Gilles de la Tourette Syndrome

The Relationship of Anxiety, Depression and OCD with Quality of Life and Tic Severity in GTS

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Author Note

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Abstract

Anxiety disorders and depression are common co-morbidities in people with the Gilles de la Tourette syndrome (GTS), yet little research has been done concerning this relationship. This study aims at exploring anxiety (disorders and symptoms), OCD (disorder and symptoms), depressive symptoms, related to tic severity and health related quality of life (HrQoL) in a large sample. The expectations were: anxious, depressive symptoms, and OCD correlate with tic severity and HrQoL; patients with pure GTS experience higher anxiety, depressive symptoms, tic severity and lower HrQoL than a control group; GTS patients with co-morbid OCD (GTS+OCD), and GTS patients with co-morbid non-OCD anxiety disorders (GTS+AD) score higher on anxiety, depressive symptoms, tic severity and lower on HrQoL than pure GTS patients and a control group. In total 187 participants with a DSM-IV-TR Gilles de la Tourette syndrome (GTS) diagnosis and 185 unaffected family members took part in the study. Participants were assessed on mental disorders using the MINI and the SCID (standardized interviews); or OCB using the Y-BOCS; on tic severity using the YGTSS; on depression and anxiety using BDI and BAI, and on health related quality of life using the EQ VAS. The results showed that tic severity was correlated and predicted by OCB, but not by anxiety or depressive symptoms. Further, HrQoL was correlated with anxiety, depressive symptoms and with OCB, and was predicted by depressive symptoms, but was not associated with tic severity. Between-group comparisons (pure GTS, GTS+OCD, GTS+AD) revealed that higher levels of anxiety and depressive symptoms in GTS were related to the presence of co-morbid OCD. In conclusion, the presence of co-morbidity leads to lower HrQoL, whereas tic severity does not lower QOL. This notion has several treatment implications.

Keywords: Gilles de la Tourette syndrome, anxiety, depressive symptoms, obsessive-compulsive disorder/behaviour, OCD, health related quality of life, tic severity, co-morbidity, adults

Preface

This master thesis was written in the context of the Master's programme in Clinical and Health Psychology at the University of Utrecht. The topic Gilles de la Tourette with the focus on co-morbid Anxiety Disorders, Depression and OCD was chosen due to personal interest, as well as, due to the fact that it offered insight in working on an on-going project (of dr. D. C. Cath and other people of the University of Utrecht) and into working with a large clinical family sample, which was seen as a practical addition to the theoretical knowledge (gained throughout the graduate en postgraduate degree at the University of Utrecht). In the scope of the longitudinal study concerning Gilles de la Tourette syndrome a large database of baseline measurement was available, though not all of the data was yet available in a digital version. Though not used for this study, we also invited participants for the second assessment of the on-going longitudinal study, enabling us to get valuable insights into the disorder Gilles de la Tourette, and this improved our knowledge of applying semi-structured interviews and neuropsychological tests. This proved very useful for the work during our internships. Due to our wide interests and the huge database, we made several attempts defining suitable research questions and developed many theories and performed many analyses before reaching the master thesis in its current form. Both authors contributed individually to this article by concentrating on specific areas. A. V. Fritz dedicated special attention to the relationship of anxiety, depressive symptoms and obsessive-compulsive behaviour with tic severity, whereas R.T.S. Stockmann focussed on the relationship of the same variables with health- related quality of life. Therefore these statistical analyses (correlations and regressions) were performed separately and later merged in one thesis. Regarding the discussion, the second paragraph was written by A. V. Fritz and the fourth by R.T.S. Stockmann. The remaining components of this article were written in cooperation. Grateful acknowledgment is hereby made to dr. D. C. Cath, for the guidance and feedback in the process of writing this article. Furthermore gratitude is shown to H. M. Huisman-van Dijk for her assistance with respect to the statistical analyses. Without their invaluable help, this thesis would not have reached its present form. Conducting this study and writing the thesis was an educative experience as well as a useful addition to the knowledge of the authors. Furthermore, we would like to thank our families and friends for bearing our behaviour in stressful times and for always having an open ear when our minds were full of fantastic ideas about the thesis. Grateful thanks to all of them!

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Gilles de la Tourette Syndrome: The Relationship of Anxiety and Depression on Quality of Life and Tic Severity in GTS

The Gilles de la Tourette syndrome (GTS) was first described by Georges Gilles de la Tourette, a French neurologist, in 1885 which earned him eponymous fame. It is a chronic neuropsychiatric disorder with childhood onset, which is characterized by multiple motor and one or more vocal (phonic) tics lasting longer than a year, with no tic-free period of more than three consecutive months (American Psychiatric Association, 2000). Tics are rapid, sudden, unexpected, irresistible, inappropriate, repetitive and involuntary muscle contractions (motor tics) or noises and words (phonic/vocal tics; Shapiro & Shapiro, 1981). Tics typically fluctuate in form, frequency, intensity, and severity (Conelea, Woods, & Brandt, 2011). Evidence supports GTS being an inherited disorder; however, the precise genetic abnormality has still to be identified (Felling & Singer, 2011). After its childhood onset (generally between the age of 5 and 7), whereby a younger age of onset is linked to more severe GTS (Khalifa & Von Knorring, 2005), GTS symptoms have a fluctuating/waxing course with a common worsening between the age of 9 and 12 years (Sukhodolsky et al., 2009). Symptom intensity and severity decreases during adolescence or early adulthood (Leckman et al., 1998), with usually some tics persisting (Robertson, 2008b). Indeed, 90% of adult patients in the research of Pappert, Goetz, Louis, Blasucci, and Leurgans (2003) still had some form of tics. The prevalence of GTS in the age group of 5 to 18 years is estimated between 0.4 % and 3.8%, meanwhile the overall prevalence is estimated to be around 1% (Robertson, 2008a). GTS affects people from all cultures and social classes (Awaad, 1999) nevertheless it is possibly more common in Western Caucasians, and less common in Oriental populations and even rare in Afro-Americans. And, so far no case was reported in Sub-Saharan coloured Africans (Robertson, 2008a). Co-morbidities are common in people with GTS, indeed research suggests that approximately 90% suffer from co-morbid disorders, including attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD) and behaviours (OCB), self-injurious behaviours, depression, anxiety and non-obscene socially inappropriate behaviours (Cavanna, Servo, Monaco, & Robertson, 2009; Freeman et al., 2000; Robertson, 2000; Servello, Porta, Sassi, Brambilla, & Robertson, 2008). In 1970, Feinstein defined the term co-morbidity as “any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study” (pp. 456-57). An extent of research has shown that co-morbidity has a negative influence on the

