Gilles de la Tourette Syndrome and Disruptive Behavior Disorders: Prevalence, Associations, and Explanation of the Relationships

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Gilles de la Tourette syndrome and conduct disorder (CD) are both heterogeneous childhood onset conditions, and although patients with CD have been described in Gilles de la Tourette syndrome cohorts, little is known about the etiology of CD in Gilles de la Tourette syndrome or of the interrelationships. A cohort of 578 consecutive patients with Gilles de la Tourette syndrome was assessed using standard assessment protocols. A total of 13.5% of participants had only Gilles de la Tourette syndrome, whereas the rest had associated comorbidities and psychopathology. CD occurred in 14.5% of Gilles de la Tourette syndrome probands. These findings suggest that CD is not an integral part of Gilles de la Tourette syndrome but rather that CD in the context of Gilles de la Tourette syndrome is related to the presence of attention deficit hyperactivity disorder, as well as, and importantly, a family history of aggressive and violent behavior and forensic encounters.

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Gilles de la Tourette syndrome is a childhood onset neuropsychiatric movement disorder characterized by multiple motor tics and one or more vocal/phonic tics, lasting longer than a year.[1,2] The clinical features of Gilles de la Tourette syndrome include a wide range of behavioral symptoms[3–6] and are similar, irrespective of the country of origin, highlighting the biological nature of Gilles de la Tourette syndrome.[5,7,8]

The predominant co-occurring clinical comorbid conditions in Gilles de la Tourette syndrome include attention deficit hyperactivity disorder (ADHD), obsessive compulsive behaviors (OCB) and disorder (OCD),[9] and, to a lesser extent, autism spectrum disorder (ASD),[10] whereas the most common coexistent psychopathologies include depressive illness, depressive symptomatology, learning difficulties, personality disorder, oppositional defiant disorder, and conduct disorder.[11]

Conduct disorder (CD) is also a heterogeneous condition with associated comorbid conditions and psychopathologies. The essential features include aggression to people or animals, destruction of property, deceitfulness or theft, and serious violation of rules.[12] There are at least two main further subdivisions. These include the 1) callous-unemotional—usually aggressive type,[13–15] which is highly heritable,[14] and the 2) noncallous type, which is associated with significant emotional and behavioral regulation difficulties.[15] It must further be highlighted that the dimensional phenotype of CD is well recognized, with opppositional defiant disorder (ODD) considered to be a milder version of CD, characterized by poor compliance, defiance, and oppositional behaviors.

Examination of the literature to date suggests that only the Comings group[16–19] have consistently suggested a genetic relationship between Gilles de la Tourette syndrome and CD. Comings and Comings[16] assessed conduct symptoms in 246 patients with Gilles de la Tourette syndrome, 47 control subjects, 17 patients with attention deficit disorder, and 15 patients with attention deficit disorder with minor tics or a family history of Gilles de la Tourette syndrome. When the components were combined for a total conduct score, only one (2.1%) of the control subjects had a score greater than 13, and he had Gilles de la Tourette syndrome. By contrast, 35% of patients with Gilles de la Tourette syndrome had scores greater than 13, which is a significant difference ($p<0.0005$). The correlation coefficient between the total conduct score and attention deficit disorder score was 0.48. Although the presence of attention deficit disorder was an important factor in determining conduct in the patients with Gilles de la Tourette syndrome, other factors such as depression and "compulsive behaviors" also played a contributing role. There was little correlation between the total conduct score and the number of tics.[16] Comings et al[17] further examined polymorphisms of three dopaminergic genes namely the dopamine D2 receptor, dopamine β-hydroxylase, and dopamine transporter in Gilles de la Tourette syndrome probands, their relatives, and control subjects. Results indicated that each gene individually

showed a significant correlation with various behavioral variables and that for 16 of 20 of the behavior scores, there was a linear progressive decrease in the mean score, with progressively lesser loading for the three gene markers. The authors therefore concluded that Gilles de la Tourette syndrome, ADHD, stuttering, ODD, and CD and other behaviors associated with Gilles de la Tourette syndrome are polygenic, due in part to these three dopaminergic genes. In another study,[18] the same researchers suggested that the male predominance in Gilles de la Tourette syndrome suggested that the X-linked androgen gene might be involved in the etiology of the Gilles de la Tourette syndrome and its associated behaviors and suggested that genetic variation at the human androgen gene gene played a role in human externalizing behaviors. Budman et al[20] attempted to investigate the potential etiological factors of rage in 12 consecutive children with Gilles de la Tourette syndrome, and the results of this pilot study suggested that "rage attacks" in Gilles de la Tourette syndrome may well be related to the presence of comorbid disorders rather than the Gilles de la Tourette syndrome per se.[20]

