Tourette’s syndrome

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As our knowledge of Gilles de la Tourette’s syndrome increases, so does our appreciation for the pathogenic complexity of this disorder and the challenges associated with its treatment. Advances in the neurosciences have led to new models of pathogenesis, whereas clinical studies have reinvigorated early hypotheses. The interdependent roles of genes and environment in disease formation have yet to be fully elucidated. Results of epidemiological studies have prompted debate on how best to characterise and diagnose this disorder. Absence of ideal anti-tic drugs, combined with knowledge that uncomplicated cases of childhood Tourette’s syndrome frequently have a favourable outcome, has led to striking changes in care and treatment of patients. This seminar focuses on these changing views and offers a new perspective on our understanding of the pathogenesis of Tourette’s syndrome and on principles for treatment of patients with this disorder.

Tic disorders have been the subject of speculation for at least the past 300 years. Despite the overt nature of tics and decades of scientific scrutiny, our ignorance remains great. Notions of cause have ranged from “hereditary degeneration” to the “irritation of the motor neural systems by toxic substances, of a self-poisoning bacteriological origin” to “a constitutional inferiority of the subcortical structures . . . [that] renders the individual defenseless against overwhelming emotional and dynamic forces”.

Predictably, each of these aetiological explanations has prompted new treatments and new ways of relating to families.

Symptoms and natural history

The cardinal features of Tourette’s syndrome are motor and phonic tics that wax and wane in severity. Motor tics usually begin between the ages of 3 and 8 years, with transient periods of intense eye blinking or some other facial tic. Phonic tics, such as repetitive bouts of sniffing or throat clearing, can begin as early as 3 years of age, but typically they follow the onset of motor tics by several years. In uncomplicated cases, severity of motor and phonic tics peaks early in the second decade of life, with many patients showing a striking reduction in tic severity by age 19 or 20 years. However, the most severe cases of Tourette’s syndrome arise in adulthood. Extreme forms of this disorder involve forceful bouts of self-injurious motor tics, such as hitting or biting, and socially unacceptable coprolalic utterances—eg, shouting obscenities, racial slurs—and gestures.

Motor and phonic tics arise in bouts over the course of a day, and change in severity over weeks and months. These episodes are characterised by stable intra-tic intervals—ie, time between successive tics—of short duration, typically 0.5–1.0 s. Less well known is the so-called self-similarity of these patterns across different times. Over minutes to hours, bouts of tics happen in groups. Over the course of weeks to months, many episodes of tics arise (figure 1).

This periodic higher-order combination of tic bouts could be the basis of the well-known waxing and waning course of Tourette’s syndrome.

Knowledge of the temporal patterning of tics is important for the doctor, because it informs decisions about when to initiate anti-tic drugs, when to change drugs, and when to be patient and simply provide close monitoring and support to the family. Stated simply, if a clinician begins or changes a treatment at the end of a waxing period, the patient’s condition will improve irrespective of the efficacy of the intervention. Furthermore, a deeper understanding of the multiplicative processes that govern these timing patterns might clarify neural events arising every few milliseconds and the natural history of tic disorders over the first two decades of life.

Many patients with tic disorders report associated sensory symptoms, including premonitory urges that incessantly prompt tics and feelings of momentary relief that follow performance of a tic. Many patients describe being besieged by these bodily sensations that are generally localised to discrete anatomical regions—eg, like an urge to stretch one’s shoulder or a need to clear one’s throat. These urges, and the internal struggle to control them, can be as debilitating as the tics themselves. Other antecedent sensory happenings include a generalised inner tension that can be relieved only by performance of a tic. A large range of auditory or visual cues can also prompt tics, but the nature of these cues is usually highly selective for individual patients—a cough, a particular word, an alignment of angles or specific shapes.

