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Blind Verification of Elevated Platelet Autoantibodies in Serum of Schizophrenic Patients – Part II: Adult Subjects

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Key Words
Schizophrenia · Diagnosis · Blood test · Platelets · Autoantibodies

Abstract
Background: In our preceding study, we assayed in a blind fashion the blood sera of young normal subjects and schizophrenic patients for levels of platelet autoantibodies (PAA). The recorded PAA titers of the schizophrenic patients were significantly higher than those of the normal subjects. This observation has lent support to this test being used as an objective evaluation of schizophrenia in young subjects in the future. In addition, this finding strongly suggested that the etiology of a distinct group of sufferers of this disorder could have originated from an autoimmune reaction against platelets which can, under certain conditions, cross-react with brain tissue. ***Aims:*** In the present study, PAA titers in the sera of adult schizophrenic patients and matched normal subjects were determined analogously to the preceding study. The effect of hospitalization and drug treatments on the apparent blood test scoring in adult subjects could thus be evaluated. ***Methods:*** A total of 46 schizophrenia patients (30 men and 16 women) aged 19–45 years (mean ± SD: 31.7 ± 8.0 years) with a minimum score of 60 on the Positive and Negative Symptom Scale and 43 healthy control subjects (22 men and 21 women) aged 21–44 years (mean ± SD: 31.9 ± 6.9 years) participated in the study. The blood titers of PAA were evaluated in a single-blind fashion using an optimized ELISA test scored by optical density (OD) units. A positive test was defined as a value above 1.3 OD units. ***Results:*** The titers of PAA in the group of schizophrenic patients (1.1 ± 0.55 OD units, range: 0.360–2.285 OD units) were significantly higher in comparison to those of the healthy control subjects (0.81 ± 0.37 OD units, range: 0.360–1.704 OD units; p = 0.004, two-tailed unpaired t-test). Significantly more schizophrenic patients showed a positive test (15 patients out of 46) than the control subjects (5 out of 43). However, significantly higher OD values of 1.55 ± 0.5 were recorded in the group of patients with less than 3 years of registered disease (n = 16, age 19–30 years), while in the group with 4–20 years of hospitalization (n = 30, age 24–45 years) the recorded OD values (0.85 ± 0.4 OD units) were practically indistinguishable from those of the control group. ***Conclusions:*** In the adult schizophrenic patients, the PAA blood test remains valid for patients who were hospitalized for less than 3 years. Drug treatment, length of disease and age can be assumed to reduce the PAA level considerably.

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Introduction

Schizophrenia is the most prevalent of all serious neuropsychiatric disorders, affecting 1% of the general population worldwide. This disorder consists of 3 principal clusters of clinical features: positive symptoms (delusions and hallucinations), negative symptoms (avolition, anhedonia, amotivation and alogia) and neural-cognitive dysfunction [1–3]. A wide range of risk factors and impairments have been suggested to be implicated in schizophrenia. These include genetic predisposition [4–6], a winter delivery [7], complications during pregnancy or birth [8], abnormal brain development, viral infection and subsequent autoimmune reactions [9–12], as well as impairment in the dopaminergic system [13–14]. This wide range of symptoms and risk factors implies that the etiology of schizophrenia is complex, hampering the development of specific therapies and objective diagnostic tests, and as a result it has remained obscure.

The chronic nature of the disease characterized by repeated outbreaks, between which there are usually calm periods, is similar to that of other diseases, particularly lupus and rheumatoid arthritis [15], where a common finding in these patients is an additional autoimmune factor. A recent study found that 'the history of every autoimmune disease is related to an increase of 45% in the risk of developing schizophrenia' [16]. Family members also have a high risk of developing autoimmune diseases, primarily type 1 diabetes and Grave's disease [17].