Of importance is that tics and Tourette syndrome, without any other associated or comorbid conditions, occur in only 10% of most clinical populations[21] and those identified in epidemiological and community settings[22–24]. Furthermore, in some community studies, up to 30% of Gilles de la Tourette syndrome individuals have been shown to have three or more diagnoses[25]. In other words, approximately 90% of Gilles de la Tourette syndrome cases in any given setting have comorbid disorders or coexistent psychopathologies. In fact, recent investigations on the phenotype by principal component factor analysis are in agreement with this notion,[26,27] and such studies[28–31] have indeed demonstrated that there are many factors/phenotypes in Gilles de la Tourette syndrome. Several studies specifically found aggressive behaviors as part of one factor/phenotype.[29,31,32] Similarly, Eapen et al[33] in a principal component factor analysis study reported two factors: one was obsessionality and the other was anxiety and depression. A consistent finding from these studies is that one factor/phenotype consisted of "pure tics only," whereas the rest included comorbidities and other psychopathologies.

Although the exact pathophysiology of Gilles de la Tourette syndrome is still unknown, there is evidence suggesting a pivotal role for dopaminergic dysregulation within the cortico-striato-thalamo-cortical pathways.[34] This model is consistent with the tic-suppressing properties of antidopaminergic agents, which are considered to be the most effective pharmacological approach for patients with Gilles de la Tourette syndrome.[35] Interestingly, distinct structural changes have been found to underpin different clinical phenotypes in patients with Gilles de la Tourette syndrome, suggesting that the presence of comorbid behavioral problems, such as obsessive-compulsive symptoms, reflects the involvement of additional brain pathways.[36]

Thus, the findings of epidemiological, clinical, and factor/hierarchical analysis studies all suggest that "pure Gilles de la Tourette syndrome" consisting of simple tics is only found in about 10% of Gilles de la Tourette syndrome community and most clinical populations, and there is an urgent need to explore in depth the remaining 90% of patients with Gilles de la Tourette syndrome, where comorbidities and coexiting psychopathologies are present and often dominate both the clinical presentation and management. Given the increasing evidence about the role of disruptive behavioral disorders on the course and outcome of patients with Gilles de la Tourette syndrome, it is critical to address these issues in the overall management of Gilles de la Tourette syndrome. In this paper, we report on a Gilles de la Tourette syndrome cohort with particular focus on disruptive behavioral disorders such as ADHD, ODD, and, more specifically, CD.

METHODS

A cohort of 578 consecutive patients fulfilling DSM diagnostic criteria (all the comorbidities and psychiatric diagnoses were made using the DSM criteria, which was updated as per the current version depending on when the patients were assessed) for Gilles de la Tourette syndrome[1,2] and clinically assessed and examined by the first author, an experienced neuropsychiatrist (M.M.R.): standardized schedules were used including the National Hospital Interview Schedule[37] and the Yale Global Tic Severity Rating Scale,[38] and results were analyzed with the aim of examining the occurrences and interrelationships between Gilles de la Tourette syndrome and related disruptive or aggressive behavioral disorders, namely CD, ODD, and ADHD. Using the National Hospital Interview Schedule and regularly updated DSM criteria, histories were taken for evidence of CD, ODD, ADHD, OCD/OCB, tic severity (Yale Global Tic Severity Rating Scale score), the presence of coprolalia, family history of depression, and family history of forensic encounters. The latter was taken to reflect a family history for significant aggressive, violent, or other behaviors that resulted in conflict with the law. In addition, a broader history for aggressive behaviors, including rage attacks, in the proband was also taken: this included physical aggression to other people or property that resulted in damage but not necessarily in forensic encounters and was noted as present only when aggressive behaviors were considered significant in the social context (in the National Hospital Interview Schedule inventory-specific examples were given). Aggressive behavior was not simply a combination of ODD and CD categories. Self-injurious behavior (SIB) was "true Gilles de la Tourette syndrome SIB" such as self-pinching, punching, picking the skin or mucosa until it bleeds, etc. The SIB within the context of Gilles de la Tourette syndrome[39] was specifically inquired about and is usually associated with OCB in Gilles de la Tourette syndrome,[39] does not overlap with ODD/CD/ADHD, and is a distinct entity.[7] Thus, the rage, aggression, SIB, ODD, and CD were all different diagnostic and categorical entities in this sample. It was hypothesized that within the Gilles de la Tourette syndrome cohort, the presence of disruptive behavioral disorders would be associated with the presence of comorbid ADHD and also with aspects of the family history—particularly

forensic encounters—and not with tic (Gilles de la Tourette syndrome) variables. Tic severity was not hypothesized to be related to disruptive behavioral difficulties.

