Post-streptococcal autoimmune disorders of the central nervous system

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Purpose of review

Autoimmune disease has long been intertwined with investigations of infectious causes. Antibodies that are formed against an infectious agent can, through the process of molecular mimicry, also recognize healthy cells. When this occurs, the immune system erroneously destroys the healthy cells causing autoimmune disease in addition to appropriately destroying the offending infectious agent and attenuating the infectious process. The first infectious agent shown to cause a post-infectious autoimmune disorder in the central nervous system was *Streptococcus pyogenes* in Sydenham's chorea. The present review summarizes the most recent published findings of central nervous system diseases that have evidence of a post-streptococcal autoimmune etiology.

Recent findings

Sydenham's chorea and other central nervous system illnesses that are hypothesized to have a post-streptococcal autoimmune etiology appear to arise from targeted dysfunction of the basal ganglia. PANDAS (pediatric autoimmune disorders associated with streptococcal infections) is the acronym applied to a subgroup of children with obsessive–compulsive disorder or tic disorders occurring in association with streptococcal infections. In addition, there are recent reports of dystonia, chorea encephalopathy, and dystonic choreoathetosis occurring as sequelae of streptococcal infection. Investigators have begun to isolate and describe antistreptococcal–antineuronal antibodies as well as possible genetic markers in patients who are susceptible to these illnesses.

Summary

Clinical and research findings in both immunology and neuropsychiatry have established the existence of post-streptococcal neuropsychiatric disorders and are beginning to shed light on possible pathobiologic processes.

Keywords

Group-A β-hemolytic streptococcal infections, autoimmune disease, post-infectious, central nervous system illness

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Abbreviations

ADEM	acute disseminated encephalomyelitis
ASO	antistreptolysin O
CNS	central nervous system
GABHS	Group A β-hemolytic streptococcus
IVIG	intravenous immunoglobulin
NIMH	National Institute of Mental Health
OCD	obsessive–compulsive disorder
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PEX	plasma exchange

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Introduction

One of the primary roles of the immune response is to provide defense against infection. The immune system must be able to recognize a pathologic agent and target it for destruction (immune response) while ignoring healthy tissue (self-tolerance). Autoimmunity is a dysfunction of the immune system where self-tolerance to healthy tissues has been suppressed or lost. The loss of self-tolerance allows the immune system to produce autoantibodies that erroneously target healthy tissue for destruction. Although our knowledge of the pathobiology of autoimmune disease in the central nervous system (CNS) has expanded greatly, the initial events that lead to the loss of self-tolerance are still unknown. It has been hypothesized that self-tolerance to CNS antigens is broken by several linked events that result in the initiation or induction of anti-CNS immune responses, which produce the inflammation and demyelination seen in these disorders [1].

The concept of molecular mimicry has been hypothesized as a possible mechanism for the induction of autoantibodies [2]. In this model, autoantibodies are produced against healthy tissue because the antigen on a pathologic organism closely resembles the structure of an antigen on healthy tissue. When the immune system induces an antibody to target the pathologic organism for destruction, there is enough overlap that the antigen on the healthy tissue is also recognized. This mistaken recognition results in a functional loss of self-tolerance and the destruction of healthy tissue by the host's own immune system. Molecular mimicry is just one possible mechanism by which post-infectious autoimmune disorders can occur. A wide variety of inciting organisms and affected tissues have been reported. This review will concentrate on evidence for autoimmune disease in the CNS caused by *Streptococcus pyogenes* or Group A β-

hemolytic streptococcus (GABHS), the infecting organism in 'strep throat' and scarlet fever.

