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Maternal History of Autoimmune Disease in Children Presenting with Tics and/or Obsessive-Compulsive Disorder

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Abstract

Objectives—A commonality across a number of pediatric neuropsychiatric disorders is a higher than typical rate of familial – and especially maternal – autoimmune disease. Of recent interest, a subtype of obsessive-compulsive disorder (OCD) and tic disorders known collectively as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) is believed to be secondary to central nervous system (CNS) autoimmunity that occurs in relation to group A streptococcal infection. Thus, we hypothesized that a sample of children with OCD and/or tics would have an increased maternal risk for an autoimmune response relative to population norms. We also expected maternal prevalence of various autoimmune diseases to be higher among those participants that met the putative criteria for PANDAS.

Methods—We examined, via structured interview, the medical history of the biological mothers of 107 children with OCD and/or tics.

Results—Autoimmune disorders were reported in 17.8% of study mothers, which is significantly greater than the general prevalence among women in the United States (approximately 5%). Further, study mothers were more likely to report having an autoimmune disease if their children were considered “likely PANDAS” cases versus “unlikely PANDAS” cases.

Conclusions—Results offer preliminary support for hypothesized links between maternal autoimmune disease and both OCD/tics and PANDAS in youth. Further research is necessary to clarify these general associations; links to specific autoimmune disease; and relevance of autoimmune disease in other family members (e.g., fathers).

Introduction

Prevalence rates suggest that autoimmune disease (AD) is not uncommon, affecting approximately 5% of women in the U.S. and 3% of men (Cooper & Stroehla, 2003). Rose and Bona propose three types of evidence that establish an autoimmune disease: direct evidence from transfer of pathogenic antibody or pathogenic T cells, indirect evidence based on reproduction of the autoimmune disease in experimental animals, and circumstantial evidence from clinical clues (Rose & Bona, 1993).

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One line of clinical support has developed from a purported link between parental AD and developmental/neurobiological disorders in children. Findings remain equivocal. In one noteworthy study, investigators compared families that had a child with Pervasive Developmental Disorder (PDD) to those that had a child with an autoimmune disease and those with a healthy child, and found that families of a child with PDD had a higher frequency of autoimmune diseases (especially Rheumatic Fever) than did either other family type (Sweeten, Bowyer, Posey, Halberstadt, & McDougle, 2003). Another study did not find a significant difference in general prevalence of maternal autoimmune disease (between youth with autism and normal controls), but did report both an association between infantile autism and maternal ulcerative colitis in a sample of 111 patient-mother pairs (as compared to 330 control pairs); and between infantile autism and paternal type I diabetes (Mouridsen, Rich, Isager, & Nedergaard, 2007). Finally, Croen and colleagues did not find a significant difference in general prevalence of maternal autoimmune disease (based upon children's PDD caseness) (Croen, Grether, Yoshida, Odouli, & Van de Water, 2005); however, psoriasis did occur more frequently among those mothers of children with autism than among those of children without the diagnosis. As the incidence of autoimmune diseases increases throughout adult life, and this latter study only took into account maternal autoimmune conditions diagnosed within the 4-year period surrounding childbirth, a longer-term study would clearly be warranted.

Autoimmune and genetic contributions have been purported in bipolar disorder as well. Vonk et al. sampled thyroperoxidase antibodies (TPO-Abs) in 22 monozygotic and 29 dizygotic bipolar twins as well as 35 healthy control twins (Vonk, van der Schot, Kahn, Nolen, & Drexhage, 2007). Twenty-seven percent of subjects with bipolar disorder were positive for autoimmune thyroiditis, while only 16% of the control subjects tested positive. Further, there were significant differences in TPO-Abs such that monozygotic non-bipolar co-twins had the highest levels; followed by significantly lower levels in dizygotic non-bipolar co-twins; and, lastly, by significantly lower levels still in control twins. While the TPO-Abs levels in bipolar patients were significantly higher than in controls, levels did not differ between those with bipolar disorder and their non-bipolar twins, suggesting that increased TPO-Abs levels may be more related to genetic vulnerability to develop the disease than to the disease process (Vonk, et al., 2007).

