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Tourette's syndrome: I. Symptomatology and Etiology

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Abstract

Tourette's syndrome (TS) is an ancient disease that belongs to a group of disorders of the developing nervous system called 'tic disorders'. It is a common inherited, neurodevelopmental, neuropsychiatric, motor disorder that may cause sudden, unwanted, and uncontrolled rapid and repeated movements or vocal sounds called 'tics'. There is a lack of consensus about its definition. In this Article, after briefly retracing the history of TS, I will present its characteristics, clinical phenomenology, neuropsychological function, and the brain structures it affects. I will then describe its signs and symptoms, and dwell at some length on its main hallmark – the tics in terms of their morphology, premonitory urges, trigger, urge to express them, onset and duration, and suppression. Subsequently, I will outline the risk and several potential causal factors of TS, including genetic, environmental, and infectious factors as well as psychosocial stress, neuroanatomical factors, neuroimmunological factors, and psychosocial or other non-genetic factors. Interestingly, it will be indicated that TS may be triggered by an autoimmune response and more generally be linked to immune-system abnormalities and immune dysregulation. I will further discuss the mechanism of TS and multiple possible co-occurring conditions. Lastly, I will present the prevalence rates and epidemiology (both genetic and environmental) of the syndrome.

Abbreviations

AAN: American Academy of Neurology; AD: Affective Disorders; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorders; APA: American Psychiatric Association; B/NG: Basal/Nuclei Ganglia; CBG: Cortico Basal Ganglia; CD: conduct disorder; CDC&P: (U.S.) Center for Disease Control & Prevention; CSTC: Cortico-striato-thalamo-cortical; DSM: Diagnostic & Statistical Manual of Mental Disorders; DZ: Dizygotic; ECG: European Clinical Guidelines; ESSTS: European Society for the Study of Tourette's Syndrome; EU: European Union; GEI: Genetic, Environmental, Infectious; GWAS: Genome-

Wide Association Studies; ICD: International Statistical Classification of Diseases & Related Health Problems; ICD: Impulse Control Disorder; MCTD: Motor Chronic (persistent) Tic Disorder; MPTD: Motor Provisional Tic Disorder; MZ: Monozygotic; NOSIB: Non-Obscene Socially Inappropriate behavior; OC/BD: Obsessive Compulsive/Behavioral Disorder; ODD: Oppositional Defiant Disorder; PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections; PANS: Pediatric Acute-onset Neuropsychiatric Syndrome; PD: Personality Disorder; PTSD: Post-Traumatic Stress Disorder; TAA: Tourette Association of America; TS: Tourette's Syndrome; TSA: Tourette Syndrome Association; TSA-ICG: Tourette Syndrome Association's International Consortium on Genetics; VTD: Vocal Tic Disorder; WCSC: Yale Child Study Center; WHO: World Health Organization (WHO).

Keywords

Attention deficit hyperactive disorder; Autoimmune dysregulation; Obsessive compulsive/behavior disorder; autism spectrum disorder; Coprolalia; Echolalia; Movement disorder; Neurodevelopmental disorder; Neuropsychiatric disorder; Tic disorders; Tourette's syndrome.

Background

The history of Tourette's syndrome (TS) dates back to the fifteenth century's book *Malleus Maleficarum* (Hammer of Witches), which describes a priest whose tics were "*believed to be related to possession by the devil*". The first clinical description of the disease was made only in 1825 by the French physician, Jean Marc Gaspard Itard. However, the true history of the disease begun only half-a-century later with Jean-Martin Charcot, an influent French physician and neurologist at the Hôpital de la Salpêtrière, Paris. Charcot entrusted one of his neurology students, Georges Gilles de La Tourette, with a study of patients to the end of defining symptoms distinct from hysteria and chorea (movements of cerebral origin that are irrepressible and beyond any volition).

Charcot and Tourette then believed that the "tic illness" they had observed was an untreatable, chronic, and progressive hereditary condition. In 1885, Tourette published a report on nine patients titled "*Étude sur une affectation nerveuse caractérisée par de l'incoordination motrice accompagnée d'écholalie et de copralalie*" (which translates as 'Study of a nervous condition characterized by motor incoordination accompanied by echolaly and copralaly) in which he pointed out the need to define a new clinical category. The name chosen by Charcot was finally that of "sickness of Gilles de la Tourette" in honor of his student. Little progress was made over the 19th century in explaining or treating tics. With limited clinical experience, involving typically very few (perhaps one or two) patients, authors advanced different ideas as a cause of the tics, including brain lesions similar to those resulting from rheumatic chorea or *encephalitis lethargica*. Such ideas also included faulty mechanisms of normal habit formation and treatment with Freudian psychoanalysis.

Following the 19th-century descriptions of the disease, a psychogenic view of it prevailed so that little progress was made in explaining or treating tics until well into the 20th- century. Then, for nearly a century, nothing came about to explain or treat the characteristic tics of the syndrome. A psychiatric approach became privileged until the twentieth century. The possibility that movement disorders, including TS, might have an organic origin began to appear when the 1918-26 *encephalitis lethargica* epidemic led to a subsequent epidemic of movement and tic disorders.

The first pharmacological treatment of the disease with *Haloperidol* (*Haldol*) was approved in the 1960s-70s for attenuating the severity of the tics. As the beneficial effects of this drug became known, the psychoanalytic

approach to TS was questioned.

In 1972, working with patients' families, the Shapiros (husband and wife team) founded the Tourette Syndrome Association (TSA), which was later renamed Tourette Association of America (TSA) in 2015. They advanced the argument that TS is a neurological, rather than a psychological, disorder and worked to persuade the media to promote information about it. In the 1990s, a more neutral view of the etiology of TS emerged in which a genetic predisposition is seen to interact with non-genetic and environmental factors. Since 1999, notwithstanding the new discoveries made in genetics, neuroimaging, neurophysiology, and neuropathology, numerous questions remained regarding how best to characterize TS and how closely it is related to other movement or psychiatric disorders. Nonetheless, epidemiological data are still insufficient and available treatments are neither without risks nor always well tolerated.

The 21st century saw the enactment of several diagnostic criteria, classifications, and guidelines by the American Psychiatric Association (APA), the European Society for the Study of Tourette's Syndrome (ESSTS), the American Academy of Neurology (AAN), the European Union (EU), and the World Health Organization (WHO) (see the Appendix).

Introduction - What is TS?

There is a lack of consensus about the definition of TS. It belongs to a group of disorders of the developing nervous system called 'tic disorders'. It is a common inherited, neurodevelopmental, neuropsychiatric, motor disorder that may cause sudden, unwanted, and uncontrolled rapid and repeated movements or vocal sounds called 'tics'. Once regarded as a rare and bizarre disorder, TS continues to be so regarded by some clinicians and scientists. It has popularly been associated with 'coprolalia' (the utterance of obscene words or socially-inappropriate and derogatory remarks). It is not a degenerative condition in that it does not continue to get worse.

The motor (involving body movement) or vocal (involving sounds made) tics of TS wax and wane and vary in type, frequency, location, and severity. Since vocal tics result from a motor event (i.e., a contracting diaphragm moving air through the upper airways), TS could be defined as a disorder of motor tics, eliminating the distinction between TS and the other tic disorders.

