Etiologies and Clinical Manifestations of Hyperprolactinemia in A Medical Center in Southern Taiwan

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Abstract

The aim of this study was to investigate the etiologies and clinical manifestations of hyperprolactinemia in a medical center. From May 1999 through October 1999, 140 consecutive patients with hyperprolactinemia were enrolled. Medical records of demographic data, presenting symptoms, departments visited, serum prolactin level, brief history, comprehensive drug history (drug name or classes of drug), pituitary imaging studies, and causes of hyperprolactinemia were analyzed. Of the 125 females patients studied, 53 (42%) had menstrual problems, 41 (33%) had galactorrhea, and 19 (15%) were infertile. In contrast, epilepsy (11 patients, 73%) was the leading symptom and cause of hyperprolactinemia in male patients. The etiologies of hyperprolactinemia included idiopathic hyperprolactinemia (46 patients, 32.9%), drug-induced hyperprolactinemia (33 patients, 23.6%), and pituitary tumors (28 patients, 20%). Four of 33 (12%) patients with drug-induced hyperprolactinemia had prolactin levels between 100 ng/mL and 200 ng/mL while another six (18%) patients had prolactin levels above 200 ng/mL. Although the prolactin levels in the macroadenoma group seem higher than in the microadenoma group (169±33.4 ng/mL vs 89±15.6 ng/mL, p = 0.105), the difference was not statistically significant. Idiopathic hyperprolactinemia, drug-induced hyperprolactinemia, and pituitary tumors were the major causes of hyperprolactinemia. There were no significant differences in clinical manifestations among patients with different etiologies. High prolactin levels were not diagnostic of prolactinoma and serum prolactin levels were not predictive of tumor size. (J Intern Med Taiwan 2004; 15: 19-24)

Key Words：Hyperprolactinemia, Etiology, Idiopathic hyperprolactinemia, Drug-induced hyperprolactinemia

Introduction

Hyperprolactinemia is a common endocrine disorder. It is a major cause of amenorrhea, infertility, and galactorrhea in women and decreased libido and

impotence in men. A prolactin-secreting pituitary adenoma and idiopathic hyperprolactinemia are common causes of spontaneous hyperprolactinemia1. Other less frequent causes are drugs, primary hypothyroidism, non-prolactin secreting pituitary adenoma that compresses the pituitary stalk, cirrhosis of the liver and chronic renal failure. Idiopathic hyperprolactinemia (IH) is diagnosed when there is sustained clinically significant elevation of serum prolactin concentrations with neither demonstrable pituitary/hypothalamic lesions nor any other recognized causes of prolactin oversecretion2. We conducted a study on a hospital-based hyperprolactinemic population, which is different from previous specialty clinic-based studies3, to study the etiologies and clinical manifestations of hyperprolactinemia in a tertiary medical center in southern Taiwan.

PATIENTS AND METHODS

Patients

From May 1999 through October 1999, 140 consecutive patients with hyperprolactinemia from a laboratory database were included in this study. All patients were diagnosed and treated at the National Cheng Kung University Hospital, a teaching and referral center in southern Taiwan.

Methods

Medical records of all patients were reviewed. Demographic data, presenting symptoms, departments visited, serum prolactin levels, brief history, comprehensive drug history (drug name or classes of drug), pituitary imaging studies, and causes of hyperprolactinemia were all recorded. Laboratory examinations and pituitary imaging depended on clinical judgment of physician. Drug-induced hyperprolactinemia was diagnosed when cessation of the responsible drugs normalized prolactin levels and clinical symptoms. In the absence of pertinent drug history and recognizable causes, it was classified as idiopathic hyperprolactinemia after 1 year of follow up.

Prolactin assay

The assay used Coat-A-Count R Prolactin IRMA (EURO/DPC Ltd., UK), a solid-phase immunoradiometric assay based on monoclonal and polyclonal anti-prolactin antibodies. Interassay and intraassay CV values were 3.2% and 1.8%, respectively. Normal range of serum prolactin is 3.1-16.5 ng/mL.

Statistical analysis

The data analysis was conducted using the JMP statistical package (SAS Institute Inc.). All data were expressed as median and ranges. The Wilcoxon's rank sum test was used to analyze the differences between the groups with regard to clinical characteristics. A $p<0.05$ was considered significant.

Results

The median age at diagnosis of 140 patients

(125 females; 15 males) was 36.7 years (range, 13 to 81 years). The serum prolactin concentrations ranged from 19.1 to 331 ng/mL (median, 46.5 ng/mL). The presenting manifestations are outlined in Table 1. Menstrual problems (53, 46%), galactorrhea (41, 33%) and infertility (19, 15%) were the most common symptoms in female patients. However, epilepsy (11, 73%) was the most common reason to measure prolactin level in male patients.

