ABSTRACT

Background: A beta hemolyticus infection can cause a number of infections by different kinds of pathogenic mechanisms in the general population. These can range from streptococcal skin infections to rheumatic valve and heart diseases, as well as brain damage like encephalitis and paediatric autoimmune neuropsychiatric disorders. Objectives: The objective of this study was to find out the presence of anti-streptococcal antibodies in bipolar affective disorder with respect to family history, educational background, and gender differences. Methodology: The sample was collected with patient consent during the past year from the Bolan Medical College Complex Hospital, the Quetta Department of Psychiatry's out-door and in-door patients and from private referrals. A cross-sectional study with a sample size of 100 patients with a history of elated mood and low-grade fever in the absence of obvious causes, or if any causes were discovered after treatment, was conducted after carrying out their general physical and systemic examinations in order to include them in this study. Results: The positive anti streptolysin-o (ASO-titer) meaning more than 200 IU, is set for a positive result for the presence of the streptococcal antibody levels. In this study, the authors found a 29% prevalence of positivity. The variables are positive psychiatric family history, no education or poor educational background, and the third variable is the way the gender-based differences are, in males, the results are 71.7% and in females, it is 70% negative. Conclusion: The female gender, poor educational background, and positive family history are the main outcomes of this study.

Keywords: Psychiatric, Anti-streptococcus, Infection, Bipolar affective disorder, Patient’s disorder, symptomatic patient.
INTRODUCTION

Generally, the streptococcus group A beta hemolyticus infection (GAS) can cause a number of infections by different kinds of pathogenic mechanisms in the general population, ranging from direct skin infections to autoimmune reactions (1). The most common somatic manifestation of streptococcal infections is boils (erysipelas, for example) which can lead to rheumatic fever. Because rheumatic fever primarily affects children and adolescents, it is sometimes preceded by a mild history of pharyngitis, which leads to pericarditis, which means that all three cardiac layers are inflamed, resulting in rheumatic heart diseases or rheumatic heart valve diseases (2).

As in this type of damage, the specific antigenic proteins that are the main culprit are present in heart, brain, lungs, and kidneys, where the immune system cross-reacts to start attacking our own heart thinking these are the "M proteins" of the body of the pathogen bacteria so that causes the rheumatic fever, pericarditis, and with its late sequela are the fibrotic valvular heart diseases, or rheumatic heart disease The same holds true for brain diseases (3). As here, the antibodies against the "M" protein of the myelin sheet of the neuronal axonal processes cause the demyelinating type of damage (4).

Recent research has shown that microglia play a role in the aetiology of paediatric autoimmune neuropsychiatric disorders (PANDAS) caused by streptococcal infections (5). Microglia cells play an important role in mediating immune reactions in the central nervous system, affecting and causing neuropsychiatric disorders in children that have been linked to this type of infection and a group of anti-neuronal autoantibodies, specifically acting as dopamine receptor-mediated stimulators acting as encephalitis within the basal ganglia and the adjacent areas of the brain (6).

There are four subtypes of IgG autoantibodies against four neuronal autoantigens that have been recognized, namely, tubulin, lysoganglioside G_{M1}, and dopamine receptors D1 and D2, which were detected in the sera of patients who are infected with streptococcal bacteria (7). As a result, antibodies, D1, D2 receptor mediators, and their sites of activity appear to cause either overactive ties, hyperexcitability, or manic reactions, or both, in their early or later lives (8-10). It was shown that besides their immunological reactions, the microglia are also involved in brain development, brain homeostasis, the blood-brain barrier for highly selective filtrations, plasticity, and adult neurogenesis (11). Further, as a ligand that binds to the transporter protein, this was expressed by active microglia. Further, it has been shown that an increase in microglia was found in the striatal volume of the children with paediatric autoimmune neuropsychiatric disorders (12). Childhood streptococcal infection has also been linked to immunological reactions involving microglia cells, which play an important role in mediating immune reactions in the central nervous system and may be involved in some adult patients with Tourette syndrome (13). The same bacterial antibodies that cause Sydenham’s chorea also cause basilar ganglia damage. In this case, the basal ganglia causes slower levels of gama-
aminobutaric acid (GABA) inputs, which leads to an increase in dopaminergic activity, which leads to rapid, irregular, and aimless involuntary uncoordinated movements of the arms, legs, and trunk muscles, resulting in weakness, stumbling and falling, slurred speech, difficulty concentrating, and writing difficulties (14). The emotional instability of Sydenham’s chorea or disease (SD) can vary from patient to patient, ranging from slight grimacing to involuntary movements that were frequent and severe to uncontrolled quasi-purposive movements.

