Complement factors in newly diagnosed Nigerian schizophrenic patients and those on antipsychotic therapy

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Summary: The role of Complement factors in the pathogenesis of psychiatric disorders is enormous, but the data on levels and functions of complement factors in patients with schizophrenia are scanty and conflicting. To address this issue, levels of Complement regulators (C1 inhibitor and C3 activator) and complement factors (C1q, C3c, C4 and C5) were determined in the serum of newly diagnosed drug free schizophrenic patients, schizophrenic patients on medication and healthy subjects using immune-plates. C1q was significantly reduced in newly diagnosed schizophrenic patients or schizophrenic patients on medication compared with the controls. C3c was significantly reduced in newly diagnosed schizophrenic patients compared with controls or schizophrenic patients on medication. The levels of C3 activators, C1 inhibitors and C4 were similar in the two groups of schizophrenic patients compared with the controls. It may be concluded from this study that C1q is deficient in schizophrenic patients; and that C3c may differentiate newly diagnosed schizophrenia from schizophrenic patients on medication.

Keywords: Schizophrenia, Complement factors, Immunity, Treatment

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INTRODUCTION

Auto-antibodies have been shown to contribute to development of schizophrenia (Real and Yehuba 2006, Matloubitt et al., 2007). Autoantibody–antigen complexes activate complement cascade which may reduce the levels of complement factors in schizophrenic patients. Few literatures that existed on the levels of complement factors and complement haemolytic activities are conflicting. To the knowledge of the authors, no study on complement regulators in schizophrenic patients was carried out on Nigerian patients.

Schizophrenics were reported to have reduced total haemolytic activities (Spivak et al, 1993), raised activation of classical and alternative pathways of complement system (Svetlana et al, 2005, Mayilyan et al, 2006). C3 and C4 were found to be higher in untreated schizophrenics compared with the controls (Maes et al, 1997). But Wong (2003) found significantly low C3 in schizophrenic patients compared with healthy controls. The present study determined the levels of complement factors (C1q, C3c, C4 and C5) and complement regulators (C1 inhibitor and C3 activator) in newly diagnosed schizophrenic patients and schizophrenic patients on medication. Our result is expected to contribute to already existing immunological explanations for the aetio-pathology of schizophrenia.

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. All subjects 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 without anticoagulant, allowed to clot and retract at room temperature. The serum was separated from retracted blood by centrifugation at 5000rpm for 20 minutes. Complement factors and complement regulators were measured using immunoplates, based on the principle of antigen-antibody precipitation reaction in agarose gel (Arinola et al., 2006).

**Statistical analysis**
The results are expressed as mean ± SEM. The data obtained was analyzed using the students’ t-test. A p value of 0.05 was considered statistically significant.

**RESULTS**
From Table 1, the levels of C1q were significantly reduced in newly diagnosed schizophrenic patients or schizophrenic patients on medication compared with the controls. C3c was significantly reduced in newly diagnosed schizophrenic patients compared with controls (p=0.00) or schizophrenic patients on medication (p=0.00). The regulators of the complement system (C3 activator and C1 inhibitor) and C4 were not significantly reduced in the two groups of schizophrenic patients compared with the controls. C5 was significantly raised in schizophrenic patients on medication compared with newly diagnosed schizophrenic patients.

**DISCUSSION**
The complement system is made up of a large number of distinct plasma proteins that react with one another to opsonize pathogens and induce a series of inflammatory responses that help to fight infection. A number of complement proteins are proteases that are themselves activated by proteolytic cleavage. The complement system is an integral part of innate immune defense. Classical pathway of Complement activation is triggered primarily by cell-bound immune complexes, and the alternative pathway is activated by foreign bodies such as microorganisms. C1q is the first complement factor involved in classical pathway of Complement activation while C3 is the 1st complement factor of alternate pathway of the complement activation. C5 is central to both classical and alternate pathways (Arinola, 2003). The products of complement activation are important in producing kinin effect (by C2a), opsonisation (by C3b), neutrophil chemotaxis (by C5a) and cytolysis (by C9). Thus, defective activation of complement system or reduced levels of complement factors might contribute to susceptibility to infectious agents. Autoantibodies (antibrain and anticytoplasmic) are present in schizophrenics ((Real and Yehuba 2006, Matloubitt et al., 2007). These

### Table 1:
Complement factors in newly diagnosed schizophrenic patients, schizophrenic patients on anti-psychotic drugs and control

<table>
<thead>
<tr>
<th>Subjects</th>
<th>C1q (g/l)</th>
<th>C3c (g/l)</th>
<th>C4 (g/l)</th>
<th>C5 (g/l)</th>
<th>C1 inhibitor (g/l)</th>
<th>C3 activator (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=20)</td>
<td>9.40±5.69</td>
<td>1.41±0.54</td>
<td>0.26±0.27</td>
<td>1.50±0.83</td>
<td>0.53±0.11</td>
<td>0.89±0.32</td>
</tr>
<tr>
<td>NDSP (n=15)</td>
<td>3.09±1.01</td>
<td>0.68±0.29</td>
<td>0.23±0.22</td>
<td>1.20±0.44</td>
<td>0.49±0.13</td>
<td>0.66±0.41</td>
</tr>
<tr>
<td>SPM (n=20)</td>
<td>3.61±1.77</td>
<td>1.30±0.62</td>
<td>0.17±0.99</td>
<td>1.55±0.51</td>
<td>1.21±1.77</td>
<td>0.75±0.41</td>
</tr>
<tr>
<td>t-, p=</td>
<td>4.23, 0.00</td>
<td>4.72, 0.00</td>
<td>0.34, 0.74</td>
<td>1.26, 0.22</td>
<td>1.05, 0.30</td>
<td>1.85, 0.74</td>
</tr>
<tr>
<td>t-, p=</td>
<td>4.33, 0.00</td>
<td>0.57, 0.58</td>
<td>1.43, 0.16</td>
<td>0.20, 0.84</td>
<td>0.57, 0.57</td>
<td>1.20, 0.24</td>
</tr>
<tr>
<td>t-, p=</td>
<td>1.03, 0.30</td>
<td>3.58, 0.00</td>
<td>1.14, 0.26</td>
<td>2.08, 0.04</td>
<td>1.02, 0.24</td>
<td>0.63, 0.53</td>
</tr>
</tbody>
</table>

NDSP: Newly diagnosed schizophrenic patients, SPM: Schizophrenic patients on antipsychotic drugs
a=Control compared with NDSP, b=Control compared with SPM, c=NDSP compared with SPM

*Complement factors in schizophrenia*
auto-antibodies combine with self-antigens to produce immune complexes which circulate in the plasma (as circulating immune complexes) or are removed by the cells of reticuloendothelial system. Circulating immune complexes activate classical pathway of the complement system. Immune complexes had been found to be elevated in schizophrenic patients (Mailian et al, 2005).

Elevated immune complexes activate classical complement system pathway causing consumption and reduction of complement factors (especially C1q) in schizophrenic patients. C3c is one of the products of C3 activation which is further degraded to C3d, C3g, C3f. Therefore, reduced C3c in newly diagnosed schizophrenic patients might indicate further activation and catabolism of Complement factors in schizophrenics reduced activation of alternative pathway of complement system.

It is concluded from this study that initiating complement factor (C1q) but not complement regulators are deficient in schizophrenic patients; and that both classical and alternate pathways may be lacking in drug free newly diagnosed schizophrenia.

REFERENCES


