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ORIGINAL ARTICLE

Tic Disorders

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Abstract

Objective: This article aims to discuss tic disorders in childhood and adolescence. **Methods:** Non-systematic review of the literature, focusing on diagnostic criteria, epidemiology, clinical features, pathophysiology, etiology, comorbidities, differential diagnosis, assessment, and treatment. **Results:** The main categories of tic disorders are Tourette's disorder, persistent motor or vocal tic disorder, and provisional tic disorder. The latter is the most prevalent. Tics can be classified as motor or vocal and simple or complex. Clinical presentation can change over time, and it is expected to exhibit a waxing and waning pattern, influenced by environmental (psychosocial) factors. Important characteristics of tic disorders are tic suggestibility, capacity to inhibit tics, and premonitory urges. Pathophysiology involves cortico-striatal-thalamo-cortical loops. Evidence suggests that there is a significant genetic contribution. Neuropsychiatric comorbidities are present in most of the patients, mainly attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. Tic disorder is a clinical diagnosis, and a comprehensive assessment is recommended in order to exclude other causes of abnormal movements. Treatment involves psychoeducation, behavioral therapy, and pharmacotherapy. Deep brain stimulation can be considered in refractory cases. **Conclusion:** Tic disorders have been extensively studied in the literature, and present research provides new evidence.

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DEFINITION AND DIAGNOSTIC CRITERIA

Tic disorders are movement disorders that can be classified as motor or vocal. They are part of neurodevelopmental disorders and are categorized into Tourette's disorder, persistent motor or vocal tic disorder, provisional tic disorder, other specified tic disorder, and unspecified tic disorder. The diagnostic criteria are described in Box 1[1].

The diagnosis is essentially clinical and accounts for time of onset of symptoms (more or less than 1 year), age at onset, types of tic (motor only, vocal only, or motor and vocal), and absence of another condition that justifies the occurrence of tics.

EPIDEMIOLOGY

Tic disorders occur in different cultures and socioeconomic contexts[2]. A Swedish study of children aged 7-15 years reported a 6.6% rate for any tic disorder in the last year, 4.8% for provisional tics, 0.6% for Tourette's disorder, 0.8% for chronic motor tic disorder, and 0.5% for chronic vocal tic disorder[3].

A systematic review and meta-analysis of studies conducted from 1985 to 2011 reported a prevalence of 2.99% for provisional tic disorder in children. The prevalence of Tourette's disorder was 0.77% in the young population, being 1.06% in boys and 0.25% in girls; in adults, the prevalence was 0.05%, without division by sex[4].

A review of studies with community sampling reported a prevalence of provisional tics of up to 20% in school-age children. The prevalence of Tourette's disorder, chronic motor tic disorder, and chronic vocal tic disorder ranged from 2.6 to 28 in every 1,000 children, 3 to 50 in every 1,000 children, and 2.5 to 9.4 in every 1,000 children, respectively[5].

Another meta-analysis, specific to the Chinese population, reported a prevalence of 6.1% for tic disorders in patients aged 3-16 years. The rates for provisional tic disorder, chronic tic disorder, and Tourette's disorder were 1.7%, 1.2%, and 0.3%, respectively[6].

A Brazilian study of children and adolescents is also worth mentioning, which reported a prevalence of 0.43% for Tourette's disorder, being 0.67% in boys and 0.22% in girls. The prevalence of tic disorders excluding Tourette's disorder was 2.47%[7].

Specifically for Tourette's disorder, a review article including studies from different countries estimated a 1% international prevalence in children and adolescents[2]. A recent population study in Canada reported a rate of 3.3 in every 1,000 adolescents aged 12-17 years, being 6.03 in every 1,000 boys and 0.48 in every 1,000 girls. For adults, the prevalence was 0.66 in every 1,000 individuals[8].

Thus, some variation can be observed in prevalence rates. However, we highlight that tic disorders are common in childhood and adolescence, with a male predominance, and that provisional tic disorder is the most prevalent type. We also emphasize that the prevalence of symptoms decreases in adulthood.

PRESENTATIONS AND CHARACTERISTICS OF TICS

Tics tend to start between 4 and 6 years of age, peaking in severity between 10 and 12 years of age[1]. In adolescence and early adulthood, symptoms tend to decrease in intensity and frequency[9].

