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RESEARCH ARTICLE

Serum Cytokine Profiles of Children with Obsessive-Compulsive Disorder Shows the Evidence of Autoimmunity

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Abstract

Background: Previous reports have described an association between autoimmunity and primary obsessive compulsive disorder. This study aimed to investigate any differences in the levels of T helper 1, 2, and 17 effector cell cytokines between obsessive compulsive disorder patients and the control group.
Methods: The study included 34 children (23 males, 11 females), aged between 7 and 17 years, with a diagnosis of obsessive compulsive disorder prior to receiving treatment. The control group consisted of age- and gender-matched children. Study participants were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version, Children's Yale Brown Obsession Compulsion Scale, and Children's Depression Inventory. Cytokine serum concentrations were measured using the BD Cytometric Bead Array Human $Th_1/Th_2/Th_{17}$ Cytokine Kit.
Results: Interleukin-17A, tumor necrosis factor-α, and interleukin-2 levels were significantly higher in obsessive compulsive disorder patients, However, there was no correlation between T helper 1 and 17 cytokine profiles in the obsessive compulsive disorder group. The duration and severity of obsessive compulsive disorder symptoms were not significantly associated with interleukin-17A, interferon-gamma-γ, interleukin-10, interleukin-6, interleukin-4, and interleukin-2 levels. Interestingly, a negative correlation was found between tumor necrosis factor-α levels and Clinical Global Impression scores.
Conclusions: These findings suggest, in some cases, obsessive compulsive disorder may develop on a background of autoimmunity, and interleukin-2, tumor necrosis factor-α, and interleukin-17A may play a role in these autoimmune processes. Therefore, we believe it is important to investigate for obsessive compulsive disorder symptoms in patients with autoimmune disease and, conversely, autoimmune diseases in obsessive compulsive disorder patients.

Keywords: obsessive compulsive disorder, cytokine, IL-17, autoimmunity, children

Introduction

Obsessive compulsive disorder (OCD) is a chronic disorder with functional impairment characterized by obsessive, unwanted, and repetitive thoughts and/or repetitive ritualistic behaviors (Murphy et al, 2006). The prevalence of OCD is 1%-3% (Heyman et al, 2001), and symptoms start in childhood in approximately 80% of cases (Pauls et al, 1995). The etiologies of OCD are largely multifactorial, involving complex interactions between genetic and environmental factors (Pauls, 2010). Moreover, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and pediatric acute-onset neuropsychiatric syndrome OCD are 2 OCD subtypes in children that are developed secondary to infection due to cross-reactive antibodies (Swedo et al, 2012; Murphy et al, 2014).

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Studies performed on pediatric subjects have provided better insight into the mechanism underlying the association of psychiatric disease with inflammation, since there are fewer confounding factors in childhood, such as duration of disease, medication, adverse effects, and comorbidities (McEwen, 2006; Mitchell and Goldstein, 2014). Therefore, the pediatric population represents an optimal study group to identify an underlying inflammatory mechanism in OCD patients (Kapczinski et al, 2008). In addition, cytokine production in children was different from adults (Lilic et al, 1997).

In OCD patients, previous studies have reported irregularities of neurotransmitters, such as glutamate, serotonin, and dopamine, in the cortico-striato-thalamo-cortical circuits (Murphy and Pigott, 1990; Russell et al., 2003; Maina et al., 2008; Pittenger et al, 2011; Rodriguez et al, 2015). It has been shown that specific cytokines may have an effect on the synthesis, release, and reuptake of these neurotransmitters (Miller et al, 2013). For example, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) have been reported to activate the enzyme indoleamine 2,3 dioxygenase, which decreases brain serotonin levels by consuming tryptophan, the serotonin precursor, via the production of kynurenine and neuroactive metabolites (Dantzer et al, 2008). In turn, neuroactive metabolites might affect the levels of dopamine and glutamate (Miller et al, 2013). Another example described is interleukin (IL)-6. The increased level of IL-6 in the central nervous system has been associated with decreased levels of tetrahydrobiopterin, a cofactor in the synthesis of serotonin and dopamine (Haroon et al, 2012), which, in turn, resulted in decreased levels of serotonin and dopamine (Felger et al, 2013). Furthermore, a mixture of IL-1β, TNF-α, and IFN-γ has been reported to enhance the release of glutamate from astrocytes (Ida et al, 2008).

