

Psychosis exacerbation following group A *Streptococcal pharyngitis*: an immune-mediated phenomenon? A case report

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Summary

According to some theories that postulate an immune involvement in the pathogenesis of Schizophrenia (SCZ), autoimmunity and infections are risk factors for SCZ.

We report the case of a 20-year-old female patient who received a diagnosis of SCZ at the age of 15, in concomitance with having contracted a streptococcal pharyngitis. Interestingly, since then, the patient repeated a number of Group A streptococcal (GAS) infections that, in each case, preceded recurrent significant psychotic exacerbation.

GAS infections are a well-known cause of post-infectious immune-mediated conditions such as Sydenham's chorea and PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections), in which a prominent SCZ-like symptomatology has been occasionally reported. The neurobiological basis of the emergence of psychotic symptoms in these cases remains largely elusive. We speculate in this article that psychotic exacerbations following GAS infections are linked to the pathophysiology of the streptococcal pharyngitis.

Key words

Schizophrenia • Streptococcal infections • Basal ganglia

Abbreviations

SCZ: Schizophrenia

GAS: Group A streptococcal

PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

SC: Sydenham's chorea

CNS: central nervous system

Background

According to literature, infections caused by *Streptococcus pyogenes*, a beta-hemolytic bacterium also known as the group A streptococcus (GAS), may be related to the onset of neuropsychiatric symptoms. Eygör et al.¹ studied 27 patients with chronic pharyngitis reporting that psychiatric disorders were 6.4 times more frequent in the patient group compared with the healthy population. All the patients involved in the study, received an Axis I DSM-IV TR diagnosis, the most frequent of which were somatization disorder (n = 8, 29.6%) and dysthymic disorder (n = 8). Huang et al.² investigated the psychopathological features of 100 pharyngitis patients and found high prevalence of somatization, obsession, interpersonal sensitivity and anxiety. Even if according to these data, psychotic symptoms appear to be less frequent and poorly-defined, they have been occasionally described as associated to the autoimmune processes involved in the post-streptococcal disorders

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Sydenham's chorea (SC) and PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) ³⁻⁵.

Our aim is to report the case of a 20-year-old female patient who received a diagnosis of SCZ at the age of 15, in concomitance with having contracted a streptococcal pharyngitis. Since then the patient repeated a number of GAS infections following which, she always presented recurrent psychotic exacerbations. After pharmacological treatment, based on antipsychotic and beta-lactam antibiotics co-administered for the first psychotic episode and for all psychotic exacerbations, a rapid psychopathological improvement could always be reported, with the patient gaining back the pre-morbid level of functioning. We speculate in this article that psychotic exacerbations following GAS infections are linked to the pathophysiology of the streptococcal pharyngitis: this clinical case could be conceptualized as an uncommon expression of a pediatric autoimmune neuropsychiatric disorder associated to strep throat infection.

Case presentation

G. came to our observation at the age of 20. The patient had a psychiatric onset at the age of 13 with a mild form of anorexia nervosa that fulfilled the diagnostic criteria. This symptomatology remitted after a few months, although a certain preoccupation about food still persisted. At the age of 15, she had her psychotic onset, preceded by a pharyngeal infection that lasted about 3 weeks. Psychotic symptoms mainly consisted in persecutory delusions accompanied by auditory hallucinations. Because of this psychotic symptomatology the patient was admitted to the hospital for about one week, undergoing treatment with risperidone and beta-lactam antibiotics. After this first psychotic episode, she received pharmacological treatment with antipsychotics (risperidone long acting injectable 25 mg im every two weeks), obtaining a remarkable effect on psychotic symptoms: even if a significant fear of being judged by others persisted, hallucinations and persecutory delusions rapidly disappeared. Since then, every single psychotic recrudescence was preceded by a streptococcal infection that presented with or without fever and was treated with a combination therapy based on antipsychotic and beta-lactam antibiotic.

Psychotic exacerbations lasted four to seven days and always occurred in the form of persecutory auditory hallucinations (voices) and delusions. In the latest years, school functioning and social functioning clearly regressed, the patient spends most of her time at home and has recently interrupted school attendance.

Discussion and conclusions

We hereby report the case of a chronic patient with a diagnosis of SCZ who experienced, from the age of 15, multiple episodes of GAS pharyngitis followed by the acute exacerbation of psychiatric symptoms.

Infections, and the resulting immune response, have recently received increased recognition as pathogenic mechanisms for neuropsychiatric disorders ⁶.