Tics are arbitrarily classified into motor tics (involving movements) and vocal tics (leading to production of sound)[10] and can be further classified as simple or complex. In the first case, they involve a single muscle group[10] and are of short duration, i.e., milliseconds[1]. Examples include blinking or shrugging (motor tics) and throat clearing, sniffing, or grunting (vocal tics)[1]. Complex tics involve behaviors that can appear to be purposeful but actually lack an obvious motive[10] and tend to last longer, i.e., seconds[1]. Complex motor tics may present as a combination of simple tics (e.g., head turning and shrugging), as sexual or obscene gestures (copropraxia), or as imitation of movements (echopraxia). Complex vocal tics can occur as a repetition of sounds or words produced by oneself (palilalia), imitation of the last word or phrase heard (echolalia), or verbalization of socially inappropriate words or phrases, such as obscenity, but lacking the typical prosody of an interactional context (coprolalia)[1]. Box 2 provides some examples of common tics according to a previously described classification[11]. Tics can also be categorized into clonic or dystonic, the latter being of longer duration, with sustained abnormal movements or posture[10].

Studies on patients with Tourette's disorder report coprolalia and copropraxia in 8%-50% and 5%-25% of patients, respectively. The age at onset of these phenomena ranges from 8 to 15 years, approximately 5 to 8 years after the onset of tics. They are more frequent in male patients[12].

Tics typically occur several times in a day. They can occur almost daily or fluctuate, increasing and decreasing over time. Changes in the anatomical location, type, frequency, and severity over the years are common[13]. Vocal tics tend to appear later than motor tics[14]. After the completion of a tic, individuals usually feel a momentary sense of relief[15]. In general, movements or vocalizations are experienced as involuntary but can be intentionally suppressed by the individual for a variable duration[1].

According to a review article, the temporal and spatial occurrence of tics is not random. Movements or vocalizations occur in a short duration and are followed by a tic-free period; movements apparently follow a rostrocaudal distribution, and craniofacial tics are more common than tics in the trunk or feet, especially in children[10]. Occurrence increases during periods of psychosocial stress, overexcitement, and fatigue. On the other hand, tics may decrease during planned activities[15].

As the disorder progresses, in most cases, a premonitory urge starts to precede tics. They are somatic sensations or intrusive feelings perceived by the individual before the tic, and they are more likely to occur before complex tics[16]. They can be classified into sensory (focal or generalized musculoskeletal or visceral sensations), cognitive (feelings of incompleteness or "just-right" perceptions), or autonomic (sweating, palpitations, and nausea)[14]. These sensations can be described as an urge to move, an impulse to perform the tic, or sensations such as itching, pressure, or pain[10]. This phenomenon is rarely extracorporeal, in another person or in the environment[17]. One hypothesis is that this premonitory urge phenomenon is an adaptive process of increasing awareness of imminent movements, which would consequently result in awareness of the movement that is about to occur and an opportunity for tic suppression[18]. The relationship between premonitory urges and this ability to suppress the movement is, however, controversial in the literature. For example, a study using video recordings of 15 adult participants diagnosed with Tourette's disorder found no relationship between the ability to inhibit tics and premonitory urges[18]. In contrast, a clinical study of 1,032 patients with this disorder found a significant positive association between premonitory urges and tic suppression[19]. This study found premonitory urge rates of 46.7%, 61.3%, and 79.7% in the age groups under 10 years, 10-12 years, and over 12 years, respectively. For these same age groups, the ability to suppress tics was 65.5%, 78.8%, and 92.6%, respectively. Thus, premonitory urges and ability to control movements increase as age increases.

PATHOPHYSIOLOGY AND ETIOLOGICAL FACTORS

The pathophysiological mechanisms and etiological factors for tic disorders are not completely understood but have been extensively studied recently.

The fact that tics resemble voluntary motor behaviors and that individuals have the ability to suppress them indicate that voluntary movement pathways are involved, specifically cortico-striatal-thalamic-cortical loops. Structural and functional changes in these pathways would thus be associated with the occurrence of symptoms, whereas tick suppression is associated with prefrontal cortex control. In contrast, premonitory urges are related to the ability to perceive interoceptive (intrabody) signals, and the insular cortex appears to be involved in this phenomenon[10,20].

