Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2009 August 31; 33(6): 967–971. doi:10.1016/j.pnpbp.2009.05.001.

A cytokine study in children and adolescents with Tourette's disorder

Vilma Gabbay[a,*], **Barbara J. Coffey**[a], **Leah E. Guttman**[a], **Lev Gottlieb**[a,1], **Yisrael Katz**[a], **James S. Babb**[b], **Mia M. Hamamoto**[a], and **Charles J. Gonzalez**[c,2]

[a] NYU Child Study Center, Child and Adolescent Psychiatry, New York University School of Medicine, 577 First Avenue, New York, NY 10016, United States

[b] Radiology, Research, New York University School of Medicine, Bellevue C&D Building 122, 462 First Avenue, New York, NY 10016, United States

[c] Immunology and Infectious Diseases, New York University School of Medicine, 550 First Avenue, New York, NY 10016, United States

Abstract

Background—While immune system dysregulation has been postulated to play a role in Tourette's disorder (TD), most research has focused on the hypothesis of an autoimmune process similar to rheumatic fever. This study examined the potential role of cytokines, modulators of the immune system. We hypothesized that children with TD would have increased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-12, IL-1β and IL-6, and decreased IL-2. We also explored whether comorbid obsessive compulsive disorder (OCD) had an effect on the cytokine profile of TD patients.

Method—Thirty-two children and adolescents with TD (27 males, ages 7–18 years), 17 with comorbid OCD (14 males), and 16 healthy comparison subjects (7 males, ages 9–19), were enrolled. Plasma cytokines were examined using an enzyme-linked immunosorbent assay. The Mann–Whitney and binary logistic regression tests were used to compare the groups.

Results—Only patients with comorbid OCD (TD+OCD; $n = 17$) had significantly elevated IL-12 plasma levels compared to controls (2.73 ± 5.12 pg/ml vs. 0.55 ± 0.88 pg/ml, *rank statistic* = 222.5; $p<0.04$). IL-2 was significantly higher in the TD+OCD subgroup compared to the non-OCD TD subgroup (0.74 ± 0.29 pg/ml vs. 0.49 ± 0.24 pg/ml, *rank statistics* = 108.5; $p<0.03$). There were no other significant cytokine differences between groups.

Conclusions—Findings suggest a role for IL-12 and IL-2 in TD, and that the TD+OCD subgroup may involve different neuroimmunological functions than the TD−OCD subgroup. Larger studies with medication-free patients should follow.

Keywords

Cytokines; Interleukin-12; Interleukin-2; Obsessive compulsive disorder; Tourette's disorder

*Corresponding author. vilma.gabbay@nyumc.org (V. Gabbay), barbara.coffey@nyumc.org (B.J. Coffey), leah.guttman@nyumc.org (L.E. Guttman), lev.gottlieb@u.northwestern.edu (L. Gottlieb), yisrael.katz@nyumc.org (Y. Katz), james.babb@nyumc.org (J.S. Babb), mmh10@stanford.edu (M.M. Hamamoto), cjg17@health.state.ny.us (C.J. Gonzalez)..

[1]Present address: Northwestern University, Feinberg School of Medicine, Abbott Hall, Suite 1205, 710 North Lake Shore Drive, Chicago, Illinois 60611, United States.

[2]Present address: New York State Department of Health, AIDS Institute, 90 Church Street, 13th Floor, New York, NY 10007, United States.

1. Introduction

Tourette's disorder (TD) is a chronic neuropsychiatric disorder of childhood onset characterized by multiple, waxing and waning, motor and vocal tics. The disorder is associated with significant impairment and disability. It is estimated that up to 3% of school-age children meet criteria for TD; the majority of clinically referred patients also meet criteria for one or more comorbid psychiatric disorders, including obsessive compulsive disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD). Findings highlight the need for biological research in pediatric samples with TD.

