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Comparison of IL-13 and IL-27 levels between schizophrenics and healthy subjects before and after antipsychotic administration

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ABSTRACT

Many new evidences suggest cytokine activities involvement in pathogenicity of schizophrenia. Therefore, the aim of this study was to assess the serum levels of IL-13 and 27 in schizophrenics, and then compares them with those of healthy individuals. This project was conducted in 2013. First, the patients and the controls were matched based on their sex and age, then serum levels of IL-13 and 27 (ELISA) were measured at the beginning of treatment with antipsychotics, Once more, after completion of antipsychotic administration for three months, the interleukins were assayed. The results indicated that IL-13 levels in the male and female patients before treatment were significantly higher than their respective control groups (P = 0.001and P = 0.002). The amount of this cytokine three month after the treatment, showed no significant difference between the two groups (P = 0.965 and P = 0.205). The results also revealed that IL-27 levels in female patients had no significant increase before the treatment comparing to their associated control group (P = 0.625) and serum level of the cytokine in male patients was significantly low before the treatment comparing to their control subjects (p=0.009). Serum level of this cytokine demonstrated no significant difference between the patients and their control groups based on their age and sex after treating for three months (P = 0.325 and P = 0.744). The results indicated that serum levels of IL-13 and IL-27 before and after the treatment were different and treating with antipsychotics returned IL-13 and IL-27 serum levels of the patients to the same level of the controls.

Key words: Schizophrenia, cytokines and antipsychotic drugs.

INTRODUCTION

Schizophrenia is a chronic and often debilitating mental disease with a prevalence of approximately 1% of the world population [1, 2]. There is evidence suggesting that immunological aspects of cytokine activities have been involved in the pathogenesis of schizophrenia [3]. Immunological activities in schizophrenics, has been highly regarded.

Immune system can cause neurological and behavioral changes and this may lead to changes in the central nervous system [4].

It is known that the disease is accompanied by an increase in nonspecific innate immunity; reduced T cells activities (Th1)and imbalance between Th1 and Th2 cells which can shift immune system towards increased Th2 response [5, 6,7]. In this regard, most studies involving/ concerning schizophrenia have focused on the role of cytokine activities especially interferon (IFN), IL-2, IL-6 and tumor necrosis factor (TNF-α). So, increased level of IL-6 has been reported continuously during the disease process [8]. Several studies have also shown that production of serum IL-2 and interferon alpha in patients with schizophrenia have been reduced whereas min case of IL-4 and IL-10 the increment was seen [8].

Regarding the roe of antipsychotics in cytokine activities, there is evidence which confirms that serum levels of anti-inflammatory interleukins after treating with antipsychotics have been decreased and serum levels of inflammatory cytokines have been increased. In this regard, a suppressive property of such drugs in vitro was determined by increasing the serum levels of IL-1R antagonist and reduction of IL-2, IFN-γ and IL-4 secretion [9]. Whereas using atypical antipsychotics inhibit significantly production of IL-1β, IL-6 TNF-α and also the release of TNF-α and IFN-γ following the activation of microglial cells [10]. Repeated injections of atypical antipsychotics in vivo revealed significant increment of inflammatory cytokines, including IL-6 and TNF-α. In addition, short-term treatment approach with these medications (median = 120 days) increase IL-6 plasma concentration [11, 12]. Study of Muller and Schwarz in 2010, indicated that increased Th2 cytokines production seen in schizophrenics can be returned to the initial status after treating with antipsychotics (13)

MATERIALS AND METHODS

This case and control study has carried out on schizophrenics admitted to rehabilitation center and nursing of Behravan (especially for the ladies) and Iran (especially for the men) in Yasuj capital city of Kohgealuyeh and Boyerahmad province.

In this study that has carried out for the first time, 34 schizophrenia patients were studied (19 male and 17 females) before and three months after treating with antipsychotics . In the meantime, thirty healthy control subjects were chosen (18 male and 12 female) their gender and age were matched. Patients were selected from those ones which were referred to Yasuj blood transfusing center without having inflammatory and, non-inflammatory disease or history of any certain disease and of course they did not take any specific drugs. The population study was chosen based on consulting a medical statistician medical statistic counselor. Then from the superintendent patients and control, informed consent was taken and patients' treatments were carried out by antipsychotic drugs according to a psychiatrist's orders.