However, cytokine production in children is different from that in adults. There is evidence of a role of inflammation in neuropsychiatric diseases in both children and adolescents (Mitchell and Goldstein, 2014), but there are inconsistent results from studies investigating cytokine levels in the serum and cerebrospinal fluid in OCD patients. Anomalies in the immune system have been identified in children diagnosed with both tic disorder, for instance, Tourette's disorder (TD), and OCD (Leckman et al, 2005; Gabbay et al, 2009; Bos-Veneman et al, 2010). Moreover, a meta-analysis of studies of adult OCD patients found reduced levels of IL-1β, but similar levels of IL-6 and TNF-α, compared with patients without OCD. To the best of our knowledge, there have been no studies investigating cytokine profiles in pediatric patients with OCD only (Gray and Bloch, 2012).

Although some studies have supported the opposite (Gause et al, 2009), other studies have reported an association between autoimmunity and primary OCD (Pearlman et al, 2014). Studies conducted in both pediatric and adult OCD patients found higher levels of antibasal ganglia antibodies and antithalamic autoantibodies compared with the control group (Dale et al, 2005; Pearlman et al, 2014). In addition, antibasal ganglia antibody was found in both seropositive (antistreptolysin O-positive) and seronegative OCD patients (Nicholson et al, 2012). Consistent with these findings, functional abnormalities in the cortico-striato-thalamo-cortical circuitry in OCD were also reported (Pittenger et al, 2011).

One way of understanding whether OCD may have an immunologic etiology is to study the cytokine profile of T-helper (Th) cells. Th cells are characterized and classified on the basis of the cytokines they secrete (Raphael et al, 2015). Th_1 effector cells produce IL-2, IFN-γ, and TNF-α (Ruffell et al, 2010); Th_2 effector cells produce IL-4, IL-10, and IL-13 (Agarwal et al, 2010); and Th_{17} effector cells produce IL-17 (Harrington et al, 2005). Both Th_1 and Th_{17} effector cells play a role in autoimmune diseases (Cosmi et al, 2014; Eyerich and Zielinski, 2014).

To our knowledge, there have been no published studies on the inflammation in children and adolescents with OCD. This study investigated any differences in the levels of IL-17A, TNF-α, IFN-γ, IL-10, IL-6, IL-4, and IL-2 in OCD patients compared with the control group. The study also aimed to determine whether there was an association between cytokine levels and the severity of OCD.

Methods

Study Participants

The study was conducted in the Department of Child Psychiatry at Dicle University Training and Research Hospital between January 2014 and December 2014. A total of 52 children with OCD were admitted during this period, of which only 41 agreed to participate in the study. Seven cases were excluded from the study based on the exclusion criteria. Thus, the study population comprised 34 children, aged between 7 and 17 years (23 males, 11 females), diagnosed with OCD prior to receiving treatment. The diagnosis of OCD was made in accordance with the DSM-V criteria. To avoid interference with biochemical parameters, the following exclusion criteria were applied: mental retardation; a history of head trauma; a history of intake of oral contraceptives, psychotropics, nonsteroidal antiinflammatory drugs, and vitamins; previous or current cortisol therapy; body mass index of 30 or greater; chronic systemic disorders; clinically active infection; clinical suspicion of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and pediatric acute-onset neuropsychiatric syndrome; and the presence of other psychiatric disorders. Simple tic disorder patients were included in the study, and simple motor tic disorder was present in 11.8% (n = 4) of the patients with OCD. The control group consisted of age-, gender-, and environmentally matched children with no medical history. Two experienced psychiatric doctors evaluated the patients. Interrater agreement was 0.70. The Non-Interventional Clinical Research Ethics Committee at Dicle University Faculty of Medicine approved the study. Parents of all study participants provided informed written consent.

