

Peripheral Blood T-Lymphocyte and T-Lymphocyte Subset Ratios before and after Treatment in Schizophrenia Patients not taking Antipsychotic Medication

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Abstract

Objective: Immune system abnormalities in schizophrenia have been previously studied. According to the present point of view, an infection or autoimmune process might be occurring in the form of cellular and/or humoral immune system abnormalities in schizophrenia. Furthermore, several effects of antipsychotic medication on the immunological profile of schizophrenic patients have been demonstrated. The present study aimed to compare the total T-lymphocytes level and the T-lymphocyte subset ratios in schizophrenia patients not treated with antipsychotics and healthy controls. The relationship between disease duration, symptom severity, and treatment response and T-lymphocyte profiles were investigated.

Methods: The study included 14 patients (11 antipsychotic naive, 3 antipsychotic free for at least 6 months) diagnosed with schizophrenia or schizophreniform disorder that were compared to age- and sex-matched healthy controls in terms of the total T-lymphocytes level and T-lymphocyte subset ratios using flow-cytometry. The relationship of the T-lymphocyte profiles, to disease duration and treatment response was investigated.

Results: The groups were not different in terms of total T-lymphocytes level and T-lymphocyte subset ratios; however, the antipsychotic naive patients and the group with disease duration < 2 years had lower rates of T8-lymphocytes. Total T-lymphocytes and the T8-lymphocyte ratio increased after treatment. Clinical improvement was correlated with total T-lymphocytes and the T4-lymphocyte subset ratio.

Conclusion: Cellular immune system abnormalities in schizophrenia may be intrinsic factors. Changes in the cellular immune system are associated with treatment response and might be candidates for biological markers

Key Words: Schizophrenia, Immunity (cellular), T-lymphocytes, Flow-cytometry

INTRODUCTION

The role of immune system changes in the pathogenesis of schizophrenia has been attracting attention since the beginning of the 20th century. The first studies in the field focused mainly on cellular immunity due to the technical limitations of the time. In 1903 Bruce and Peebles (1903) reported an increase in the peripheric T-lymphocyte ratio during the initial phases of the disorder. Dameshek (1930) reported a decrease in T-lymphocyte ratios and eosinophilia, in addition to T-lymphocyte increases in schizophrenic patients. In the 1930's Molholm reported a decrease in the delayed hypersensitivity response and Vaughan reported a decrease in the immune response to pertussis vaccine (De Lisi, 1982). These studies are important because they were conducted during

the era prior to the use of antipsychotics and they support the view that there is in vivo damage in to cellular immune system functions in schizophrenic patients.

T-lymphocyte subset ratios supply valuable information about the state of the cellular immune system. An increase in T8-lymphocytes suppresses cellular immunity, whereas a decrease could cause excessive functioning. The appropriate T4/T8-lymphocyte ratio is expected to be 2:1. Ratios below 1:1 indicate serious disorder of the immune system (Kouttab et al., 1989). It has also been suggested that changes in the T-lymphocyte ratio reflect changes in the metabolism of central nervous system cells and that they could be used as neural markers in the analysis of psychiatric disorders (Gladkevich et al., 2004). Many studies have been conducted on T-lym-

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phocyte subset ratios in schizophrenia and the following findings have been reported: a decrease in peripheral blood T-lymphocytes (Loseva and Khondkarian, 1978; Vartarian et al., 1978; Zarrabi and Zucker, 1979; Nyland and Ness, 1980; Koliassinka and Burbaeva, 1979), an increase in the T4-lymphocyte level (Henneberg and Riedl, 1980), and an increase in the T8-lymphocyte level (Cazullo et al., 1998).

In the studies mentioned above sheep red-blood cells were used for the purpose of detecting T-lymphocytes and decreases in T-lymphocytes were associated with thymic antibodies. Flow-cytometry is a modern, highly sensitive method used for the investigation of T-lymphocyte subsets within peripheral blood (Rudolf et al., 2004; Schiavon et al., 1996).

Using flow-cytometry, Mazzarello et al. (2004) found a lower T8-lymphocyte level in schizophrenia patients than in controls. Rudolf et al. (2004), on the other hand, did not find any differences in the T-lymphocyte subset ratios of schizophrenic patients and controls. Moreover, some studies observed an increase in total T-lymphocytes (De Lisi and Goodman, 1982). Pirildar et al. (2001) reported that there were no differences between the schizophrenic patients with damage and those without damage in terms of T4- and T8-lymphocyte levels.

