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Published in:
Pediatric neurology

DOI:
10.1016/j.pediatrneurol.2023.04.013

Pediatric Neurology 144 (2023) 90–96

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Moderating Role of Depression on the Association of Tic Severity With Functional Impairment in Children

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ARTICLE INFO

Article history:
Received 10 July 2022
Accepted 17 April 2023
Available online 21 April 2023

Keywords:
Chronic tic disorder
Tics
Tourette syndrome
Depression
ADHD
OCD

ABSTRACT

Background: Chronic tic disorders (CTDs) commonly co-occur with other psychiatric disorders. CTDs have been linked to functional impairment and reduction in quality of life. Insufficient research is available on depressive symptoms in patients with CTD, especially children and adolescents, yielding conflicting findings. To investigate the presence of depressive symptoms in a cohort of children and young adolescents with CTD and to test whether they moderate the link between tic severity and functional impairment.

Methods: The sample consisted of 85 children and adolescents (six to 18 years) with a CTD who were treated in a large referral center. Participants were evaluated using gold-standard self- and clinician-reporting instruments to measure tic symptom severity and tic-related functional impairment (Yale Global Tic Severity Scale), depression (Child Depression Inventory), and obsessive-compulsive symptoms (Children Yale Brown Obsessive Compulsive Scale).

Results: Depressive symptoms (mild to severe) were exhibited by 21% of our sample. Study participants with CTD and comorbid obsessive-compulsive disorder (OCD) and/or attention-deficit/hyperactivity disorder had higher rates of depressive symptoms compared with those without comorbidities. Significant correlations were found within and among all tic-related and OCD-related measures, yet depressive symptoms only correlated to tic-related functional impairment. Depression significantly and positively moderated the correlation between tic severity and tic-related functional impairment.

Conclusions: Findings suggest that depression plays an important part as a moderator in the link between tic severity and functional impairment in children and adolescents. Our study highlights the importance of screening for and treating depression in patients with CTD.

Funding: The longitudinal European Multicentre Tics in Children Study (EMTICS) has received funding from the European Union's Seventh Framework Programme for research, technological development, and demonstration under Grant agreement no. 278367.

Ethics approval: The study was approved by the Institutional Review Board of the Rabin Medical Center, Petah Tikva, Israel.

Consent to participate: Written informed consent was obtained from all participants.

Consent for publication: All authors gave their consent for publication.

Data availability: Raw data were generated at Schneider Children's Medical Center. Derived data supporting the findings of this study are available from the corresponding author on request.

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https://doi.org/10.1016/j.pediatrneurol.2023.04.013
0887-8994/

Introduction

Chronic tic disorders (CTDs), including Tourette Syndrome (TS), are neurodevelopmental disorders that typically begin during childhood years,[1] and they are characterized by the presence of motor and/or vocal tics, appearing in bouts, over a period of at least one year. Tics are sudden, rapid, recurrent, nonrhythmic movements or sounds that vary significantly in complexity and intensity.[2] Community samples of children between the ages 10 and 17 years estimate the prevalence of CTDs to be as high as 1% to 2%. CTDs occur more frequently in males and are usually diagnosed around age seven years.[3]

CTDs co-occur with other psychiatric disorders in over 85% of cases,[4] with the most common being attention-deficit/hyperactivity disorder (ADHD, 60% to 80%), and obsessive-compulsive disorder (OCD, 30% to 50%).[1,4-7] Other conditions such as anxiety, sleeping problems, learning disorders, and behavioral problems were also found as comorbidities.[6,7] Patients with CTD suffering from comorbid psychiatric conditions tend to accumulate greater and more pervasive functional impairments in familial relationships, academic performance, and social functioning.[8,9]

Much less research is available on depressive symptoms in patients with CTD, yielding conflicting findings, depending on the study characteristics. Population-based data suggest that depressive disorders do not appear in higher rates among children and youth with tics, compared with controls.[6,10] Evidence to the contrary appears in clinical sample-based studies,[11-13] with depression prevalence in patients with CTD ranging between 13% and 76% depending on the sample population, diagnostic criteria, symptom severity, and age.[5,11,14,15] More recent studies replicate these findings, confirming that patients with TS are at increased risk of developing depression, particularly those diagnosed with comorbid OCD, when compared with non-TS patients.[5,11,16-18] Some recent reports have even pointed to a link between CTD and suicidality in both adult and youth samples.[19,20] The etiology of depression in CTD is likely multifactorial; it could, at least in part, be explained by new findings of a shared genetic background directly linking CTD and depression.[21] In addition, depression in patients with CTD may be a secondary condition caused by adversity, stress, and suffering related to tic symptomology and comorbid conditions.[11] However, not much is known about the complex inter-relation, in which each comorbid disorder may affect the other.

