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ORIGINAL CONTRIBUTION

Tic disorders in children and adolescents: does the clinical presentation differ in males and females? A report by the EMTICS group

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Abstract

Tic disorders have a strong male predominance, with a male-to-female ratio of 4:1 in Tourette syndrome (TS) and 2:1 in persistent tic disorders. In other neurodevelopmental conditions, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), the disparity in sex distribution has been partially related to differences in symptom presentation between males and females. In tic disorders, however, little research has been conducted on this topic, probably due to the limited access to large samples with a significant proportion of females. The aim of this study was to describe sex differences in the clinical presentation of tic disorders in children and adolescents in one of the largest pediatric samples with TS/persistent tic disorders ($n = 709$, 23.3% females) recruited as part of the *European Multicenter Tics in Children Study* (EMTICS). Validated measures assessed the severity of tics and comorbid psychiatric symptoms. Using mixed-effect models, we found that sex had a significant influence on the severity of tics, ADHD symptoms, ASD symptoms, and emotional problems. Males had more severe symptoms than females, except for emotional problems. We also observed a statistically significant interaction between sex and age on the severity of tics and compulsions, with females showing higher symptom severity with increasing age than males. These findings indicate that the clinical presentation of TS/persistent tic disorders varies with sex. Males seem to exhibit a more noticeable pattern of clinical symptoms at a younger age that may contribute to their earlier detection in comparison to females.

Keywords Tourette syndrome · Children · Adolescents · Sex differences

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by persistent motor and at least one vocal tic, whereas persistent tic disorder includes only motor or vocal

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tics [1]. Tics usually begin around the age of 4–6 years, increase in severity around age 10–12 years, and often undergo a spontaneous amelioration throughout adolescence [2, 3]. In addition to tics, the majority of individuals with TS exhibit other psychiatric symptoms that contribute to a broader impairment in daily functioning [4]. Attention-deficit/hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) are the most common comorbid conditions, with prevalence rates up to 50% in clinical samples [5, 6]. Elevated rates of autism spectrum disorder (ASD), disruptive behavior disorders, anxiety disorders, and mood disorders have also been reported [7].

Comorbid psychiatric conditions are often the primary reason for referral of children with tics. In a population study with 4479 children and adolescents aged 7–15, those diagnosed with TS ($n = 25$, 0.6%) or chronic/persistent tic disorders ($n = 58$, 1.3%) were primarily referred for attention problems/hyperactivity, comorbid neurodevelopmental conditions, and disruptive behaviors [8]. Behavioral problems were also reported to be frequent at tic onset in an early study with 92 children with TS [9]. In that study, the authors specified that behavioral problems were more common in boys than in girls and suggested that this difference could facilitate the detection of tic disorders in males, while possibly delaying the diagnosis in females.

In other neurodevelopmental disorders, sex differences in symptom presentation have also been related to under- or misdiagnosis in females. In ASD, girls have been reported to present better non-verbal communication than boys, a characteristic that has been thought to camouflage their condition [10]. In ADHD, it has been suggested that females may be more easily missed in the diagnostic process unless they have prominent hyperactivity-impulsivity or behavioral problems [11]. With regard to TS, little research has been conducted on this topic, probably due to the limited access to large clinical pediatric samples with a significant proportion of females, a limitation that has only been overcome by the recent foundation of large-scale collaborative projects.

One of the early exceptions was the international study of Freeman et al. (2000), who examined sex differences in the rates of comorbid psychiatric disorders from a sample with 3500 children and adults with TS (18.7% females) collected by referral to tertiary centers [12]. In that study, ADHD, conduct disorder (CD)/oppositional defiant disorder (ODD), and ASD were more frequent in males, whereas self-injurious behaviors were more frequent in females. More recently, Hirschtritt et al. (2015) reported similar findings from a sample with more than 1000 participants with a clinical diagnosis of TS (26.8% females, mean age 19.1 ± 13.5 years) [6]. In that cross-sectional study, ADHD and disruptive behavior disorders (ODD/CD) were more frequent in males, whereas OCD, anxiety, and mood disorders were more frequent in females. This distribution, with externalizing disorders more frequent in pre-pubertal males, is in line with prevalence studies of psychiatric disorders in non-TS samples [13]. Despite their contribution to the understanding of TS, the previously mentioned studies had some limitations. First, despite the wide age range of their samples, which included children and adult participants, they did not explore relations between sex and age. Second, they only focused on the presence or absence of comorbid diagnoses and did not consider the severity of comorbid conditions in TS. Although important, diagnoses do not capture the dimensional nature of comorbid problems across non-clinical to clinical levels [14].

