Immunologic Basis of Premature Ovarian Failure (A Case Related Clinical Review)

PREMATÜR OVARYAN YETMEZLİĞİNİN İMMÜNOLOJİK TEMELİ

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SUMMARY

10 Patients with premature ovarian failure were studied. Among the families of 6 of these, at least one member in each family was found to have had amenorrhoea or idiopathic premature ovarian failure. Among the remaining 4 patients one had a sister who had breast cancer and a brother suffering from dia betes mellitus. These patients were tested for antiovarian antibody, counts of white blood cells (WBC). Lymphocytes, B cells and T cedes. The patient with a family history af breast cancer and diabetes mellitus was tested for a range of autoantibodies. Next of kin of the patients were also tested for antiovarian antibo dy. 2 of the patients were positive for antiovarian antibody (20%). The patient with a family history of breast cancer and diabetes mellitus was positive for antinuclear antibody (10%). Also the next of kin of two antibody positive for patients were found positive for antiovarian antibody. Patients with autoantibodies had moderately higher B cell counts, but slightly elevated WBC, Iympocytc and T cell counts.

Key Words: Iiuumiiology, Premature ovarian failure

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ÖZET

Prematür ovaryan yatmezlikli 10 hasta çalışmaya alındı. Bunlardan 6 'sının ailesinin en az bir bireyinde amenorc veya idiopatik ovaryan yetmezlik vardı. Geri kalan 4 hastanın birinin kız kardeşinde meme kanseri, erkek kardeşinde de diabetes mellitus vardı. Bu hastalarda antiovaryan antikor bakıldı, beyaz küre, lenfosit, B ve BT lenfosit sayımı yapıldı. Ailesinde meme kanseri ve diabetes mellitus olan hastada otoantikor dağlımı ölçüldü. Hastaların yakın akrabalarında da antiovaryan antikor bulundu, iki hastada antiovaryan antikor pozitif bulundu (%20). Ailesinde meme kanseri ve diabet olan hastada antinükleer antikor ve pozitifti (% 10). Antiovaryan antikor pozitif olan iki hastanın yakın akrabalarında da pozitif bulundu. Otoaıtikoru yüksek olan hastalarda orta derecede yüksek B lenfosit, hafif derecede de yüksek beyaz küre, lenfosit ve T lenfosit saptandı.

Analılar Kelimeler: İmmünoloji, Prematür ovaryan yetmezlik

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Although the etiology is not known in many of the patients with premature ovarian failure, it may be associated with chromosomal abnormalities, surgical castration, radiothreapy and use of cytotoxic drugs. In some of these patients, there are some evidence that autoimmun mechanisms may be the cause of ovarian failure: 1. Widely existing circula-

Table 1.

Case No	Age	FSH (nilU/ml)	LH (mlll/ML)	PRL (mlU/ml)	Estradiol (pg/nil)	Antibody
1	27	82	69	220	28	
2	28	100	114	340	33	+
3	28	120	68	132	26	+
4	29	120	96	90	38	—
5	34	57	77	1 16	57	—
e	39	65	67	197	26	—
7	33	131	113	384	42	—
8	39	100	74	398	69	—
9	36	52	60	243	34	—
10	34	69	88	173	38	—

Table 2.

Case No	WBCCIO'/L)	LympliocyledO'/L)	E-rosetle (lO'/L)	B cell (10'/L)	Antibody
1	7.94	1.92	1.52	0.37	+
2	7.04	1.85	1.48	0.42	
3	6.94	2.06	1,78	0.30	
4	5.76	1.77	1.40	0.27	—
5	6 07	1.68	1.38	0.29	—
6	7.54	1.73	1.44	0.23	—
7	5.96	i.70	1.37	0.34	—
8	6.13	1.74	1.50	0.26	—
9	5.94	1.79	1.39	0.34	—
10	6.28	1.68	1.41	0.28	—

