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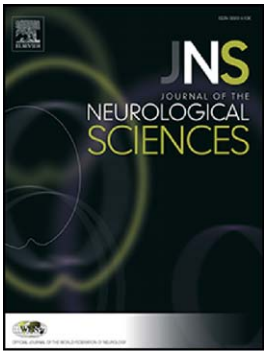

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Clinical Research Article

Depression in Tourette syndrome: A controlled and comparison study

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Abstract

Background. Tourette syndrome (TS) is a neurodevelopmental condition characterised by multiple tics and co-morbid behavioural problems. Previous research found that up to 76% of patients with TS experience affective symptoms, with 13% fulfilling diagnostic criteria for depression.
Objectives. We aimed to assess the severity of depression and profile of depressive symptoms in adult patients with TS compared to patients with major depression and healthy controls.
Methods. Depression ratings were collected from patients with TS (*N*=65) using the BDI-II and from patients with recurrent major depressive disorder (rMDD, *N*=696) and healthy controls (*N*=293) using the Beck Depression Inventory (BDI)-IA. Direct comparisons were possible for 14/21 BDI items.
Results. Patients with TS scored significantly higher on the BDI than controls (*P*<.001) and all individual symptoms were reported more frequently by patients with TS than by controls (*P*<.001). Total BDI score in TS was not significantly different to that in rMDD, however irritability was significantly more frequently reported in the TS group and this remained significant after controlling for age and gender differences between the two groups (OR 5.24, 95% CI 1.97-14.00; *P*=.001).
Conclusions. Our findings show that depression is a prominent feature in TS and may present with a more irritable phenotype than rMDD. Patients with TS should be routinely screened for depression to implement treatment as appropriate.

Key Words: Tourette syndrome; Tics; Affective disorders; Depression; Irritability.

1. INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by multiple motor and phonic tics [1]. TS is estimated to affect up to 1% of children and adolescents, as well as adults in a less severe form [2]. Symptoms wax and wane in severity over weeks, months and years, but over time patients usually show marked reductions in their symptoms [3], regardless of treatment [4].

TS is associated with a spectrum of behavioural co-morbidities in about 90% of patients [5], particularly attention-deficit and hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), impulse control disorders and affective disorders [6]. Evidence from both controlled and uncontrolled studies suggest that depression is prevalent in TS, with an epidemiological meta-analysis estimating that 13% of patients with TS fulfil diagnostic criteria for depression and 76% experience sub-threshold depressive symptoms [7]. In a large population-based cohort study conducted on 1337 patients with TS, the risk of developing depression was about 5 times higher in the TS population compared to the control cohort [8].

In a sample of children and adolescents with TS, it was found that the presence of affective disorders significantly predicted psychiatric hospitalisation [9]. Moreover, a number of studies showed that depression is associated with significant impairments to health-related quality of life [10,11], in both children [12,13] and adults [14,15] with TS. Recent research has suggested that depressive symptoms, alongside anxiety, moderate the relationship between tic severity and functional impairment in adult patients with chronic tic disorders [16]. Despite extensive research into the behavioural symptoms in young patients with TS, relatively little is known about the clinical presentation of depressive symptoms in adults with TS, apart from a recently identified association between co-morbid depression and increased values of the 'threatened self' or narcissistic vulnerability [17].

The aim of this study was to examine the severity of depression and phenomenology of depressive symptoms in adults with TS in comparison to patients with major depression and healthy controls. We anticipated to find higher depressive symptom severity in patients with TS than healthy controls and partially overlapping affective profiles between TS and major depression, in line with the documented presence of mood disorder and suicidality in patients with 'malignant' TS [18]. This is of particular relevance to clinical practice, as adult patients with TS have been shown to have a greater prevalence of mood disorders than children with TS [19].