Over the past decade, the role of the immune system in TD has been increasingly investigated. Most research has focused on the hypothesis that an autoimmune process similar to Sydenham's chorea may occur in a putative subgroup of children with a lifetime history of OCD and/or a tic disorder [referred to as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)] in whom the onset and/or exacerbation of symptoms is observed to be precipitated by Group A β-hemolytic streptococcus (GABHS), with inconclusive findings to date (Giedd et al., 2000; Luo et al., 2004; Murphy and Pichichero, 2002; Singer et al., 2008; Swedo et al., 1998; Leslie et al., 2008). Recently, Kawikova et al. (2007) found fewer T regulatory (Treg) cells in a combined group of children with TD and/or OCD compared to controls, suggesting impaired capacity to inhibit auto-activation of the immune system. Another investigative approach has focused on the possible role of cytokines, glycopeptide signaling molecules that mediate key steps in cellular and humoral immunity. Peripheral cytokines can cross the blood-brain barrier and influence complex brain functions (Kronfol and Remick, 2000; Pollmacher et al., 2002). Only two studies examined cytokines in TD. Leckman et al. (2005) found increased serum tumor necrosis factor (TNF)-α and interleukin (IL)-12 at baseline and during symptom exacerbation in a combined sample of children with TD and/or OCD compared to controls. IL-2, which plays a key role in Treg cell production, was not different between patients and controls (Leckman et al., 2005). One confounder in Leckman et al.'s study is that the patient sample included patients with OCD without tics, which may have affected findings and decreased statistical power. Further, cytokine studies in adults with OCD without tics have yielded different findings, with the majority of studies reporting decreased TNF-α, increased IL-6, decreased IL-1β, and decreased natural killer (NK) cell activity (Brambilla et al., 1997; Denys et al., 2004; Monteleone et al., 1998). It is still unclear why these related disorders have opposite patterns in cytokine secretion, but these findings do suggest that the neuroimmunological pathways involved in OCD, not in the context of a tic disorder, are distinct from TD. It may be that increased TNF-α and IL-12 are linked to a local inflammatory reaction in TD. In addition, animal studies have shown that TNF-α treatment can result in an increase or decrease of monoamine concentrations in specific brain regions, suggesting the involvement of distinct brain areas in each disorder (Mossner et al., 1998; Brebner et al., 2000).

Based on findings to date, reporting differences in the cytokine profile of patients with TD and OCD, our overall aim was to examine the cytokine profile of a homogenous group of children and adolescents with TD, and the possible effect of comorbid OCD. Hypotheses were that: 1) children and adolescents with TD would have significantly elevated plasma levels of TNF-α, IL-12, IL-6, and IL-1β, and decreased IL-2 compared to controls as suggested by prior studies in TD, and 2) children and adolescents with TD+OCD would have decreased levels of TNF-α and IL-1β, and increased IL-12, IL-6, and IL-2 compared to the TD−OCD group and controls. Relationships between severity of tics and OCD symptoms and the above measures were also examined in the patient groups.

2. Materials and methods

2.1. Subjects

Two subject groups were established for this study: subjects with TD and healthy comparison subjects. The TD sample consisted of 32 children (27 males), ages 7–18 years (11.2 ± 3.2), who met DSM-IV-TR criteria for TD [mean total tic Yale Global Tic Severity Scale (YGTSS) score = 22.0 ± 6.11]. The TD sample was further divided into two subgroups: one consisting of 17 subjects (14 males) with TD plus comorbid OCD (TD+OCD), and a second consisting of 15 subjects (13 males) with TD without comorbid OCD (TD−OCD). Demographics, diagnoses, and treatment profiles are compiled in Table 1. Patients were recruited from the Institute for Tourette and Tic Disorders at the New York University (NYU) Child Study Center and from the Tourette Syndrome Association. Sixteen healthy comparisons (7 males), ages 9–19 (15.1 ± 3.3), were recruited from families of NYU staff. Data on 15 of the controls were reported elsewhere (Gabbay et al., 2009).