The effect of antipsychotics on the immune system has been the subject of a number of studies. Atypical T-lymphocytes observed in schizophrenic patients have been associated with antipsychotic use (McAllister et al., 1989) and it has been shown that chlorpromazine disrupts T-lymphocyte functions in vitro (Zarrabi and Zucker, 1979). Bilici et al. (2003) observed a decrease in the T4/T8-lymphocyte ratio in the third month of olanzapine therapy. It has been demonstrated that atypical antipsychotics disrupt interleukin-6 and interleukin-1RA levels (Maes et al., 2000), and cause changes to interleukin receptor levels (Akiyama, 1999). It has been reported that clozapine and haloperidol change T-lymphocyte enzyme activity (Whatley et al., 1998).

In summary, cellular immune system dysfunction in schizophrenia could be due to the presence of an infection or autoimmune process. A thorough review by Rothermundt et al. (2001) emphasized that the results of studies in this field are contradictory. Against all the effort put into the field, it has not been possible to define a study area to focus on and it has not been possible to show whether the findings were the outcome or the cause. On the other hand, most of the studies were conducted with patients that were taking antipsychotics and

most employed technical methods of dubious sensitivity, which could provide an explanation for the contradictory results (De Lisi and Goodman, 1982; Rothermundt et al., 2001).

In the present study, the following hypotheses were tested using the flow-cytometry method, which is considered one of the most sensitive measurement methods (Sachivion et al., 1996): 1. In schizophrenia, when the antipsychotic effect is excluded, there are differences in the parameters of cellular immunity compared to healthy controls; 2. These parameters change following therapy and this change could be a marker of improvement in clinical symptoms.

METHODS

Sample

The study included 14 patients that presented to Ankara University Medical Faculty, Department of Psychiatry between 2000 and 2002 that were subsequently diagnosed with schizophrenia (n= 7) or schizophreniform disorder (n= 7) (based on DSM-IV criteria), and 14 healthy age- and sex-matched controls. The local ethics committee approved the study protocol. Inclusion criteria were as follows: aged between 15 and 65 years, not having used antipsychotic drugs in the past 6 months, diagnosed with schizophrenia or schizophreniform disorder, and agreeing to take part in the study. Because immune system disorders have also been observed in other psychiatric disorders (Sperner-Unterweger 2005), patients with an Axis I or II disorder other than schizophrenia were not included in the study. Due to the potential effects on the immune system, exclusion criteria included the presence of any medical, surgical, or neurological disease, alcohol/substance addiction or abuse, use of any drug within the past 6 months with a potential to influence the immune system, history of frequent infections, and history of allergy suggestive of an immune system disorder. The patients who met the inclusion criteria were invited to join the study and the patients who had consented to take part in the study were included. Of the 25 patients that were invited to join the study, 21 agreed to take part. Of those 21 patients, 14 were recruited because they did not meet the exclusion criteria. The study expenses were paid for by the researchers.

Methods

Sociodemographic data on the patients and controls were gathered using a sociodemographic information form, and data about the general medical conditions and

allergy profiles of the patients were gathered using a systems examination form; both forms were prepared by the researchers.

The severity of patient clinical symptoms was measured with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen and Olsen, 1982; Erkoç et al., 1991a) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen and Olsen, 1982; Erkoç et al., 1991b).

Total T-lymphocyte level, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratio were determined by FAC SORT (Becton DICKSON) flow-cytometry.

Procedure

Of the patients invited to join the study, those who agreed to take part were evaluated by each of 2 psychiatrists (SÇB, HDÖ) and the patients with a consensus diagnosis that met the inclusion criteria were included in the study. The patients included in the study and their first-degree relatives were informed by the first author (SÇB) and written informed consent was provided by the patients and their first-degree relatives. Then, physical and neurological examinations were performed, the sociodemographic data and systems examination forms were administered, symptom severity was evaluated with SANS and SAPS, and blood samples were taken into tubes containing EDTA. The blood samples were transported to Ankara University Medical Faculty, Department of Immunology and Rheumatology Laboratory, Department of Flow Cytometry within 30 min. The control group was also informed about the study and their written informed consents were obtained, after which all of the steps described above, apart from SANS and SAPS, were performed in the same order. At the end of this process the patients began taking antipsychotics prescribed by the doctors at the outpatient clinic. The patients were invited for a re-evaluation during the third week of treatment. In all, 10 patients came for re-evaluation 3 weeks after the initiation of treatment, whereas of the remaining 4 patients, 1 did not show up for the re-evaluation appointment and the other 3 refused to provide a second blood sample. It was seen that of the 10 patients who came for re-evaluation, 4 patients were taking olanzapine 5-10 mg/day, 2 were taking quetiapine 600-800 mg/day, 2 were taking pimozid 4 mg/day, 1 was taking risperidone 4 mg/day, and 1 patient was taking trifluoperazine 10 mg/day. SANS and SAPS were administered to the 10 re-evaluated patients by the first author (SÇB), who was blind to their treatment, in order

to determine the changes in symptom severity.

