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REVIEW OF GILLES DE LA TOURETTE SYNDROME

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REVIEW OPEN ACCESS

ABSTRACT

Gilles de la Tourette syndrome is a neurodevelopmental disorder characterized by chronic motor and vocal tics that develop in childhood. The etiology of this disorder is complex and multifactorial with the final result being functional and structural brain anomalies and the involvement of cortico-striato-thamo- cortical neural circuits and neurotransmitters. GTS is considered polygenic and also be non-genetic, such as perinatal events and immunological factors, which contribute to heterogeneous manifestations. GTS generally has onset before 10 years of age, exhibit a waxing and waning clinical course, with peaks in adolescence and generally remits in adulthood. Diagnosis based on DSM-5 is made through history taking, physical and psychiatric examination using validated assessment instruments. Management is based on clinical and severity, including psychoeducation, behavioral therapy, and pharmacology to deep brain stimulation.

Keywords: Tourette syndrome, pathophysiology, management.

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INTRODUCTION

Gilles de la Tourette syndrome (GTS) is a complex idiopathic neuropsychiatric disorder with unclear pathophysiological mechanisms. This neurodevelopmental disorder is quite common with a prevalence up to 1% world's population.[1] GTS is phenotypically heterogeneous and manifests as motoric and behavioral disorders with an onset before adulthood with tics become the main clinical feature. Tics was complex disorder because it typically exhibited episodic symptoms, improvement and worsening, often preceded by a premonitor somatosensory sensation before an attack occurs.[2] This disorder is often comorbid with obsessive-compulsive disorder (OCD) and Attention deficit and hyperactivity disorder (ADHD), so it is said to be an epigenetic spectrum disorder, which is a neurodevelopmental spectrum disorder (neurodevelopmental) with a complex genetic profile.[3] GTS has a childhood onset, occurs disproportionately in male, and shows spontaneous symptomatic attenuation in adulthood in the majority of suffered persons. Although not fully understood, its neurobiological basis is related to dysfunction in the cortico-striato-thalamo-cortical circuit (CSTC).[4] Treatment modalities for Tourette's syndrome include behavioral, pharmacological and surgical interventions, but there is currently no medicine for the disorder.[5]

The aim of this article is to present data and findings of the scientific and clinical relevance of various methods and provide up-to-date information on the current understanding of the underlying pathomechanisms and management of Tourette's syndrome.

METHOD

This review provides a comprehensive overview of the current state of knowledge based on literature review.

DISCUSSION

GTS refers to Tourette's disorder in the *Diagnosis and Statistical Manual of Mental Disorder* (DSM-5) which falls within the large umbrella of tic disorders.[5] Based on the DSM-5, tic disorders include *provisional tic disorder* (temporary tic disorder), tic motor disorder or sedentary vocal (persistent), Tourette disorder (multiple motor and combined vocal disorders), and other tic disorders.[6]

Temporary tic disorders are characterized by the presence of tics motor and / or vocal, single or multiple, for less than 1 year, with an onset of age <18 years. Persistent vocal or motor tic disorder was defined as the presence of either motor or vocal tics, but not both, for more than 1 year. Then, Tourette's disorder was defined as the presence of multiple motor tics DAN one or more vocal tics over 1 year, with an onset of age <18 years. [6]

Epidemiology

The prevalence of GTS is estimated to occur in 0.66% of the school age child population. If only boys were counted, the prevalence would be around 1%, which is consistent with the finding that GTS is more common in boys than girls at a ratio of 3-4 : 1. [2,7] Furthermore, the onset of age of GTS is 4-6 years, then reaches its heaviest level at 10-12 years of age, then decreases in severity during adolescence. These tics can persist into adulthood and the case that causes the most decline in quality of life is in adulthood.[4]

Consistently, GTS has an incidence 4-5 times higher in children than adults. This symptomatology decline during adulthood supports the theory that GTS is a neurodevelopmental disorder on structures and / or certain immature brain processes.[2]