People with TS are commonly affected by other co-occurring conditions such as attention deficit hyperactivity disorder (ADHD) or/and obsessive compulsive/behavior disorder (OC/BD) and sensory phenomena, all disorders that I will address only briefly in this Article. Questions remain as to whether such disorders should also be part of the core definition of TS, and why sensory phenomena, which are a core part of TS, are not part of the diagnostic criteria. In addition, since individuals who have only tics may not be functionally impaired, the question was raised as to whether TS, as currently defined, should be a diagnosis in the Diagnosis & Statistical Manual (DSM) of Mental Disorders (Appendix).

Characteristics of TS

TS is characterized by the presence of multiple movement (motor) tics and at least one vocal (phonic) tic. Common tics are: blinking, coughing, throat clearing, sniffing, and facial movements. These are typically preceded by an unwanted urge or sensation in the affected muscles known as a 'premonitory urge'. They can sometimes be suppressed temporarily and, characteristically, change in location, strength, and frequency. TS is at the more severe end of a spectrum of tic disorders. The tics often go unnoticed by casual observers.

There are no specific tests for diagnosing TS. It is not

always correctly identified because most cases are mild, and the severity of tics decreases for most children as they pass through adolescence. Therefore, many go undiagnosed or may never seek medical attention. Though sensationalized in the media, extreme TS in adulthood is rare but, for a small minority, severely debilitating tics can persist into adulthood. TS does not affect intelligence or life expectancy.

There is currently no cure for TS and no single most effective medication. In most cases, medication for tics is not necessary and behavioral therapies are the first-line treatment. Education is an important part of any treatment plan, and explanation alone often provides sufficient reassurance that no other treatment is necessary.

The co-occurring conditions (ADHD, OC/BD, and others) are more likely to be present among those who are referred to specialty clinics than they are among the broader population of persons with TS. They often cause more impairment to the individual than the tics; hence, it is important to correctly distinguish co-occurring conditions and treat them.

Clinical phenomenology - Onset and progression of TS

TS is the primary tic disorder that reaches most commonly medical attention and monitoring. Motor and phonic tics are its core features. In addition to their well-characterized phenomenology, tics display a peculiar variability over time, which is strongly influenced by a variety of contextual factors. The sensory phenomena of TS are increasingly recognized as another crucial symptom of TS and consist of premonitory urges and somatic hypersensitivity.

A relevant proportion of patients with TS display complex, tic-like, repetitive behaviors that include echophenomena, coprophenomena, and non-obscene socially inappropriate behaviors (NOSIBs). The burden of behavioral co-morbidities is very important in determining the degree of disability of TS patients. Only a small minority of TS patients presents exclusively with a tic disorder (so-called 'TS-only' or 'pure-TS'). OCDs are common and the clinical distinction between compulsions and complex tics may be difficult in some cases. Probably, the presence of co-morbid ADHD is the main determinant of cognitive dysfunction in TS patients that influences heavily also the risk of developing disruptive behaviors. Affective disorders (AD), impulse control disorders (ICD), autism spectrum disorders (ASD), and personality disorders (PD) complete the wide psychopathological spectrum of this condition, but have been less investigated than OCD and ADHD.

The complexity of TS has been confirmed by cluster and factor analytical approaches, and is likely to inform the study of the genetic basis of this disorder as well as future reappraisal of its nosography, with the development of novel clinical subtypes.

There is no typical case of TS but the age of onset and the severity of symptoms follow a fairly reliable course. Although onset may occur anytime before 18 years, the typical age of onset of tics is 5-7, and is usually before adolescence. A 1998 study from the Yale Child Study Center (YCSC) showed that tic severity increased with age until it reached its highest point between 8-12. Severity then declines steadily for most children as they pass through adolescence when half to two-thirds of children see a dramatic decrease in tics.

In people with TS, the first tics to appear usually affect the head, face, and shoulders, and include blinking, facial movements, sniffing, and throat clearing. Vocal tics often appear months or years after motor tics but can appear first. Among people who experience more severe tics, complex tics may develop, including "arm straightening, touching, tapping, jumping, hopping, and twirling". There are different movements in contrasting disorders (for example, the autism spectrum disorders,

ASD), such as self-stimulation and stereotypes.

The severity of symptoms varies widely among people with TS and many cases may be undetected. Most cases are mild and almost unnoticeable, Many people with TS may not realize they have tics. Because tics are more commonly expressed in private, TS may go unrecognized and casual observers might not notice them. Most studies of TS involve males, who have a higher prevalence of TS than females, and gender-based differences are not well studied. A 2021 review suggested that the characteristics and progression for females, particularly in adulthood, may differ pointing to the need for better studies.

Most adults with TS have mild symptoms and do not seek medical attention. While tics subside for the majority after adolescence, some of the "most severe and debilitating forms of tic disorders are encountered" in adults.

In some cases, what appear to be adult-onset tics can be childhood tics re-surfacing. Unfortunately, because people with milder symptoms are unlikely to be referred to specialty clinics, TS studies have an inherent bias towards more severe cases.

Neuropsychological function

There are no major impairments in neuropsychological function among people with TS, but conditions that occur along with tics can cause variation in neurocognitive function.

A better understanding of co-morbid conditions is needed to untangle any neuropsychological differences between TS-only individuals and those with co-morbid conditions.

Several psychiatric and behavioral disorders are associated with TS including, as previously indicated, ADHD, OC/BD, learning disabilities, anxiety, and emotional swings. Only slight impairments are found in intellectual ability, attentional ability, nonverbal memory, and social cognition, but not in the ability to plan or make decisions.

Learning disabilities may be present, but whether they are due to tics or co-morbid conditions is controversial. Older studies that reported higher rates of learning disability did not control well for the presence of co-morbid conditions. There are often difficulties with handwriting, and disabilities in written expression and math are reported in those with TS plus other conditions.

Brain structures affected by TS

The brain structures affected by TS include the cerebellum and basal/nuclei ganglia (B/NG):