With regard to tic severity, previous studies have not identified sex differences: in an internet-based study with 460 adults with TS (40.2% females), scores on the *Yale Global Tic Severity Scale* (YGTSS) were similar for both sexes [15]. The same finding was reported in a study with 74 youth and young adults (ages 5–21 years) with TS, in which the severity of tics was assessed using the *Parent Tic Questionnaire* [16]. In terms of sex differences regarding the course of tics over time, findings have been scarce and inconsistent. While some studies have suggested that females may exhibit a less favorable course than males [17], others have concluded that sex does not affect the course of tics, since both sexes showed a similar decline in symptom severity with age [18].

Capitalizing on one of the largest clinical pediatric samples collected to date, in this study, we investigated sex differences and their interaction with age in the clinical presentation of TS/persistent tic disorders. Based on the present literature, we expected externalizing/neurodevelopmental problems to be more severe in boys and internalizing problems to be more severe in females.

Methods

Participants

The sample consisted of 709 children and adolescents aged 3–16 years with TS/persistent tic disorder who participated in the baseline assessment of the *European Multicenter Tics in Children Study* (EMTICS). EMTICS is a longitudinal study that examines the role of genes, immunity, and psychosocial stress on the onset and course of tics (see for a more detailed description: [19]). Participants were recruited from 16 specialized outpatient clinics across Europe (i.e., child and adolescent psychiatry clinics and pediatric neurology clinics), through referrals from clinicians or advertisements with patient organizations. Exclusion criteria were a serious medical illness, antibiotic treatment in the past month, and/or inability to understand and comply with the study protocol.

Participants' diagnoses (TS/chronic tic disorder, OCD, or ADHD) were established by an experienced clinician using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [20]. For cases of diagnostic uncertainty, we used consensus scoring by an expert team at each clinical center. The study clinician also rated the severity of tics and OCD symptoms (see below). Parent-reported questionnaires completed within 2 weeks before the visit were used to assess participants' symptoms of ADHD, ODD, CD, ASD, and emotional problems. The clinician also recorded parental education level, as a proxy for socio-economic status, using a 6-point scale (1 = 7 years of schooling, 2 = junior high school, 3 = high school diploma, 4 = associate degree, 5 = bachelor degree, and 6 = post graduate/graduate/professional degree). The use of psychotropic medication in the previous 2 weeks was also recorded and classified in one or more of the following categories: typical antipsychotics, atypical antipsychotics, alpha agonists (clonidine), ADHD medications (stimulants/atomoxetine), serotonin reuptake inhibitors, or others.

The EMTICS study was approved by the local research ethics committees of each participating center. Written informed consent was obtained from all parents or legal guardians, and children and adolescents were asked to sign informed assent forms when appropriate.

Clinical measures

Clinician-rated interviews

The *Yale Global Tic Severity Scale* (YGTSS), a semi-structured interview, was used to measure tic severity [21] (Cronbach's alpha in our study $\alpha = 0.87$). Motor and vocal tics present during the previous week were rated separately on a 0- to 5-point scale across five dimensions: number, frequency, intensity, complexity, and interference. The Total Motor Tic severity score (YGTSS motor range, 0–25) and the Total Vocal Tic severity score (YGTSS vocal range, 0–25) were added to produce the Total Tic severity score (YGTSS total range, 0–50). Higher scores indicate greater severity.

The *Children's Yale–Brown Obsessive Compulsive Scale* (CY-BOCS), another semi-structured interview, was used to assess the severity of obsessive–compulsive symptoms [22] (Cronbach's alpha in our study $\alpha = 0.93$). Obsessions and compulsions present during the previous week were rated separately on a 0- to 4-point scale across five dimensions: time spent, interference, distress, resistance, and control. The CY-BOCS Obsession score (CY-BOCS obsessions range, 0–20) and CY-BOCS Compulsion score (CY-BOCS compulsions range, 0–20) were added to obtain the CY-BOCS Total score (CY-BOCS total range, 0- 40). CY-BOCS total scores above 14 were considered clinically significant [23].