The emotional instability of Sydenham’s chorea or disease (SD) can vary from patient to patient, ranging from slight grimacing to involuntary movements that were frequent and severe to uncontrolled quasi-purposive movements. The Sydenham’s chorea or disease is a childhood neurological disorder caused by an infection with a group A beta haemolytic streptococcus bacterium (15). This bacterium resides in the throat, as described above, and causes rheumatic fever. Then its antibodies act against the neurons and neuronal coverings by virtue of cross-reacting with their "M" proteins resulting from childhood infection (16).

Dyskinesia is also a psychiatric disorder caused by antipsychotics and streptococcal infections (17). PANDAS vs. PANS: a paediatric neuropsychiatric syndrome with an acute onset (17). While PANDAS is a condition characterized by the sudden onset of obsessive-compulsive disorder, tics, or disturbed food intake along with various psychiatric distortions, which is similar to PANDAS. In contrast to the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), the PANS syndrome does not always necessitate prior GAS infection (18).

The most serious form of end-stage renal failure, referred to as rapidly progressing post-streptococcal glomerulonephritis, is also caused by the beta hemolyticus infection streptococcus group. (19). It is the most dangerous type because it starts so rapidly and becomes irreversible by the time it is recognized, mostly leading to end-stage renal disease and transplantation.

The pathogenesis of post-streptococcal glomerulonephritis is different from that of heart and brain diseases or damage (20). Antigens from the pathogen and antibodies from the host are present in glomerulonephritis. Then these bacterial antigens combined with the antibodies and complement system to grow inside the glomeruli of the host, where they formed insoluble complexes that caused local immune reactions and inflammation, which is known as type II hypersensitivity damage (21). This condition is a malignant end-stage renal disease that clinically presents with granular renal casts, malignant hypertension, mild to moderate protein urea, and oligourea leading to chronic renal failure (22).

**METHODOLOGY**

**Objective of the Study**

As psychiatric patients seem to have visited a number of various subspecialty consultants, including the psychiatrists who have treated them with electroconvulsive therapy (ECTs), even without response.

The objective of this study was to find out the presence of anti-streptococcal antibodies in bipolar affective disorder with respect to family history, educational background, and gender differences. (1). So, we aimed to carry out the study.
Type of Study and Sample Size
To diagnose a case, we had to complete the following: first consent, history, general physical examination, and systemic examination. Many variables have been included here in order to target a specific population for a specific cause and later find a specific, tailored treatment for them. For that matter, we had to include all those patients with bipolar disorder symptoms, including outpatients, inpatients, and those referred by other consultants or psychiatrists. Authors interviewed after the administration of various disease-specific scales, such as the maniac rating scale (1).
A cross-sectional study declared, with data collected for over a year and a total sample size of 100 patients with a history of elated mood and low-grade fever from the department of psychiatry's outpatient and inpatient department, as well as referrals from physicians and other consultants, at Bolan Medical College Complex Hospital Quetta. The type of psychiatric patients were mostly the older people and having a repeated treatment history without a response or a poor response are the reasons they were referred from various consultants, particularly physicians.
These study patients just needed a careful history (if one doesn’t ask patients) because most of the time patients think that psychiatrists don’t need tests, or they may think that if they’re taking cardiac or anti-tuberculosis drugs, for example, there’s no need to mention it or that it has nothing to do with psychopharmacology. Another historical pitfall is that it is usually taken by a junior colleague, such as a house officer or a medical officer (not in all cases) and not rechecked for reasons of work overload.

Inclusion Criteria
This study included patients who were age 18 or older.

Exclusion Criteria
All those patients were excluded from this study because they were minors or mentally retarded and not able to give their consent.
Although many patients with a history of low-grade fever but, at the time of the study, also had another emergency requiring urgent medical or psychiatric attention for which taking a history was risky. Patients over the age of 75 and those with debilitating health issues were also excluded.

Instruments
SPSS 20 was used; please see the charts below. Anti-streptolysin titer (ASO-titer) levels are measured using instruments; if it is greater than 200, it is considered positive (23). ASO titer kits for testing were from labs. (See below in investigations) For diagnosing the patients using ICD-10 criteria and the Mania Rating Scale (24).