clinical course by, for example, affecting the time of detection, the prognostic anticipation, therapeutic selection, the post-therapeutic outcome, also, it may alter statistical categories of diagnostic classification (Feinstein, 1970; Merikangas & Kalaydjian, 2007). Furthermore, effectiveness of interventions will be improved by systematical inclusion of co-morbidity into clinical evaluation and treatment (Merikangas & Kalaydjian, 2007). This study aims at exploring anxiety (disorders and symptoms), OCD (disorder and symptoms), depressive symptoms, and tic severity and HrQoL in a large sample of GTS and unaffected family members.

To give an overview and understanding of the topic, first the relation of GTS with anxiety and depressive symptoms will be described. Second, OCD and its multifaceted links with GTS, as well as the relation of co-morbid non-OCD anxiety disorders with GTS, will be clarified. Third, there will be an description of research findings of the relation between tic severity and various domains of quality of life.

Co-morbidity with Anxiety and Depression

In 1885 Gilles de la Tourette stated that fears and phobias often co-occurred with GTS (as cited in Robertson, 1989). Recent research has indicated that co-morbid anxiety disorders are quite common in people with GTS (Coffey et al., 2000). In a clinical study by Corbett, Mathews, Connell and Shapiro (1969) anxiety symptoms were documented to be the most frequent co-morbid symptoms in GTS, occurring in 57 of the 171 participants with GTS. Freeman and colleagues found in 2000, in the largest clinical database to date (containing 3500 GTS patients worldwide [from 22 countries]) a prevalence rate of anxiety disorders of 18%. Thus, even though the precise prevalence of anxiety disorders has yet to be determined anxiety symptoms seem to be somewhat more common in people with GTS than in the general population (11%; Grant et al., 2004).

Besides anxiety, clinical literature suggests that depression is also common in people with GTS (Cavanna et al., 2009; Cohen, Sade, Benarroch, Pollak, & Gross-Tsur, 2008; Comings & Comings, 1987; Müller-Vahl et al., 2010; Robertson & Orth, 2006; Snijders, Robertson, & Orth, 2006) with a suggested prevalence of 18-30% (Chee & Sachdev, 1994; Snijders et al., 2006). The presence of co-morbid Anxiety and Depression are well known to be associated with chronicity and severity of psychopathology, worsen treatment outcome and psychological functioning (e.g., Katon, 2003; Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Especially, depression may lead to hospitalization and even suicide in some

instances (Robertson, 2006), and therefore appropriate assessment and treatment is essential. Some research argues that the increased frequencies of co-morbid anxiety and depression in GTS are secondary to disease burden, as GTS is a chronic, socially doubling and stigmatising disease, which inter alia can have a negative effect on self-esteem (Snijders et al., 2006) and on quality of life (Elstner, Selai, Trimble, & Robertson, 2001). Other research states that the occurrence of anxiety and depression in patients with GTS could be attributed to co-morbidity with OCD and ADHD instead of to the disorder itself, due the fact that the patients suffer from more than one disorder (Cavanna et al., 2009). Indeed, Spencer and colleagues (1998) showed that children with GTS and co-morbid ADHD showed higher scores on anxiety and depression than children with "only" GTS. Furthermore, according to Cavanna and colleagues (2009) anxiety and depressive symptoms are both associated with more severe tics. This is in line with the study of Elstner and colleagues (2001), which showed that GTS patients with anxiety and depression had higher tic severity. Coffey and colleagues (2000) even hypothesized that anxiety has an aggravating effect on tic severity. Interestingly in the research of Cohen and colleagues (2008), tic severity in children was found to correlate significantly with depression but not with anxiety symptoms. On the other hand, even though some research has found relations between tic severity and depressive symptoms, Hornsey, Banerjee, Zeitlin, and Robertson (2001) and Findley and colleagues (2003) suggested that milder tic severity might not result in depressive symptomatology whereas higher severity and co-morbidity might. Indeed, Sukhodolsky and colleagues (2009) showed that participants with GTS without co-morbidity did not experience more depressive symptoms than the comparison groups (as cited in Cavanna et al., 2009). The research of Coffey and colleagues (2000) showed a relation between tic severity and co-morbid anxiety disorders (non-OCD), but unfortunately without comparing the results to a pure GTS group.

In summary, anxiety and depressive symptoms seem common in people with GTS and are associated with negative outcomes in physical and mental health, as well as with a worse clinical course and hospitalization and in some cases even suicide. Further, either due to the disorder itself or due to co-morbidity, multiple research studies have shown relations between GTS and depressive and anxiety symptoms. And it is suggested that anxiety and depressive symptoms are related to tics severity, but the direction is yet unclear.

Co-morbidity with OCD (and non-OCD Anxiety Disorders)

Clinical literature has shown multifaceted links between OCD and GTS on basis of co-morbidity, family genetics, clinical phenomenology, and neurophysiology (Chang & Piacentini, 2002 as cited in Chang, McCracken & Piacentini, 2007). Obsessive-compulsive disorder (OCD) is defined as an anxiety disorder, which is characterized by the presents of obsessions and compulsions. Obsessions are recurrent and persistent ideas, thoughts or impulses that are perceived as intrusive and inappropriate and cause marked distress or anxiety (Cath, 2000; Sheppard, Bradshaw, Purcell, & Pantelis, 1999). OCD is characterized by the presence of obsessions and/or compulsions that the patient perceive to be excessive at some time during the disorder. Common obsessive thoughts include fears of contamination, to harm/injury/kill someone beloved, or of shameful thoughts (Fullana et al., 2009; Leonard et al., 1992, as cited in Sheppard et al., 1999; Singer & Walkup, 1991), and repeated doubts about one's actions (Cath, 2000). Compulsions are repetitive and seemingly purposeful behaviour, usually performed in response to an obsession aiming to reduce distress and anxiety, not to obtain pleasure or gratification (Sheppard et al, 1999; Cath, 2000). Typical compulsions include excessive cleaning (e.g., repeated hand-washing, showering), checking rituals, reordering or arranging habits, repeating rituals, and counting (Leonard et al., 1992 as cited in Sheppard et al., 1999; Singer & Walkup, 1991). The patients experience the compulsion as excessive and unreasonable.