The results of etiologies of hyperprolactinemia are outlined in Table 2. Idiopathic hyperprolactinemia (46, 32.9%), drug-induced hyperprolactinemia (33, 23.6%), and pituitary lesions (28, 20%) were the major common causes. Other causes included epilepsy (16, 11.4%), hypothyroidism (6, 4.3%), pregnancy (5, 3.6%), and renal insufficiency (1, 0.7%).

Among 28 patients with identifiable tumors on pituitary imaging (CT scan or MRI) studies, 23 (82 %) patients had microadenoma (<1cm), while five patients (18%) had macroadenoma (≧1cm).

The median prolactin level in patients with IH was 31.8 ng/mL. Seven of 46 (15.2%) patients had prolactin levels between 100 ng/mL and 200 ng/mL, while one (2%) patient had a prolactin level above 200 ng/mL.

The median of prolactin level in patients with drug-induced hyperprolactinemia was 52.5 ng/mL (range, 19.9 to 272.2 ng/mL). Range of serum prolactin level in drug-induced hyperprolactinemia varied widely (Table 3). Four of 33 (12%) patients had prolactin levels between 100 ng/mL and 200 ng/mL, while another six (18%) patients had prolactin levels above 200 ng/mL.

The median of prolactin level in patients with pituitary adenoma was 76.4 ng/mL. The prolactin levels in the macroadenoma group seemed higher than those in the microadenoma group (median / range: 90/68.9~331 ng/mL vs 72.6/19.2~272.4 ng/mL, $p = 0.105$ by Wilcoxon's rank sum test).

No significant differences in serum prolactin levels were noted among these study groups. Distributions of serum prolactin levels among patients with different etiologies are shown in Figure 1.

Discussion

Our study showed that IH caused hyperprolactinemia in one-third of the patients. The results are similar with those previously reported 3. None of the patients with IH resolved or developed new signs after at least 1 year of follow up. It has been estimated that IH constituted 40% of the total patients with hyperprolactinemia 4. Many patients with IH complained of symptoms of oligomenorrhea, amenorrhea, galactorrhea, and infertility 4. Other long-term follow up studies showed that about one third of IH resolved spontaneously 5 and progression to pituitary prolactinoma seldom occurred 3. Thus, it is probable that the disease is an entity different from

prolactinoma 2.

The mechanism of IH is still not well elucidated. Most investigators assume that patients with IH may actually be harboring tiny microadenomas that are not visible with current imaging techniques6. Macroprolactinemia is another major possibility. Prolactin molecules in the serum of healthy subjects and the majority of patients with hyperprolactinemia have a molecule weight of about 23 kDa (little PRL), the remainder consisting of big PRL (MW 50kDa), and big- big PRL (MW greater than 150 kDa). However, patients with macroprolactinemia have a high proportion of big-big PRL in their serum. The reported incidence of macroprolactinemia in hyperprolactinemic populations varied from 16 to 26% and anti-PRL autoantibodies were considered to be major contributors to the cause of macroprolactinemia 7-8. It has been suggested that either because of its size, partial glycosylation 8-12, or polymerization, the access of these IgG-bound PRL to target cells through the capillary wall may be restricted thus devoid of biological action 7,13. Hattori and Inagak demonstrated that delayed clearance accounted for the increased serum prolactin levels in such patients 8. Most patients with macroprolactinemia are clinically characterized by the lack of hyperprolactinemia-related symptoms such as amenorrhea and galactorrhea and retain fertility despite hyperprolactinemia 7,14. Some patients with IH had a relative resistance to dopamine, which was presumably caused by a change in affinity for or in the number of dopamine receptors of the lactotrophs 15.

In view of the benign and self-limited course of IH, it appears justified to treat these patients only when troublesome galactorrhea or anovulatory infertility occurs and to prevent osteoporosis in connection with hypogonadism 6.

Drug-induced hyperprolactinemia was the second most common cause of hyperprolactinemia in our study. The finding is similar to that reported by Suliman et al 3. In addition, it is remarkable that the most common offending agents are gastrointestinal drugs (including sulpiride used as ulcer-healing promoter) in our study population.

Serum prolactin concentrations in drug-induced hyperprolactinemia widely varied. It is a common belief that with very rare exceptions, basal prolactin levels greater than 200 ng/mL are virtually diagnostic of prolactinoma. Similarly, if the serum prolactin level is between 100 and 200 ng/mL, the cause is usually prolactinoma 16-19. However, nearly one third of the patients with drug-induced hyperprolactinemia in this study had serum prolactin levels more than 100 ng/mL. One fifth of patients even had prolactin level above 200 ng/mL. The results imply that complete history taking of medications is essential to minimize unnecessary radiation exposure and medical cost for diagnosis even if the patients has very high serum prolactin level.

