Effect of Anger Patterns and Depression on Serum IgA and NK Cell Frequency

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ABSTRACT

Background: There are conflicting findings about relationship between depression and anger with immunological parameters. **Objective:** To investigate the relationship between anger patterns and immune system in depressed patients. **Methods:** Thirty-five patients with major depressive disorder were selected according to DSM-IV criteria. The Hamilton Depression Scale and Spielberger Anger questionnaires were used to determine severity of depression and "anger expression pattern", respectively. The control group without a previous history of mental illness was also selected. In the group of patients with moderate depression, serum IgA levels and NK cell percentage were measured. **Results:** Mean differences of all types of "anger expression pattern", including; "state-trait anger", "anger expression out", "anger expression in", "anger control out" and "anger control in", between study and control groups, were statistically significant (p<0.05). Difference in mean serum levels of IgA in either group was not significant (p=0.9), but the mean difference was significant in terms of NK-cell percentage in both groups (p=0.04). There was no significant relationship between IgA levels and percentage of NK-cell with all types of "anger expression pattern" in both groups. Only in the control group, IgA had significant correlation with Anger control out (p=0.04). **Conclusion:** Moderately depressed patients versus control group had higher Spielberger scores in all types of anger expression pattern except anger control-out and anger control-in. We found no evidence supporting the relationship between" anger expression pattern" and IgA levels and NK cell percentage; however, it seems that depression itself causes reduced number of NK cells and increased IgA levels.

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INTRODUCTION

Major depression is the most common mood disorder, which affects 20% of women and 10% of men in all periods of life. Anger turned inward is one of the oldest psychodynamic explanations for the occurrence of depression; which was presented for the first time by Freud, Karl Abraham and Sandor Rado. According to this theory the anger that occurs about the important persons, whom their images has been internalized priory, causes self-damage and the resultant depression (1). It seems that anger has a crucial role in depression (2). Patients with depression, show higher levels of anger expression than the normal population (3). It has been shown that depression severity is correlated with that of anger, but an external or internal anger expression patterns were similar (4). The effects of depression on neurochemical, electrophysiological, endocrine and immunological systems have been investigated, previously. Though some studies have shown that the levels of some immunoglobulins; such as IgG and IgA, were significantly higher in depressed patients compared to healthy individuals (5), other studies have shown that the titers of IgG, IgM, and IgA in depressed patients and healthy ones were similar (6). On the matter of anger and serum immunoglobulin levels, studies showed that anger expression was not related to the serum levels of IgG, IgE, IgM but serum IgA levels in patients with suppressed anger were higher than those who were able to express their anger (7). The association between depression and immunological changes were studied frequently but the reported results are inconsistent (8-10). Although a causal relationship between suppressed anger and depression have been confirmed, several studies have shown conflicting results in this regard. Reduction in anger-out has been reported in depressed patients compared to normal subjects. Snaith *et al.* have reported contrary findings, 37% of patients hospitalized with depression, had moderate to severe externalizing anger, which was significant comparing to the control group (11). Goldman *et al.* pointed out that these patients may express less anger due to fear of the consequences of expressing anger, and this fear exhibit high correlation with suppressed anger in depressed patients compared with non-depressed individuals (12) .

Also depressed patients who were in remission phase, in comparison to those who have never been depressed, show a higher level of suppressed anger and fear of the anger expression (13). Though a direct relationship between the severity of depression and suppressed anger has been displayed, other studies have found no significant difference in the level of hostility and severity of depression. There are also conflicting findings whether depression remission could be able to reduce the anger and hostility level (14). Depression and anger expression type separately affect the inflammatory indices, but few studies have been undertaken regarding the complementary effect of these two psychological factors on the inflammatory processes. Consequently, there is a need for further research in this area for two reasons: First, depression and anger are related to each other, so they may co-occur with each other. Second, depression and anger are associated with different physiological and psychological alterations which potentially causing considerable synergic effects of them (15).

People with the characteristics of anger and hostility, show depression and higher levels of inflammatory biomarkers over time(16).

Pettingale *et al.* in a study that was conducted on patients with breast cancer, showed that the serum levels of IgA were significantly higher in patients with suppressed

anger compared to the people who were capable of anger expression (7). Penedo *et al.* showed that higher levels of optimism were correlated with lower rates of depression and anger suppression, and higher percentage of NK cell (17). So, according to aforementioned conflicting reports in the present study we aimed to investigate the relationship between the patterns of anger expression and immune system activity in depressed patients.

MATERIALS AND METHODS

The study population contained patients older than 18 years with the desire to participate in the present study. After completing the written informed consent prior to the study, patients with no history of physical and mental disorders were included. After the diagnosis of major depressive disorder according to DSM-IV criteria by a psychiatrist the study population were selected. Patients completed Hamilton Depression Inventory and Spielberger (STAXI-2) questionnaires. Then, the serum IgA levels and peripheral blood NK cell percentage were investigated in 35 patients with moderate depression. Control group with the age of 18 years or older without any previous history of mental or physical illness was selected. The same questionnaires and tests were conducted on this group, too.