OCD appears to be one of the most common co-morbidity in people with GTS (Freeman et al., 2000). The overall co-morbidity rate between GTS and OCD is estimated to be around 11% to 80% (Cavanna et al., 2009). Chang and colleagues suggested in 2007 that this co-morbidity is bi-directional; they found that 20–60% of GTS patients met OCD criteria, and that 20 - 38% of children with OCD had co-morbid tics. In line with this, other findings suggest that the majority of people with GTS experience obsessive-compulsive behaviours in the course of the disorder, while simple and/or complex tics often occur in OCD (Sheppard et al., 1999). OCD and GTS relate in several aspects. In both disorders people report some extend of voluntary control over the repetitions (Sheppard et al., 1999). Furthermore, patients often experience raising tension if they supress/ inhibit the behaviour, and when the act is carried out it is followed by relief. Symptoms of both, GTS and OCD are also worsened by stressful situations, fatigue, and emotional states (Como, 1995 as cited in Sheppard et al., 1999; Singer & Walkup, 1991). Both, GTS and OCD have a similar progression: They have a chronic fluctuating course and juvenile onset. Further they experience failure to inhibit

voluntary and involuntary repetitive behaviour, higher familial occurrence and stress reactivity, and neuroanatomical dysfunctions have overlapping sites (Sheppard et al., 1999). As seen, OCD and GTS have several similarities, suggesting that GTS is closely associated with OCD in GTS families. Indeed, family studies on the relation between GTS and OCD have indicated that, in GTS families, OCD/OCB is an alternative expressions of the same underlying disorder (Paul, Leckman, Towbin, Zalmer, & Cohen, 1986; Eapen, Pauls & Robertson, 1993). Sex of the family member of the proband with GTS matters; female relatives develop in more instances OCD whereas male relatives develop GTS or tics (Pauls & Leckman, 1986; Pauls, Raymond, Stevenson, & Leckman, 1991). The relation of OCD with tic severity seems still inconsistent. On the one hand Elstner and colleagues (2001) found that GTS patients with high scores on obsessive compulsive behaviour (OCB) did not differ in tic severity from people without OCB. On the other hand, several investigations have shown that OCD is associated with more severe tic severity (Comings & Comings, 1987; Sheppard et al., 1999). Furthermore, due to the close relation to GTS a lot of research has been concentrating on co-morbid OCD. Less research has been done about the influence of other co-morbid non-OCD anxiety disorders in people with GTS. As mentioned above, they are also associated with worsened illness and according to Coffey and colleagues (2000) with higher tic severity.

In summary, OCD has multifaceted links with GTS on basis of co-morbidity, family genetics, clinical phenomenology, and neurophysiology. One question rising up is whether OCB would be higher in people without co-morbid OCD as well, thus in patients with pure GTS or co-morbid non-OCD anxiety disorders. Further, as mentioned before, some research suggests that the occurrence of anxiety, depression symptoms, and tic severity are more related to co-morbidity than to the disorder itself. Here the question is if co-morbid OCD or non-OCD anxiety disorders actually heighten tic severity and depressive symptoms?

GTS and Quality of Life

Quality of Life (QoL) is an extremely multifactorial, abstract, and diffuse concept difficult to define (Fernández-Ballesteros, 1997). Usually it means the evaluation of the general well-being of individuals and includes many factors, like physical and mental health, education, social well-being, freedom, human rights and happiness.

Several studies have looked into the many different domains of QoL and demonstrated that in people with GTS QoL was lowered in many of these domains. For example, studies of

young people with GTS show a lower QoL opposed to their unaffected peers, particularly within the emotional, social and school domains (Cutler, Murphy, Gilmour, & Heyman, 2009; Storch et al., 2007), but not for physical functioning (Storch et al., 2007). Furthermore, children and adolescents with GTS reported that tics had a negative academic impact, resulted in peer problems and problems with dating and keeping friends (Packer, 2005; Champion, Fulton, & Shady, 1988). Thus, in children and young people with GTS, tics seem to have a negative impact on QoL, in particular in social and academic functioning. Furthermore, Elstner and colleagues (2001) found that adult out-patients with severe GTS, had lower scores on QoL in the domains of social functioning and role limitation due to emotional problems and general health perception. They concluded that general QoL is impaired in patients with GTS, and that associated disorders like depression, anxiety and OCD also contributed to this impairment. Indeed, research found that the presence of both ADHD and OCD could lead to more widespread problems in QoL of the person (Eddy et al., 2011b). It seems that different mental disorders each could have a profound negative impact on different aspects of the QoL. For instance, co-morbid OCD might have a profound impact on the vitality (Elstner et al., 2001), the self and the relationship domain (Eddy et al., 2011b). Depression and anxiety negatively influenced all domains measured by the Short Form Health Survey (SF-36; Ware, Kosinski, & Keller, 1994), except the physical functioning domain (Elstner et al., 2001).

Meanwhile general QoL is a broader concept; the concept of health related quality of life (HrQoL) is more specific and in this study based on the subjective evaluation of their general health. Müller-Vahl and colleagues (2010) studied the HrQoL in adults with GTS and found depression to be a major determinant, whereas tic severity only contributed minimally.

In summary, QoL is an immense broad concept with various relations with GTS. This study will focus on HrQoL. Not much is known yet about the relation between HrQoL with anxiety, depression, OCD and non-OCD anxiety disorders in adults with GTS.

