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Involvement of immunologic and biochemical mechanisms in the pathogenesis of Tourette's syndrome

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Abstract

Tourette's syndrome is a neurodevelopmental disorder clinically characterized by multiple motor and phonic tics. It is likely that a neurobiological susceptibility to the disorder is established during development by the interaction of genetic, biochemical, immunological, and environmental factors. This study sought to investigate the possible correlation of several immunological and biochemical markers with Tourette's syndrome. Children with Tourette's syndrome attending a tertiary pediatric medical center from May 2008 to April 2010, and healthy age-matched control subjects underwent a comprehensive biochemical and immunological work-up. Demographic data were abstracted from the medical records. Findings were compared between the groups and analyzed statistically. Sixty-eight children with Tourette's syndrome (58 males, 85.3%) and 36 healthy children (25 males, 69.4%) were recruited. Compared with the control group, the Tourette's syndrome group had significantly higher levels of ferritin ($p = 0.01$) and hemoglobin ($p = 0.02$), a lower level of zinc ($p = 0.05$), and a lower percentage of non-ceruloplasmin copper ($p = 0.01$). Analysis of the immunological markers revealed no significant between-group differences in IgA, IgM or IgG; however, IgE and IgG-4 levels were significantly higher in the Tourette's syndrome group ($p = 0.04$ and $p = 0.02$, respectively). Children with Tourette's syndrome have high levels of biochemical indices of oxidative stress and the quantitative immunoglobulins. These findings add to the still-limited knowledge on the pathogenesis of Tourette's syndrome and may have implications for the development of novel therapeutic modalities.

Keywords

Tourette syndrome; Oxidative stress; Heavy metals metabolism; Autoimmunity; Immunoglobulins

Introduction

Tourette's syndrome (TS) is a neurodevelopmental disorder that begins in childhood and is clinically characterized by multiple motor and phonic tics (Kurlan 2010; Martino et al. 2009). It is one of the spectrum of tic disorders, and many of its aspects remain poorly understood despite years of scrutiny. The underlying mechanism has been variably attributed to hereditary degeneration, irritation of the motor neural systems by toxic substances, and a constitutional inferiority of the subcortical structures, among other factors (Kushner 1999a; Leckman 2002). The perception of TS as a rare, bizarre, psychological disorder began to change after reports of the benefit of neuroleptic drugs on tic severity (Kushner 1999b), which prompted research into its epidemiology and pathogenesis. TS is now recognized as a relatively common, genetic/biologic disorder with neuro-behavioral manifestations that wax and wane (Jankovic 2001). The high-order combination of tic bouts could be the basis of the fluctuating course of the disorder (Leckman 2002).

The natural history of TS, its high heritability in the absence of a single causative gene, and the many related psychiatric comorbidities support a multifactorial etiology. Researchers suggest that genetic, biochemical, immunological, and other environmental factors interact during development to establish a neurobiological susceptibility to TS (Martino et al. 2009; Murphy et al. 2010; Swain et al. 2007). Numerous biochemical, neuroimaging, neurophysiological, and genetic studies support the theory that TS is an inherited and developmental disorder of synaptic transmission of the cortico-striatal-thalamic-cortical circuitry (Jankovic 2001; Leckman et al. 2001).

The proposed link between environmental factors that induce immune activation and TS is based partly on the similarity of TS to Sydenham's chorea and other neuropsychiatric disorders that occur or worsen after group A streptococcal infections (Kiessling et al. 1993). Other environment-related cellular metabolites and trace elements involved in reduction-oxygenation processes and oxidative stress modulation have also been associated with neurodegenerative (Deibel et al. 1996; Yao et al. 2006) and movement disorders (Yamamoto et al. 2007), including TS (Gorman et al. 2006; Peterson et al. 1994; Robertson et al. 1987). The oxidative stress theory has gained popularity in the past decade with the onset of research into possible therapeutic agents. For example, the synthesized free radical scavenger, MCI-186, was found to significantly decrease hydroxyl radical levels and was hypothesized to be effective against TS in an animal model (Nomoto 2004).

The aim of the present controlled prospective study was to investigate possible correlations of immunological and biochemical markers with TS in the context of the immune system dysregulation theory and the oxidative stress theory of the pathogenesis of TS.

Methods

Study design, patients, and inclusion and exclusion criteria

The study was performed at the Tourette's syndrome Center of the Psychological Medicine Clinics at Schneider Children's Medical Center of Israel which serves as a multidisciplinary local and national referral center for the treatment of children with TS. Patients aged <18 years who consecutively attended the TS center from May 2008 to April 2010 were prospectively recruited. All had been diagnosed according to the DSM IV criteria by a senior child and adolescent psychiatrist or a pediatric neurologist with extensive experience in TS. For the control group, we recruited healthy age-matched children referred to the Endocrinology Clinic of the same medical center. Patients with significant acute or chronic

disease (e.g. acute febrile disease, chronic renal failure, malignancy) were excluded from either the study group or the control group.