Chronic tic disorder and Tourette's disorder have been understood as conditions with a strong genetic component, with a 77% estimated heritability. The relative risk for first-, second-, and third-degree relatives is 18.69%, 4.58%, and 3.07%, respectively. The risk is greater for siblings (17.68%) than for half-siblings (4.41%)[21]. In the 1980s and early 1990s, inheritance was believed to be single-gene autosomal dominant[22]; however, with the advancement of research, the current understanding is that there is a complex inheritance mechanism involving multiple genes[22,23].

In relation to non-endogenous influence, perinatal factors have been investigated. A systematic review identified that several variables have been correlated with the development of Tourette's disorder, including maternal age, antenatal care features, slight physical anomalies, pregnancy complications, exposure to antibiotics during pregnancy, maternal smoking, 5-minute Apgar score, pre-and post-natal adverse events, and birth weight. However, maternal smoking and low birth weight are the variables of more consistent association[24]. A recent population study with a large number of participants corroborated the association between adverse perinatal events (fetal growth restriction, prematurity, breech presentation, and cesarean section) and higher risk of Tourette's and chronic tic disorders. This same study also found an association between these disorders and maternal smoking, but that was explained by family factors and comorbidity with attention-deficit hyperactivity disorder (ADHD)[25].

Other non-endogenous factors that have been investigated are immune mechanisms and infections[26], vaccination[27], parents' mental disorders[28], and psychosocial stressors and responses to stress[29].

NEUROPSYCHIATRIC COMORBIDITIES

Between 80% and 90% of patients with Tourette's disorder present at least one neuropsychiatric comorbidity[16,30] and approximately 50% have two or more[30]. These cases with other concurrent mental disorders are referred to as Tourette syndrome plus, to enable distinction from pure cases[16,31].

The most common associations in clinical studies are with ADHD (17%-68%) and obsessive-compulsive disorder (OCD, 10%-60%). Associations have also been described with learning disabilities (20%-30%), autism spectrum disorder (2.9%-20%), depression (11%-37%), anxiety disorders (2%-45%), sleep disorders (9%-53%), externalizing/conduct disorders (5%-30%), and intellectual disability (3.4%)[32]. Patients with comorbid disorders have more significant loss of quality of life[31].

DIFFERENTIAL DIAGNOSIS OF TIC DISORDERS

The clinical diagnosis of tics is usually quite evident. However, a few situations need more attention: misdiagnosis or the false interpretation that the tics are due to psychological factors; abnormal movements coexisting with tic disorder, but mistakenly identified as tics; the presence of tics as a clinical presentation of another condition; another movement disorder confused with tics[33].

In the evaluation of abnormal movements that can be confused with tics, it is important to consider akathisia (restlessness, a side effect of antipsychotics), ballismus

(ample, intermittent movements with outward and forward projection, usually unilateral, resulting from lesions of the subthalamus or the contralateral striatum), chorea (dance-like, sudden, nonrepetitive, anarchic movements resulting from infectious or degenerative processes), dystonia (sustained or intermittent, repetitive contraction movements progressing to abnormal postures, including twisting dystonias such as spasmodic torticollis and blepharospasm), myoclonus (sudden, brief muscle contractions, restricted to muscle groups or portions, with possible displacement of a body segment), stereotypy (voluntary, repetitive behavior, apparently with no purpose, more common in patients with cognitive deficit, psychotic disorders, or hyperactivity), movements caused by restless legs syndrome, and compulsions (acts or rituals usually performed in response to obsessive thoughts, with the aim of preventing some supposed damage)[11].

Among the causes of secondary tics, there are developmental disorders (cognitive deficit, autism spectrum disorder, Rett syndrome, genetic and chromosomal abnormalities, dystrophies, and congenital adrenal hyperplasia, etc.), acute brain injuries (post-traumatic, vascular, or infectious), post-infectious conditions (e.g., Sydenham's chorea and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), neurodegenerative diseases (e.g., Huntington's disease, neuroacanthocytosis syndromes, and neurodegeneration associated to iron accumulation), systemic diseases (e.g., Behçet's disease and antiphospholipid syndrome), use of medications and other substances, and functional tics[10,34]. Medications or substances that may induce or exacerbate tics are pemoline, amphetamines, cocaine, heroin, methylphenidate, antipsychotics (fluphenazine, perphenazine, thiothixene), antidepressants, anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), and L-DOPA[10].