Ethical permission was obtained from the relevant institutions, and all patients (and parents in the case of young people) gave written informed consent. We only had 12 declinations for institutional review board/consent, and these patients were not used for the study. We thus had 578 consecutive patients with Gilles de la Tourette syndrome patients with institutional review board/consent from two institutions. With regards to coexisting medical conditions and exclusions, we elicited information using the National Hospital Interview Schedule (based on existing literature and clinical experience) about headache, essential tremor, epilepsy, diabetes, asthma, allergies, cardiac disease, brain trauma, and infections, as well as streptococcal infections. As would be expected from a cohort of this size, it is inevitable that there would be some missing data. This occurred when the items in the National Hospital Interview Schedule were left blank. No cutoff was used: a patient was assigned a diagnosis of CD, ODD, ADHD, anxiety disorder, major depressive disorder, bipolar disorder, etc. because they feature as distinct diagnostic categories in the National Hospital Interview Schedule. However, when using rating scales such as the Child Behavior Checklist, cutoff scores were used. Some of the missing data on certain scales were accounted for in the analysis using imputation.

A series of chi-square analyses, using Yates continuity correction, was used to examine the relationships between disruptive behavioral difficulties (CD and ODD) and other aspects of the proband's clinical phenotype and family history, specifically of ADHD, OCD/OCB, coprolalia, and a family history of forensic encounters and depression. Fisher's exact test was used in cases where cell sizes were small. In all cases, Phi values were reported to document the strength of the relationship between the variables. Phi values of 0.1, 0.3, and 0.5 are commonly thought to denote small, medium, and large effect sizes, respectively. Odds ratios were also reported for all comparisons. Differences in tic severity, as assessed using the Yale Global Tic Severity Rating Scale, between probands affected or not affected by CD, ODD, or aggressive behaviors were evaluated using independent samples t tests. Cohen's *d* effect sizes were reported for these comparisons, with *d* values of 0.2, 0.5, and 0.8 taken to reflect small, medium, and large effect sizes, respectively. Two-tailed test results are reported in all instances, with p values of less than 0.05 taken to denote statistical significance.

RESULTS

In this cohort of 578 patients withe Gilles de la Tourette syndrome (see Table 1 for descriptive characteristics of the sample), "Gilles de la Tourette syndrome only" or "pure Gilles de la Tourette syndrome" (tics only) was found in 13.5% of the sample, CD was present in 14.5% of Gilles de la Tourette syndrome cases, and aggressive behaviors was found in 29.5%. There were some cases of missing data as not all aspects of the clinical interview were completed with all participants, particularly with respect to family history variables.

In patients with Gilles de la Tourette syndrome, CD and ODD in the proband were significantly associated with ADHD: χ^2 (1, N=522) = 46.10, p<0.0001, Φ=0.30 and χ^2 (1, N=403) = 79.74, p<0.0001, Φ=0.45, respectively. In both the CD and ODD diagnosis groups, 80% of probands had ADHD, whereas in the CD- and ODD-negative groups, approximately one third of probands had ADHD. Family history for forensic encounters was associated with the presence of CD (p=0.04; Fisher's exact test; odds ratio = 4.12, 95% confidence interval = 1.00–18.01) but not ODD. In the CD diagnosis group, 64% of probands reported a family history for forensic encounters, whereas 36% did not. Coprolalia was associated with the presence of ODD, χ^2 (1, N=214) = 4.97, p=0.03, Φ=0.16), but not CD. OCD/OCB and family history for depression were not significantly associated with CD or ODD (Tables 2 and 3).

It was also noted that aggressive behaviors were more likely to occur in men than women, with 42% of men and 30% of women having such a history: χ^2 (1, N=352) = 4.02, p=0.045, Φ=0.11. Age (less than or equal to 18 years compared with greater than 18 years) was not significantly associated with the presence of a history of aggressive behaviors: χ^2 (1, N=404) = 2.34, p=0.13, Φ=0.08.

Tic severity was not significantly different between probands with or without CD or ODD (Table 4). However, a significant difference was evident between probands with a broader history of aggressive behaviors, such as rage attacks, relative to those without such a history: $t(391)=-2.12$, p=0.04, Cohen's d=0.23.

