European Psychiatry 30 (2015) 334–340

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Influence of gender on Tourette syndrome beyond adolescence

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ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form 2 July 2014
Accepted 9 July 2014
Available online 2 September 2014

Keywords:
Sex differences (Neuropsychiatric aspects)
Basal ganglia disorders
Childhood neuropsychiatric disorders
Tourette syndrome

ABSTRACT

Although boys are disproportionately affected by tics in Tourette syndrome (TS), this gender bias is attenuated in adulthood and a recent study has suggested that women may experience greater functional interference from tics than men. The authors assessed the gender distribution of adults in a tertiary University-based TS clinic population and the relative influence of gender and other variables on adult tic severity (YGTSS score) and psychosocial functioning (GAF score). We also determined retrospectively the influence of gender on change in global tic severity and overall TS impairment (YGTSS) since adolescence. Females were over-represented in relation to previously published epidemiologic surveys of both TS children and adults. Female gender was associated with a greater likelihood of tic worsening as opposed to tic improvement in adulthood; a greater likelihood of expansion as opposed to contraction of motor tic distribution; and with increased current motor tic severity and tic-related impairment. However, gender explained only a small percentage of the variance of the YGTSS global severity score and none of the variance of the GAF scale score. Psychosocial functioning was influenced most strongly by tic severity but also by a variety of comorbid neuropsychiatric disorders.

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1. Introduction

Although at least two thirds of individuals with Tourette syndrome (TS) experience amelioration of tics by adulthood [4,6,8,21,27,29,36], tic persistence and significant tic-related impairment in adulthood are problematic for an important subset of patients [4,14,33]. Predictors of adult tic severity include former tic severity, particularly in adolescence [6,27], fine motor skill deficits in childhood [7], and reduced childhood caudate volumes on MRI [5]. A previous history of more complex and vocal tics [4,17] and psychosocial stress and depression [39] may also predict future tic severity, while the seeking of nonpharmacologic treatment for tics has been associated with a later age of tic improvement [1].

The possibility of an independent gender influence on the natural history of TS is suggested by findings of frequent later diagnosis and treatment of TS in females compared with males, and a stronger male bias in sex distribution of TS in children than in adolescents or adults [2,11,12,24,37,46]. Thus, in a large international sample of 3500 individuals with TS, the mean age at TS diagnosis was 12.7 years in males compared with 15.3 years in females and the male preponderance was less pronounced in adults than it was in youth (3:1 versus 5.2:1) [24]. Similarly, the ratio of TS females to males in a North American state-wide prevalence study was almost three times higher in adulthood (1:3.4) than in childhood (1:9.3) [11,12]. In a German insurance database study, the administrative prevalence of TS, diagnosed and reported by physicians to obtain reimbursement for services provided, also showed a steady decline in the higher male to female ratio with increasing age [47]. Indeed, tic disorders in the latter study were somewhat more frequently reported in females than in males in the age groups above 30 years. A long-term follow-up of the North Dakota childhood study showed that males demonstrated more variability in improvement over time but more improvement overall than females [10]. Recent data have also suggested that women may experience greater functional interference from tics than men [37].

The primary aim of this study was to assess the unique influence of gender, relative to other clinical factors, on global tic severity, tic-related functional impairment and global psychosocial functioning in an adult TS clinic population. A secondary aim

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http://dx.doi.org/10.1016/j.eurpsy.2014.07.003
0924-9338/Published by Elsevier Masson SAS.

was to estimate retrospectively the effect of gender in this cohort on the course of tics after adolescence.

2. Subjects and methods

Of 90 adult TS patients evaluated consecutively at a University-based TS clinic, 75 subjects were included in the study. Fifteen patients (6 women and 9 men), with IQ < 70 ($n = 2$), active psychosis ($n = 1$), pervasive developmental disorder ($n = 3$), individuals with a single evaluation only ($n = 3$) and those without adequate documentation of juvenile tic severity ($n = 6$) were excluded. Study subjects had been followed in the clinic for a period of 9.1 ± 7.6 yrs. Twenty-seven (36%) (5 women and 22 men) had also previously been evaluated by one of the authors (DGL) during childhood or adolescence. At the time of their adulthood rating, subjects had been stable on current treatment without significant change in their tic disorder for a period of at least three months. The study cohort were Caucasian, except for one African-American male, and consisted of 52 males and 23 females, aged 20.0–80.0 (mean 36.6 ± 13.4) years.