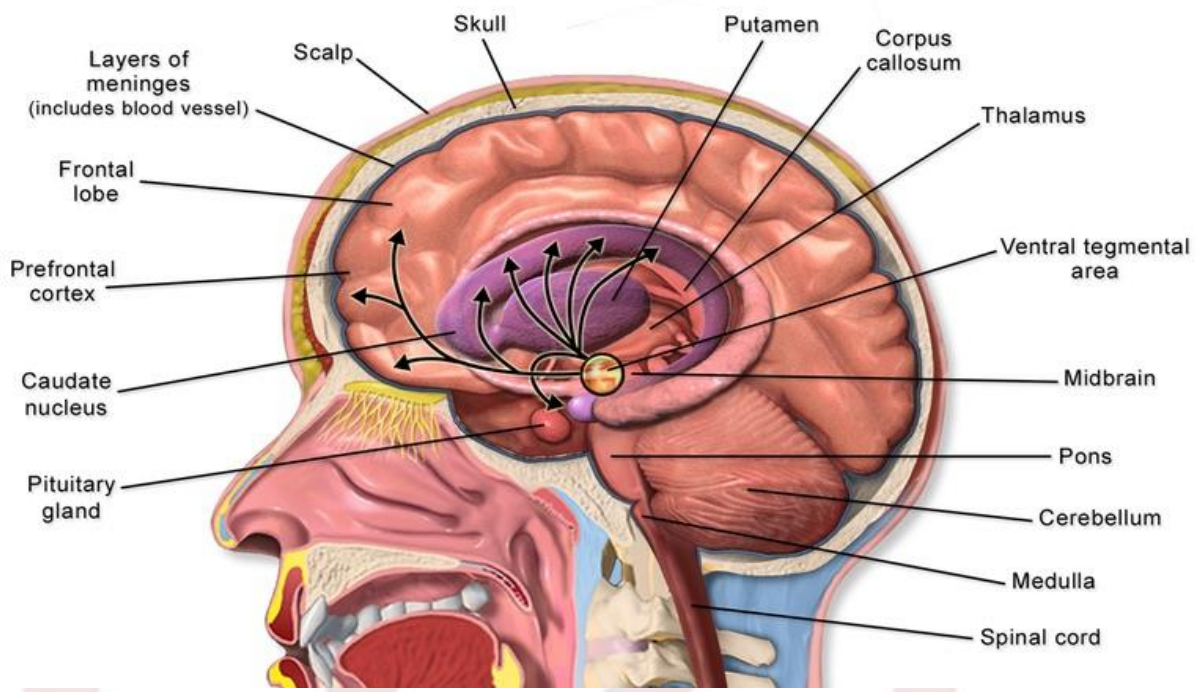
The cerebellum

The cerebellum (Latin for "little brain") is a major feature of the hindbrain (Figure 1). It appears as a separate structure attached to the bottom of the brain, tucked underneath the cerebral hemispheres. Although usually smaller than the cerebrum, the cerebellum plays an important role in motor control.

While definitely associated with movement-related functions, it may also be involved in some cognitive functions (such as attention and language) as well as emotional control (such as regulating fear and pleasure responses).

It does not initiate movement, but contributes to coordination, precision, and accurate timing. Cerebellar damage produces disorders in fine movement, equilibrium, posture, and motor learning.

In addition to its direct role in motor control, the cerebellum is necessary for several types of motor learning, most notably learning to adjust to changes in sensorimotor relationships.



Reference: Bruce Baus

Figure 1 – The cerebellum

The basal/nuclei ganglia

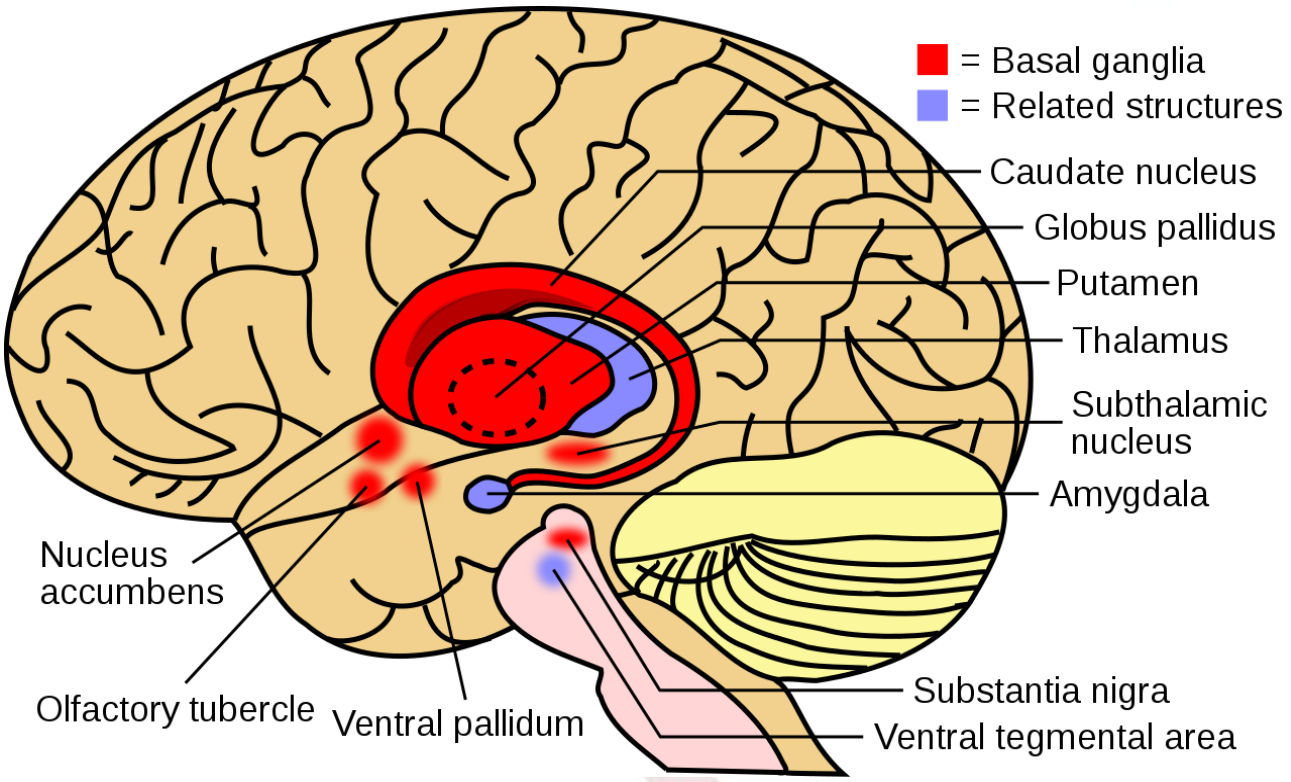
The B/NG (in red color in Figure 2) are a group of subcortical nuclei of varied origin situated between the forebrain and the midbrain forming a group of interconnected structures in the brain. They are strongly interconnected with the cerebral cortex (in beige color), the thalamus (blue/purple color), and the brainstem as well as several other brain areas. They are associated with a variety of functions, including control of voluntary motor movements, learning (procedural, habit, conditional), eye movements, cognition, and emotion.

Defined functionally, the main BG components are the striatum, globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus (see all these brain components in the different red areas of Figure 2). Each of these components has a complex internal anatomical and neurochemical organization.

It has been hypothesized that the B/NG are not only responsible for motor action selection (that is helping to decide which of several possible behaviors to execute at any given time) but also for the selection of more cognitive actions. They are of major importance for normal brain function and behavior. Their dysfunction results in a wide range of neurological conditions including disorders of behavior control and movement, as well as cognitive deficits that are similar to those that result from damage to the prefrontal cortex.

Impact of TS

Having TS can impact on many areas of life, particularly when children have another additional condition. Using data from the (U.S.) Center for Disease Control & Prevention (CDC&P), the following impact examples have been noted on education (children with TS experience being treated differently by teachers and other adults), health and health care, parenting, social competence, bullying involvement (most common among peers), and public health impact.



Reference: BrainCaudatePutamen.svg

Figure 2 – Brain structures affected by TS: Basal ganglia and related structures

The CDC&P and other public and private organizations are working to better understand TS, to improve the health and well-being of people with TS, and what public health can do to bridge the gaps in knowledge to help individuals with TS.

Signs and symptoms of TS

Tics are the main symptoms of TS. They usually begin when a child is 5 to 10 years of age, although many people may experience them into adulthood. In most cases, tics decrease during adolescence and early adulthood, and sometimes even disappear entirely. In some cases, however, tics can become worse during adulthood. The types of tics, and how often a person has them, changes a lot over time. Even though the symptoms might appear, disappear, and reappear, these conditions are considered chronic.

Although the media often portray people with TS as involuntarily shouting-out swear words (coprolalia) or constantly repeating the words of other people

(echolalia), these symptoms are rare and are not required for a diagnosis of TS.