DISCUSSION

First, our finding that only 13.5% of the patients had "pure Gilles de la Tourette syndrome," whereas the remainder had associated comorbidities and psychopathology concurs with the findings from previous studies.[8,21] For instance, a clinical investigation[21] embracing 3500 clinic patients with Gilles de la Tourette syndrome worldwide demonstrated that at all ages, 88% of individuals had reported comorbidity/psychopathology. The most common was ADHD, followed by OCB and OCD. Anger control problems, sleep difficulties, coprolalia, and SIB only reached high levels in patients with comorbidity. Males were more likely than females to have comorbid disorders. This has also been shown to be true in community studies, with around 90% of individuals with Gilles de la Tourette syndrome having attracted other diagnoses (for studies, see ref. 5). Thus, both in clinical populations and in the community, only approximately 10% of people with Gilles de la Tourette syndrome have solely tics ("pure Gilles de la Tourette syndrome"/"Gilles de la Tourette syndrome-only"), and 90% have other psychiatric comorbid diagnoses or coexistent psychopathology.

Our finding that the coexistent CD in our patients with Gilles de la Tourette syndrome was associated with a positive family history of forensic encounters in the proband's family—taken to be a measure of aggressive, violent, or other

TABLE 1. Descriptive Characteristics of the Sample

Variable	Distribution
Age	Mean 25.4 years (SD 14.3)
Sex	Male 73%
Gilles de la Tourette syndrome only	13.5%
Comorbidities	
CD	14.5%
Aggressive behaviors	29.5%
ADHD	56%
Obsessive compulsive behaviors/ disorder	40%
Self-injurious behaviors	29.5%
Anxiety	43%
Autism spectrum disorder	10%
Learning disabilities/problems	18%
Depression	49%
Bipolar disorder	2%
Nonobscene socially inappropriate behaviors	8%
Coprophenomena	42%
Echophenomena	42%
Family history	
Family history for forensic encounters	29.5%
Family history for tics and/or Gilles de la Tourette syndrome	60%
Family history for obsessive compulsive disorder/behaviors/ symptoms	46%
Family history for ADHD	13%
Family history for depression	66%
Family history for anxiety	40%

Given some cases of missing data, percentages are calculated on different sample sizes (mean=360). ADHD, attention deficit hyperactivity disorder; CD, conduct disorder.

illegal behaviors that has resulted in a conflict with the law—is interesting. Further, CD in the Gilles de la Tourette syndrome proband was also significantly related to the presence of ADHD, which is in keeping with several previous studies that have demonstrated a link between ADHD and other disruptive behaviors, including CD and ODD,[40–47] and the findings from other studies showing that CD is linked to other factors, including ADHD and family history of CD, forensic encounters, or depression.[48,49] Thus, investigators have separated patients with Gilles de la Tourette syndrome on the basis of clinical symptoms into subgroups, specifically demonstrating significant differences between patients with and without ADHD. These studies have examined cohorts of children, including children with Gilles de la Tourette syndrome only, and compared them with other groups such as Gilles de la Tourette syndrome + ADHD, ADHD-only, and unaffected control subjects (for reviews, see refs. 4 and 5). These studies have generally indicated that patients with Gilles de la Tourette syndrome only appear to be similar to healthy control subjects, but are significantly different from those with Gilles de la Tourette syndrome + ADHD.[4,47,49]

In our patients, the DSM diagnoses of CD and ODD were used consistently, and the DSM was updated with the passage of time. Although the current DSM is DSM-V, for Gilles de la Tourette syndrome, it is not practically different from DSM-IV-TR. The major difference for Gilles de la Tourette syndrome was between DSM-IV and DSM-IV-TR. In the former, impairment and distress were stipulated, as were other features, but after several criticisms,[50] these criteria were dropped from DSM-IV-TR. Our diagnoses were always based on the clinical judgment, and there was no cut-off: that is, the patients were either given a positive diagnosis of CD, ODD, or ADHD, depending on whether or not they fulfilled the DSM diagnostic criteria. In our cohort, when we separated the patients into males and females, a history of violence/aggression was significantly associated with male sex. This is also in accordance with the recent literature,[51] where it has been reported that in a large sample, significantly more males were the perpetrators of violent crime and injury. In our