2. METHODS

All consecutive adult patients attending the specialist TS clinic at the Department of Neuropsychiatry, BSMHFT and University of Birmingham, UK, were invited to take part in this study. Patients with a lifetime diagnosis of recurrent major depressive disorder (rMDD) and healthy controls were recruited by the multi-centre (Cardiff and Birmingham, UK) Mood Disorders Research Group (MDRG) as part of an ongoing programme of research into the genetic and non-genetic determinants of affective disorders [20]. The MDRG recruited patients with affective disorders and controls via Community Mental Health Teams across the UK and advertisements through GP surgeries, patient support organisations (e.g., Depression Alliance) and local media. Patients with rMDD were recruited when they were judged by their medical team to be well enough to participate. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (DSM-IV-TR) criteria were used for the diagnosis of TS [21], whereas the DSM-IV criteria were applied to the rMDD group [22]. Patients with rMDD were recruited when relatively well and the healthy controls had no personal or family history of psychiatric illness. The studies received both local and national ethics approval and informed consent was obtained from each participant.

The demographic and clinical data of the patients with TS were gathered from participants' medical records. Each patient underwent a comprehensive clinical assessment using the National Hospital Interview Schedule for TS (NHIS-TS) [23]. The NHIS-TS is a detailed semi-structured interview schedule which covers personal and family histories and demographic details. For the diagnosis of various TS-associated psychiatric disorders, the NHIS-TS was originally developed by incorporating the relevant questions and items from the Diagnostic Interview Schedule and WHO criteria to yield a lifetime diagnosis as per DSM-III-R and ICD-10, and was subsequently updated based on the DSM-IV-TR criteria. The treating clinician (AEC) ascertained lifetime recurrent major depression. The Yale Global Tic Severity Score (YGTSS) [24] and the Diagnostic Confidence Index (DCI) [25] were completed as ratings of tic severity and lifetime cumulative symptomatology, respectively. Both the YGTSS and DCI scores range from 0 to 100, with higher scores indicating higher tic severity and diagnostic confidence of TS.

The 21-item Beck Depression Inventory (BDI) is a widely used self-report scale which measures the psychological and biological symptoms of depression over the week prior to completion. The first edition (BDI-IA) was amended to simplify the scoring structure [26], with the second edition (BDI-II) subsequently developed to reflect DSM-IV criteria for affective disorders [27]. A study comparing self-report scales for affective symptoms proposed the BDI-II as the instrument of choice for assessing depression in patients with TS [28]. In our study, all patients with TS completed the BDI-II, whilst patients with rMDD and controls completed the BDI-IA, as their recruitment preceded the enrolment of patients with TS. In developing the BDI-II, 4 items (self-image, occupational functioning, weight loss and hypochondriasis) were removed from the original BDI-IA list and replaced with questions addressing agitation, feelings of worthlessness, loss of energy and concentration difficulty. These items were excluded from our analysis, along with the items on self-dislike, sleeping pattern and appetite, because the scoring anchor points were different between the two BDI versions. The remaining 14 items had minor wording changes with intact anchor points, which allowed reliable comparisons of symptom severity. Total BDI-II scores from the TS sample were converted to BDI-IA scores using the recommended equipercentile equating method [27]. With scoring adjustments, the BDI-IA and BDI-II self-reports have previously been compared in psychiatric outpatients [29]. In the present study, to compare the frequency of different BDI items across the diagnostic groups, we assigned '0' and '1' responses as non-clinically significant ('absent'), with '2' and '3' being clinically significant ('present').

Statistical analyses were performed using the SPSS statistical package version 20.0 (IBM, Armonk, NY, USA). Continuous variables (e.g., total BDI score) were compared between diagnostic groups using Kruskal-Wallis tests (*KWH*) followed by pairwise post-hoc comparisons using Mann-Whitney tests (*MWU*). Categorical variables (e.g., presence/absence of each BDI symptom) were compared between diagnostic groups using X^2/Fisher's exact tests. Within group associations between continuous variables (e.g., between total BDI score and age) were explored using correlation analyses (Spearman's rho; ρ). The Bonferroni method was used to

adjust the cut-off for a significant *P* value to .025 and control for α-inflation by multiple testing. We also carried out logistic regression analyses (enter method) to explore i) whether BDI total score and ii) which combination of BDI symptoms was/were associated with diagnostic group after controlling for demographic differences between groups (gender, age).

