Acute phase proteins and immunoglobulin classes in newly diagnosed Nigerian schizophrenic patients and those on anti psychotic drug treatment

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Abstract

Background: No single organic cause has been found for schizophrenia and its management has been difficult. More so, there are few data on the immune parameters of Nigerian schizophrenic patients on drug treatment and those that are not on treatment.
Methodology: This study determines the levels of immunoglobulin classes (IgG, IgA, and IgM) and acute phase proteins (caeruloplasmin, haptoglobin, transferrin and alpha 2-macroglobulin) in schizophrenic patients that are on drug treatment and those that are not on drug treatment compared with the controls.
Results: The mean level of IgG was significantly reduced in newly diagnosed drug free schizophrenic patients compared with controls (p=0.00) or with those on treatment (p=0.00). The mean level of transferrin was significantly reduced in newly diagnosed drug free schizophrenic patients compared with controls (p=0.00) or with those on treatment (p=0.00).
Conclusion: This study suggests the use of IgG and transferrin as indicators of drug compliance/efficacy in schizophrenic and in assessing the severity of schizophrenia.

Keywords: Schizophrenia, transferrin, anti-psychotic drugs, Nigeria and immunoglobulin.

Introduction

Schizophrenia is a psychiatric disease in which multiple aetiopathogenic factors have been implicated [(1)]. Till date, no acceptable biological marker or laboratory test currently exist for the monitoring or predicting schizophrenia. The capacities of the immune systems are diminished after frequent activation of the autonomic nervous system by chronic stress [(2)]. Having a positive attitude correlates with an increased ability of the immune system in fighting diseases [(2)]. In schizophrenic patient chronic stress, clinical depression, violence and negative attitudes and anxiety disorders are common [(3)].
Research into immune function in psychiatry is challenging because it represents an interface between two rapidly changing fields. Revitalization of interest in this area began with work demonstrating changes in immune function with stress [(4)]. Also, recognition of autoimmunity and dysfunction of the immune system secondary to the primary disease process, to long-term pharmacological treatment, or a result of an unrecognised concurrent, but unrelated medical disorder were reported in schizophrenia [(5)]. Based on the above report, immune responses in schizophrenic patients are expected to be deficient. To investigate this, our study determines the levels of certain humoral immune factors (IgG, IgA, IgM, caeruloplasmin, haptoglobin, transferrin and alpha 2-macroglobulin) in schizophrenic patients that are on drug treatment and those that are not on drug treatment.

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Materials and methods

Ethical Approval was obtained from Uselu Psychiatric Hospital's Management Ethical Committee before the commencement of the study and informed consent was obtained from guardians and families of the subjects. A total of thirty-five patients suffering from schizophrenia (20 males and 15 females between ages of 18 and 50 years) were recruited from Uselu Psychiatric Hospital, Benin, Nigeria. The schizophrenic patients were divided into two groups consisting of 20 on antipsychotic drugs for at least 2 weeks, and 15 newly diagnosed and not taking antipsychotic drugs. The patients were diagnosed by a Consultant Psychiatrist according to axis 1 of DSM –IV (the fourth edition of the diagnostic and statistical manual of mental disorders) criteria.

Twenty (20) healthy volunteers (12 males and 8 females) who were age and sex matched with the patients served as controls for this study. The control group has no previous history of any psychiatric disorders or any medical disease that can affect the immune system. A history was obtained and a clinical psychiatric examination performed. All patients were evaluated clinically (history and clinical examination), searching for signs of immunological changes, e.g. recurrent viral infection and searching for any diseases that can affect immunity, e.g. sore throat, bronchitis, liver diseases, thyroid enlargement etc. The following laboratory investigations were carried out:

1) Complete blood count to exclude anaemia, leucopenia, leucocytosis, eosinophilia or any other abnormal figures in blood count.
2) Thyroid function tests to exclude increased T3 and T4 serum levels or to exclude patients with low serum T3 and T4 levels.
3) Renal function tests (blood urea and serum creatinine) to exclude renal impairment.
4) Liver function tests to exclude liver affection, especially those with high liver enzymes or those with diminished albumin levels or high globulin levels.
5) Urine and stool analysis to exclude urinary tract infection or parasitic infestations. Other exclusion criteria were subjects with rheumatic fever, rheumatoid arthritis, subjects who received oral contraceptives, nonsteroidal anti-inflammatory drugs, corticosteroids, anticonvulsants and antidepressants.

About five milliliters (5ml) of venous blood was collected from each subject into a plain bottle, allowed to clot and retract at room temperature. The serum was separated from retracted blood by centrifugation at 5000rpm for 20 minutes. Acute phase proteins (Caeruloplasmin, transferrin, haptoglobin and alpha 2-macroglobulin) and immunoglobulin classes (IgG, IgA, and IgM) were quantified by the single radial immunodiffusion method as previously described [(6)]. It is

based on the principle of antigen-antibody precipitation reaction in agarose gel.

Results

Table 1 presents the levels of immunoglobulin classes (IgG, IgA and IgM) in schizophrenic patients compared with controls. The mean level of IgG was significantly reduced in newly diagnosed drug free schizophrenic patients compared with controls (p=0.00) or with those on treatment (p=0.00). The mean levels of IgA and IgM were not significantly different in newly diagnosed drug free schizophrenic patients compared with controls or with those on treatment. Table 2 presents the levels of acute phase proteins (Caeruloplasmin, transferrin, haptoglobin and alpha 2-macroglobulin) in schizophrenic patients compared with controls. The mean level of transferrin was significantly reduced in newly diagnosed drug free schizophrenic patients compared with controls (p=0.00) or with those on treatment (p=0.00). The mean levels of caeruloplasmin, haptoglobin and alpha 2-macroglobulin were not significantly different in newly diagnosed drug free schizophrenic patients compared with controls or with those on treatment.