The potential autoimmune contribution to Tourette Syndrome (TS) has recently gained research attention. For instance, although the sample size was modest, Yeh et al. found antineural antibodies in the sera of four patients with TS as well as in their family members (Yeh, et al., 2006); in contrast, antineural antibodies were not found in normal healthy controls. This presumed link between autoimmune processes and certain mental disorders has also sparked the study of neuroimmunological processes as they potentially relate to the pathophysiology of obsessive compulsive disorder (OCD). Indeed, the finding of anti-brain antibodies in patients with OCD offers circumstantial evidence for central nervous system (CNS) autoimmunity (Murphy, Sajid, & Goodman, 2006). Also pointing to a link, patients with Sydenham's chorea (SC), systemic lupus erythromatosus, and other autoimmune diseases have evidenced a high rate of comorbid OCD (Murphy, et al., 2006; Slattery, et al., 2004). In fact, relative to the general population, individuals with systemic lupus erythromatosus are 10 to 15 times more likely to have OCD (Bachen, Chesney, & Criswell, 2009; Slattery, et al., 2004). Further, OCD was more prevalent among relatives of subjects with Rheumatic Fever (RF) than among control relatives – even when RF-affected relatives were taken out of the analyses (Hounie, et al., 2007) – suggesting that psychiatric disorders are associated with autoimmune disease in both affected patients and their relatives.

Rheumatic Fever is a classic example of an autoimmune illness triggered by an infection. With RF, the pathogen involved is group A streptococcus (GAS), the most common cause of

childhood bacterial pharyngitis (Cunningham, 2000). GAS infections have been implicated to trigger pediatric onset neuropsychiatric disorders, most notably OCD and tic disorders. This presentation of OCD and tic disorders with presumed association to GAS infection has been collectively categorized as Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) (Murphy, et al., 2004; Swedo, et al., 1998). As yet, PANDAS has not been universally accepted as an official diagnosis, nor is it clear what features will clearly delineate this subtype from other youth with tics and OCD. For example; in an examination of rates of neuropsychiatric disorders in 139 first degree relative (FDR) of 54 subjects with PANDAS, 26% of PANDAS subjects had a FDR with OCD. While this rate is significantly higher than the general population, it is similar to that reported for subjects with OCD and tic disorders (Lougee, Perlmutter, Nicolson, Garvey, & Swedo, 2000). This study did not report rates of autoimmunity in FDR.

Although a causal relationship between streptococcus and both OCD and tic disorders has yet to be determined, mounting evidence suggests immune dysfunction in a subset of patients with OCD and tics (Dale, Heyman, Giovannoni, & Church, 2005; Hoekstra & Minderaa, 2005; Maina, et al., 2009; Morer, et al., 2008); as well as neuropsychiatric risks from repeated streptococcal infections (Mell, Davis, & Owens, 2005; Murphy, et al., 2006; Perrin, et al., 2004). The underlying pathophysiology is not known. Maternal antibodies are transferred during pregnancy (Lee, et al., 2009); but some have postulated this transplacental passage of antibodies may affect brain development via inflammation or via interaction with neurotransmitter receptors (Vincent, Dalton, Clover, Palace, & Lang, 2003). Circumstantial evidence for autoimmunity includes environmental triggers of relapses, familial risk, and response to immune modulating therapies (Murphy, Sajid, & Goodman, 2006). Recreating the illness either by animal models via recreation of autoimmune pathology or by passive transfer of antibodies has been mixed (Loiselle, Lee, Moran, & Singer, 2004; Yaddanapudi, et al., 2009). In addition, poor standardization in the field for phenotype characterization and assay methodology has hampered progress thus far. Duration of illness at the time of assay may have a significant impact on the level of evidence for autoimmunity, yet this characteristic is generally not mentioned in studies examining autoimmunity in OCD/tics. For example, studies in diabetes have shown levels of markers for autoimmunity to depend upon both time of onset and duration of illness (Hathout, et al., 2000; Mayer, et al., 2007).