Participants ages 18 years and over signed informed consent; those under age 18 provided assent, and a parent or guardian provided signed consent as approved by the NYU School of Medicine IRB.

A board-certified child and adolescent psychiatrist with expertise in diagnosis and treatment of TD, OCD, and PANDAS (VG or BC) interviewed all subjects (patients with TD and controls) and parents using the Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version for Children (K-SADS-PL) (Kaufman et al., 1997). Full DSM-IV-TR criteria had to be fulfilled to meet diagnostic criteria for TD and OCD. Tic severity was rated on the YGTSS (Leckman et al., 1989), and OCD severity on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997). PANDAS was diagnosed using Swedo et al.'s five research diagnostic criteria (Swedo et al., 1998). Baseline medical evaluation incorporated medical history and laboratory studies, including complete blood count, metabolic panel, liver functions, throat culture, and a urine toxicology test.

Exclusion criteria for all subjects were: immune-affecting medications taken in the past 6 months (other than psychotropic medications), any immunological or hematological disorder, Sydenham's chorea, any infectious disease in the month prior to enrollment (including a common cold), and significant medical or neurological disorders (other than a tic disorder). Exclusionary diagnoses for subjects with TD were bipolar disorder, major depressive disorder, pervasive developmental disorder, psychotic disorder, and a substance-related disorder in the past 12 months (based on history and urine toxicology test). Control subjects could not meet criteria for any current or past DSM-IV-TR psychiatric disorder. In addition, control subjects who endorsed taking allergy medication(s) were excluded.

2.2. Cytokine measurements

Venous blood samples of 10 ml were drawn directly into plastic tubes containing EDTA-K3. All blood samples (10 ml) were drawn between 08:00 and 09:00 AM after an overnight fast; the EDTA blood was processed within 20 min of collection. Aliquots of the plasma samples were stored at −80 °C for appropriate serial immunoassay analysis.

The quantitative determinations of the plasma levels of TNF-α, IL-1β, IL-12, IL-6, and IL-2 were performed in duplicate for each of the serial aliquots by commercial enzyme-linked immunosorbent assays (ELISA) in accordance with the manufacturers' instructions. The TNF-α, also known as cachectin and TNFSF1A, the Quantikine Human TNF-α/TNFSF1A assay (R&D Systems, Minneapolis, MN) was used; for IL-1β, also known as IL-1F2, the Quantikine HS Human IL-1β/ILF2 immunoassay (R&D Systems, Minneapolis, MN) was used. For IL-12, the High Sensitivity Human Quantikine IL-12 (R&D Systems, Minneapolis, MN) was used;

IL-6 was assayed with High Sensitivity Human Quantikine IL-6 (R&D Systems, Minneapolis, MN); and for IL-2, the QuantiGlo Human IL-2 immunoassay (R&D Systems, Minneapolis, MN) was used.

The lower limits of detection of the assays were: 0.038 pg/ml, 0.057 pg/ml, 0.18 pg/ml, 0.039 pg/ml, and 0.1 pg/ml, respectively. Intra-assay variability was less than 10%. The mean of the duplicate sample values was used. All assays were performed by CG, who was blind to the subjects' clinical status.

2.3. Statistical analysis

As data were not normally distributed, the non-parametric Mann–Whitney test was used to compare subjects with TD and controls. A separate analysis was conducted for each cytokine. When cytokine levels were too low for detection, cytokines were given the lowest detectable value. Additionally, when cytokines were not detectable for more than 20% of either controls or subjects with TD, a binary logistic regression analysis was conducted to compare the groups in terms of the percentage of subjects with detectable levels. Further, ANCOVA based on ranks was used to assess the interaction of subject group with age and gender in terms of their impact on each measure.

Significance levels were set at $p \leq 0.05$. Spearman rank correlation coefficients were used to characterize the association of cytokine levels with severity of TD symptoms on the YGTSS and severity of OCD symptoms on the CY-BOCS, as well as with age and gender. SAS version 9.0 (SAS Institute, Cary, NC) was used for all statistical computations.