The study has been approved by the Institutional Review Board of Schneider Children's Medical Center of Israel and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons, parents and children, gave their informed consent prior to their inclusion in the study.

Data collection and blood assays

The following data were obtained from the medical records: age, sex, and medical background. Every child underwent blinded blood assays as follows:

1. Complete blood count: white blood cells and differential, red blood cells with indices, and platelets.
2. Quantitative immunoglobulins: IgG, IgM, IgA, and IgE and IgG subclasses (IgG-1, IgG-2, IgG-3, and IgG-4).
3. Biochemical markers: copper, ceruloplasmin, zinc, iron, transferrin, and ferritin. Additionally, equations of copper and ceruloplasmin were calculated (Twomey et al. 2006), as follows: non-ceruloplasmin-bound copper level = total copper (mcg/dL) – 3 × ceruloplasmin (mg/dL); percentage non-ceruloplasmin copper = non-ceruloplasmin copper/total copper (mcg/dL) × 100; and adjusted copper (copper index) = total copper (umol/L) – 0.052 × ceruloplasmin (mg/L) + 17.5.

Statistical analysis

Data were analyzed using BMDP software (Chief Editor: A. J. Dixon, University of California Press, 1993). Discrete variables were compared between groups with Fisher's exact test, and continuous variables, with analysis of variance (ANOVA). To determine significant differences between variances, we applied Levene's test, which when significant, was followed by the Brown-Forsythe method for comparing means, assuming variances to be unequal. For the variables with a non-Gaussian distribution (e.g., IgE), we applied log-transformation before ANOVA. Variables with a *p* value of 0.10 were entered into a stepwise logistic regression model to identify those most significantly associated with TS. A *p* value of 0.05 was considered significant.

Results

Sixty-eight children with TS (58 male, 85.3%; study group) and 36 healthy age-matched children (25 males, 69.4%; control group) were included in the study. Mean age of the study group was 11.4 ± 3 years, and of the control group, 10.9 ± 2.9 years.

Forty children with TS (58.8%) had one or more comorbid conditions. The most prevalent was attention-deficit and hyperactivity disorder (28 children, 41.2%), followed by obsessive-compulsive disorder (8 children, 11.8%), learning disabilities (8 children, 11.8%), anxiety disorders (7 children, 10.3%), mood disorder (3 children, 4.4%), oppositional defiant disorder (3 children, 4.4%), and conduct disorder (2 children, 2.9%). Forty-four children (64.7%) had received one or more medications to treat symptoms of TS or the associated comorbidities. The most commonly used medication was Methylphenidate (18 children, 26.5%), followed by Clonidine (13 children, 19.1%), selective serotonin reuptake inhibitors (12 children, 17.6%), Risperidone (10 children, 14.7%), Pimozide (9 children, 13.2%), Tetrabenazine (7 children, 10.3%), Haloperidol (3 children, 4.4%), and Clonazepam (2 children, 2.9%). Twenty-seven children (39.7%) were assisted with psychotherapy during the study period, of whom 21 were receiving concurrent medication. None of these factors

was found to influence the assay results, apparently owing to the small size of these subgroups (data not shown).

Analysis of iron, copper, and zinc metabolism as well as the complete blood count and blood parameters yielded several significant between-group differences (Table 1). Compared with the control group, the TS group was characterized by significantly higher levels of ferritin and hemoglobin levels ($p = 0.02$), a significantly lower level of zinc ($p = 0.05$), and a significantly lower percentage of non-ceruloplasmin copper ($p = 0.01$). Among the immunological markers (Table 2), there was no significant difference between the TS and control groups for IgA, IgM or IgG. However, the TS group had significantly higher levels of IgE ($p = 0.04$) and IgG-4 ($p = 0.02$). Moreover, the TS group had significantly higher IgE level range (0–1,680 IU/ml) than the normal reference range (0–100 IU/ml) and the control group level range (6–604 IU/ml), which further supports the presumed immunomodulatory etiology underlying the pathogenesis of TS.

When the variables with a p value of <0.10 were entered into a stepwise logistic regression, four factors were found to be significantly associated with TS: high ferritin level ($p = 0.016$), low zinc level ($p = 0.025$), high hemoglobin level ($p = 0.015$), and high IgG-4 level ($p = 0.044$).

Discussion

The main findings of the present study of the possible involvement of biochemical and immunological factors in TS were the significant differences between the TS and control groups in measures of ferritin, hemoglobin, IgG-4, IgE (higher in the TS group), and zinc (lower in the TS group).