The influence of prenatal exposure to maternal immune activation upon CNS development and behavior has yet to be fully explored. Prenatal exposure to cytokine levels is dependent upon plethora factors including: estrogen levels, autoimmune disease type (Th1 vs. Th2 predominant), disease activity, concurrent medications, and many other factors. Some autoimmune diseases such as rheumatoid arthritis and autoimmune thyroid diseases tend to improve during pregnancy. However, evidence exists suggesting that in subsets of immune disease-represented by lupus, certain viral and other infections-the fetus is subjected to sequelae of maternal immune dysregulation (Atladdottir, et al., 2009; Doria, et al., 2006). These factors such as elevated cytokines and autoantibodies, in concert with genetic predisposition, may act to increase fetal cytokine signaling and expression, disrupt trophic factor and apoptotic signaling, as well as modulate cytoarchitecture in the CNS (Golan, Lev, Hallak, Sorokin, & Huleihel, 2005). For example, animal models of prenatal administration of various cytokines have shown that increased levels of specifically IL-6 in the maternal serum play an important role in influencing the behavior of offspring (Croonenberghs, Bosmans, Deboutte, Kenis, & Maes, 2002) (Smith, Li, Garbett, Mirnics, & Patterson, 2007).

In this study, we examined the rates of reported autoimmune illness in the mothers of children with OCD/tics. We hypothesized that rates would be higher in these mothers than among those of the general population, and that those children determined to have the PANDAS phenotype would have mothers with the highest rates of autoimmunity.

Method

Subjects

Along with their biological mothers, 107 children (65 males) participated. The average age of the subjects was 9.2 years ($SD \pm 2.4$; range = 4.1–17.0). Six of the subjects were of Hispanic ethnicity, three were Asian, one was African-American, and ninety-seven were Caucasian. Subjects with co-morbid depression, ADHD, or other compulsive disorders were included as long as OCD or a tic disorder comprised the primary diagnosis. To ensure that a medical disorder could not explain the presence of OCD and/or tics, subjects were excluded if they had a history of rheumatic fever or major autoimmune disease or a diagnosis of autism; mental retardation; schizophrenia-spectrum disorder; or a chronic degenerative neurological disorder. For mothers who provided it (i.e., 51 of 101), the average age was 38.33 years ($SD \pm 4.86$ years). The discrepancy between number of child participants and number of mothers (107 and 101, respectively) is due to the presence of four sibling pairs and one sibling trio.

Procedures

Once informed consent and assent were granted, eligible subjects underwent a comprehensive neuropsychiatric evaluation with the first author. This evaluation typically lasted three hours and included: 1) an interview for demographic information and maternal history; 2) semi-structured psychiatric diagnostic interviews to establish psychiatric diagnoses and to monitor severity of psychiatric symptoms, particularly obsessive-compulsive symptoms and tics; 3) comprehensive parent, child, and clinician ratings and assessments – primarily with regard to OCD and tics; 4) the Clinical Global Impression Scales (Severity and Improvement) (Guy, 1976); 5) questionnaires to elicit information regarding infections and PANDAS stigmata; 6) laboratory measures, including streptococcal antibodies and upper respiratory cultures; and 7) physical examinations including Tanner staging and neurological assessment that was comprised of standard neurological examination, fine motor battery, soft neurological examination, and brief executive function testing. After assessments were completed, final diagnoses of subjects were made by a consensus of study physicians and clinicians (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982).

Maternal History

Data were collected via parent report followed by physician interview with the biological mother for maternal history of both medical and psychiatric illnesses. Mothers' diagnostic histories were specifically elicited (via self-report) on a number of autoimmune diseases, specifically: rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes, Behcet disease, Hashimoto's thyroiditis, Graves' disease, Crohn's disease, Guillain-Barré, and multiple sclerosis. However, mothers were granted the opportunity to list any other (i.e., unlisted) autoimmune diagnoses. All reported autoimmune diagnoses were then confirmed by a study physician via interview.

Clinician-Administered Measures

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime (K-SAD-PL) is a semi-structured psychiatric interview for children used for diagnostic assessment (Kaufman, et al., 1997).