Depression Evaluation. The Hamilton Depression Rating Scale, 17-item version was used by the therapist to assess the severity of depression in patients. People with a score of 14-17 in the test group(with moderate depression), and willing to continue participating in the study were selected.

Anger Evaluation. Spielberger State-Trait Anger Expression Inventory-2 (STAXI-2) is a valid tool to study different aspects of anger expression pattern with adequate validity and reliability. Its reliability has been confirmed in numerous researches. This psychometric tool evaluates anger isolated from hostility and aggression, covering the anger experience and expression. The 57-part questionnaire consists of six scales, five subscales and an anger expression index which is a general measure of expression and control of anger based on formula of questionnaire.

The first part of the STAXI-2 is the state anger (SANG) scale. It consists of fifteen items measuring how intensely an individual experiences anger during either the testing period, or a time or situation specified by the test administrator. The state anger scale consists of three subscales: state anger/feeling angry (SANGF), state anger/feel like expressing anger verbally (SANGV), and state anger/feel like expressing anger physically (SANGP).

The second part of the STAXI-2 is the trait anger (TANG) scale. This scale consists of ten items measuring an individual's proneness to experience angry feelings. Two subscales are used to comprise the TANG scale: Trait anger/angry temperament (TANGT) and trait anger/angry reaction (TANGR).

The final part of this inventory measures the ways in which an individual expresses and controls anger. These scales consist of 32 items. The following scales make up this final part of 22 the STAXI-2: The anger expression-out (AX-O) scale, the anger expression-in (AX-I) scale, the anger control-out (AC-O) scale, the anger control-in (AC-I) scale, and the anger expression index (AX).

To reply to a questionnaire, participants should have at least had the ability to read. This questionnaire is a self-assessment test which was responded by depressed patients and the control group after the necessary explanations by a trained interviewer to individual participants. While answering each of the 57 sections of the questionnaire, participants rated their situation on a 4 point scale from almost never (1) to almost always (4) and thereby the intensity of feelings of anger in certain time and frequency of experiences, expression, suppression or control were measured.

Serum IgA Measurement. 1-2 ml of blood samples were collected from each of the patients with moderate depression (according to Hamilton questionnaire) and control participants. The samples were placed at 37°C for one hour and centrifuged at 3000 rpm 1008 ×g, then, for the measurement of IgA by nephelometry method, the separated serum was frozen at -20°C and the serum levels of IgA in both patients and controls measured at the end of sampling.

The Percent of Peripheral Blood NK cell. A total of 5-10 ml of blood were taken from each of the patients and the control individuals, and poured in heparinized tubes and immediately prepared for the CBC (complete blood count) measurement by the H1® analyser and determination of NK cell percentage via flowcytometry method in Shahid-Ghazi Hospital of Tabriz University of medical sciences. To determine the percentage of NK cells, anti-CD16 FITC and anti-CD56 PE (Coulter Immunotech), in a BD FACS calibourflowcytometer were used.

Statistical Methods. The data obtained from the study were analyzed using descriptive statistics (mean ± SD and frequency percent) and Spearman's correlation coefficient to evaluate correlation of variables. Also independent sample's *t-test* or U Mann Whitney test were used for comparison between groups. Normal data distribution was assessed using Kolmogorov-Smirnov test and Q-Q plot. All data were analyzed via SPSS-18 software. The p values less than 0.05 were considered statistically significant.

RESULTS

Pattern of Anger Expression. The primary objective of this study was to determine the pattern of anger expression in both groups of depressed and healthy individuals. The obtained results showed that there were significant mean differences in all types of state-trait anger, anger expression out, anger expression in, anger control out and anger control in, between two groups ($p<0.05$) (Table 1).

State anger includes feeling, verbal and physical parameters (S-Ang / F, V and P) and trait anger includes temperament and reaction parameters (T-Ang / T, R).

Serum IgA Levels and Depression. The mean serum levels of IgA in the case and control groups were 1.68 ± 0.67 and 1.66 ± 0.59 (g/L), respectively; for which the difference was not statistically significant ($p=0.9$).

Peripheral Blood NK cell Percentage and Depression. The mean percentage of NK cells in the case and control group were 15.97 ± 6.82% and 19.90 ± 8.75% respectively. This difference was statistically significant ($p=0.04$). The frequencies of NK cells in the case and control groups are shown in Table 2.

Serum IgA Levels and Anger Expression Pattern. Spearman correlation test results showed that in the case group there were no significant relation between the serum levels of IgA and all kinds of State -Trait anger and "anger expression out", "anger

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expression in", "anger control out" and "anger control in". In the control group, however, levels of IgA had significant correlation with anger control out (AC-O) (r_s = 0.36, N = 35, p=0.04,) but other pattern of anger showedno statistically significant correlation.

Table 1. Comparison of the anger expression pattern in people with moderate depression and control group.