TABLE 2. Tourette Syndrome, CD, and Related Characteristics

Variable	Contingency table			Test value	p value	Phi	OR (95% CI)
ADHD		CD+	CD−	46.10[a]	<0.0001[b]	0.30	6.43 (3.49–11.98)
	ADHD+	66 (80%)	172 (39%)				
	ADHD−	16 (20%)	268 (61%)				
OCD/OCB		CD+	CD−	2.55[a]	0.11	−0.08	0.62 (0.34–1.11)
	OCD/OCB+	19 (24%)	147 (34%)				
	OCD/OCB−	59 (76%)	281 (66%)				
Coprolalia		CD+	CD−	0.94[a]	0.33	0.06	1.38 (0.75–2.53)
	Coprolalia+	27 (46%)	102 (38%)				
	Coprolalia−	32 (54%)	167 (62%)				
FH Forensic		CD+	CD−	Fisher's exact	0.04[c]	0.20	4.12 (1.00–18.01)
	FHForensic+	7 (64%)	37 (30%)				
	FHForensic−	4 (36%)	87 (70%)				
FH Depression		CD+	CD−	Fisher's exact	0.73	0.07	1.84 (0.34–13.02)
	FHDepression+	9 (82%)	88 (71%)				
	FHDepression−	2 (18%)	36 (29%)				

Percentages reported are for column totals. CD: conduct disorder; CI: confidence interval; FH Depression: family history for depression; FH Forensic: Family history for forensic encounters; OCD/OCB: obsessive compulsive behaviors/disorder; OR: odds ratio.
[a] Chi-square test with Yates continuity correction.
[b] $p<0.0001$.
[c] $p<0.05$.

TABLE 3. Tourette Syndrome, Oppositional Defiant Disorder, and Related Characteristics

Variable	Contingency table			Test value	p value	Phi	OR (95% CI)
ADHD		ODD+	ODD−	79.74[a]	<0.0001[b]	0.45	7.94 (4.80–13.19)
	ADHD+	122 (80%)	85 (34%)				
	ADHD−	30 (20%)	166 (66%)				
OCD/OCB		ODD+	ODD−	0.61[a]	0.43	−0.05	0.82 (0.52–1.30)
	OCD/OCB+	46 (31%)	89 (36%)				
	OCD/OCB−	102 (69%)	162 (65%)				
Coprolalia		ODD+	ODD−	4.97[a]	0.03[c]	0.16	1.95 (1.08–3.54)
	Coprolalia+	45 (52%)	45 (35%)				
	Coprolalia−	42 (48%)	82 (65%)				
FH Forensic		ODD+	ODD−	1.89[a]	0.17	0.14	1.83 (0.80–4.17)
	FHForensic+	18 (42%)	26 (28%)				
	FHForensic−	25 (58%)	66 (72%)				
FH Depression		ODD+	ODD−	0.03	0.87	−0.03	0.86 (0.36–2.06)
	FHDepression+	30 (70%)	67 (73%)				
	FHDepression−	13 (30%)	25 (27%)				

Percentages reported are column for column totals. CI: confidence interval; FH Depression: family history for depression; FH Forensic: family history for forensic encounters; OCD/OCB: obsessive compulsive behaviors/disorder; ODD: oppositional defiant disorder: OR: odds ratio.
[a] Chi-square test with Yates continuity correction.
[b] $p<0.0001$.
[c] $p<0.05$.

patients with Gilles de la Tourette syndrome, 29.5% had SIB, and this is in agreement with the literature,[39] where one third of 90 patients with Gilles de la Tourette syndrome was found to also have SIB. The SIB in that early Gilles de la Tourette syndrome cohort was significantly associated with OCB. Subsequently, Mathews et al[52] also described the SIB in nearly 300 patients with Gilles de la Tourette syndrome and showed that mild to moderate SIB was correlated with OCD, as well as the presence of obsessive and compulsive symptoms and the overall number of obsessions. Severe SIB was correlated with variables related to affect or impulse dysregulation, in particular, with the presence of episodic rages and risk taking behaviors. Both mild and moderate SIB was correlated with tic severity. In our patients, there was no correlation between tic severity and externalizing behaviors, and the latter were related to ADHD, which may breed true and independently from Gilles de la Tourette syndrome. These results are in keeping with the increasing literature suggesting that it is by and large the Gilles de la Tourette syndrome comorbidities and not Gilles de la Tourette syndrome per se that result in externalizing behaviors.

