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Serum Prolactin Level in Chronic Urticaria: Is promocriptine inducing remission in chronic urticaria?

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Abstract

Background: Chronic urticaria (CU) is a disturbing disease with a negative impact on quality of life. Despite of several clinical studies on CU patients, its pathogenesis is poorly understood. Prolactin (PRL) is peptide hormone has immunomodulatory effects in some immune inflammatory skin diseases.

Aim: To elucidate any possible relationship between the immunomodulatory effects of Prolactin (PRL) and CU. Besides, the study aims to investigate the crucial role of antiprolactin drugs in the management of CU patients.

Patients and Methods: The serum PRL level of 80 female patients with CU was measured using the electrochemiluminescence immunoassay. The activity of CU was assessed by European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum (EAACI/GA2LEN/EDF) activity score. Patients with high PRL level had been given anti prolactin therapy to normalize their PRL levels. Then, the disease activity was reassessed in these patients.

Results: The serum PRL level was high in 8 of 40 (20%) patients (43.18 ± 12.81). Half of patients with high PRL level had remission after treatment of hyperprolactinemia ($p = 0.001$).

Conclusion: Serum PRL levels could not be considered as a marker of the disease activity in CU patients.

Key Words: Prolactin; chronic urticaria, bromocriptine

Introduction

Chronic urticaria (CU) is a common disorder characterized by wheals with or without angioedema for more than six weeks. It is a recurrent disease caused by release of mast cells mediators within the dermis. The CU affects 0.5% to 1% of the population, most commonly women aged 20 to 40 years. It has a negative impact on quality of life [1-3]. The pathogenesis of CU is poorly understood. Autoimmune etiology is the most accepted mechanism involving about 30 to 50% of cases. Most of patients have autoimmune antibodies to the IgE receptor α subunit. Mast cells play a key role in its pathophysiology. The treatment of CU is palliative and despite of extensive investigations, its etiology is still elusive. Non immunologic mechanism, which based on substance P, endorphins, endogenous peptides has also been implicated in some patients. The findings of many previous studies documented other factors including emotional disorders, food allergy, intolerance to food additives and chronic infections like *Helicobacter pylori* [3-6].

Prolactin (PRL) is a peptide hormone secreted from the anterior pituitary and its secretion is controlled by dopamine. In addition to gland and stimulates mammary gland growth and differentiation. The PRL is produced also by extrapituitary sources. Prolactin receptors have been expressed on several cells including keratinocytes, fibroblasts and

macrophages. PRL activates immune cells such as T cell, B cells, neutrophils and macrophages [7-9,10]. It stimulates antibody production and it has immunomodulatory effects. PRL level is elevated in many autoimmune diseases as psoriasis, alopecia, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjogren's Syndrome in Graves' disease, Hashimoto's thyroiditis (HT) and type 1 diabetes mellitus [11-13].

PATIENTS AND METHODS

Patients

This study was conducted at the department of Dermatology, Venereology and Andrology, Zagazig University Hospitals from March 2014 to March 2015. The study was approved by the Institutional Review Board (IRB) at Zagazig University Hospital. Forty female patients had CU with their ages at reproductive age were included in this study and they were symptomatic (had active disease) at the time of their enrollment.

The diagnosis in each patient was made on the basis of history and clinical presentation. Written informed consent taken from all patients.

Inclusion criteria

Female patients at reproductive age with CU with or without angioedema for more than 6 weeks.

Exclusion criteria

Patients who had been receiving any therapies for urticaria within 10 days before the study, Pregnant or lactating females or females with any past history of hormonal contraception, any medication affecting prolactin level (antidepressants, antipsychotics, estrogens, H2 blockers, methyldopa, phenothiazines, reserpine, verapamil) patients who had been on systemic steroid therapy within 6 months prior to recruitment, all other identified causes of urticaria had been excluded.

Methods

All patients were subjected to complete history taking, general and dermatological examination. The diagnosis of CU was clinically established by appearance of continuous or recurrent wheals and itching anywhere on the body with or without angioedema for more than 6 weeks.

Assessment of urticaria activity

Disease activity was assessed by European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network;

European Dermatology Forum (EAACI/GA2LEN/EDF) activity score which is composed of Wheals score (none = 0, 1 for 1-20 wheals, 2 for 20-50 wheals, 3 for > 50 lesions in 24 hours) and itching score (none = 0, mild = 1, moderate = 2, intense = 3)

The disease activity is scored from 0 to 6 (summation of wheals and itching scores). Zero score considered as none, score 1-2 as mild, score 3-4 as moderate and score 5-6 as severe disease activity [14-15].

Morning fasting blood samples at 8:00 and 10:00 a.m. were obtained from all patients for measurement of basal concentrations of serum PRL level. Normal level of serum PRL in non-pregnant non-lactating women were ranged from 10–25 ng/ml (106 -487.6 mIU/L).