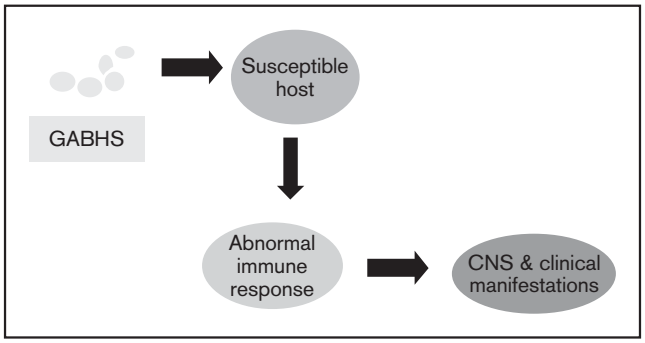
Pathogenesis of post-streptococcal illness

GABHS colonize the throat or skin and are responsible for a number of suppurative infections and nonsuppurative sequelae. As pathogens they have developed complex virulence mechanisms to avoid host defenses. GABHS has been investigated for its significant role in the development of post-streptococcal infection sequelae. The basic pathogenesis begins with an infection with GABHS. There are multiple serotypes of GABHS and there is evidence that only specific serotypes will cause rheumatic fever. There is not evidence for this selectivity in any of the other post-streptococcal CNS disorders at this point. Although there is a high prevalence of GABHS throat infections among pediatric populations, only a small percentage of individuals develop post-streptococcal autoimmune illnesses. Studies of families suggest that rheumatic fever is an autosomal recessive illness with limited penetrance [3]. This implies that these illnesses will only develop in a susceptible host that has been infected by a specific GABHS serotype. It is this infection with GABHS that primes the host's immune system and causes an abnormal response. The healthy tissues of the CNS can become the targets of this abnormal immune response causing neuropsychatric sequelae through an inflammatory process [3] (Fig. 1).

Sydenham's chorea

Sydenham's chorea, the neuropsychiatric manifestation of rheumatic fever, has been proposed as a possible medical model for post-streptococcal autoimmune neuropsychiatric disorders [4]. Molecular mimicry is implicated in this illness through the demonstration of antineuronal antibodies in serum samples from patients with Sydenham's chorea [5]. These antineuronal antibodies are postulated to arise in response to an infection with GABHS and then to cross-react with antigens from neurons in the basal ganglia. The first antineuronal antibodies isolated from patients with Sydenham's chorea were found to react with cytoplasm from the caudate and subthalamic nucleus. In these 30 Sydenham's chorea patients, the presence of antineuronal antibodies correlated with the severity and duration of the chorea [5]. These results were replicated in 11 children diagnosed with Sydenham's chorea at the National Institute of Mental Health (NIMH). Antineuronal antibodies directed against human caudate tissue were demonstrated in 10 of the 11 patients [6].

Figure 1. Proposed pathogenesis of post-streptococcal autoimmune disorders



CNS, central nervous system; GABHS, Group A β-hemolytic streptococcus.

Post-mortem studies as well as functional and structural brain imaging support the involvement of the basal ganglia in Sydenham's chorea. In a study conducted at the NIMH, 24 patients with Sydenham's chorea were compared with 48 matched controls using cerebral magnetic resonance imaging. The Sydenham's chorea group showed increased volumes of the caudate, putamen, and globus pallidus when compared with the controls [7]. The current evidence for Sydenham's chorea being a post-streptococcal autoimmune disorder is growing stronger. Once preliminary work on the bioactivity of these antineuronal antibodies has been established, the pathobiology of this illness will be confirmed.

PANDAS

Swedo and colleagues [8] published the first description of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) in 1998. This cohort of children had the abrupt onset of obsessive-compulsive disorder (OCD) or tic disorder following an infection with GABHS. Five criteria were established for inclusion in the PANDAS subgroup: presence of OCD and/or a tic disorder, prepubertal onset, acute onset and episodic course of symptom severity, association with GABHS infection, and association with neurologic abnormalities. The children had a very young age of illness onset, 6.3 ($\pm$2.7 SD) years for tics and 7.4 ($\pm$2.7 SD) years for OCD. Children in the PANDAS subgroup were also found to have larger volumes of the caudate, putamen, and globus pallidus than healthy children by cerebral magnetic resonance imaging [9] (Table 1).