3. Results

3.1. Subjects

Seven (22%) of the 32 TD subjects were psychotropic medication-naïve, and 25 (78%) were taking psychotropic medication(s) at the time of assessment. All subjects on psychotropic medication(s) had active tics at the time of the study. Many of these subjects were taking multiple medications, including psychostimulants [amphetamine, methylphenidate, (n = 12)], α_2-adrenergic agonists [guanfacine, clonidine (n = 11)], antidepressants [fluvoxamine, venlafaxine, fluoxetine, citalopram, paroxetine, sertraline (n = 8)], and atypical neuroleptics [risperidone, olanzapine, aripiprazole (n = 5)]. Two patients met research diagnostic criteria for PANDAS (Swedo et al., 1998).

3.2. Cytokine findings

Means and standard deviations of plasma cytokine levels are summarized in Table 2.

IL-2 plasma levels were not analyzed for most of the controls, precluding meaningful analysis between patients and controls. IL-2 levels were available for 27/32 (84%) patients with TD, of whom 16/27 (59%) had comorbid OCD. Therefore, analysis for IL-2 only compared TD patients with and without OCD.

Only the subgroup of patients with comorbid OCD (TD+OCD; n = 17) had significantly elevated IL-12 plasma levels compared to controls (2.73 ± 5.12 pg/ml vs. 0.55 ± 0.88 pg/ml, *rank statistic* = 222.5; p<0.04). Analysis was repeated using binary logistic regression to compare patient groups in terms of the percentage of subjects with detectable IL-12, since more than 20% of the samples had undetectable IL-12 [controls: 13/16 (81%); TD+OCD: 8/17 (47%); TD−OCD: 9/15 (60%)]. Only TD patients with comorbid OCD had a significantly higher percentage of IL-12 detected compared to controls (χ^2 = 3.88; p<0.05).

Comparing the two subgroups of patients, IL-2 was significantly increased in the TD+OCD subgroup compared to the TD−OCD subgroup (0.74 ± 0.29 pg/ml vs. 0.49 ± 0.24 pg/ml, *rank statistics* = 108.5; $p<0.03$).

There were no other cytokine differences between any of the groups, and no significant differences in IL-12 and IL-2 plasma levels with respect to psychotropic medication treatment. Additionally, there were no significant interactions between any of the cytokines with age and gender in any of the subject groups.

3.3. Correlations

While cytokine plasma levels were not significantly correlated with clinical measures (YGTSS, CY-BOCS), several trends were identified: IL-2 was positively correlated with OCD severity as measured by the CY-BOCS ($r = 0.36$; $p<0.07$), and TNF-α was inversely correlated with OCD severity as measured by the CY-BOCS ($r = -0.31$; $p<0.09$). (A trend was defined when findings would have been significant on the basis of a one-sided test; such results may be indicative of a real result that the study did not have adequate statistical power to detect. These results can be considered hypotheses for further study).

4. Discussion

The present study examined cytokine profiles in children and adolescents with TD with an additional focus on possible differences between two clinical subgroups: one with and one without comorbid OCD. Interestingly, IL-12 was significantly elevated only in the TD+OCD subgroup compared to the control group. Additionally, IL-2 was significantly elevated in the TD+OCD subgroup compared to the TD−OCD subgroup.

