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Altered immunoglobulin profiles in children with Tourette syndrome

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ABSTRACT

Background: Post-infectious autoimmunity and immune deficiency have been implicated in the pathogenesis of Tourette syndrome (TS). We asked here whether B cell immunity of patients with TS differs from healthy subjects.
Methods: In two independent cross-sectional samples, we compared serum levels of IgG1, IgG2, IgG3, IgG4, IgM, IgA, and IgE in 21 patients with TS from Yale University (17 males, 4 females, 8–16 years) versus 21 healthy controls (13 males, 8 females, 7–17 years); and in 53 patients with TS from Groningen University (45 males, 8 females, 6–18 years) versus 53 healthy controls (22 males, 31 females, 6–18 years), respectively. We also investigated correlations between Ig concentrations and symptom severity. In 13 additional patients (9 males, 4 females, age range 9–14), we established Ig profiles at time points before, during, and after symptom exacerbations.
Results: IgG3 levels were significantly lower in Yale patients compared to healthy children (medians 0.28 versus 0.49 mg/ml, $p = .04$), while levels of IgG2, IgG4, and IgM in patients were lower at trend-level significance ($p \leqslant .10$). Decreased IgG3 (medians 0.45 versus 0.52 mg/ml; $p = .05$) and IgM (medians 0.30 versus 0.38 mg/ml; $p = .04$) levels were replicated in the Groningen patients. Ig levels did not correlate with symptom severity. There was a trend-level elevation of IgG1 during symptom exacerbations ($p = .09$).
Conclusion: These pilot data indicate that at least some patients with TS have decreased serum IgG3, and possibly also IgM levels, though only few subjects had fully expressed Ig immunodeficiency. Whether these changes are related to TS pathogenesis needs to be investigated.

1. Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterized by the presence of involuntary, rapid, recurrent, non-rhythmic movements, and/or vocalizations, often accompanied by obsessions and/or compulsions. The onset of symptoms occurs mostly between 5 and 7 years of age, symptoms typically wax and wane over time, and the disorder is often outgrown by young adulthood, except in a minority of cases (Leckman, 2002; Lombroso and Scahill, 2008).

Strong evidence indicates that the disorder is hereditary, but the exact mechanisms involved in the genetic transmission are not resolved (Hoekstra et al., 2004). It appears that TS is genetically heterogeneous and that environmental factors may influence the onset, course, and severity of symptoms. Among multiple environmental factors, infections with group A beta hemolytic streptococcus (GABHS) have been proposed to play a key role in the pathogenesis of TS in at least some patients. This has received significant attention after a wave of infections with GABHS in Rhode Island was followed by increased frequency of tic disorders in pediatric practice (Kiessling et al., 1993). A subgroup of patients with TS with a medical history of GABHS infection prior to the onset of TS symptoms was designated as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) (Swedo et al., 1998). In addition, other infections were implicated in TS by studies demonstrating that common cold preceded TS symptom exacerbations (Hoekstra et al., 2005) and that antibodies against mycoplasma pneumoniae are elevated in patients with TS (Muller et al., 2004), and by case reports suggesting relations of TS with Lyme disease (Riedel et al., 1998) or

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toxoplasmosis (Brynska et al., 2001). Establishing evidence for the role of post-infectious autoimmunity in the pathogenesis of TS has proven quite challenging and the concept remains controversial (reviewed in (Giovannoni, 2006; Martino et al., 2009). This is mainly due to the complexity of neuro-immune interactions and the limited accessibility to the site of pathology, particularly in children. Nevertheless, this line of investigation is important as it may prove relevant not only to TS itself, but also to other pediatric neuropsychiatric diseases, for example autism spectrum disorders, where a role of the immune system was implicated and which has a well-established clinical link with TS (Baron-Cohen et al., 1999; Ivarsson and Melin, 2008).