Flow-cytometry Evaluation

Step 1: T-lymphocyte Labeling.

For this step, CD3, CD4, and CD8 surface fluorescent antibodies for T-lymphocytes and T-lymphocyte subsets were used. The tubes were prepared according to these antibody panels, 10 µl of the monoclonal antibody and 100 µl of the blood sample were distributed into the tubes and incubated under room temperature for 20 min. Then, the erythrocytes were removed from the medium with approximately 2 ml of lytic solution and the cells were washed with PBS, resuspended, and fixed.

Step 2: Measuring Process.

Before measurement of the tubes labeled with the appropriate antibodies, flow-cytometry (FAC SORT, Becton DICKSON) was checked, and prepared for measurement every day. Measurement was carried out with FAC SORT, which has a 450-mm argon laser source. The T-lymphocytes were separated and their quantity determined according to the amount and magnitude of fluorescence they were carrying, using the simul set program of the device, the side scatter (SSC) and forward scatter diagrams, and the optical system. The tube with the isotopic controls, chosen according to the monoclonal antibodies that were being used, was also included in the evaluations. Thus, any possible non-specific monoclonal antibody ligation was detected. For the measurement process, the percentage of positive cells, with the boundaries determined according to the isotopic control tube, was used as a measure. After that, the printouts were obtained and the data were recorded.

Analysis

Sociodemographic, clinical, and laboratory data were statistically analyzed with the SPSS v.11.0 package program. The Mann-Whitney U test was used for inter group comparison of total T-lymphocyte levels, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratios, Wilcoxon signed rank test was used for inter group comparison of the pre- and post-treatment variables, and Spearman's correlation test was used to determine the relationship between clinical improvement and change in T-lymphocyte level. Patients without any prior antipsychotic medication use were compared with the control group using the Mann-Whitney U test.

Table I. Comparison of T-lymphocyte levels, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratio between the patient and control groups (Mann-Whitney U test).

	Patient (n = 14) X ± SD	Control (n = 14) X ± SD	U	P
T-lymphocyte (%)	70.3 ± 5.6	72.8 ± 6.2	73	0.26
T4-lymphocyte (%)	43 ± 7.2	41.8 ± 6.8	89.5	0.70
T8-lymphocyte (%)	26.7 ± 5.9	30.9 ± 6.8	57.5	0.06
Ratio (T4/T8)	1.6 ± 0.4	1.4 ± 0.3	65	0.13

SD: standard deviation; X: mean.

RESULTS

Mean age of the patients was 27.7 ± 10.7 years (range: 15-49 years). Average disease duration was 27 months (range: 2-6 months in patients with a diagnosis of schizophreniform disorder; 1-20 years in patients with a diagnosis of schizophrenia) and 8 of the cases were female (57.14%). The age and gender distribution of the controls were similar to those of the patients. In all, 78.3% of the patients (n = 11) did not have a history of antipsychotic medication use. Although 3 patients previously used antipsychotics (total duration of use: 2 months, 4 years, and 20 years), 1 patient was drug-free for the past 12 months and the other 2 were drug-free for the past 6 months.

When the patients were compared to the controls in terms of the T-lymphocyte level, T-lymphocyte subset ratios, T4- and T8-lymphocyte levels, and T4/T8-lymphocyte ratio, there were no significant differences between the groups (Table I). Among the participants, 4 in the patient group and 1 in the control group had T-lymphocyte values that were at the lower end of the normal range (15%-20% of total leukocyte levels).

Because life-long duration of antipsychotic use in 2 of the 3 patients who had stopped antipsychotic use were long (4 years and 20 years) and because the effect of long-term antipsychotic use on the immune system has been previously demonstrated (Muller et al., 1991; Maes et al., 2000), the patients without any prior use of antipsychotics (n= 11) were compared to the control group separately. As a result of this comparison, no significant differences in T-lymphocyte level, T-lymphocyte subset ratios, T4-lymphocyte level, or T4/T8 lymphocyte ratio were found; however, the T8-lymphocyte level was significantly lower in the drug naive patient group than in the controls (P = 0.02) (Table II).

In the group with disease duration of less than 2 years (n= 7) the T8-lymphocyte level was significantly lower than in the control group (P = 0.02, u = 19.5); there were no significant differences in any of the variables between the patient group with disease duration of more than 2 years (n = 7) and the controls.