Blood samples were collected between 8-12 hours of admission and then serum centrifuged at 2500 rpm for 10-minutes and then they were stored under -80˚ until the testing time. .

Weight of persons were measured by a scale (up to 150 kg and accurately 01 / kg Made in Germany) and their height in standing position and based on cm and finally, the body mass index (index BMI) was calculated.

Patients' information were obtained by psychiatrist through demographic cards serum IL-13 and IL-27 concentration were measured using ELISA kits purchased from eBioscience Co., (USA) and by Elisa reader Biotek machine (USA). The sensitivity for IL-13 and IL-27, has obtained as 0.7 and 9.5 Pg/ml respectively. Various tests were performed on different samples, standard test controls, before and after the treatment.

After evaluating the serum concentrations of IL-13 and IL-27, concentrations of these two cytokines were analyzed by SPSS 19 software. Initially for evaluation normal or abnormal distribution of the data, One-sample Kolmogorov-Smirnov Test was used. Due to lack of normal data, non-parametric Independent-Samples Tests -2 of Maan-Whitney U and Wilcoxon tests were used.

All results were evaluated based on the mean ± standard deviation (SD) and the level of $p>0.05$ was considered as non-significant.

RESULTS

The result of this study showed 55.8% of patients were male whereas in control group, 60% were male. Characteristics of participants such as age, sex, smoking, body mass index (BMI), type of symptoms, type of

diseases and family history of the disease, are shown in Table 1. The subjects' ages age were 21 to 62 years old and the results showed statistically significant differences between the patients and the controls (P=0.041).

Other results of the table indicated that some factors, including the quantity of smoking, body mass index, symptoms positive and negative syndrome scale (SPNS) did not show significant difference between males and females patients (P = .0.690), (P = 0.128) and (P=0.353) respectively.

Table 1: Mean and standard deviation of characteristics in patients and healthy control

Participants / Parameters	Female patient mean ± standard deviation n=15	Male patient mean ± standard deviation n=19	Female healthy mean ± standard deviation n=12	Male healthy mean ± standard deviation n=18
Age	42/06±9/397	41/10±10/73	35/17±11/296	33/85±9/78
BMI	25/2±5/4	24/19±3/41	24/5±3/45	26/45±3/1
Cigarette	smokers:4 non- smokers**:** 11	smokers:11 non- smokers**:** 8	smokers **:** 2 non- smokers**:** 10	smokers **:** 7 non- smokers**:** 11
Type of symptoms	positive:10**:** negative**:** 4 cognitive:1	positive **:**11 negative**:** 5 cognitive **:** 3	-	-
Type of disease	paranoid : 10 unorganized: 0 catatonic: 0 non-distinctive:1 reset;4	paranoid : 9 unorganized: 4 catatonic: 2 non-distinctive: 1 rest: 3	-	-
Family history of the disease	yes:6 no:9	yes:6 no:13	-	-

Regarding the results obtained from IL-13 and IL-27 serum levels in schizophrenics before treatment, our results showed that IL-13 level in both male and female patients with schizophrenia before treating with antipsychotics was significantly increased compared to control group (P=0.002) and (P = 0.001) respectively (table 2 and fig 1). Our results also revealed that IL-27 serum level in male patients with schizophrenia was significantly increased before the treatment compared to the control group (P=0.007) and was not increased in female patients compared to the control group (P=0.625) (table 2 and fig 2).

Based on the effect of antipsychotics on IL-13serum level, our results demonstrated that after treating with anti psychotics for three months, IL-13 level in both male and female patients with schizophrenia was not significantly increased compared to the healthy control group after treating with anti psychotics for three months (P=0.205) and (P = 0.965) respectively (table 2 and fig 1). Our results also indicated that IL-27 serum levels in both male and female patients with schizophrenia treated with antipsychotics for three months were not significantly increased compared to the healthy control group (P=0.744) and (P = 0.325) respectively (table 2 and fig 2).