Morphology of tics

Generally, tics are movements or sounds that take place "*intermittently and unpredictably out of a background of normal motor activity*", having the appearance of "*normal behaviors gone wrong*". They may also occur in "*bouts of bouts*", which may vary among people. The variation in tic severity may occur over hours, days, or weeks. They are involuntary movements and vocalizations that affected people do repeatedly. They may increase when someone is experiencing stress, fatigue, anxiety, or illness or when engaged in relaxing activities like watching TV. They sometimes improve (decrease) when an individual is engrossed in, or focused on, an activity like playing a musical instrument.

The first tics often are motor tics that occur in the head and neck area. They are sudden, repetitive, nonrhythmic, and uncontrollable movements that involve discrete muscle groups. By contrast, vocal (phonic) tics produce a sound, involving laryngeal, pharyngeal, oral, nasal or respiratory muscles to produce sounds. Both motor and vocal tics can either be simple or complex.

Tics can occur in any body part, such as the face, shoulders, hands, arms, or legs. Most tics are mild and hardly noticeable, however, in some cases, they are frequent and severe, and can affect many areas of a child's life. They are the primary symptoms of a group of childhood-onset neurological conditions known collectively as 'tic disorders' and individually as Tourette's syndrome (TS), vocal tic disorder (VTD), motor chronic (persistent) tic disorder (MCTD), and motor provisional tic disorder (MPTD). These latter three tic disorders are named based on the types of tics present (*vocal/phonic, motor, or both*) and by the length of time during which the tics have been present. Now, to be considered as tics, they must not be explained by other medical conditions or substance use.

Premonitory urges

Some tics are preceded by an urge or sensation in the affected muscle group (a premonitory urge). One may feel like having to complete a tic in a certain way or a certain number of times to relieve the urge or decrease the sensation. Children may be less aware than are adults, but their awareness tends to increase with maturity. By the age of ten, most children recognize the premonitory urge. On the other hand, some people with TS may not be aware of the premonitory urge associated with tics.

Urge to express the tics

People describe the urge to express the tic as a build-up of tension, pressure, or energy which they ultimately choose consciously to release, as if they "*had to do it*" to relieve the sensation or until it feels "*just right*". The urge may cause a distressing sensation in the part of the body associated with the resulting tic. The tic is actually a response that relieves the urge in the anatomical location of the tic. Examples of this urge are the feeling of having something in one's throat, leading to a tic to clear one's throat, or a localized discomfort in the shoulders leading to shrugging the shoulders. The actual tic may be felt as relieving this tension or sensation, similar to scratching an itch or blinking to relieve an uncomfortable feeling in the eye.

Typical onset and duration

Tics typically emerge between the ages of 5 and 7 years, usually with a motor tic in the head or neck region. They tend to increase in frequency and severity between the ages of 8 and 12 years, and can range from mild to severe. Most people with TS see improvements by late adolescence, with some becoming tic-free. A minority of people with TS continue to have persistent, severe tics into adulthood.

Tics can range from mild to severe and, in some cases, can be self-injurious and debilitating. They regularly change in type, frequency, and severity—sometimes for reasons unknown and sometimes in response to specific internal and external factors, including stress, anxiety, excitement, fatigue, and illness.

Tic triggers

Tics may worsen with excitement or anxiety and get better during calm, focused activities. Certain physical experiences can trigger or worsen tics; for example, tight collars may trigger neck tics. Hearing another person sniff or clear the throat may trigger similar sounds. Tics do not go away during light sleep but are often significantly diminished; they go away completely in deep sleep.

Although the symptoms of TS are unwanted and unintentional (involuntary), some people can suppress or otherwise manage their tics to minimize their impact on functioning. However, people with TS often report a substantial build-up in tension when suppressing their tics to the point where they feel that the tic must be expressed (against their will). Tics in response to an environmental trigger can appear to be voluntary or purposeful, but are not.

Tic suppression

The premonitory urges that precede the tic make suppression of the impending tic possible. Because of the urges that precede them, tics are described as 'semi-voluntary' or 'involuntary' rather than specifically involuntary. They may be experienced as a voluntary, suppressible response to the unwanted premonitory urge. The ability to suppress tics varies among individuals, and may be more developed in adults than children. People with tics are sometimes able to suppress them for limited periods of time, but doing so often results in tension or mental exhaustion.

Tics can be stopped voluntarily for brief periods but it is hard and, eventually, the person has 'to do the tic'. Generally, people who have tics cannot stop their body from "*doing these things*". Having tics is a little bit like having hiccups. Even though one might not want to hiccup, the body does it anyway.

Tics simplicity/complexity

Motor and vocal tics can be either simple or complex, and may range from very mild to severe although most cases are mild. Thus:

- **Simple motor tics:** They are sudden, brief, repetitive movements that involve a few muscle groups or just a few parts of the body. They are more common than complex tics and often precede them. Examples include: Eye blinking, squinting, or other movement; facial grimacing; jaw movements; neck stretching; and sniffing.

- **Complex motor tics:** They usually involve multiple several different parts of the body (muscle groups or combinations of movements) and tend to be slower (for some) but more purposeful in appearance. They can have a pattern. Examples include: Arm jerking; bending; bobbing the head while jerking an arm and then jumping up; facial grimacing combined with a head twist and a shoulder shrug; hopping; jumping; shrugging the shoulders; sniffing or touching an object; twirling; and twisting.

- **Simple vocal tics:** Examples include: Barking; grunting; hooting; humming; shouting; sniffing; throat clearing; and yelling out a word or phrase,

Complex vocal tics: They are words or phrases that may or may not be recognizable but that consistently occur out of context. In 10%-15% of cases, the words may be inappropriate and often portrayed or mocked in the media as a common symptom of TS. Examples include: Repeating one's own or others' words or phrases; vulgar, obscene, or swear words; ethnic slurs; or other socially-unacceptable words or phrases (see section below on complex tics related to speech).

Children with TS have both body and vocal tics. As previously indicated, some tics disappear by early adulthood, and some continue. They may also have problems with attention and/or learning disorders. They may act impulsively. Some may even develop obsessions and compulsions.

Complex tics related to speech

Complex tics related to speech include coprolalia, echolalia and palilalia:

- **Coprolalia:** This is the spontaneous utterance or blurting out of obscene words; insults to others; obscene gestures or movements; socially-inappropriate and derogatory remarks; or taboo words or phrases. TSers cannot control these sounds and movements and should not be blamed for them. Punishment by parents, teasing by classmates, and scolding by teachers will not help the child to control the tics but will hurt the child's self-esteem and increase their distress. Although coprolalia is the most publicized symptom of TS, only about 10% of people with TS exhibit it, and it is not required for a diagnosis;

- **Echolalia:** This is repeating the words of others. These tics may be some of the most dramatic and disabling ones and may result in self-harm such as punching one's own face; and

- **Palilalia:** This is repeating one's own words. It occurs in a minority of cases.

On the other hand, corresponding to the above three speech tics, are complex motor tics that include:

- **Copropraxia:** The obscene or forbidden gestures, or inappropriate touching;

- **Echopraxia:** The repetition or imitation of another person's actions; and

- **Palipraxia:** The repeating of one's own movements.

Risk and potential causal factors of TS

Despite extensive research and numerous clinical trials, the risk and causal factors of TS are still not well understood.

Risk factors

Research has evidenced the following factors:

- TS is inherent as a dominant gene with about 50% chance of parents passing the gene to their children. Actually, TS is a complex epigenetic disorder that likely occurs as a result of the effects of multiple genes interacting with other factors in the environment;

- Boys with the gene(s) are 3-4 times more likely than girls to display symptoms of TS; and

- TS can be triggered by abnormal metabolism (breakdown) of dopamine in the brain.

