline, amisulpride, fluoxetine, estrogen, and nortriptyline, and one patient having a history of herbal medicine intake (Peruvian Maca Extract; Figure 1). Fourteen patients followed within a week after stopping drug consumption for repeat prolactin estimation, another 14 patients followed in the second week, and the remaining patients followed after that. All patients had repeated prolactin levels of less than 25 ng/mL. Microprolactinoma was found in 15 subjects, whereas macroadenoma was found in 16 patients. Among pituitary macroadenoma subjects, 5 were labeled as non-functional pituitary adenoma, 3 had associated acromegaly (2 somatotroph adenoma and one mammosomatotroph adenoma) and eight had macroprolactinoma. Two patients had multiple endocrine neoplasia type 1 (MEN 1)-related hyperprolactinemia, each harboring macroadenoma or microadenoma. All seven males had a diagnosis of pituitary macroadenoma, with two patients having associated acromegaly. The mean serum prolactin level, according to the etiology, is given in Table 3. The mean prolactin level in hypothyroidism-related HP was 81.25 ng/mL.

Table 1. Clinical features of hyperprolactinemic patients.

Symptom	Number of patients (Percentage)
Galactorrhea	64 (64%)
Amenorrhea	38 (38%)
Oligomenorrhea	22 (22%)
Infertility	10 (10%)
Headache	19 (19%)
Visual Disturbances	14 (14%)
Erectile dysfunction (Males)	6/7 (85.71%)
Headache	
Microadenoma	7 (46.66%)
Macroadenoma	12 (75%)
Visual Disturbances	
Microadenoma	3 (20%)
Macroadenoma	11 (68.75%)

Table 2. Etiology of hyperprolactinemia.

Etiological class	No. of cases (Percentage)
Drug induced	59 (59%)
Microprolactinoma	15 (15%)
Macroprolactinoma	9 (9%)
Non functioning pituitary macroadenoma	7 (7%)
Hypothyroidism	4 (4%)
Idiopathic hyperprolactinemia	4 (4%)
PCOD	1 (1%)
Rathke's cyst	1 (1%)

Discussion

The present study was conducted to study the etiological profile of documented HP. Most of the patients were in the 3rd or 4th decade of life. The presence of galactorrhea and visible effect on gonadal function (oligomenorrhea or amenorrhea) in females makes them to present early. Most of the female patients presenting in the 3rd decade of life could be explained by the fact that most of the marriages are arranged in this decade in our culture, and any abnormality in gonadal function leads to an evaluation in most cases. Females with prolactinomas present earlier as compared to males; in males, these are usually macroadenomas (5).

Symptoms(s) of amenorrhea and/or galactorrhea was the most common presentation in females. The incidence of galactorrhea in women with HP varies among different reports and occurs in 30-80% of subjects (11,12). Around 19% of our subjects had a history of headaches. Headache is usually a

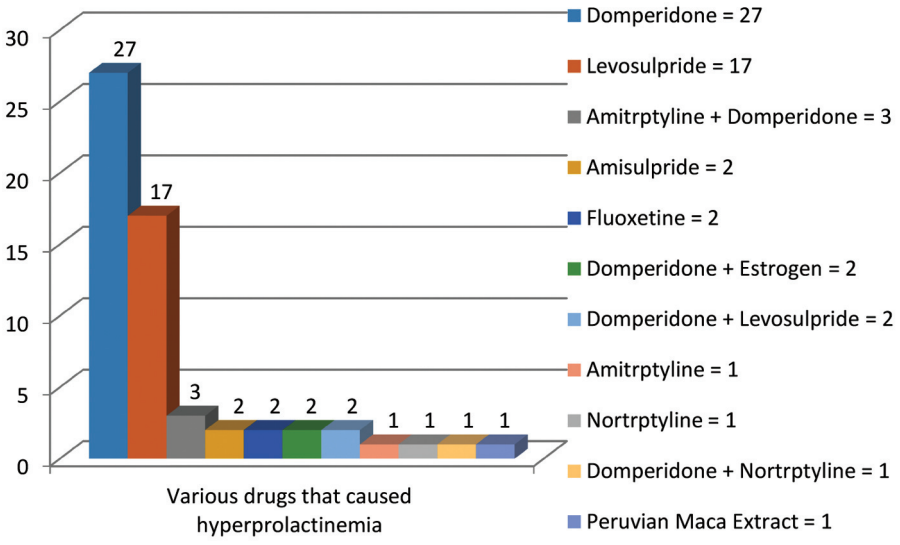

Figure 1. Drug-induced hyperprolactinemia.

feature of macroadenoma, but a higher frequency of patients with microprolactinoma present with headache. In a study by Kemmann et al., 58% of females with documented HP and normal pituitary imaging had more than one severe headache per week as compared to 27% of the control group. The precise correlation between HP and headache is not clear, particularly in the presence of normal pituitary imaging (13). In our study, as the most common cause of HP was drugs and not pituitary tumors, we observed a lower prevalence of headache compared to previous studies. The prevalence of drug-induced HP is on the rise and constituted 59% of cases in the present study. A study conducted by Zargar et al. approximately two decades ago at our center reported drug use in only 5% of 187 HP cases (9). Pituitary microadenoma was the most common cause seen in 35.8% of cases in that series (Table 4). This shows a change in the trend of the etiology of HP with drugs overtaking pituitary adenoma. In a recent study conducted in North India by 'Kulshreshtha et al.', 30.4% of HP patients had drugs as etiology (8). Prokinetics were taken by 52 of our patients, either alone or in combination with other drugs, including neuroleptics (Figure 1), whereas previous studies have shown that neuroleptics were the most common cause (14). Most of the literature regarding drug-related HP includes neuroleptics (15,16). There are only a few case reports that show prokinetics causing HP. Our study showed them responsible in more than half of the cases (52 patients). It is due to a recent increase in the use of pro-

Table 3. Prolactin levels according to gender/etiology.