Parent-rated questionnaires

The *Swanson, Nolan, and Pelham Scale, version IV* (SNAP-IV), a 26-item questionnaire, was used to assess the severity of ADHD and ODD symptoms [24] (Cronbach's alpha in our study $\alpha = 0.95$). Parents rated their child's inattentive (SNAP inattention items 1–9), hyperactive-impulsive (SNAP hyperactivity/impulsivity, items 10–18), and oppositional defiant (SNAP ODD, items 19–26) behaviors present during the previous week using a 4-point scale ranging from 0 (*not at all*) to 3 (*very much*). Mean scores were calculated for each subscale. A severity score for combined ADHD symptoms was calculated by adding the inattentive and hyperactive-impulsive subscales (items 1–18). Scores above 1.78 for inattention, 1.44 for hyperactivity-impulsivity, 1.67 for combined symptoms, and 1.88 for defiant behaviors were considered clinically significant [24].

The *Autism Spectrum Screening Questionnaire* (ASSQ), a 27-item questionnaire assessed the severity of ASD symptoms [25] (Cronbach's alpha in our study $\alpha = 0.91$). Parents rated their children's autistic symptoms on a 3-point scale ranging from 0 (*not true*) to 2 (*certainly true*). A total score was calculated by summing all items (range 0–54), with a cutoff score of ≥ 19 in clinical settings indicating the likelihood of high-functioning ASD [25].

The *Strengths and Difficulties Questionnaire* (SDQ), a 25-item scale, was used to evaluate emotional and behavioral problems [26] (Cronbach's alpha in our study $\alpha = 0.95$). Parents rated their children's emotional problems (SDQ emotional) and conduct problems (SDQ conduct) present during the previous two weeks on a 0- to 3-point scale ranging from 0 (*not true*) to 2 (*certainly true*). Subscale scores ≥ 5 were considered clinically relevant [26].

Statistical analyses

Preliminary analyses

We removed potential outliers ($\geq |3.0|$ standard deviations away from the mean). We checked the distribution of residuals and used log-transformation to normalize scale scores where appropriate (i.e. for the CY-BOCS subscales). The percentage of missing data was below 4.6% for all clinical measures and related to incomplete questionnaires. Mean imputation was used to replace missing variables if at least 20% of the items on that (sub) scale were answered. Otherwise, scores for that (sub) scale were recorded as missing.

In preliminary analyses, we tested whether there were sex differences in demographic characteristics or use of psychotropic medication using t tests for continuous variables and chi-squared tests for categorical variables. All variables that were significant (alpha level 0.05) and related to the severity of tics and/or other comorbid psychiatric symptoms

(outcome measures) were included as fixed effects in the main analyses.

Main analyses

The association of sex with tic severity (YGTSS) and comorbid symptom scales (CY-BOCS, SNAP, ASSQ, SDQ) was investigated by means of mixed-effects models with sex and use of medication as fixed effects and recruitment center as the random effect. Then, sex differences in the severity of clinical measures were analyzed using post-hoc comparisons with Bonferroni adjustments. Similarly, the interaction between sex and age on tic severity (YGTSS) and comorbid symptom scales (CY-BOCS, SNAP, ASSQ, SDQ) was investigated by means of mixed-effects models with sex, age, their interaction, and use of medication as fixed effects and recruitment center as the random effect. Significant interaction effects were further explored repeating the analyses using a categorical age variable (children ≤ 12 years *vs*. adolescents > 12 years). Sex differences in the severity of clinical measures within each age group were also analyzed using post-hoc comparisons with Bonferroni adjustments. Cohen's *d* was calculated to facilitate the interpretation of results, with *d*-values of 0.2, 0.5, and 0.8 taken to reflect small, medium, and large effect sizes, respectively. All analyses were performed using IBM SPSS, Version 22.0 (IBM Corp., Armonk, NY), using an alpha level of 0.05.