Indirect support for the assumption that schizophrenia has an autoimmune basis is provided by the negative relationship that exists between schizophrenia and rheumatoid arthritis [18–26]. In general, the risk of schizophrenic patients for developing this disease is 4–6 times less than in the general population. It was suggested that these 2 diseases may share a common immunological etiology, and when a person develops one of the diseases, he/she becomes relatively immune to the other [25]. Another piece of indirect evidence is indicated in a case report showing a marked improvement in the psychiatric symptoms of a schizophrenic patient treated with the immunosuppressant azathioprine [27].

It was suggested that a central autoimmune process in schizophrenia occurs in the peripheral blood, and the autoantibodies penetrate the brain under certain conditions, such as physical, mental or physiological stress [27–31]. The target tissue in the autoimmune process must meet 2 conditions: first, it should rapidly regenerate and, secondly, it must present cross-reactive sites in the brain. The platelets meet these 2 conditions [32–34]. Platelets share many characteristics of nerve tissue [33, 35], in particular with respect to the serotonin [32, 34] and the dopamine [36] systems. They may thus act as a peripheral catalyst for the creation and spread of autoantibodies that can cross-react with brain structures [31]. In our previous studies, high levels of autoantibodies against platelets were detected in schizophrenic patients [28–31], and were found to inhibit dopamine uptake [29], which in turn lends support to their relevance to the etiology of schizophrenia.

The open screenings that we carried out [28–31] led us to conduct analogous tests in a blind fashion. In the preceding single-blind study, we observed a highly significant elevation of PAA levels in the blood serum of young schizophrenic patients as compared to control subjects [37]. The aim of the present study was to investigate in an analogous controlled single-blind design (blind for the laboratory) the blood levels of PAA in adult schizophrenic patients.

Methods

Subjects

Schizophrenia patients (age range: 19–45 years), who were initially admitted to the Ness-Ziona Mental Health Center in an acute psychotic state, participated in the study. Inclusion criteria for participation required compliance with a DSM-IV diagnosis of schizophrenia according to the Structured Clinical Interview for Axis-I DSM-IV Disorders – Patient Version [38], as well as a minimal score of 60 on the Positive and Negative Symptom Scale (PANSS) [39]. All patients had to have normal routine laboratory tests. Patients with an unstable physical medical condition, past or current medical or neurological illness, past or current alcohol or any other substance abuse, or a current major routine laboratory abnormality were excluded from the study. Patients treated with any non-psychotropic medication or with clozapine were also excluded. A total of 46 schizophrenic patients (30 men and 16 women) between the ages of 19 and 45 years (mean ± SD: 31.7 ± 8.0 years; disease duration: 7.8 ± 6.2 years, number of hospitalizations: 3.6 ± 3.4) participated in the study. In the schizophrenia group, the total PANSS score was 91.3 ± 12.0 points, of which the positive symptom PANSS scores averaged 24.8 ± 4.9 points and the negative symptoms PANSS scores averaged 30.0 ± 5.2 points.

The healthy control group consisted of 22 men and 21 women (age 21–44 years, mean ± SD: 31.9 ± 6.9 years). The control volunteers all had a normal medical history, did not suffer from any chronic or current psychological or physical disturbances, and were not receiving medical treatment. Both groups were similar in age range and average age (two-tailed unpaired t test: $p > 0.91$).

All participants, both the schizophrenic and the healthy subjects, underwent an assessment of physical diseases using a special questionnaire and a physical examination. The details of the study were fully explained to all potential participants prior to