Previous studies stated that 52% of children with GTS have a family history. They have a first degree relative with a GTS 10 times higher than the general population, and the concordance ratio in monozygotic twins is 5: 1 compared to dizygotic. Therefore, Tourette's syndrome is well known to be one of the most commonly inherited neuropsychiatric disorders.[1]

Etiology

The causes of GTS can be genetic or non-genetic. The last category includes cases related with streptococcal infection, namely (*pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection* (PANDAS)) and cases following other brain injuries.[8,9]

GTS is known to be familial; the prevalence of GTS in first-degree relatives is 5-15%, or at least 10 times higher than that of the general population. In a study on twins, it was shown that the concordance ratio in monozygotic twins versus dizygotic twins around 5 : 1.[10] Furthermore, many studies have identified gene mutations in GTS, but have not been able to significantly explain this disorder so that it is concluded that this disorder is polygenic.[1] Several candidate genes in the manifestation of GTS include *DLGAP3*, single nucleotide polymorphisms on *NTN4* (axon molecular guide encodings expressed in the growth striatum), deletion *NRXN1* and duplication *CNTN6*, and gene micro deletion *AADAC*.[4,11]

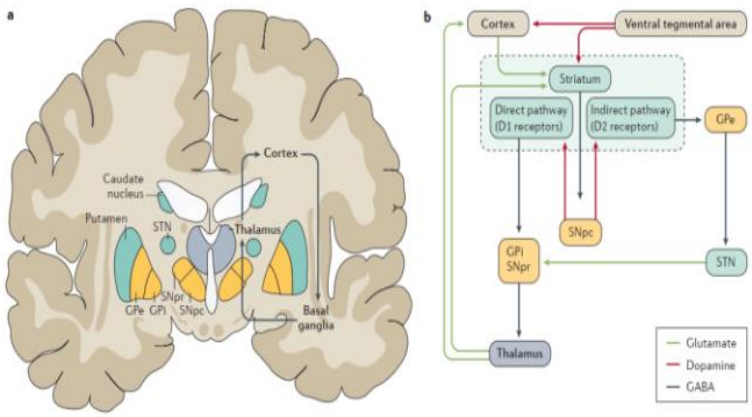
The etiologic model of GTS declares an existence disorder in CSTC circuits and neurotransmitters.[12] Neurochemical evidence concludes that dopamine dysfunction is a principal factor in the manifestation of GTS. The GTS dopaminergic hypothesis declares an existence pre-synaptic, intra-synaptic, and post-synaptic dysfunction.[12] Other neurotransmitters that play a role in GTS include decreased excitatory agent glutamate in the postmortem basal ganglia GTS, striatal interneurone GABA deficiency, decreased acetylcholine amount in striatal interneurones, decreased serotonin and tryptophan amount in the cerebrospinal liquor GTS, as well as noradrenaline and histamine.[9,12–14]

In recent years, there has been increasing interest in the possibility that streptococcal infection can produce not only chorea, in this case Sydenham's chorea, but also tics, obsession and compulsion disorders. In some cases, tics occurred immediately after streptococcal infection and the investigators submitted research for post-streptococcal autoimmune neuropsychiatric disorders related with group A beta-hemolytic streptococcal infection (PANDAS).[8]

Pathophysiology. A recapitulation of models previously proposed for psychosis, prenatal and perinatal factors (e.g., infection, maternal stress during pregnancy and smoking during pregnancy) can, based on increased genetic susceptibility, trigger *priming* microglia (i.e. glial cells of the macrophage / monocyte group involved in the formation of and synapse elimination).[4] The next attacks (eg, psychosocial stressors or infections) can, at the central level, activate microglia, so that affecting synaptic plasticity close to the emergence of symptoms, and increase the peripheral inflammatory or immune response. For example, the predictive effect from psychosocial stressors on tic severity and obsessive-compulsivity was three times stronger when an infection (such as group A streptococcal pharyngitis) coincided with increased levels of psychosocial stress.[4,10]

The currently accepted hypothesis is a dysregulation cortico-striato-thalamo-cortical (CSTC) circuit which parallel and interacting, linking specific regions in the frontal cortex with subcortical structures (including the basal ganglia and thalamus), providing a framework for understanding GTS (Picture 1).[12,14,15] In the CSTC dysregulation hypothesis, it can be seen that there is involvement of the neurotransmitters dopamine, glutamate, and GABA.[14]