This Study

This study aims at exploring anxiety (disorders and symptoms), OCD (disorder and symptoms), depressive symptoms, tic severity and HrQoL in a large sample of GTS and unaffected family members.

Questions:

(A) What is the relationship of anxiety, depressive symptoms and OCD/OCB with tic severity and HrQoL?

It is expected that:

1) There is an association between a) anxiety, b) depressive symptoms and c) OCB with tic severity.
   These variables predict tic severity.
2) Tic severity and HrQoL correlate.
3) There is an association between a) anxiety, b) depressive symptoms and c) OCB with HrQoL,
   These variables predict HrQoL.

(B) What are the differences between pure GTS, co-morbid OCD (GTS+OCD) and co-morbid non-OCD anxiety disorders (GTS+AD) and a control group in anxiety, depressive symptoms, tic severity and HrQoL?

It is expected that:

1) Participants in the pure GTS group have higher anxiety, depressive symptoms, tic severity and lower HrQoL than those in the control group.
2) The groups GTS+OCD and GTS+AD score higher on anxiety, depressive symptoms, tic severity and lower on HrQoL compared to the pure GTS and the control group

Methods

Participants

Clinical data were obtained from 596 participants, 224 participants were excluded. Reasons for exclusion were: 1) missing data (only blood samples; *n* = 36); 2) age younger than 18 (*n* = 111) and older than 65 (*n* = 30); 3) missing GTS diagnosis (*n* = 4); 4) a diagnosis of CMT (*n* = 39) and CVT (*n* = 2) and 5) drug- induced co-morbid disorders (*n* = 2). In total 372 participants were included in the analysis. Of those participants 187 had a DSM-IV-TR diagnosis of GTS (72 females and 115 males, with an average age of 36.61; age range: 18-65[see Table1]) and the control group consisted of 185 family members, who had no diagnosis of GTS (96 females and 89 males with an average age of 46.64; age range: 18-65[see Table1]). Of the 372 participants, 322 have been assessed for mental disorders, either by the M.I.N.I. (*n* = 176), SCID (*n* = 141) or clinical interview (*n* = 5). The frequencies of (co-morbid) mental disorders are shown in Table 2. The numbers of mental disorders of participants with GTS and of unaffected family members are shown in Table 3. Participants with GTS had significantly more co-morbid disorders: one or more mental disorders (other

than GTS) were found in 87 of the 149 participants with a GTS diagnosis (58.4%), and in only 14 of the 172 participants without a GTS diagnosis (8.1%). Fifty-one participants had missing co-morbidity diagnoses. Half of the participants with GTS had anxiety disorders (50%), with OCD being the most common co-morbid mental disorder (38%). Of the unaffected family members 7% had one or more anxiety disorders. Mood disorders were found in 25% of the people with GTS and in 3% of the unaffected family members. Major depression was found in 18% of the participants with GTS (see Table 2).

Procedure

Participant recruitment was carried out from 2001 to 2008. Participants were recruited via the GGZ Buitenamstel outpatient clinic, and the Dutch Tourette's syndrome patients' association and the National Tourette days, in the scope of a genetic study on Tourette's disorder. Participants with GTS and their family members (siblings, parents, children, spouses) were invited for an assessment using both self-report questionnaires and interviewing. After agreeing to participate (and written informed consent) participants were sent self-report questionnaires (consisting of BAI, BDI, QOL and other measurements). They were asked to fill out the forms and bring them along for the interview. During the interview trained personnel assessed the participants' co-morbidities including OCD diagnosis with the help of either the M.I.N.I. or the SCID, the YGTSS (tic symptoms and severity) and the Y-BOCS (OCD symptoms and severity). Interviews and self-reports took in total 4 hours. Afterwards participants were reimbursed for travel expenses.

Materials

Establishment of clinical diagnoses/Co-morbidities: Co-morbidities were assessed either by using the Dutch version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, &Williams, 1996; Groenestijn, Akkerhuis, Kupka, Schneider, & Nolen, 1999) or the Dutch version of the Mini International Neuropsychiatric Interview (M.I.N.I.), version 5.0.0 (Overbeek, Schruers, & Griez, 1999). Both instruments are semi-structured clinician or trained mental health professional rated standardised interviews used to systematically diagnose the most prevalent DSM-IV Axis I disorders. Research on the English version of the SCID has shown good till high reliability for all disorders (Lobbestael, Leurgans, & Arntz, 2010; Williams et al., 1992; Segal, Kabacoff, Hersen, Van Hasselt, & Ryan, 1995) and high validity (Shear et al., 2000). With respect to the MINI, good to very

good interater reliability has been established (Lecrubier et al., 1997; Sheehan et al., 1998). Further, sensitivity and specificity for all diagnoses except for generalized anxiety disorder (GAD; kappa = .36), agoraphobia (sensitivity = .59) and bulimia (kappa = .53) was good, as well as test-retest reliability. The validity and reliability of the Dutch version of the M.I.N.I. have yet to be determined (Vliet & Beurs, 2007).

Severity of tics: The severity of tics was measured using the Dutch version of the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). This semi-structured clinician-rated instrument assesses the characteristics and severity of motor and vocal tics, during the course of a one week interval before clinical assessment. The clinician separately rates the severity of motor and vocal tics on five separate dimensions: Number, frequency, intensity, complexity and interference. In addition, there is one question which measures the overall impairment in daily functioning due to tics. The 10 items are rated on a 6-point ordinal scale. The total score of both vocal and motor tics is calculated by adding up the scores of the five dimensions (range 0-25). The global severity scale is derived by summing the totals scores of the vocal scale, motor scale and the overall impairment rating (range 0-50), creating a total score (range 0-100). According to Storch and colleagues (2005), the YGTSS is a reliable and valid instrument with excellent internal consistency. Cronbach's alpha of current study is .95.

Anxiety symptom severity: The level of anxiety was assessed via the Dutch Version of the Beck Anxiety Inventory (BAI; Beck & Steer, 1990). This 21 item self-report measure assesses the severity of anxiety symptoms on a 4-point scale ranging from 0 ('*not at all'*) to 3 (*severe).* Numerous studies have supported the reliability, internal consistency and validity of this instrument (e.g., Beck, Epstein, Brown, & Steer, 1988; Beck & Steer, 1990; 1991). In current study Cronbach's alpha is .91.