Other possible causes and environmental risk factors that might contribute to TS continue to be studied, including possibly: Smoking during pregnancy; pregnancy complications; and low birthweight. Certain children might perhaps be more likely to develop tics following an infection. However, even if such associations were to be elucidated, let us remember

ourselves that associations are not causations!

Possible causal factors

Genetic factors: Genetic epidemiology studies have shown that TS is highly heritable, and 10-100 times more likely to be found among close family members than in the general population. TS runs in families and its symptoms seem to pass from parent to child. TS tics and other symptoms are more prevalent in children who have parents with these symptoms. Some scientific theories suggest that the genes involved in TS and its symptoms are also responsible for the sex differences in the incidence of TS. Thus, boys are more likely to have tics with associated conditions such as ADHD and OCD, whereas girls are less likely to have tics and more likely to have associated conditions such as anxiety and OCD.

However, the exact mode of inheritance is not known, no single gene has been identified, and hundreds of genes are likely involved. Not everyone who inherits the genes for TS will show symptoms, though. The overall risk for a parent, child, or sibling having TS is between 5% and 15%.

Genome-wide association studies (GWAS) were published in 2013 and 2015 in which no finding reached a threshold for significance. Also, a 2019 meta-analysis found only a single genome-wide significant locus on **chromosome 13**, but that result was not found in broader samples. Twin studies show that 50%-77% of identical twins share a TS diagnosis, while only 10%-23% of fraternal twins do. But, not everyone who inherits the genetic vulnerability will show symptoms. Although there may be a few genes with substantial effects, it is also possible that many genes with smaller effects and environmental factors may play a role in the development of TS. Genetic studies also suggest that some forms of ADHD and OCD are genetically related to TS, but there is less evidence for a genetic relationship between TS and other neurobehavioral problems that commonly co-occur with TS.

It is important to understand that genetic tendency may not necessarily result in TS; instead, it may express itself as a milder tic disorder or as obsessive-compulsive behaviors. It is also possible that children who inherit the gene abnormality will not develop any TS symptoms. Gender also plays an important role in TS gene expression. At-risk males are more likely to have tics and at-risk females are more likely to have obsessive-compulsive symptoms. Genetic counseling of people with TS should include a full review of all potentially hereditary conditions in the family.

• **Environmental factors:** Environmental exposures during the prenatal period, perinatal stages, and postnatal life may contribute to the onset and course of TS. Pregnancy-related noxious exposures may be more frequent in pregnancies of children who will develop TS, particularly maternal smoking and prenatal life stressors. Lower birth-weight and use of forceps at delivery may be associated with tic severity in the offspring. Moreover, low birth-weight and maternal smoking during pregnancy may affect the risk of co-morbid ADHD/OCD.

• **Infectious factors:** Group A streptococcal infections as risk-modifier for TS have not been convincingly demonstrated to date, although an interaction with stressors was suggested. The PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) hypothesis is currently undergoing a nosological revision. Only limited anecdotal evidence supports a link of TS to other pathogens. Nevertheless, the relationship between infections and TS may be complex. Recent data point to intrinsically altered immune regulation in TS, which might predispose to both infections and autoimmune mechanisms; however, evidence of cell-mediated and antibody-mediated autoimmunity in TS is still insufficient.

Other factors may also include:

• **Psychosocial stress:** It remains the most important contextual factor influencing tic severity, as confirmed by prospective studies. This might in part be related to enhanced reactivity of the stress response in TS patients, the mechanisms of which need to be explored further. New studies on large prospective cohorts of patients of different age and the identification of reliable biomarkers or endophenotypes indicating early, prenatal exposure to environmental insults are needed.

• **Neuroanatomical factors:** Some neurotransmitters responsible for communication between nerve cells (neurons) play a role in TS and its treatment. Three, in particular, seem related to TS (dopamine, noradrenaline, and serotonin). The dopamine neurotransmitter is known for its important inhibiting role in actions and behaviors. The tics are supposed to originate from dysfunctions in the cortical and subcortical regions of the thalamus, the basal ganglia, and the frontal cortex. Neuroanatomical models imply lesions in the circuits connecting the cortex and subcortex. Brain imaging techniques have also shown involvement of the basal ganglia at the basis of the frontal cortex. This points to abnormalities in other brain regions, including the frontal lobes and cortex as well as the circuits that connect these regions (refer to Figures 1 and 2).

• **Neuroimmunological factors:** Several perturbations of numerous immunological parameters suggest a possible immunological causal contribution. Having observed that sometimes, after an infection, the immune system seems to behave differently, some neuroscientists believe that TS can be triggered by an autoimmune response after a childhood infection. In other words, autoimmune processes may affect the onset of tics or exacerbate them. Both OCD and tic disorders are hypothesized to arise in a subset of children as a result of a post-streptococcal autoimmune process. Its potential effect is described by the controversial PANDAS hypothesis which proposes five criteria for diagnosis in children. PANDAS and the newer pediatric acute-onset neuropsychiatric syndrome (PANS) hypothesis are the focus of clinical and laboratory research, but remain unproven and a controversial subject. There is also a broader hypothesis that links immune-system abnormalities and immune dysregulation with TS.

• **Psychosocial or other non-genetic factors:** While not causing TS, psychosocial or other non-genetic factors can affect the severity of TS in vulnerable individuals and influence the expression of the inherited genes. Pre-natal and peri-natal events increase the risk that a tic disorder or co-morbid OCD will be expressed in those with the genetic vulnerability. These include: Paternal age; forceps delivery; stress or severe nausea during pregnancy; use of tobacco, caffeine, alcohol, and cannabis during pregnancy. Babies who are born premature with low birthweight, or who have low Apgar scores, are also at increased risk. In premature twins, the lower birthweight twin is more likely to develop TS.

TS Mechanism

The exact mechanism affecting the inherited vulnerability to TS is not well established. Tics are believed to result from dysfunction in cortical and subcortical brain regions: the thalamus, basal ganglia and the frontal cortex. Neuroanatomical models suggest failures in circuits connecting the brain's cortex and subcortex. Neuroimaging techniques and *post mortem* brain studies, as well as animal and genetic studies, made progress towards a better understanding of the neurobiological mechanisms leading to TS. These studies support the basal ganglia model, in which neurons in the striatum are activated and inhibit outputs from the basal ganglia.

Cortico-striato-thalamo-cortical (CSTC) circuits, or neural pathways, provide inputs to the basal ganglia

from the cortex. These circuits connect the basal ganglia with other areas of the brain to transfer information that regulates planning and control of movements, behavior, decision-making, and learning. Behavior is regulated by cross-connections that allow the integration of information from these circuits. Involuntary movements may result from impairments in these CSTC circuits, including the sensorimotor, limbic, language, and decision making pathways. Abnormalities in these circuits may be responsible for tics and premonitory urges.

The caudate nuclei may be smaller in subjects with tics compared to those without tics, supporting the hypothesis of pathology in CSTC circuits in TS. The ability to suppress tics depends on brain circuits that regulate the response inhibition and cognitive control of motor behavior. Children with TS are found to have a larger prefrontal cortex, which may be the result of an adaptation to help regulate tics. It is likely that tics decrease with age as the capacity of the frontal cortex increases. Corticobasal ganglia (CBG) circuits may also be impaired, contributing to sensory, limbic and executive features. The release of dopamine in the basal ganglia is higher in people with TS, implicating biochemical changes from overactive and dysregulated dopaminergic transmissions.