4.1. IL-12

Our finding of increased IL-12 is consistent with the findings of Leckman et al. (2005), the only prior controlled study of cytokines in pediatric TD. However, the increased IL-12 plasma levels in our TD sample were present only in the subgroup of children with TD+OCD. Importantly, while we are not aware of cytokine studies in pediatric populations with non-tic OCD, none of the cytokine studies in adults with non-tic OCD detected increased IL-12 (Brambilla et al., 1997; Denys et al., 2004; Konuk et al., 2007; Monteleone et al., 1998; Weizman et al., 1996). As such, our finding, as well as the prior study by Leckman et al., may suggest that the pathophysiology of OCD in the context of TD differs from that of OCD alone, a concept supported biologically by genetic studies (Miguel et al., 2005), and phenomenologically by clinical presentation and pharmacological response (Bloch et al., 2006; Coffey et al., 1998; Kwak et al., 2003). For example, patients with TD+OCD are reported to have more impairment, including increased rates of mood and anxiety disorders, compared to those with TD or OCD alone (Coffey et al., 1998). They are also likely to manifest symmetry and exactness obsessions, and pharmacologically, have a beneficial response when treatment with serotonin reuptake inhibitors is augmented with neuroleptics (Bloch et al., 2006; Kwak et al., 2003).

IL-12 plays a central role in activating a T-helper (Th)-1 (cellular mediated) immunological response through activation of NK and T cells (Trinchieri et al., 2003). IL-12 has also been shown to suppress Treg activity and restore the ability of $CD4^{+}CD25^{-}$ T cells to proliferate in the presence of Treg (King and Segal, 2005), potentially implicating another pathway through which IL-12 may lead to immune system activation in TD+OCD. While several autoimmune diseases have been linked to IL-12 action, its association in multiple sclerosis (MS) (Comabella et al., 1998) has particular relevance to TD because of the involvement of the central nervous system. One of the hypothesized pathways linking IL-12 to MS is through an immunological

response against myelin oligodendrocyte glycoprotein (MOG); 50% of MS patients have peripheral mononuclear cells directed toward MOG protein (Genain et al., 1999). Related to our study, a specific polymorphism in the MOG gene has been linked to OCD (Zai et al., 2004), but not to TD (Huang et al., 2004), providing additional evidence that the subgroup of TD+OCD may involve different neuroimmunological pathways than the TD−OCD subgroup.

4.2. IL-2

Our second finding is of increased IL-2 in the TD+OCD subgroup compared to the TD−OCD subgroup. Recent evidence suggests that IL-2 is essential for $CD4^+CD25^+$ Treg development (Malek, 2008). As such, our finding of decreased IL-2 in children with TD−OCD compared to TD+OCD and the low count of Treg found in TD in a prior study may be linked (Kawikova et al., 2007). However, the lack of a healthy comparison group for this cytokine limits our interpretation of this finding.

At the same time, IL-2 also affects central dopamine activity and behavior associated with the mesocorticolimbic system, processes that are hypothesized to play a role in TD. Most relevant to tic and other movement disorders, central administration of IL-2 into the caudate nucleus or substantia nigra evokes asymmetric body posture, with ipsilateral turning behavior and periodic ipsilateral circling in animals (De Sarro et al., 1990); thus, the effects of IL-2 on dopaminergic activity in these regions may play a role in the abnormal movements that occur in TD.

We also found a trend for an inverse correlation between TNF-α plasma levels and OCD severity as measured by the CY-BOCS in children with TD. TNF-α is produced by macrophages and circulating monocytes, and plays an important role in a wide range of immune reactions, including autoimmune conditions (Vassalli, 1992). While the only prior study of cytokines in youth with TD and/or OCD detected increased TNF-α compared to controls and during illness exacerbation (Leckman et al., 2005), several studies in adults with OCD have reported decreased TNF-α (Brambilla et al., 1997; Denys et al., 2004; Monteleone et al., 1998).

4.3. Limitations

While our findings support our hypothesis that cytokines may play a role in TD, they should be considered preliminary in light of several limiting factors: first, the cohort size is relatively modest; second, many patients (78%) were receiving psychotropic medications at the time of the study which can induce an anti-inflammatory effect. Indeed, Type II errors are possible explanations for failing to detect other cytokine alterations. Further, due to the small sample, we did not apply a multiple comparison correction in order to preserve statistical power, but this may have increased our rate of Type I errors. Finally, the patient and control groups were not matched with respect to gender.