Table 2: Comparison of mean and standard deviation of serum level of IL-27 and IL-13 in patients and healthy controls

Participants / Time of treatment based on kind of cytokines	Mean ± S.D Female patients	Mean ± S.D Female healthy control	Mean ± S.D Male patients	Mean ± S.D Male healthy controls
before treatment IL-13 (pg/ml)	5.184± 2.14	2.05 ± 0.21	3.636 ±.51	2.03 ±0.144
IL-27(pg/ml) before treatment	227.458 ± 78.324	180.733 ± 56. 910	115.78 ± 54.312	282.800 ±62.4
IL-13 (pg/ml) three months after treatment	2.501 ±1.62	2.05 ± 0.21	1.96 ± 0.23	2.03 ±0.144
IL-27 (pg/ml) three months after treatment	151.576 ± 26.608	180.733± 56. 910	196.763 ± 50.4	282.80 ±62.42

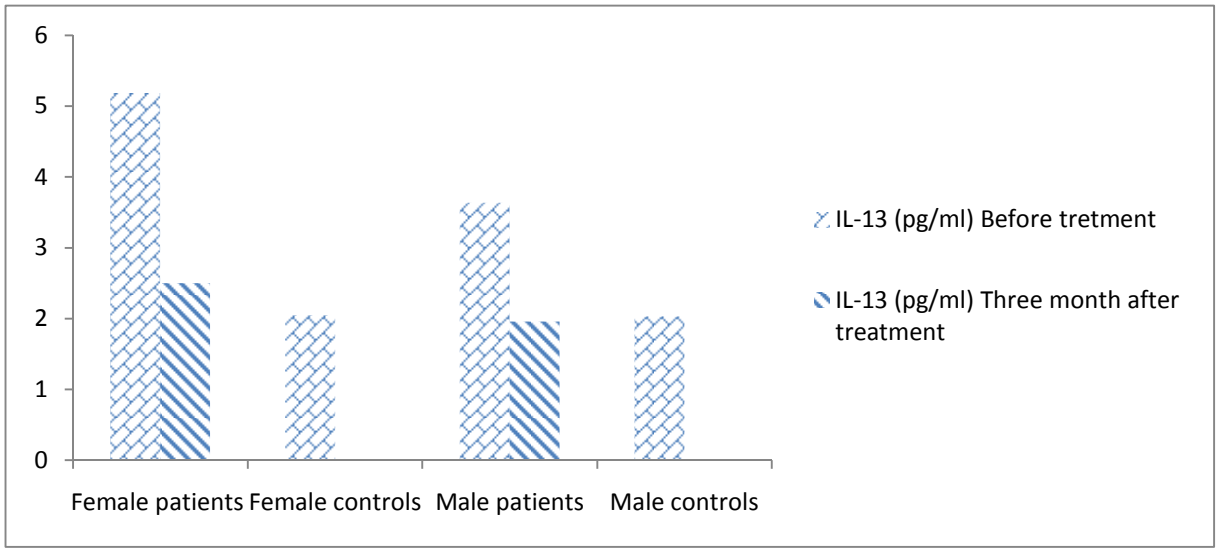

Fig 1: Comparison of IL-13 (pg/ml) between schizophrenics and healthy controls before and three month after treating with antipsychotics

