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Increased Th_1 and Th_2 Immune Reactivity with Relative Th_2 Dominance in Patients with Acute Exacerbation of Schizophrenia

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Aim To determine concentration of T helper (Th_1) cytokines and Th_2 cytokines in patients with acute exacerbation of schizophrenia and compare the cytokine profiles between subtypes of schizophrenia.

Method One hundred inpatients with acute exacerbation of schizophrenia and 34 matched healthy subjects from the same population without psychiatric history were included in the study. According to predominant symptom complexes the patients were divided into three subgroups: hallucinations and delusions (n = 36); disorganized behavior (n = 33), and primary, enduring negative or deficit symptoms (n = 31). *In vitro* IFN-γ and IL-4 secretion by peripheral blood mononuclear cells after stimulation with ionomycin and phorbol 12 myristate 13 acetate was measured by enzyme-linked immunosorbent assay (ELISA) tests.

Results Significant increase in *in vitro* secretion of IFN-γ (21,505 vs 14,915 pg/mL; $P = 0.037$; independent samples *t* test) and IL-4 (32 vs 15 pg/mL; $P < 0.001$) with a shift to the Th_2 (1,022 vs 1,432 pg/mL; $P = 0.005$) immune response was observed in patients with schizophrenia compared to healthy controls. We found pronounced effects of age and age at first hospitalisation on the Th_1/Th_2 immune balance ($R^2 = 0.068$; $P = 0.037$). There were no significant differences in *in vitro* secretion of IFN-γ ($P = 0.734$; one-way analysis of variance), IL-4 ($P = 0.485$) and IFN-γ/IL-4 ratio ($P = 0.293$) between the subgroups of patients with schizophrenia.

Conclusion Our findings indicate a simultaneous increase of *in vitro* reactivity of both Th_1 and Th_2 arm of cell mediated immunity, with a relative predominance of Th_2 immunity in patients with acute exacerbation of schizophrenia.

Alterations of cytokine levels represent the most consistent finding in the studies on the involvement of the immune system in the etiology of schizophrenia (1,2). According to their cytokine profile, T helper (Th) cells are classified into at least two functionally antagonistic subsets, Th_1 and Th_2. Human Th_1 lymphocytes secrete more interferon (IFN)-γ and stimulate type 1 immunity, which is characterized by intense phagocytic activity. Conversely, Th_2 cells secrete more interleukin (IL)-4 and stimulate type 2 immunity, which is characterized by high antibody titers (3). Cytokines and soluble cytokine receptors have been measured under various *in vitro* conditions (4), as well as *in vivo* in various body fluids (5,6) of patients with schizophrenia. A dysbalance between the Th_1 and Th_2 arms of cell mediated immunity, with over-activation of the Th_2 response and a decreased Th_1 response (7-9) and an activation of the monocytic arms of cell mediated immunity, were reported (2,6). Immune differences between the subtypes of patients with schizophrenia were also described (9-12).

The reports on the *in vitro* secretion pattern of Th_1 cytokine IFN-γ in schizophrenia are

controversial (4). Taken together, altered *in vitro* secretion of IFN-γ by peripheral blood cells seems to be a trend in schizophrenia. Eight studies reported decreased *in vitro* secretion of IFN-γ (1,10,11,13-16), one reported increased *in vitro* secretion (17), and two reported no difference between patients and controls (9,18). In the acute schizophrenia both decreased (10,14-16) and increased (17) *in vitro* IFN-γ secretion were reported. Differential production of IFN-γ in patients with schizophrenia, depending on the psychopathology was reported (10). In schizophrenia, few studies measured *in vitro* IL-4 secretion. *In vitro* production of IL-4 in a whole-blood assay after stimulation with PHA was not significantly increased in the group of patients with schizophrenia (10,17).