Search strategy and selection criteria

A computerised and manual search on PubMed of published work was done to identify studies about the pathogenesis of Tourette’s syndrome and its treatment, with particular focus on original reports published over the past 5 years. Selection criteria included a judgment about novelty and importance of studies and their relevance to the well-informed general medical doctor. In the case of treatment studies, only those interventions whose efficacy has been supported by at least one randomised, double-blind, clinical trial are cited. Keywords used included: “Tourette”, “tic”, “obsessive-compulsive”, “attention deficit hyperactivity disorder”, and “PANDAS”, among others.
In addition to tics, many patients with Tourette’s syndrome have symptoms of hyperkinetic disorder (known as attention-deficit hyperactivity disorder in the USA), obsessive-compulsive disorder, or both. These coexisting disorders can add greatly to morbidity associated with Tourette’s syndrome and detract from the patient’s overall quality of life.8–11 (figure 2). Tics typically have the greatest effect on a patient’s self-esteem and peer and family relationships from age 7–12 years, especially during periods of waxing forceful motor tics and loud phonic tics that can go on for hours virtually nonstop. Hyperkinetic disorder takes a heavy toll from onset, with a negative effect on peer acceptance, school performance, and self-esteem. Increased irritability and rage attacks, and an increased vulnerability for drug abuse, depression, and antisocial behaviour are also not uncommon among patients with Tourette’s syndrome and hyperkinetic disorder.8–11 Lesser variants are typical in individuals with Tourette’s syndrome. Normal obsessive-compulsive-like symptoms are present in many young children, peaking at 2–5 years of age. This disorder when associated with tics generally has a prepubertal age of onset. When present, obsessive-compulsive symptoms are usually done in secret, and are most disabling in the home environment. They can lead to periods of depression.8–11

Epidemiology and genetics

Once thought to be a rare disorder,12 the prevalence of Tourette’s syndrome is presently estimated to be between 31 and 157 cases per 1000 in children aged 13–14 years.13 Frequency of the disorder varies by age, sex, source of sample, and method of assessment. For example, studies on direct classroom observation and that use multiple informants consistently yield substantially higher prevalence estimates than do other assessment methods. Many patients identified with these techniques have mild characteristics and do not need long-term intervention apart from educational and other support. However, behavioural problems, in particular hyperkinetic disorder, are frequently associated with Tourette’s syndrome. Once diagnosed, these problems usually need prompt intervention to prevent or keep to a minimum adverse long-term results. In part, because of this association, children in special-education settings are more likely to be diagnosed with a tic disorder than children in community-based samples.14

Genes

Genetic studies in twins and families provide compelling evidence that genetic factors are implicated in vertical transmission in families with a vulnerability to Tourette’s syndrome and related disorders. At present, the nature of vulnerability genes that predispose individuals to develop the disorder are unknown. Many genes probably have a role. Clarity about the nature and normal expression of even a few of the susceptibility genes in Tourette’s syndrome is likely to provide a major step forward in understanding the pathogenesis of this disorder. Future progress could also depend on identification of characteristic, biologically established, endophenotypes that are closely associated with specific vulnerability genes. Endophenotypes are measurable aspects of human psychiatric disorders that can either be used in linkage analyses as quantitative traits, be modelled in animals with the disease, or both. Promising endophenotypes include neurophysiological and neuroanatomical measures and patterns of treatment response (see section on neural substrates).

The pattern of vertical transmission in family members suggests major gene effects, and results of segregation analyses accord with models of autosomal transmission.15,16 Historically, efforts to identify susceptibility genes within these high-density families with traditional linkage strategies have met with limited success. However, investigators studying a large French-Canadian family have reported evidence for linkage at 11q23.17

Figure 1: Fractal character of temporal occurrence of tics
Progressively longer time scales (seconds to months) are depicted.

Figure 2: Age at which tics and coexisting disorders affect patients
Width of bars shows schematically the amount the disorder affects a patient at a particular age.
Non-parametric approaches with families in which two or more siblings are affected with Tourette’s syndrome have also been undertaken. This sib-pair approach is suitable for diseases with an unclear mode of inheritance, and has been used successfully in studies of other complex disorders, such as type 1 diabetes mellitus and essential hypertension. In one sib-pair study of Tourette’s syndrome, two areas were suggestive of linkage, one on chromosome 4q and another on chromosome 8p. A genome scan of hoarding symptoms (a component of obsessive-compulsive disorder that can be seen in some patients with Tourette’s syndrome) as a quantitative phenotype was done with the same affected sib-pair data obtained by the Tourette’s Syndrome Association International Consortium for Genetics. Significant allele sharing was noted for hoarding phenotypes for markers at 4g34–35, 5q35, and 17q25. 4q is in close proximity to the region linked to Tourette’s syndrome.