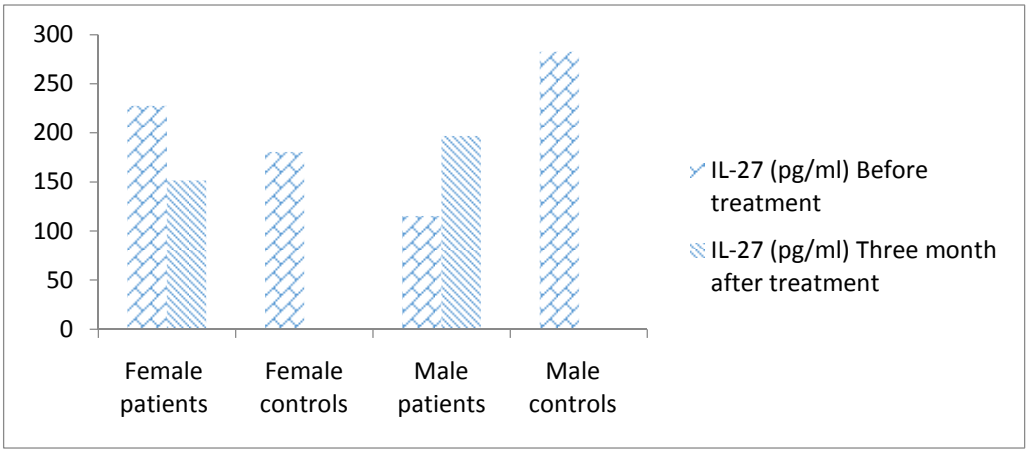

Fig 2: Comparison of IL-27 (pg/ml) between schizophrenics and healthy controls before and three month after treating with antipsychotics

Fig 3: Comparison of serum levels of IL-13 among female and male groups (patients and healthy controls)

Furthermore, our results showed that the IL-13 level in female patients was higher than male patients but the difference was not significant (P=0.227) and the level of this cytokine in healthy male and female was not different significantly/had no significant difference (P = 0.984) (fig 3). Our results also revealed that IL-27 serum level in the

male patients with schizophrenia was significantly decreased compared to the female patients (P=0.019) and there was no significant difference between male and female healthy control groups (P=0.922) (fig 4).

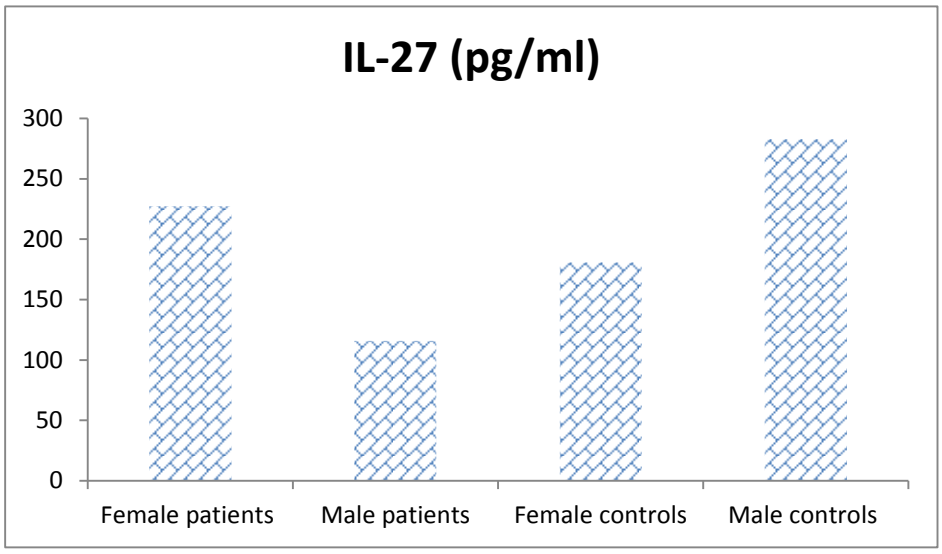

Fig 4: Comparison of serum levels of IL-27 among female and male groups (patients and healthy controls)

DISCUSSION

Studies on the role of immune functions in schizophrenia has been rarely performed and most of them have focused on the role of cytokines especially IL-4 and 10 [20]. Hence we focused on the role of IL-13 and IL-27 as cytokine family of IL-4 and IL-10 in these patients for the first time to find out any immunopathgenicity relevant to the disease. We started first with the evaluation of IL-13 followed by IL-27 in schizophrenics before and three month after treating with antipsychotics compared with healthy subjects as well as comparative study of these interleukins levels between male and female patients before and three month after the treatment.

One of the findings of this study was a significant increment of IL-13 levels before the treatment in both sexes comparing to the controls.

While Chi-Un Pae and colleagues in South Korea (2006) reported that serum levels of IL-13 in patients with schizophrenia and 8 weeks after treatment with antipsychotics has been significantly different, therefore their result is consistent with ours [3].

