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 amenorrhea or idiopathic premature ovarian failure. Among the remaining 4 patients one had a sister who had breast cancer and a brother suffering from diabetes mellitus. These patients were tested for antiovarian antibody, counts of white blood cells (WBC), lymphocytes, B cells and T cells. The patient with a family history of breast cancer and diabetes mellitus was tested for a range of autoantibodies. Next of kin of the patients were also tested for antiovarian antibody. 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 patients were found positive for antiovarian antibody. Patients with autoantibodies had moderately higher B cell counts, but slightly elevated WBC, lymphocyte and T cell counts.

Key Words: Immunology, Premature ovarian failure

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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, radiotherapy and use of cytotoxic drugs. In some of these patients, there are some evidence that autoimmune mechanisms may be the cause of ovarian failure: 1. Widely existing circula-
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 amenorrhea 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 mIU/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, T and B cell 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 condition 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 indirect immunofluorescence 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 with 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 mIU/ml and plasma LH was 80.6+22.8 mIU/ml. The plasma PRL was within normal 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 of 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 Addison's disease in the patients under study. Also no autoimmune disorders 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 amenorrhoea, 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 mIU/ml exclude possibilities of laboratory error and measurements of a gonadotropin surge. Serum concentrations of LH and FSH that do not vary in tyclic fashion but do reflect the pulsatile secretion (9). The baseline of these pulses is always greater than 40 to 50 mIU/ml.

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

The diagnosis of our patients was based on persistently elevated plasma FSH level (over 50 mIU/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 immunofluorescence techniques on human tissue, the incidence of antiovarian antibody was 33%-30% in Addison's disease and positive antidiadrenal antibody (11-12). If the patients had ovarian failure in addition to Addison's disease the incidence was 100% (11). Using a technique to test the binding of circulating antibodies to 125I-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 immunofluorescence 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 antibody (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 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 anti ovarian 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 disorders. 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 suppressor 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 necessary before a conclusion can be drawn.

REFERENCES