In a manner neuroimaging, patients with GTS show increased cerebral blood flow (CBF) and tic-related hypoperfusion in the left caudate nucleus and anterior cingulatum cortex, as well as hypoperfusion in the left dorsolateral prefrontal cortex, which is related with mood. Hypoperfusion in the striatal, frontal, and temporal areas was also observed. Furthermore, a smaller caudate nucleus volume in children with GTS was related with more severe tic symptoms in adulthood.[9,14]



Picture 1. CSTC Circuit. [2,14]

Description: a) CSTC circuit is a complex interconnection between the cortex, basal ganglia and thalamus, which regulates complex behavior and includes many neurotransmitters (NT) (including dopamine, glutamate and GABA). This imbalance in one or more NTs may explain some of the characteristics of GTS**. b)** The CSTC circuit (simplified) includes a projection pathways from excitatory glutamaergic pyramidal neurons located in the frontal cortex up to neurons *spiny* GABA-ergic medium in the striatum. Striatal output includes a direct pathways that transmits striatal information monosynaptically to the internal Globus pallidus (GPi) and substantia nigra pars reticulata (SNpr); and indirect pathways that transmit information to these regions via a disynaptic relay from the GPe to the subtalamic nucleus (STN). Each of these pathways has the opposite effect; the direct pathway inhibits and the indirect pathway stimulates. Specifically, direct pathways facilitate motor activity, whereas indirect pathway activation inhibits motor activity.

Clinical Manifestations

Many individuals with TD characterize their tics as voluntary responses to feelings of discomfort that precede them. These feelings, or premonitory *sensations*, are described by the majority of individuals with Tourette's disorder; can be localized or general, and it can be physical or mental characteristics. This premonitory sensation distinguishes tic disorders from other movement disorders.[5]

A comprehensive and detailed Anamnesis with observations derived from multiple sources is the basis of the clinical evaluation of the tics and comorbid neurodevelopmental and psychiatric disorders. Neurological check-up, laboratory, and imaging in patients with tic disorder are generally normal. Because this disorder is diagnosed on the basis of history, reliable sources of information are essential.[5]

Tic vocal and motor has three components, namely: [1.5]

1. The sensation of premonition *(premonitory* sensation)
2. Physical expression from attacks tic
3. Relief *(sense of* relief) after the attack happened.

From the anamnesis, it can be found that the onset of the disorder is before adulthood, generally at the age of 5-6 years. Questions in the anamnesis include medical and growth-development information, medical history (including recreational substance use), employment and educational data, social and interpersonal history, and pedigree of at least 3 generations. Descriptive and longitudinal assessments are important, including onset, journey of disease, current severity, the existence of premonitory sensation and capacity patient to suppress tics, quality of life and management to date.[5]

Standard video-recorded interview and evaluation procedures were used in some research studies; it can also be used in clinical settings. However, the absence of tics observed at baseline does not rule out a diagnosis of tic disorders. An unusual history, concomitant change in mental status, or the presence of a seizure always requires referral for a thorough neurological evaluation.[5]

Motoric Tic is a sudden, rapid and repetitive, stereotypical non-rhythmic motor movement, usually preceded by a *premonitory sensation*. The motor movement can affect any part of the body but is most common in the face, head and neck area. Vocal tic includes all the tics that make a sound: sniff, grunt, hum, clicking, shout the word repeatedly. Coprolalia, shouting crude or other profane language, affects less than 10% of GTS patients.