Results

Sample characteristics

Most of the 709 participants were Caucasian ($n = 600$; 84.6%) males ($n = 544$; 76.7%) with a mid-level parental education (mean score of 4 ± 1.15). The mean age was 10.7 ± 2.8 years. Four hundred eighty-one ($n = 481$, 67.8%) participants were classified as children (112 females, mean age 9.1 ± 1.8 years) and 228 (32.2%) as adolescents (53 females, mean age 14 ± 1.4 years). Regarding the tic disorder diagnosis, 624 (88%) participants met criteria for TS, 79 (11.1%) for persistent motor tic disorder, and 6 (0.9%) for persistent vocal tic disorder. Almost half of the sample met DSM-IV criteria for comorbid ADHD and/or OCD: ADHD alone ($n = 121$; 17.1%), OCD alone ($n = 119$; 16.8%), or ADHD + OCD ($n = 74$; 10.4%). Scores were above the clinical cutoff in 98 (13.8%) participants for ODD symptoms, 94 (13.3%) for CD symptoms, 122 (17.2%) for ASD symptoms, and 258 (36.4%) for emotional problems. Around one third of the subjects ($n = 235$; 33.1%) were currently (past 2 weeks) using psychotropic medication. There were no statistically significant sex differences in terms of age, ethnicity, or parental education. However, sex was linked to statistically significant differences in the use of specific psychotropic medications (see Table 1). In particular, typical antipsychotics and ADHD medication were prescribed significantly more often in males, while antidepressant medication was more frequently prescribed in females.

Sex in relation to clinical measures

Sex had a statistically significant association with the severity of motor and total tics (YGTSS motor, $F(1, 693) = 6.06$, $p = 0.01$; YGTSS total, $F(1, 694) = 4.21$, $p = 0.04$). It was also significantly associated with the following comorbid symptoms: ADHD symptoms (SNAP-IV inattention, $F(1, 676) = 4.24$, $p = 0.04$; SNAP-IV hyperactivity/impulsivity, $F(1, 675) = 10.05$, $p = 0.01$); SNAP-IV combined, $F(1, 674) = 7.84$, $p = 0.01$), ASD symptoms (ASSQ, $F(1, 662) = 10.44$, $p = 0.01$), and emotional problems (SDQ emotional, $F(1, 680) = 4.21$, $p = 0.04$). For all of these clinical measures except emotional problems, males exhibited higher scores than females (see Table 2). Sex did not have a statistically significant main effect on the severity of OCD (CY-BOCS obsessions, CY-BOCS compulsions, CY-BOCS total scores) or disruptive behaviors (SNAP ODD, SDQ conduct).

Effect of the interaction between sex and age on clinical measures

There was a statistically significant interaction between sex and age, with an effect on the severity of total tics (YGTSS total, $F(1, 692) = 4.76$, $p = 0.03$) and compulsions (CY-BOCS compulsions, $F(1, 686) = 6.36$, $p = 0.012$). For both clinical measures, the effect of higher levels of symptom severity with higher age was more pronounced in females than in males (see Fig. 1). In participants aged ≤ 12 years ($n = 481$), YGTSS total and CY-BOCS compulsion scores were higher in males than females (YGTSS total, diff = 2.53, $p = 0.01$; CY-BOCS compulsions, diff = 1.06, $p = 0.04$). These differences were not present in participants older than 12 years ($n = 228$), in whom YGTSS total and CY-BOCs scores were similar for both sexes (YGTSS total, diff = − 0.76, $p = 0.55$; CY-BOCS compulsions, *diff* = − 1.30, $p = 0.09$). Interaction between sex and age was not statistically significant for any of the other clinical measures.

Discussion

We describe sex differences in the symptom presentation of TS/persistent tic disorders in a large European clinical pediatric sample in the age range of 3–16 years. The study included 165 females (23.3%), a sex distribution that is representative of clinical samples [12]. Our study confirmed that tic severity and severity of most comorbid psychiatric

Table 1 Demographic and clinical characteristics of the sample ($n = 709$)