Study Procedures

Socio-demographic features and clinical data of the participants were recorded by the psychiatrists. A structured psychiatric interview (Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version [K-SADS-PL] and Children's Yale Brown Obsession Compulsion Scale [CY-BOC]) was conducted, and self-reported Children's Depression Inventory (CDI) given to the participants. Heights and weights were measured, and the body mass index was calculated.

K-SADS-PL

The K-SADS-PL schedule, originally developed by Kaufman et al. (1997) and adapted to the Turkish version by Gökler et al. (2004) evaluates the presence of common psychopathologies, primarily OCD, in children and adolescents. It was administered as part of the structured psychiatric interview with the parents and children. The final evaluation was performed using input from all data sources.

CY-BOC

The CY-BOC is a semistructured tool to measure the severity of OCD signs within the past week (Scahill et al, 1997). It comprises 5 main sections: instructions, an obsession screening list, items to determine the severity of obsessions, a compulsion screening list, and items to determine the severity of compulsions. Information was gathered from the child and his/her parents. The validity and reliability study of the Turkish version of this scale was carried out by Yucelen et al. (2006).

CDI

The CDI was developed by Kovacs (1985), based on the Beck Depression Scale, and we used the CDI scale adapted in Turkish by Öy (1991). Of note, questions specific to the childhood period, such as school success and relationship with friends, were added. The scale contains 27 items, and each item is scored as "0", "1", or "2" points depending on the severity of the symptoms. The maximum score is 54 points. High scores indicate the level or severity of depression. The cutoff point for the scale is 19 points.

Clinical Global Impression Scale

The Clinical Global Impression (CGI) scale is a standardized evaluation tool used to rate disease severity, disease course over time, and drug effects according to the clinical condition of the patient and the severity of the side effects. CGI is rated on a 7-point scale, from 1 (normal) to 7 (severe disease) (Guy, 1976).

Cytokine Bead Array

Blood samples were obtained between 10:00 and 12:00 AM. The samples were collected in gel tubes and stored at 4°C until centrifugation later on the same day. All blood samples were then centrifuged at 5000 rpm for 6 minutes. The sera were transferred to 1.5-mL polypropylene tubes and stored at –80°C for subsequent analysis. The BD Cytometric Bead Array Human $Th_1/Th_2/Th_{17}$ Cytokine Kit (cat. no. 560484, BD Biosciences), FCAP Array v3.0 software (23-13454-00, BD Biosciences), and BD FACSVerse system (23-13453-00, BD Biosciences) were used for the measurement and analysis of the concentrations of the cytokines IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α. Sera were used without dilutions for BD Cytometric Bead Array analysis.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 software package (SPSS Inc, Chicago, IL). The chi-square test was used to evaluate any difference between the groups in terms of gender, consanguinity between parents, and history of psychiatric disorders. The Student's *t* test was used to compare normally distributed variables in independent groups, and the Mann-Whitney test was used to compare nonnormally distributed variables. The effects of age and gender were adjusted using 2-way ANOVA and ANCOVA tests. The Pearson's test was used to determine correlation coefficients and statistical significance of normally distributed variables, and the Spearman's test was used for nonnormally distributed variables. $P < .05$ was considered statistically significant.

Results

There was no significant difference in age or gender between the OCD group (male/female: 23/11; age: 12.8 ± 2.7 years) and the control group (male/female: 17/17; age: 12.8 ± 2.6 years). No differences were detected in the occupation of the parents and the presence of consanguinity between the parents in either group. The frequency of psychiatric diseases in the family and close relatives was significantly higher in the OCD group ($P = .00$) compared with the control group. The socio-demographic data are shown in Table 1.

No significant difference was found in the depression scores between the OCD and control groups ($P = .76$). The duration of OCD symptoms was 19.0 ± 19.8 months. Patients reported that the severity of their OCD symptoms had increased to a level that impaired functioning over a mean of 4.0 ± 3.5 months. Data from the psychiatric evaluation using the K-SADS-PL, CY-BOC, and CDI scales are shown in Table 1. IL-17A, TNF-α, and IL-2 levels were significantly higher in OCD patients compared with the control group ($P = .03$, 0.01, and 0.02, respectively). When 2-way ANOVA and ANCOVA were performed to assess the confounding impact of age and gender on the results, the statistical significance of differences did not change between the OCD