Table 1: The levels of immunoglobulin classes in newly diagnosed schizophrenic patients, schizophrenic patients on anti-psychotic drugs and control.

	IgG (g/dl)	IgA (g/dl)	IgM (g/dl)
Control (n=20)	10.15±4.43	1.82±0.82	1.26±0.70
NDS (n=15)	4.67±2.96	1.13±0.57	1.59±2.64
DS (n=20)	8.66±4.19	1.54±0.60	1.13±0.78
t-, p^a	4.14, 0.00	2.78, 0.09	0.54, 0.59
t-, p^b	1.09, 0.28	1.22, 0.23	0.53, 0.59
t-, p^c	3.14, 0.00	2.04, 0.49	0.73, 0.47

NDS: Newly diagnosed drug free schizophrenic patients
DS: Schizophrenic patients on antipsychotic drugs
a=Control compared with NDS b=Control compared with DS
c=Control compared with DS

Table 2: The levels of acute phase proteins in newly diagnosed schizophrenic patients, schizophrenic patients on anti-psychotic drugs and control

	Caerulop lasmin	**Transferrin**	**Alpha2-macroglo bulin**	**Haptoglobulin**
Control:(n=20)	**0.21±0.92**	**1.89±0.50**	**1.19±0.29**	**3.19±1.80**
NDS : (n=15)	**0.19±0.79**	**1.29±0.49**	**1.13±0.56**	**2.34±1.23**
DS : (n=20)	**0.23±0.11**	**2.07±0.47**	**1.27±0.46**	**3.07±1.29**
t-, p^a	**0.49, 0.63**	**3.52, 0.00**	**0.37, 0.71**	**1.59, 0.12**
t-, p^b	**0.66, 0.51**	**1.16, 0.25**	**0.69, 0.49**	**0.25, 0.80**
t-, p^c	**1.08, 0.29**	**4.76, 0.00**	**0.80, 0.43**	**1.70, 0.09**

NDS: Newly diagnosed drug free schizophrenic patients
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Discussion

Schizophrenia is a psychiatric disorder that has been shown to have multiple aetiopathogenic factors including genetic, environmental, immunological, inflammatory, and nutritional deprivation among others. In schizophrenic patients, acute phase response was reported to be modulated by chronic treatment with antipsychotic drugs, thus making acute phase proteins possible biological markers for schizophrenia [(7)].

In the present study, the level of caeruloplasmin was slightly reduced in untreated schizophrenic patients compared with the controls. Caeruloplasmin is a positive acute phase protein, which binds Cu and oxidizes iron, thereby inhibiting iron uptake by microbes. Reduced caeruloplasmin in our newly diagnosed schizophrenic patients may explain their susceptibility to infections. Caeruloplasmin is a potent antioxidant, even more than albumin and superoxide dismutase. Reduced level of total antioxidant activity and lipid peroxidation is high in schizophrenic patients [(8)]. Given that lipid peroxidation is high in schizophrenic patients, therefore low level of caeruloplasmin is expected in them as reported by this study.

Transferrin is an iron transporting glycoprotein and a negative acute phase protein whose level decreases with progressing inflammation and regresses with improvement in the inflammatory condition. Several studies have provided evidence that abnormalities in oligodendrocytes and myelin function may contribute to the aetiopathology of schizophrenia. Transferrin plays an important role in the synthesis of myelin and the development of oligodendrocytes.[(9)] The reduction in the level of transferrin may lead to a decrease synthesis of myelin and oligodendrocytes, this will lead to impaired neurotransmission causing brain damage resulting in schizophrenia. Therefore significantly low level of transferrin in newly diagnosed drug free schizophrenic patients and raised level of transferrin in schizophrenic patients on drugs indicate that transferrin might have contributed to aetiopathology of schizophrenia.

Haptoglobin binds haemoglobin thereby inhibiting up-take of iron by microbes. Therefore reduced levels of haptoglobin may make free Fe available for the growth of microbes thus raised the susceptibility of schizophrenic patients to infections. Alpha 2-macroglobulin is an inhibitor of coagulation by inhibiting thrombin [(10)], and also inhibitor of fibrinolysis by inhibiting plasmin; thus low of level alpha 2-macroglobulin may compromise defense mechanism in schizophrenic patients.

In the present study, there were increases in the mean levels of IgA (non-significant) and IgG (significant) when untreated schizophrenic patients were compared with schizophrenic on drug treatment. This means that the use of antipsychotics enhanced the synthesis of IgA and IgG schizophrenic on drug treatment. The cause of slightly raised IgA in newly diagnosed drug free schizophrenic patients may be hypothesised to be indiscriminate ingestion of contaminated materials. This will stimulate production of secretory IgA in the gut which might have entered into circulation through the wall of the gut.

From this study, the levels of IgG and transferrin were increased with the use of antipsychotic medications in schizophrenics; thereby suggesting the use of these

parameters as indicators of drug compliance and efficacy in schizophrenic. The inclusion of IgG and transferrin in the criteria for assessing the severity of schizophrenia should be investigated.

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