Confidentiality
In this study, the majority of the names in the data were not the real ones for confidentiality and security reasons. A number was allotted to a person with a fake name attached to its information. The original identity is with the patient on his informed consent and in the author's records. If any of the participants requested that his/her original name be included with his/her original data, it was done so.
**Investigations**

All tests, including the ASO titer, were available in the government hospitals at the time of the study. If someone had wanted it from outside, from a private lab, one lab was made available at a subsidiary rate of Rs 150 per test in 2021. For the disease screening, the majority of the patients didn’t need any further laboratory tests because they had already carried them out from head to toe (sometimes more than once). The tests were, e.g., MRIs, CT scans, X-rays, ultrasounds, so these patients did not need any additional tests unless a grass infection was discovered, for example, in the chest (referral) or the UTI (send the urine examination, treat with antibiotics).

**RESULTS**

However, we found that there was a substantial genetic causal relationship with the positive psychiatric family history and poor educational background history. Both of which were associated with a significantly increased number of ASO-titre positive disordered organic patients with symptoms of bipolar affective disorder per se; it was discovered in those patients that a positive ASO titer, defined as more than 200 IU, is set for a positive result for the presence of streptococcal antibodies levels. In this study, the authors found a 29% prevalence of positivity. In this study, the variables, as shown in Table 1, are:

1. The positive psychiatric family history value is less than 0.05%.

There was a substantial causal relationship between genetics and bipolar affective disorder.

2. The education variable, consisting of either a poor educational background or no educational subgroup variable, is more associated with significantly positive cases examined of ASO-titre levels in affective disordered symptoms patients found, meaning the $p$ value is less than 0.05%. That is, there was a substantial causal relationship with a positive but poor educational background or no education, and people suffered more from paediatric autoimmune neuropsychiatric disorders than from actual bipolar affective disorders, says the Person correlation equation.

3. The ASO titer was positive at 17 and 12 for men and women, respectively, for the third variable, negative cross tabulation in case processing, where the predicted count for males was 60 and for women was 40, demonstrating potential reduced T cell functionality in females (possibly due to frequent hormonal fluctuations).
Table 1. Overall prevalence of ASO titer antibodies in population

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (&lt;200)</td>
<td>71</td>
<td>71.0</td>
<td>71.0</td>
</tr>
<tr>
<td>Positive (&gt;200)</td>
<td>29</td>
<td>29.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Prevalence of ASO Titer Antibodies with Reference to Family History

There was also a significant relationship found in family history, i.e., the p value is less than 0.05. The fact that bipolar affective disorder runs in families may be linked to the T cell defect. This, in turn, leads to unchecked antibody production by B cells. The overall count for ASO titer was 57 where family history was present, compared to 43 where there was no family history in the patients, as shown in Table 2.

Table 2. Prevalence of ASO titer antibodies with reference to family history

<table>
<thead>
<tr>
<th>Family history</th>
<th>YES</th>
<th>NO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASO Titer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>40</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Expected</td>
<td>40.5</td>
<td>30.5</td>
<td>71.0</td>
</tr>
<tr>
<td>Negative (&lt;200)</td>
<td>Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>17</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Expected</td>
<td>16.5</td>
<td>12.5</td>
<td>29.0</td>
</tr>
<tr>
<td>Positive (&gt;200)</td>
<td>Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>57</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Expected</td>
<td>57.0</td>
<td>43.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Prevalence of ASO Titer Antibodies with Reference to Gender

The sex differences, or gender-based, in males and females were 71.7% and 70% negative in cross-tabulation in case processing, in which the expected count for men was 60 and for women was 40, while the ASO titer was positive for 17 and 12 for men and women, respectively, as shown in Table 3.
Table 3. Prevalence of ASO titer antibodies with reference to gender

<table>
<thead>
<tr>
<th>ASO_titer</th>
<th>Sex</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
</tr>
<tr>
<td>Negative (&lt;200)</td>
<td>Count</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>42.6</td>
<td>28.4</td>
</tr>
<tr>
<td>Positive (&gt;200)</td>
<td>Count</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>17.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Total</td>
<td>% within ASO_titer</td>
<td>60.0</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Prevalence in sex (%)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Total (%)</td>
<td>60.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Prevalence of ASO Titer Antibodies with Reference to Educational Background

The education variable, consisting of either a poor educational background or no educational background, was more associated with significantly positive cases examined of ASO-titre levels in affective disordered symptoms patients found, meaning the "P" value is less than 0.05%. As shown in table 4, there was a significant causal relationship between a positive but poor educational background or no education and people suffering from paediatric autoimmune neuropsychiatric disorders (PANDAS) rather than actual bipolar affective disorder.