Table 1. Data Related to Some Sociodemographic Variables and Scales

	OCD (n = 34) (mean ± SD)	Control (n = 34) (mean ± SD)	z or t Value	*P* Value
Age (years)	12.8 ± 2.7	12.8 ± 2.6	t = 0.00	1.00
Sex (M/F)	23/11	17/17	chi-square	0.22
Mother's age (y)	42.7 ± 8.2	37.4 ± 4.9	z = -2.55	**0.01**
Father's age (y)	46.8 ± 4.9	42.9 ± 5.8	t = 2.12	**0.04**
Consanguineous marriages (yes/no)	12/22	10/24	chi-square	0.80
History of psychiatric disorders in the family (yes/no)	20/14	2/32	chi-square	**0.00**
BMI (kg/m^2)	19.7 ± 4.1	19.7 ± 2.8	t = 0.04	0.97
CDI	13.3 ± 6.8	12.7 ± 6.3		0.76
Duration of OCD symptoms (mo)	19.0 ± 19.8	NA		
CY-BOC				
Obsession	12.1 ± 3.4	NA		
Compulsion	10.8 ± 4.1	NA		
Total	22.8 ± 7.2	NA		
CGI	3.9 ± 0.8	NA		

Abbreviations: BMI, body mass index; CDI, The Children's Depression Inventory; CY-BOC, Children's Yale Brown Obsession Compulsion Scale; CDI*, cutoff point for the scale is 19 points. CGI, Clinical Global Impression Scale; NA, not applicable; OCD, Obsessive Compulsive Disorder.

and control groups in terms of IL-17A, TNF-α, and IL-2 levels (F = 6.547, P = .013; F = 11.175, P = .001; F = 5.109, P = .027, respectively). However, there was no correlation between Th_1 and Th_{17} cytokine profiles in the OCD group. Data from the biochemical analysis are presented in Table 2. The duration and severity of OCD symptoms were not significantly associated with IL-17A, IFN-γ, IL-10, IL-6, IL-4, and IL-2 levels. A negative correlation was found between TNF-α levels and CGI scores (r = -0.46, P = .02).

Discussion

The most important finding of the present study was the significant increase in the levels of the Th_1 cytokines IL-2 and TNF-α as well as levels of the Th_{17} cytokine IL-17 in the OCD group. A further important finding was the lack of correlation between the severity and duration of the OCD symptoms and cytokine levels. Interestingly, a negative correlation was found between disease severity and TNF-α levels.

There are inconsistent results from studies investigating the serum and cerebrospinal fluid levels of cytokines in OCD patients. The IL-2 level has been found higher in children who had TD together with OCD compared with the non-OCD TD group, whereas no significant difference has been found in TNF-α and IL-6 levels between the groups. Additionally, a negative correlation has been reported between OCD symptom severity and TNF-α levels (Gabbay et al, 2009). In children with tic disorder, the serum levels of IL-2 have been found to negatively correlate with OCD symptom severity (N. G. Bos-Veneman et al, 2010). Only one study has investigated IL-2 levels in adult OCD patients and found that levels were similar to those in healthy control subjects (Weizman et al, 1996). A meta-analysis of studies conducted in adult OCD patients found reduced levels of IL-1β and similar levels of IL-6 and TNF-α compared with healthy subjects. Additionally, TNF-α levels were increased in OCD patients who also had depression (Gray and Bloch, 2012).

Consistent with our findings, a study by Leckman et al. reported increased levels of TNF-α in pediatric and adolescent OCD and/or TD patients compared with healthy control subjects (Leckman et al, 2005). The authors also reported a negative correlation between OCD symptom severity and TNF-α levels, also in agreement with our data (Gabbay et al, 2009). Moreover, one report showed that TNF receptor 1 (TNFR1: p55) and TNF receptor 2 (TNFR2: p75) might have opposite effects on neurons, with TNFR1 having a damaging impact on neuronal cells and TNFR2 having a neuroprotective effect (Fontaine et al, 2002). These findings indicate that low TNF-α concentrations may stimulate TNFR1, whereas TNFR2 stimulation may require high TNF-α concentrations. In other words, TNF-α affinity to TNFR1 may be high, but lower to TNFR2. In fact, Frishman et al. (2000) showed that TNF-α affinity to the TNFR2 receptor is 40-fold lower than that to TNFR1. Our findings suggest that high TNF-α levels might ameliorate OCD pathology via TNFR2, whereas low TNF-α levels might contribute to create OCD or make it worse via TNFR1. On the other hand, Konuk et al. reported that TNF-α levels were higher in patients with childhood-onset OCD than in patients with adult-onset OCD (Konuk et al, 2007). These inconsistencies in findings between pediatric and adult OCD patients might be explained by the variation in cytokine levels by age (Lilic et al, 1997; Geller et al, 2001).