In children with severe symptoms who met criteria for the PANDAS subgroup, immunomodulatory treatment with plasma exchange (PEX) and intravenous immunoglobulin (IVIG) was found to be effective in lessening the neuropsychiatric symptom severity [10]. A double-blind randomized study compared PEX with IVIG and sham IVIG (placebo) for the treatment of tics and obses-

Table 1. The five clinical criteria of the PANDAS subgroup

(1) Presence of obsessive–compulsive disorder and/or tic disorder (meeting DSM-IV criteria).
(2) Prepubertal symptom onset.
(3) Episodic course characterized by acute, severe onset and dramatic symptom exacerbations.
(4) Neurological abnormalities (e.g. choreiform movements) present during symptom exacerbations.
(5) Temporal relationship between GABHS infections and symptom exacerbations.

PANDAS, pediatric autoimmune disorders associated with streptococcal infections; GABHS, Group A β-hemolytic streptococcus.

sive–compulsive symptoms in children with PANDAS. Twenty-nine children completed the trial, which found that both PEX and IVIG produced dramatic improvements in obsessive–compulsive symptoms, anxiety, depression, emotional lability, and global functioning. Global change scores revealed that patients in both the PEX and IVIG groups were much improved [CGI (clinical global impression) – change = 1.9 ($\pm$1.1) and 2.4 ($\pm$1.1), mean improvement of 48% and 41%, respectively]. In the PEX group, symptom improvement was often observed near the end of the first week of treatment, whereas in the IVIG group, improvement was not usually seen until 3 weeks after treatment. The PEX group also appeared to have greater symptom relief than did the IVIG group, with particularly striking individual improvements seen for obsessive–compulsive symptomatology. In contrast, placebo administration was associated with little or no change in overall symptom severity [CGI-change = 4.1 ($\pm$0.6), mean change of -2%].

The results of this investigation suggest that PEX and IVIG may be beneficial to a subgroup of patients with tics and obsessive–compulsive symptoms, but require replication. These treatments carry significant risks and therefore should be reserved for only individuals with acute and severe neuropsychiatric symptoms that have a definite post-streptococcal autoimmune etiology. This study does not provide support for the routine use of immunomodulatory agents in OCD and tic disorders that do not have an immune mediated etiology.

In the past year, two community-based case series of children in the PANDAS subgroup have been described. The first was a prospective case study done in a general pediatric practice in Rochester, New York over a 3-year period. Twelve children presented with the abrupt onset of OCD and also met criteria for inclusion in the PANDAS subgroup. Of the 12 patients reported, six had a positive culture or rapid antigen-detection assay for GABHS at presentation of their OCD symptoms and four were positive within the month prior to presentation. One patient had a negative rapid antigen-detection assay for GABHS at presentation, but elevated antistreptococcal antibody titers. The remaining child had a tonsillectomy performed 1 month prior to onset because of a history of recurrent GABHS infections during the previous year. In the children who did not experience a recurrence of neuropsychiatric symptoms, a complete resolution of OCD symptoms occurred in 5–21 days [11••].

In order to determine if a parent-reported upper respiratory infection might be a valid screening tool for children found to be in the PANDAS subgroup, 83 consecutive children and adolescents referred to an academic child psychiatry clinic with the primary diagnosis of OCD were evaluated for symptoms of an upper respiratory infection at the onset of their neuropsychiatric symptoms. The children with a history of an upper respiratory infection were more likely to experience a sudden rather than insidious onset of OCD symptoms and also to have a comorbid tic disorder. To determine that a child meets criteria for membership in the PANDAS subgroup, however, a prospectively determined association between neuropsychiatric symptoms and GABHS infection must be established. Validated biomarkers will be necessary to confirm a retrospective diagnosis. Until they are available, a history that abrupt onset OCD began around the time of an upper respiratory infection should alert a clinician to look prospectively for a GABHS association [12•].