3. RESULTS

A total of *N*=1054 participants were included in the study. Demographic data for the three groups are illustrated in **Table 1**. The TS group was significantly younger (*KWH*=106.03, *P*<.001), and comprised significantly more males X^2=58.26, *P*<.001), than the rMDD and control groups, reflecting the higher male:female ratio in TS populations. The vast majority of participants in all groups were White British.

Table 1. Demographic characteristics of the study participants.

	Controls	**TS**	**rMDD**
***N* (% female)**	293 (60.8)	65 (32.3)	696 (71.7)
Age – median (range) years	50.0 (24.0-63.0)	26.0 (16.0-65.0)	48.0 (18.0-65.0)
Ethnicity – %			
White British	100.0	89.2	97.7
White Other	-	3.1	2.2
Asian	-	6.2	-
African	-	1.5	0.1

Abbreviations: ***TS****, Tourette syndrome;* ***rMDD****, recurrent major depressive disorder*

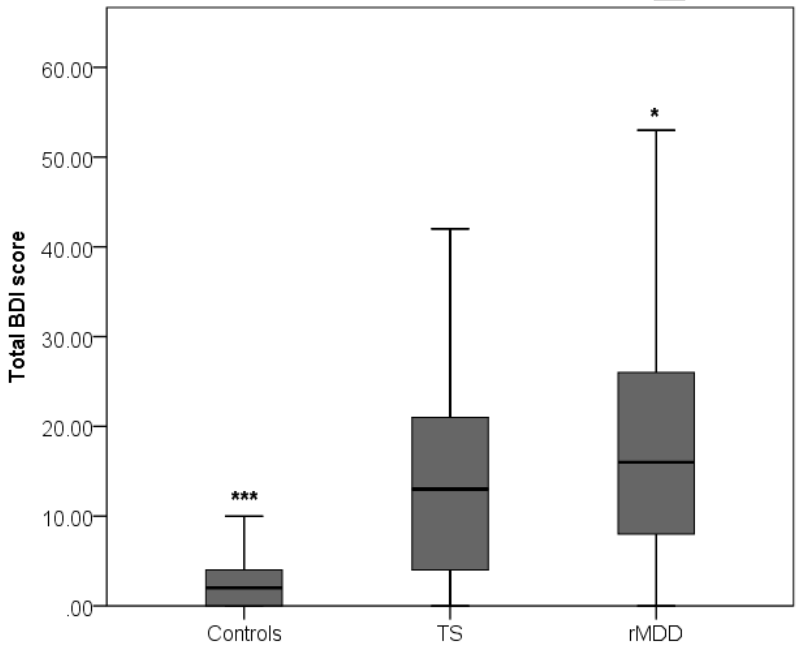
The TS group was representative of a clinic population with characteristic symptoms (median TS DCI score 68.0% [range 33.0-100.0]) and moderate-to-marked tic severity (median YGTSS tic severity score 25.0/50 [range 11.0-46.0], with overall impairment score 20.0/50 [range 10.0-50.0]). Co-morbid diagnoses included depression (40.0%), ADHD (24.6%), OCD (23.1%, with 49.2% of patients presenting obsessive-compulsive symptoms of different degrees of severity) and bipolar disorder (7.7%). With regards to pharmacotherapy, patients were mainly treated with neuroleptics (46.2%), clonidine (21.5%) and antidepressants (30.8%). A family history of affective disorders was present in 24.6% of patients with TS.

