

Tourette syndrome¹

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Creation Date: May 2003

Update: October 2004

Scientific Editor: Professor Alessandro Filla

¹Adapted and modified from Jankovic J. Tourette's syndrome. *N Engl J Med* 2001; 345:1184-1192.

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Abstract

Tourette syndrome (TS) is a genetic neurological disorder with childhood-onset tics that may be associated with comorbid behavioral problems. Tics, which represent the clinical hallmark of TS, are sudden, brief and intermittent, involuntary or semi-voluntary, movements (motor tics) or sounds (phonic or vocal tics). Motor tics include blinking, nose twitching, and head and limb jerking. Phonic tics include sniffing, throat clearing, grunting, coughing, and there may be the use of obscene words or phrases. Tics may be voluntarily suppressed for short periods, be exacerbated by stress, excitement, fatigue. Besides tics, patients with TS often exhibit a variety of behavioral symptoms, particularly attention deficit-hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Manifestations are characterized by marked fluctuations in severity and frequency during the disease course, and wide variation among patients. The disorder typically begins between 3 and 8 years of age and half of the patients are tic-free by 18 years. Prevalence rates have been estimated to vary between 0.7% and 4.2% in school populations. Evidence indicates a developmental disorder of synaptic neurotransmission as the underlying etiology. To date, a TS gene has not been isolated. The diagnosis of TS is based on a history and an observation of tics and a family history of similar symptoms. The first step in the management is proper education of the patients, family members, teachers. Medication is considered when symptoms are functionally disabling. Classes of medication used in the treatment of patients with TS include neuroleptics, central nervous system (CNS) stimulants, and selective serotonin uptake inhibitors (SSRIs).

Keywords

Attention-Deficit Disorder with Hyperactivity, Obsessive-Compulsive Disorder, Tics, Tourette Syndrome

Disease name

Tourette syndrome (TS)

Definition/Diagnosis criteria

TS is a neurological disorder named after the French neurologist Georges Gilles de la Tourette who, in 1885, described nine patients with childhood-onset tics, accompanied in some by

uncontrollable noises and utterances, features of attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), poor impulse control, and other comorbid behavioral problems (1-3). TS is now recognized as a relatively common biologic, genetic disorder with a rich spectrum of neurobehavioral manifestations that fluctuate markedly in severity

and frequency of symptoms during its natural course, and vary greatly from one individual to another, contributing to frequent misdiagnoses (4). Patient's symptoms may sometimes be wrongly attributed to "hyperactivity", "nervousness", "habits", "allergies", "asthma", "dermatitis", and other conditions (5,6).

To aid in the diagnosis of TS, the Tourette Syndrome Classification Study Group (TSCSG) (7) formulated the following criteria for definite TS:

1. both multiple motor and one or more phonic tics have to be present at some time during the illness, although not necessarily concurrently;
2. tics must occur many times a day, nearly every day, or intermittently throughout a period of more than one year;
3. the anatomic location, number, frequency, type, complexity, or severity of tics must change over time;
4. onset must be before age 21;
5. involuntary movements and noises cannot be explained by other medical conditions;
6. motor and/or phonic tics must be witnessed by a reliable examiner directly at some point during the illness or be recorded by videotape or cinematography. These and other diagnostic criteria (8,9), are designed to assist in accurate diagnosis, in genetic linkage studies, and in differentiating TS from other tic disorders (10,11) (see Differential diagnosis).

Differential diagnosis

Diseases associated with tics disorders are listed below:

Primary causes of tics

A. Sporadic

1. Transient motor or phonic tics (<1 year)
2. Chronic motor or phonic tics (>1 year)
3. Adult-onset (recurrent) tics
4. Tourette syndrome
5. Primary dystonia

B. Inherited

1. Tourette syndrome
2. [Huntington disease](#)
3. Primary dystonia
4. Neuroacanthocytosis
5. Neurodegeneration with Brain Iron Accumulation, type 1 (NBIA 1) (previously Hallervorden-Spatz syndrome)
6. [Tuberous sclerosis](#)
7. [Wilson disease](#)

Secondary causes of tics

A. Infections

Encephalitis, Creutzfeldt-Jakob disease, neurosyphilis, Sydenham's chorea

B. Drugs

Amphetamines, methylphenidate, pemoline, levodopa, cocaine, carbamazepine, phenytoin, phenobarbital, lamotrigine, antipsychotics and other dopamine receptor blocking drugs (tardive tics, tardive tourettism)