We compared the *in vitro* secretion of IFN-γ, IL-4 and their ratio by peripheral blood mononuclear cells (PBMC) after stimulation with ionomycin (IONO) and phorbol 12-myristate 13-acetate (PMA) between patients with acute exacerbation of schizophrenia and healthy volunteers. Next, we compared the immunological parameters between subtypes of schizophrenia, classified according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM IV) classification (21). We assessed the influence of several confounding factors on the *in vitro* cytokine secretion in patients with schizophrenia. The IFN-γ and IL-4 secretion were assessed in our own model of *in vitro* cytokine production. The procedure was previously designed for monitoring the subtle changes in cytokine responses occurring *in vivo* due to the pathological processes and/or immunointerventions (19,20).

Patients and Methods

Patients

One hundred patients (49 women and 51 men) who met the DSM-IV criteria for schizophrenia (21) and 34 matched healthy volunteers from the same population, without psychiatric history (19 women and 15 men) were included in the study (Table1). There were no significant differences in age ($t=0.132$, $P=0.059$) between the patients with schizophrenia (mean ± standard deviation, 38 ± 12 years) and control group (32 ± 11 years). Patients were hospitalized for an acute exacerbation of psychosis. According to predominant symptom complexes the patients were divided into three subtypes: group 1 – hallucinations and delusions: (n = 36; 22 women and 14 men); group 2 – disorganized behavior, including positive formal thought disorder, bizarre behavior, and inappropriate affect (n = 33; 11 women and 22 men); and group 3 – primary, presenting negative or deficit symptoms (n = 31; 16 women and 15 men). The patients in different subgroups did not

Table 1. Demographic and clinical characteristics of patients with schizophrenia*

Parameter*	Schizophrenia subgroups			P†
	paranoid (n=36)	disorganized (n=33)	residual (n=31)	
Gender (men/women)	14/22	22/11	15/16	0.068
Age (years, mean±SD)	34±10.7	39±13.4	44±10.9	0.054
Age at first hospitalization (years, mean±SD)	27±9.7	25±8.7	33±11.5	0.069
Antipsychotic treatment:				
first generation	7	16	17	0.169
second generation	22	11	8	0.031
clozapine	7	6	6	0.949
chlorpromazine equivalents (mg, mean±SD)	728±610	884±662	682±437	0.345
Additional therapy:				
antidepressants	1/36	4/33	4/31	0.368
anxiolytics and hypnotics	24/36	23/33	19/31	0.727
anticholinergic	13/36	19/33	18/31	0.538
Positive and negative syndrome scale (mean±SD):				
positive symptoms	24.9±5.2	23.4±6	18.6±7.3	<0.001
negative symptoms	21.3±4.4	21.6±7.5	23.1±9.7	0.596
general psychopathology	44±7.8	41.8±10.7	43.7±8.9	0.573
total scores	90±14.7	86±21.3	88.3±18.3	0.739
PANSS subsyndrome (mean±SD):				
positive symptoms	15.3±3.6	13.2±4.2	12.1±3.8	0.005
negative symptoms	17.6±4.1	17.2±6.5	20.7±6.8	0.042
cognitive symptoms	14.7±2.6	15.9±4.2	14.9±2.9	0.313
excitement symptoms	11.5±2.9	11±3.6	9.5±3.1	0.037
depressive symptoms	14.3±3.5	11.1±3.5	13.9±4.1	<0.001
Smoking (no/yes)	15/21	6/27	12/19	0.460

*Abbreviations: PANSS – Positive and Negative Syndrome Scale (23); SD – standard deviation.
†Analysis of variance (ANOVA).

differ significantly with respect to age ($P=0.069$) and gender ($P=0.068$) (Table 1).

All patients included in the study had been receiving antipsychotic medications for at least three weeks before entering the study (Table 1). The daily dose of antipsychotics was converted to chlorpromazine equivalents using standard conversion tables (22). Antidepressants, benzodiazepines, and anticholinergic drug biperidone were used according to indications. The severity of the psychopathology of the patients was measured by the Positive and Negative Syndrome Scale (PANSS) by the same rater (23). All patients gave a written consent to participate in the study. The study was approved by the Ethics' Committee of the Slovenian Ministry of Health.