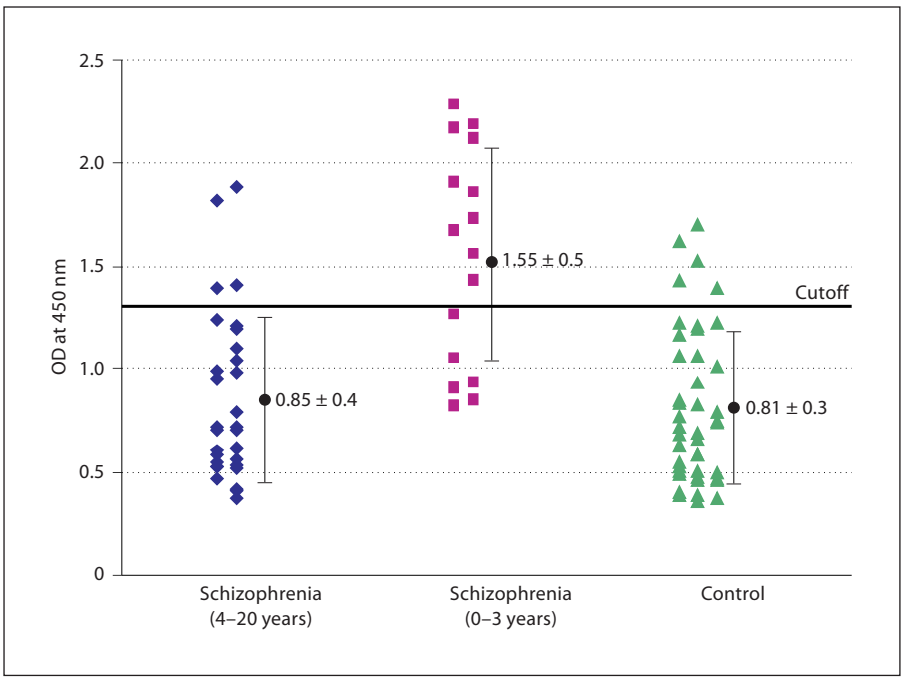

Fig. 1. PAA scores of the adult control group (n = 43; age 21–40 years) and adult schizophrenic patients after 0–3 years (n = 16; age 19–30 years) and 4–20 years (n = 30; age 24–45 years) of hospitalization.

study commencement, who then signed a written informed consent. The study protocol was approved by the Ness-Ziona and Beer Yaakov Hospital Institutional Review Board.

Laboratory Procedure

Twenty milliliters of venous blood was drawn from each of the participants and then encoded and transferred to the laboratory at the Weizmann Institute (M.Sh. and M.Sc.). Serum samples obtained from the venous blood were stored at –20°C until assay. The titers of PAA were evaluated using the optimized ELISA test expressed in a linear scale of optical density (OD) proportional to the level of the tested PAA. In this test, an immobilized dimmer of a peptide epitope from a platelet antigen provided the binder of circulating PAA, followed by an enzymatic color release proportional to the level of bound PAA expressed in OD units. The cutoff value was pre-evaluated with a battery of stored serum samples of registered normal subjects and schizophrenic patients, and was defined as 1.3 OD units. For this cutoff value, the sensitivity in our registered samples was 63%, while the percent of negative recordings in the registered normal samples, i.e. the specificity, was 88%. It should be noted that in this method, the magnitude of the recorded OD provides just a relative measure for the level of PAA. More details on the test were given in the preceding paper [37].

It is important to emphasize that the blood samples of all participants were transferred to the Weizmann Institute anonymously, with only a code number appearing on the test tube. The exact record and coding of the examined subjects were filed (by Y.S.) and concealed. After termination of the study, the coding and the ELISA results, together with the rest of the clinical information, were opened and analyzed.

Statistical Analysis

Titers of the PAA of the schizophrenic patients were compared to the PAA titers of the control subjects, using a two-tailed unpaired Student's t test. Categorical data were analyzed using the two-tailed Fisher's exact test. All results are expressed as means ± SD.

Results

A total of 46 schizophrenia patients (30 men and 16 women) between the ages of 19 and 45 years (mean ± SD: 31.7 ± 8.0 years, disease duration: 7.8 ± 6.2 years, number of hospitalizations: 3.6 ± 3.4) participated in the study. The healthy control group consisted of 22 men and 21 women, aged 21–44 years (mean ± SD: 31.9 ± 6.9 years). Both groups were similar in age range and average age (two-tailed unpaired t test: $p > 0.91$). In the schizophrenia group, the total PANSS scores were 91.3 ± 12.0 points, of which the positive symptoms PANSS scores averaged 24.8 ± 4.9 points and the negative symptoms PANSS scores averaged 30.0 ± 5.2 points.