Patients with high PRL level had been given anti prolactin therapy e.g. bromocriptine one tablet (2.5 mg) daily with food, to decrease nausea occurring with bromocriptine until level of prolactin decreased to the normal range then the disease activity was reassessed.

The samples from CU patients were subjected to:

- Routine investigations were done as complete and differential blood cell count, Liver and kidney function tests and erythrocyte sedimentation rate.

- Serum PRL was determined by the electrochemiluminescence immunoassay ECLIA by using cobas e 411 immunoassay analyzer and Elecsys prolactin II reagent kits (Roche Diagnostics, Germany)

Statistical analysis

The data were analyzed using SPSS program (Statistical Package for Social Science) version 18.0. Quantitative data were expressed as mean $\pm$ SD (Standard deviation).

The following tests were used; Fisher -exact test, Mann-whitney test, Spearman's correlation coefficient (r) and Wilcoxon Signed Ranks test. P value of less than 0.5 was considered to be significant.

RESULTS

Forty female patients had CU with mean age 32.83 ± 7.87 were enrolled in the study. The demographic data of the patients are presented in (Table 1).

Twenty percent of the studied CU patients had hyperprolactinemia and 80% had a normal level of PRL (Figure 1).

There was statistically significant difference in 50% of the studied patients who had positive family history of CU and with high PRL level ($p = 0.000$) than patients who have positive family history with normal PRL level (Table 2). The presence of helicobacter pylori showed no statistical significant difference.

There was no statistical significant difference between patients having normal or high PRL level as regard age and duration of disease but there was highly statistical significance difference between CU patients with

normal and high PRL level as regard level of PRL hormone (Table 3). There was no correlation between duration of CU and level of PRL (Figure 1). 50 % of the studied CU patients with high PRL had no disease activity (remission) after treatment of hyperprolactinemia (Figure 2).

Table (4) showed that 50% of CU patients with high PRL level had mild wheal score and the other 50% of them had moderate wheal score. Also 25% of them had mild itching score, 50% of them had moderate itching score and 25% of them had intense itching score. Concerning the disease activities 25% of patients with high PRL level had mild disease activity, 50% of them had moderate disease activity and 25% of them had severe disease activity.

Table (5) showed that the disease activity of CU among patients with high PRL level before and after the treatment of hyperprolactinemia had no statistically significant difference.

DISCUSSION

Urticaria is characterized by activation of mast cells by immunologic or non-immunologic processes inducing mast cells degranulation that results in the release of inflammatory mediators as histamine, leukotrienes, and prostaglandins. These mediators induce pruritus, enhance vascular permeability and tissue edema [15]. Patients with CU have impaired

quality of life. It has been suggested that psychosocial factors may play a role in its pathogenesis [16-18]. Stress leads to dysfunctions of the neuroendocrine immune system which precipitate the attack of the disease. PRL binds to specific skin receptors and leads to modulation of cytokine release in the skin. The autoimmune diseases are more common in females especially during the reproductive period. Estrogen and PRL modulate the immune response, hyperprolactinemia observed in some autoimmune diseases [19,20].

In the last decades, some studies evaluated the clinical significance of PRL in different skin diseases. Moreover, a prolactin-lowering drug has been shown to decrease both peripheral and pituitary PRL production and could be used as adjuvant therapy especially in refractory disease.

The aim of this study was to evaluate the association between serum concentrations of prolactin hormone in patients with CU and the possible role of anti prolactin drugs in the management of the disease.

No previous published studies had demonstrated the role of anti prolactin therapy such as bromocriptine for treating cases of CU associated with hyperprolactinemia.

During our work, serum PRL levels in patients with CU were ranged from 4.41 to 60 ng/ml and mean value was 11.28 ng/ml. Only eight patients (20%) had high PRL level among the studied CU patients and

80% had a normal level of PRL hormone. There was no statistically significant difference in other variables as age and marital status. 50% of the studied patients who had a positive family history of CU and with high PRL level had statistically significant difference $p = 0.000$ than patients who had positive family history with normal PRL level.

In the present study, when we investigated our patients for PRL level, we accidentally found that only 12.5% of the CU patients had positive helicobacter pylori. This finding was consistent with the study of Loh et al.[21] who found that 16.5 % of CU patients had Helicobacter pylori infection.

Brzoza et al.[22] were the first authors who previously investigated the relationship between PRL and CU. They observed a nonsignificant elevation of PRL levels among autologous serum skin test (ASST) positive patients as compared to ASST-negative patients and controls. They concluded that hyperprolactinemia does not accompany the immune-inflammatory processes associated with CU; also they suggested that the lack of abnormalities in peripherally detectable hormones does not exclude the possibility of PRL exerting immunomodulatory effects in urticaria.