IL-17, the signature cytokine of Th_{17} cells, has been shown to play a role in the pathogenesis of important psychiatric diseases such as anxiety disorder and TD (Vieira et al, 2010; Cheng et al, 2012). Cheng et al. (2012) found significantly higher IL-17 levels in children and adolescents with TD than in healthy control subjects. Our study was the first to investigate the levels of IL-17A in children and adolescents with OCD, showing significantly higher levels of IL-17A in the OCD group than in healthy controls.

Both Th_1 and Th_{17} effector T cells play a role in organ-specific, as well as systemic, autoimmune disease development (Steinman, 2007), while Th_2 effector cells are crucial for allergic diseases (Cosmi L, 2014). Th_{17} cells may show plasticity and can be converted into Th_1 or Th_2 effector cells (Cosmi et al, 2014; Ivanova and Orekhov, 2015; Maggi et al, 2012). Increased levels of TNF-α and IL-17 are associated with numerous autoimmune diseases and blockade of these cytokines have been shown to have therapeutic benefits in various autoimmune diseases (Kodama et al, 2005; Lai and Dong, 2015; Waisman et al, 2015). Our results showed that the levels of the Th_1 cytokines IL-2 and TNF-α, as well as the levels of the Th_{17} cytokine IL-17A, were significantly higher in the sera of OCD children. However, there was no correlation between Th1 and Th17 cytokine profiles in the OCD group. These findings indicate that the two distinct populations of Th cells, namely Th_1 and Th_{17}, may play a role in the pathogenesis of OCD.

The present study had some limitations. The cross-sectional study design allowed the measurement of cytokine levels at only a single time point. Also, the small study sample size meant that it was inadequate to be representative of the general population. In addition, we did not assess the antistreptolysin O titration levels.

In conclusion, the present study found significantly higher levels of the Th_1 cytokines IL-2 and TNF-α, and the Th_{17} cytokine IL-17 in children with OCD. Moreover, there was an inverse correlation between TNF-α levels and disease severity. However, there was no correlation between Th_1 and Th_{17} cytokine profiles in the OCD group. These findings suggest that OCD might be mediated by Th_1 or Th_{17} effector T cells, according to serum cytokine profiles. It might be necessary to investigate for OCD symptoms in patients with autoimmune disease, and conversely for autoimmune diseases in OCD patients. Additionally, the possible effects of adding immunomodulatory and antiinflammatory agents to conventional treatment of OCD should be investigated.

Table 2. Biochemical Parameters in Patients with or without OCD

(pg/mL)	OCD (n = 34) (mean ± SD)	Control (n = 34) (mean ± SD)	z or t Value	P Value
IL-17A	15.4 ± 26.7	2.9 ± 9.9	z = -2.18	**0.03**
IFN-γ	ND	1.04 ± 6.07	z = -1.00	0.32
TNF-α	22.7 ± 32.1	4.9 ± 5.6	z = -2.63	**0.01**
IL-10	6.9 ± 4.6	7.1 ± 4.2	z = -0.25	0.81
IL-6	6.8 ± 18.1	4.0 ± 9.3	z = -0.10	0.93
IL-4	33.1 ± 12.3	28.6 ± 4.6	t = 1.96	0.06
IL-2	21.4 ± 9.0	15.8 ± 10.5	t = 2.34	**0.02**

Abbreviations: ND, not detected; OCD, Obsessive Compulsive Disorder.

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Interest Statement

None.

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