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Parental Attitude in Women with Hyperprolactinemia: a Controlled Cross-Sectional Study

[Ailesel tutumun hiperprolaktinemi üzerine etkisi: kesitsel kontrollü bir çalışma]

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ABSTRACT

Objective: Prolactin hormone affects the brain, attitude and mood. Secretion of prolactin may be stimulated by environmental factors. The aim of this study was to demonstrate any possible effect of poor child-parent relationship on hyperprolactinemia. We hypothesize that women with hyperprolactinemia may have been subjected to poor child-parent relationship and neglect.

Method: The present study was designed in a maternity hospital and included women with gynecologic complaints referred from the gynaecology outpatient clinic for serum prolactin assessments. An 85-item, self-rated EMBU Scale questionnaire (a scale for perceived parental attitude) was applied. Fifty women were enrolled over a period of 5 months.

Results: Women with hyperprolactinemia (prolactin levels above 26 ng/ml) constituted the patient group (Group 1) (n=34) and those with normal serum prolactin levels (below 26 ng/ml) served as the controls (Group 2) (n=16). The mean±SD levels of prolactin for group 1 and 2 were 57.25±38.7 ng/ml and 18.81±4.4 ng/ml, respectively. Group 1 patients believe that their parents did not show enough emotional warmth and had rejective behavior. Emotional warmth parameters of patients' mothers and fathers were significantly lower (p=0.002 and p=0.01, respectively) than those of the control group. We also found that the patients believed that their mothers and fathers both had rejective behaviors (p=0.008 and p= 0.009, respectively).

Conclusion: Prolactin secretion is regulated by the dopaminergic system and since dopamine is responsible of pleasure and satisfaction sensations, the negative affection of both mothers and fathers in childhood may play a role in the etiology of chronic low-grade hyperprolactinemia in women.

Conflict of Interest: Authors did not declare any conflict of interest.

Key Words: Hyperprolactinemia, parents, attitude, behavior.

ÖZET

Amaç: Santral sinir sistemi ve kişinin davranış ve duygulanımını etkileyen bir hormon olan prolaktin salınımını çevresel faktörler etkileyebilmektedir. Bu çalışmanın amacı geçmişteki kötü çocuk-ebeveyn ilişkisinin hiperprolaktinemi üzerine olası etkisinin ortaya koyulmasıdır. Hiperprolaktinemili kadınların geçmişte kötü çocuk-ebeveyn ilişkisine ve ihmale maruz kalmış olabilecekleri düşünülmüştür.

Yöntem: Bu çalışma bir Kadın Doğum Hastanesinde planlanmış ve jinekolojik yakınmaları olup jinekoloji polikliniğinden serum prolaktin testi istemi yapılan kadınlarda tasarlanmıştır. Hastalara 85 soruluk EMBU Skalası anketi (algılanan ebeveyn tutumu skalası) bir psikolog tarafından verilmiştir. Anket isteğe bağlı olarak uygulanmış ve 5 ay süresince 50 kadın anketi doldurmayı kabul etmiştir.

Bulgular: Hasta grubu serum prolaktin değeri >26 ng/ml olan hiperprolaktinemili hastalardan (Grup 1) (n=34), kontrol grubu ise <26 ng/ml olan 16 gönüllüden (Grup 2) oluşturulmuştur. Grup 1 ve Grup 2 prolaktin düzeyleri sırasıyla, ortalama±SS olarak 57,25±38,7 ng/ml ve 18,81±4,4 ng/ml idi. Uygulanan anket sonucunda Grup 1'deki bireylere anne ve babanın bireylere duygusal sıcaklık göstermediği ve reddedici tutum takındığını gözlendi. Duygusal sıcaklık parametreleri hasta grubu (Grup 1) anne ve babaları için kontrol grubuna göre anlamlı olarak düşük (sırasıyla, p= 0,002 ve p= 0,01) bulundu. Ayrıca hastaların anne ve babalarının reddedici bir tutum sergilediğine inandıkları saptandı (sırasıyla, p= 0,008 ve p= 0,009).