As illustrated by **Figure 1A**, there was a significant difference in total BDI score across diagnostic groups (*KWH*=411.52, *P*<.001). Pairwise comparisons between TS and control and rMDD groups identified a statistically significant difference between TS and controls (*P*<.001) with TS patients scoring significantly higher than controls, but not between TS and rMDD (*P*=.030). **Figure 1B** illustrates the frequencies of participants reporting the presence of each BDI symptom in each diagnostic group. There was a significant difference between groups for every symptom (all *P*<.001). Pairwise X^2 comparisons showed significantly higher reporting of every symptom in the TS and rMDD groups compared to controls (all *P*<.001). When comparing the TS and the rMDD groups, the only significant differences were that sadness (*P*=.005) and loss of libido (*P*=.008) were more frequently reported in the rMDD group, and irritability (*P*=.006) was more frequently reported in the TS group.

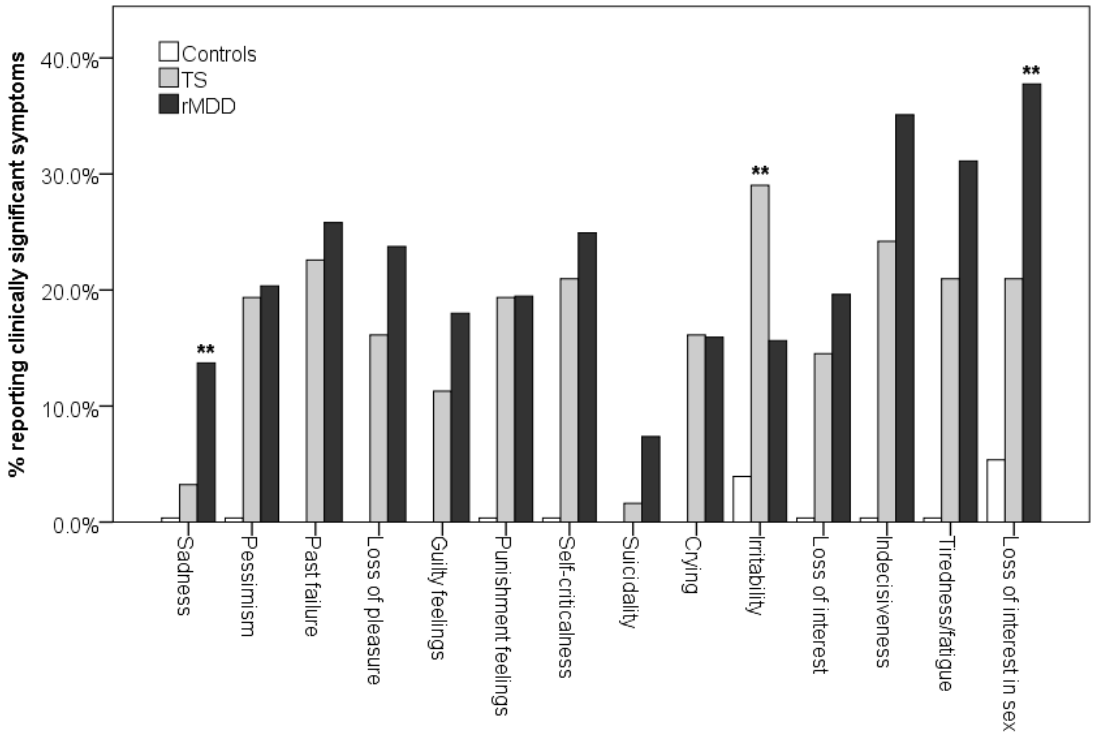
Logistic regression showed that, after controlling for age and gender, total BDI score was predictive of a diagnosis of TS compared to controls (odds ratio [OR] 1.50, 95% confidence intervals [CI] 1.33-1.69; *P*<.001), but not compared to rMDD. Further analysis showed that, after controlling for age and gender, the only BDI symptom that predicted TS compared to rMDD was irritability (OR 5.24; 95% CI 1.97-14.00; *P*=.001).

Figure 1. Comparison of median total BDI scores (**A**) and frequency of reporting individual BDI symptoms (**B**) across three diagnostic groups: healthy controls, Tourette syndrome (TS) and recurrent major depressive disorder (rMDD).