The Infection-Related OCD/TS Evaluation (IROTE) is an assessment of infection-triggered symptoms and history of autoimmune illness devised by the first author (Murphy, et al., 2004). This clinician-on-parent-administered questionnaire elicits information germane to the diagnosis of immunological conditions, infections, RF, SC, and other movement

disorders. This instrument also screens for personal and family history of autoimmune illnesses. Physician review of the IROTE in addition to physical and neurological examination of the child contributed greatly to children's PANDAS classification.

Group Assignment

Participants were assigned to two subgroups based on physician evaluation of the children, consideration of their medical histories, and the children's overall adherence (determined via consensus) to existing PANDAS criteria (Swedo & Grant, 2005). The two groups were as follows: "likely PANDAS" (i.e., deemed to closely match existing PANDAS criteria; evidencing a history of GAS associated with dramatic onset and fluctuating course; $n = 40$) and "unlikely PANDAS" (i.e., showing limited or no history of required combination of: GAS, dramatic onset, and/or a fluctuating course; $n = 67$). All had OCD and/or tics, all were children, and all had onset of symptoms pre- or early puberty.

Data Analyses

First, a series of binomial tests was run to determine whether prevalence of autoimmune diseases among study mothers (overall) differed from those among similarly-aged women in the general population. Second, between-group risk ratios (i.e., of "likely PANDAS" mothers to "unlikely PANDAS" mothers) were determined for presence of a) any autoimmune disease; and b) specific autoimmune diseases. For comparative analyses examining PANDAS caseness, the child was the unit of analysis; thus, all participating youth were included in analyses ($n = 107$). For analyses of mothers relative to the general female population, the unit of analysis was the individual mother ($n = 101$).

Results

Prevalence of Maternal Autoimmune Disease in All Subjects

Among subjects' mothers ($N = 101$), 17.8% ($n = 18$) had an autoimmune disease. Specifically, 11.9% ($n = 12$) had Hashimoto's thyroiditis, 3.0% ($n = 3$) had SLE, 3.0% ($n = 3$) had rheumatic fever, 2.0% ($n = 2$) had rheumatoid arthritis, and 2.0% ($n = 2$) had Graves' disease. No respondents had a history of diabetes, Behcet disease, Crohn's disease, or Guillain-Barré. The proportion of subjects' mothers with any AD differed significantly from that found among women in the general population (approximately 5% (Cooper & Stroehla, 2003), $p < 0.01$; See Table 1). As for specific disorders, only the proportion of subjects' mothers with SLE (more in subjects' mothers; $p < 0.01$) (Dray-Spira, Gary, & Brancati, 2008), and the proportion of subjects' mothers with diabetes (less in subjects' mothers; $p < 0.05$) (Jacobson, Gange, Rose, & Graham, 1997), differed significantly from those found among similarly-aged women in the general population.

Likelihood of Maternal Autoimmune Disease Based on Child OCD/Tic Disorder

As children with PANDAS are frequently described to have OCD with comorbid tics and this comorbid state implies a more complex neuropsychiatric state, a comparison of the influence of comorbid OCD and tics to tics only and OCD only was performed. As compared to mothers of children without OCD, mothers of children with OCD were 1.73 times more likely to report having at least one autoimmune disease. Mothers of children with and without tic disorders did not differ in rates of reported autoimmune disease. As compared to mothers of children without the comorbid condition, mothers of children with both OCD and a tic disorder were 1.25 times more likely to report having at least one autoimmune disease.

Risk Ratios of Maternal Autoimmune Disease, based on Child's PANDAS Group

Among “likely PANDAS” mothers, 25.0% reported having at least one autoimmune disease – compared with 13.4% of “unlikely PANDAS” mothers. Accordingly, “likely PANDAS” mothers were 1.86 times more likely than were “unlikely PANDAS” mothers to report having at least one autoimmune disease. For a breakdown by autoimmune condition, and corresponding risk ratios, refer to Table 1.