Sonuç: Prolaktin salgılanmasının dopaminerjik yolaklarla regüle edildiği ve dopaminin haz ve doyum alma işlevlerinden sorumlu olduğu göz önüne alınırsa, hastalara çocukluk evresinde ebeveynlerinin tutumlarının olumsuz olması, kronik düşük seviyeli hiperprolaktineminin etiyolojisinde rol oynayabilir.

Çıkar Çatışması: Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Anahtar Kelimeler: Hiperprolaktinemi, ebeveyn, tutum, davranış

Introduction

Prolactin, a 199 amino acid peptide hormone, regulates neuroendocrine and emotional stress responses in the brain [1]**.** It modulates some of the features of reproduction and maternal functions, and is also associated with learning, stimulation of immune response, reduction of body temperature, and involved in behavior. Hyperprolactinemia is seen in 0.4% of the normal population throughout reproductive ages [2]. Psychological factors are reported to play a role in its etiology [2,3]. There is evidence that the young girls in families characterized by absent or alcoholic fathers may be predisposed in developing hyperprolactinemia later in life as a reaction to those losses [4]. Paternal alcoholism or violence in early developmental period leads to problems, e.g. anxiety, depression and hostility in later life [5] and hyperprolactinemia could be predicted in such women [6]. In view of neurobiological aspect, prolactin release is under inhibitory control of dopamine and its increase is inversely proportional to dopamine secretion [4,7].

Patients admitted to the gynecology outpatient clinic of a maternity hospital in Izmir with hyperprolactinemia showed galactorrhea, infertility issues and emotional problems. They often require prolonged therapy. Up to date, psychological studies on hyperprolactinemia are mainly a comparison between behaviors of hyperprolactinemic and normal women in view of their absent or alcoholic fathers [5]. We believe that, comparison of not only paternal, but parental attitude towards children, and children's attitude towards their parents would provide more comprehensive information.

The aim of the present study was to investigate if there was any underlying psychological problem in chronic low-grade hyperprolactinemic patients, namely poor parental manners towards the patients, and the approach of patients towards their parents.

Material and Methods

Subject selection: The present study was conducted in a maternity hospital, among patients with gynaecologic complaints registered to the outpatient gynaecology clinic and referred consecutively to the biochemistry laboratory for serum prolactin analysis. Subjects between 20-50 years old who agree to fill in the 85 item questionnaire and being referred to the laboratory for a serum prolactin test were included in the study. Exclusion criteria consisted of having a previous history of drug abuse, alcoholism, mental retardation, organic brain disorders, hypothyroidism, renal failure, liver disease, seizures, and treatment with antipsychotics or medications known to elevate prolactin levels. Women who were breast-feeding or pregnant or in depression were not included in the study. High-grade hyperprolactinemic patients (serum prolactin level over 100 ng/ml) who were documented by cranial CT to have a prolactin-secreting tumor were also excluded. One patient was excluded because of incomplete questionnaire.

Information about the participants was gathered via the EMBU Scale (Egna Minnen Betraffande Uppfostran Scale, a scale for perceived parental attitude), an 85-item, self-rated questionnaire. It was applied by a psychologist and patients undergoing prolactin test were asked to complete it before the test results were obtained. The questionnaire was voluntary and 18 women did not accept to complete the questionnaire. Over a span of 5 months, 50 questionnaires were collected from women fulfilling our criteria. Psychologist's private room was used for the completion of the questionnaire. Out of the 50 patients who completed the questionnaire, the ones with prolactin level above the normal range (>26.6 ng/ml; manufacturer based information, Roche Diagnostics, USA) were assigned as the hyperprolactinemia group (Group 1) (n=34) and the ones found within the normal range as the control group (Group 2) (n=16).

