Special Article

Gilles de la Tourette Syndrome: An Overview

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Abstract

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental condition characterized by multiple motor and vocal tics with a chronic course. With its multifaceted range of symptoms, GTS lies at the crossroads of neurology and psychiatry. This review article provides an outline of GTS, encompassing its extended clinical phenomenology, pathophysiology, and treatment options. Tics are the most common hyperkinetic manifestations in childhood, and the majority of patients present with comorbid behavioral conditions, such as obsessive-compulsive disorder, attention-deficit hyperactivity disorder, anxiety, and affective symptoms. Most patients report that their tics are preceded by sensory experiences (premonitory urges), i.e., unpleasant sensations characterized by pressure, tension, tightness, pain, itch, or vague inner discomfort. Tics can be temporarily suppressed and delayed for seconds to minutes, at the expense of mounting inner tension until the subjective feeling becomes unbearable, and the tic must be released. A better understanding of the mechanisms at the root of tic production can pave the way to the development of more effective treatment interventions for patients with GTS in order to improve their health-related quality of life (QOL). Specific instruments for measuring health-related QOL based on standardized assessments allow to appraise the impact of both tics and behavioral comorbidities and tailor treatment strategies to individual patients.

Keywords: Behavior, Gilles de la Tourette syndrome, health-related quality of life, premonitory urges, tics

Introduction

Gilles de la Tourette syndrome (GTS) was famously described as a complex tic disorder by the French physician Georges Gilles de la Tourette.[1] Although Gilles de la Tourette's landmark paper dates back to 1885, GTS is still poorly understood and largely underdiagnosed.[2] Current epidemiological studies show that GTS has a prevalence ranging between 0.4% and 1% across all cultures.[3,4] Tics as isolated symptoms are known to be more common than GTS, potentially affecting around 5% of the general population, albeit prevalence figures are highly variable.[5,6] Overall, the prevalence of tic disorders in the pediatric population could be around 3%, with declining prevalence figures in adulthood.[3,7]

GTS is a neurodevelopmental disorder characterized by the presence of multiple tics with a chronic course: according to the current diagnostic criteria, at least two motor tics and one vocal tic.[8-10] Tics are defined as rapid, sudden, involuntary, recurrent, nonrhythmic movements and vocalizations, usually accompanied by specific behavioral symptoms and considered to be the result of altered neurodevelopmental pathways.[11,12] In consideration of its multifaceted clinical features, it is not surprising that GTS is present in both neurological and psychiatric classification systems, such as those developed by the Movement Disorders Society[13] and the American Psychiatric Association.[8] Furthermore, the clinical heterogeneity of GTS makes it a challenging condition in terms of identifying therapeutic targets and implementing effective treatment interventions aimed at improving patients' health-related quality of life (QOL).[14,15]

Progress in research over the last few years has led to a better understanding of the sensorimotor processes at the basis of GTS, paving the way for the development of evidence-based therapeutic interventions tailored to the needs

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of individual patients. Key advances in translating research findings into clinical settings have been facilitated by the availability of disease-specific instruments for the assessment of health-related QOL in both children and adults with GTS.[16,17] The present article provides an overview of GTS, encompassing its diagnostic criteria, epidemiology, clinical features, behavioral comorbidities, etiology, pathophysiology, and treatment options.

Diagnostic Criteria and Classification of Tics

Individuals affected by chronic tic disorders characteristically exhibit a tic repertoire which is both dynamic and stereotyped, with the re-occurrence of specific tic types at multiple life stages.[11,12] Tics have an average age at onset of 6–8 years and are reported three to four times more frequently by males than females.[18] In the majority of patients, motor tics develop earlier than vocal tics, and the most frequently observed motor tic at onset is eye blinking.[19]

Both motor and vocal tics can be simple or complex.[20,21] Commonly reported simple motor tics include eye blinking, eye rolling, face grimacing, mouth opening, neck jerking, shoulder shrugging, abdominal contractions, arm stretching, and kicking. Among the most frequently reported simple vocal tics are grunting, sniffing, coughing, throat clearing, humming, snorting, and squeaking. Complex motor tics usually develop after the onset of simple motor tics and are characterized by the engagement of several muscular segments, often resembling intentional actions. Complex motor tics can result in copropraxia (involuntary production of obscene gestures), palipraxia (repetition of own movements a set number of times or until they feel "just right"), and echopraxia (imitation of others' movements). Complex vocal tics often include recognizable and meaningful words, resulting in coprolalia (involuntary swearing), palilalia (repeating own words and movements a set number of times or until they feel "just right"), and echolalia (repeating others' words). Other complex vocal tics include the production of apparently random words and animal sounds. Complex tics involving coprophenomena are characteristically accompanied by attempts at camouflaging and can be followed by sincere apologies. Despite their extensive coverage in the media and in lay literature, coprophenomena are not included within the current diagnostic criteria for any tic disorder. It has been estimated that these socially inappropriate symptoms affect a minority of patients with GTS, about 10% in the community and up to 30% in specialist clinics, where more severe and complex cases tend to be referred.[16,22]