Research findings suggest that patients with TS suffer from lower quality of life compared with the healthy population.[22] Moreover, depressive symptoms have a significant and widespread impact on the quality of life of patients with TS,[14,23] with some authors suggesting that this effect is unique, predicting an aspect of the variance in quality of life unexplained by tic severity itself.[24] Robertson[13] argued that the functional prognosis among patients with CTD may be hampered due to comorbid depression, particularly when it is related to tic severity. Indeed, research interest has shifted in recent years toward functional impairments associated with CTD and its correlates. Some of the evidence points to a link between TS and impairments across several life domains. Storch and colleagues[25] showed that in a clinical sample of youth with TS, parents' reports indicated at least one significant problem area in which tic-related impairment was evident. Self-esteem and a variety of school-related, social and familial aspects of functioning have indeed been reported to be adversely impacted by CTD.[25-30]

The degree of functional impairment of patients with CTD may be related to tic severity. However, two main gaps are evident in the limited literature on tic-related functional impairment.[31] First, results are mixed with regard to the relationship between functional impairment and tic severity, with some research yielding a positive relationship,[25,28,30,32] whereas others failing to demonstrate an association.[33-35] Second, in light of the frequent comorbidity between CTDs and other psychiatric disorders, the adverse impact of CTDs on functioning needs to be disentangled from that of co-occurring conditions. From the current evidence available in the literature, it remains unclear to what degree CTDs alone impact functional impairment, and to what degree it can be attributed to comorbid psychopathology,[15,28] particularly depression, which is closely linked with life stressors and dysfunction.[14] Lewin and colleagues showed an enhancing moderation effect of affective symptoms on the correlation between tic severity and functional impairment in a sample of adults with TS. For patients with more depressive or anxious symptoms, stronger relationships were reported between tic severity and impairment.[31]

The aim of this prospective cross-sectional study was to explore the role of co-occurring depression as a potential factor influencing tic-related functional impairment, along with tic severity in children and adolescents with CTD, an underexplored area so far. We hypothesized that depression as an enhancing moderator might be a significant missing piece of the puzzle, and we tested whether such an effect is evident in a pediatric sample, similar to what is found in adults, and whether it is significant above and beyond other comorbidities. Identifying such effects would have relevant clinical implications, given that everyday functioning is a central treatment outcome.[31]

Methods

Participants

The study sample consisted of 85 children and adolescents with a CTD aged between six and 18 years, attending a tertiary pediatric neuropsychiatric tic clinic in Schneider Children's Medical Center in Israel. Fifty participants also participated in the baseline measurement of the longitudinal European Multicenter Tics in Children Study. This study aims to identify the role of genes, autoimmunity, and psychosocial stress on the onset and course of tics.[36] Excluded were patients suffering from serious medical illnesses, mental retardation, schizophrenia, head injuries, focal neurological disabilities, those treated with antibiotics during the last month, and those unable to understand and comply with the study procedures. Written informed consent forms were provided by the families. The study was approved by the Rabin Medical Centre Research Ethics Committee.

Procedure

In this prospective cross-sectional study, all participants were evaluated by two senior child psychiatrists (N.B.-M. and A.A.), during which diagnoses of CTD, OCD, ADHD, depressive disorder, anxiety disorders, and behavior problems were validated according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) criteria. All study participants and their families were interviewed using gold-standard instruments for tic severity and OCD (see below) by three doctoral clinical psychologists with a special training in tic disorders. This interview was followed in the same session by self-report questionnaire for depressive symptoms completed by the participants (see below) while clinicians were unaware of the depressive symptoms score.

Measures

Yale Global Tic Severity Scale

Tic severity and tic-related functional impairments were assessed via the Yale Global Tic Severity Scale (YGTSS),[37] a

semistructured clinician-rated measure, designed to assess tic severity across five impact categories (number, frequency, intensity, complexity, and interference). The YGTSS also includes a separate tic-related functional impairment item, which allows for capturing the clinician's impression of overall functional impairment, evident in the patient's everyday life. All items are rated on a six-point Likert scale in relation to the previous week. The YGTSS yields one rank score for tic-related functional impairment (range 0 to 50) as well as three summary scores: total tic severity (range 0 to 50), total phonic tics score (range 0 to 25), and total motor tics score (range 0 to 25). Severity cutoffs for total tic severity of the YGTSS are minimal tics <10, 10 ≤ mild tics <20, 20 ≤ moderate tics <40, and 40 ≤ severe tics <50, based on Leckman and colleagues.[38] The internal reliability of the Hebrew version of the YGTSS used in the tic disorder clinic was Cronbach alpha = 0.83.[39]