The most common comorbidity in Gilles de la Tourette syndrome is ADHD, with reported prevalence rates ranging between 35% and 90% in different studies (average, 60%), followed by OCB/OCD, occurring in 30%−50%. Gilles de la Tourette syndrome is overrepresented in special education cohorts, occurring in up to 25% of cases.[53] Similarly, ASD occurs in between 6% and 15% of probands.[54–57] Many other coexistent psychopathologies such as depressive symptoms, mood disorders, anxiety, aggression/rage attacks, and sleeping disorders have also been documented in patients with Gilles de la Tourette syndrome.[8,59]

A number of studies have investigated whether the symptoms of comorbid ADHD are the same in patients who do not present with tics and whether the presence of ADHD symptoms or tic severity has a greater impact on normal functioning in patients with Gilles de la Tourette syndrome. One of the earliest studies to examine this issue compared patients in four groups: Gilles de la Tourette syndrome, attention deficit disorder, attention deficit disorder and epilepsy, and control subjects in relation to their perceptual, motor, and neuro-maturational competence.[60] The results found patients with Gilles de la Tourette syndrome to be similar to the normal/healthy controls, whereas both the attention deficit disorder only and attention deficit disorder-epilepsy groups had lower (worse) scores. This and other subsequent studies have shown that comorbid ADHD symptoms rather than tics per se are associated with social, behavioral, and educational problems in patients with Gilles de la Tourette syndrome.[8] Similarly, studies that examined the impact of other behavioral disorders in the context of Gilles de la Tourette syndrome found that aggression, rage, ODD, and CD also have a profound negative impact on the patient's ability to function (physically, physiologically, emotionally, and academically). For example, aggressive behavior in

TABLE 4. Differences in Tic Severity Between Patients With Tourette Syndrome Affected and Not Affected by Comorbid Disruptive Behavioral Problems

	Mean	Standard deviation	N	Test value	p value	Cohen's *d*
CD+	40.93	20.9	61	0.16	0.87	0.02
CD−	41.4	21.0	316			
Aggressive behaviors+	45.17	19.29	133	−2.12	0.04[a]	0.23
Aggressive behaviors−	40.42	21.85	260			
ODD+	38.73	20.72	128	0.59	0.55	0.07
ODD−	40.15	21.28	197			

CD: conduct disorder; ODD: oppositional defiant disorder.
[a] $p<0.05$.

children with Gilles de la Tourette syndrome and comorbid ADHD/OCD was investigated in a Canadian study,[40] which found that "Gilles de la Tourette syndrome only" children did not statistically differ from healthy control subjects in the measures of aggressive behavior or conduct problems. However, children with comorbid ADHD or OCD were more likely to have aggression and conduct problems in either home or school environments in comparison to children with "Gilles de la Tourette syndrome only". Carter and colleagues[42] studied the social and emotional adjustment of children with Gilles de la Tourette syndrome, assessing the impact of comorbid ADHD, and highlighted the increased levels of internalizing behaviors, as well as a broader range of social-emotional difficulties associated with comorbid ADHD. Another study[43] assessed the impact in terms of functional impairment of disruptive behavior in children with Gilles de la Tourette syndrome and comorbid ADHD and found that the presence of comorbid ADHD in children with Gilles de la Tourette syndrome is associated with high rates of delinquent behavior, resulting in significant functional impairment. It is often the presence of the comorbidities and psychopathologies, rather than the presence or severity of tics, that seem to be related to the psychosocial and psychological functional impairment associated with Gilles de la Tourette syndrome.

The impact of tics, ADHD, and OCD symptoms on internalizing (i.e., anxiety/depression) and externalizing behaviors (i.e., aggression) in patients with Gilles de la Tourette syndrome has received recent attention. In a study of patients with Gilles de la Tourette syndrome by Pollak and colleagues,[61] it was observed that tic severity, inattention, hyperactivity, and impulsivity were predicted by externalizing behaviors (OCD symptoms being unrelated), whereas internalizing behaviors were predicted by inattention and OCD symptoms (tic severity and hyperactivity/impulsivity being unrelated). The results of this investigation suggested that tics and comorbid conditions independently contribute to the internalizing and externalizing psychopathology in Gilles de la Tourette syndrome. In a cohort of child psychiatric patients who had Gilles de la Tourette syndrome with comorbidities, patients with disruptive behavioral disorders were found to have significantly higher mean scores on the Child Behavior Checklist than patients without disruptive behavioral disorders on the externalizing scale, social problems, attention problems, delinquent, and aggression scales. Comorbidity of anxiety disorders was not related to the Child Behavior Checklist scores.[44]

Only one study from our group (Haddad et al[47]) has examined these phenomena in adults, comparing patients with Gilles de la Tourette syndrome only with those with Gilles de la Tourette syndrome + ADHD. The patients with combined Gilles de la Tourette syndrome + ADHD had significantly more depression, anxiety, OCB, and maladaptive behaviors (e.g., aggression to property, attacking other people, having had forensic encounters, alcohol/drug abuse). The patients with Gilles de la Tourette syndrome + ADHD were significantly more likely to have copro- and echo-phenomena and reported significantly more relatives with a history of ADHD than the "Gilles de la Tourette syndrome only" group. These findings further suggest that many of the maladaptive behaviors encountered are due to the ADHD comorbidity and not Gilles de la Tourette syndrome per se. They also support suggestions from research in young people that individuals with "Gilles de la Tourette syndrome only" and individuals with Gilles de la Tourette syndrome + ADHD are different from each other. Thus, in the context of the present study, it seems that the antisocial disorders in childhood can result in antisocial disorders in adults, including aggression and forensic encounters, and that these are related to ADHD in the proband and not Gilles de la Tourette syndrome per se.