Identity-by-descent approaches have been used in populations in South Africa and Costa Rica. These techniques assume that a few so-called founder individuals contributed the vulnerability genes that are now distributed within a much larger population. The South African study implicated regions near the centromere of chromosome 2, and on 6p, 8q, 11q, 14q, 20q, and 21q. The marker in the French-Canadian family that was associated with the highest LOD score was the same marker for which significant linkage disequilibrium with Tourette’s syndrome was detected in the South African population. However, none of the chromosomal regions in which cytogenetic abnormalities have been found to co-segregate with phenotypes of Tourette’s syndrome has shown any convincing evidence for linkage in the high-density families, the sib-pair study, or the identity-by-descent studies.

Several candidate genes have been assessed in people with Tourette’s syndrome, including various dopamine receptors (DRD1, DRD2, DRD4, and DRD5), the dopamine transporter, various noradrenergic genes (ADRA2a, ADRA2C, and DBH), and a few serotonergic genes (5HTT). Genetic variation at any one of these loci is unlikely to be a major source of vulnerability to the disorder, but in concert, these alleles could have an important cumulative effect.

Environment

Many epigenetic factors have been implicated in the pathogenesis of Tourette’s syndrome (panel 1). For example, children with a low birthweight with ischaemic parenchymal brain lesions are more likely to have tics and hyperkinetic symptoms by age 6 years than controls. Low Apgar scores recorded 5 min after birth have also been associated with an increased risk for tic symptoms. Males are more often affected with Tourette’s syndrome than females. Although this association could be attributable to genetic mechanisms, frequent male-to-male transmissions within families seem to rule out the presence of an X-linked vulnerability gene. This observation has led to the hypothesis that androgenic steroids during critical periods in fetal development could have a role in later development of the syndrome. It has also led investigators to test the efficacy of antiandrogenic drugs in treatment of refractory tics.

Tic disorders have long been identified as stress-sensitive problems. Typically, symptoms follow in the wake of stressful life-events. These events need not be adverse in character, as long as there is a high level of emotional excitement—eg, the start of school, impending holidays or birthdays, vacation trips. Stress-related neurotransmitters and hormones have also been implicated in Tourette’s syndrome. For example, compared with healthy controls, patients with the disorder have been reported to excrete substantially more norepinephrine in the 20 h preceding a lumbar puncture, to have raised concentrations of adrenocorticotropic hormone after this procedure, and to have high concentrations of norepinephrine and corticotropin-releasing factor in their cerebrospinal fluid. Taken together, these findings suggest that a subset of patients with Tourette’s syndrome could be characterised by heightened reactivity of the hypothalamic-pituitary-adrenal axis and related noradrenergic sympathetic systems.

The past decade has seen the re-emergence of the hypothesis that post-infectious autoimmune mechanisms contribute to the pathogenesis of some cases of Tourette’s syndrome. Speculation about a post-infectious (or at least autoimmune) cause for symptoms of tic disorder dates from the late 1800s. Group A β haemolytic streptococci (GABHS) are known to be a possible trigger of immune-mediated disease in genetically predisposed individuals. Acute rheumatic fever is a delayed sequela of these bacteria, arising about 3 weeks after an inadequately treated infection of the upper respiratory tract. Rheumatic fever is characterised by inflammatory lesions of the joints, heart, or central nervous system (Sydenham’s chorea). This disorder and Tourette’s syndrome probably affect common anatomic areas—the basal ganglia of the brain and related cortical and thalamic sites. Some patients with Sydenham’s chorea have motor and phonic tics and symptoms of obsessive-compulsive and attention-deficit hyperactivity disorder, suggesting that, at least in some instances, these disorders share a common cause. As in Sydenham’s chorea, antinuclear antibodies have been reported to be raised in the sera of some patients with Tourette’s.