Physical Check-up. Physical check-up includes height, weight (anthropometric status), presence or absence of body dysmorphic features, posture, gait, reflexes and assessment for abnormal motor movements.[16] *Abnormal Involuntary Movement Scale* (AIMS) is a systematic assessment procedure (and rating form) that can be adapted use to children. The standard of interview which recorded video and evaluation procedures were used in some research studies; it can also be used in clinical settings. However, the absence of tics which observed at initial check-up does not get rid diagnosis of tic disorders. An unusual anamnesis, concomitant change in mental status, or the presence of a cramp always requires referral for a thorough neurological evaluation.[5]

Psychiatric Check-up. Psychiatric evaluation should include a formal assessment from behavioral and emotional problems that are known clinically to classify tic disorders, including ADHD, OCD, anxiety disorders, mood disorders, and manifestations from disorder or affective dysregulation (eg, aggression). Standard grading scales developed specifically for this population of disorders have increased diagnostic reliability in research studies and may also be helpful in clinical settings. The *Yale Global Tic Severity Scale* (Y-GTSS) and *Tourette Syndrome Symptom List* (TSSL) Grades Scale, assesses tics, compulsions, and other related features. Because the assessment instrument can provide baseline data that can be measured, such as frequency and intensity of tics, these data can also be used to measure treatment response (Table 1). [17]

Table 1. The Scoring of Scale [5,17]

Domain	Type	Reliability and Validity	Sensitive to Changes
Tics			
• Yale Global Tic Severity Scale (YGTSS)	*Clinician*	*Excellent*	*Yes*
• Abnormal Involuntary Movement Scale (AIMS)	*Clinician*	*Excellent*	*Yes*
• Tic Symptom Self-Report	*Parent/patient*	*Good*	*Yes*
Gangguan Pemusatan Perhatian dan Hiperaktivitas			
• Swanson, Nolan, and Pelham-IV (SNAP-IV)	*Parent/Teacher*	*Excellent*	*Yes*
• Abbreviated Conners Questionnaire	*Parent/Teacher*	*Excellent*	*Yes*
Gangguan Obsesif-Kompulsif			
• Yale-Brown Obsessive Compulsive Scale (YBOCS) & Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS)	*Parent/Teacher*	*Excellent*	*Yes*
• National Institute of Mental Health Global	*Parent/Teacher*	*Excellent*	*Yes*
Gangguan Mood dan Cemas			
• Children's Depression Inventory (CDI)	*Clinician*	*Good*	*Yes*
• Children's Depression Rating Scale (CDRS)	*Patient*	*Good*	*Yes*
• Multidimensional Anxiety Scale for Children (MASC)	*Patient*	*Good*	*Yes*
General			
• Achenbach Child Behaviour Checklist (CBCL)	*Parent/Teacher*	*Excellent*	*No*
• Clinical Global Impression Scale (CGI)	*Clinician*	*Excellent*	*Yes*

Children with GTS have a high rate of comorbid neurobehavioral disorders. ADHD or Obsessive-Compulsive Disorder is seen in the majority of patients. Children with GTS often experience a lot of anxiety, sleep disorders, poor impulse control, or other behavioral disorders. These comorbid neurobehavioral disorders often cause more psychosocial distress to the child than the severity of tics. *Echophenomenon is* found in more than half of children with GTS. Echolalia refers to words that are repeated, whereas echopraxia is a repetitive movement. This is common in GTS patients who have comorbid OCD. This can be a problem when dealing with authority figures, such as teachers or police officers, who do not understand GTS.[1,5]

Laboratory Check-up. In general, laboratory testing is indicated only to get rid of other disorders when such conditions are deeply involved in the appeal diagnosis of a given patient. For example, specific tests are available for the definitive diagnosis of Huntington's disease, Wilson's disease, and neuroakantocytosis.[5]

Radiology Check-up. At present, there are no specific lab or radiological tests available to diagnose GTS. MRI of the brain or CT scan of the head is generally normal. Recent MRI studies have shown a decrease in the volume of the caudate nucleus in children with GTS, and the rate of this volume loss correlates with the OCD symptoms accompanying.[9] However, these results were obtained by careful measurement, and existing techniques are not currently available for most public health services.[1]

The Establishment of Diagnosis. The diagnosis of GTS is based on data obtained from the anamnesis of the complete medical history, general check-up physical and psychiatric, and comorbidities. The DSM-5 diagnosis criteria for Gilles de la Tourette Syndrome are : [6]

- Multiple motor tics AND ≥ 1 vocal tics occurring at one time during illness, although not necessarily concurrent. (Tic is motor movement or vocalization sudden, rapid, repetitive, non-rhythmic, stereotypical)
- Tic occurs several times a day, almost every day or intermittently over a period of > 1 year, and during this period there is never a tic free period > 3 consecutive months
- Onset before age 18 years
- The disorder is not due to a direct physiological effect of a substance (eg stimulants) or a general medical condition (eg, Huntington's disease or posviral encephalitis).