As we already discussed, biological action of IL-13 is to inhibit production of proinflammatory mediators by monocytes and macrophages, therefore this phenomenon has been a subject of interest to many investigators especially considering on the role of this cytokine in the central nerve system (CNS). The study conducted by Shin et al. (2003), their results showed that, cooperation of neurons and microglial cells by inducing the production of IL-13 by microglia, reduces inflammatory factors and cause programmed death apoptosis of microglia[21].

Our results also revealed that IL -27 levels in female schizophrenics before and after three month of the treatment compare comparing with the control group despite of increase in the control group, were not significantly different. It was also indicated that IL -27 levels in male patients with schizophrenia was significantly lower than male healthy controls before the treatment. In a research carried out by Milica Borovcanin et al. (2013) studied patients with schizophrenia and patients with first episode psychosis (FEP), their results showed the levels of serum IL-4, IL-27 and IL-6 in patients (FEP) after treatment with antipsychotic was significantly reduced. The concentration of IL-4 in patients with schizophrenia after treating with antipsychotics was significantly reduced [19].

On the other hand, IL-27 has also anti-inflammatory and proinflammatory effects [22]. In this regard an in vitro study was done by Fitzgerald et al. colleagues on stimulated encephalitogenic T-cells with IL-27, as a result, the cells reduced IFN-γ production [22].

Another study reported the effect of IL-27 on CD4 T-cells; this effect has been dependent on what conditions these cells may have had as IL-27 did not affect production of IFN-γ and IL-17 by CD4 T-cells in the early stages of their

activation. While this cytokine will suppress IFN-γ and IL-17 production by CD4 T-cells, they are at the peak in the beginning of activation. So this will explain the role of IL-27 in the male schizophrenics comparing to the healthy control group [23].

On the other hand, our findings showed that IL-27 level of between men and women with schizophrenia before treatment was significantly different which can be caused by interference of with sexual hormones called sex hormones this phenomena can have effect(s) on immunological mechanisms in the CNS [24]. Study of Trotter et al. (2001) also demonstrated that IL-10 levels in female infants and children gone through cardiopulmonary bypass were higher than boys [25].

Other findings of this study was the levels of interleukin -13 in male and female schizophrenics after three months of the treatment compared to the control groups was not significantly different and this has been observed similarly in case of IL-27. Typical antipsychotic drugs (type 1 drugs) inflammatory cytokines such as IL-1β, IL-6, TNF-α in patients with schizophrenia. Studies on animal models have shown that this group of drug significantly inhibits production of stimulated IL-1β and TNF-α in a dose-dependent manner [26]. In contrast, atypical antipsychotics drugs (type 2 drugs) have been associated with an increased inflammatory response, and many studies have reported that clozapine can increase inflammatory cytokines [27].

In the analysis of several inflammatory markers in treatment with antipsychotic drugs, a study showed that after 18 months the level of C-reactive protein (CRP) has been increased significantly. In this study the level of variety of different inflammatory markers according to used antipsychotic drugs has been changed (28 and 20). Interestingly some investigators have reported increased CD4+ CD45 + RO cells as major sources of IFN-γ production during treating with antipsychotic drugs [13, 29] as well as increased serum levels of IL-18, which plays a pivotal role in the type 1 immune response in schizophrenia [30]. Therefore reduction of serum level of interleukin-13 and increase increment of serum level of interleukin-27 following treatment of schizophrenia patients, are consistent with the hypothesis that cytokine levels shifts toward Th2 cytokines (such as IL-4, 10 and 13) before treatment but treating the patients with antipsychotic drugs, increase the response of type1 cytokines (such as IL-27, 12 and TNF-α) and decrease responses of type 2 T-cells. Thus, our results are consistent with this hypothesis.

CONCLUSION

The results of this study indicated that the level of IL-13 and IL-27 before and after treatment was different and the amount of IL-13 and IL-27 cytokines in combination with usage of antipsychotic medications may play a role in the pathophysiology of schizophrenia disease. Further investigations and studies are needed to be done to explain this relation better in the future.

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