Mean age for the study group (Group 1) was 35.2±6.1. Their presenting sypmtoms were menstrual irregularities (n=19), infertility (n=8), galactorrhea (n=1), and miscellaneous (alopecia, hypertrichosis, etc). Control group (Group 2) consisted of 16 women with normal prolactin levels (<26 ng/ml) matched for age (mean 31.7+8.5) and marital status with Group 1**.** There was no difference between study and control groups in terms of age ($p>0.05$) and marital status ($p>0.05$).

Blood samples were taken after a 12-hour fasting period, within 2 hours after waking up, between 3rd and 8th day of their menstrual cycles, and assessments were done the next day by chemiluminescence method on an Elecsys 2010 Auto analyzer (Roche Diagnostics, USA). The detectable range of the system was 0.0470 – 470 ng/ml. Intra assay CV value for 33.7 ng/ml was 42.2%; inter assay CV value for 33.7 ng/ml was 3.6%. Comparison with a different method revealed a linear regression equation of $y = 0.76x – 21.21$ and "r" was calculated to be 0.998 (Manufacturer based information, Roche Diagnostics, USA).

Serums were stored at +4 °C properly in capped tubes overnight.

EMBU Scale (a scale for perceived parental attitude) [8] was used for the evaluation. It is an 85-item self rated Likert type questionnaire, taking into consideration their own mothers' and fathers' attitudes and behaviors, as they were growing up. The first 81 items were related with parental attitudes towards the child. The following three items consists of general evaluation, and the last item asks the child to evaluate the parent by giving a score between 0 and 100, regarding their affection towards themselves. The first 81 items provide evaluation of parental attitudes in 5 domains: emotional warmth, rejection, overprotection, favoring subject, and others. The questionnaire, originally in English, was translated by trained interpreters into Turkish and retranslated. The resulted text was piloted among 20 patients and staff, and revised before it was distributed to the patients to be

filled. Validation tests are currently in use at Celal Bayar University Department of Psychiatry.

Statistical methods: Data were analyzed using SPSS package program version 10.0. Levere normality test (test of homogeneity of variance) indicated that the variables were not normally distributed. Relation of the nominal values (age, prolactin level) was analyzed by Student's t-test; whereas, cross tabulation and chi-square tests were used for categorical variables (education, occupation, socioeconomical and marital status). Since the groups did not have a normal distribution with high standard deviations, nonparametric Mann-Whitney U test was used to compare the prolactin levels and emotional warmth and rejective behavior parameters of mothers and fathers. Levere normality tests, t test and chi-square tests were used for statistical analyses with SPSS v.10.0 program (license code cf3e8064683bb72de4c0). For statistical significance, $p< 0.05$ was accepted.

Ethics approval for the study was obtained from our institutional Research and Ethics Committee. Written consent was obtained from all participants.

Results

There were no significant differences (p= 0.551 and p= 0.451, respectively) regarding occupation and marital status of patients between study and control groups (Group 1 and 2). The groups were statistically different (p= 0.017) with regard to educational status. The mean (±SD) prolactin levels in groups 1 and 2 were 57.25±38.7 ng/ml and 18.81±4.4 ng/ml, respectively (z= -5.658, p<0.0001). When the two groups were compared with the attained results of EMBU Scale by Mann Whitney U test, it was seen that both the mothers and the fathers lacked emotional warmth toward women in Group 1. As seen in Table 1, the differences were found significant (z=-2.979, p=0.003 for mothers and z= -2.443, p=0.015 for fathers). Also, the mothers and fathers were noted to be rather rejectional towards women in Group 1. As seen in Table 2, the difference was again found significant by t-test (p=0.008 and p=0.009). There was no statistically significant difference between the two groups in both maternal and paternal attitudes in regard to overprotection and favoring subject parameters. In the evaluation of EMBU Scale total scoring, although we could not find a correlation between the total scoring of the parents with prolactin levels in either group, it was observed that, the last item, the total score of parents attained by Group 1 (75.76±22.4) was significantly lower (87.88±14.0, p=0.024) than that of Group 2 (Table 2).

