

Association of psychosis, affective disorders and diseases affecting the immune system

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Abstract

Purpose of the article

There are indications of altered immune activity in depressed and psychotic patients compared to healthy controls in several studies. To explore the clinical importance of this phenomenon we examined the relation between different disorders affecting the immune system and psychoses and depression respectively.

Materials and methods

A total of 276 patients consecutively admitted to a psychiatric acute ward were included in the study. Of these 41 patients fulfilled the criteria for ICD-10 F20-F29 (psychotic) diagnosis and 157 patients a F30-F39 (affective) diagnosis. Information on diseases affecting the immune system in patients themselves and family members of the patients were obtained by a self-report questionnaire.

Results

Comparing the two groups showed a significant correlation between the F20-29 group and eczema ($r=-0.116$, $p=0.037$). Comparing what patients reported for family members showed a significantly higher frequency of epilepsy ($p = 0.033$) in the F20-29 group. Summarizing all immunological diseases for family members showed a significantly higher frequency in the F30-39 group compared to the F20-29 group ($\chi^2 = 4, 82$, $df = 1$, $p = 0.028$)

Conclusions

There may be differences between the F20-29 and F30-39 groups and their family members regarding risk for diseases affecting the immune system. This is in line with different activity of the immune system measured in blood for the disorders and may add information regarding etiology and pathology of these psychiatric diseases. Further studies including a greater number of subjects, as well as confirmation of the immunological diseases through blood samples is needed.

Keywords: Depression; Psychoses; Schizophrenia; Immune; Autoimmune; Allergy; Eczema.

Background and aim

There are several reports on altered immune activity measured as biological markers in blood or cerebrospinal fluid (CSF) in patients with psychotic and affective disorders compared to healthy controls [1]. Also genetic [2] and pharmacological data indicate a potential connection between immune system and psychiatry [3]. Finally, several mechanisms by which the immune system can affect the nerve system are described [4]. This has led to curiosity and optimism regarding a role for the immune system in aetiology, pathology and potentially treatment of psychiatric disorders. Two important remaining questions in this expanding field of research are whether the immune deviations found are specific to certain psychiatric diagnoses or a more general phenomenon in psychiatric suffering, and whether the immune findings are of clinical importance [5]. Studying comorbidity between different immune disorders and different psychiatric disorders is a way to explore this further.

The immune system has many effector mechanisms and may respond in a variety of ways. Immune responses often are divided into Type 1 (T1), Type 2 (T2) or Type 17 (T17) responses with different profiles of effector mechanisms. T1 often is referred to as pro-inflammatory, it is typically associated with biological markers like IFN- γ and IL-2 [6]. It is necessary in protection against bacterial infections and involved in pathogenesis of certain autoimmune disorders like coeliac disease and diabetes mellitus type 1 [6, 7]. T2 often is regarded as the opposite of T1. It is associated with biological markers like IL-4. It is necessary for protection against helminths and parasites, and is associated with diseases like hay fever and atopic eczema [8]. T17 is associated with biological markers like TGF- β and is considered a contributor in the mechanisms of several autoimmune disorders including multiple sclerosis (MS) and also certain disease stages of rheumatoid arthritis (RA) [9, 10]. However, the biology of the immune system is complicated and in real life immune responses usually are not as distinct as described above, though patterns can be found.

Studies on biological markers have indicated that also psychiatric disorders are associated with certain types of immune responses. There are indications of a T1 response in major depressive disorder [11], but results are conflicting [3]. Regarding psychotic disorders, there are also discrepancies in the results regarding immune profile [12, 13] but some studies indicate an increased T2 response [14]. Findings still are deviating and most data so far are based on comparing a distinct

psychiatric diagnostic group with healthy controls, not clarifying the specific role of immune activity in specific psychiatric disorders versus an effect on general psychiatric suffering.

There are some previous studies on the association between disorders of the immune system and psychiatric disorders. Autoimmune diseases like Graves' disease, psoriasis and type 1 diabetes as well as atopy and asthma have been associated with schizophrenia [15, 16]. Depression is frequently seen as a co-morbid disorder to diseases affecting the immune system, and is found more often in patients with inflammatory bowel diseases, RA and MS than in physically healthy persons [17, 18, 19]. Interestingly, active inflammatory bowel disease is associated with both increased depressive symptoms and proinflammatory cytokines [20]. An association between depression and hypothyroidism have been hypothesized for many years, but the results are conflicting [21, 22]. In a large cohort in Denmark several diseases affecting the immune system were associated with increased risk of developing bipolar disorder [23]. MS has been associated with both depression and bipolar disorder, but not with schizophrenia [24].

In summary, findings on comorbidity are deviating and mainly psychiatric disorders have been compared to healthy controls only. It is not known if the immunological changes seen in psychiatric disorders are related to general psychiatric stress or specific psychiatric disorders. In order to explore this question, we wanted to examine the relation between different immune disorders (representing different immunological profiles) and psychoses and depression respectively.

