PANDAS, Autism Spectrum Disorders and Involvement of Streptococcus Organisms

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ABSTRACT: The term “Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections”, or PANDAS, was coined in the late 1990s by Susan Swedo and colleagues of the National Institute of Mental Health. The term refers to a subgroup of childhood obsessive-compulsive and tic disorders triggered or exacerbated by group A beta-hemolytic streptococcus (GABHS) infection. GABHS is believed to elicit production of antibodies that cross-react with neural tissues and thereby provoke the neurobehavioral symptoms associated with PANDAS. Similar anti-GABHS antibodies have been found in a subset of persons with Autism Spectrum Disorders (ASD) giving rise to concerns that other streptococcal organisms, including the probiotic species S. thermophilus, may be capable of provoking an autoimmune response. A review of the literature reveals no evidence that S. thermophilus promotes production of cross-reactive anti-streptococcal antibodies and no indication that any streptococcal organism other than GABHS is associated with PANDAS or ASD. S. thermophilus lacks the virulence factors found in pathogenic streptococcal species such as GABHS rendering it a benign organism that has, in fact, demonstrated a variety of health benefits for humans.

THE EVOLUTION OF PANDAS

The belief that neuropsychiatric symptoms might be associated with streptococcal infection dates back to 1894 when Sir William Osler described “a certain perseverativeness of behavior” in patients with Sydenham’s chorea, a movement disorder associated with rheumatic fever and triggered by infection with GABHS.1 Later observations that persons with Sydenham’s chorea often manifest symptoms of obsessive-compulsive disorder, and vice versa,2,4 raised suspicions that perhaps these and other neurological and neurobehavioral illnesses have a common streptococcal etiology. Neuroimaging studies demonstrating basal ganglia dysfunction and findings of antineural antibodies in both obsessive compulsive disorder and Sydenham’s chorea supported this hypothesis.2 A pathophysiological model emerged in which antibodies against GABHS were believed to cross-react with neural tissue in the basal ganglia leading to dysfunctional movements, tics, and/or other neuropsychiatric symptoms. The term PANDAS (Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders) was introduced to summarize the essential features of a subgroup of patients with obsessive-compulsive disorder or tics (including Tourette’s syndrome) whose symptoms were triggered or exacerbated by bacterial or viral infections.6 Swedo and colleagues later refined these areas.

AUTISM SPECTRUM DISORDERS AND AUTOIMMUNITY

ASD is a neurodevelopmental disorder characterized by social withdrawal, communication deficits, and often repetitive or restrictive behaviors. While its etiology remains unclear, ASD is believed to be a heritable disorder in which genetic and environmental factors combine to produce an array of neurological, immunological, and metabolic derangements. The possibility of a link between autism and autoimmunity was first posited in 1971 by researchers at the Johns Hopkins Hospital who observed symptoms of autism in a child with primary Addison’s disease and a strong family history of autoimmunity. Since then, a variety of immune abnormalities have been described in ASD including T- and B-cell dysfunctions,10 a proinflammatory cytokine pattern,11 and anti-neural antibodies,11 the latter providing the clearest evidence of autoimmune dysregulation. Autoimmunity in ASD has been attributed to abnormal antibody response to the measles component of MMR vaccination, dietary peptides from dairy and wheat, specific bacterial antigens from Chlamydia pneumoniae and GABHS, and possibly the ethyl mercury component of thimerosal.11-14 Maternal antibodies crossing the placental barrier have also been postulated as a source of autoantibody production in infants.15 The growing number of reports of autoreactivity in ASD patients has lent support to a model of autoimmune pathogenesis in which antibodies cross-react with one or more components of the brain giving rise to dysfunction in these areas.11

IMPLICATION OF S. THERMOPHILUS IN PANDAS AND ASD?