Reduction-oxygenation processes and oxidative stress

There is recent cumulative evidence of a central pathogenic role for reduction-oxygenation processes and the resultant oxidative stress in several neurologic diseases (e.g. Parkinson disease, autism, Alzheimer disease) (Yamamoto et al. 2007; Yao et al. 2006; Zhu et al. 2007), in addition to Behcet's disease, a multifactorial autoimmune disorder that sometimes presents with neuropsychiatric symptoms of motor tics and obsessive-compulsive behavior (Budman and Sarcevic 2002; Najim et al. 2007; Taysi et al. 2007). The biochemical metabolites that mediate oxidative stress induction pathways include iron, copper (Hultberg et al. 2007), and zinc (Zhou et al. 2005). Iron metabolism has been implicated in the development of Alzheimer disease (Smith 2006), and copper metabolism, in postpartum depression (Crayton and Walsh 2007).

Accordingly, early studies of TS suggested that some patients have altered metabolism of iron (Gorman et al. 2006; Peterson et al. 1994) or copper (Mezaki et al. 2001; Robertson et al. 1987; Tagawa et al. 2001). However, the present analysis of biochemical markers in a cohort of patients with TS and control subjects failed to replicate these findings. Indeed, levels of ferritin and hemoglobin, the “iron-storage” molecules, were actually significantly elevated in the TS group ($p = 0.02$ for both). At the same time, the level of zinc, which possesses many anti-oxidant features, was significantly low in the patients with TS ($p = 0.05$). These three significant differences support a working model, based on which there is a potential etiologic role for oxidative stress. Of note, most of the quantitative copper parameters were not significantly different between the two groups. Surprisingly, the control group had a significantly higher percentage of non-ceruloplasmin copper than the TS group; we expected the opposite on the basis of the oxidative stress theory. Although there are clear clinical differences in the characteristics of the patients investigated across the different studies (adult to childhood age range; level of symptom severity; medicated vs. unmedicated

states), it appears less likely that peripheral measures of oxidative stress will emerge as validated biomarkers in the majority of cases of TS. Consistent with this conclusion is the failure of the recent study by Hsieh et al. (Hsieh et al. 2010) to detect abnormalities in the levels of copper, ceruloplasmin, iron, ferritin, and hemoglobin in a group of 15, mostly adult, patients with TS during a period of symptom exacerbation.

Pathogenetic immunomodulatory concepts

Recent views on the pathophysiology of TS have pointed to a role for abnormal immune responses. Supportive findings (Martino et al. 2009; Murphy et al. 2010) include changes in the expression of genes modulating cytotoxicity, antigen presentation of T lymphocytes, and the D5 dopamine receptor; changes in lymphocyte subpopulation numbers (i.e., a correlation of the percentage of T-regulatory cells with disease severity); and changes in the synthesis of effector molecules by immune-competent cells (i.e., increased plasma levels of TNF- α and IL-12). This body of evidence is still growing, and research is progressively unveiling a complex interplay between neural transmission and immune response regulation (Martino et al. 2009; Murphy et al. 2010).

In agreement with these studies, the present study demonstrated two significant differences in the immunological profile of patients with TS and healthy control subjects (Table 2). First, the children with TS had significantly higher values of the IgG-4 subclass. This finding, together with earlier reports showing an association of elevated IgG-4 level with autoimmunity (Morselli-Labate and Pezzilli 2009; Takahashi et al. 2010), implies that the immune system plays a complex and intricate role in the pathogenesis of TS. Interestingly, in a recent study of the immunoglobulin profile in TS (Bos-Veneman et al. 2010), the only consistently significant finding in two independent cross-sectional samples was a lower-than-normal level of IgG-3. Our TS group also had a low level of IgG-3, with the difference from controls reaching nearly trend-level significance ($p = 0.12$). IgG-3 is one of the most potent activators of the classical complement pathway, and it is also involved in phagocytosis (Bos-Veneman et al. 2010). The less-than-significant result in our study may have been due to other subclassification features (disease severity, comorbidity, medication regimen), and further studies of this factor are warranted.

The second important immunological finding in our TS group was the significantly high IgE level relative to the control group. Our search of the literature yielded only two small reports from non-controlled studies of IgE levels in adults or children with TS (Finegold 1985; Hsieh et al. 2010). To the best of our knowledge, this is the first controlled study to show that IgE may play a role in the pathogenesis of TS, and together with the aforementioned higher values of IgG-4, these findings further establish the working model, by which there is a major role for immune dysregulation in the pathogenesis of TS.

None of the other immunological markers tested in our study, including white blood count and blood components, were significantly different between the children with TS and the healthy matched controls. This finding, like for IgG-3, may be explained by the relatively mild spectrum of TS in our study group. Larger longitudinal studies are needed in children with more severe disease to clarify this issue.