Another study [23] was assessed the level of prolactin and dehydroepiandrosterone Sulfate in female patients with CU. They found

that Prolactin was significantly higher among ASST positive patients than among ASST negative patients and controls. They found elevated PRL levels among CU patients, support and highlight on the PRL in autoimmunity. Moreover, they reported that PRL levels were significantly and positively associated with the grade of disease severity of CU patients. In contrast, the activity of CU according to EAACI/GA2LEN/EDF activity score was done on the hyperprolactinemic patients. We founded that 50% of the studied CU patients with high PRL level had no disease activity after treatment of hyperprolactinemia. In 37.5% of them, the disease activity became moderate and 12.5% of them had become mild disease activity which was not significant.

The controversy about the correlation between PRL and CU activity may be due to the heterogeneity of the studied patients, by the inclusion of patients with variable disease duration or by the diverse methodologies used for PRL testing.

Limitations in our study were due to lack of studying the serum PRL levels in different disease durations. Patients with CU have frequently exacerbation and remission. They are on treatment regimens most of the time; hence, finding patients who were not on therapeutic regimens and new cases of CU was a big challenge and the reason for a smaller sample

size. Studies with larger sample sizes are still necessary. Further studies are recommended either to support our results or to clarify any diagnostic role of PRL in CU.

CONCLUSION

In this study there was no significant higher serum PRL level in CU patients.

The analysis of the data suggests that chronic inflammation may affect serum PRL concentration. So serum PRL levels are not likely to be used as a marker of the disease activity in CU patients.

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Table 1 Frequency Distribution of demographic Criteria of the Studied CU Patients

Variable	Frequency (No=40)	Percentage (%)
1)Age (years): • Mean±SD • Range	32.83±7.87 18-50	
2) Marital status: • Married • Unmarried	34 6	85 15
3) Occupation: • Not working • Worker	30 10	75 25
4) Residence: • Rural • Urban	29 11	72.5 27.5

Table2 Comparing the characteristics features regarding family history and helicobacter pylori infection between the studied normal and high PRL level among CU patients

VARIABLE	TOTAL	CU WITH NORMAL PRL (NO=32)		CU WITH HIGH PRL (NO=8)		TEST	P-VALUE
		No	N	%	N	%	
Family History : • Positive • Negative	4 36	0 32	0 100.0	4 4	50.0 50.0	Fisher -exact test	0.000 (HS)
Helicobacter Pylori • Positive • Negative	5 35	3 29	9.4 90.6	2 6	25.0 75.0	Fisher -exact test	0.257 (NS)

Fisher – exact test

Table 3 Comparing demographic characteristics between the studied normal and high PRL level among CU patients (No =40)

VARIABLE	CU WITH NORMAL PRL	CU WITH HIGH PRL	TEST	P-VALUE
Age (years): Mean $\pm$ SD Range	33.50 $\pm$ 8.60 18-50	30.12 $\pm$ 2.75 27-34	1.871*	.070 (NS)
Duration of disease (months): Mean $\pm$ SD Median (Range)	12.81 $\pm$ 11.35 7.50(2-48)	13.25 $\pm$ 8.75 13.0(2-24)	119.500#	0.772 (NS)
Prolactin Level (ng/ml): Mean $\pm$ SD Median (Range)	10.21 $\pm$ 4.61 9.0(4.41-20)	43.18 $\pm$ 12.81 43.13(24.20-60)	.000	.000 (HS)

*T –test; #Mann-whitney test

Table 4 Frequency distribution of disease activity of CU among patients with high PRL level according to EAACI/ GA2LEN/ EDF activity score (No =8)

Item	Frequency	Percentage %
Wheals score:		
• Mild	4	50%
• Moderate	4	50%
Itching score :		
• Mild	2	25%
• Moderate	4	50%
• Intense	2	25%
The disease activity:		
• Mild	2	25%
• Moderate	4	50%
• Severe	2	25%

Table 5 Relation of disease activity of CU among patients with high PRL level according to EAACI/GA2LEN/EDF activity score before and after treatment of hyperprolactinemia (No =8)

Item	EAACI/GA2LEN/EDF activity score before ttt	EAACI/GA2LEN/EDF activity score after ttt	Test	P-value
	No.(=8)	No.(=8)		
The disease activity:				
• None	0	4	1.897-	0.058 (NS)
• Mild	2	1		
• Moderate	4	3		
• Severe	2	0		

Wilcoxon Signed Ranks test

Figure legends

Figure 1 Scatter diagram showing correlation between duration of disease and PRL level among CU patients (No =80)

Figure 2 Multiple Bar charts showing Percentage distribution of disease activity score among CU patients with high PRL level before and after treatment of hyperprolactinemia