Some features of the clinical presentation of primary tic disorders can assist in more complex cases, mainly rostrocaudal distribution; suggestibility; premonitory urges; inhibition capacity; presence of echolalia, palilalia, echopraxia, coprolalia, or copropraxia phenomena; personal history of typical psychiatric comorbidities (especially ADHD and OCD); and family history. On the other hand, late onset (end of adolescence or adulthood), abrupt onset, and association with other neurological manifestations are signs that indicate the need to exclude secondary causes[10,33].

Functional tics, also called psychogenic or pseudo-tics, are included in the functional movement disorders and are considered rare. They are difficult to diagnose because they lack specific diagnostic criteria. Their presentation can be quite similar to that of true tics and, similarly, to other movement conditions, and they can coexist with a tic disorder[35,36]. To identify them, the following data might be useful: the presence of triggering events, other functional neurological symptoms, or depressive or anxiety disorder and failed response to drug treatment for tics[36].

INVESTIGATION

Investigation for tic disorders should be very broad and include the detailed characterization of abnormal movements [age at onset, duration, location, type (motor, vocal, simple or complex), variation over time, factors of improvement and worsening, suppression capability, presence of premonitory urges], family history, use of medications or substances, and psychiatric comorbidities (particularly ADHD, OCD, and neurodevelopmental disorders). It is important to detect other neurological signs and symptoms as well as general comorbidities to rule out secondary causes. Assessing the impact of tics on the patient's quality of life is essential.

Using specific scales can help characterize the clinical picture. To assess the severity of symptoms, the recommended scales are the Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression (TS-CGI), Tourette's Disorder Scale, Shapiro Tourette Syndrome Severity Scale, and Premonitory Urges for Tics Scale. YGTSS is the most used internationally; it assesses the number, frequency, intensity, complexity, and interference from motor and vocal tics, in addition to overall impairment of the individual[37].

Requesting additional tests should be considered. In cases of sudden onset of severe tics, atypical tics, and mental status changes suggestive of an organic process, a more thorough assessment should be quickly performed. General laboratory tests (complete blood count; renal, liver, and thyroid function; ferritin levels) and a toxicology examination can be requested. Tics of sudden onset and severe symptom exacerbation require acute infectious disease investigation (cultures and rapid virus tests). Electroencephalogram and neuroimaging examination are not routinely performed and are indicated in presence of other neurological findings[38].

TREATMENT

Based on extensive research, a proper conduct can be established. A key aspect of the treatment is psychoeducation. The patient and family receive information on the characteristics of the tic disorder, including the neurobiological basis, course of the disease, fluctuating pattern, influence of non-endogenous factors, and the spectrum of associated neuropsychiatric conditions. Access to this information promotes better understanding of the disorder, increases the perception of symptoms, and facilitates acceptance by children/adolescents and their families[39]. Guidance for teachers and adaptations in the school context may be necessary, e.g., ignoring the tics and giving the child or adolescent permission to leave the classroom when necessary[38].

Some cases, however, may require more specific (psychotherapeutic or pharmacological) treatment. The decision must be shared with the patient and family, considering the severity of the symptoms and the damage they cause. In case there are comorbidities that are the main reason of suffering or damage, they should be treated first[38].

Specific treatment begins with behavioral therapy (first-line treatment, considering its effectiveness and less chance of side effects) and progresses to medication (second-, third-, and fourth-line treatments, considering their effectiveness and potential adverse events)[40].

Different approaches are used in behavioral therapy, including habit reversal training, exposure and response prevention, and a more extensive model called Comprehensive Behavioral Intervention for Tics (CBIT)[41]. Several randomized controlled studies and review studies show the benefits of these types of intervention. For example, a study of 126 patients aged 9-17 years with Tourette's disorder or chronic tic disorder reported that patients undergoing CBIT showed a 7.6-point reduction in the YGTSS scale compared with 3.5 points in the control group. Therapeutic gains persisted through the 6 months of follow-up[42].