In summary, our preliminary results support the concept that TD may be linked to cytokine dysregulation, specifically the role of IL-12 in the TD+OCD subgroup is suggested. These findings require replication in a larger sample of medication-free youth with an additional focus on other immunological markers, including T cell subtypes (e.g., T regulatory), other comorbid disorders such as ADHD, and the utilization of molecular biology techniques.

Acknowledgments

This study was supported by grants from NIH (AT002395, MH077072), the Tourette Syndrome Association, the NYU School of Medicine General Clinical Research Center grant (M01-RR00096), and generous gifts from the Anita Saltz Foundation, and from Bruce and Claude Wasserstein. The authors thank Dr. Rachel G. Klein for her helpful comments on this manuscript.

Financial disclosures:

Drs. Vilma Gabbay, James S. Babb, and Charles J. Gonzalez report no biomedical financial interests or potential conflicts of interest. Dr. Barbara J. Coffey reports research support from Boehringer Ingelheim, Bristol Myers Squibb, and Eli Lilly. Dr. Coffey also reports serving on the advisory board for Jazz Pharmaceuticals, Eli Lilly, and Novartis. Leah E. Guttman, Lev Gottlieb, Yisrael Katz, and Mia M. Hamamoto report no biomedical financial interests or potential conflicts of interest.

Abbreviations

ADHD, attention deficit hyperactivity disorder
CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale
ELISA, enzyme-linked immunosorbent assay
GABHS, Group A β-hemolytic streptococcus
IL, interleukin
K-SADS-PL, Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version for Children
MOG, myelin oligodendrocyte glycoprotein
MS, multiple sclerosis
NK, natural killer
NYU, New York University
OCD, obsessive compulsive disorder
PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcus
TD, Tourette's disorder
Th1, T-helper1
Th2, T-helper2
TNF, tumor necrosis factor
Treg, T regulatory
YGTSS, Yale Global Tic Severity Scale

References

Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry 2006;11:622–32. [PubMed: 16585942]

Brambilla F, Perna G, Bellodi L, Arancio C, Bertani A, Perini G, et al. Plasma interleukin-1 beta and tumor necrosis factor concentrations in obsessive-compulsive disorders. Biol Psychiatry 1997;42:976–81. [PubMed: 9386848]

Brebner K, Hayley S, Zacharko R, Merali Z, Anisman H. Synergistic effects of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha: central monoamine, corticosterone, and behavioral variations. Neuropsychopharmacology 2000;22:566–80. [PubMed: 10788757]

Coffey BJ, Miguel EC, Biederman J, Baer L, Rauch SL, O'Sullivan RL, et al. Tourette's disorder with and without obsessive-compulsive disorder in adults: are they different? J Nerv Ment Dis 1998;186:201–6. [PubMed: 9569887]

Comabella M, Balashov K, Issazadeh S, Smith D, Weiner HL, Khoury SJ. Elevated interleukin-12 in progressive multiple sclerosis correlates with disease activity and is normalized by pulse cyclophosphamide therapy. J Clin Invest 1998;102:671–8. [PubMed: 9710434]

De Sarro GB, Masuda Y, Ascioti C, Audino MG, Nistico G. Behavioural and ECoG spectrum changes induced by intracerebral infusion of interferons and interleukin 2 in rats are antagonized by naloxone. Neuropharmacology 1990;29:167–79. [PubMed: 1691831]

Denys D, Fluitman S, Kavelaars A, Heijnen C, Westenberg H. Decreased TNF-alpha and NK activity in obsessive-compulsive disorder. Psychoneuroendocrinology 2004;29:945–52. [PubMed: 15177711]

Gabbay V, Klein R, Alonso C, Babb JS, Nishawala M, De Jesus G, et al. Immune system dysregulation in adolescent major depressive disorder. J Affect Disord 2009;115(1–2):177–82. [PubMed: 18790541]

Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med 1999;5:170–5. [PubMed: 9930864]

Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. Am J Psychiatry 2000;157:281–3. [PubMed: 10671403]

Huang Y, Li T, Wang Y, Ansar J, Lanting G, Liu X, et al. Linkage disequilibrium analysis of polymorphisms in the gene for myelin oligodendrocyte glycoprotein in Tourette's syndrome patients from a Chinese sample. Am J Med Genet B Neuropsychiatr Genet 2004;124B:76–80. [PubMed: 14681920]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psych 1997;36:980–8.