The overall titers of PAA in the schizophrenia patients were in the range of 0.36–2.28 OD units with an average of 1.1 ± 0.55 OD units. Among them, 33% displayed OD above the cutoff level of 1.3. The titers of PAA in the healthy control subjects ranged from 0.35 to 1.70 OD units with an average of 0.81 ± 0.37 OD units, and 12%

recorded OD >1.3 units. Significantly more schizophrenic patients showed a positive test (15 out of 46) than control subjects (5 out of 43): Fisher's exact test, p = 0.02, OR = 3.67 (95% CI = 1.2–11.2). However, this difference was considerably less significant than the one observed in the preceding study with young patients and their control subjects [37].

The effect of length of disease, which includes the effects of both age and treatments, was tested by dividing the previous results between 2 durations: 0–3 years (n = 16, age 19–30 years) and 4–20 years (n = 30, age 24–45 years). Figure 1 presents the OD results for these 2 patient groups and the control group. As clearly indicated, the disease duration had a remarkable effect on the PAA titers. The adult patient group of less than 3 years' duration averaged an OD of 1.55 ± 0.5, with 68% of the members above 1.3, while the adult patient group of over 4 years' duration averaged an OD of 0.85 ± 0.40, with only 13% above the cutoff value; this was practically indistinguishable from the control group. The recorded level and spread of PAA values in the group of 0–3 years' hospitalization were practically identical to those observed in the preceding study for young patients [37].

Statistical evaluation of a possible effect of gender on the recorded PAA levels indicated that there were no statistical differences in the rate of positive tests between females and males, either in the patient group (7/9 vs. 8/22) or in the control group (3/18 vs. 2/20); Fisher's exact test: for patients p = 0.32, and for controls p = 0.66.

Discussion

The etiology of schizophrenia is still an enigmatic conundrum despite the enormous amount of investigations carried out. As with all other diseases of unknown etiology, no specific therapy or biochemical diagnosis could have been developed so far for schizophrenia. Yet, the hypothesis that schizophrenia, in some cases, originates from an autoimmune reaction opened the route for identifying putative target antigens responsible for triggering this reaction, and from there on to develop strategies for diagnosis and therapeutic approaches.

Many of the immunological functions in schizophrenic patients were found to be abnormal. In the circulatory dimension, increases in the immunoglobulin levels [15, 40], increases in interleukin (IL)-2 receptor [41–43], and decreases in the production of IL-2 [42, 44, 45], interferon-γ [43] and IL-6 [46] were recorded. On the cellular level, a decrease in the reactivity of lymphocytes [47–48] and the presence of large morphologically abnormal lymphocytes [47] were reported. A decrease in the percentage of T cells in schizophrenic patients with a severe recurrence was also observed [49], whereas in untreated patients an increase in T suppressor lymphocytes was noted [50]. In addition, an increase in the ratio of T helper cells to T suppressor cells was found to correlate with the patients' psychiatric condition [51]. All of these findings point to a significant impairment of the immunological functions in schizophrenic patients, which in principle may activate an autoimmune response that can propagate to the brain [52]. The detection of autoantibodies in brain structures of schizophrenic patients [53–56] that may cause behavioral changes when injected into animals [57] provided further support for the aforesaid assumption. Lastly, our previous findings of an autoimmune reaction against blood platelets in schizophrenia [28–31] and the identification of the target platelet antigen [58] may provide for the first time a basis for the development of a specific diagnostic tool, which was presented in this study and the preceding one [37].

In the preceding study, we demonstrated that recording the level of PAA in the blood serum of young subjects through a relatively simple ELISA test is a reliable diagnostic test. In this paper, we found that this test can be extended to the diagnosis of schizophrenia, even after a short period of hospitalization. However, for patients hospitalized for over 3 years, the PAA level is reduced to the levels found in healthy individuals, which is probably mainly due to the effect of pharmacological treatment. The possibility that a substantial proportion of the patients with high PAA titers carry an autoimmune arm in their pathophysiology suggests the application of immunosuppressive therapeutic treatment in addition to the conventional antipsychotic treatment.

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