Interestingly, there are numerous descriptions of an association between infection, chronic inflammation of the central nervous system (CNS), and SCZ ⁷. An increased level of proinflammatory markers, like cytokines, has been described both in blood and cerebrospinal fluid of patients suffering from SCZ. Animal models have shown that a first hit to the immune system occurring in early life might trigger a lifelong increased immune reactivity. Many epidemiological and clinical studies show the role of various infectious agents as risk factors for SCZ with overlap to other psychoses. A large-scale epidemiological study from Denmark clearly demonstrates severe infections and autoimmune disorders during lifetime to be risk factors for SCZ ⁸.

SCZ-like symptoms have moreover been described in the autoimmune processes of the post-streptococcal disorders, such as SC and PANDAS ^{4 5 9 10}.

Being SC the most well characterized post-streptococcal syndrome and the most widely recognized post-streptococcal autoimmune disorder, it represents a model for this proposed pathogenesis ⁶. SC is considered a medical complication of group A beta-hemolytic streptococcal infection and it constitutes one of the major criteria for the diagnosis of Acute Rheumatic Fever ⁵. SC, in addition to chorea, is mainly characterized by psychiatric symptoms such as irritability, obsessions and compulsions, tics, and psychotic symptoms ³. The link between SC and psychosis is unclear, in recent decades, clinicians and researchers have continued to conduct studies in this field.

Some authors discussed the increased incidence of psychotic symptoms in SC ¹¹. While retrospective chart reviews suggested that patients with SC present a higher risk of developing SCZ if compared to the general population ^{11 13}. Nausieda et al. hypothesized an increased potential for aberrant thought processing in a subgroup of Sydenham's patients who demonstrated a significant elevation in the psychotic tetrad of the MMPI and adverse reactions to central stimulants ¹².

A dysregulated immune response to GAS infection is hypothesized to be linked to the onset of a process of inflammation that can involve clusters of neurons that principally constitute the basal ganglia, the most vulnerable CNS region in post-streptococcal autoimmune disorders. ¹⁴ The resulting dysfunction of the basal ganglia nuclei are hypothesized to be for the constellation

of psychiatric symptoms described in these clinical frames⁶.

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections) has been proposed as a variant of SC, with which it is hypothesized to share a pathogenic mechanism, despite showing a unique, predominantly psychiatric, symptom profile⁶.

PANDAS is defined by the presence of obsessive compulsive disorder and/or a tic disorder, prepubertal symptom onset, sudden or episodic course, temporal association of symptom exacerbation and streptococcal infections and associated neurological abnormalities. An autoimmune process triggered by a streptococcal epitope directed to CNS neurons is thought to be responsible for the characteristic symptom profile and for the course of illness⁴.

PANDAS may arise when antibodies directed against the invading bacteria happen to cross-react, such as in SC, with basal ganglia structures.

As most symptoms of SC and PANDAS may be considered the result of a basal ganglia dysfunction determined by autoimmune mechanisms elicited by streptococcal infection¹⁵, we speculate that psychotic symptoms in our clinical case report, may have been determined by the same pathophysiological process.

According to literature, when patients with PANDAS are not treated for long periods, SCZ-like symptoms are an unavoidable manifestation¹⁶. Thus, it could be assumed that the involvement of the basal ganglia may lower the threshold for the emergence of SCZ-like symptoms. Indeed, evidence from various studies suggest that a basal ganglia disturbance has a role in SCZ and may contribute to the understanding of the pathophysiology of this complex disorder¹⁷⁻¹⁹.

The dopaminergic system of the basal ganglia manifests several anomalies in SCZ²⁰. Conversely, prominent psychotic symptoms are often reported in organic disorders with specific involvement of these subcortical nuclei (i.e. Sydenham's chorea, Wilson's disease, Huntington's chorea, Hallervorden-Spatz disease, post-encephalitic psychoses)²¹.

The reason why psychosis is not so frequent in post-streptococcal conditions is, however, a matter of debate and the relationship existing between SCZ and post-

streptococcal related diseases, specifically PANDAS, has not been completely understood yet.

In conclusion, in this case report we hypothesize the involvement of a basal ganglia dysfunction in the pathogenesis of SCZ, adding interesting and potentially useful information to the international literature related to immune-mediated neuropsychiatric complications following GAS infection.

We presume that our patient suffered from an immune-related post-infectious psychosis triggered by GAS infection that may be an uncommon expression of pediatric autoimmune neuropsychiatric disorder associated with a streptococcal infection.

In spite of the speculative nature of our paper, we have tried to temper our speculations supporting our theory with solid data that have been derived from the scientific international literature.

Conflict of interest

The Authors declare to have no conflict of interest.

Ethics approval and consent to participate

We carefully considered the utility of this case against the likelihood of identification or potential distress.

Consent for publication

The Authors of this article declare to have obtained the written and signed consent from the patient to publish the case report.

Availability of data and materials

Not applicable.

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Author's contributions

All Authors analyzed and interpreted the patient data regarding her psychiatric disorder.

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