Discussion

Similar to prior reports on relationships between parental AD and both autism and PDD (Mouridsen, et al., 2007; Sweeten, et al., 2003) our results suggest a general association between maternal AD and PANDAS. In addition, our preliminary data suggest specific links between PANDAS and maternal presence of a number of autoimmune diseases – namely hypothyroidism (i.e., Hashimoto's thyroiditis). Although Hashimoto's thyroiditis is a common autoimmune disorder in women, our results of an increased prevalence in mothers of children classified with PANDAS subtype of OCD and tics suggest that perhaps a genetic diatheses for autoimmunity exists in these children. Shared risk factors (eg. cytokine or cellular dysfunction, genetic or HLA variations, environmental factors, etc.) among autoimmune illnesses are frequently reported (Brown, 2009) as well as the increased risk of individuals having a second autoimmune disorder (Boelaert, et al., 2010). Of interest are case reports of co-occurrence of Hashimoto's thyroiditis and rheumatic fever (Yildiz, Gokcay, Gokcay, & Karasoy) (Ertugrul, et al., 2008). In summary, the present study supports prior reports of an association between maternal autoimmune disease and pediatric neuropsychiatric disorders (Croen, et al., 2005; Mouridsen, et al., 2007). To further elucidate a specific link between pediatric OCD and especially the PANDAS subtype with familial autoimmune disease, we encourage more widespread and validated examination of the autoimmune histories of family members of youth with OCD, tics, and PANDAS.

Limitations

Within the present study's methodology, several limitations should be noted: 1) Access to medical records was limited – and, thus, maternal diagnoses relied predominantly upon self-report and physician review; 2) Maternal diagnoses were reviewed by a single physician (versus multiple physicians); 3) Only youth with primary OCD and/or tics were included in the study and, thus, comparisons of maternal autoimmune disease prevalence rates with other childhood disorders were not possible; and 4) A nonclinical comparison control group was not included.

Implications

Autoimmunity in the mother may be one additional risk factor for development of OCD and tics in young children. In addition to assessing for GAS history among youth, evaluations for PANDAS should include careful survey of familial autoimmune history and examination of parental risk factors for autoimmunity. If a definitive link is found in a subset of patients, new possibilities for treating OCD/tics could be therapeutics that modulate immune function. For example, as demonstrated in animal studies, blocking IL-6 with neutralizing antibody attenuates the associated behavioral and pathological symptoms in exposed offspring (Smith, et al., 2007). Interventions that target immune function may provide a tolerable and effective treatment option for these neuropsychiatric symptoms in young children.

Focus Points

- As compared to the general female population in the United States, mothers in our study (i.e., mothers of children with OCD and/or a tic disorder) were significantly more likely to have an autoimmune disease.
- In cases of “likely PANDAS” (versus “unlikely PANDAS”), presence of maternal autoimmune disease was generally greater. In particular, these mothers evidenced a greater prevalence of Hashimoto’s thyroiditis; rheumatic fever; rheumatoid arthritis; and Graves’ disease/hyperthyroidism.
- Taken together, our findings suggest preliminary evidence for a relationship between PANDAS and maternal autoimmune disease.

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Table 1
Prevalence of Autoimmune Disorders in Comparison Populations and Study Mothers.

Autoimmune Disorder	Overall Prevalence in Study Mothers		Prevalence by PANDAS group		
	Expected	Observed	Likely (n=40)	Unlikely (n = 67)	Risk Ratio
Any	4.67%	17.8% **	25.0%	13.4%	1.86
Diabetes	2.82%	0% *	0%	0%	-
Rheumatoid Arthritis	2.40%	2.0%	2.5%	1.5%	1.68
Hashimoto's Thyroiditis	6.63%	11.9%	20.0%	6.0%	3.35
Guillain-Barre	0.98%	0%	0%	0%	-
Systemic Lupus	0.09%	3.0% **	2.5%	4.5%	0.56
Erythematosis					
Graves' /Hyperthyroidism	2.07%	2.0%	2.5%	1.5%	1.68
Rheumatic Fever	1.49%	3.0%	5.0%	1.5%	3.35
Behcet Disease	0.0019%	0%	0%	0%	-
Crohn's Disease	0.17%	0%	0%	0%	-

* = $p < 0.05$

** = $p < 0.01$