Only 20% of patients in present study had prolactinoma. Prolactin levels in the macroadenoma group seem higher than those in the microadenoma group, but the difference did not reach statistical significance. From this study, serum concentrations of prolactin did not predict whether micro-prolactinoma or macro-prolactinoma was present for any patient with hyperprolactinemia in clinical practice.

Sixteen (11%) patients in our study had epilepsy-related hyperprolactinemia. It is known that serum levels of prolactin may increase as a consequence of epileptic seizure. The hormone release is caused by the propagation of epileptic activity, usually from the temporal lobe to the hypothalamic-pituitary axis 20. Serum prolactin rises after virtually all generalized tonic-clonic seizures, most complex partial seizure, and some simple partial seizure. Absence, myoclonic seizure, and psychogenic seizure do not affect serum prolactin levels. Therefore, it is a useful diagnostic test in the differentiation between psychogenic and epileptic seizures. Blood sampling should be done within 30 min after a seizure episode, since the prolactin levels decreases with a half-life of 32 minutes and reach normal values 2 hours after a seizure episode 21.

The limitations of our study should be noted. First, few patients categorized as idiopathic hyperprolactinemia did not have thyroid function test. To minimize possibility of miscategorization, medical chart was reviewed comprehensively in such cases to rule out overt hypothyroidism. Second, not all patients undergo pituitary imaging studies so that, inevitably, the etiological diagnosis could be biased. However, it faithfully reflects the scenario in physician's daily practice and we learned the importance of history taking as stated above.

In conclusion, hyperprolactinemia is a disorder of heterogeneous etiologies. Idiopathic hyperprolactinemia, drug-induced hyperprolactinemia, and pituitary tumors were the major causes of hyperprolactinemia. We could not differentiate the etiologies from serum prolactin levels. In addition, serum prolactin levels were not predictive for tumor size of prolactinoma.

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南台灣一醫學中心高泌乳素血症之病因與臨床表現

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摘　　要

目的：本研究之目的乃在探討某一醫學中心中高泌乳素血症之病因與臨床表現。方法：從 1999 年 5 月到 1999 年 10 月，共有 140 位高泌乳素血症之病患進入研究，分析之要項包括：人口學資料、最初症狀、看診科別、血清泌乳素值、簡要病史、完整藥物史（包括藥物名稱或藥物類別）、腦下垂體影像學檢查結果以及高泌乳素血症之原因。結果：125 位女性病人中，53 位（42％）女性有月經的問題，41 位（33％）出現溢乳，19 位（15％）不孕；而 15 位男性病人中，癲癇（11 位，73%)是最常見的症狀與病因。就病因學來分析，不明原因之高泌乳素血症的病患有 46 位，藥物引起之高泌乳素血症的病患有 33 位（23.6％），腦下垂體腫瘤則有 28 位（20％）。33 位藥物引起之高泌乳素血症病患中，血清泌乳素值介於 100 ng/mL 到 200 ng/mL 有 4 位（12％），而血清泌乳素值大於 200 ng/mL 有 6 位（18％），血清泌乳素值在巨腺瘤患者似乎較微腺瘤患者高（169 ± 33.4 ng/mL vs 89 ±15.6 ng/mL, p=0.105），但未達統計顯著差異。結論：不明原因之高泌乳素血症、藥物引起之高泌乳素血症以及腦下垂體腫瘤是高泌乳素血症之主要原因。不同病因引起的高泌乳素血症間之臨床表現並沒有顯著差異。高血清泌乳素值無法確診爲有泌乳素瘤也無法預測腫瘤之大小。

Table 1. Clinical presentation of hyperprolactinemia

Clinical presentation	**Number (%)**	
	Male	**Female**
	(*n* = 15)	**(*n* = 125)**

Menstrual problems	0 (0)	53 (42)
Galactorrhea	0(0)	41 (33)
Infertility	0(0)	19 (15)
Headache	1 (7)	8 (6)
Epilepsy	11 (73)	7 (6)
Others	4 (27)	25 (20)

Table2. Causes of hyperprolactinemia

Causes	**Number**	**%**
Idiopathic	46	32.9
Drug-induced	33	23.6
Pituitary lesions	28	20.0
Epilepsy	16	11.4
Hypothyroidism	6	4.3
Pregnancy	5	3.6
Hepatic cirrhosis	5	3.6
Renal insufficiency	1	0.7
Total	**140**	**100**

Table3. Range of serum prolactin level in drug-induced hyperprolactinemia

Drugs	**Prolactin level (μg/L)**	***n***
Antipsychotics/antidepressants		
Sulpiride	20.4-225.3	10
Other	37.5-58.8	4
Gastrointestinal medications		
Metoclopramide	58-272.2	5
Cimetidine	23.4-262.1	4
Cardiovascular drug		
Verapamil	31.6	1
Estrogen	19.9-112.5	6
Herb	20.4-52.5	6