Depression symptom severity: The Dutch version of the revised Beck Depression Inventory (BDI; Beck & Steer, 1987, Bouman, Luteijn, Albersnagel, & Van der Ploeg, 1985) was used. It is a 21-item self-report questionnaire in which each item is rated on a 4-point scale, ranging from 0 ('*not at all'*) to 3 (*severely),* indicating severity of depressive symptoms over the past week. Scores for all 21 items are summed to yield one single depression score. The internal consistency of the BDI, based on a number of clinical samples, is good to excellent (Beck & Steer, 1987). Cronbach's alpha of this study is .89.

Severity of OCB symptoms: The severity of OCB symptoms was assessed using the clinician-administered version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS;

Goodman et al., 1989b). The Y-BOCS is a semi-structured interview used to assess the severity of OCD symptoms differentiating between the following levels: Subclinical (scores of 0–7), mild (8–15), moderate (16–23), severe (24–31) and extreme (32-40). The scale consists of 10 items with separate questions about obsessions and compulsions. Further, the time that the individual spends on obsessions and compulsions, and impairment, distress, resistance and control is assessed. Goodman and colleagues (1989a) found an excellent validity, high inter-rater reliability and internal consistency.

Quality of life: The VAS scale of the EQ-5D (EuroQol Group, 1990) is used as a quantitative measure of health related quality of life (HrQoL) as judged by the individual respondents. The EQ VAS is a one item, self-report standardised instrument and global rating scale for current health, measured with a visual analog scale (VAS), rating from 0 *('worst imaginable'*) to 100 (*'best imaginable'*). Convergent validity of the EuroQol is moderate to strong and reliability good, however the EuroQol is supposed to be better at detecting large than small changes in health (Dyer, Goldsmith, Sharples, & Buxton, 2010).

Statistical Analyses

All analyses were performed using the statistical software SPSS (version 16). A significance level of $p \leq .05$ was adopted and all tests were analysed two-tailed. Alpha levels of $p < .10$ are interpreted as trend-level significance. As this study is predominantly interested in the disorders in the more severe spectrum, it was decided not to take specific phobia into account in the calculations.

An independent samples t-test was used to analyse differences between participants with GTS and controls (unaffected family members; independent variables) in the number of DSM IV axis 1 diagnoses (dependent variable).

Pearson's correlation cofficients (r) were used for the entire sample of participants with GTS to test for significant intercorrelations between tic severity (YGTSS), anxiety symptoms (BAI), depressive symptoms (BDI), severity of OCB (Y-BOCS severity), number of co-morbidities and health related QoL (EQ VAS) scores. The interpretation of the associations is: $r = .10$ is a small correlation, $r = .30$ is a medium correlation and $r = .50$ is a large correlation.

To predict which variables were mostly related with tic severity and HrQoL, the entire sample of GTS patients was used in a two step forward regression analyses with YGTSS scores (only as predictor of HrQoL), BAI scores, BDI scores and Y-BOCS severity scores as

independent variables and YGTSS and EQ VAS score (item of EQ-5D) as dependent variables. The regressions were adjusted for gender and age. For both regressions the assumption of no multicollinearity was met.

One-way analyses of variance (one-way ANOVAs) were performed to investigate quantitative difference between groups in tic severity, anxiety, depressive symptoms, severity of OCB and HrQoL (dependent variables). Four groups were compared: (a) a control group, consisting of family members without GTS, (b) a pure GTS group, of participants with GTS and no co-morbid mental disorder, (c) a GTS with OCD group (GTS+OCD), participants with GTS and co-morbid OCD, without any other anxiety disorder, and (d) a GTS with non-OCD anxiety disorder group (GTS+AD), participants with GTS and an anxiety disorder other than (subthreshold) OCD. If necessary to control for unequal variance between groups the Welch's t-test was used. Scheffe's Post Hoc Tests were performed to investigate (significant) differences between groups.

Results

Between Groups Comparison of the Number of Mental Disorders

An independent samples t-test showed that participants with GTS (M = 1.17; SD = 1.32) had significantly more often one or more mental disorders than the control group (M = 0.15; SD = 0.61), $t(202) = -8.67$, $p < .001$. For the number of mental disorders see Table 3.

Exploratory Data Analysis Between Variables

Pearson's correlation coefficients (r) of the statistical intercorrelations between age, YGTSS (total, motor and phonic), BAI, BDI, Y-BOCS severity, number of co-morbidities and EQ VAS scores are shown in Table 4. The data shows that BAI positively correlates with BDI ($r(108) = .66$, $p < .001$), Y-BOCS severity ($r(103) = .43$, $p < .001$), as well as with number of co-morbidities ($r(85) = .48$, $p < .001$). BDI correlates with Y-BOCS ($r(104) = .48$, $p < .001$) and with number of co-morbidities ($r(85) = .65$, $p < .001$). Furthermore, Y-BOCS and number of co-morbidites positively correlate ($r(144) = .52$, $p < .001$). EQ VAS seems negatively related with BAI ($r(61) = -.53$, $p < .001$), BDI ($r(60) = -.63$, $p < .001$), Y-BOCS severity ($r(70) = -.45$, $p < .001$) and with number of co-morbidities ($r(52) = -.54$, $p < .001$).

Predictors of YGTSS and EQ VAS Score

A stepwise forward multivariate regression showed that of the expected predictors Y-BOCS severity scores, BDI scores and BAI scores, only Y-BOCS severity significantly predicted YGTSS scores (β = 0.20, $t(98) = 2.04$, $p = .044$) explaining approximately 4% of the variance ($R^2 = .04$, $F(1, 98) = 4.18$, $p = .044$).

Furthermore, analysing the predicting value of BDI scores, BAI scores, Y-BOCS severity scores and YGTSS scores on EQ VAS scores, it was found that only BDI significantly predicted lower EQ VAS scores (β = -0.59, $t(52) = -5.30$, $p < .001$), explaining 35% of variance ($R^2 = .35$, $F(1, 52) = 28.13$, $p < .001$). The other variables did not significantly add to the model.