When the pre- and post-treatment immunological and clinical variables were compared, a significant decrease in the post-treatment SAPS and SANS scores (P

Table II. Comparison of T-lymphocyte levels, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratio between drug-naive patients and the control group (Mann-Whitney U test).

	Patient (n = 11) X ± SD	Control (n = 14) X ± SD	U	P
T-lymphocyte (%)	69.4 ± 5.9	72.8 ± 6.2	50	0.14
T4-lymphocyte (%)	41.7 ± 7.1	41.8 ± 6.8	74	0.89
T8-lymphocyte (%)	25.8 ± 5.1	30.9 ± 6.8	36	0.02*
Ratio (T4/T8)	1.6 ± 0.4	1.4 ± 0.3	48	0.12

SD: standard deviation; X: mean; *statistically significant.

Table III. Comparison of pre- and post-treatment clinical characteristics, T-lymphocyte levels, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratio of the patient group (Wilcoxon signed rank test).

	Pre-treatment (n = 10) X ± SD	Post-treatment (= 10) X ± SD	Z	P
T-lymphocyte (%)	70.6 ± 6.4	75.9 ± 3.5	-2.14	0.03*
T4-lymphocyte (%)	42.7 ± 8.5	43.8 ± 7.4	-0.11	0.90
T8-lymphocyte (%)	26.5 ± 5.6	30.7 ± 6.1	-1.96	0.05*
Ratio (T4/T8)	1.6 ± 0.5	1.5 ± 0.5	-1.27	0.20
SAPS	39 ± 18.3	24.1 ± 15.6	-2.80	0.005*
SANS	61.8 ± 16.5	53.6 ± 18.8	-2.44	0.01*

SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; *statistically significant.

= 0.005, $z = -2.80$; $P = 0.01$, $z = -2.44$, respectively) was observed, and there was a significant increase in total T-lymphocyte and T8-lymphocyte levels ($P = 0.03$, $z = -2.14$; $P = 0.05$, $z = 1.96$, respectively) (Table III).

The relationship between the changes in post-treatment SAPS and SANS total scores, and the changes in T-lymphocyte counts, T-lymphocyte subset ratios, and T4/T8-lymphocyte ratios were tested with correlation analysis (Table IV). An inverse relationship between the change in SAPS scores and the change in total T-lymphocyte counts ($r = -0.63$, $P = 0.05$), and a positive relationship between the change in SANS scores and the change in T4-lymphocyte subset ratio ($r = 0.74$, $P = 0.01$) were observed.

DISCUSSION

The present study was an experimental, controlled clinical study in which certain markers of the cellular immune system in schizophrenia patients without antipsychotic medication use were compared to healthy age- and gender-matched controls, and the relationships between these markers, and disease duration and treatment response were investigated.

The observation of a lack of a significant difference in total T-lymphocyte levels and T-lymphocyte subset ratios between schizophrenia patients without antipsychotic medication use and healthy controls contradicts studies that reported an increase (Henneberg et al. 1980, Cazullo et al. 1998) or a decrease in the total T-lymphocyte level (Loseva and Khondkarian, 1978; Vartarian et al., 1978; Zarrabi and Zucker, 1979; Nyland and Ness, 1980; Koliassinka and Burbaeva, 1979). The changes in

T-lymphocyte levels reported in previous studies could have been due to antipsychotic use.

The results of the studies conducted with patients that had stopped antipsychotic treatment have been contradictory. Some studies reported no differences in the T-lymphocyte level (Schleifer and Keller, 1985; Oral and Ceylan, 1991; Achirion et al., 1994) and others that reported a significant decrease in total T-lymphocyte level (Coffey et al., 1983) and T8-lymphocyte level (Villemeine et al., 1999).

Among these studies, the length of time without antipsychotic use was at least 6 months only in the study by Coffey, whereas this period varied between 2 weeks and 3 months in all the other studies. In the present study we observed a significant decrease in the T8-lymphocyte level only when drug naive patients were compared to the controls. The fact that this effect was absent when the patients that stopped antipsychotic treatment for at least 6 months were added to this group suggests that antipsychotic medication use could have had long-term effects on the cellular immune system or that the observed decrease could also have been caused by the small sample size.

There are 2 studies about T-lymphocyte and T-lymphocyte subset ratios conducted in drug naive patients. Unterweger et al. (1999) observed an increase in the T4-lymphocyte level of schizophrenia patients and did not find any significant differences in terms of the other variables. In contrast, Theodoropoulou et al. (2001) did not find any significant differences between groups in any of the variables. With the addition of the present study, it can be seen that contradictory results remain even af-

Table IV. The relationship between change in SANS and SAPS scores, and T-lymphocyte levels, T-lymphocyte subset ratios, and T4/T8 lymphocyte ratio (Spearman's correlation analysis).