One criterion for inclusion in the PANDAS subgroup is a prepubertal age of onset. A recent case report described a 28-year-old male who had the onset of debilitating OCD at 25 years of age following a sore throat. His pharyngitis went untreated for 3 weeks before he was brought to medical attention and treated with antibiotics. As his pharyngitis resolved, he developed acute OCD symptoms that severely interfered with his life. Since this patient had a post-pubertal onset of symptoms he cannot be included in the PANDAS subgroup. The report suggests that the subgroup may be larger than originally described, but inclusion of adult cases must await the development of more specific diagnostic tests [13•]. Children undergoing tonsillectomy for recurrent streptococcal pharyngitis who also have OCD and tic disorders have had reported improvements in their neuropsychiatric symptoms following surgery [14]. Since otolaryngologists evaluate a large proportion of pediatric patients with recurrent GABHS infections it is important that these subspecialists are aware of the association of GABHS infection and the onset of neuropsychiatric symptoms (Table 2).

Obsessive–compulsive disorder

OCD is generally conceptualized as a neurobiologic disorder with a multifactorial etiology. There is increasing evidence that a post-streptococcal autoimmune-

Table 2. Current treatment guidelines for children in the PANDAS subgroup

(1) Assessment for GABHS infection by 48 h culture in a young child with abrupt onset OCD and/or tic disorder. A positive culture should be treated promptly with a standard 10-day course of antibiotics.
(2) If the abrupt onset of the OCD and/or tic symptoms occurred at least 4–6 weeks prior to the visit, then a blood test for antistreptococcal antibody titers (ASO and anti-Dnase B) should be done (along with a 48 h throat culture) to attempt to document a preceding GABHS infection. Antibiotic treatment of elevated titers is not appropriate in the absence of a positive GABHS culture.
(3) Prospective assessment for GABHS infections in a child with an episodic course of symptoms should be done. Throat cultures for GABHS should be obtained at the time of relapse of OCD and/or tic symptoms or antistreptococcal titers should be drawn 4–6 weeks later.
(4) The decision to begin antibiotic prophylaxis should be based on clinical indications in each individual child after obtaining evidence that they are in the PANDAS subgroup. The prompt diagnosis and adequate treatment of GABHS infections in this subgroup of patients is clearly indicated.
(5) Treatment with immunomodulatory therapies (like plasma exchange and intravenous immunoglobulin) should be reserved for children with acute, severe symptoms who fit the PANDAS designation. These treatments carry significant risks and should be used only for the most severely affected patients.

PANDAS, pediatric autoimmune disorders associated with streptococcal infections; GABHS, Group A β-hemolytic streptococcus; OCD, obsessive–compulsive disorder; ASO, antistreptolysin O; anti-Dnase B, antideoxyribonuclease B.

mediated process is occurring in the PANDAS subtype of OCD. Both radiologic and immunologic evidence supports this postulated etiology. Radiologic evidence from imaging studies of children in the PANDAS subgroup implicates the basal ganglia as the primary site of dysfunction [15•]. Magnetic resonance imaging studies on these children have revealed reduced caudate nucleus volumes in children with longstanding OCD but acutely increased volumes after the onset of neuropsychiatric symptoms [15•]. This acute increase in volume could be secondary to a post-infectious inflammation, while the reduced volumes found in chronic OCD could be secondary to another process or repeated bouts of inflammation. The serologic evidence documenting that Sydenham's chorea is a post-streptococcal autoimmune disease is now being acquired from children in the PANDAS subgroup. Both antineuronal antibodies against the basal ganglia and cytokine profiles similar to those found in Sydenham's chorea have been reported in the PANDAS subgroup [15•].