Table 4. Prevalence of ASO titer antibodies with reference to educational background

<table>
<thead>
<tr>
<th>ASO_titer</th>
<th>Under Matric</th>
<th>Bachelor</th>
<th>Postgrad</th>
<th>Religious Education</th>
<th>Uneducated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>22</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Expected</td>
<td>22.0</td>
<td>7.1</td>
<td>7.1</td>
<td>0.7</td>
<td>34.1</td>
</tr>
<tr>
<td>Positive (&gt;200)</td>
<td>Count</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Expected</td>
<td>9.0</td>
<td>2.9</td>
<td>2.9</td>
<td>.3</td>
<td>13.9</td>
</tr>
</tbody>
</table>
DISCUSSION

The neuropsychiatric syndromes or obsessive-compulsive disordered spectrum disorders present with hyperactive behaviours and are frequently misdiagnosed as just obsessive-compulsive disorder and attention deficit hyperactivity disorders, then inadvertently treated with serotonergic drugs, which usually ruin the patient's and their family's lives. Although it appears to be a difficult and laborious type of illness, it has a very simple treatment; otherwise, such patients are very resistant to all psychiatric medicines if only psychotropic drugs are used; when both penicillin and psychotropic medications are used, the results are dramatic.

Those patients, whether heavily medicated with antipsychotics or supplemented with low or high doses of serotonergic drugs, were found to be counterproductive. The serotonergic drug worsens the bipolar affective disorder symptomatic patient’s symptoms; the mood stabilisers indicated. The future prognosis would be a poor if improperly managed now (25). Although antipsychotic drugs in low doses are the only effective drugs used to treat the streptococcal group A beta hemolyticus infection’s movement disorders, when patients are labelled with their face value and treated with both serotonergic and antipsychotic drugs in the mistaken belief that either will work. Small doses of antipsychotic drugs were commonly used in the past in the treatment of obsessive-compulsive disorder and in patients suffering from post-streptococcal...
infection or antibody damage against neuronal cell damage in the past. However, recent evidence shows that such small doses of antipsychotics on dopamine receptors (D1) have worsened the cases (26). Although antipsychotic drugs in small doses were the mainstay treatment for movement disorders.

The other clinicians observed that symptoms improved for more than 80% of the paediatric autoimmune neuropsychiatric disorder subjects during their 6-month follow-up, and serum autoantibody titers decreased significantly (27). These results were reported previously in published studies. that their laboratory findings indicate that the antibody biomarkers could be a useful adjunct to clinical diagnosis of paediatric autoimmune neuropsychiatric disorders and related disorders, and that they were the first known group of autoantibodies detecting dopamine receptor-mediated encephalitis in children (27). In general, the majority of our patients did not recover from their disease or symptoms despite receiving extensive treatment from other clinicians.

However, in our sporadic clinical case observation, we could not find any depressive levels in the patient's anti-streptolysin antibodies when we checked some cases again after the 6-month period (but the disease symptoms disappeared quickly after the antibiotics were administered) (28). Throughout all of these studies, i.e., "prevalence cases of Streptococcus group A beta hemolyticus infection antibodies presence in psychiatric patients," which are currently or will soon be published as articles in various journals under various titles (e.g., obsessive-compulsive disorder symptoms, depressive illnesses, bipolar affective disorder, epilepsy, conversion disorder, psychosis/schizophrenia, and mental retardation) (26, 29).

During the study, it was discovered that patients infected with gram-negative endotoxin and viral infection in bipolar affective disorder symptomatic cases experienced anxiety, panic attacks, dysphonia, or depression mood/shivering, and at times, fleeting delusional ideations, which were relieved by acetaminophen, diazepam, or their relevant antibiotics. On the other hand, gram-positive exotoxins are usually associated with an elated mood, agitation, shouting, and aggressiveness, mostly restlessness. Another finding from this study was that subclinical co-morbidities were the sustaining factors for many different types of psychiatric and medical illness (30).

CONCLUSION

The objective of this study was to find out the presence of anti-streptococcus antibodies in bipolar affective disorder with respect to family history, educational background, and gender differences. Positive psychiatric family history, poor educational background history and poor socioeconomic conditions were discovered to have a significant genetic causal relationship. In conclusion, the female sex, the poor educational background, and the positive family history are the main outcomes of this study.

ACKNOWLEDGEMENTS

None
DECLARATIONS
Authors’ Contributions
MUM contributed to study concept; BT and MUM contributed to study design, data collection. HM contributed in data analysis and interpretation. IM did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical Approval
Ethical Approval was obtained from Research Ethics committee of Bolan Medical Complex Hospital, Quetta.

Conflict of Interest
The author declared no conflict of interest among them.

Funding
None

REFERENCES