All primary tic disorders are currently classed as hyperkinetic movement disorders that develop before 18 years of age.[8] Similar to GTS, persistent motor or vocal tic disorders are characterized by the chronic presence of motor or vocal tics, but their diagnostic criteria reflect the presence of only one category of tics. In the current classification system (Diagnostic and Statistical Manual of Mental Disorders. 5th Edition), the diagnosis of "transient tic disorder" was replaced by "provisional tic disorder," reflecting the uncertainties about the evolution of tic symptomatology, that is, if newly developed tics will improve and disappear or become chronic [Table 1].

Sensorimotor Components of Tics

Patients with GTS can exhibit a variety of tics with different degrees of severity; some tics can be mild and hardly noticeable, whereas other tics can be forceful and compel the person to produce violent movements or loud noises, resulting in physical and/or psychological distress. Both categories of tics (motor and vocal) typically fluctuate over time, following a waxing and waning course, usually with a peak in severity during early teenage years and improvement in adulthood.[23-25] Of note, environmental tic-modulating factors have been consistently reported in clinical research.[9,10,14] Anxiety, stress, excitement, tiredness, and boredom are among the conditions known to induce and exacerbate tics. Tics can also be triggered by talking about them or by seeing other persons with tics. In contrast, when patients are engaged in certain activities requiring both mental and physical effort, such as playing music or sports, tic severity and/or frequency can improve.[26]

Most patients with GTS report that tics are preceded and/or accompanied by specific sensations that are often referred to as "premonitory urges."[27] Premonitory urges are unpleasant sensory experiences characterized by pressure, tension, tightness, pain, itch, or vague inner discomfort, often localized in the muscular districts involved by tics.[28,29] These sensations have been suggested to be similar to the sensations preceding an itch or a sneeze: tic expression provides temporary relief from premonitory urges, similar to the relief that follows scratching an itch or sneezing.[30] Importantly, most patients with GTS can voluntarily suppress their tics for a variable length of time (from a few seconds to several minutes). However, tic suppression is typically accompanied by a distressing sensation of mounting inner tension, until the tension caused by the

Table 1: Key diagnostic features of primary tic disorders (onset before 18 years)

Tic disorder	Presence of vocal tics	Presence of motor tics	Chronic course
GTS	Yes (at least 1)	Yes (at least 2)	Yes
Persistent motor tic disorder	No	Yes (at least 1)	Yes
Persistent vocal tic disorder	Yes (at least 1)	No	Yes
Provisional tic disorder*	Yes/no	Yes/no	No

*Patients with provisional tic disorder present with at least 1 motor or vocal tic. GTS: Gilles de la Tourette syndrome

premonitory urge becomes unbearable and the tic has to be released.[31,32] Recent research has provided confirmation to the clinical observations that premonitory urges are related to interoceptive awareness.[33,34]

The mechanisms underlying tic expression are complex and poorly understood, reflecting the blurred distinction between voluntary and involuntary movements. The compelling nature of premonitory urges leads to repetitive behaviors that are performed against the individual's will; however, the decision to release the tic is usually perceived as voluntary.[35,36] Therefore, it has been suggested that the tics released in response to specific urges might be thought of as "unvoluntary," to indicate a third category of movements that is halfway between voluntary and involuntary actions.[37] The simultaneous presence of both voluntary and involuntary components in the expression of tics is in line with the hypothesis that tics may have the same neurophysiologic substrate as voluntary acts, even though they are misperceived as being involuntary. This interpretation supports the view of GTS as a hyperkinetic movement disorder affecting the conscious experience of action.[36,38]

The assessment of sensory experiences is of central importance to the diagnosis of GTS, which remains essentially clinical. Based on the presence and characteristics of the premonitory urges, clinicians can reliably discriminate GTS from other hyperkinetic movement disorders.[39] Moreover, patients' awareness of their urges to tic is a prerequisite for some of the most frequently used behavioral treatment approaches for tic management, such as habit-reversal training.[40] Over the last few years, there has been progress in our understanding of the neural correlates of premonitory urges, as neuroimaging studies have shown patterns of activation in extramotor regions, including the insula and the cingulate cortex, that are implicated in the conscious monitoring of the internal environment.[17,34,41,42]

Comorbid Behavioral Symptoms

It has been reported that in about 90% of cases, patients with GTS present with behavioral symptoms in addition to tics[43-45] [Table 2].