Kawikova I, Leckman JF, Kronig H, Katsovich L, Bessen DE, Ghebremichael M, et al. Decreased numbers of regulatory T cells suggest impaired immune tolerance in children with Tourette syndrome: a preliminary study. Biol Psychiatry 2007;61:273–8. [PubMed: 16996487]

King IL, Segal BM. Cutting edge: IL-12 induces $CD4^{+}CD25^{-}$ T cell activation in the presence of T regulatory cells. J Immunol 2005;175:641–5. [PubMed: 16002658]

Konuk N, Tekin IO, Ozturk U, Atik L, Atasoy N, Bektas S, et al. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. Mediators Inflamm 2007:65704. [PubMed: 17497035]

Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatr 2000;157:683–94. [PubMed: 10784457]

Kwak C, Dat Vuong K, Jankovic J. Premonitory sensory phenomenon in Tourette's syndrome. Mov Disord 2003;18:1530–3. [PubMed: 14673893]

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28:566–73. [PubMed: 2768151]

Leckman JF, Katsovich L, Kawikova I, Lin H, Zhang H, Kronig H, et al. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. Biol Psychiatry 2005;57:667–73. [PubMed: 15780855]

Leslie DL, Kozma L, Martin A, Landeros A, Katsovich L, King RA, et al. Neuropsychiatric disorders associated with streptococcal infection: a case–control study among privately insured children. J Am Acad Child Adolesc Psychiatry 2008;47(10):1166–72. [PubMed: 18724258]

Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. Pediatrics 2004;113:e578–85. [PubMed: 15173540]

Malek TR. The biology of interleukin-2. Annu Rev Immunol 2008;26:453–79. [PubMed: 18062768]

Miguel EC, Leckman JF, Rauch S, do Rosario-Campos MC, Hounie AG, Mercadante MT, et al. Obsessive-compulsive disorder phenotypes: implications for genetic studies. Mol Psychiatry 2005;10:258–75. [PubMed: 15611786]

Monteleone P, Catapano F, Fabrazzo M, Tortorella A, Maj M. Decreased blood levels of tumor necrosis factor-alpha in patients with obsessive-compulsive disorder. Neuropsychobiology 1998;37:182–5. [PubMed: 9648125]

Mossner R, Heils A, Stober G, Okladnova O, Daniel S, Lesch KP. Enhancement of serotonin transporter function by tumor necrosis factor alpha but not by interleukin-6. Neurochem Int 1998;33:251–4. [PubMed: 9759920]

Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med 2002;156:356–61. [PubMed: 11929370]

Pollmacher T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines—do they affect human brain functions? Brain Behav Immun 2002;16:525–32. [PubMed: 12401466]

Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997;36:844–52. [PubMed: 9183141]

Singer HS, Gause C, Morris C, Lopez P. Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Pediatrics 2008;121:1198–205. [PubMed: 18519490]

Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 1998;155:264–71. [PubMed: 9464208]

Trinchieri G, Pflanz S, Kastelein RA. The IL-12 family of heterodimeric cytokines: new players in the regulation of T cell responses. Immunity 2003;19:641–4. [PubMed: 14614851]

Vassalli P. The pathophysiology of tumor necrosis factors. Annu Rev Immunol 1992;10:411–52. [PubMed: 1590993]

Weizman R, Laor N, Barber Y, Hermesh H, Notti I, Djaldetti M, et al. Cytokine production in obsessive-compulsive disorder. Biol Psychiatry 1996;40:908–12. [PubMed: 8896778]

Zai G, Bezchlibnyk YB, Richter MA, Arnold P, Burroughs E, Barr CL, et al. Myelin oligodendrocyte glycoprotein (MOG) gene is associated with obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet 2004;129B:64–8. [PubMed: 15274043]

Table 1

Demographic and clinical characteristics of children and adolescents with Tourette's disorder (TD) and healthy control subjects.