Possible risk factors

Genetic vulnerability

- Severe nausea and vomiting during the first trimester
- Severe psychosocial stress of the mother during pregnancy
- Maternal use during pregnancy of coffee (more than 2 cups a day), cigarettes (more than ten a day), or alcohol (fewer than two drinks a day)
- Identical twin with a lower birthweight
- Low-birthweight children with evidence of parenchymal lesions, ventricular enlargement, or both
- Transient hypoxia or ischaemia during birth (labour >24 h), use of forceps, nuchal cord, evidence of fetal distress
- Low Apgar scores

Severe psychosocial trauma, recurrent daily stresses (eg, teasing by peers), or extreme emotional excitement

Recurrent streptococcal infections with post-infectious autoimmune response

Drug abuse

- Exposure to androgenic drugs
- Chronic intermittent use of cocaine and other psychostimulants

Co-existing medical or psychiatric disorders

- Hyperkinetic disorders
- Learning disabilities
- Depression
- Manic depression

Gestational and perinatal risk factors

- Severe psychostimulants
Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) has been suggested to represent a distinct clinical entity and include cases of Tourette’s syndrome and obsessive-compulsive disorder, in which a GABHS infection is likely to have preceded symptom onset. Although the importance of antibodies against neurons in relation to cause, and the association with previous GABHS infections, remains a topic of great debate, treatments based on this mechanism show some promise. Furthermore, if specific immunological alterations are associated with onset or acute clinical exacerbations, then the nature of these alterations should provide insight into the genetic, neuroanatomical, and immunological mechanisms implicated. This knowledge could provide a basis for rational design of therapeutic or preventative interventions.

Neural substrates of habit formation and tics

Habits are assembled routines that link sensory cues with motor action. Ideas at present have suggested neural substrates of habit formation are crucial for a better understanding of Tourette’s syndrome. Neuroscientists who are interested in learning and habit formation have focused on the motor, sensorimotor, association, inhibitory, and limbic (motivational and threat detection) neural circuits that course through the basal ganglia. These circuits direct neural circuits that course through the subcortex, and then back to specific regions of the cortex, thereby forming multiple cortical-subcortical loops (figure 3).

Cortical neurons projecting to the striatum outnumber striatal neurons by about a factor of ten. These cortical projection neurons to the striatum segregate into two structurally similar, but neurochemically distinct, compartments: striosomes and matrix (figure 4). These two compartments differ by their cortical inputs, with the striosomal medium spiny projection neurons mainly receiving convergent limbic and prefrontal inputs, and neurons in the matrix mainly receiving convergent input from ipsilateral primary motor and sensory motor cortices and contralateral primary motor cortices. The response of particular medium spiny projection neurons in the striatum is partly dependent on perceptual cues that are judged salient, so rewarding and aversive stimuli can both serve as cues.

Several other less abundant striatal cell types probably have a key role in this form of habit learning, including cholinergic tonically active neurons and fast spiking interneurons. Tonically active neurons are very sensitive to salient perceptual cues because they signal the networks within the cortico-basal ganglia learning circuits when these cues arise (figure 4). They are responsive to dopaminergic inputs from the substantia nigra, and these signals probably participate in calculation of the perceived salience (reward value) of perceptual cues along with excitatory inputs from midline thalamic nuclei. The fast spiking spiny interneurons of the striatum are electrically coupled via gap junctions that connect adjacent dendrites. Once activated, these fast spiking neurons can inhibit many striatal projection neurons synchronously. The characteristic electrophysiological properties of the striatal fast spiking neurons—e.g., irregular bursting with stable intra burst frequencies—are reminiscent of temporal patterning of tics. These fast spiking interneurons are also very sensitive to cholinergic drugs, suggesting that they are functionally related to tonically active neurons.

Under normal circumstances, peak metabolic activity happens in the matrix compartment (matrix>striosome), as shown in figure 5. However, when this balance is reversed (striosome>matrix), tics and stereotypes are likely to arise.