Importantly, GTS is not related to intellectual disability; on the contrary, among individuals with GTS, there are persons with exceptional talents in different fields.[46] Obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD) are the most commonly associated behavioral comorbidities. Prevalence figures for comorbid ADHD in children and adolescents with GTS vary from 38% (in community settings) to over 60% (in specialist clinics).[43] The diagnosis of comorbid ADHD can be challenging and requires in-depth assessments by experienced clinicians: by definition, tics implicate restlessness and hyperactivity, and the continuous effort to suppress tics can interfere with the patient's ability to sustain concentration.[47] Distressing and time-consuming repetitive behaviors (compulsions) and/or thoughts (obsessions) are commonly reported by patients with GTS, with prevalence figures for comorbid OCD ranging from 11% to 66%.[48] Of note, converging evidence from multiple clinical studies has shown that patients with tics tend to report specific obsessive-compulsive symptoms, which are different from the ones described by patients with OCD only. For instance, evening-up behaviors, obsessional counting (arithmomania), ordering, concerns for symmetry, and "just right" perceptions have been shown to be more prevalent in patients with GTS, whereas concerns for contamination and cleaning/washing rituals have been shown to be more prevalent in patients with pure forms of OCD.[48] Such phenomenological differences are likely to reflect different pathophysiological underpinnings and have clinically relevant implications for both diagnosis and treatment.

Patients with GTS often report problems with impulse control, anxiety, and affective symptoms.[49-51] The relationship between GTS and its behavioral comorbidities is not fully elucidated. For example, the relationship between GTS and depression is thought to be multifactorial. It is not surprising that living with a potentially disabling and stigmatizing condition can lead to depression. Moreover, disruption in the corticostriatal system, especially within monoaminergic pathways, has been associated with both motor dysfunction and emotional dysregulation. Finally, treatment of tics with antidopaminergic agents can exacerbate affective symptoms.[52] With regard to autism spectrum disorder, it has been shown that there is a high frequency of both tics and stereotypies in patients with pervasive developmental disorders.[53] Clinical data show that there might be an association between GTS and specific personality disorders, although the relationship between tics and personality traits is likely to be mediated by the presence of psychiatric comorbidities.[54]

Both diagnostic approaches and treatment strategies for patients with GTS are complicated by the presence of comorbid behavioral conditions. From a clinical perspective, it has been proposed to differentiate different groups of patients with GTS, based on neurobehavioral presentations and care needs, as

Table 2: Examples of comorbid behavioral symptoms in patients with Gilles de la Tourette syndrome

Behavioral symptoms	Examples
Obsessive-compulsive behaviors	Counting, concerns of symmetry, "just right" or evening-up behaviors
Attention-deficit hyperactivity symptoms	Lack of concentration, restlessness, and difficulty completing tasks
Affective symptoms	Mood swings, feelings of being isolated, and hopelessness
Anxiety symptoms	Generalized anxiety, panic attacks, and feelings of self-consciousness in public

follows: patients with motor and vocal tics only ("pure" GTS); patients who report additional complex tics and tic-related symptoms ("full-blown" GTS); and patients with behavioral comorbidities (GTS "plus"). In particular, the therapeutic management of this last group of patients poses considerable challenges and requires the input of experienced clinicians.[21,55]

Little is known about the factors capable of influencing the long-term prognosis of patients with GTS. A few longitudinal studies have investigated the influence of tic severity and behavioral comorbidities on health-related QOL.[24,56,57] Recently developed disease-specific tools to measure health-related QOL in patients with GTS of all ages (GTS-QOL and C and A-GTS-QOL) can assist clinicians in the assessment of the impact of both tics and related behavioral symptoms on patients' lives.[58,59] A more detailed understanding of the neurobehavioral spectrum of GTS can promote informed decisions about treatment interventions and contribute to an improved assessment of therapeutic outcomes.

Etiological and Pathophysiological Mechanisms

Both genetic and environmental factors are thought to have a role in the etiology of tics. GTS is a complex neurodevelopmental disorder characterized by a high clinical heterogeneity, suggesting an equally complex interplay of pathophysiological mechanisms. In particular, it has been proposed that GTS may originate from the interaction between heterogeneous genetic vulnerability patterns and environmental factors, such as pre- and perinatal difficulties and postinfectious autoimmunity.[60,61]

Genetic tests do not currently play any role in the diagnostic process of GTS; however, both twin and family studies have provided evidence that GTS is one of the most heritable, non-Mendelian neurodevelopmental disorders, characterized by a heritability risk of 0.77.[62-64] The risk can be higher and more accurately predictable in families where specific chromosomal abnormalities have been detected.[65-68]

Although the role of autoimmune mechanisms in GTS has been questioned, the hypothesis that a subgroup of patients with GTS presents with a set of conditions called "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" is still under investigation.[69,70] The findings of epidemiological studies have shown that pregnancy-related noxious exposures (especially maternal smoking and prenatal life stressors) may be more frequent in pregnancies of children who will develop GTS.[71] The mechanisms by which pre- and perinatal adversities could lead to the development of GTS or tic severity are unknown, but have been suggested to be possibly related to changes in the dopaminergic system as a result of early brain injury.[72]