Children's Yale Brown Obsessive Compulsive Scale

OCD symptoms were assessed via the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS).[40] This scale is a clinician-rated 10-item scale, designed for assessing the severity of obsessive-compulsive symptoms in children and adolescents. CY-BOCS is composed of question related to obsessions and compulsions regarding the amount of time consumed by symptoms, degree of interference, distress, resistance, and control over symptoms. All items are rated on a five-point Likert scale in relation to the previous week. The CY-BOCS yields three summary scores: obsessions severity score (ranges 0 to 20), compulsions severity score (range 0 to 20, $\alpha = 0.85$), and total OCD score (range 0 to 40). Severity cutoffs for the CY-BOCS are subclinical 0 to 7, mild 8 to 15, moderate 16 to 23, severe 24 to 31, and extreme 32 to 40. The CY-BOCS has demonstrated acceptable internal consistency and convergent validity.[41] The internal reliability of the Hebrew version of the CY-BOCS used in the tic disorder clinic was Cronbach alpha = 0.90.[39]

Child Depression Inventory

Depression symptoms were measured using the Child Depression Inventory (CDI),[42] a self-report scale designed to capture emotional, cognitive, behavioral, and somatic symptoms of depression in children and adolescents in relation to the previous two weeks. Each item is ranked on a scale of 0 to 2, and items are then summed to a total severity scale in which higher scores represent more severe depressive symptoms (0 to 54). A total score of 20 is considered the cutoff for a diagnosis of a depressive disorder in community samples. Previous studies proposed severity ranks of 15 for mild, 20 for moderate, and 25 for severe depression.[43] The internal reliability of the Hebrew version of the CDI used in the tic disorder clinic was Cronbach alpha = 0.89.[39]

Data analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) (IBM Corp., Released 2011; IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). *t* Tests were used to compare tic severity, OCD, and depressive symptoms between males and females. *t* Test was also used to compare tic severity between patient's with or without depression (CDI ≥15). Chi-square test was used to compare rates of ADHD diagnoses between males and females. A *t* test was used to compare depressive symptoms between study participants with or without comorbidities (ADHD and/or OCD). A correlation matrix of all study variables was carried out; all correlations were calculated using both Pearson and Spearman rho correlations, as there was a positive right-skewed distribution of CDI scores.

To test our hypothesis regarding the moderating role of depression, a hierarchal regression analysis was conducted with depressive symptoms, tic severity, and the interaction between them as predictors of tic-related functional impairment. Variables were initially standardized and then entered consecutively into the model in a four-block design, to control for age, sex, and comorbidity symptoms (OCD symptoms, ADHD diagnosis) and account for the added contribution of the interaction effect to the explained variance, beyond all controlled, independent factor effects. The model R^2, ΔR^2, ΔF, the standardized and unstandardized coefficients, and their significance were all analyzed.

To illustrate the moderator effect, a simple slope analysis was conducted and shown in a graph. The graph presents the simple correlation between the independent (tic severity) and dependent (tic-related functional impairment) standardized variables for two different cutoff points of the standardized moderator variable (depressive symptoms). Therefore, one S.D. above or below the mean of standardized CDI score was considered as high or low depressive symptoms correspondingly and was used as a cutoff creating two simple correlations. All results were considered statistically significant if $P < 0.05$.

Results

Sample characteristics

Table 1 provides the demographic and clinical information about participants. The sample included 85 children and adolescents with CTD, 50 (58.8%) of whom had TS and 35 (41.2%) of whom had CTDs. Mean age of the study group was 10.9 ± 2.63 years. There were 68 (80%) males, with a mean age of 11.0 ± 2.63 years, and 17 (20%) females, with a mean age of 10.5 ± 2.68 years (see Table 1). The mean total tic severity score (YGTSS) was 15.1 ± 8.61. Most (42%) study participants exhibited mild tic severity; 30.6% and 25.9% of the participants had minimal and moderate tic severity, respectively, and only one participant (1.1%) displayed severe level of tics.

Additional diagnoses (defined according to DSM-IV-TR criteria) at the time of evaluation included ADHD and OCD, present in 43 (50.6%) and 11 (12.9%) participants, respectively; 25 (29.4%) young patients suffered from an anxiety disorder and six (7.1%) from behavioral problems. Depressive disorders were diagnosed in six (7.1%) patients according to DSM-IV-TR criteria (see Table 1).

Males had a significantly higher YGTSS total tic severity score when compared with females (16.19 ± 8.80 vs 10.65 ± 6.26; $t_{83} = 2.44$, $P < 0.05$), but there were no significant differences between males and females when comparing tic-related functional impairment, depressive symptoms, and comorbidities.

Depressive symptoms

The mean CDI depression score for the whole sample was 9.18 ± 7.58 (range 0 to 33), with a mean of 9.35 ± 7.85 for males (range 0 to 33) and 8.47 ± 6.52 for females (range 0 to 23). No significant differences were evident between the sexes. Most participants (78.8%) exhibited none to minimal severity depressive symptoms according to the CDI, six (7.1%) participants reported mild depressive symptoms, seven (8.2%) had moderate symptoms, and five (5.9%) had severe symptoms. A total of 12 (14.1%) participants were above the clinical cutoff (≥20), indicating a suspected depression according to CDI score. When comparing patients with none to minimal depressive symptoms (n = 67, 78.8%) with patients with mild, moderate, or severe symptoms (n = 18, 21.2%) there were no significant differences in the total tic severity score (14.3 ± 7.68 vs 18 ± 11.21, $P = 0.20$). However, marginal significance