C. Toxins

Carbon monoxide

D. Developmental

Static encephalopathy, mental retardation syndromes, chromosomal abnormalities, autistic spectrum disorders (Asperger's syndrome)

E. Chromosomal disorders

[Down's syndrome](#), [Klinefelter's syndrome](#), XYY karyotype, Fragile X, Triple X and 9p mosaicism, partial trisomy 16, 9p monosomy, citrullinemia, [Beckwith-Wiedemann syndrome](#)

F. Other

Head trauma, stroke, neurocutaneous syndromes, schizophrenia, neurodegenerative diseases

Related manifestations and disorders

1. Stereotypies/habits/mannerisms
2. Self-injurious behaviors
3. Motor restlessness
4. Akathisia
5. Compulsions
6. Excessive startle
7. Jumping Frenchman

Clinical description

Tics represent the clinical hallmark of TS: they are sudden, brief and intermittent, involuntary or semi-voluntary, movements (motor tics) or sounds (phonic or vocal tics). They typically consist of simple or coordinated, repetitive or sequential, movements, gestures and utterances that mimic fragments of normal behavior (3,12).

Simple motor tics

They involve only a single muscle or a group of muscles, causing a brief, jerk-like movement called "clonic tics", which include blinking, nose twitching, and head and limb jerking. Movements may be also slower causing a briefly sustained abnormal posture referred as to "dystonic tics", such as blepharospasm, ocular deviations, bruxism, mouth opening, torticollis, and shoulder rotation. They may also result into an isometric contraction called "tonic tics" (12), which are typically manifested by tensing of abdominal or limb muscles.

Complex motor tics

They include head shaking, trunk bending or gyrating, brushing hair, touching, throwing, hitting, jumping, and kicking. Additional examples of complex motor tics include gesturing "the finger", grabbing one's genitalia and other lewd and obscene gestures (termed "copropraxia"), or imitating other's gestures (termed "echopraxia").

Simple phonic tics

They typically consist of sniffing, throat clearing, grunting, squeaking, screaming, coughing, barking, blowing and sucking sounds.

Complex phonic tics

They include linguistically meaningful utterances and verbalizations, such as shouting of obscenities, profanities, or otherwise socially inappropriate words or phrases (termed "coprolalia"), repetition of someone else's words or phrases (termed "echolalia") and repetition of one's own utterances particularly the last syllable, word or phrase in a sentence (termed "palilalia"). Coprolalia, perhaps the most recognizable and certainly one of the most distressing symptoms of TS, is actually present in less than half of patients with TS.

Motor and phonic tics are often preceded by premonitory sensations, which consist of localizable paresthesias or discomforts, temporarily relieved after the execution of the tic. Examples include "a burning feeling" in the eye before an eye blink, "a tension or a crick in the neck" relieved by stretching of the neck or jerking of the head, "a feeling of tightness or constriction" relieved by arm or leg extension, "nasal stuffiness" before a sniff, "dry or sore throat" before throat clearing or grunting, and "itching" before a rotatory movement of the scapula (12). In a recent study, some patients describe motor tics as a voluntary movement in response to an involuntary sensation, rather than a completely involuntary movement (13). Besides the local or regional premonitory sensations, this premonitory phenomenon may be non-localizable and less specific, such as an urge, anxiety, anger, and other psychic sensations.

The ability of patients to volitionally suppress their tics helps differentiate tics from other hyperkinetic movement disorders such as chorea, dystonia, athetosis, myoclonus, and paroxysmal dyskinesias (14). Besides temporary suppressibility, tics are also characterized by suggestibility, exacerbation with stress, relaxation after a period of stress, excitement, boredom, fatigue, and with an exposure to heat. Although diagnostic criteria for TS require that the onset is present before the age of 21, in 96%

of patients the disorder is manifested by age 11, typically beginning between 3 and 8 years of age (15). According to one study, the average age at onset of tics is 5.6 years and tics usually become most severe at age 10; by 18 years half of the patients are tic-free (16). Tics may persist into adulthood, although their severity usually gradually improves (17). The vast majority of adults with tics represent persistence or recurrence of childhood-onset tics (18), but rare patients may have their first tic occurrence during adulthood (19). In these adults with new onset tics, it is important to search for secondary causes such as infection, stroke, trauma, illicit drugs, neuroleptic exposure, and neuroacanthocytosis (10,19, 20) (see Differential diagnosis).

