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Original Article

The Presence of Anti Thyroid and Anti Ovarian Auto-Antibodies in Familial Premature Ovarian Failure

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Abstract

Background: Premature ovarian failure (POF) is a disorder of multi causal etiology. Autoimmunity has been proposed as a mechanism for some cases of ovarian follicle dysfunction which is evident in POF. The aim of this study was to identify the level of auto-antibodies in POF and familial POF patients.

Materials and Methods: In this study, auto-antibodies including anti-ovarian antibody (AOA), anti thyroid peroxidase (TPO) and anti thyroglobulin (TG) antibodies were assessed in the sera of 43 cases with spontaneous POF including 12 cases affected by familial POF. The control samples were obtained from sera of 39 women with normal ovulatory or post menopause women.

Results: AOA were detected in 46.5% of the POF group, 41.7% of the familial POF group and 41% of the control group without significant statistical difference between the three groups. Thyroid peroxidase (TPO) antibody was found in 32.6% of the POF group, 41.6% of the familial POF group and 10.3% of the control group. Anti TPO was detected significantly high in both POF and familial POF groups ($p<0.02$ and $p<0.01$, respectively). Thyroglobulin (TG) antibody was found in 48.8% of the POF group, 75% of the familial POF group and 23.1% of the control group with meaningful difference ($p<0.02$ and $p<0.001$, respectively). TG antibody was significantly higher in familial POF group in comparison to POF group ($p<0.03$).

Conclusion: Although measurement of AOA is not a reliable method for diagnosis of auto-immune POF, but existence of anti thyroid antibodies in familial POF (mainly anti TG) can potentially represent an autoimmune mechanism. It is possible to propose a genetic component for developing autoimmune POF supported by presence of anti thyroid antibodies in familial POF.

Keywords: Auto-antibodies, Premature Ovarian Failure, Familial POF

Introduction

Premature ovarian failure (POF) is a non physiological cessation of menstrual cycle before the age of 40 years and after puberty (hence, in fact, secondary amenorrhea) (1). Women with POF have a hyper gonadotropic-hypoestrogenic hormone profile (2, 3). POF is a heterogeneous disorder with a multi causal pathogenesis. Chromosomal (4), genetic (5), enzymatic (6), iatrogenic (7) or infectious (8) factors may all form the basis for the disappearance of ovarian follicles (2).

A large proportion of women with primary ovarian failure have no identified causes .The etiology of POF can be divided into two broad categories: ovarian follicle depletion and ovarian follicle dysfunction .Ovarian autoimmunity is a possible cause of both afollicular and follicular forms of POF and both follicle depletion and dysfunction occur (2, 9).

POF is frequently associated with autoimmune disorders, particularly autoimmune thyroid disease. In the absence of clinically overt disease, some patients have serological evidence of autoimmunity mainly against thyroid (10). These observations suggest that autoimmunity may be an important cause of idiopathic POF. Using microsomal ovarian antibodies and oocyte antibodies, an autoimmune basis was detected in as many as 69% of women (11). The aim of this study was to assay the presence of circulating AOA, anti TPO and

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anti TG antibodies in the POF and familial POF cases in comparison to the control group.

Materials and Methods

This case control study was performed between 2004 and 2005. Sera from 43 women with spontaneous POF (12 cases with familial POF) were assessed for the presence of AOA, anti TPO and anti TG antibodies. These cases referred sequentially to Royan institute and gynecology clinic in Taleghani teaching hospital affiliated to Shahid Beheshti University of Medical Sciences in Tehran, Iran. All patients in case group had cessations of menstrual cycles before the age of 40 in association with raised serum levels of FSH more than 10 IU/ml (12). All of cases had secondary amenorrhea. Familial POF was defined as existence of POF in the first or second degree relatives.

The control group consisted of 39 women including 31 women with normal ovulation referred for choosing some contraceptive methods and the other 8 women were in post menopausal period.

The project was approved by Royan Institute ethics committee. All cases and controls signed the consent form. None of them had clinical evidence of autoimmune disease. All laboratory tests were done in the laboratory of Royan Institute.

Inclusion criteria included: spontaneous cessation of menstrual cycle before 40 year with secondary amenorrhea. Exclusion criteria were surgical menopause or POF due to chemotherapy or radiotherapy. Neither cases nor control had overt autoimmune disease. None of the cases and controls had familial relationship with each other. SPSS version 13 was used for data entry. The chi-square test on 2×2 contingency tables was used for statistical analysis. The subjects were screened for immunological markers associated with autoimmune disease including anti TPO, TG, AOA and also were evaluated for some related hormonal and biochemical agents such as FSH, LH, Prolactin, TSH.