There is a growing body of evidence that post-streptococcal autoimmunity plays a role in pediatric OCD. To explore the possible association between compromised immune function and OCD, adult OCD patients were compared with patients with other psychiatric disorders to determine if there was a higher incidence of recurrent infections or other evidence of compromised immune function among the patients with OCD. A chart review from an anxiety disorders clinic revealed an increased rate of immune related syndromes among OCD patients in comparison to other anxiety and mood disorder groups. One implication of this finding is that prolonged immunologic stress may be a risk factor for OCD. It is possible that immunologic stress may compromise the blood brain barrier and permit the influx of antineuronal antibodies into the central nervous system [16••].

Reports of post-streptococcal autoimmunity in PANDAS have spurred interest in studying immune parameters in non-PANDAS OCD. Studies that have assessed immunologic measures in patients with OCD have not found consistent evidence of this connection in non-PANDAS OCD [17••]. Although OCD is felt to have a genetic basis, no specific genetic factors have been conclusively identified to date. This has led researchers to look for possible environmental risk factors that may be interacting with underlying genetic susceptibility in individuals with OCD. The similarities between Sydenham's chorea, PANDAS and OCD with respect to genetic susceptibility have encouraged researchers to look for a post-streptococcal association for non-PANDAS OCD. To date, however, there is no evidence for this among nonselected patients with OCD [18•].

Movement disorders

In the past decade there has been increasing evidence that movement disorders can develop in the context of streptococcal infections. Reports to date suggest that post-streptococcal neurologic sequelae include extrapyramidal movement disorders such as chorea, tics, and dystonia [19•]. The relationship between tic disorders and GABHS infection has been reported in the literature frequently, yet very few studies have looked systematically for evidence of GABHS infection in children with tic disorders. A well designed case-control study of the relationship between childhood tic disorders and GABHS infections in Italian school-aged children was conducted using mean antistreptolysin O (ASO) titer. (ASO titers become elevated 4–6 weeks after a preceding GABHS infection.) In the children with a tic disorder, mean ASO titer was significantly higher compared with that of controls [20••].

A variety of movement disorders have been proposed to have an immune-mediated or post-streptococcal etiology. In the recent literature there are three clinical reports of particular interest. Two children with serologic evidence of a recent GABHS infection presented with infantile bilateral striatal necrosis, a dystonic movement disorder with basal ganglia imaging abnormalities. Both

of these children had antineuronal antibodies reactive against the basal ganglia [21]. Paroxysmal dystonic choreoathetosis is an episodic, nonkinesogenic (not induced by movement), extrapyramidal movement disorder. A sporadic case of this disorder was described in an 8-year-old boy who was found to have serum antibasal ganglia antibodies and a history of a preceding GABHS infection [22]. A childhood syndrome of immune-mediated choreatic encephalopathy was reported in four previously healthy girls aged 3–8 years. These girls presented with encephalopathy and an extrapyramidal movement disorder without evidence of a preceding streptococcal infection but with cerebral spinal fluid specific oligoclonal bands [23•].

An 8-month longitudinal observational study of school-aged children was conducted to determine the monthly point prevalence of motor tics. The investigators found that the incidence of motor tics was significantly higher during the winter months of November through February when compared with the spring months of March through June. Although no direct streptococcal infection rates were determined, this time period overlaps with the high seasonal prevalence of streptococcal infections seen in this age group. This study provides indirect evidence of a temporal correlation between GABHS infections and tic disorders [24].

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an immune-related inflammatory disease of the CNS, affecting predominantly gray matter. Viruses, bacteria and live vaccines have all been implicated as possible pathogens. In a recent case series, 10 patients with ADEM occurring in association with a preceding GABHS infection had significantly elevated antibasal ganglia antibodies when compared with patients with ADEM without preceding GABHS infection, encephalitis, or a recent streptococcal infection [25••]. A case of ADEM in a 10-year-old boy with concomitant acute glomerulonephritis has also been reported following a GABHS infection [26•]. By evaluating patients with ADEM systematically for evidence of a recent GABHS infection, investigators have been able to define a subgroup characterized by basal ganglia involvement, dystonic movement disorders, behavioral disturbance, and the presence of defining autoreactive antibodies against the basal ganglia [26•].