Between Group Comparisons of Co-morbid Anxiety Disorders on YGTSS, BAI, BDI, Y-BOCS and EQ VAS Scores

A one-way ANOVA revealed significant differences in YGTSS scores between the groups (pure GTS, GTS+OCD and GTS+AD), $F(2, 87) = 5.91$, $p = .004$. The pure GTS (M = 15.73; SD = 11.06; n = 48) and GTS+AD group (M = 17.67; SD = 8.58; n = 21) did not significantly differ (p = .915). The GTS+OCD group (M = 24.67; SD = 8.49; n = 21) scored significantly higher on YGTSS compared to the pure GTS group (p = .004), and there is a trend that they score higher compared to the GTS+AD group (p = .081).

Significant differences were found in BAI scores between the groups (controls, pure GTS, GTS+OCD and GTS+AD), $F(3, 29) = 3.21$, p = .028. Post hoc tests indicated the control group (M = 5.07; SD = 6.17) did not significantly differ on the BAI compared to the pure GTS group (M = 5.83; SD = 6.24; p = .796) and compared to the GTS+AD group (M = 11.30; SD = 9.53; p = .111), but scored significantly lower on the BAI compared to the GTS+OCD group (M = 11.75; SD = 9.28; p = .021). There was a trend that the pure GTS group scored lower compared to the GTS+OCD group (p = .061), but the pure GTS group did not score different compared to the GTS+AD group (p = .211) and the GTS+OCD group did not differ from the GTS+AD group (p = .999).

The groups showed significant differences in BDI scores, $F(3, 97) = 4.92$, p = .002. Post hoc tests indicated that the control group (M = 5.92; SD = 6.20) did not significantly differ on the BDI compared to the pure GTS (M = 5.34; SD = 5.32; p = .985) and the GTS+AD group (M = 11.60; SD = 6.48; p = .115). However, the GTS+OCD group (M = 11.62; SD = 9.19) scored significantly higher on BDI compared to the controls (p = .038) and

the pure GTS group (p = .021). The GTS+OCD group did not differ from the GTS+AD group (p = 1.000). There was a trend of the pure GTS group to score different from the GTS+AD group (p = .073).

The groups showed significant differences in EQ VAS scores between the groups, $F(3, 125) = 3.64$, p = .015. Post hoc tests indicated that the GTS+OCD group (M = 65.33; SD = 20.27) scored significantly lower on the EQ VAS compared to the control group (M = 80.21; SD = 13.71; p = .028) and the pure GTS (M = 81.35; SD = 12.90; p = .040). The control group did not significantly differ in EQ VAS scores compared to the pure GTS group (p = .989). The GTS+AD group (M = 73.20; SD = 5.45) did not score different compared to any of the groups (vs. controls, p = .752; vs. pure GTS, p = .704; vs. GTS+OCD, p = .794). The mean, standard deviation and group size are shown in Table 5.

Furthermore, significant differences in Y-BOCS scores between the groups were found (control, pure GTS and GTS+AD), $F(2, 44) = 8.37$, p = .001. Post hoc tests indicated that the control group (M = 0.70; SD = 2.89; n = 182) scored significantly lower on Y-BOCS scores compared to the pure GTS group (M = 2.98; SD = 4.55; n = 51; $p < .001$) and the GTS+AD group (M = 3.59; SD = 5.26; n = 22; p = .002). The pure GTS group and the GTS+AD group were not significantly different (p = .794).

Discussion

This is the first large scale study attempting to explore the relationship between anxiety, depression, tic and OCB severity in participants with GTS. The hypotheses regarding the correlations were only partly supported. Tic severity was correlated with OCB, and was also predicted by it, though with a very small proportion of explained variance. However, the other co-morbidities showed no association with tic severity. Further, there was an association of HrQoL with anxiety, depressive symptoms and OCB, but not with tic severity. Poorer HrQoL was only predicted by depressive symptoms. Looking into the differences in anxiety, depressive symptoms, tic severity and HrQoL between the following groups: pure GTS, co-morbid OCD, co-morbid non-OCD anxiety disorders (AD) and the control group revealed the following: first, contrary to the assumptions, participants with pure GTS did not experience more anxiety and depressive symptoms, nor did they have a lower HrQoL compared to the control group. Second, in line with the expectation participants with co-morbid OCD experienced higher tic severity, depressive symptoms and a lower HrQoL compared to pure GTS, and showed a trend of a higher anxiety level. Third, contrary to the expectation GTS

participants with a co-morbid AD did not significantly differ in tic severity, anxiety, nor in HrQoL. Moreover, there was only a trend of higher depressive symptom levels compared to pure GTS.

Research suggests that anxiety and depressive symptoms are associated with and aggravate tic severity (Cavanna et al., 2009; Elstner et al., 2001;Coffey et al., 2000). This study could not find any relation, neither a correlation nor a predictive relation between anxiety and tic severity. This is in line with Shapiro, Shapiro, Young and Feinberg, who stated in 1988 that repetitive tics in GTS patients, contrary to the compulsions in people with OCD "only", are performed automatically or as a consequence of a failure to withstand an impulse and are non-anxiety related. Indeed, there was an association between anxiety and OCB. Furthermore, no relation (neither correlation nor regression) between depressive symptoms and tic severity was found. Instead, depressive symptoms were associated with OCB, suggesting a link between depression and OCB, also noted before by Eapen, Fox-Hiley, Banerjee & Roberson colleagues (2004). Further, this is in line with the findings of Perugi, Toni, Travierso, Hantouche, and Akiskal (2002), who suggest that depression is very common in people with OCD, ranging from 13-75%. The exact relation between tic severity and OCB has been a topic of controversy in the literature. Contrary to Elstner and colleagues (2001) and in line with several other studies (see Sheppard et al., 1999), this research showed that OCB was associated with tic severity, and even predicts it, though only with a small proportion of variance explained. Interestingly, even though OCB and tics seem closely related, and (according to Paul and colleagues [1986] and Eapen and colleagues [1993]) seem to be variant expressions of the same genetic susceptibility, they seem to have one important difference: OCB is associated with anxiety and depressive symptoms, whereas tics are not. In conclusion, tic severity is neither associated with anxiety nor with depressive symptoms, but with OCB.