The precise brain mechanisms underlying tic expression are still largely unknown. Dopaminergic dysfunction in the cortico-striato-cortico-frontal circuitries has been suggested to play a key role in the pathophysiology of GTS, though other neurochemical systems (in particular histaminergic and noradrenergic pathways) have been proposed to be possibly involved.[73-75] The possible effects of brain plastic remodeling in response to both tic expression and tic suppression across the lifespan are among the brain mechanisms underlying GTS that deserve further investigation.[76]

Treatment Approaches

Pharmacotherapy, behavioral strategies, and functional neurosurgery (deep brain stimulation [DBS]) have been used as therapeutic strategies for GTS. In 2011, the European Society for the Study of Tourette Syndrome published the first set of evidence-based guidelines on four key aspects of GTS care, namely assessment, pharmacological therapy, behavioral and psychosocial interventions, and DBS.[77-80] The European guidelines were complemented by expert consensus on the optimal management of GTS.[81,82] At around the same time, the Canadian guidelines for the evidence-based treatment of tic disorders were published.[83,84] After these collaborative enterprises, experts from the United States proposed a practice parameter for the assessment and treatment of children and adolescents with tic disorders,[85] and the International Deep Brain Stimulation Database and Registry Study Group published a set of recommendations on the use of DBS in GTS.[86] In 2016, a team of experts based in the United Kingdom published a health technology assessment on the treatment strategies for tics in children and adolescents with GTS.[87] More recently, an international group of experts developed the American Academy of Neurology practice guideline recommendations on the treatment of tics in people with GTS and other chronic tic disorders.[88,89]

The most effective treatments for tics are pharmacological agents, although patients' response is characterized by high interindividual variability. Anti-tic medications can be divided into antidopaminergic and nonantidopaminergic agents. First-generation antidopaminergic medications (neuroleptics) such as haloperidol have long been employed, despite the high prevalence of adverse effects (sedation, depression, metabolic adverse effects, and extrapyramidal symptoms). Selected second-generation antidopaminergic medications (atypical antipsychotics) such as risperidone have been shown to have similar efficacy but better tolerability (especially in terms of extrapyramidal symptoms) compared to neuroleptics. Aripiprazole, a partial dopamine agonist that is sometimes referred to as a third-generation antidopaminergic agent, is characterized by a particularly favorable efficacy-to-tolerability ratio and is currently included among the first-line pharmacological options for the treatment of tics. The presynaptic dopamine depletor tetrabenazine is frequently employed as a second- or third-line option because of its adverse effects. Overall, tolerability is often the main limiting factor for the use of antidopaminergic agents in patients with GTS.[90] With regard to nondopaminergic agents, alpha-2 agonists (clonidine and guanfacine) have proven useful both for the treatment of tics and ADHD symptoms.

Pharmacological studies have indicated that other medications, such as antiepileptic drug topiramate, can have good efficacy against tics.[88,89,91]

With regard to the behavioral strategies for tic management, habit-reversal training and exposure and response prevention are among the most extensively investigated techniques.[92,93] Habit-reversal training is a method based on sustained resistance to the premonitory urge with the help of tic-specific competing responses; it is a key component of a broader treatment intervention called comprehensive behavioral intervention for tics.[94] The role of cognitive behavioral therapy in patients with GTS might be particularly relevant, in consideration of the neurobehavioral spectrum that characterizes most clinical presentations.[95-97]

More invasive treatment approaches, such as DBS, have been used in severe and refractory cases of GTS. Among the potential brain targets, the pars interna of the globus pallidus and the centromedian–parafascicular nuclei of the thalamus have been shown to be associated with more favorable outcomes.[86] There are both similarities and differences in the perspectives on the use of DBS for GTS across different specialist centers and countries.[98,99]

Conclusion

In consideration of its multifaceted range of symptoms, including both motor and nonmotor features, GTS lies at the crossroads of neurology and psychiatry. There is growing evidence that GTS is not a unitary condition, as originally believed, but a cluster of different clinical phenotypes. An improved understanding of the multiple clinical presentations of GTS results in an increased attention to their individual care needs. Operationalization and standardization of both assessment and treatment strategies, promoted by the publication of national and international sets of guidelines and by the development of disease-specific instruments to evaluate health-related QOL, have considerably improved the standards of care for this patient population. A number of questions remain open for future research. These include the characterization of phenotype–genotype correlations and the elucidation of the complex interplay between genetic and environmental factors. A better understanding of these aspects will be of key importance to implement more accurate diagnostic protocols and more effective treatment interventions to improve the quality of patients' lives.

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Conflicts of interest

There are no conflicts of interest.

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