Characteristics	Mean Prolactin levels (ng/mL)
Male	1950±2818
Female	171.8±430
Microadenoma	143.3±81.1
Macroadenoma	1193±2153
Drug Induced	126.10±66.49
Levosulpiride Group	144.82±83.55
Hypothyroidism	81.25

Table 4. Comparison of etiological profiles between the present series and the previous study done by Zargar et al.[9]

Etiology	Present series (%)	Zargar et al. (%)
Drug induced	59	5.3
Microadenoma	15	35.8
Macroadenoma	16	16
Idiopathic	4	27.8
Hypothyroidism	4	2.1
Polycystic ovarian syndrome	1	12.8

kinetics for non-specific symptoms and due to their easy availability as an over-the-counter medication. Similar to our study, Horng-Yih et al. found that the most common offending drugs in HP are gastrointestinal drugs such as sulpiride (17). In one case in our study, HP was due to the consumption of a herb (Peruvian Maca) extract, which was prescribed to the patient as an aphrodisiac in the form of capsules. In an earlier study conducted in Southern Taiwan, herbal extracts were reported to induce HP (17). In most of the cases of drug-induced HP, documentation of levels of prolactin into the normal range after stopping/substituting the offending drug was carried out between week 1 and week 4 from the time of initial contact with the patient. However, in the case of six patients, it took more than eight weeks from the point of initial contact for the normalization of their prolactin levels due to the compelling need for reusing the same or a different offending drug, mostly for acute migraine episodes or bothersome acid peptic disorder that led to the delay in normalization.

About 15% of our subjects had pituitary microadenoma, and 16% had macroadenoma on MRI together, constituting the second most common cause of HP in our study population. Two patients had MEN 1-related hyperprolactinemia, one harboring macroadenoma and the other microadenoma.

Idiopathic HP continues to be an important cause of high prolactin. The prevalence of idiopathic HP has decreased over time as in our study; only 4% of patients represented it as compared to 27% of patients representing it in the study conducted two decades ago at the same center (9). Due to the availability of high-resolution MRI, the disorder labeled as idiopathic hyperprolactinemia was later proved to be a microadenoma. It is believed that many patients harbored such small microadenomas that were beyond the resolution of imaging tools used in the past, such as hypocycloidal polysomnography, CT, and MRI (18).

Four percent of our cases had hypothyroidism as the cause of HP. Elevation of the thyrotropin-releasing hormone causes increased release of prolactin. The mean prolactin level in this group was 81.25 ng/mL. Treatment of primary hypothyroidism corrected hyperprolactinemic state (19). Vilar et al. found that 6.3% of cases of HP were due to primary hypothyroidism in their study (20). Earlier. Zargar et al. had found hypothyroidism to be responsible for 2.1% of hyperprolactinemia cases (9).

Polycystic ovarian disease (PCOD) was the sole cause of HP in one of our subjects. In comparison, a previous study showed that PCOD was responsible for 14% of hyperprolactinemia cases. The exact prevalence of HP in PCOD is not known. Increased prolactin levels lead to increased production of dehydroepiandrosterone sulfate (DHEAS) from adrenals, which decreases following the treatment of HP (21). Although a large number (13%) of PCOD patients reported HP in 1984, recent data have suggested that HP does not seem to be more frequent in PCOD women than in healthy subjects (20,21).

Conclusion

HP is a common endocrinological problem. Every effort should be made to find the cause of HP. Drug-induced HP was the most frequent identifiable etiology, with prokinetics being the most common cause in our study. This was in contrast to the findings of previous studies as found in the literature, where pituitary adenoma followed by neuroleptic drugs was the most common cause of HP. Discontinuation of the offending drug resolves HP in all the patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Arshad Iqbal Wani, Junaid Rashid Dar, Moomin Hussain Bhat; Design: Shariq Rashid Masoodi, Moomin Hussain Bhat; Control/Supervision: Arshad Iqbal Wani, Mir Iftikhar Bashir, Raiz Ahmad Misgar; Data Collection and/or Processing: Junaid Rashid Dar, Javaid Ahmad Bhat, Moomin Hussain Bhat; Analysis and/or Interpretation: Arshad Iqbal Wani, Raiz Ahmad Misgar; Literature Review: Moomin Hussain Bhat, Junaid Rashid Dar; Writing the Article: Moomin Hussain Bhat, Junaid Rashid Dar; Critical Review: Shariq Rashid Masoodi, Mir Iftikhar Bashir; References and Fundings: Raiz Ahmad Misgar; Materials: Arshad Iqbal Wani, Moomin Hussain Bhat.

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