Table 1: The results of the EMBU scale; Mann Whitney U test

	Group1 (n=34)	Group2 (n=16)	z	p
Prolactin	44.71±6.64 ng/ml	19.00±1.10 ng/ml	-5.658	< 0.0001
Mothers-Emotional Warmth	43.00±2.09	58.00±3.00	-2.979	0.003
Fathers-Emotional Warmth	43.00±1.97	56.50±3.21	-2.443	0.015
Mothers- rejective behavior	31.00±2.37	28.00±1.02	-1.525	0.127
Fathers- rejective behavior	31.00±2.35	28.00±1.19	-1.529	0.126
P85	80.00±3.83	92.5±3.50	-1.684	0.092

Group 1: Hyperprolactinemic, Group 2: Controls. Results are given as median ±standard error of the mean
P85= Child's evaluation of the parent over 100 points

Table 2: The results of the EMBU scale; t test

	Group 1 (n=34)	Group 2 (n=16)	p
Mothers-Overprotection	30.26±7.0	29.38±7.3	NS
Fathers-Overprotection	28.73±6.3	27.69±8.2	NS
Mothers-Emotional Warmth	42.24±12.2	54.06±12.0	0.002
Fathers-Emotional Warmth	40.85±11.3	50.50±12.8	0.010
Mothers- favouring subject	6.94±2.7	6.56±3.7	NS
Fathers- favouring subject	7.67±3.3	6.38±2.9	NS
Mothers- rejective behaviour	36.03±13.8	28.81±4.1	0.008
Fathers- rejective behaviour	34.91±13.5	27.69±4.8	0.009
Mothers- other behaviour	34.85±5.5	34.88±4.6	NS
Fathers- other behaviour	33.27±5.8	32.62±4.5	NS
P85	75.76±22.4	87.88±14.0	0.024

Group 1: Hyperprolactinemic, Group 2: Controls. Results are given as mean ±standard deviation
P85= Child's evaluation of the parent over 100 points; NS= Not significant

Discussion

Prolactin is a 199 amino acid peptide hormone of the anterior pituitary gland so named for promoting lactation in response to the suckling stimulus of the neonate. However, prolactin is not as simple as originally described; the biological actions of prolactin are not limited solely to the aspect of reproduction. Chemically it appears in a multiplicity of post translational forms [4], even plays a role in homeostasis. In addition, it regulates emotional and neuroendocrine stress responses in the brain [9]. Changes in its secretion cause variations in mood, emotion and behaviour. On the other hand, personality traits and environmental factors may stimulate secretion of prolactin and thus may play a role in the development of hyperprolactinemia [3].

There is evidence that young girls may be prone to develop hyperprolactinemia later in life in families characterized by paternal deprivation, alcoholism and/or violation [4,10,11]. These observations support the argument that paternal deprivation during childhood could be associated with a predisposition to develop chronic hyperprolactinemia and galactorrhea later in life as a response to specific environmental changes [5,10]. However, in the present study not only the negative attitudes of the fathers but also of the mothers were shown to be as effective on prolactin over secretion. The results of EMBU Scale showed that, the mothers significantly ($p=0.002$) lacked emotional warmth toward women in Group 1 compared to those in Group 2. In addition, they were neither overprotective nor showed extra favoring toward them. We believe that, not only paternal but also maternal, or better, parental negative attitudes could be accepted as the culprit in hyperprolactinemia.

Studies on sessions of evocation of memories under hypnosis show that, there is a significant negative association between prolactin and cortisol peaks [12]. Prolactin surges were related to the evocation, with the range of humiliating experiences, but not with the fantasy of nursing experience [12]. These findings show that the role of prolactin is much more complex than lactation and favoring care for the young.