Materials and methods

Study design

This cross-sectional study was performed in acute psychiatric wards of St. Olav's University Hospital, Trondheim, Norway. At the time of the inclusion period, the psychiatric department served a catchment area of 140.000 inhabitants from age 18 years and above. Clinical psychiatric diagnoses were set in a consensus meeting with the doctors and psychologists of the hospital always including at least two senior psychiatrists. Patients were diagnosed according to the International Classification of Diseases 10th revision (ICD-10) research criteria [25]. All participants gave written informed consent.

The study was approved by the regional committee for ethics in medical research (REK number 2011/1448) and reported in Clinicaltrials.gov (NCT 00184418).

Sample

A total of 835 patients were included in the study. The patients were asked to fill out a questionnaire regarding diseases affecting the immune system, and 276 patients were willing and able to fill out the questionnaire satisfactory. Of these 41 patients had a non-affective psychosis (ICD-10 F20-F29 diagnosis) and 126 patients an affective disorder (F30-F39 diagnosis). These two diagnostic groups were compared for prevalence of diseases affecting the immune system among patients themselves and family members.

Inclusion and exclusion criteria

All patients admitted to the acute wards in the period October 2004 until November 2006 were eligible for inclusion. The only exclusion criteria were lack of patient consent or non-ability to give consent.

Assessments

Patients were given a self-administrated questionnaire asking if they themselves, or relatives of the patients, had a disease affecting the immune system. The following diseases were included in the questionnaire; multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatic, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, coeliac disease, Grave's disease, hypothyroidism, diabetes mellitus type 1, Addison's disease, eczema, asthma, hay-fever, food allergies and epilepsy. The patients were also asked if they had any liver, eye, skin or kidney diseases in addition to the diseases listed above. If they answered yes, they were asked to specify what disease. If they answered yes for a disease among their relatives, they were asked to specify their relation. Only diseases among first and second degree relatives were included in the analysis.

Statistical analyses

Statistical analyses were performed using SPSS software version 18 for Windows. All tests are two-sided with a preset level of significance of 0.05. The F20- and F30-group was dichotomized and descriptive analysis was performed with the chi-square statistic or Fischer exact test. A chi-square test was preformed to analyze if there were any differences in frequency of immunological diseases

between the two dichotomized psychiatric groups. The relationship between the dichotomized groups and diseases affecting the immune system was analyzed using Pearson correlation coefficient. A negative correlation coefficient would indicate an association between F20-diagnoses and diseases affecting the immune system, whereas a positive coefficient would indicate an association between F30-diagnoses and immune diseases.

Results

Study sample characteristics

The demographic characteristics of the F20-group and the F30-group are shown in table 1. Of the 835 **patients participating in the larger study**, 150 were grouped in the F20-29-category and 288 patients were grouped in the F30-39-category **of whom respectively 41 and 126 patients were able to fill out the questionnaire**. There were statistically significant ($\chi^2 = 11.268$, $df = 1$, $p = 0.001$) differences between the two groups regarding response rate to the questionnaire. The distribution of age and sex were similar in the two groups.

Differences in frequencies of diseases affecting the immune system

No significant difference in self-reported diseases affecting the immune system was found between the affective and the psychotic group using chi-square test (table 2). When comparing what patients reported for family members a significantly higher frequency of epilepsy was found in the F20-29-group ($p < 0.033$). Family members of the F30-39-group showed a significantly higher frequency for all immunological diseases combined ($p < 0,028$) (table 3). Prevalence of diseases affecting the immune system among our patients group as well as frequencies reported for the general population are listed in supplementary file 1.

Correlation of psychiatric disorders and diseases affecting the immune system

We used Pearson's correlation coefficient (r) to explore the association between the two psychiatric diseases and diseases affecting the immune system. Eczema among patients themselves was significantly correlated with the F20-29-group ($r = -0.116$, $p = 0.037$). Regarding what patients reported for family members, a significantly positive correlation between the F20-29-group and epilepsy ($r = -0.189$, $p = 0.014$) was found, and a significantly positive correlation between the F30-39-group and all

diseases affecting the immune system collectively ($r = 0.170$, $p = 0,028$). These results are shown in supplementary file 2 and 3.

Discussion

The present study may indicate a difference in frequency of immune related disorders, and thus in immune activity, between patients with disorders grouped as F20-29 and F30-39. The data indicate that F20 – 29 is associated with more epilepsy **in relatives** and **more** eczema in patients than the F30 – 39 group, while the total burden of immune related disorders seems to be higher in the relatives of the F30 – 39 group.

A significant association between eczema and F20-29-diagnoses was found among patients themselves. Not better specified eczema may be mediated both by T1 and T2 responses. Our finding is in line with Weber *et al.* who found an increased frequency of eczema among schizophrenic patients compared to healthy controls [26]. Also, there are indications that asthma and other atopic disorders (T2 responses) increases the risk of schizophrenia [16]. In a large cohort in Taiwan, however, no significant association between schizophrenia and atopic dermatitis was found and the risk for the T2 related urticarial reaction was reduced compared to healthy controls [27]. Thus, the immune activity in F20 – 29 is not clear, and thus not either the potential role of immune activity in pathogenesis and treatment.