	Males ($n = 544$)	Females ($n = 165$)	p
Age (years)	10.7 ± 2.8 (3.4–16.9)	10.7 ± 2.9 (4.4–16.9)	0.91
Parental education level [a] (mean between mother and father)	4.3 ± 1.2	4.4 ± 1.2	0.26
Ethnicity (white Caucasian)	461 (84.7%)	139 (84.2%)	0.84
Comorbid diagnoses[b]			
OCD	152 (27.9%)	41 (24.8%)	0.43
ADHD	157 (28.9%)	38 (23.0%)	0.15
ODD	79 (14.5%)	19 (11.5%)	0.28
CD	74 (13.6%)	20 (12.1%)	0.55
ASD	103 (18.9%)	19 (11.5%)	**0.02**
Emotional problems	185 (34%)	73 (44.2%)	**0.03**
Use of psychotropic medication			
Typical antipsychotics	30 (5.5%)	2 (1.2%)	**0.02**
Atypical antipsychotics	105 (19.3%)	25 (15.2%)	0.22
Alpha-agonist (clonidine)	16 (2.9%)	4 (2.4%)	0.99
ADHD medication (stimulants/atomoxetine)	63 (11.6%)	10 (6.1%)	**0.04**
SRIs	14 (2.6%)	10 (6.1%)	**0.03**

Data are given as mean ± standard deviation (range) for continuous variables and number (percentage) for categorical variables

Between-group differences were tested by t tests for continuous variables and chi-squared tests for categorical variables

Statistically significant differences at 0.05 level are shown in bold

OCD Obsessive–compulsive disorder, *ADHD* Attention-deficit/hyperactivity disorder, *ODD* Oppositional defiant disorder, *CD* Conduct disorder, *ASD* Autism spectrum disorder, *SRIs* Serotonin Reuptake Inhibitors

[a]Parental education level, as a proxy for socio-economic status, was recorded using a 6-point scale (1 = 7 years of schooling, 2 = junior high school, 3 = high school diploma, 4 = associate degree, 5 = bachelor degree, and 6 = post graduate/graduate/professional degree)

[b]Comorbid diagnoses were defined using DSM-IV criteria for OCD and ADHD, and clinical cutoff scores for ODD symptoms, CD symptoms, ASD symptoms and emotional problems

symptoms differed between males and females, largely in line with the sex distribution of neurodevelopmental/psychiatric diagnoses in TS samples and in the general population.

Regarding tics, we found that motor and total tic scores (including both motor and vocal tics) were more severe in boys than in girls. Previous studies found similar tic severity scores between males and females [15, 16], but their samples were smaller and included older participants. An additional finding was that females exhibited higher total tic severity scores with age than their male counterparts, with lower tic severity during childhood but similar scores into adolescence. Despite the cross-sectional nature of our study, this finding could suggest a less favorable course of tic severity in females compared to males. This hypothesis was also proposed by Lichter et al. (2015), who reported that females were associated with a greater likelihood of tic worsening in adulthood, as opposed to improvement, in a retrospective study with 75 adult participants (52 males and 23 females, ages 20–80 years) [17]. In a more recent large prospective study, however, sex was not found to affect the course of tics, which were reported to decline in both sexes over a 6-year follow-up period; yet the study sample included participants up to age 26 years in contrast to our study [18].

Looking at OCD symptoms, we found that females exhibited higher severity of compulsions with age than males, with lower scores during childhood years and similar scores during adolescence. This finding might point to sex differences in the course of OCD symptoms. This proposition was first suggested by Bloch et al. (2015), who reported that females were associated with a greater likelihood of OCD symptom persistence into adulthood in a longitudinal study with 45 children with OCD (34 males, mean age at baseline 12.1 ± 2.0 years) [27]. However, findings reported by Groth et al. (2017) do not support this hypothesis, as sex was not found to affect the course of OCD symptoms over the follow-up period [18]. Surprisingly, the overall severity of OCD symptoms did not differ between boys and girls in our sample. This negative finding could be related to the mean age of our sample (close to 11 years), as previous studies have suggested that OCD symptoms may be more common

Table 2 Sex differences in severity of tics and comorbid psychiatric symptoms in TS/CTD