Limitations of the study

Importantly, this study has few limitations, of which it is essential to be aware. First, the study sample has been consecutively recruited based on the patients attending the Tourette's syndrome Center. Therefore, the study could be potentially prone to selection bias, as the patients adhering to the scheduled appointments might be more adherent to the therapeutic recommendations and better managed. On the other hand, they might have more severe

disease which requires close follow-up. Therefore, the selection bias could potentially be associated with opposite effects.

Furthermore, the study and control groups were relatively not large enough, and consequently we could not appropriately investigate the different subgroups, based on the comorbidities or therapeutic modalities, which potentially could have differential effects on the study endpoints. Also, the sample size limitation required us to make no control for multiple comparisons, as it would have blunted potentially significant results, which could be further investigated in the future. Therefore, it will be important to investigate different immunomodulatory and oxidative stress-related aspects in the future in larger study groups to address these intriguing theories presumably underlying the pathogenesis of Tourette's syndrome.

Implications of the study

Both the immunological and oxidative stress of the present study may have practical implications for the medical treatment of TS. If immune alterations and autoimmunity underlie the onset or exacerbation of tic disorder, the affected children might respond to immunomodulatory treatments. Some authors reported that symptom severity lessened following treatment with plasma exchange or intravenous immunoglobulin (Hamilton et al. 2001; Perlmuter et al. 1999). The number of studies investigating the relationship of oxidative stress and TS are increasing (Twomey et al. 2006), but therapeutic research is only just beginning.

Summary

The present study highlights important differences between children with TS and healthy children in immunological and oxidative stress profiles. These differences expand our knowledge about the pathogenic mechanisms of TS and encourage further research. They may also be helpful in the development of novel therapeutic modalities.

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Table 1

Biochemical and hematological markers in children with Tourette's syndrome and healthy controls

Markers (normal reference range)	Tourette group (n = 68)		Control group (n = 36)		P value
	Mean	SD	Mean	SD	
Iron (50–120 mcg/dL)	77	32.8	68.3	23.6	0.16
Transferrin (200–400 mg/dL)	289	34.2	277	32.2	0.09
Ferritin (10–80 ng/ml)	30.6	22.2	22.2	13.4	0.01
Zinc (70–140 mcg/dL)	79.3	10.8	83.2	8.2	0.05
Copper (70–140 mcg/dL)	115.3	23.3	112.9	24.4	0.63
Ceruloplasmin (20–45 mg/dL)	22.6	4	21.1	3.7	0.06
Non-ceruloplasmin-bound copper	47.4	16.9	49.7	15.9	0.50
Percentage non-ceruloplasmin copper	40.5	7.2	43.5	4.8	0.01
Adjusted copper (copper index)	23.8	2.6	24.3	2.4	0.41
White blood cells ($4.5\text{--}11 \times 1,000$ cells/mm ³)	7.4	1.6	7.1	1.9	0.35
Absolute neutrophil count ($2\text{--}8 \times 1000$ cells/mm ³)	3.8	1.2	3.5	1.3	0.25
Absolute lymphocyte count ($1.3\text{--}4.7 \times 1,000$ cells/mm ³)	2.67	0.63	2.68	0.77	0.95
Absolute eosinophil count ($0\text{--}0.4 \times 1,000$ cells/mm ³)	0.352	0.222	0.364	0.252	0.81
Hemoglobin (12–16 g/dL)	13.25	1.18	12.7	0.98	0.02
Mean corpuscular volume (78–93 μm^3)	79.1	4.6	78	4.5	0.25
Red blood cell distribution width (11.5–14.5)	13.1	0.78	13.3	0.81	0.18
Platelets ($150\text{--}400 \times 1,000/\text{mm}^3$)	290	64.9	317	67.5	0.05

Table 2

Immunoglobulin levels in children with Tourette's syndrome and healthy controls

Immunoglobulin (normal reference range)	Tourette group (n = 68)		Control group (n = 36)		P value
	Median	Range	Median	Range	
IgA (90–430 mg/dL)	123	2–273	152	41–291	0.17
IgM (35–200 mg/dL)	108	52–277	95	44–223	0.37
IgE (0–100 IU/mL)	81	0–1,680	49	6–604	0.04
IgG (600–1,400 mg/dL)	1,070	773–1,610	1,083	576–1,720	0.77
IgG-1 (350–1,000 mg/dL)	656	315–1,263	681	359–1,400	0.12
IgG-2 (120–550 mg/dL)	236	5–560	232	67–592	0.85
IgG-3 (10–230 mg/dL)	64	20–114	83	24–125	0.12
IgG-4 (6–100 mg/dL)	41	2–55	20	1–55	0.02