First-choice drugs, considered a second-line treatment intervention, are clonidine (an alpha-2 agonist, therapeutic range: 0.025-0.3 mg/day) and sulpiride (a dopamine antagonist of the benzamide group, therapeutic range: 50-200 mg/day). As third-line treatment interventions, we highlight baclofen (a GABA receptor agonist, therapeutic range: 10-60 mg/day) and topiramate (an anticonvulsant, therapeutic range: 1-9 mg/kg/day; doses above 200 mg are usually not well tolerated). Fourth-line drugs are typical and atypical antipsychotics. The former group comprises haloperidol (therapeutic range: 0.5-3 mg/day), pimozide (0.5-4 mg/day), and fluphenazine (0.25-3 mg/day). In the latter group, the initial choice is either risperidone (therapeutic range: 0.25-3 mg/day) or aripiprazole (2-15 mg/day), but other options include olanzapine (2.5-10 mg/day), quetiapine (50-250 mg/day), and ziprasidone (20-40 mg/day)[39,40].

Other drugs of the aforementioned groups are also indicated, but they are not available in Brazil at this time, e.g., guanfacine (an alpha-2 agonist, second line) and tetrabenazine (a VMAT2 inhibitor, third line)[40].

The side-effect profile of the drugs and patient monitoring should be considered for proper prescription. With clonidine, orthostatic hypotension, sedation, and drowsiness are frequent reactions. Blood pressure control and electrocardiogram are recommended. Antipsychotics require attention to extrapyramidal side effects, sedation, increased appetite, agitation, akathisia, and orthostatic hypotension. It is important to monitor weight, electrocardiogram, blood count, transaminases, blood glucose, lipid profile, electrolytes, and prolactin[43]. For the use of topiramate, monitoring cognitive side effects, mood changes, and weight loss is suggested[39].

Drug treatment reduces tic occurrence in 25%-50%, on an average. However, some patients can reach complete or nearly complete control of the symptoms[39].

Figure 1 is a suggested flowchart for the treatment of tic disorders (adaptation[39]).

Transcranial magnetic stimulation, cannabinoids, special diets, and vitamin supplements are not recommended for the treatment of tic disorders in children and adolescents due to lack of scientific evidence[10,38]. Application of botulinum toxin is an intervention that has been studied but is currently only recommended on an individual basis[39].