Although alterations in the structure of the basal ganglia, including loss of right-left asymmetry in the volumes of the lenticular nuclei, in patients with Tourette’s syndrome have been reported, present data from in-vivo neuroimaging and neurophysiological studies suggest that broadly distributed cortical systems (or their thalamic inputs) might be even more important...

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**Figure 3:** Schematic diagram of the major connections of the basal ganglia
**Figure 4:** Schematic diagram of the major inputs into the medium spiny GABAergic projection neurons of the striatum
Syndrome. This finding provides a possible explanation for why the cortical silent period is shortened and intracortical prepulse inhibition of startle responses—have shown that studies—eg, transcranial magnetic stimulation and behavioural inhibition paradigms, neurophysiological findings might also be useful for clarifying the role of specific vulnerability genes. Early results of functional in-vivo neuroimaging studies have shown that voluntary tic suppression involves activation of regions of the prefrontal cortex and caudate nucleus and bilateral deactivation of the putamen and globus pallidus. If confirmed, these findings accord with the well-known finding that chemical or electrical stimulation of inputs into the putamen can provoke motor and phonic responses that resemble tics. They also reinforce the view that prefrontal cortical regions have a crucial role in expression of tic symptoms. In addition to behavioural inhibition paradigms, neurophysiological studies—eg, transcranial magnetic stimulation and prepulse inhibition of startle responses—have shown that the cortical silent period is shortened and intracortical inhibition is defective in patients with Tourette's syndrome. This finding provides a possible explanation for the reduced motor inhibition and intrusive sensory occurrence in Tourette's syndrome and obsessive-compulsive disorder. These in-vivo neuroimaging and neurophysiological findings might also be useful endophenotypes that could be proven to have value in prediction of treatment response to specific drugs or in clarification of the role of specific vulnerability genes.

Recent neurosurgical procedures reinforce the functional importance of thalamic regions that are part of these cortical-subcortical loops. Results of one case study showed that high frequency stimulation of the median and rostral intralaminar thalamic nuclei produced an important reduction of tics. This effect could be caused by the effect of these midline thalamic nuclei on the tonically active neurons (figure 4), or on broadly distributed cortical systems and their corticostriatal projections. As in other movement disorders, a deeper understanding of the circuitry involved in Tourette's syndrome could lead to specific circuit-based therapies, with deep-brain stimulation to treat refractory cases. As with habits and stereotypies, ascending dopaminergic pathways probably have a key role in consolidation and performance of tics. First, dopamine D2 receptor-blocking drugs are the mainstay of traditional pharmacological approaches to treatment of tics. Second, studies of monozygotic twins suggest that developmental shifts in the balance of tonic-phasic dopaminergic tone arise as a result of epigenetic differences, and density of dopamine D2 receptors might affect severity of Tourette's syndrome. Third, further evidence shows that a range of alterations in dopamine pathways, such as an increase in dopamine transporter capacity, are possible, but not necessary, features of pathophysiology.

**Developmental models**

Future progress in elucidation of the pathogenesis and treatment of Tourette's syndrome could be greatly accelerated with development of animal models. Thus far, the use of psychomotor stimulants, direct dopamine receptor agonists, behavioural stress sensitisation conditioning paradigms, and immune-based challenges to induce different levels of stereotypy in rats and other species seem to offer the greatest promise in modelling key components of the disorder's phenotype. If tics, like stereotypies, vary in accordance with the balance of activity of medium spiny projection neurons in the striosome and matrix compartments of the striatum, then it should be possible to investigate the clinical effect of genetics, developmental insults, or both, that affect the number and sensitivity of medium spiny projection neurons in the two striatal compartments. For example, perinatal ischaemic and hypoxic insults involving parenchymal lesions strikingly increase risk of tic disorders.

Furthermore, this model could provide a meaningful integration of knowledge about tics drawn from several perspectives. These include the stress responsiveness of tics (limbic activation), the presence of premonitory sensory urges (as sensory motor and primary motor cortical inputs converge on the fewer medium spiny projection neurons in the matrix), the reduction of tics when an individual is engaged in acts that need selective attention, and guided motor action (heightened activity within the matrix compartment).