Why children with TS would be prone to post-infectious autoimmune disorders remains unclear. Two recent epidemiological studies brought new insight into possible immune mechanisms in these patients by revealing that children with a newly diagnosed tic disorder or obsessive–compulsive disorder (OCD) were significantly more likely to have had a GABHS infection in the previous year than unaffected control subjects (Leslie et al., 2008; Mell et al., 2005). A higher vulnerability to infections may be due to some form of immune deficiency. Patients with immune deficiencies (even the isolated deficiencies that were originally considered to be benign, such as isolated immunoglobulin (Ig) A deficiency) are now known to have increased occurrence of autoimmune disorders (Bussone and Mouthon, 2009; Woof and Kerr, 2006). Previous studies have suggested that patients with TS may have enhanced activity of T cell immunity (Gabbay et al., 2009; Leckman et al., 2005) (Moller et al., 2008), implying that the deficient immune mechanisms may concern humoral branch of the immunity. In our first pilot study, we found decreased plasma IgA levels in patients with TS and/or OCD, particularly in the subgroup fulfilling the PANDAS criteria, implying that mucosal immunity may be compromised in these patients (Kawikova et al., 2010).

In this second pilot study, we continued to investigate the hypothesis that humoral immune deficiency may be present in patients with TS. We used existing archived samples and included a larger number of subjects from two clinical sites, focused on patients with mostly non-PANDAS TS and established detailed serum Ig profiles (including IgG subclasses and IgE). We chose to not specifically enrich the sample for PANDAS cases as we did in an earlier pilot study (Kawikova et al., 2010), since other microorganisms than GABHS have been implicated in TS (Hoekstra et al., 2005; Muller et al., 2004, 2000).

2. Methods

2.1. Subjects

The study involved samples of convenience from cross-sectional collections that were obtained and archived at two distinct clinical sites. Additionally, we assessed changes during symptom exacerbations in serum samples collected longitudinally in one of the sites. Table 1 shows demographic and clinical characteristics of all subjects.

Selection of samples from these collections was performed based on the diagnosis of TS (TS patients with and without OCD

Table 1
Demographic and clinical characteristics of patients with TS and healthy subjects.

	Yale University cross-sectional sample		Groningen University cross-sectional sample		Yale University longitudinal sample
	Patients (n = 21)	Healthy subjects (n = 21)	Patients (n = 53)	Healthy subjects (n = 53)	(n = 13)
Male, n (%)	17 (81.0)	13 (61.9)	45 (84.9)	22 (42)	9 (69.0)
Age, Mean (SD), range (years)	11.9 (2.6), 8–16	12.2 (2.7), 7–17	12.3 (3.2), 6–18	12.2 (3.0), 6–18	10.6 (1.7), 9–14
	n (%)		n (%)		n (%)
Type of tic disorder					
Tourette's disorder	18 (85.7)		52 (98.1)		12 (92.3)
Chronic motor tic disorder	3 (14.3)		1 (1.9)		1 (7.7)
Patients fulfilling PANDAS criteria	3 (14.3)		0		5 (38.5)
Psychotropic medication use					
Antipsychotic agents	1 (4.8)		9 (17.0)		0
Antidepressive agents	2 (9.5)		1 (1.9)		1 (7.7)
Clonidine	5 (23.8)		3 (5.7)		5 (3.8)
Psychostimulants	0		4 (7.5)		0
Atomoxetine	0		4 (7.5)		0
Combination of two or more agents	8 (38.1)		12 (22.6)		6 (4.6)
No psychotropic medication	5 (23.8)		20 (37.8)		1 (7.7)
Antibiotics	0		0		4(33.1)
	Mean (SD), range (n = 21)		Mean (SD), range (n = 21)		Mean (SD), range (n = 13)
YGTSS ratings					
Total	18.5 (7.6), 5–32		22.1 (8.1), 3–39		
Motor	10.3 (4.5), 0–18		13.7 (4.2), 0–22		
Vocal	8.2 (4.8), 0–15		8.5 (5.5), 0–19		
Δ YGTSS before – during exacerbation					15.6 (7.5), 9–31
Δ YGTSS after – during exacerbation					10.4 (5.5), 2–20
	Mean (SD), range (n = 12)		Mean (SD), range (n = 30)		
CY-BOCS ratings					
Total	14.8 (8.0) 5–30		11.1 (6.7) 3–28		
Obsessive	7.2 (3.9) 0–15		4.2(4.9) 0–16		
Compulsive	7.7 (5.2) 0–15		6.9 (3.7) 0–14		

PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; YGTSS, Yale Global Tic Severity Scale; CY-BOCS, Children's Yale-Brown Obsessive–Compulsive Scale.