	Males (*n* = 544) Mean (95% CI)	Females (*n* = 165) Mean (95% CI)	Differences Mean (95% CI)	*Cohen's d*
Tics (YGTSS)				
Motor	12.75 (11.83–13.67)	11.80 (10.74–12.86)	**0.95 (0.19–1.71)**	**0.19**
Vocal	7.58 (6.76–8.39)	7.07 (6.01–8.12)	0.51 (− 0.43–1.45)	0.08
Total	20.29 (18.70–21.88)	18.81 (16.94–20.68)	**1.48 (0.06–2.89)**	**0.16**
OCD symptoms (CY-BOCS)[a]				
Obsessions	0.71 (0.44–0.98)	0.72 (0.42–1.01)	− 0.01 (− 0.17–0.16)	0.01
	n = 538	*n* = 160		
Compulsions	0.92 (0.70–1.14)	0.85 (0.59–1.11)	0.07 (− 0.12–0.26)	0.06
	n = 539	*n* = 164		
Total	1.21 (0.90–1.52)	1.16 (0.81–1.50)	0.06 (− 0.16–0.27)	0.04
ADHD symptoms (SNAP-IV)	*n* = 539	*n* = 161		
Inattention	1.29 (1.19–1.39)	1.15 (1.01–1.28)	**0.14 (0.01–0.27)**	**0.16**
	n = 525	*n* = 162		
Hyperactivity/impulsivity	1.06 (0.97–1.15)	0.86 (0.73–0.98)	**0.20 (0.08–0.33)**	**0.24**
	n = 524	*n* = 161		
Combined	1.17 (1.08–1.26)	1.00 (0.88–1.13)	**0.17 (0.05–0.29)**	**0.21**
	n = 523	*n* = 162		
Disruptive behaviors				
ODD symptoms (SNAP-IV ODD)	1.03 (0.90–1.16)	0.92 (0.76–1.07)	0.12 (− 0.01–0.25)	0.14
	n = 524	*n* = 162		
CD symptoms (SDQ conduct)	2.48 (2.14–2.82)	2.43 (2.02–2.84)	**0.05 (− 0.28–0.38)**	**0.02**
	n = 528	*n* = 164		
ASD symptoms (ASSQ)	11.82 (10.32–13.33)	9.49 (7.68–11.29)	**2.34 (0.92–3.76)**	**0.25**
	n = 517	*n* = 159		
Emotional problems (SDQ Emotional)	3.98 (3.60–4.35)	4.44 (3.95–4.92)	**-0.46 (− 0.90–0.02)**	**0.16**
	n = 527	*n* = 164		

ns are lower for some measures due to missing data

Data are given as mean (95% confidence interval)

Statistically significant differences at 0.05 level are shown in bold

TS Tourette syndrome, *CTD* Chronic tic disorder, *d* Cohen's d, *YGTSS* Yale Global Tics Severity Scale, *OCD* Obsessive–Compulsive disorder, *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale, *ADHD* Attention deficit/hyperactivity disorder, *SNAP-IV* Swanson Nolan and Pelham-IV rating scale, *ODD* Oppositional Defiant Disorder, *CD* Conduct Disorder, *ASD* Autism Spectrum Disorder, *ASSQ* Autism Spectrum Screening Questionnaire, *SDQ* Strengths and Difficulties Questionnaire

[a]Log transformed scores

and severe among males in childhood, but are more common and severe among females in adolescence and adulthood [28–30].

As hypothesized, we found more severe ADHD and ASD symptoms in males than in females. The male predominance in these neurodevelopmental disorders is well documented, with a male-to-female ratio reported to be close to 3:1 for ASD [31] and 2:1 for ADHD in community-based studies [32]. In terms of ADHD, males in our sample exhibited more severe symptoms than females in all ADHD subdomains, including inattention, hyperactivity/impulsivity, and combined ADHD symptoms. In line with previous studies with non-TS samples [33, 34], the sex difference was most pronounced for hyperactivity/impulsivity symptoms. Looking at ASD, previous studies have also reported more severe ASD symptoms in males (especially restrictive and repetitive behaviors), but male–female differences in ASD are much debated and the literature is inconsistent at large, with many other studies that have found no significant sex differences in the phenotypic presentation or severity of ASD (for review see [35, 36]). Considering that ADHD and ASD symptoms have been reported to be one of the primary reasons for referral of children and adolescents with persistent tics [8], one could suggest that this pattern of comorbid symptoms could facilitate the more timely detection of tic disorders in males than in females.