Epilepsy was included as it is a relatively frequent neurological condition and - as for many neurological conditions – may be mediated by immune activity [28]. Based on reports from the patients, we found a significantly increased frequency of familial epilepsy in the F20-29-group. Although this finding is statistically significant, it is difficult to draw any firm conclusions from it due to small numbers in each group and needs further exploration. However, this finding is in line with previous reports [29], where both being diagnosed with epilepsy and having family members with epilepsy are associated with increased risk for developing schizophrenia [30]. In our material we did not find an association between mood disorders and epilepsy though it has been reported by others [31, 32], however, their reports were based on comparison with healthy controls. Epilepsy obviously is important in psychiatric morbidity, either mediated by immune activity or other mechanisms.

For family members, patients with F30 – 39 diagnoses reported increased frequency of diseases affecting the immune system collectively compared to family members of the F20-29-group. In a cohort study investigating the prevalence of 30 autoimmune diseases in family members of patients with bipolar disorder [23] an association of pernicious anemia in parents or siblings was found. No association was found upon investigation the 30 autoimmune diseases combined. This study differed from ours as comparison against healthy controls was performed. However, several studies indicate increased occurrence of autoimmune disorders in persons with F30 – 39 diagnoses [17, 18, 19], and as these disorders have a genetic component an increased risk also in family members is expected. To our knowledge no other studies have explored the difference between different psychiatric groups regarding these immune disorders and immune functions and thus the present report adds important knowledge to the field.

We expected to find an increased risk for RA in patients with F30-39-diagnoses and an inverse relationship for the F20-group [33]. Neither was found. RA is a disease affecting only 0.5-1% of the population [34]. The low prevalence may not give positive results in a study sized like ours.

Limitations and strengths

A limitation in our study is that immune related disorders are only self-reported in a questionnaire. We did not validate the diagnoses by collecting laboratory data or examining medical files. This should be strived for in future studies. Another limitation is the rarity of most diseases affecting the immune system and the sample size of the study. This may cause difficulties in discovering associations (Type 2 errors). Also, many diseases affecting the immune system have onset later than schizophrenia and mood disorders, which can result in a lower prevalence than expected. Due to a small number of participants in each group, no firm conclusions on disease prevalence can be drawn from this study. Also, as we have no healthy control group the study is not designed to reveal anything regarding prevalence compared to the general population.

Assessment of diagnosis by a self-report questionnaire is challenging in many psychotic patients. They may have cognitive impairment and neglect due to the psychosis. This together with isolation and social withdrawal may interfere with their knowledge on disorders in the family. A potential bias is therefore that patients with psychotic disorders may report family factors differently

from patients with affective disorders. Also, a higher frequency of patients with F30 – 39 than F20-29 answered the questionnaires, this is another potential source of bias.

Previous studies on the subject compared isolated psychiatric disorders with healthy controls. To further develop this field, we have compared the different psychiatric disorders with each other. The lack of a healthy control group is a weakness. However, our study may contribute with new information regarding whether the immune associations are related to certain psychiatric diagnoses or to psychopathology and psychiatric suffering in general.

Another strength is that the study is performed in the only available acute psychiatric inpatient service in the catchment area, reducing the effect of socioeconomic factors. Further, patients included are severely ill (as they are admitted to inpatient service). Thus, we are able to study a group often not recruited to studies. Finally, the sample size in the study is relatively large considering the rarity of F20-29-diagnoses like schizophrenia. To our knowledge this is the first study examining the comorbid immune pathology in such an ill population.

Conclusions

In this study we have explored the associations between psychiatric disorders and diseases possibly affecting the immune system. Psychotic and affective disorders may be associated with different immune diseases (epilepsy and eczema in relation to psychosis, and overall immune burden in affective disorders). The findings indicate that the immune system may have deviating activity in the two groups of psychiatric disorders, potentially leading to consequences regarding immune related pathology and treatment of F20 – 29 and F30 – 39 respectively in the future. However, no conclusions on prevalence can be drawn from this study. Further analyses on more psychiatric groups are necessary, as are calculations on the co-occurrence of clinical diagnoses and lab tests in the material.

Abbreviations

ICD-10 = International Classification of Diseases 10th revision, MS = multiple sclerosis, RA = rheumatoid arthritis, T_H cells = T-helper cells,

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Declaration of interest statement

The authors declare that they have no competing interests.

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Tables

Table 1: Demographic characteristics of the F20- and F30-group

Table 2: Frequency of diseases affecting the immune system among patients

Table 3: Differences in familial diseases affecting the immune system reports by the patients

Supplementary files

Supplementary file 1 - frequency of immunological diseases among patients themselves compared to general population

Supplementary file 2 - Correlation (r) between psychiatric disorders and diseases affecting the immune system among patients

Supplementary file 3 - Correlation (r) between psychiatric disorders and diseases affecting the immune system among family members.