Also, histamine level in the H3-receptor may play a role in the alterations of neural circuitry. A reduced level may result in an increase in other neurotransmitters, causing tics. *Post-mortem* studies have also implicated dysregulation of neuroinflammatory processes. The mechanism appears to involve dysfunction in neural circuits between the basal ganglia and related structures in the brain.

Co-occurring conditions

People with TS often have other mental, behavioral, or developmental conditions that may be present prior to the onset of tics. These will merely be sketched here as they would require separate detailed treatments that would lie outside the scope of this Article. While tics are the primary symptoms, these co-occurring conditions may cause more problems and can be more bothersome than the tics themselves. Among people diagnosed with TS, it is estimated that 86% of them have been diagnosed with at least one of these additional conditions. The most common co-occurring conditions include: Anxiety; ADHD; OC/BD; behavioral or conduct problems (such as oppositional defiant disorder, ODD; conduct disorder, CD; and rage); depression; learning disability; sensory processing issues; sleep disorders; deficits in social skills; and social functioning.

Children with TS can also have other health conditions that require care. Among the more common health conditions that can occur with TS are: Asthma; hearing loss or vision problems; bone, joint, or muscle problems; and brain injury or concussion problems. In addition, children with TS are also less likely to receive effective coordination of care. They may additionally have educational concerns although, as a group, having levels of intelligence similar to those children without TS, children with TS might be more likely to have learning differences, a learning disability, or a developmental delay that affects their ability to learn. Many may have problems with writing, organizing, paying attention, and problems processing what they hear or see. This can affect the person's ability to learn by listening to, or watching, a teacher. Or, others might have problems with their other senses (such as how things feel, smell, taste, and move) that affect learning and behavior.

As a result of these challenges, children with TS might need extra help in school. Many times, these concerns can be addressed with accommodations and behavioral interventions (for example, help with social skills). Accommodations can include things such as providing a different testing location or extra testing time,

providing tips on how to be more organized, giving the child less homework, or letting the child use a computer to take notes in class. Children also might need behavioral interventions, therapy, or they may need to learn strategies to help with stress, paying attention, or other symptoms.

Prevalence Rates and Epidemiology Of TS

TS was once thought to be a rare disease, however, recognizing that tics may often be undiagnosed and hard to detect, newer studies use direct classroom observations and multiple informants (parents, teachers, trained observers) and, consequently, record more cases than older studies. Further, as the diagnostic threshold and assessment methodology have moved towards recognition of milder cases, the estimated prevalence has increased. Thus, under such considerations, TS may actually be a common but under-diagnosed condition that reaches across all social, racial, and ethnic groups. Since 2000, numerous published studies have indeed consistently demonstrated that the prevalence is much higher than previously registered or believed to exist. Nonetheless, a word of caution is appropriate here as the gathered data depend on the definition of TS which, as indicated earlier, lacks consensus at the present time.

Prevalence rates

Recent data suggest that TS is not a unitary condition and with possibly different types. The prevalence in these individual subtypes is unknown. For the future, it is suggested that a new nomenclature be adopted for TS pending further genetic and phenomenological studies. To what extent the etiology affects the phenotype and, thus, the prevalence is still unclear.

TS is found in all cultures, although to possibly differing degrees. In those cultures where it has been reported, the phenomenology is similar, highlighting the biological underpinnings of the disorder. Prevalence depends, at least in part, on the definition of TS, the type of ascertainment, and the epidemiological methods employed. Indeed, the reported prevalence rates vary according to the source, age, sex, ascertainment procedures, and diagnostic system. They are (see also Table 1):

• **Range for children and adolescents:** For adolescents, 0.15%-3.0% with a best prevalence

• **In the overall general population:** 0.3%-1% which, according to turn-of-the-century census data, translated to half-a-million children in the U.S. and also the U.K., although symptoms in many older individuals would be almost unrecognizable. A study of 420,312 young people suggested that a figure of 1% would be appropriate for the overall international prevalence figure. There were, however, "outliers", for TS seems to be substantially rarer in African-American people and sub-Saharan black African people.

• **By gender:** It is three to four times more frequent in males than in females. Because of the high male prevalence, there is limited data on females from which conclusions about gender-based differences could be drawn. A 2021 review stated that females may see a later peak than males in symptoms, with less remission over time, along with a higher prevalence of anxiety and mood disorders.

• **By age:** Observed prevalence rates are higher among children than adults because tics tend to remit or subside with maturity and a diagnosis may no longer be warranted for many adults. Using similar multi-stage methods, two recent pilot studies and 12 large definitive studies in mainstream school and school-age youngsters have documented remarkably consistent findings, demonstrating prevalence figures of between 0.4% and 3.8% for youngsters between the ages of 5 and 18 years.

estimate of 1.4% in adolescents and 1% in children. People with TS also experience chronic (or persistent) tics (5% in children) and transient (or provisional, or unspecified) tics (up to 20% in children).

• **Range for school-aged children:** 0.3%-0.7% with a conservative estimate of around 0.5% (that is, one child in 200, or 10 times the accepted rate for a rare disease).

Prevalence rate	General population	By gender	By age	Children	Adolescents
U.S.A.	0.3-1.0	Males: 3-4 times females	5-18 years: 0.4-4.8	o Children: - Best 1.0 - Chronic: 5.0 - Provisional: up to 20.0 o School-aged: 0.3-0.7 Best: 0.5	o Adolescents: 0.15-3.0 => best 1.4

Table 1 – Approximate percent prevalence rates in the U.S.A.

The tentative explanations advanced for the differing prevalence figures include: The waxing-and-waning of symptoms; the multidimensional nature of tics; co-morbid disorders that may mask tics; the psychosocial stresses that can lead to increased tic severity; and problems with the diagnosis (lack of diagnostic tests and absence of a definitive diagnosis other than a clinical one). The varying methods of study employed can also affect prevalence. There may be some regional differences as well, which may be due to a lack of awareness or a true reflection of low prevalence as, in some populations, TS does indeed appear to be rare. The apparent rarity in some populations may include: Other medical priorities with less propensity to seek health care; lack of awareness; chance; ethnic and epigenetic differences and reasons; genetic and allelic differences in different races; and admixture of races.

The etiology of TS is also complex, with influences from complex genetic mechanisms, pre- and perinatal difficulties and, in a subgroup, some infections possibly by epigenetic mechanisms. These may well affect phenotype and, thus, prevalence.

Data and statistics for U.S. children

We do not know exactly how many children have TS. Among children diagnosed with TS in 2016-2017:

• Studies that included children with diagnosed and undiagnosed TS have estimated that 1 out of every 162 children (0.6%) have TS.
• A CDC&P study using parent-reported data found that 1 out of every 333 (0.3%) children 3–17 years of age have received a diagnosis of TS; this is about 174,000 children in 2016–2019.
• This suggests that about half of children with TS may not be diagnosed.
• Children 12–17 years of age were more than twice as likely to have a diagnosis of TS than children 6–11 years of age.