Characteristic	Healthy controls (*n* = 16)	Children and adolescents with TD (*n* = 32)		
		Total (*n* = 32)	TD+OCD (*n* = 17)	TD–OCD (*n* = 15)
Age (years)	15.1±3.30	11.2±3.15	12.6±3.35	9.67±2.12
Gender (male/female)	7/9 (44/56%)[a]	27/5 (84/16%)[a]	14/3 (82/18%)[a]	13/2 (87/13%)[a]
Illness history				
Medication-naïve/Medicated	16/0 (100/0%)[a]	7/25 (22/78%)[a]	2/15 (12/88%)[a]	5/10 (33/67%)[a]
YGTSS[b]	N/A	22.0±6.11 (6–35)[c]	22.8±6.24 (9–35)[c]	21.1±6.06 (6–27)[c]
CY-BOCS[d]	N/A	9.03±7.37 (0–27)[c]	13.1±7.28 (0–27)[c]	4.40±4.07 (0–14)[c]
Current comorbid disorder				
OCD[e]	0	17 (53%)[a]	17 (100%)[a]	0
PANDAS[f]	0	2 (6%)[a]	1 (6%)[a]	1 (7%)[a]
ADHD (any subtype)[g]	0	20 (63%)[a]	11 (65%)[a]	9 (60%)[a]
Any non-OCD anxiety disorder	0	7 (22%)[a]	5 (29%)[a]	2 (13%)[a]
ODD[h]	0	2 (6%)[a]	0	2 (13%)[a]
SAD[i]	0	2 (6%)[a]	0	2 (13%)[a]
Speech or language disorder	0	3 (9%)[a]	0	3 (20%)[a]
Any comorbid disorder	0	27 (84%)[a]	17 (100%)[a]	10 (67%)[a]

[a] Respective percentages (may not add up to 100% due to rounding).

[b] Yale Global Tic Severity Scale.

[c] Range.

[d] Childrens' Yale-Brown Obsessive Compulsive Scale.

[e] Obsessive Compulsive Disorder.

[f] Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus.

[g] Attention Deficit Hyperactivity Disorder.

[h] Oppositional Defiant Disorder.

[i] Separation Anxiety Disorder.

Table 2

Mean (SD) levels of plasma cytokines in children and adolescents with Tourette's disorder (TD), TD and obsessive compulsive disorder (OCD; TD+OCD), and TD without OCD (TD–OCD), compared to controls and within subgroups.

Cytokine measure	Healthy controls (*n*=16)	Children and adolescents with TD (*n*=32)		
		Total (*n*=32)	TD+OCD (*n*=17)	TD–OCD (*n*=15)
Tumor necrosis factor (TNF)-α	3.92 (13.0)	3.67 (17.2)	0.53 (0.29)	7.22 (25.1)
Interleukin (IL)-1β	0.16 (0.05)	0.23 (0.28)	0.27 (0.38)	0.18 (0.09)
IL-12	0.55 (0.88)	1.84 (3.87)[a]	2.73 (5.12)[b]	0.83 (1.09)
IL-6	0.74 (1.33)	0.68 (0.91)	0.54 (0.70)	0.83 (1.11)
IL-2	NA	0.64 (0.29)	0.74 (0.29)[c]	0.49 (0.24)

NA, not assessed.

[a] Compared to controls, p=0.06.

[b] Compared to controls, p<0.04.

[c] Compared to TD–OCD, p< 0.03.