ting antibodies in the sera of women with premature ovarion failure against ovarion tissue (1,2,3). 2. The histologic finding of lymphocyte infiltration within ovaries (3,4). 3. The association with the other immune disorders (3,5). The initiating factor of the autoimmune mechanism is not known. According to Newman et al (6) supressor T cell functions or counts were altered by an unknown mechanism in the patients with active systemic lupus erythematosus. Using monoclonal antibodies against CD4 and CD8 antigens to identify helper and supressor T cells, respectively, Morimoto et al (7) found a selective decrease in supressor T cells ratio in most of the patients with Sjogren's syndrome and systemic lupus erythematosus. Ho et al (8) reported that patients with premature ovarian failure demonstrate a significant increase in supressor T cells was more marked in these patients. Their results in the patients with autoantibodies showed a significant decrease in the percentage of T cells.

Patients with premature ovarian failure were tested for antiovarian antibody and the patient with a family history of diabetes mellitus and breast cancer was present. The next of kin of patients with amenorrhoea or idiopathic premature ovarian failure were also tested for antiovarian antibody to determine whether an autoimmune reaction was present, and whether there was a familial tendency to the disease. Afterwards in order to detect any alteration in the immune response of these patients, WBC, lymphocyte, B cell and T cell counts were studied.

MATERIAL AND METHODS

We studied 10 patients with idiopathic ovarian failure defined as ovarian failure before the age of 40

years. The diagnosis of ovarian failure was based on persistently elevated plasma follicle stimulating hormone (FSH) levels over 50 mlU/ml. Karyotype, follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin (PRL), 17-Beta estradiol and antiovarian antibody tests were run on all the patients. The patient with a family history of diabetes mellitus and breast cancer was also tested for a range of autoantibodies. We performed WBC counts, differential, lymphocyte, B and Tcell counts for all of the studied patients. Not taking in account the patient with a family history of diabetes mellitus and breast cancer, 6 of the patients were found to have at least one member among their families having amenorrhoea or idiopathic ovarian failure. These next of kin were then tested for antiovarian antibody. But since some of them reside elsewhere or are not regular patients at our clinic, further evaluation and follow up was impossible. However their medical histories were reviewed in detail and there was no indication of anything remarkable or related to the condirion under study. None of the patients had received any hormonal preparation for a period of two months prior to the tests.

Plasma FSH, LH, PRL, and 17-Beta estradiol were measured by radioimmunoassay. Antiovarian antibody and antinuclear factor was detected by indrect immunofluoresence technique. B cell counts were performed by identifying lymphocytes with surface membrane immunoglobulin. T cells counts were performed by using E-rosette method. Ovarian biopsy was operated for a benign pelvic condition.

RESULTS

A total of 10 patient swith premature ovarian failure were studied. The mean age (+SD) of the patients was 32.7+4.5 years. The plasma estradiol was 39.1 + 18.0 pg/ml, plasma FSH was 89.6+28.6 mlU/ml and plasma LH was 80.6+22.8 mlU/ml. The plasma PRL was within nonnal limits in all the patients (229.3+10.0) (Table 1).

Antiovarian antibody was detected in two of the 10 patients (20%). One of the patients with a family history of diabetes mellitus and breast cancer was positive for antinuclear antibody (10%). In total, 30% of the our patients were positive for autoantibodies. The relatives of those 2 antiovarian antibody positive patients were also found to be positive for this antibody. One fo them was the three years older sister of the first antibody positive patients, the other was the 52 year old mother of the second antibody positive patient, respectively. There was no clinical and laboratory evidence of Addisson's disease in the patients under study. Also no autoimmune disoders were detected.

The results of the WBC, lymphocyte, T cell and B cell were analysed and compared with the results of the antibody positive and negative patients. Patients with autoantibodies were found to have moderately high B cell counts, but slightly higher lymphocyte and T cell counts (Table 2).