A



B



**TS-rMDD pairwise comparison P=.03*
***TS-rMDD pairwise comparison P=<.01*
****TS-healthy controls pairwise comparison P<.01*

4. DISCUSSION

This is the largest study to date to explore depressive symptoms in adult patients with TS in comparison to patients with major depression and healthy controls. Gender ratios in our patient populations were representative of clinical samples, with male predominance in TS and female predominance in major depression [2,30]. According to our results, patients with TS reported higher depressive scores than healthy controls, and their scores were comparable to patients with a primary diagnosis of recurrent major depression.

Previous studies employing a variety of clinical rating scales for depression in child, adolescent and some adult cohorts have consistently found higher scores in patients with TS compared to healthy controls [31-37]. Only one study examining *N*=17 children and adolescents with TS and an equal number of age and sex-matched control subjects failed to find consistent group differences on the Children's Depression Inventory scores, although the TS group reported higher scores on the depression sub-scale of the Child Behavior Checklist [38]. The results of this isolated study are to be interpreted in the light of the known differences between self- and proxy-ratings in young patients with TS [39-41].

The present study validates the findings of a previous smaller study, in which adult patients diagnosed with TS (*N*=22) and depression (*N*=19) were compared to healthy controls (*N*=21) across a variety of psychopathological indices, including depression ratings [42]. *Post hoc* analyses indicated that both patients with TS and patients with depression experienced more severe depressive symptoms than controls, and in turn patients with depression had higher scores than those with TS (all $P<.0001$). Besides the considerable difference in sample size, the recruitment setting (psychiatric outpatient clinics only) suggests that patients with more severe forms of depression were included in the patient control group of this earlier study. It is therefore not surprising that he difference between the TS and depressed groups was not replicated in our study (adjusted *P* value was trend-level significant only).

The presence of depressive symptoms in TS is likely to have a multifactorial aetiology, which includes the psychological consequences of having a socially disabling and chronic condition, the high co-morbidity rate with ADHD and OCD, the side-effects of pharmacotherapy for tics and associated co-morbidities, the family history for tics and/or behavioural problems, shared biological risk factors for both disorders and the possibility of chance co-morbidity, as both depression and TS are relatively common disorders [7].

Our results also highlight the prominence of irritability in TS compared to the rMDD group. Impulse control disorders, including aggressive behaviours, rage attacks and conduct problems, are frequently reported in TS [43,44] and usually related to the presence of co-morbid ADHD [45-47]. Given that irritability is a common feature of neuropsychiatric disorders [48], this may be independent of depression and due to TS-related factors [49]. However, our findings raise the possibility that irritability could act as a mediator between affective disturbances and impulse dyscontrol, especially in patients with TS who also have a diagnosis of ADHD.

Our study has limitations. Firstly, the study design was cross-sectional, and future studies would benefit from implementing a prospective design in order to capture the development of depressive features. Secondly, the healthy control group was 'super-normal', i.e. without any personal or family history of psychiatric disorders, which maximised the chances of finding differences between controls and patient groups. Thirdly, there may be some discrepancy with different versions of the BDI used, although the conversion of BDI-II to BDI-IA was validated by previous research by the BDI developers. Fourthly, the fact that no data about antidepressant use were available for analysis from the rMDD group could be a relevant confounder, as irritability symptoms have been shown to be potentially responsive to antidepressants, as well as antipsychotics and mood stabilisers [50]. Finally, the TS group was recruited from a specialist clinic within a tertiary care setting, and due to referral bias might not be representative of the overall TS population.

In conclusion, depression appears to be a prominent feature in TS, particularly the symptom of irritability which may be related to aggressive symptoms and impulse dyscontrol, often reported by patients with TS and co-

morbid ADHD. We therefore suggest that patients with TS should be routinely screened for specific depressive symptoms in order to provide appropriate management of psychological and behavioural problems.

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Highlights

We assessed depressive symptoms in adults with Tourette syndrome (TS) and controls.

TS patients reported similar depressive scores to patients with major depression.

Both patient groups reported higher depressive scores than healthy controls.

TS patients presented with irritability features in association with depression.

TS patients should be routinely screened for depression to implement treatment.