With regard to depression (an internalizing behavior), in the present cohort, 49% of patients with Gilles de la Tourette syndrome had a diagnosis of depressive disorder. This is in agreement with the literature suggesting that patients with Gilles de la Tourette syndrome are often depressed. In a review, Robertson[62] documented that in 16 uncontrolled studies in specialist centers examining mood changes among 5409 patients with Gilles de la Tourette syndrome, depressive symptomatology, dysthymia, mood swings, and/or major depressive disorder or depressive illness were found in 13%–76%. The main diagnosis was that of major depressive disorder. In addition, 13 controlled investigations also found both young people and adults with Gilles de la Tourette syndrome (N=741) to be significantly more depressed than age- and sex-matched healthy control subjects using standardized measures. The correlates of the depression were increasing age, tic severity, and the presence of ADHD, OCD/B, and, surprisingly, CD.[48]

It is true that in the DSM evolving criteria of, for example, CD, there is some ambiguity. For example the callous-unemotional-usually aggressive subtype falls within the limited prosocial category (DSM-V, 2013). It encompasses the aggressive type listed in the DSM-III-R but was removed in DSM-IV and is present in ICD 10, but not ICD 9. Thus, the names in the various classifications may well be somewhat artificial categories and may clearly change. In the description of the comorbidities and coexistent psychopathology in our cohort, we used DSM criteria, updated with the passage of time, namely DSM-111, DSM-111-R, and DSM-IV-TR (but not DSM-IV for Gilles de la Tourette syndrome as we disagreed with the criteria[50]), whereas DSM IV was used for comorbidities.

Our finding in the present study that CD in the Gilles de la Tourette syndrome proband is related to a positive family history of aggressive/violent behaviors in the family is in agreement with studies that have suggested that some types of CD including the callous-unemotional-usually aggressive type,[13,14] which emerges in early childhood and exhibits specific ties to negative emotionality and executive dysfunction, is highly heritable.[14] However, genetic predisposition to Gilles de la Tourette syndrome and genetic predisposition to CD and ODD seem to be occurring independently in those families. Similar findings exist for at least some forms of ADHD as

segregating independently to Gilles de la Tourette syndrome.[63] In this regard, it is also noteworthy that the genetic predisposition to aggression has been reported to be greatly affected by specific genetic variants, including functional polymorphisms in both the monoamine oxidase A gene and serotonin transporter due to the relationship between these variants and the limbic system involvement in aggressive people.[64] The monoamine oxidase A genotype is associated with aggressive behavior, especially in interaction with childhood trauma or other early adverse events, particularly in men: male carriers of monoamine oxidase A-L (low-expressing variant) with childhood trauma or other early adverse events seem to be more aggressive, whereas female carriers with the high-expressing variant (monoamine oxidase A-H) with childhood trauma/early adverse events may be more aggressive.[65] It would seem that CD occurring in the context of Gilles de la Tourette syndrome is linked to gene–environment interactions in these families that are segregating independently to the "Gilles de la Tourette syndrome-genetic" influences. This coupled with the finding that the presence of CD in the proband was not significantly related to tic severity, the presence of coprolalia, the presence of OCB/OCD, or a family history of depression seems to suggest that the CD is not "Gilles de la Tourette syndrome or tic specific" or related to other frequently co-occurring disorders such as OCB/OCD, which are generally regarded as genetically linked and integral to Gilles de la Tourette syndrome.[66] The finding of a positive association between coprolalia and ODD may seem to argue somewhat against this hypothesis; however, we would contend that given the absence of an association with coprolalia in the CD group, it is likely that coprolalia was effectively masquerading as a feature of oppositionality in the ODD group. Our finding of greater tic severity in the group with a history of aggressive behaviors, including rage attacks, is in keeping with existing studies. This suggests that, although CD and ODD per se are not related to tic severity, certain dysregulated and impulsive aggressive behaviors may indeed be overrepresented in cases where Gilles de la Tourette syndrome symptoms are more severe and especially when associated with coprolalia. This could be an important area for future research.