In line with expectations, we found that females exhibited more severe emotional problems than males. This female

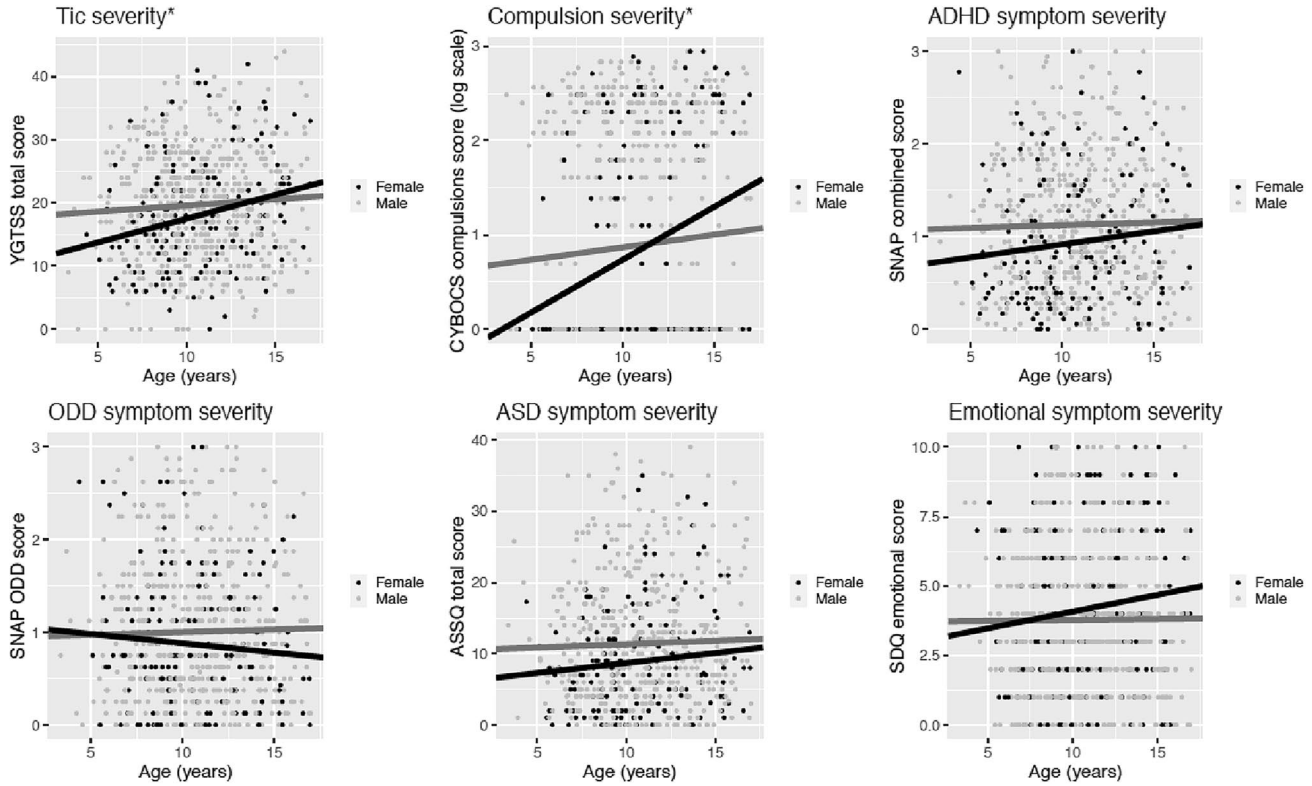

Fig. 1 Interaction between sex and age for the severity of tics and other comorbid psychiatric symptoms. * statistical significant at 0.05 level. *YGTSS* Yale Global Tics Severity Scale, *CY-BOCS* Children's Yale-Brown Obsessive Compulsive Scale, *ADHD* Attention/Deficit and HyperactivityDisorder, SNAP-IV Swanson Nolan and Pelham-IV rating scale, *ASD* Autism SpectrumDisorder, *ASSQ* Autism Spectrum Screening Questionnaire, *SDQ* Strengths andDifficulties Questionnaire

predominance in emotional conditions and associated symptom severity has been widely reported in studies of both the general population [37] and clinical samples with TS [6, 15]. In an online survey of 460 adults with TS or chronic/persistent tic disorder [15], females ($n = 185$) were shown to be 2.75 times more likely to report having non-OCD anxiety disorders and 1.83 times more likely to report mood disorders than males. In that study, women were also more likely to report more severe anxiety and depressive symptoms than males on dimensional measures. Hirschtritt et al. (2015) also found that anxiety disorders and mood disorders were more frequent in females than in males [6]. Emotional conditions may be more difficult to identify than behavioral problems [38], but their early detection and treatment are crucial to improve quality of life in individuals with TS [39].