Exclusion criteria for patients and healthy controls were acute or chronic infection or inflammatory responses as well as other chronic medical illnesses known to be accompanied by changes in immune functions, neurological disorder, and alcohol and/or drug abuse.

In Vitro Cytokine Production and Measurement

Venous blood was collected from patients and healthy controls in EDTA-coated venipunction tubes. PBMC were isolated by centrifugation on Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient. PBMC were suspended in RPMI 1640 (Sigma, Munich, Germany) supplemented with antibiotics and 5% fetal calf serum (Sigma, St. Louis, MO, USA) and plated at 6.66×10^5/mL in 24-well cell culture plates (T grade, NUNC, Roskilde, Denmark). Polyclonal activators PMA (3.33 ng/mL) and IONO (500 nM) were added. PBMC cultures were incubated 40 hours in a CO_2 incubator, at 37 °C in humidified atmosphere with 5% CO_2. After the incubation, the concentration of IFN-γ and IL-4 in the culture supernatants was measured using ELISA kits (Pierce Endogen, Woburn, MA, USA). The ratios of Th_1 against Th_2 cytokines (IFN-γ vs IL-4), as introduced by Kallmann et al (24) and later modified by us (19,20), were calculated.

Statistical Analysis

In vitro cytokine secretion values were log-transformed in order to achieve a normal distribution of data. The differences in means between patients and healthy controls were tested with independent samples *t* test. The proportions between groups were compared with χ^2 test. One-way analysis of variance (ANOVA) was used to compare the differences in the means between different subgroups of patients with schizophrenia. Scheffe test was used for *post hoc* multiple comparisons between the groups. Linear multiple regression analysis was used to investigate the influence of confounding factors on the *in vitro* cytokine secretion. *P*-values less than 0.05 were considered statistically significant. Windows Statistical Package for Social Sciences, version 10.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

In Vitro Cytokine Secretion in Patients with Schizophrenia

In vitro secretion of IFN-γ ($t=2.108$, $P=0.037$) and IL-4 ($t=4.519$, $P<0.001$) by PBMC after stimulation with IONO and PMA was significantly increased in patients with schizophrenia compared to healthy controls (Table 2). IFN-γ/IL-4 ratio showed a statistically significant shift towards the Th_2 immune response in patients with schizophrenia compared with healthy controls ($t=2.924$, $P=0.005$) (Table 2).

Predictors of the Immune Parameters

Linear multiple regression analysis was used to investigate the influence of confounding factors on the *in vitro* cytokine secretion (Fig. 1). The age at first hospitalization (Beta=-0.262, standard error SE=0.004) and the age of the patients (Beta=-0.043, SE=0.004) significantly influ-

Table 2. *In vitro* secretion of IFN-γ and IL-4 by PBMC and their ratio in patients with acute exacerbation of schizophrenia and healthy controls*

	Finding (pg/mL, mean±standard deviation) in the group			
Variable	schizophrenia	control	*t*	*P*†
IFN-γ	21505±14068	14915±5128	2.108	0.037
IL-4	32±26	15±10	4.519	<0.001
IFN-γ/IL-4	1022±783	1432±1069	2.924	0.005

*Abbreviations: PBMC – peripheral blood mononuclear cells; IFN-γ – interferon-γ; IL-4 – interleukin-4.
†Independent samples *t* test.

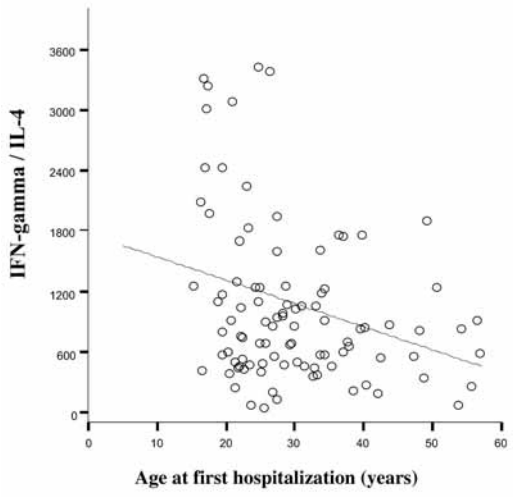

Figure 1. Correlation between the age at first hospitalization and IFN-γ/IL-4 ratio was significant; Pearson correlation: r=-0.260, *P*=0.01.