Group	Depressed	Non-Depressed	P Value
State-anger/ Feeling (S-Ang / F)	13.80 ± 3.20	7.00 ± 3.31	<0.001
State-anger/ Verbal (S-Ang / V)	9.74 ± 4.13	6.57 ± 3.17	0.001
State-anger/ Physical (S-Ang / P)	7.62 ± 3.64	5.75 ± 2.65	0.018
Trait-anger/Temperament (T-Ang/T)	10.54 ± 3.92	6.45 ± 2.57	<0.001
Trait-anger/ Reaction (T-Ang/R)	14.97 ± 3.62	12.21 ± 4.32	0.006
Anger expression out (Ax-O)	18.48 ± 4.85	15.15 ± 4.74	0.006
Anger expression in (Ax-I)	20.25 ± 3.46	18.33 ± 5.57	0.04
Anger control out (Ac -O)	19.31 ± 5.79	23.72 ± 6.48	0.004
Anger control in (Ac-I)	18.77 ± 4.97	22.87 ± 6.97	0.006
Anger index	41.65 ± 13.48	34.87 ± 11.95	<0.001

Peripheral blood NK cell percentage and anger expression pattern. In both groups, the percentage of NK cell counts had no relationship with all kinds of State - Trait anger and anger expression out, anger expression in, anger control out and anger control in subscales.

Index of anger, serum IgA levels and peripheral blood NK cell percentage. The Spearman correlation coefficient test showed no statistically significant correlation between the indices of anger with the percentage of NK cell and IgA in the two groups (p>0.05).

Table 2. Frequency of NK cells in the Depressed and Non-depressed groups.

NK cell percentage	< 5%	5%-30%	> 30 %
Depressed group	5.7%	91.4%	2.9%
Non-depressed group	2.9%	88.2%	8.8%

DISCUSSION

The aim of the current study was to examine the relationship between anger expression pattern with serum levels of IgA and the percentages of NK cells in depressed patients in comparison with non-depressed people. There have been few studies to determine the relationship between the anger expression patterns with depression. One of our findings indicates that there is a significant correlation between the anger expression patterns and depression. Normally, healthy people are able to control the anger expression; while, depressed individuals manifest anger more intensely and faster with a delayed extinguishment, which is due to the autonomic instability caused by depression. The current findings are parallel to previous studies that have shown anger outbursts were more common in depressed patients than in healthy individuals (14).

Considering the role of anger and depression in formation of many diseases, like cardiovascular and inflammatory diseases and since the mortality rate in the mentioned diseases are notably high, previous studies have suggested that further studies are needed to confirm the possible relationship between anger and depression with inflammatory markers; in order to determine whether behavioral intervention programs for reducing violence and harmful behavior could be effective on the prognosis of the such disease (1,18,19).

In a study by Painuly *et al.*, depression was reported as the strongest predictor of anger outbursts; also it has been shown that the level of depression is correlated with the hostility and anger expression, and to some extent, linked to anger suppression (14). In the present study, in order to eliminate the possibility of error due to the impact of depression on the anger, the study population selectively contained patients with moderate degrees of depression.

The results of our study show that people with moderate depression in comparison with control group have significantly higher scores in variables of state-trait anger expression inventory including "feeling angry", "verbal and physical expressions of anger", "angry temperament"," angry reactions", "anger expression-out", "anger expression-in" and "anger index". Meanwhile, in "anger control-out" and" anger control-in" scales (which are positive aspects of anger management) they had a lower score than non-depressed group.

We also presumed that subtypes of anger expression may directly lead to changes in immune system, but interestingly we found that depression is associated with higher serum levels of IgA and lower NK cell percentage without any relationship with anger expression pattern. No evidence was found regarding the anger expression pattern and serum levels of IgA and NK cell percentage. It means that anger expression pattern does not directly affect the immune system but instead, it is the depression itself that leads to above mentioned changes in immune system although this requires further investigation.

In one study conducted by Acton *et al.* the serum IgA levels in patients with untreated depression in the recovery phase were evaluated and it was concluded that serum levels of IgA in these patients were lower than the control group, while no significant difference was observed about IgM and IgG (20). Another study about the relationship between depression and immune system has shown that the titer of immunoglobulins (IgA, IgM, IgG) are similar in both depressed and healthy cases (6), both of the above studies have results incompatible with ours.

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Ishihara *et al.* studied the relationship between immune response and psychological factors and they found that lower anger expression and higher anger control scores significantly increase the NK cell activity (21). Though, this study's results are not in accordance with ours, but we should mention that in our study, we measured NK cell percentage and not their activity.

Penedo *et al.* examined the relationships between optimism, depression and suppressed anger with NK cell cytotoxicity in men treated for prostate cancer, and they found that optimism was associated with higher frequencies of NK cells. Also optimism increased the ability to develop appropriate and consistent pattern of anger and was associated with less anger suppression and less depressive symptoms. It also found that depression is not associated with higher levels of NK cell counts (17), which is consistent with the results of the present study.

These results suggest that people with moderate depression have higher scores in all subscales of anger according to STAXI-2 except in "anger control-out" and "anger control-in" (which consist of the positive aspects of anger management), for them the rates is less than the control group. There is no relationship between anger expression pattern with IgA levels and NK cell percentage; but patients with moderate depression have reduced NK cell count and increased IgA levels in comparison with healthy individuals.

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