TABLE 1.
Demographic and Clinical Characteristics of the Sample (n = 85)

Variables	n = 85
Demographic characteristics	
Male gender, n (%)	68 (80)
Age (Mean ± S.D.)	10.90 ± 2.64
Clinical characteristics	
Tourette disorder, n (%)*	50 (58.8)
Total tic severity (mean ± S.D.)	15.08 ± 8.61
Motor tics (mean ± S.D.)	9.56 ± 4.97
Vocal tics (mean ± S.D.)	5.52 ± 5.56
Tic impairment (mean ± S.D.)	10.47 ± 13.53
ADHD, n (%)*	43 (50.6)
OCD, n (%)*	11 (12.9)
Obsessions (mean ± S.D.)	2.12 ± 3.74
Compulsions (mean ± S.D.)	2.84 ± 4.33
Total OCD score (mean ± S.D.)	4.96 ± 7.02
Anxiety disorders, n (%)*	25 (29.8)
Behavioral problems, n (%)*	6 (7.1)
Depressive disorders, n (%)*	6 (7.1)

Abbreviations:
ADHD = Attention-deficit/hyperactive disorder
OCD = Obsessive-compulsive disorder
* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.OCD, Obsessive Compulsive Disorder

was found in impairment with higher score for patients with depressive symptoms (8.8 ± 12.37 vs 16.6 ± 16.1, $P = 0.07$).

Differences in depressive symptoms between participants with CTD alone and with CTD and comorbidities were assessed. A *t* test revealed a significant difference between the CTD group and the comorbidity group (7.30 ± 7.03 vs 10.63 ± 7.74; $t_{(83)} = -2.05$, $P < 0.05$), indicating higher rates of depressive symptoms among study participants also presenting with OCD, ADHD, or both.

Correlations between study variables

Table 2 shows the correlation analyses among all study variables (Pearson and Spearman rho correlations are presented). Depressive symptoms were only correlated to tic-related functional impairment and not to tic or OCD severity. Correlation analyses among all study variables revealed significant correlations within tic and OCD measures so that total tic severity and tic functional impairment were significantly and positively correlated to each other and symptoms of obsessions and compulsions were also significantly and positively correlated (large effect sizes, see Table 2). However, ADHD diagnosis was not significantly correlated with either tic or OCD measures.

Predicting tic functional impairment and the moderation effect of depression

To test our hypothesis regarding the moderating role of depression, hierarchal regression analysis was conducted with depressive symptoms, tic severity, and interactions between them as predictors of tic-related functional impairment (for the purpose of this analysis all variables were standardized). Table 3 shows the results of the regression analysis, as well as the hierarchal block sequence. Within this final model, tic severity had the largest contribution to the prediction model of tic functional impairment, followed by the interaction effect, and finally depressive symptoms. OCD symptoms had a marginal effect after accounting for tic severity, depression, and their interaction; ADHD diagnosis, age, and sex remained insignificant in their contribution. According to the regression model, more severe tics as well as depressive symptoms predicted greater functional impairment.

The significant interaction effect indicates that depression acts as an enhancing moderator on the correlation between tic severity and tic-related functional impairment. Simple slope analysis was used to illustrate the interaction (see Fig). The graph presents the simple correlation between the independent (tic severity) and dependent (tic impairment) standardized variables for two different cutoff points of the standardized moderator variable (depressive symptoms). Therefore, one S.D. above or below the mean of standardized CDI score was considered as high or low depressive symptoms correspondingly and was used as a

TABLE 2.
Correlations* Matrix for Study Measures (n = 85)

Spearman Rho / Pearson Correlation	Depressive Symptoms (CDI)	Total Tic Severity (YGTSS)	Tic Impairment (YGTSS)	OCD Symptom Severity (CY-BOCS)	Obsessive Symptom Severity (CY-BOCS)	Compulsive Symptom Severity (CY-BOCS)	ADHD Diagnosis (Yes/No, According to Psychiatric Evaluation)
Depressive symptoms (CDI)		0.03 0.08	0.23† 0.23†	0.09 0.08	0.09 0.05	0.07 0.08	0.17 0.14
Total tic severity (YGTSS)			0.52‡ 0.56‡	0.13 0.31‡	0.08 0.24†	0.2 0.29‡	0.1 0.06
Tic impairment (YGTSS)				0.34‡ 0.33‡	0.3‡ 0.24†	0.38‡ 0.33‡	−0.08 −0.04
OCD symptom severity (CY-BOCS)					0.82‡ 0.89‡	0.87‡ 0.85‡	0.05 0.08
Obsessive symptoms severity (CY-BOCS)						0.5‡ 0.51‡	0.04 0.01
Compulsive symptom severity (CY-BOCS)							0.06 0.12
ADHD diagnosis (yes/no, according to psychiatric evaluation)							

Abbreviations:
ADHD = Attention-deficit/hyperactive disorder
CDI = Child Depression Inventory
CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale
OCD = Obsessive-compulsive disorder
YGTSS = Yale Global Tic Severity Scale
Spearman's rho correlations are shown on the top right side of each cell.
* Pearson correlations are shown on the bottom left side of each cell.
† $P < 0.05$.
‡ $P < 0.01$.