enced the IFN-γ/IL-4 ratio (R = 0.260, R^2 = 0.068, F = 3.417, *P* = 0.037). Our analysis did not reveal any significant influence of gender, severity of the psychopathology, measured by the PANSS, duration of the disease, number of hospitalizations, and antipsychotic dosage on *in vitro* cytokine secretion.

Effects of Schizophrenia Subtypes and Antipsychotic Medication on in Vitro Secretion of the Cytokines

No significant difference of the *in vitro* secretion of IFN-γ (F = 0.310, *P* = 0.734), IL-4 (F = 0.729, *P* = 0.485), and IFN-γ/IL-4 ratio (F = 1.243, *P* = 0.293) was found between the subgroups of patients with schizophrenia, classified according to DSM IV.

In vitro cytokine secretion was compared according to the type of antipsychotic medication. *In vitro* secretion of IFN-γ was significantly increased in the subgroup of patients treated with typical antipsychotics (26,341 ± 17,533 pg/mL) compared to other subgroups treated with either atypical antipsychotic (18,446 ± 10,920 pg/mL) or clozapine (17,925 ± 8,404 pg/mL) (F = 3.713, *P* = 0.028). *In vitro* secretion of IL-4 (F = 1.920, *P* = 0.152) and IFN-γ/IL-4 ratio (F = 2.065, *P* = 0.132) did not differ according to the type of antipsychotic medication. Our analysis did not reveal any significant effect of antipsychotic dosage (see Table 1) on *in vitro* cytokine secretion (data not shown).

Discussion

The most important finding of this study is significantly increased *in vitro* secretion of IFN-γ and IL-4 after stimulation with PMA and IONO in patients with acute exacerbation of schizophrenia in comparison with healthy controls. The results indicate increased *in vitro* reactivity of both Th_1 and Th_2 arm of the cell mediated immunity, with a relative shift towards Th_2 immune reactivity in patients with acute exacerbation of schizophrenia in comparison with healthy controls. Increased pro-inflammatory Th_1 and anti-inflammatory Th_2 cytokine activity in the acute exacerbation of schizophrenia is in accordance with previous findings that schizophrenia is accompanied by the activation of the pro-inflammatory and anti-inflammatory aspects of cell mediated immunity (2,6). Contradictory results have been published on the Th_1 immune activity in schizophrenia. Increased *in vitro* secretion of IFN-γ by PBMC after stimulation with a mitogen in drug-naive or drug-free patients with schizophrenia (17) and significantly higher plasma IFN-γ detection rate in untreated patients with acute exacerbation of schizophrenia (25) have been reported. Others, however, reported significantly decreased *in vitro* IFN-γ secretion in patients with acute schizophrenia (10,14-16). The inconsistency of the results of the *in vitro* studies could be explained by the heterogeneity of the patients included in the studies, the potential influence of drug treatment on cytokine production, differences in experimental design, and other possible confounding factors (4). The *in vitro* studies used different cellular source preparations, different durations of *in vitro* culture and stimulatory procedures and ELISA kits from different suppliers. Other indicators of increased Th_1 cytokine activity in schizophrenia are increased serum concentrations of the IL-2R and increased concentrations of IL-2 in serum or cerebrospinal fluid (12,26). The increase of Th_2 immune activity in our study is in accordance with previous findings of elevated serum levels of IL-6 (12,27) and cerebrospinal fluid levels of IL-4 (28).

The *in vitro* reactivity of Th_1 and Th_2 arm of cell mediated immunity did not differ significantly between the subtypes of patients with schizophrenia. This is in accordance with previous reports, which have shown the Th_2 shift of immune response in patients with predominantly negative symptoms (5). It should be noted, how-

ever, that the variances within the subgroups for these values were high. These findings suggest that there could be a possible immunological heterogeneity of patients among schizophrenia subtypes classified according to the DSM-IV criteria.