DISCUSSION

Premature ovarian failure is usually defined by the triad of amenorhoea, estradiol deficiency and elevated plasma concentrations of follicle stimulating hormone (FSH) and luteinising hormone (LH) in women under 40 years of age. There are no unique clinical features that univocally establish the diagnosis of ovarian failure.

Concentrations of LH and FSH that consistently exceed 50 mlU/ml exclude possiblities of laboratory error and measurements of a gonadotropin surge. Serum concentrations of LH and FSH that do not vary in cylic fashion but do reflect the pulsatile secretion (9). The baseline of these pulses is always greater than 40 to 50 mlU/ml.

This suggests that a single measurement of LH and FSH is a reliable indicator of ovarion failure when the value exceeds 50 mlU/ml.

The diagnosis of our patients was based on persistently elevated plasma FSH level (over 50 mlU/ml).

The incidence of autoantibodies varies in different studies according to the type of the patients studied and the technique used to detect antiovarian antibody. The finding of autoantibodies against ovarian constituents has been reported in 15%- 40% of follicular type ovarian failure (10). Using indirect immunofluoresence techniques on human tissue, the incidence of antiovarian antibody was 33%- 30% with Addisson's disease and positive antiadrenal antibody (11-12). If the patients had ovarian failure in addition to Addisson's disease the incidence was 100% (11). Using a technique to test the binding of circulating antibodies to 1251-Labeled proteins from human menopausal ovaries, Coulam and Ryan (1) reported an incidence of 27% in the patients with premature ovarian failure. By studying 45 Chinese patients with premature ovarian failure, Ho et al (8) reported that only one of these patients had antiova-

rian antibody (18%) were positive at least for one antibody.

By using indirect immunofluoresence technique we found that the patient with a family history of breast cancer and diabetes mellitus was positive for antinuclear antibody (10%). In total, 3 of our patients were positive at least for one anibody (30%).

Aiman and Smentek (13) reported that none of their 35 patients had a family history of amenorrhoea or idiopathic premature ovarian failure. But three of those women had brothers with diabetes mellitus, and the ovarian failure of these three women was of undetermined etiology. Similarly the brother of one of our patients was suffering from diabetes mellitus. However, conversely, 6 of the next of kin of our patients had amenorrhoea or idiopathic ovarian failure. To test if there was a familial tendency for immunological aspect of premature ovarian failure, we also studied these 6 cases for antiovarian antibody. Although the result for antibody positivity was not statistically valid after studying just 10 patients, it allowed us to form an idea: because 2 of the antibody positive patients relatives were also found to be positive for the same antibody. This suggests that some genetic features may be responsible for this type of ovarian insufficiency as in the other autoimmune disoders. It also suggests that there may be an associated immune disease in the patients with premature ovarian failure. In fact, some studies on the subject showed that 13-18% of the patients with premature ovarian failure had also an associated immune disorder or other antibodies (5,13,14). However non of our patients with autoantibodies had a moderately high percentage of B cells. Whereas WBC, lymphocyte and T cell counts were slightly higher in these patients compared to the antibody negative patients (Table 2). Alteration in the immune system may be primary or secondary to other abnormalities in these patients. The changes in lymphocytes and lymphocyte subpopulations in premature ovarian failure may be due to estrogen deficiency. Estrogen is a well known immunomodulator. It may be effective on lymphocyte counts. Mathur et al (15) reported that there was a negative corelation of lymphocyte counts with estradiol levels and that the minimum lymphocyte counts coincided with the preovulatory estradiol surge. Estrogen depletion was more marked in our antibody positive patients. It may be the cause of that slight elevation of lymphocytes. Estrogen also enhances human B cell maturation via inhibition of supressor T cells (16). It can be possible cause of B cell elevation of B cell elevations in these patients or this moderate elevation of B cells in antibody positive patients is probably due to the other abnormalities in immunoregulation. Consequently, further studies on the immune response of these patients are necesarry before a conclusion can be drawn.

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