In addition to involuntary noises, some patients have speech dysfluencies that resemble developmental stuttering and up to half of all patients with developmental stuttering may have undiagnosed TS (21). Except for tics, increased blink rates (22), subtle oculomotor disturbances related to saccadic eye movements (23), and other evidence of mild impairment of motor control (e.g. poor penmanship), the neurological examination in patients with TS is otherwise normal.

Besides motor and phonic tics, patients with TS often exhibit a variety of behavioral symptoms, particularly ADHD and OCD. These comorbid behavioral conditions often interfere with overall functioning and with academic and work performance more than tics and, if left untreated, may lead to social and emotional maladjustment. While 3-6% of school-aged population suffers from ADHD (24), a majority of patients with TS have symptoms of ADHD, OCD, or both sometime during the course of their illness (25). Other behavioral comorbidities may include poor impulse control and inability to control anger. One of the most distressing symptoms of TS is a self-injurious behavior (2,5,26). A common form of self-injurious behavior is compulsive, repetitive damage to the skin by biting, scratching, cutting, engraving (5), hitting (particularly in the eye and throat), often accompanied by an irresistible urge (obsession). Besides comorbid behavioral conditions, TS has been reported to be frequently associated with migraine headaches (27), present in 26.6% of patients in one study (28).

Etiology

Various biochemical, imaging, neurophysiologic and genetic studies support the notion that TS is an inherited, developmental disorder of synaptic neurotransmission resulting in disinhibition of the cortico-striatal-thalamic-cortical circuitry (1). Although postmortem neuropathological

examinations of brains of patients with TS have not revealed any specific pathological changes (29), the basal ganglia, particularly the caudate nucleus, and the inferior prefrontal cortex, have been implicated (via dopaminergic abnormalities (30)) in the pathogenesis of TS, as well as OCD and ADHD (31).

The TS gene has not been isolated as yet. A systematic genome scan using 76 affected sib-pair families with a total of 110 sib-pairs showed two regions, 4q and 8p, with increased lod scores suggesting that these loci may contain TS-related genes (32). Future genetic studies must consider the common observation that both parents of a TS child often exhibit TS or a forme fruste of TS. Such bilineal transmission is noted in 25 to 41% of TS families (33,34). Twin studies, showing 89 – 94% concordance for TS, also provide strong support for the genetic etiology of TS (35).

There is also evidence that Tourette syndrome may occur in a subset of patients as a result of basal ganglia dysfunction secondary to post-streptococcal immunity (36,37,38,39).

Epidemiology

TS affects males approximately three times more frequently than females.

While observational studies in public schools have suggested a prevalence of TS to be about 0.7% (33,40), the prevalence rates have been estimated to be as high as 4.2% when all types of tic disorders are included (41,42). Different ascertainment methods, different study populations, and different clinical criteria are likely to explain this wide variation in prevalence.

Diagnostic methods

The diagnosis of TS is based on a history and an observation of tics, often supported by the co-existence of behavioral disorders, particularly ADHD and OCD, and a family history of similar symptoms.

Treatment

The first step in the management of patients with TS is proper education of the patients, family members, teachers and other individuals who interact with the patient. Behavioral therapies, habit reversal or supportive psychotherapy, may be useful ancillary techniques in patients whose response to other therapies, including pharmacotherapy, is not entirely satisfactory (43, 44). Medications are usually considered when symptoms begin to interfere with peer relationships, social interactions, academic or job performance, or with activities of daily living. In a small percentage of patients, however, symptoms are intractable to any conservative treatment and various attempts have been made

to treat these patients through ablative procedures, and recently, deep brain stimulation (DBS) (45). Because of the broad range of neurologic and behavioral manifestation and varying severity, therapy of TS must be individualized and tailored specifically to the needs of the patient and the most troublesome symptoms should be targeted first (46) (**Table 1**).