TABLE 3.
Hierarchal Regression Model for Predicting Tic-Related Functional Impairment in 85 Children and Adolescents (Six to 18 years) With CTD

Variables	Unstandardized Coefficients		Standardized Coefficients		ΔR^2	ΔF	$P_{\Delta F}$
	B	SE	β	*P*			
Step 1							
Age	0.037	0.103	0.038	0.724	4.014	0.090 (2.76)	0.022
Sex	−0.200	0.112	−0.193	0.078			
ADHD diagnosis (according to psychiatric evaluation)	−0.053	0.104	−0.054	0.612			
OCD Severity (CY-BOCS)	0.217	0.113	0.302	0.006			
Step 2							
Age	0.075	0.088	0.077	0.399	15.978	0.258 (2.74)	<0.001
Sex	−0.072	0.097	−0.069	0.463			
ADHD diagnosis (according to psychiatric evaluation)	−0.138	0.090	−0.142	0.130			
OCD severity (CY-BOCS)	0.159	0.100	0.152	0.114			
Depressive symptoms (CDI)	0.200	0.091	0.202	0.032			
Total tic severity (YGTSS)	0.488	0.094	0.506	<0.001			
Step 3							
Age	0.116	0.087	0.120	0.186	5.922	0.045 (1.73)	0.017
Sex	−0.089	0.094	−0.086	0.349			
ADHD diagnosis (according to psychiatric evaluation)	−0.113	0.088	−0.116	0.204			
OCD severity (CY-BOCS)	0.193	0.097	0.184	0.052			
Depressive symptoms (CDI)	0.194	0.089	0.197	0.032			
Total tic severity (YGTSS)	0.427	0.095	0.442	<0.001			
Interaction (total tic severity × depressive symptoms)	0.188	0.077	0.226	0.017			

Abbreviations:
ADHD = Attention-deficit/hyperactive disorder
CDI = Child Depression Inventory
CTD = Chronic tic disorder
CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale
OCD = Obsessive-compulsive disorder
YGTSS = Yale Global Tic Severity Scale
SE = Standard error.
For the full model $R^2 = 0.45$, $F_{(7,80)} = 8.47$, $P < 0.001$.

cutoff creating two simple correlations, thus revealing that the positive correlation between tic severity and tic-related functional impairment was stronger at high level of depressive symptoms ($r = 0.76$, $P < 0.001$) compared with low level ($r = 0.37$, $P < 0.01$) as shown in Fig.

Discussion

The current study set out to understand an understudied phenomenon, namely, depression and depressive symptoms in CTDs, in a sample of 85 children and adolescents attending a tertiary pediatric neuropsychiatric tic clinic. Primarily, we found that over a fifth of our CTD sample exhibited mild to severe depressive symptoms; patients with CTD and comorbid OCD and/or ADHD had higher rates of depressive symptoms compared with those with no comorbidity.[12]

The main finding of the current study was a moderating role of depressive symptoms strengthening the adverse effect of tic severity on tic-related functional impairment. Lewin and colleagues[31] reported similar results in their sample of non–treatment-seeking adults with TS. Therefore, those findings suggest that the mere presence of depressive symptomatology has an important harmful effect, not only as a comorbid disorder but also on patients' subjective experience of tic-related functional impairment.

Hanks et al.[44] found that severe tic symptoms predict lower self-concept, which shapes the child's self-perspective and in turn predicts more depressive symptoms. Furthermore, the interaction between tic impairment and youth's reliance on avoidant coping strategies moderated their self-concept. Our findings, combined with those, highlight the need to estimate depressive symptoms in patients with CTD of all ages, which can be accomplished via well-validated self-report measures to guide clinical work.

Our results show that 14% of children and adolescents scored above cutoff for depression on the CDI, whereas only 7% were clinically diagnosed before entering the study with depression. These rates are considerably higher than the prevalence of depression in children and adolescents in the general population.[11] Nevertheless, our rates are slightly lower than those seen in other clinical samples, possibly due to the low average age in our study and relatively low tic severity, which was measured by the YGTSS.[11,45] Mood disorders are more dominant in females with TS, and the median onset age among patients with TS is approximately 13 years.[5] Consistent with this, the lack of sex differences in depressive symptoms may also be explained by the average age (11 years) of our sample.[46] These findings indicate the need to address depressive symptomatology clinically and empirically in children and adolescents diagnosed with CTD.