Looking at disruptive behaviors, we did not find sex differences in the severity of ODD and CD symptoms. This finding is not in line with previous studies in TS, which have found disruptive behaviors to be more prevalent [6, 12] and severe [40] in males than in females. Our negative finding could be related to the questionnaires used to assess behavioral problems, which only included a restricted range of symptoms and did not differentiate between dimensions of ODD/CD [41, 42]. Also, the age range was limited to 16 years in our sample; although ODD symptoms occur frequently in young children, CD symptoms are increasingly common during adolescence [43].

The findings of our study should be interpreted in the context of several limitations. First, the multi-center design may have produced site differences in scoring and clinical populations. To limit this potential bias, we discussed the standardization of procedures biannually during the study and used statistical methods that account for the effect of site. Second, the inclusion of mostly Caucasian participants with mid-level parental educational levels limits our ability to generalize the results to groups with different demographic characteristics. Third, despite the wide age range, our sample did not include participants in their late adolescence, a period where psychiatric disorders may appear or be more pronounced, such as affective disorders particularly in females or conduct problems in males, suggesting a possible underestimation of effects. Also, no direct inferences can be made about the sex differences in the clinical course of tics and other comorbid symptoms given the cross-sectional nature of this study, as the inter-individual differences related to age could be the result of a referral bias. Fourth,

the mean severity scores for tics and other comorbid psychiatric symptoms were below the clinical cutoff for a diagnosis [23–26], suggesting that our cohort had mild symptom levels and that the results may not be generalizable to populations at the more severe end of the disease spectrum. Fifth, despite the large sample size, negative results could be related to inadequate statistical power in specific age groups (i.e. female adolescents). Finally, although the instruments administered to assess the severity of tics and most comorbid conditions were considered gold standard measures, the use of a structured diagnostic interview to detect comorbid disorders and more elaborate questionnaires to assess behavioral and emotional problems could have been more informative.

In conclusion, we found small but significant sex differences in the clinical presentation of TS and persistent tic disorders in children and adolescents aged 3–16 years. Our findings indicate that tics and comorbid symptoms relating to neurodevelopmental disorders (ADHD and ASD) are more severe in boys than in girls. In contrast, emotional problems appear to be more severe in females. Also in females, tics and compulsions were more severe particularly with increasing age, perhaps suggesting a less favorable course of tic and OCD symptomatology in this group. Given the early occurrence of neurodevelopmental disorders, which often are the cause for primary clinical referral rather than the tics themselves, this symptom presentation could facilitate the detection of TS and persistent tic disorders in males and/or impede their timely diagnosis in females. Clinicians should be aware of sex-specific differences in the clinical presentation varying across age. Research into sex differences during the developmental course of tic disorders is warranted to promote the early detection of clinical symptoms, eventually contributing to a sex-based personalized treatment of tic disorders and comorbid symptoms. Those studies should be based on large international samples with clinical and community participants to understand the real influence of sex on neurodevelopmental conditions.

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Declarations

Conflict of interest Coffey is on the Scientific Advisory Board of Abide Therapeutics and Teva/ Nuvelution, has received honoraria from the American Academy of Child and Adolescent Psychiatry, Partners Healthcare, Harvard Medical School, Teva, CME Outfitters, University of Cincinnati, University of Texas Medical Branch, and University of Florida, and has received research support from Teva/ Nuvelution, Inc., Neurocrine Biosciences, Emalex, the National Institute of Mental Health (Grant No. 5R01MH115959-02), and University of California San Francisco. Müller-Vahl received funding for research from the EU (FP7-PEOPLE-2012-ITN No. 316978), the German Research Society (DFG: GZ MU 1527/3–1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), GW, Almirall, Abide Therapeutics, and Therapix Biosiences, and consultant's honoraria from Abide Therapeutics, Fundacion Canna, and Therapix Biosiences. On behalf of all other authors, the corresponding author declares that the other authors have no conflict of interest.

Ethics approval and consent to participate The EMTICS study was approved by the local research ethics committees of each participating center and in accordance with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all parents or legal guardians, and children and adolescents were asked to sign informed assent forms when appropriate.

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