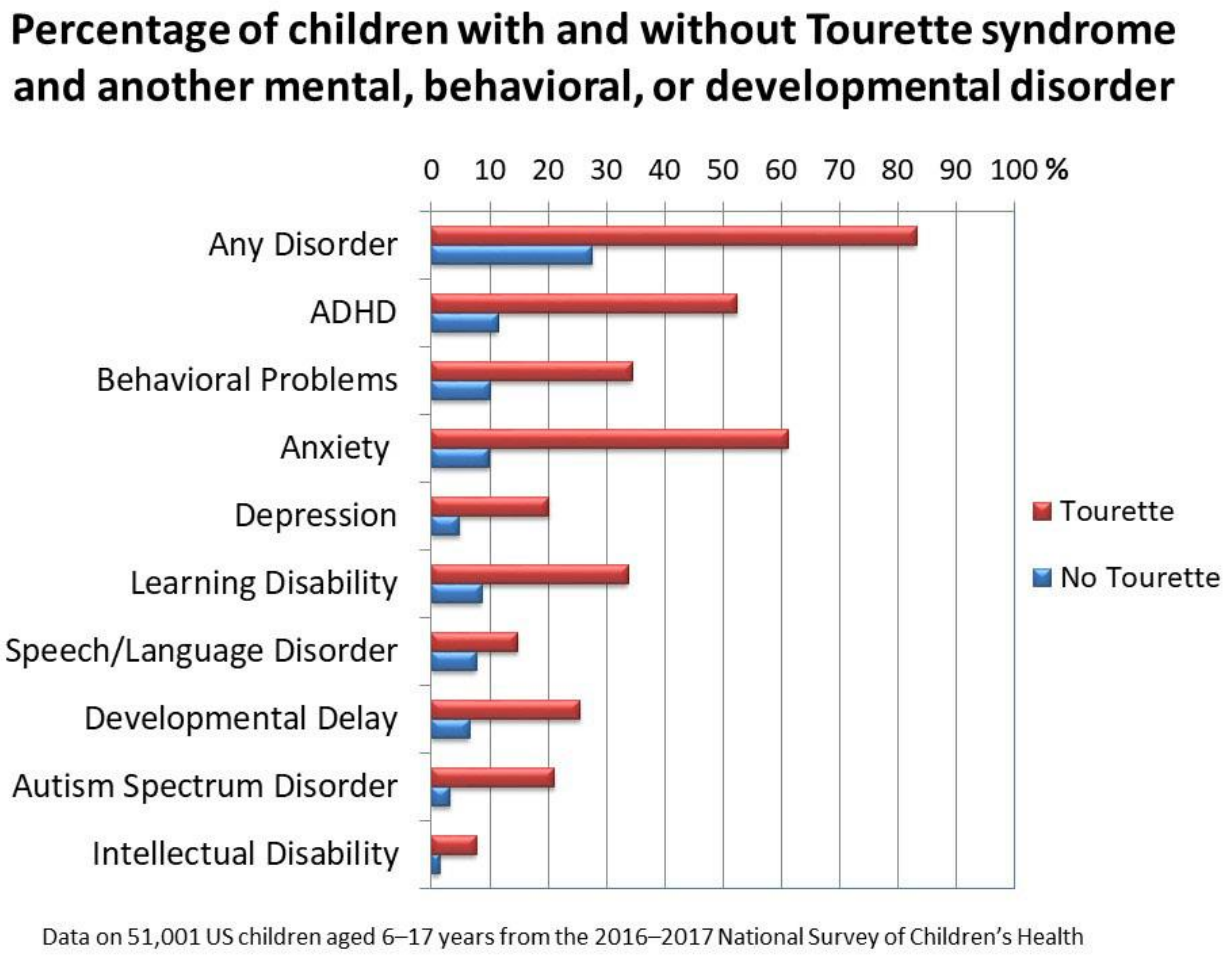


Figure: 3

Among children diagnosed with TS and co-occurring conditions (Figure 3):

- 44% have been reported as having moderate or severe TS.
- Boys were about three times more likely to have TS than girls.
- Children from all racial and ethnic groups or socio-economic backgrounds had similar estimates for diagnosis of TS.
- 83% have been diagnosed with at least one additional mental, behavioral, or developmental disorder.
- 61% had anxiety problems.
- 52% had ADHD.
- 34% had behavioral problems, such as ODD or CD.
- 34% had learning disabilities.
- 26% had developmental delays.
- 21% had ASD.
- 20% had depression.
- 15% had speech or language problems.
- 8% had intellectual disabilities.
- More than 33% have OCD.

The epidemiology and prevalence of TS are complex and, in order to understand them, one must take the disorder in context with regard to clinical

phenomenology, psychopathology, and possible phenotypes, as well as the complex etiological theories as they almost certainly all affect the prevalence data.

Epidemiology

Epidemiologists investigate the magnitude, distribution, and determinants of diseases in populations. Understanding how the frequency and expression of a disease varies over time, place, and person may yield important clues to its cause. Additionally, public health planners depend on accurate epidemiologic data to develop effective prevention and treatment strategies.

Many individuals with tics do not know they have tics, or do not seek a diagnosis, so epidemiological studies of TS reflect a strong “ascertainment bias" towards those with co-occurring conditions.

In adults there is no solid epidemiological data although we may extrapolate from the pediatric findings. Assuming that two-thirds of patients with TS remit when entering adulthood, around 0.2% of adults might still suffer from TS, which still does not fulfill any of the defined diagnostic criteria for rare diseases.

(But, this is merely a data extrapolation result!) However, a 2019 meta-analysis based on only three studies, suggested a prevalence rate of 0.012%, which would make adult TS indeed a rare disease. Clearly, more epidemiological research is warranted in the field of adult TS.

• **Genetic epidemiology:** Although the genetic basis of TS is rather well established, uncertainty about how best to define and assess the phenotype has hampered efforts to identify the genes responsible for susceptibility to the disorder. To help in this effort, the Tourette Syndrome Association's International Consortium on Genetics (TSA-ICG) was formed by more than a dozen research groups from around the world to develop common approaches to uniformly phenotype the syndrome.

As a result, the genome-wide scans of affected sibling-pairs and large families were completed. These studies show real promise for identifying TS susceptibility genes. Further, recent discoveries in the field of molecular biology and increased attention to genetic epidemiology have stimulated renewed interest in the genetics of psychiatric disorders. In these studies, TS is a model to describe the research strategies employed in the genetic epidemiology of child psychiatric disorders.

• **Environmental epidemiology:** TS and tics often appear to be more frequent in some families than in the general population. This suggests that either tics have a hereditary component or that family members may unconsciously copy tics from each other. To disentangle the environmental influence from a genetic effect, twin studies are useful.

In these studies the association of a trait (in our case tics) are compared between monozygotic (MZ) or identical twin-pairs (twins with identical DNA) and dizygotic (DZ) or fraternal twin-pairs (who share half of their DNA).

When a trait is genetic, MZ twins are more likely to share that trait than DZ twins. When the trait is found equally in both MZ and DZ twin-pairs, then, we may assume that the family environment is probably causing the similarities.

The above observation was investigated in a large epidemiological sample of adult Dutch twins, their siblings, parents, and spouses. Only one small clinical study of 43 twin pairs (30 MZ, 13 DZ) with TS (53% for MZ, 8% for DZ) has been reported.

The findings of that study strongly suggest that environmental factors (such as low birth weight and maternal smoking during pregnancy) may affect tic

expression (Table 2):

Twin type	Number of samples	TS tics	All tics	Co-morbid OCD
MZ	30	53%	77%	52%
DZ	13	8%	23%	15%

Table 2: Dutch twin study showing the relative contribution of genetic and environmental factors on tic expression

To date, however, no large-scale epidemiological twin studies have investigated the relative contribution of genes and environmental factors on tic expression.