In line with previous findings,[12] our results show that patients with CTD presenting with comorbidities are more likely to exhibit depressive symptoms than those without comorbidities. This observation may be explained by the high comorbidity that ADHD and OCD have with depression. Depression may occur either as a complication of OCD and/or ADHD, or because of shared genetic and psychosocial factors.[11] Moreover, contrary to expectations, tic severity did not correlate with depressive symptomology, corroborating the major role of comorbidity. Rather, we found that patients with more severe tics are more likely to have more severe OCD symptoms and to show greater functional impairment, as has been previously reported.[11,13]

The lack of correlation between depressive symptoms and OCD symptoms was surprising. There is ample literature pointing to the link between OCD and depression, although more commonly reported in adult and adolescent samples than in children.[47] In concordance with our results, another study in youth with TS 1[14] reported that OCD symptoms did not differentiate between

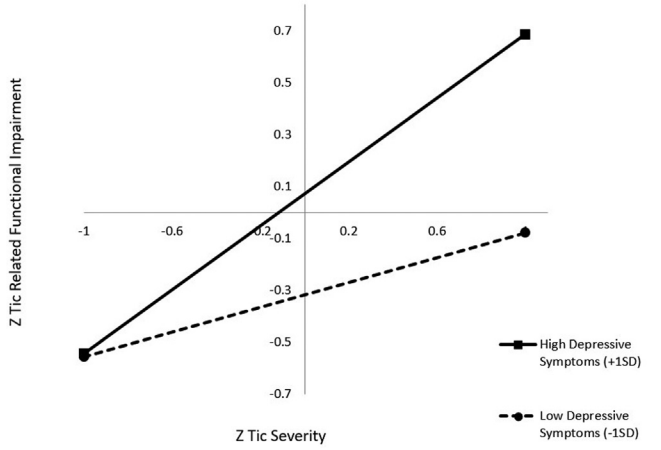

Figure. Depressive symptoms moderate the correlation between total tic severity and tic-related functional impairment (n = 85). Simple slope analysis was conducted to illustrate the interaction. The graph presents the simple correlations between tic severity and tic-related functional impairment for high and low cutoff points of depressive symptoms. One S.D. above or below the mean was considered as high or low depressive symptoms, respectively (CDI = 2; CDI = 17).

depressed and nondepressed patients. Another possible explanation is that co-occurring OCD in patients with CTD differs from non-tic-related OCD. Tic-related OCD is more commonly characteristic of younger patients and males, and patients with tic-related OCD commonly exhibit more sensory phenomena, higher rates of symmetry/ordering symptoms, and more "just right" and incompleteness feelings underlying compulsive behaviors compared with non-tic-related OCD. Thus, tic-related OCD is less anxiety related, and therefore might be less related to depression.[48,49]

It is well-documented in the literature that severe tic symptomology may have deleterious implications on the functional impairment and quality of life of patients and their families, causing considerable suffering by itself or in combination with other related psychopathology.[50] The etiology of depression in patients with CTD is likely multifaceted. Depression, particularly in those with more severe tics, may be explained by the distress and suffering associated with having a chronic, socially disabling, and often stigmatizing condition.[8] For example, being bullied may be a cause of depressive symptoms, which in turn may affect daily functioning, such as at school. Other possible origins may include a shared genetic etiology between CTD and depression,[21] a familial history of depression, side effects of medications, or the presence of other comorbidities.[11]

Strengths and limitations

The present study has several notable strengths, including its focus on an understudied area—depressive symptoms and tic-related functional impairment in a middle childhood sample. The importance of this study is that the moderating effect of depression on the association between tic severity and tic impairment was found above and beyond other comorbidities, which has further clinical implications. Nevertheless, the current study has some limitations. First, the restricted sample size and low number of females are shortcomings. Second, the sample exhibited relatively low tic symptom severity, despite recruitment from an outpatient pediatric neuropsychiatric clinic, limiting the generalizability of our results to other, more severe, samples. Moreover, all subjects were treated in the same clinic, which might have resulted in a selection bias. Furthermore, we used DSM-IV-TR criteria, as the study was designed before 2013. Unfortunately, no severity or count measure was available for ADHD. In addition, tic-related functional impairment was measured by a single item of the YGTSS and the measures are not fully independent; for example, tic impairment clinician ratings may still be influenced by depressive symptoms of both the children and their parents. Nevertheless, the clinicians were unaware of the CDI depressive symptoms scores and depression diagnoses, because the main conclusion of the study relies on the lack of bias in YGTSS ratings (especially the 0 to 50 functional impairment scales).

Future studies should use known validated measures such as The Gilles de la Tourette Syndrome-Quality of Life Scale.[51] Last, a major limitation of this study is its cross-sectional nature, not assessing reciprocity of the comorbid conditions and developmental aspects.