Relatively few studies have specifically examined the significance of CD in the context of Gilles de la Tourette syndrome. Kurlan et al[67] documented nonobscene socially inappropriate behaviors in Gilles de la Tourette syndrome for the first time and interestingly reported that nonobscene socially inappropriate behaviors were associated with CD and ADHD (i.e., impulse control) but not with OCB/D. Snijders et al[48] studied depressive symptomatology in adult patients with Gilles de la Tourette syndrome and reported an association between childhood CD and depressive symptomatology, as measured by the Beck Depression Inventory. Both these studies argue against an intimate relationship between CD and Gilles de la Tourette syndrome. The only exception is the suggestion of a relationship between Gilles de la Tourette syndrome and CD by Comings et al,[18] who demonstrated an association between the androgen receptor gene with ADHD and CD in both Gilles de la Tourette syndrome and control subjects. A suggested genetic relationship between Gilles de la Tourette syndrome and CD[17] has, however, never been replicated.

Thus, our current findings are in agreement with the argument that CD is not an integral part of Gilles de la Tourette syndrome. When considered together with our findings that ODD and CD in the proband were associated with the presence of ADHD, and in the case of CD with a family history of forensic encounters, the results imply that the Gilles de la Tourette syndrome gene(s) are not responsible for aggressive/violent behaviors.

Our results would thus suggest for the first time that the Gilles de la Tourette syndrome and CD are not genetically related, but that the CD-type externalizing behaviors are genetically related and breed true within families. However, in the absence of a positive family history, sociocultural and environmental determinants are known to be important in CD. This was demonstrated in a cross-cultural study by Eapen and Robertson,[68] who examined the presentation and correlates of Gilles de la Tourette syndrome in two distinctly different populations: the United Kingdom and the United Arab Emirates. Results indicated the similarity of core Gilles de la Tourette syndrome symptoms including the rates of ADHD and OCD between the two populations, but the rates of ODD and CD were significantly higher in the UK cohort, but were not related to any other clinical features or severity of Gilles de la Tourette syndrome, suggesting socio-cultural origins. Thus, the phenotypic heterogeneity seen in Gilles de la Tourette syndrome and the presence of associated comorbidities and psychopathology are likely to be determined by a complex interplay of genetic and environmental factors. Another study that is worth citing in this context is that of Rizzo et al,[69] who examined the long-term clinical course of Gilles de la Tourette syndrome and in fact reported changing phenotypes. They retrospectively studied 100 patients with Gilles de la Tourette syndrome and reassessed the patients 10 years after their initial assessment. Their results showed that those who presented with "Gilles de la Tourette syndrome only" or "pure Gilles de la Tourette syndrome" had a good long-term prognosis, with 58% maintaining the same phenotype. Those patients who presented with Gilles de la Tourette syndrome and comorbidity (ADHD and/or OCD) tended not only to change the phenotype, but also had a poorer prognosis, required medication, and had reduced quality of life, all being due to the comorbidities.

Thus, understanding the nature, occurrence, and course of comorbidities in the context of Gilles de la Tourette syndrome is critical. Our findings suggest that the CD and ODD encountered in patients with Gilles de la Tourette syndrome are not an integral part of Gilles de la Tourette syndrome but are related to the presence of ADHD in the proband and also a positive family history of forensic encounters which in turn has both etiological and management implications.

LIMITATIONS

Despite the fact that we have a large sample, there are limitations in our study, consistent with any naturalistic clinic-based study, with regard to data collection and missing data. We are no longer able to access the original case notes and therefore we inevitably have missing data. The current study would also have been enhanced by the inclusion of greater sample sizes for certain comparisons. However, detailed assessment of the Gilles de la Tourette syndrome phenomenology and psychopathology using standardized protocols adds to the strength of this study. Further, data on the association with other medical comorbidities are less extensive in our sample. For example, originally epilepsy was rarely reported in Gilles de la Tourette syndrome cohorts (Eapen et al[69]) or only noted as an incorrect previous differential diagnosis,[27] although this may no longer be true.[70] Rizzo et al[71] questioned the triple comorbidity of Gilles de la Tourette syndrome, ADHD, and epilepsy in eight patients with all three disorders.

CONCLUSIONS

We suggest that aggressive delinquent externalizing behaviors epitomized by CD occur in patients with Gilles de la Tourette syndrome but are not related to any Gilles de la Tourette syndrome variables. They are, however, significantly associated with a positive family history of forensic encounters and violent, aggressive behaviors and also with a diagnosis of ADHD in the patient.

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