Blood samples were allowed to clot; sera were separated by centrifugation and stored at -20°C until assayed. The subjects were assessed for the presence of auto-antibodies raised against thyroid (anti TPO and TG antibodies) and ovaries (AOA) by using ELISA method. Values were equal or greater than 10 IU for AOA, 75 IU for anti TPO and 100 IU for anti TG considered as positive.

Serum samples were evaluated for the presence of auto-antibodies raised against thyroid (Thyroid Peroxidase Antibody; ELISA, GENESIS, Cambridge shire CB6 1SE, UK, anti Thyroglobulin antibody; ELISA, GENESIS, Cambridge shire CB6 1SE, UK.) and human ovarian tissues (Anti-Ovary antibody, ELISA, Bioserv Diagnostics, Rostock, Germany). They were also evaluated for measurement of Follicle Stimulating Hormone concentration (FSH, IRMA, Pooyesh Tashkhis, Tehran, Iran), Luteizing Hormone concentration (LH, IRMA, Pooyesh Tashkhis, Tehran, Iran), Prolactin concentration (PRL, IRMA, Pooyesh Tashkhis, Tehran, Iran), and Thyroid Stimulating Hormone concentration (TSH, IRMA, Pooyesh Tashkhis, Tehran, Iran).

Results

In this study, 43 women with POF were compared with 39 women as the control group. Mean age of patients in POF group was 27.87±3.1 (15-39 year). Mean values of FSH were 71.24±9.42 for the POF group and 6.8±0.63 IU for the control group. TSH and Prolactin levels were within normal limits in both groups.

ELISA for anti-ovarian antibody revealed that 46.5% of the POF group (20 out of 43), 41.7% of the familial POF group (5 out of 12) and 41% of the control group (16 out of 39 patients) had AOA .

The difference between the case and control groups were not statistical meaningful. The POF group was divided into two subgroups based on the onset of POF (before or after the age of 25 year). Non-parametric test of Mann-Whitney did not show any difference in existence of AOA between the two subgroups.

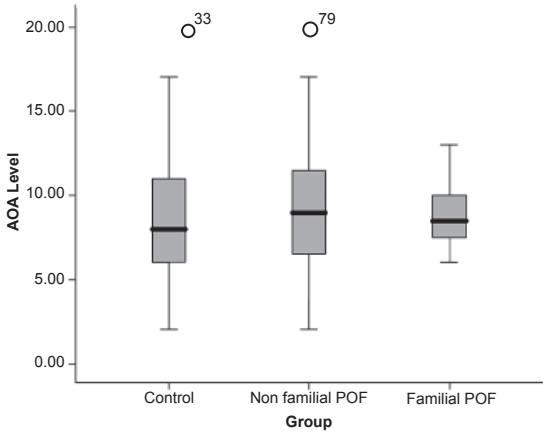

Fig 1: Bar graph of AOA level distribution in the studied groups

Table 1: Auto-antibodies in POF and control groups

Auto-antibody	*POF cases*	*Controls*	*Risk Ratio Confidence Interval (%95)*	*P Value*
AOA	46.5%	41.0%	1.250(0.521-3.000)	0.617
anti TG	48.8%	23.1%	3.182(1.224 -8.270)	*0.02
anti TPO	32.6%	10.3%	4.224(1.253-14.241)	*0.02
Auto-antibodies	72.1%	56.4%	1.996(0.796-5.004)	0.14

**** Significant Difference***

Table 2: Auto-antibodies in POF and Familial POF

Auto antibodies	*Familial POF*	*Non Familial POF*	*Risk Ratio Confidence Interval (%95)*	*P Value*
AOA	41.7%	48.4%	0.762(0.198-2.929)	0.69
anti TG	75%	38.7%	4.750(1.067-21.144)	*0.03
anti TPO	41.7%	29%	1.746(0.437-6.976)	0.43
Auto antibodies	75%	71%	1.227(0.269-5.608)	0.79

**** Significant Difference***

Table 3 . Auto-antibodies in Familial POF and Control groups

Auto antibodies	*Familial POF*	*Controls*	*Risk Ratio Confidence Interval (%95)*	*P Value*
AOA	41.7%	41%	1.027(0.276-3.817)	0.97
anti TG	75%	23.1%	10.000(2.222-44.999)	*0.001
anti TPO	41.7%	10.3%	6.250(1.333-29.301)	*0.01
Auto antibodies	75%	56.4%	2.318(0.543-9.901)	0.23