Conclusions

Our study has made an important step in pointing to the need of assessing and treating depression in children and adolescents with tic disorders. Even though the study population consisted of middle childhood, we found a high prevalence of depressive symptoms. Tic-related functional impairments seem to be mainly affected by tic severity but are also highly linked with co-occurring depressive symptoms. Our findings highlight the importance of screening for depression in the clinical evaluation of patients with CTD. Future studies should explore the role of depression on broader domains of CTD patients' quality of life than in our study, using validated tools such as a CTD-specific quality-of-life scale.[52] In addition, longitudinal studies are needed to understand the temporal and directional influence of tic disorders and comorbidities across development.

Declaration of Competing Interest

The authors have no conflicts of interest.

Acknowledgments

The authors are deeply grateful to all the children and their parents who willingly participated to make this research possible. The longitudinal European Multicentre Tics in Children Study (EMTICS) has received funding from the European Union's Seventh Framework Program for research, technological development, and demonstration under Grant agreement no. 278367. The authors thank Sharona Shmuel-Baruch, Chen Regev, and Ella Gev (Department of Psychological Medicine, Schneider Children's Medical Center of Israel, Petah Tikva, Israel) for their invaluable help in data collection. We thank Adi Moka for her assistance in editing and proofreading. We thank the Schneider Children's Medical Center physicians' committee and editorial board for their help in proofreading the article.

References

1. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. J Psychosom Res. 2009;67:497–501.
2. American Psychiatric Association. In: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
3. Knight T, Steeves T, Day L. Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol. 2012;47:77–90.
4. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. Dev Med Child Neurol. 2007;42:436–447.
5. Hirschtritt ME, Lee PC, Pauls DL. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in tourette syndrome. JAMA Psychiatr. 2015;72:325–333.