The significance of immune alterations in schizophrenia is not clear at the moment. The immune system could be related to the pathophysiology or etiology of schizophrenia. The combination immune abnormalities could also be a "by product" of the complex physiological changes in schizophrenia. The combination of immune activation and genetic (29-31) or other modulating factors may be an important underlying pathogenetic mechanism of schizophrenia. Different factors which may modulate the immune system and contribute to the etiology of schizophrenia such as infection (9,30-32), neuroendocrine (33), psychological (34), and physical (35) stress have been studied. Infectious agents may play a role in the etiopathogenesis of some cases of schizophrenia and activate the cytokine cascade (9,30-32). Th_1 and the Th_2 cytokines were shown to be elevated in the central nervous system during infection. One of the proposed hypothesis for the activation of both Th_1 and Th_2 immune response with predominant Th_2 immunity in schizophrenia is, that the Th_1 immune responses, due to unknown reasons is never able to completely clear the infection. In that case, a continual stimulation of T cells can induce chronic Th_2 response, leading to host tissue damage (9).

On the other hand, the immune changes in schizophrenia could be the result of a non-specific stress response and stress-related overactivation of the hypothalamic-pituitary-adrenal axis (33), as well as sympathetic nervous system axis (34) in the acute phase of schizophrenia. Repeated or sustained psychological stress due to psychosis can have profound emotional intensity. The patients with schizophrenia are exposed to intense psychological stress as early as in the prodromal phase of the illness (36). The prodrome appears to combine generic stress responses, such as dysphoric mood states, sleep disturbances, and social withdrawal, with the early features of the psychotic episode such as perceptual and information processing defects. In addition to the direct influences of psychological states on physiological function, distressed individuals are more likely to have health habits that put them at greater risk, including a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise.

Another important finding of this study was a pronounced age effect at first hospitalization on the Th_1/Th_2 immune balance in the group of patients with schizophrenia. This finding suggests that there is an immune difference between patients with early-onset and patients with late-onset psychosis. This supports the neurodevelopmental approach to the classification of schizophrenia, with an early-onset category, where a number of developmental risk factors have been established, and adult-onset schizophrenia (29). We also found a significant age effect of the patients on the Th_1/Th_2 immune balance. In accordance with previous studies (37,38) these findings indicate increased Th_2 immunity with aging.

There are several limitations to our study. All patients received antipychotics due to the acute exacerbation of schizophrenia for at least three weeks before the study. Drug naive, first time hospitalized patients with first episode psychosis did not meet the inclusion criteria for schizophrenia. Drug free patients with acute exacerbation of schizophrenia were not included in the study due to ethical reasons. We found significantly increased *in vitro* secretion of IFN-γ in the subgroup of patients who were receiving typical antipsychotics in comparison to the patients who were receiving atypical antipsychotics or clozapine. Typical and atypical antipsychotic drugs have been shown to modulate the production of cytokines, however, the data are limited and often controversial (2,12,39). The reasons for the differences are uncertain, and we cannot conclude whether the differences in cytokine secretion are related to the choice of antipsychotic drug or duration of the treatment. Secondly, due to the cross sectional design of our study, we included only the patients during the acute exacerbation of schizophrenia. It would have been interesting to perform a longitudinal study of the same patients in different phases of the illness and during the remission phase.

In conclusion, our findings indicate a simultaneous increase of *in vitro* reactivity of both Th_1 and Th_2 arm of cell mediated immunity with a relative predominance of Th_2 immunity in a large sample of patients with acute exacerbation of schizophrenia. The reasons for the immune dysbalance and its role in the etiology of schizo-

phrenia are unclear at the moment. Further investigations are planned to focus on patients in early, prodromal phase of schizophrenia, the interactions between the neuroendocrine and immune system, and the role of the regulatory T cells.

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