Treatment of Tics

The goal of treatment should not be to completely eliminate all the tics, but to relieve tic-related discomfort or embarrassment and to achieve a control of tics that allows the patient to function as normally as possible. Although controlled, double-blind, placebo-controlled trials, are lacking the dopamine receptor blocking drugs (neuroleptics) are considered the most effective anti-tic agents (**Table 1**). Haloperidol and pimozide are the only neuroleptics currently approved by the Food and Drug Administration for the treatment of TS. In one randomized, double-blind, controlled study pimozide was found to be superior to haloperidol with respect to efficacy and side effects (47). Some clinicians, however, prefer risperidone (48,49), fluphenazine, thioridazine, trifluoperazine, molindone, thiothixene, and tiapride. It is not clear whether the atypical neuroleptics, such as clozapine, olanzapine, or quetiapine will be effective in the treatment of tics and other manifestations of TS, but ziprasidone was found in one study to decrease tic severity by 35% (50). Tetrabenazine, a monoamine depleting and dopamine receptor blocking drug (not yet available in the US), is a powerful anti-tic drug, and it has the advantage over the conventional neuroleptics in that it does not cause tardive dyskinesias (51). Besides tardive dyskinesia, other side effects possibly associated with neuroleptics include sedation, depression, weight gain, school phobia, and hepatotoxicity. In addition, pimozide may prolong the QT interval and, therefore, it is recommended that an electrocardiogram is performed before starting pimozide, and that electrocardiogram is repeated three months later and at least once a year thereafter. Other drugs found to be useful in the treatment of tics include clonazepam, pergolide, cannabinoids, nicotine gum and transdermal nicotine patch, but none of these drugs have been studied by well-designed, placebo-controlled trials (52). Focal motor and vocal tics have been also successfully treated with botulinum toxin injections in the affected muscles (53-55). Such local chemodenervation ameliorates not only the involuntary movements but may also eliminate the premonitory sensory component. The benefits last on the average 3

to 4 months and no serious complications have been reported.

Treatment of Comorbid Behavioral Symptoms

Central nervous system (CNS) stimulants, such as methylphenidate (Ritalin), controlled-release methylphenidate, dextroamphetamine, mixture of amphetamine salts, pemoline, and atomoxetine are clearly the most effective agents in the treatment of ADHD (56). These agents have been found useful also as a short-term therapy of conduct disorders (57). Although CNS stimulants may initially increase the frequency and intensity of tics, with continued use these drugs can be well tolerated without sustained tic exacerbation (57). The antidopaminergic drugs can be combined with the CNS stimulants if the latter produce unacceptable exacerbation of tics. Alpha-2 agonists are also useful in the treatment of ADHD, particularly if CNS stimulants are not well tolerated or are contraindicated. Clonidine, a presynaptic a2-adrenergic agonist, used as an antihypertensive because it decreases plasma norepinephrine, improves symptoms of ADHD, impulse control problem, and may ameliorate tics. Pharmacologically similar to clonidine, guanfacine may be effective in patients in whom clonidine failed to control the behavioral symptoms (58). Guanfacine may have some advantages over clonidine in that it has a longer half-life, it appears to be less sedating, and it produces less hypotension. Other drugs occasionally used in the treatment of mild cases of ADHD include tricyclic antidepressants, such as imipramine, nortriptyline, and desipramine. The selective serotonin uptake inhibitors (SSRIs) are effective in the treatment of TS-associated OCD (59-61). These include fluoxetine, fluvoxamine, clomipramine, paroxetine, sertraline, venlafaxine, and citalopram.

Table 1: Pharmacology of Tourette syndrome

DRUGS	INITIAL DOSAGE (MG/DAY)	CLINICAL EFFECT
DOPAMINE RECEPTOR BLOCKERS		TICS
1. Fluphenazine	1	+++
2. Pimozide	2	+++
3. Haloperidol	0.5	+++
4. Risperidone	0.5	++
5. Ziprasidone	20	++
6. Thiothixene	1	++
7. Trifluoperazine	1	++
8. Molindone	5	++
DOPAMINE DEPLETERS		TICS
1. Tetrabenazine	25	++
CNS STIMULANTS		ADHD
1. Methylphenidate	5	+++

2. Pemoline	18.75	++
3. Dextroamphetamine	5	++
NORADRENERGIC DRUGS		IMPULSE CONTROL/ADHD
1. Clonidine	0.1	++
2. Guanfacine	1.0	++
SEROTONINERGIC DRUGS		OCD
1. Fluoxetine	20	+++
2. Clomipramine	25	+++
3. Sertraline	50	+++
4. Paroxetine	20	+++
5. Fluvoxamine	50	+++
6. Venlafaxine	25	+++

+ = minimal improvement, ++ = moderate improvement, +++ = marked improvement

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