6. Kurlan R, Como P, Miller B. The behavioral spectrum of tic disorders a community-based study. Neurology. 2002;59:414–420.
7. Sambrani T, Jakubovski E, Müller-Vahl KR. New insights into clinical characteristics of Gilles de la Tourette syndrome: findings in 1032 patients from a single German center. Front Neurosci. 2016;10:415.
8. Eapen V, Cavanna AE, Robertson MM. Comorbidities, social impact, and quality of life in tourette syndrome. Front Psychiatry. 2016;7:5–10.
9. Rizzo R, Gulisano M, Calì PV, Curatolo P. Tourette Syndrome and comorbid ADHD: current pharmacological treatment options. Eur J Paediatr Neurol. 2013;17:421–428.
10. Chou IC, Lin HC, Lin CC. Tourette syndrome and risk of depression: a population-based cohort study in Taiwan. J Dev Behav Pediatr. 2013;34:181–185.
11. Robertson MM. Mood disorders and Gilles de la Tourette's syndrome: an update on prevalence, etiology, comorbidity, clinical associations, and implications. J Psychosom Res. 2006;61:349–358.
12. Debes Mol N, Hjalgrim H, Skov L. Validation of the presence of comorbidities in a Danish clinical cohort of children with Tourette syndrome. J Child Neurol. 2008;23:1017–1027.
13. Robertson MM, Williamson F, Eapen V. Depressive symptomatology in young people with Gilles de la Tourette syndrome - a comparison of self-report scales. J Affect Disord. 2006;91:265–268.
14. Rizzo R, Gulisano M, Martino D, Robertson MM. Gilles de la Tourette syndrome, depression, depressive illness, and correlates in a child and adolescent population. J Child Adolesc Psychopharmacol. 2017;27:243–249.
15. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. Brain. 2000;123:425–462.
16. Lebowitz ER, Motlagh MG, Katsovich L, King RA, Lombroso PJ, Grantz H. Tourette syndrome in youth with and without obsessive compulsive disorder and attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry. 2012;21:451–457.
17. Rizzo R, Gulisano M, Pellico A. Tourette syndrome and comorbid conditions: a spectrum of different severities and complexities. J Child Neurol. 2014;29:1383–1389.
18. Termine C, Selvini C, Balottin U. Self-, parent-, and teacher-reported behavioral symptoms in youngsters with Tourette syndrome: a case-control study. Eur J Paediatr Neurol. 2011;15:95–100.
19. de la Cruz F, Rydell M, Runeson B. Suicide in Tourette's and chronic tic disorders. Biol Psychiatry. 2017;82:111–118.
20. Johnco C, McGuire JF, McBride NM. Suicidal ideation in youth with tic disorders. J Affect Disord. 2016;200:204–211.
21. Brainstorm C, Anttila V, Bulik-Sullivan B. Analysis of shared heritability in common disorders of the brain. Science. 2018;360, eaap8757.
22. Jalenques I, Galland F, Malet L, et al. Quality of life in adults with Gilles de la Tourette syndrome. BMC Psychiatry. 2012;12:109.
23. Eddy CM, Rizzo R, Gulisano M. Quality of life in young people with Tourette syndrome: a controlled study. J Neurol. 2011;258:291–301.
24. Müller-Vahl K, Dodel I, Müller N. Health-related quality of life in patients with Gilles de la Tourette's syndrome. Mov Disord. 2010;25:309–314.
25. Storch EA, Lack CW, Simons LE. A measure of functional impairment in youth with Tourette's syndrome. J Pediatr Psychol. 2007;32:950–959.
26. Altman G, Staley JD, Wener P. Children with tourette disorder: a follow-up study in adulthood. J Nerv Ment Dis. 2009;197:305–310.
27. Zinner SH, Conelea CA, Glew GM. Peer victimization in youth with Tourette syndrome and other chronic tic disorders. Child Psychiatry Hum Dev. 2012;43:124–136.
28. Conelea CA, Woods DW, Zinner SH. Exploring the impact of chronic tic disorders on youth: results from the Tourette syndrome impact survey. Child Psychiatry Hum Dev. 2011;42:219–242.
29. Lee MY, Chen YC, Wang HS, Chen DR. Parenting stress and related factors in parents of children with tourette syndrome. J Nurs Res. 2007;15:165–174.
30. Wilkinson BJ, Marshall RM, Curtwright B. Impact of Tourette's disorder on parent reported stress. J Child Fam Stud. 2008;17:582–598.
31. Lewin AB, Storch EA, Conelea CA. The roles of anxiety and depression in connecting tic severity and functional impairment. J Anxiety Disord. 2011;25:164–168.
32. Storch EA, Murphy TK, Chase RM. Peer victimization in youth with Tourette's syndrome and chronic tic disorder: relations with tic severity and internalizing symptoms. J Psychopathol Behav Assess. 2007;29:211–219.
33. Eddy CM, Cavanna AE, Gulisano M. Clinical correlates of quality of life in Tourette syndrome. Mov Disord. 2011;26:735–738.
34. Stokes A, Bawden HN, Backman JE, Dooley JM, Camfield PR. Peer problems in Tourette's disorder. Pediatrics. 1991;87:936–942.
35. Bernard B, Stebbins G, Siegel S. Determinants of quality of life in children with Gilles de la Tourette syndrome. Mov Disord. 2009;24:1070–1073.
36. Schrag A, Martino D, Apter A. European Multicentre Tics in Children Studies (EMTICS): protocol for two cohort studies to assess risk factors for tic onset and exacerbation in children and adolescents. Eur Child Adolesc Psychiatry. 2019;28:91–109.
37. Leckman JF, Riddle MA, Hardin MT. The Yale Global tic severity scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989;28:566–573.
38. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in tourette syndrome: the first two decades. Pediatrics. 1998;102:14–19.
39. Benaroya-Milshtein N, Shmuel-Baruch S, Apter A. Aggressive symptoms in children with tic disorders. Eur Child Adolesc Psychiatry. 2020;29:617–624.
40. Scahill L, Riddle MA, McSwiggin-Hardin M. Children's Yale-Brown obsessive compulsive scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:844–852.
41. Stewart ES, Ceranoglu AT, O'Hanley T, Geller D. Performance of clinician versus self-report measures to identify obsessive-compulsive disorder in children and adolescents. J Child Adolesc Psychopharmacol. 2005;15:956–963.
42. Kovacs M. Children's Depression Inventory: Technical Manual. Toronto, Canada: Multi-Health Systems Inc; 2001.
43. Bang YR, Park JH, Kim SH. Cut-off scores of the children's depression inventory for screening and rating severity in Korean adolescents. Psychiatry Investig. 2015;12:23–28.
44. Hanks CE, McGuire JF, Lewin AB, Storch EA, Murphy TK. Clinical correlates and mediators of self-concept in youth with chronic tic disorders. Child Psychiatry Hum Dev. 2016;47:64–74.
45. Marwitz L, Pringsheim T. Clinical utility of screening for anxiety and depression in children with Tourette syndrome. J Can Acad Child Adolesc Psychiatry. 2018;27:15–21.
46. Kouros CD, Garber J. Trajectories of individual depressive symptoms in adolescents: sex and family relationships as predictors. Dev Psychol. 2014;50:2633–2643.
47. Jones PJ, Mair P, Riemann BC. A network perspective on comorbid depression in adolescents with obsessive-compulsive disorder. J Anxiety Disord. 2018;53:1–8.
48. Leckman JF, Grice DE, Barr LC. Tic-related vs. non-tic-related obsessive compulsive disorder. Anxiety. 1994;1995:208–215.
49. de Vries F, Cath D, Hoogendoorn A. Tic-related versus tic-free obsessive-compulsive disorder. J Clin Psychiatry. 2016;77:e1240–e1247.
50. Leckman JF, Bloch MH, Scahill L, King RA. Tourette syndrome: the self under siege. J Child Neurol. 2006;21:642–649.
51. Cavanna AE, Schrag A, Morley D, et al. The Gilles de la Tourette syndrome–quality of life scale (GTS-QOL): development and validation. Neurology. 2008;71:1410–1416.
52. Cavanna AE, David K, Bandera V. Health-related quality of life in Gilles de la Tourette syndrome: a decade of research. Behav Neurol. 2013;27:83–93.