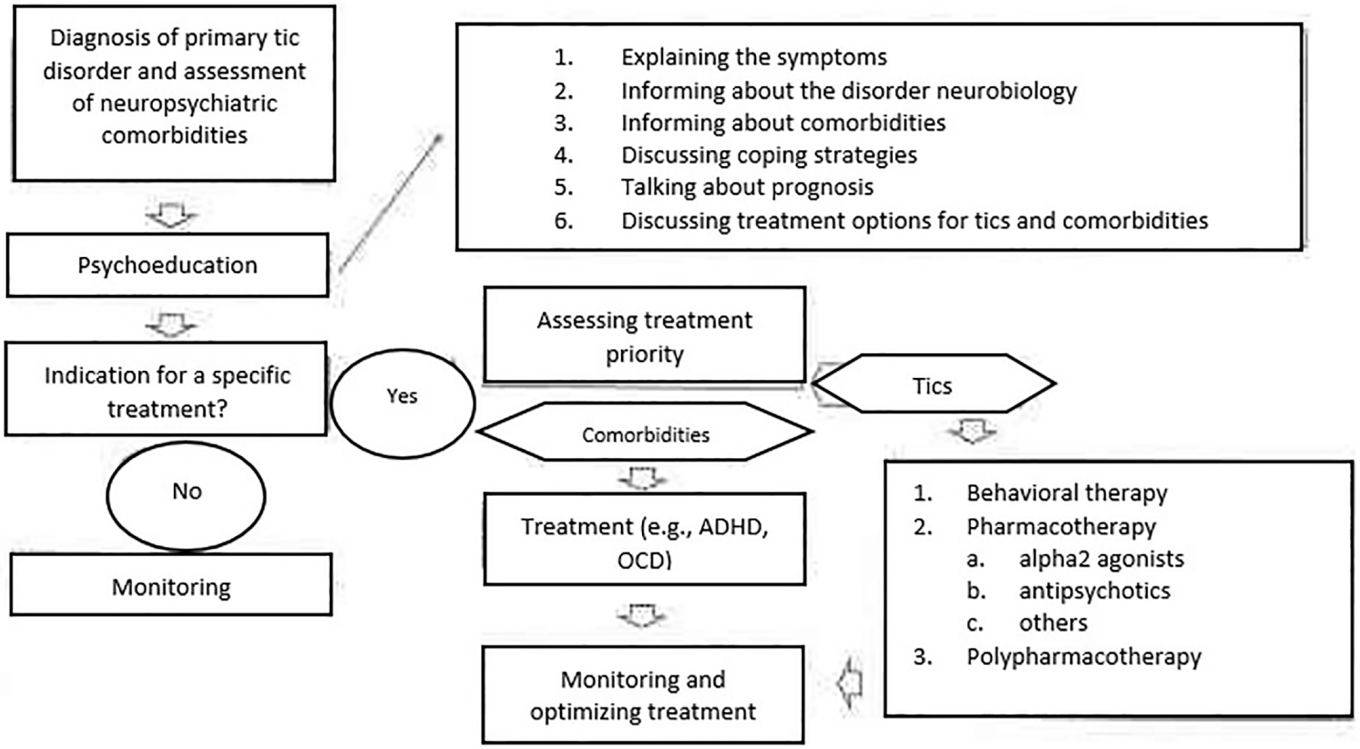


Figure 1 - Flowchart for the treatment of tic disorders in childhood and adolescence (ADHD: attention-deficit hyperactivity disorder; OCD: obsessive-compulsive disorder).

Deep brain stimulation (DBS) is also not indicated as an initial treatment protocol[38] but can be considered in refractory patients with Tourette's disorder with severe symptoms unresponsive to drug treatment and behavioral therapy. If DBS is considered for patients aged under 18 years, the current recommendation is to have an evaluation by a multidisciplinary team and an ethics committee or hospital committee[44]. The main targets of DBS in Tourette's disorder are the thalamic nuclei and the internal globus pallidus. Other less frequent targets are the subthalamic nucleus, the external globus pallidus, the internal capsule, and the nucleus accumbens[45]. A meta-analysis of 57 studies and 156 cases reported a 52.86% rate of improvement in YGTSS after treatment with DBS. There was no statistically significant difference in improvement between different sites of stimulation[46]. Another recent study examining an international database of 171 patients with Tourette's disorder who underwent DBS reported that the total score in YGTSS improved by 45.1% at 1 year after implantation. The prevalence of adverse events was 35.4%, the most common being dysarthria (6.3%) and paresthesia (8.2%). Severe events were reported, such as intracranial hemorrhage (1.3%), infection (3.2%), and implant dislocation (0.6%)[47].

FINAL CONSIDERATIONS

Tic disorders are common in childhood and adolescence and can cause significant suffering and loss of quality of life. It is understood that this group of disorders has a neurobiological, organic basis, with involvement of cortico-striatal-thalamic-cortical loops and a strong genetic component. The clinical presentation involves different (motor, vocal) manifestations, which can be simple or complex and change over time. Symptoms of tic disorders exhibit a waxing and waning pattern, influenced by non-endogenous factors. Suggestibility, suppression capability, and the presence of premonitory urges are important characteristics. Most patients have neuropsychiatric comorbidities, especially ADHD, OCD, and other neurodevelopmental disorders. To diagnose a primary tic disorder, a broad assessment should be undertaken, which can also exclude other neurological conditions or secondary causes. The treatment involves psychoeducation and, if indicated, behavioral therapy and drug treatment. Drugs used include clonidine, baclofen, topiramate, and typical and atypical antipsychotics. Side effects should always be assessed when prescribing these medications. DBS can be considered in refractory cases. Finally, tic disorders have been widely researched recently, with literature reporting new evidence. In this context, the present article is an update on this theme for resident physicians and other health care professionals.

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