On the other side, the diagnostic criteria for GTS based on the *Tourette Syndrome Study Group*¸ are : [10]

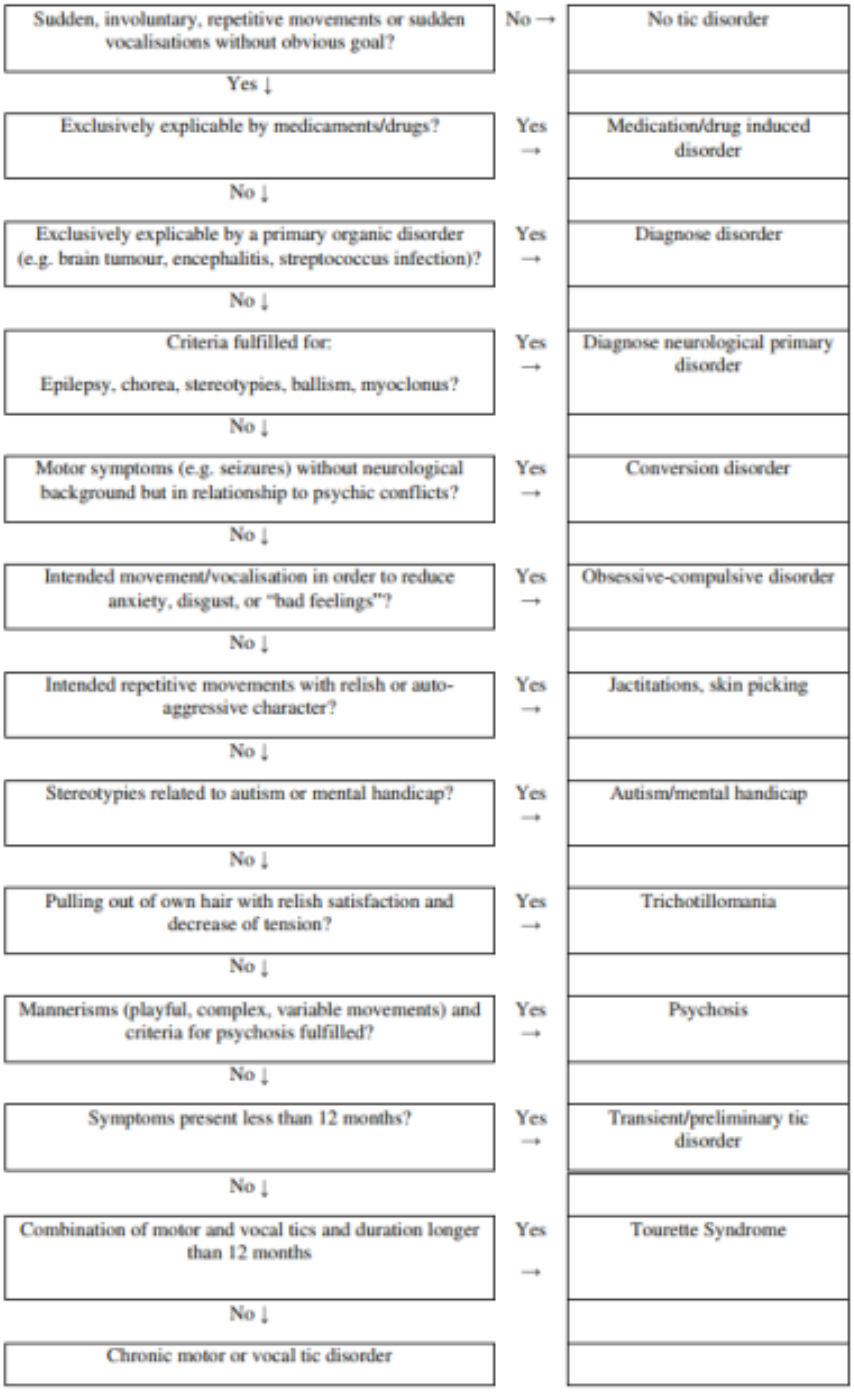
- Multiple motor tics AND ≥ 1 vocal tics occurring at one time during illness, although not necessarily concurrent
- Tic appears several times a day, almost every day, or intermittently for > 1 year
- Anatomical location, amount, frequency, complexity, type or severity of tics change over time
- Onset before age 21 years
- Involuntary movements and voices cannot be explained by other medical conditions
- Tic motor and / or vocals must be witnessed by a trustworthy examiner live at some point during illness or recorded with videotape or cinematography (for sure GTS) OR (if the tic is not witnessed by the examiner) the tics must be witnessed by a trusted family member or close friend, and tic descriptions described should be validated by a reliable examiner (for GTS by anamnesis).