Most of the active endogenous substances regulating prolactin secretion have multiple sites of action. They can act at the hypothalamic level as neurotransmitter and also at the pituitary as a neurohormone. At the pituitary level, only a few substances play role as primary neurohormones by robustly affecting hormone secretion (e.g., dopamine, thyrotropin releasing hormone-TRH), while many others can act as modulators by amplifying or diminishing the effect of a primary neurohormone (e.g., neuropeptide Y, galanin, enkephalin). The distinction between the two modes of action is rather intuitive, and the possibility to shift from one mode to another remains open. Under different physiological circumstances (e.g., proestrus, pregnancy, lactation, long-term exposure to a noxious stimulus, aging) a modulator can become a principal factor in regulating hormone secretion [9]. One example for a superior neuroendocrine mechanism that can control stress effects on both hypothalamic-pituitary-adrenal (HPA) system and prolactin secretion, and possibly even more aspects of the stress response, is the recently discovered prolactin-releasing peptide (PrRP). Despite its name giving ability to stimulate prolactin release, studies on its localization and physiology showed that PrRP is not a hypophysiotropic hormone. Rather, it is located in the brain stem solitary tract nucleus and is thought to modulate the activity of several specific nuclei of the amygdala, thalamus, and hypothalamus that are involved in generating a stress response. Various forms of experimental stress, including conditioned fear, were shown to increase central nervous PrRP activity [13].

Dopamine has an inhibitory effect on prolactin secretion [4,9]. In the present study it was seen that women in Group 1 were not raised in warm and cozy home conditions, neither felt protected nor preferred. We thought that lack of well being, pleasure and contentment together with dopamine deficiency might lead to hyperprolactinemia. We believe that such speculations might form the base in predicting the role of negative environmental factors and parental attitudes in the pathogenesis of hyperprolactinemia.

In women, menstrual irregularity, galactorrhea, and infertility symptoms are common. In addition, a small group of women who have these symptoms actually have hyperprolactinemia. This group needs further investigation and possibly treatment with dopamine agonists. Therefore serum prolactin assessment is the key investigation used to identify this particular group of patients who have hyperprolactinemia. On the other hand, the laboratory finding of hyperprolactinemia is not specific because increased serum immunoreactive prolactin may be caused by the presence of a high-molecular-mass complex of prolactin (macroprolactin). It is found in asymptomatic patients and therefore appears to lack the biological activity associated with the normal, monomeric 23-kDa form of prolactin [14]. One of the limitations of the present study is the absence of macroprolactin assessment. Also, prolactin-releasing peptide (PrRP), dopamine receptor or polymorphism studies would have helped for better understanding of the relationship between parental attitude and serum prolactin levels. Repeating the study with different clinical populations and investigating its test-retest reliability in larger samples would definitely increase the value of this study. Another limitation is that we tested only female offspring**.** However, to avoid the methodological difficulties due to circadian rhythm and menstrual cycle changes, we drew blood after a 12-hour fasting period, within 2 hours after waking up, between 3rd and 8th day of their menstrual cycles. Another weakness is that we could not test subjects younger than 18 years old due to legal reasons. However, a specific strength of our study is that our sample

was based on a representative survey randomly selected from the general population. This avoids the response bias usually associated with recruitment of participants by public announcements.

We are aware of the fact that, drawing conclusions from peripheral endocrine findings on underlying central nervous processes is difficult. Nevertheless, this view implies that future research on genetic and physiological mechanisms underlying the risk conveyed by gene-stress-prolactin interactions might be most promising.

Conclusion

Prolactin affects the brain and mood. In the present study, it is shown that negative environmental factors and lack of not only paternal but parental affection are common among women with hyperprolactinemia. Prolactin is regulated by the dopaminergic system and dopamine is responsible for pleasure and contentment. Deficient parental warmth and neglect may play a role through dopamine in the genesis of hyperprolactinemia.

Ethical Considerations

The study was approved by the ethical council of Celal Bayar University, Faculty of Medicine (2003/71).Written consent was obtained from all participants.

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Conflict of Interest

Authors did not declare any conflict of interest.

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