Antineuronal antibodies

Antibodies to nuclear and cytoplasmic antigens are frequently observed in autoimmune disorders. The picture is less clear with regard to antinuclear antibodies in Sydenham's chorea, tic disorders, and PANDAS. In a cohort of children referred to a neurodevelopmental clinic serum antibodies against human caudate were found to be significantly higher in the children with new onset movement disorders (Tourette's syndrome, chronic motor or vocal tics, chorea, choreiform movements) than those without movement disorders [27]. The presence of antibodies directed against the caudate and putamen were also found to be significantly higher in a cohort of children presenting with new onset OCD or pervasive obsessive–compulsive symptoms than clinical controls without such symptoms [28].

There have been multiple reports of the isolation of antineuronal antibodies from patients with Tourette's syndrome. Serum antibodies against human caudate, but not to the putamen or globus pallidus, were found to be significantly higher in patients with Tourette's syndrome over controls [29]. Antibodies against a neuron-like HTB-10 neuroblastoma cell have been demonstrated in children with Tourette's syndrome, but were also found in a healthy control group [30]. In a more recent study, Tourette's syndrome patients were found to have significantly higher levels of total antineural and antinuclear antibodies than healthy controls [31••]. Similar results have also been described in patients with Sydenham's chorea. Acute Sydenham's chorea patients had significantly higher titers of anti-basal ganglia antibodies than patients with convalescent Sydenham's chorea, rheumatic fever without Sydenham's chorea, or healthy pediatric controls [32•].

There is substantial evidence for elevated antineuronal antibodies in children with Tourette's syndrome, but further work needs to be done to define the specific antibodies and determine their functional abilities. Recent work has focused on possible animal models of Tourette's syndrome, which has allowed more specific immunohistochemical studies to be done. Stereotypies and episodic utterances, hypothesized to be analogous to the involuntary movements seen in Tourette's syndrome, were induced in rats by intrastriatal microinfusions of gamma globulins from patients with Tourette's syndrome. Post infusion immunohistochemical analysis confirmed the presence of gamma globulin selectively bound to striatal neurons [33]. An increased rate of oral stereotypies has also been demonstrated in rats who had bilateral infusions into the ventrolateral striatum with sera from patients with Tourette's syndrome. The oral sterotypies were significantly increased in the rats infused with the sera from patients with the highest levels of antineural antibodies [34].

D8/17 immunologic marker for central nervous system disorders

Elevated D8/17 expression on B lymphocytes is a known susceptibility marker of rheumatic fever and has also been reported among patients with OCD [35,36]. An overexpression of D8/17 on B lymphocytes was found in

a group of patients with tic disorders when compared with healthy volunteers [37••]. Although overexpression of D8/17 on B lymphocytes has been reported among several groups of patients with OCD and tic disorders, recent data suggest that the discriminatory ability of D8/17 expression to identify patients with streptococcal related OCD or tic disorders has declined from the initial findings [38•]. Methodological limitations of the current D8/17 assay need to be addressed prior to its use as a diagnostic tool in post-streptococcal OCD or tic disorders [39•].

Conclusion

The primary evidence for post-streptococcal autoimmune CNS disease is provided by studies of Sydenham's chorea, the neurologic manifestation of rheumatic fever. Reports of OCD, tic disorders and other neuropsychiatric symptoms occurring in association with GABHS infections suggest that a variety of CNS sequelae may be triggered by post-streptococcal autoimmunity; however, many questions remain unanswered. In order for this field to advance, carefully designed clinical trials must be conducted on well defined neuropsychiatric disorders that have a post-streptococcal onset. These trials should continue to refine the phenomenology of these illnesses, determine antineuronal antibodies specific to the disorders, determine the pathobiologic processes and biologic activity of the antineuronal antibodies, and advance our understanding of the risk factors and possible markers for disease state that allow for improved diagnosis and treatment.

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