The GTS and Tic Disorders Diagnostic Consideration Tree to guide the examiner's justification can be seen in Picture 2. [15]

Appeal Diagnosis. The tic needs to be distinguished from other hyperkinetic and psychogenic movement disorders. The characteristics that distinguish tic from other movement disorders - with the exception of akathisia and psychogenic movement disorders - are (1) the ability to temporarily

suppress it, and (2) the patient's experience of tic as a (partially) voluntary movement to relieve inner tension or sensation sensory inner focus (*premonitory sensation*). These features can be used to help differentiate from other movement disorders that typically worsen with action and cannot be suppressed.

Some of the appeal diagnoses of GTS are akathisia, autism spectrum disorders, chorea in adults, *complex partial seizures*, frontal lobe syndrome, and Huntington's disease and neuroakantocytosis.[10.15]



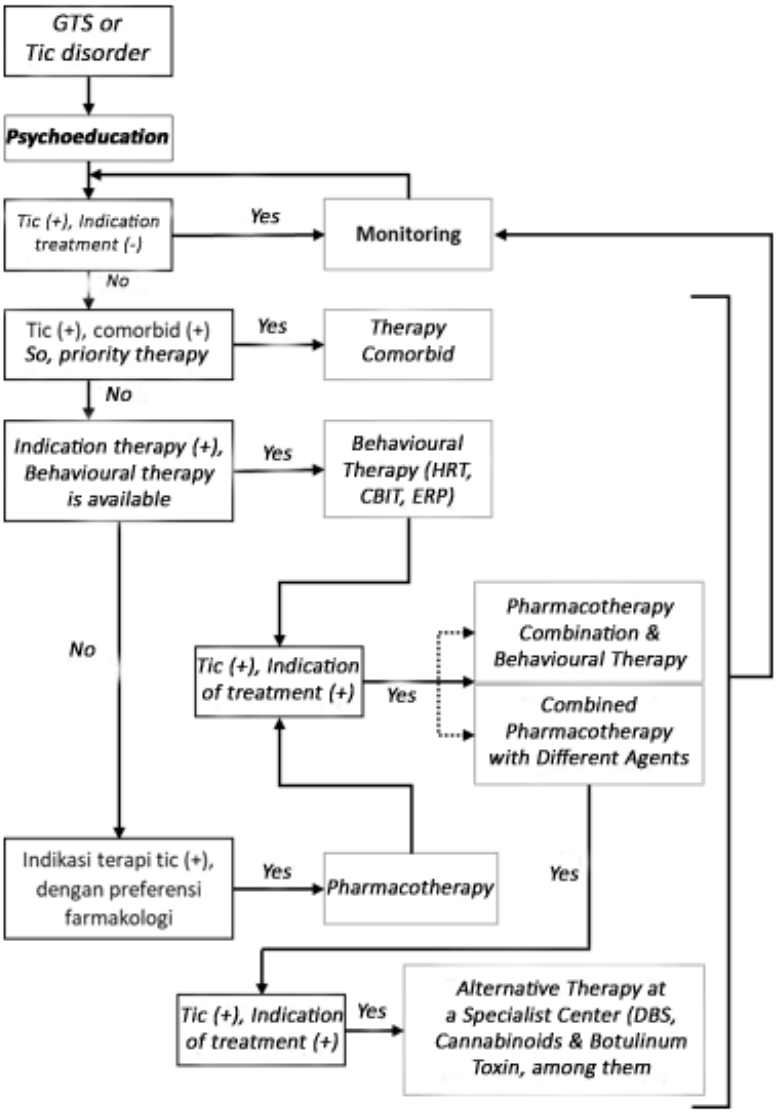
Picture 2. Tic Disorder Diagnostic Consideration Tree [15]