Research shows contradicting findings concerning the influence of GTS and tic severity on QoL (Eddy et al., 2011b). It would be expected that tic severity has a profound impact on QoL, given that people with GTS often report that tics affect their daily lives (Champion et al., 1988; Singer & Rosenberg, 1989). Interestingly, when subdivided into motor and vocal tics, motor tics did seem to be associated with a lower HrQoL. In Elstner and colleagues' (2001) study, participants with GTS most frequently mentioned motor tics to give problems in the physical functioning domain of QoL, through physical injury, exhaustion and interfering with daily activities. This could explain why HrQoL is more related to motor tics

and not to vocal or total tic severity. It could be suggested that tic severity only has an influence on certain domains of QoL, such as physical functioning (Eddy et al., 2011b; Elstner et al., 2001). However, this study shows that the severity of tics does not have a profound impact on overall HrQoL.

Research suggests that a lower QoL in people with GTS could be more related to co-morbid mental disorders than to the disorder itself (Cavanna et al., 2009; Bernard et al., 2009; Eddy et al., 2011a). Indeed, this study found that anxiety, depressive symptoms and severity of OCB were all negatively related to HrQoL. This is consistent with previous research, showing that people with high levels of anxiety, depressive symptoms and OCB have a poorer QoL (Elstner et al., 2001). Contrary to the expectations, when added in a regression simultaneously, only depressive symptoms predicted a poorer HrQoL. This is in contrast to other research, which found that anxiety and co-morbid OCD exert a negative impact (Eddy et al., 2011a; Eddy et al., 2011b). Eddy and colleagues (2011a) found that the domains of QoL were affected by different co-morbid disorders. In their study, using a specific and extensive tic-related rating scale of QOL, depressive symptoms only had a negative impact on the relationship domain, whereas severity of obsessive-compulsive symptoms was predictive of a lower QoL in general. Current study looked into the general health related domain of QoL, which could suggest that depressive symptoms best predict this domain. Furthermore, Eddy and colleagues (2011a) research consisted of young people, whereas current study looked into the influence of co-morbidity on HrQoL in adult participants. Since depression mostly develops in the course of adolescence (Burke, Burke, Rae, & Regier, 1991) and OCD has an age of onset in preadolescent childhood (Geller, 2006), depressive symptoms could have a more profound impact in QoL in later life. A study including adults with GTS conducted by Müller-Vahl and colleagues (2010), confirmed that depressive symptoms have a profound effect on HrQoL. Thus, in adults with GTS, depressive symptoms are the best predictor of a poorer HrQoL.

Besides the influence of continuous severity scales, this study looked into between groups comparison. Despite large sample size of participants with GTS and the large quantity of data collected, through the strict and specific criteria used to form the co-morbid OCD and AD groups, the sample sizes became quite small. This reduced the power of the analyses, and significance thresholds were possibly not reached, in particular for the co-morbid AD group. Therefore, the negative findings in the between-group comparisons should be interpreted with caution, especially with regard to anxiety, depressive symptoms and HrQoL. However,

investigating the rough means of the comparisons between the groups of GTS+OCD and GTS+AD, this reveals that groups are comparable and that anxiety and depressive symptoms seem to be elevated compared to the control and the pure GTS groups. Thus, it seems plausible to expect that the GTS+AD group are in between the pure GTS and GTS+OCD group, but that the sample size of the GTS+AD group was too small to pick up between-group differences.

Anxiety and depression in GTS are complex in origin, with multiple biological and psychosocial factors. So far it is not established whether depressive illness or depressive symptomatology is part of the GTS phenotype or has etiological relations with GTS (Robertson, 2006). Furthermore, research suggested that having a socially disabling and stigmatizing disorder (which can lead to negative social behaviour(Salmon, James, & Smith, 1998; Cavanna et al., 2009) can result in higher depression and anxiety in GTS patients. Indeed, half of the people with GTS had anxiety disorders and a quarter of them had depression. However, the current study implies that having GTS itself might not result in higher anxiety and depressive symptoms, but co-morbid OCD does. Indeed, the GTS + OCD group experienced the highest tic severity, whereas co-morbid AD did not heighten it. This is consistent with the fact that no correlation was found between tic severity and anxiety, but between tic severity and OCB.

Regarding HrQoL, the findings of this study suggest that lower QoL could be more due to co-morbidity than the disorder GTS. This is consistent with Bernard and colleagues' (2009) findings, showing that a lower HrQoL in people with mild to moderate GTS, relates primary to OCB and ADHD, but not to tic severity. As mentioned before, maybe due to the small group size, co-morbid AD was not found to be significantly different from the pure GTS nor from the co-morbid OCD group. However, comparing the mean of the groups, the reported HrQoL in the co-morbid AD group was in-between the means of the pure GTS and the OCD group, with the latter having the lowest. Thus, HrQoL seemed to be lowered by co-morbid OCD and presumably by co-morbid AD, but not by the disorder GTS itself.

However, considering small size of the GTS+AD group, further research should be performed on the co-morbid AD group using larger samples. Other suggestions for further research would be to study whether interactions between the variables anxiety, depressive symptoms, OCD (tic severity) would predict tic severity and HrQoL.

Next to the power problem, this study had another limitation: It did not include a disease specific QoL measurement (Cavanna et al., 2008), and thus has been unable to detect

more subtle domains of QoL besides the health related domain (Eddy et al., 2011a; Elstner et al., 2001). Furthermore, this study did not control for ADHD, although it has shown to affect QoL (Eddy et al., 2011a; Eddy et al., 2011b).

Implications for clinical practice: This study would suggest that the focus in GTS patients should be more on their co-morbidity than on tics. The presence of co-morbidity (especially OCD) should dictate a high index of suspicion of depression, anxiety and a lower HrQoL, and treatment of these issues may be as important as tic reduction. Further reduction of OCB might also contribute to a lower tic severity. Regarding the high percentage of co-morbidities in participants with GTS (58.4%) effectiveness of interventions will improve by systematic inclusion of co-morbidity into evaluation in treatment.