• **Epidemiological association with co-morbid diseases:** It was observed that blood samples taken from children with TS and/or OCD who attended specialist clinics indicated that 30%-40% of them had previously been infected by Streptococcus. However, it is not known whether such an association also exists in the general community. As a result, some scientists and clinicians believe that the symptoms of TS, as well as a range of other neuropsychiatric syndromes including OCD, may begin after a bacterial (streptococcal) throat infection. While further epidemiological investigations of this observation are being conducted, this is only an 'association' and perhaps at best a risk factor for the development of TS/OCD.

There is some controversy about which of several associated behaviors (e.g. OCD, ADHD) is genetically related to TS. As seen in the clinics, whereas OCD and ADHD are common during childhood, the pattern of their occurrence in families may not be an accurate reflection of the general population. It is increasingly becoming recognized that there may be a familial pattern to the inheritance of OCD ("pure OCD" not related to TS). Nonetheless, there are some forms of OCD seen in TS subjects that may be an alternative way that the TS gene expresses itself. Some have also speculated that there may be subgroups within OCD, namely, those with a family history of tics or TS, and those without. If this is so, it may be argued that there are differences between the two groups at a genetic, symptomatic or biochemical level. However, all the available data so far are limited because the studies have been conducted in clinic samples. Similar studies in the community would be needed.

Summary And Conclusions

TS is a common inherited neurodevelopmental, neuropsychiatric, and non-degenerative motor disorder with no consensus on its definition. It may cause sudden, unwanted, and uncontrolled rapid and repeated movements or vocal sounds called tics. It is one of a group of disorders of the developing nervous system called 'tic disorders'. It can be a chronic condition with symptoms that may last into and, in some cases, worsen in adulthood but there is no typical case. Generally, tics are movements or sounds that take place intermittently and unpredictably out of a background of normal motor activity, having the appearance of normal behaviors gone wrong. They may also occur in bouts of bouts, which may vary among people. They are the primary symptoms of a group of childhood-onset neurological conditions known collectively as 'tic disorders'. They are typically preceded by a 'premonitory urge' or sensation that enables tic suppression in some individuals, a possibility more developed in adults than children. The severity of symptoms varies widely among people with TS and many cases may go undetected. Notwithstanding the several different definitions of tics, genetic studies indicate that tic disorders cover a spectrum that is not

recognized by the clear-cut distinctions in the current diagnostic framework. Further, TS is not a unitary condition with a distinct mechanism, as described in the existing classification systems and subtypes should be recognized to distinguish "pure TS" from TS that is accompanied by co-occurring conditions (such as ADHD and OCD) that can cause variations in neurocognitive function.

The causes of TS are complex and the exact causes are unknown. However, it is well established that genetic, environmental, infectious, and possibly other factors (neuroanatomical, immunological, psychosocial, and other non-genetic factors) are involved and may influence the severity of the disease. The exact mechanism affecting the inherited vulnerability to TS is not well established. Prevalence depends, at least in part, on the definition of TS, the type of ascertainment, and epidemiological methods used. The reported prevalence rates vary according to the source, age, sex, ascertainment procedures, and diagnostic system. The differing prevalence rates might be tentatively explained by the waxing-and-waning of symptoms; the multidimensional nature of tics; co-morbid disorders that may mask tics; psychosocial stresses that can lead to increased tic severity; and problems with the diagnosis.

Of note, some scientists and clinicians believe that the symptoms of TS, as well as a range of other neuropsychiatric syndromes including OCD, may begin after a bacterial (streptococcal) throat infection. This is, however, only an 'association' (not a causation) and perhaps at best a risk factor for the development of TS/OCD.

Appendix - Official definitions of tics

There are several different definitions:

Here, TS is defined as a "*chronic tic disorder with the presence of at least two motor and one vocal tics over a period >12 months in someone under the age of 18 after excluding secondary causes*" (American Psychiatric Association, 2013). This essentially descriptive vision of TS has its merits as it is difficult if not impossible to define operational criteria for what can be considered debilitating. Also, the *waxing and waning nature of tics*, both phenomenologically and with regard to severity, means that impairment may vary over time, even if the overall condition can be considered chronic. However, this very broad definition of TS also means that many people likely fall under this diagnostic umbrella category who do not at all require medical attention at any time during their life.

TS is further classified as a motor disorder (i.e., a disorder of the nervous system that causes abnormal and involuntary movements). It is listed in the neurodevelopmental disorder category and at the more severe end of the spectrum of tic disorders. The most common tic disorder is called **provisional tic disorder** (previously known as 'transient tic disorder'). Provisional tics go away by themselves in less than a year. Some may get worse with anxiety, tiredness, and some medications. However, some tics do not go away. Tics which last one year or more are called **persistent (chronic)** motor or vocal tics in which one type of tic (motor or vocal, but not both) has been present for more than a year. **Some experts now believe that TS and persistent (chronic) motor or vocal tic disorder should be considered the same condition**, because vocal tics are also motor tics in the sense that they are muscular contractions of nasal or respiratory muscles.

DSM-5 has ben critiqued for number of its features: Disruptive mood dysregulation disorder for temper tantrums; major depressive disorder that includes normal grief; minor neurocognitive disorder for normal forgetfulness in old age; adult attention deficit disorder that encourages psychiatric prescriptions of stimulants; binge eating disorder for excessive eating; autism definition possibly leading to decreased rates of

diagnosis and the disruption of school services; first-time drug users lumped in with addicts; behavioral addictions that may make a mental disorder out of everything we like to do a lot; generalized anxiety disorder that includes everyday worries; and post-traumatic stress disorder (PTSD), which opens the gate even further to the already existing problem of misdiagnosis of PTSD in forensic settings.

European Clinical Guidelines (ECG) definition

The European Society for the Study of Tourette Syndrome (ESSTS) published its guidelines in 2011. They are divided into four parts: I. Assessment; II. Psychological interventions; III. Pharmacological treatment; and IV. Deep Brain Stimulation.

However, notwithstanding the above definitions, genetic studies indicate that **tic disorders cover a spectrum that is not recognized by the clear-cut distinctions in the current diagnostic framework**. Since 2008, studies have suggested that TS is not a unitary condition with a distinct mechanism, as described in the existing classification systems. Instead, the studies suggest that subtypes should be recognized to distinguish "pure-TS or TS-only" from TS that is accompanied by attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD) or other disorders, similar to the way that subtypes have been established for other conditions (such as, for example, type 1 and type 2 diabetes). Elucidation of these subtypes awaits a fuller understanding of the genetic and other causes of tic disorders.

World Health Organization (WHO) definition

In its International Statistical Classification of Diseases & Related Health Problems, version 11 (ICD-11), the WHO defines TS only slightly differently. It classifies it as a disease of the nervous system and a neurodevelopmental disorder, and only one motor tic is required for diagnosis. Older versions of the ICD called it "combined vocal and multiple motor tic disorder [de la Tourette]".

The DSM-5 definition is preferred over the World Health Organization (WHO)'s classification because a number of different criticisms have been leveled against it and its usefulness as a diagnostic manual, including: Reliability and validity; diagnosis based on superficial symptoms; obscuring the root causes of psychological distress; overdiagnosis; dividing lines between disorders and use of arbitrary cut-offs between normal and abnormal; cultural bias; medicalization and financial conflicts of interest; and potential harm of labels that invite social stigma and discrimination. Further, diagnoses can become internalized and affect an individual's self-identity so that the healing process can be inhibited and symptoms can worsen as a result. Additionally, it has been noted that the DSM often uses definitions and terminology that are inconsistent with a disease-recovery model.

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