	Change in T-lymphocyte level	Change in T4-lymphocyte level	Change in T8-lymphocyte level	Change in T4/T8-lymphocyte ratio
Change in SAPS scores	r = -0.63 P = 0.05*	r = 0.024 P = 0.95	r = -0.16 P = 0.65	r = 0.30 P = 0.39
Change in SANS scores	r = -0.51 P = 0.13	r = 0.74 P = 0.01*	r = 0.48 P = 0.16	r = -0.05 p=0.88

SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; r: Spearman's correlation constant; *statistically significant.

ter the exclusion of the antipsychotic effect. A possible variable with a potential to cause these contradictions could have been disease duration. Rothermundt et al. (2001) proposed that the immune system parameters in schizophrenia should be studied with patients experiencing their first psychotic attack or with those patient groups with short disease duration. In the present study the relationship of total T-lymphocyte level and T-lymphocyte subset ratios to disease duration was also studied. In our sample the group with disease duration of less than 2 years consisted entirely of schizophrenia patients experiencing their first psychotic attack. In this group it was observed that only the T8-lymphocyte level was significantly lower than in the control group, and that there were no significant differences between the patient group with disease duration of more than 2 years and the controls. In schizophrenia patients experiencing their first psychotic attack, low T8-lymphocyte levels could be due to an intrinsic effect pertaining to the immune system.

When pre- and post-treatment total T-lymphocyte level and T-lymphocyte subset ratios were compared, it was seen that during the third week of treatment there was an increase in the total T-lymphocyte level. This change could have been related to antipsychotic treatment. The effect of antipsychotic medications on the immune system has been demonstrated in previous studies (Maes et al., 2000; Dettling et al., 2001). Furthermore, it has been reported that the use of immune-modulators in schizophrenia does not improve lymphocyte abnormalities, whereas haloperidol has a beneficial effect (Oral and Ceylan, 1991). This post-treatment change that we detected could be indicative of an immune system abnormality. It has been shown that in schizophrenia the synthesis of D2 receptors on peripheral blood lymphocytes can be increased, in-

dependent of antipsychotic medication (Zvara et al., 2005).

It has been suggested that T-lymphocyte level and T-lymphocyte subset ratios could be laboratory markers for treatment response in schizophrenia (Muller et al., 1993). Zhang et al. (2006) have shown that post-treatment clinical improvement in schizophrenia is associated with an increase in the T4-lymphocyte level. In our study the association between improvement in negative symptoms and increase in T4-lymphocyte level were in line with these findings. Muller et al. (2000) suggested that there are schizophrenic clinical subgroups characterized by differences in the immune system. In the present study the correlations detected between the change in SAPS scores and the change in total T-lymphocyte level, and between the change in SANS scores and the change in T4-lymphocyte level suggest that in the future these parameters can be used to predict treatment outcome or for follow-up, and that there is a need for studies focusing on new and specific variables.

The fact that our study was conducted with patients not taking antipsychotic medication has allowed us to exclude immune system changes caused by these medications (Zarrabi and Zucker 1979), which is a strength of the study; however, it also resulted in a small sample size. Excluding such factors as allergy and drug use, and controlling such factors as age and gender between the groups excludes immune system changes that could have been caused by those factors and facilitated the interpretation of the results. Another strength of our study is the use of flow-cytometry, which is technically the most sensitive method for measuring T-lymphocytes and T-lymphocyte subsets (Rudolf et al., 2004; Schiavon et al., 1996).

The most important limitation of the present study

is the small sample size, which could have been the cause of the lack of difference between the patients and the controls in terms of the parameters associated with the immune system. Another important limitation is the variability in the medication and drug dosages of the patients who were evaluated pre- and post-treatment. On the other hand, changes in the immune system cannot be narrowed down to total T-lymphocyte level and T-lymphocyte subset ratios, and it is not possible to reach a conclusion about the presence or the absence of an immune system abnormality in schizophrenia based

on these findings. In future studies the threshold for exclusion criteria should be as high as it was in this study; however, a small sample size also needs to be avoided by, for example, planning a multi-centered study. Preferably, studies that include samples consisting of drug naive patients with short disease duration should be conducted by standardizing drug treatment and examining other immune system parameters (Zarrabi and Zucker 1979) if the aim is to obtain data about the general condition of the immune system and to clarify the contradictions in the literature.

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