Therapy. Individuals with mild and even moderate tics may not need treatment at all, if the tic does not cause significant pressure or distraction. Active monitoring may be needed for some individuals with mild tics. Indications for tics therapy are physical pain or discomfort, disruption in social interactions, and disruption in any aspect of educational or work functioning.[5]

Based on the Competency Standards for Indonesian Doctors, the competence of general practitioners in the management of GTS is 2, namely to diagnose and refer. However, before to referral to a psychiatric specialist, counseling, information, and education for the patient and family regarding the disorder and its management plan.[18]

The first step in treatment is proper education for the patient, family members, teachers, and others with whom the patient interacts. Parents, educators, and doctors should work as partners to advocate for an optimal school environment for children with tic disorders.[5]

Picture 3 is a tree of considerations in the management of GTS.



Picture 3. Tree of GTS Management Considerations[14]

Behavioral therapy is the first-line GTS is *habit reversal therapy* (HRT), which includes: training of self-consciousness *(awareness)* (to pay attention to premonition sensation and the onset of tic), competitive response training (to act that is incompatible with the tic target) and social support. Other behavioral therapies are CBIT (*comprehensive behavioral intervention for tics*) and ERP (*exposure and response prevention*).[3]

Psychopharmacological management can be implemented if behavioral therapy is less effective. This therapy is indicated for tic and GTS disorders that cause pain or physical trauma, social and emotional problems, and / or interference with life functions (e.g: academic performance).[19] Historically, the pharmacological management of tics has involved dopamine receptor blockers (neuroleptics) and α2-adrenergic agonists. Atypical antipsychotics, such as risperidone and aripriprazole, are an option because they are easily tolerated by patients.[19] α2-adrenergic agonists (clonidine and guanfacine) are considered first-line therapy especially in children with ADHD comorbid GTS.[3]

Another therapy if pharmacology and behavioral therapy is less effective is *deep brain stimulation* (DBS, which is functional neurosurgery to modulate pathological neuronal activity in specific brain tissue using high-frequency electric currents transmitted through implantation of electrodes connected by a neuropacemaker) with target the thalamus, the globus pallidus and nucleus accumbens. However, further research on this method still needs to be done because the number of populations studied is still small and limited.[2,14]

Prognosis. The prognosis of good GTS, because tics and GTS are generally in remission in adulthood (about 50% remission by age 18 years), but other neuropsychiatric conditions can be persistent. Many tics sufferer live a normal sufficient life. However, even mild tics can reduce a patient's quality of life, with disabilities being most common in the social sector. Patients with loud vocalizations or large movements experience substantial criticism and withdraw from many activities. In the clinical sample, most morbidity caused by inattention, impulsivity, obsessions, compulsions, or complex behavioral symptoms such as inappropriate social behavior, or attacks of anger.[1,10]

CONCLUSION

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by chronic motor and vocal tics that

begins in childhood. The etiology is unclear, complex and multifactorial. The clinical manifestations of GTS follow a fluctuating pattern, namely the top of symptoms at puberty and the condition begins to improve when the patient reaches adulthood. This condition generally has a comorbidity of other neuropsychiatric disorders. The diagnosis of GTS is confirmed by anamnesis as well as physical and psychiatric check-up using validated instruments. Management of GTS is based on symptoms and severity, including psycho-education, behavioral therapy, pharmacological therapy with atypical neuroleptics or α2-adrenergic agonists, and alternative therapy in the form of DBS.

Conflict of interest

No conflict of interest in this study.

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