In conclusion, this research suggests that in GTS, there is no relationship between tic severity with anxiety and depressive symptoms or with HrQoL. OCD and OC symptom severity are related to tic severity, and co-morbid depressive symptoms are related to lowered HrQOL. Treatment interventions should focus more on abating co-morbidities than on tic reduction.

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Appendices

Table 1

Participants characteristics

	n	Mean age (range)	*n* female	*n* male
Participants with GTS	187	36.61 (18 - 65)	72	115
Without anxiety disorder	62	35.53 (18 - 63)	21	41
With anxiety disorder	67	36.48 (18 - 65)	28	39
With OCD	24	35.08 (19 - 65)	7	17
With non-OCD anxiety disorder	22	40.73 (23 - 62)	10	12
With both	21	33.62 (18 - 58)	11	10
Missing	58	-	-	-
Control group/ Unaffected family members	185	46.64 (18 - 65)	96	89
Total	372	41.60 (18 - 65)	168	204

Table 2

Co-morbid Mental Disorders in Participants with GTS and Unaffected Family Members (Measured with M.I.N.I., SCID or Clinical Interview)

Disorders	Frequencies of Mental Disorders			
	GTS participants[a]		Unaffected family members[b]	
	Current	Past	Current	Past
	n (%)	*n* (%)	*n* (%)	*n* (%)
Anxiety Disorder	75 (50)	7 (4)	12 (7)	7 (4)
OCD*	57 (38)	-	6 (3)	-
PTSD	5 (3)	-	1 (< 1)	-
GAD	25 (17)	-	7 (4)	-
Social Phobia	21 (14)	-	1 (< 1)	-
Panic Disorder				
With agoraphobia	5 (3)	2 (1)	1 (< 1)	1 (< 1)
Without agoraphobia	8 (5)	5 (3)	-	6 (3)
Agoraphobia	-	-	2 (1)	-
Hypochondria	2 (1)	-	-	-
Specific phobia*	16 (11)	-	1 (< 1)	-
Mood Disorder	37 (25)	32 (21)	5 (3)	3 (2)
Depression	27 (18)	30 (20)	1 (< 1)	2 (1)
Depression with melancholic features	5 (3)	-	2 (1)	-
Dysthymia	7 (5)	-	3 (2)	-
Bipolar 1	1 (< 1)	-	-	-
Bipolar 2	1 (< 1)	-	-	-
Hypomania Episode	-	2 (1)	-	-
Manisch	-	-	-	1 (< 1)
Dependency and Abuse	19 (13)	12 (8)	2 (1)	2 (1)
Substance abuse and dependency	19 (13)	10 (7)	2 (1)	1 (< 1)
Abuse	8 (5)	4 (3)	1 (< 1)	-
Alcohol	6 (4)	3 (2)	1 (< 1)	-
Drugs	2 (1)	2 (1)	1 (< 1)	-
Dependency	14 (9)	8 (5)	2 (1)	1 (< 1)
Alcohol	9 (6)	3 (2)	2 (1)	1 (< 1)
Drugs	6 (4)	7 (5)	1 (< 1)	-
Drug Induced Disorders	-	3 (2)	-	1 (< 1)
Eating Disorders	4 (3)	1 (< 1)	-	-
Anorexia Nervosa	1 (< 1)	1 (< 1)	-	-
Bulimia Nervosa	1 (< 1)	1 (< 1)	-	-
Binge Eating Disorder	2 (1)	-	-	-
Other Disorders	6 (4)	2 (1)	1 (< 1)	1 (< 1)
Psychotic Disorders	1 (< 1)	-	-	1 (< 1)
Psychotic Disorder NAO	1 (< 1)	1 (< 1)	-	-
Cyclothymia	1 (< 1)	-	-	-
Undifferentiated Somatoform Disorder	-	-	1 (< 1)	-
Pain Disorder	1 (< 1)	-	-	-
Impulse Control Disorders*	2 (1)	1 (< 1)	-	-

Note. 50 participants had missing diagnosis data.
*diagnoses were only assessed in the SCID but not in the M.I.N.I.
[a] $n = 150$ [b] $n = 172$

Table 3

Number of Mental Disorders across Groups (Assessed with the SCID, M.I.N.I. or Clinical Interview)

Number of Mental Disorders	Frequencies of the number of Mental Disorders	
	Participants with GTS[a]	Unaffected family members[b]
	n (%)	*n* (%)
0	62 (42)	158 (92)
1	41 (28)	7 (4)
2	17 (12)	5 (3)
3	18 (12)	0 (0)
4	9 (6)	1 (1)
5	2 (1)	1 (1)

Notes. [a] $n = 149$ [b] $n = 172$

Table 4

Intercorrelations Between Variables for Participants with GTS

	1	2	2a	2b	3	4	5	6	7
1. Age	--	-.11	-.10	-.09	.18	.11	-.08	.07	.11
2. YGTSS total		--	.88***	.88***	.11	.16	.20**	.07	-.20
2a. YGTSS motor			--	.55***	.14	.18	.16*	.13	-.31**
2b. YGTSS vocal				--	.05	.12	.19*	-.01	-.03
3. BAI					--	.66***	.43***	.48***	-.53***
4. BDI						--	.48***	.65***	-.63***
5. Y-BOCS severity							--	.52***	-.45***
6. Number of co-morbidities								--	-.54***
7. EQ VAS									--

Notes. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 5

Between-Group Differences on BAI, BDI and EQ VAS Scores

	BAI			BDI			EQ VAS		
Groups	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*
Control	5.07	6.17	41	5.92	6.20	40	80.21	13.71	92
Pure GTS	5.83	6.24	35	5.34	5.32	35	81.35	14.47	23
GTS+OCD	11.75	9.28	16	11.62	9.19	16	65.33	20.27	9
GTS+AD	11.30	9.53	10	11.60	6.48	10	73.20	5.45	5
Total	6.99	7.52	102	7.19	6.93	101	79.10	14.33	129