There is little doubt that streptococcal infection can be a causative or contributory factor in a number of neurological disorders.16,17 By definition, the onset of symptoms in PANDAS is temporally associated with streptococcal infection.7 Additionally, serum samples of autistic patients have been found to produce higher than normal levels of anti-streptococcal antibodies that cross-react with neural tissue.13 The etiological role of streptococcal infection in PANDAS and possibly ASD has led some to question whether non-pathogenic species of streptococcus, such as the commonly ingested probiotic organism S. thermophilus, may trigger autoantibody production in either of these disorders. While this is an understandable concern, it must be emphasized that GABHS, or Streptococcus pyogenes, is the only streptococcal organism that has been shown to evoke immunological reactivity in either PANDAS or ASD. A search of the medical literature reveals no evidence of production of cross-reactive antibodies in PANDAS or ASD patients exposed to other species of streptococcus, such as S. thermophilus. In contrast to the human pathogen GABHS, S. thermophilus is a food-source organism that ferments dairy products (it is one of the probiotic organisms commonly used in the culturing of yogurt) and has been associated with a variety of health benefits in humans.18-21 Though belonging to the same genus as disease-causing GABHS, an examination of the genome of S. thermophilus reveals a lack of the most important genetic determinants of pathogenicity.22 Of note, one of these determinants, a specific M protein (STM6P) found in GABHS, to which autistic children have demonstrated immune reactivity,13 is not present in S. thermophilus.23 Other M proteins known to evoke antibodies that cross react with human brain tissue, such as serotypes 5 and 19,24 are also specific to various strains of GABHS but are not found in S. thermophilus.23 In fact, of the more than 60 different microbial peptides that to date have been reported to cross-react with human brain tissue, none derive from S. thermophilus.16,24,25 Additionally, streptolysin O, a virulence factor against which the human immune system produces antistreptolysin O (ASO), is expressed only by pyogenic streptococcal species such as
GBS and has never been associated with *S. thermophilus*. Therefore, elevated ASO titers should not be considered indicative of the presence of *S. thermophilus* in the body. A recent review of the molecular biology and physiology of *S. thermophilus* by Hols, et al. makes clear that *S. thermophilus*:

- “… has followed an evolutionary path divergent to that of pathogenic species due to its adaptation to the rather narrow and well-defined ecological niche, milk.”
- “… has lost many virulence related functions common among pathogenic streptococci.”

Thus all evidence indicates that both PANDAS and ASD are associated solely with GBS. No other species of *Streptococcus*, including *S. thermophilus*, has ever been implicated in either of these disorders.

On the contrary, research shows that *S. thermophilus* along with other probiotic organisms can actually improve human resistance against pathogens such as GABHS. In one study, consumption of milk cultured with *S. thermophilus* and other lactic acid bacteria was found to reduce or eliminate the presence of GABHS and *S. pneumoniae* in the nasal cavities of study participants. *S. thermophilus* may also favorably modulate specific aspects of immune dysfunction in ASD. Studies have found that persons with ASD exhibit a polarity in Th1/Th2 lymphocyte responses such that Th2 responses predominate. This type of imbalance is believed to predispose to towards allergic (IgE-mediated) and autoimmune (antineuronal antibody-mediated) processes that can exacerbate symptomatology in autism and possibly contribute to its pathogenesis. Preliminary research suggests that *S. thermophilus* may help balance Th1/Th2 responses. In one study, mice challenged with the antigenic protein ovalbumin produced significantly more Th1-associated IFN-gamma and significantly less Th2-associated IgE when fed milk fermented with *S. thermophilus* than when fed unfermented milk. In another study, mesenteric lymph nodes from colitis-prone mice orally gavaged with *S. thermophilus* and *B. breve* organisms displayed a cytokine secretory profile polarized towards a TH1 response. These studies suggest probiotic organisms like *S. thermophilus* may favorably influence immune function and provide therapeutic benefit in TH2–dominant conditions such as ASD.

**SUMMARY**

PANDAS is a recently described neurobehavioral disorder characterized by pediatric onset of obsessive-compulsive disorder and/or tics following infection with mycoplasma group A beta-hemolytic streptococcus (GABHS). Findings of anti-streptococcal antibodies capable of cross reacting with neural tissue in some persons with Autism Spectrum Disorders (ASD) has given rise to concerns that the probiotic organism *S. thermophilus* may also trigger production of antineuronal antibodies. This concern in unfounded as the onset of PANDAS or presence of anti-streptococcal antibodies in ASD has never been associated with streptococcal organisms other than GABHS. GABHS-associated autoimmune reactions in PANDAS and ASD appear to be mediated by surface proteins specific to *S. pyogenes* and not carried by *S. thermophilus*. *S. thermophilus* has a long history of safe use around the world as a probiotic component of yogurt and other fermented dairy products and has demonstrated health benefits for humans. Current evidence indicates there is no basis for believing *S. thermophilus* provokes autoimmune reactions as does GABHS and rather suggests this probiotic organism can protect against growth of GABHS and other potentially harmful streptococcal species in humans.

**References**