**** Significant Difference***

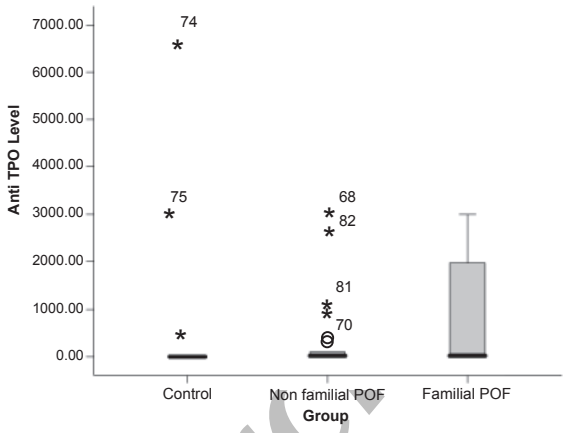

Fig 2: Bar graph of anti TPO level distribution in the studied groups

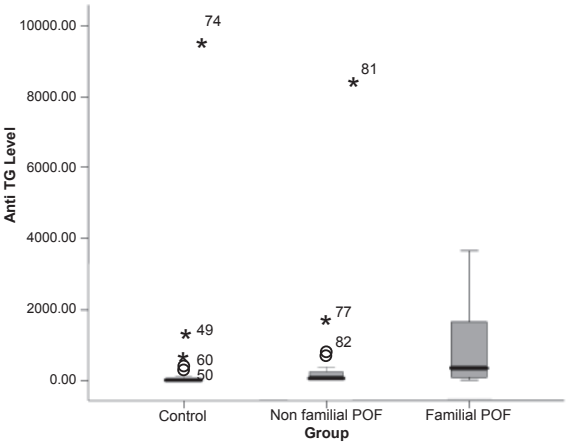

Fig 3: Bar graph of anti TG level distribution in the studied groups

Anti TPO antibody was detected in 32.6% of the POF group, 41.7% of the familial POF group and 10.3% of the control group .The difference between the POF and familial POF groups was statistically significant compared to the control group ($p<0.02$ and $p<0.01$, respectively).

Anti TG was found in 48.8% of the POF group, 77.5% in the familial POF group and 23.1% of the control group. There was significantly higher positive anti TG in the POF and familial POF groups compared to the control group; ($p<0.02$ and $p<0.001$, respectively). Anti TG antibody was detected more prevalent in the familial POF group compared to the POF group ($p<0.03$).The results are shown in the tables 1-3 and figures 1-3.

Discussion

Since fluorescent method has less specificity and sensitivity than ELISA (13), ELISA was used for the present study. Autoimmune POF has been considered to be a mechanism possibly responsible for primary idiopathic POF. Several studies revealed the association of AOA with POF. The incidence of AOA in patients with POF ranges widely (20-67%), according to the type of antibody, methods used for selection of patients and measurement of auto antibodies (14, 15).

It is possible that AOA has cross reaction with other tissues. Although one specific antigen is not determined, several antigens must be considered (14).

It is suggested that initiation of autoimmune process and production of AOA is secondary to every procedure causing invasion to ovaries such as IVF, ovarian biopsy or puncture and other mechanical procedures, although this trauma is unknown in primary POF (14).

Although there are evidences against autoimmune pathogenesis of POF because oophoritis or inflamma-

tion of ovaries is not seen in all cases of POF (it is seen only in less than 3%); in animal models being immunized against zona plucida, reduction of ovarian follicles and fibrosis (similarly to POF) are reported (2).
Massin et al (16) evaluated presence of ovarian follicles in POF patients by biopsy .Their results showed that ovarian follicles more than 2 mm were seen in 56% of POF patients. In present study, ovarian biopsy was not done because of its invasive nature.

Conclusion

AOA was not a suitable marker for diagnosis of POF in our study, but thyroid auto-antibodies such as anti TPO and especially anti TG were detected more significantly in POF cases. Findings of our study revealed we need to detect some specific auto-antibodies except AOA and anti ZP antibodies for diagnosis of POF.
Presence of antithyroid antibodies in our study shows that in POF cases, one should consider other endocrinopathies not limited to ovary, like involvement of thyroid.

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