All subjects underwent a clinical interview and examination, which included assessment of tic onset, distribution, course and severity in childhood, adolescence and adulthood, as well as questions designed to assess comorbid conditions commonly associated with TS. The assessment included a modified version of The Centre for Addiction and Mental Health Concurrent Disorders Screener (CAMH-CDS) [41] which incorporated the following Axis 1 conditions: OCD, major depressive disorder, bipolar disorder (BD), generalized anxiety disorder, panic disorder with and without agoraphobia, and substance abuse or dependence [38]. With this tool, sensitive screening questions are asked for each disorder. A "yes" answer to a screening question is followed by the minimum number of questions required to meet DSM-IV criteria [18] for that particular disorder. DSM-IV criteria were used for diagnosis of TS and all comorbid disorders, currently active and in remission, except for adult ADHD, where DSM-V criteria were employed [3]. Rage, which was defined as the presence of intermittent episodes of sudden, uncontrollable explosive or aggressive behaviors grossly out of proportion to provocation and atypical for the individual's normal personality, was assessed using a modification of DSM-IV criteria for intermittent explosive disorder (IED), omitting criterion C (i.e., that aggressive episodes are not better accounted for by another mental disorder, medication or drug, or general medical condition) [9].

All of the study ratings were performed by a single investigator (DGL). Assessment of current symptom severity and psychosocial functioning included the following measures: the Global Assessment of Functioning (GAF) Scale, [18]; the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [28]; and the Yale Global Tic Severity Scale (YGTSS), which rates severity of motor and vocal tics experienced during the past week according to tic number, frequency, intensity, complexity and interference [34]. The latter scale includes a measure of psychosocial and occupational impairment related to TS, the overall TS impairment rating, which is added to the total tic score to obtain a YGTSS global severity measure. The overall TS impairment rating is anchored by six descriptors. A rating of moderate impairment (30) on this scale is applied where tics are associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning. We also assessed current global tic severity using an anchored seven-point Clinical Global Impression (TS-CGI) scale [35]. Scores on the latter scale, originally developed at the Yale Child Study Center, are highly correlated with YGTSS global ratings [36].

Prior history of juvenile ADHD and OCD and the distribution, characteristics and severity of tics in adolescence was based on a synthesis of data obtained from interview of the patient and any accompanying relatives, and all available records. The involvement by tics of the following five bodily regions was assessed: The eyes, face and mouth; the neck; the upper extremities; the trunk; and the lower extremities. Best-estimate ratings of maximum adolescent tic severity were made using the overall TS impairment measure of the YGTSS and the TS-CGI scale. A judgement was also made regarding the latest age of maximum tic severity, recognizing that, with tic waxing and waning, more than one worst-ever time point for tics may be reported [35]. This age was determined by asking subjects whether or not their tics had improved significantly with age and, if so, the latest age at which their tics "individually or collectively", had been "most troublesome".

3. Statistical analysis

Males and females were compared using Pearson's Chi^2 tests or Fisher's exact tests for categorical data, the Kruskal-Wallis test for ordinal data, and the Student's t test for continuous data. "Moderate" cut-off scores for the YGTSS overall TS impairment rating were used, to capture functionally relevant differences. The relative contribution of motor and vocal tic severity to the latter measure was determined by ANOVA. Based on the results of univariate analyses, stepwise multiple regression analysis was used to determine the unique effects of gender and other clinical factors first on current adult tic severity (YGTSS score) and, secondly, on psychosocial functioning (GAF scale score). For the stepwise variable selection procedures, the probability of F both to enter and leave the regression equations was set at 0.10. Model fit was checked by examination of residuals. Probability values were two-tailed, with an alpha ≤ 0.05. To minimize type II errors when testing the primary hypothesis concerning gender effect on clinical variables, P values were not corrected for multiple comparisons. Statistical analyses were performed using SAS software (JMP release 7; SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Subject demographics and clinical characteristics

Women and men were similar in age, duration of monitored clinic follow-up and age at tic onset (Table 1), although two females (9%) and no males experienced motor tic onset after age nineteen. Prevalence of ADHD in childhood and OCD in adolescence was also similar by gender. There was no gender difference in adolescent global tic severity (TS-CGI), but there was a trend for adolescent overall TS impairment (YGTSS) to be lower in females (see below). There was no gender difference in current adult Y-BOCS or GAF ratings, nor in prevalence in adulthood of comorbid psychiatric disorders or use of neuroleptics, SSRIs, or stimulant drugs (Table 1).

4.2. Tic distribution in adolescence and adulthood

Tic distribution in adulthood did not differ significantly from that in adolescence. Thus, the percentage of adults exhibiting tics involving the eyes, face or mouth (77%), neck (69%), upper limbs (73%), lower limbs (37%) and trunk (35%) was comparable to the percentage of adolescents exhibiting tics in each of these regions (85%, 71%, 72%, 39%, and 25% respectively). However, compared to their juvenile tic phenotype, women were more likely than men to show an expansion as opposed to contraction in adulthood of number of body regions affected by tics. Thus, while 32 (43%) subjects showed no change over time in body regions affected by tics, 10 (44%) women and 10 (19%) men exhibited a wider tic distribution in adulthood, 3 (13%) women and 20 (39%) men