Results of two studies have shown an increase in oral stereotypes in rats after infusion of sera from patients with Tourette’s syndrome with high concentrations of antibodies against neurons compared with controls. One plausible hypothesis is that these antibodies could alter synaptic transmission and alter the balance between the striosomal and matrix compartments of the striatum.

From a developmental perspective, many GABAergic interneurons of the cerebral cortex clearly migrate tangentially from the same embryonic regions in the ganglionic eminence that also give rise to the GABAergic medium spiny projection neurons of the striatum. Could adverse events arising at a specific point in development—eg, the differential loss of medium spiny projection neurons in the matrix compartment—account for the striatal imbalance and intracortical deficits in inhibition seen in some patients with Tourette’s syndrome?

**Assessment and diagnosis**

Clinical examination of a child with tics should include an assessment of the child or adolescent as a whole not merely as someone with tics. During the examination, the full range of difficulties and competencies should be charted: the clinician, family, and child must collaborate to reconstruct the child’s history, tic symptoms (onset, progression, waxing and waning, and factors that have worsened or ameliorated tic status), and present functioning. An important question is the extent to which tics are interfering with the child’s emotional, social, familial, and school experiences. To establish this fact, it is useful to monitor symptoms over a few months to assess their severity and fluctuation, effect on the family, and adaptation of the child and family to them. This monitoring can be helpful if the family keeps records or uses standard forms.

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**Figure 5:** Effect of an imbalance between medium spiny neurons in the two striatal compartments

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A central task of assessment is to explicate, clarify, and address family issues. Diagnostic assessment is closely connected with the first steps of treatment. During the process of clinical inquiry, the doctor can approach sensitive issues through clarification, education, and an opening therapeutic discussion with the child and family.

As with other children with school-performance problems, the child with Tourette's syndrome needs careful assessment of cognitive functioning and school achievement. Children with this disorder tend to have difficulties in attentional deployment, perseverance, and ability to keep themselves and their work organised. Many have poor penmanship. Schoolwork can be impaired by compulsions, such as the need to scratch out words or return to the beginning of a sentence.

Neurological examination of a child with Tourette's syndrome can be of great value. Tics are sudden habitual movements or utterances that typically mimic some fragment of normal behaviour and that use discrete muscle groups. As such, they can be confused with normal coordinated movements or vocalisations. Tics can also be mistaken for akathisia, tardive dyskinesia, or other hyperkinetic movement disorders.64 Once established, any given tic tends to persist for a time, and may wax and wane. Tics are often exacerbated by stress and fatigue. By contrast with other movement disorders, tics can arise during sleep, but are usually much attenuated. Some severely affected patients have immaturities or atypicalities on the neuromaturational examination (so-called soft signs). These signs might suggest disturbances in the body schema and in integration of motor control, but their relevance is not really clear. Findings on electroencephalography and structural MRI are generally normal and are not yet of proven clinical use (apart from patients in whom other neurological suspicions are present). Similarly, laboratory studies can establish a child's general health profile and assist in differential diagnosis of other movement disorders, but there are no laboratory tests for positive diagnosis of Tourette's syndrome or other tic disorders.

Diagnostic criteria presently in use include the international classification of disease and related health problems, 10th revision (ICD-10)65 and diagnostic and statistical manual, 4th edition text revision (DSM-IVTR).66 Although clear differences exist between these classification schemes, they are broadly congruent with each other. To keep error to a minimum in case ascertainment and to produce an instrument measuring the likelihood of having Tourette's syndrome, an international team of experts has published a diagnostic confidence index.67 Scores on this index are highly correlated with present tic severity, as measured by a psychometrically sound, widely used, clinician-rating scale, the Yale global tic severity scale.68

Once diagnosis of tic disorder has been established, careful assessment will allow the clinician to learn about fluctuation of symptoms. As the child becomes more comfortable, he or she will show his or her symptoms with less suppression or inhibition. Patients or family members might recognise a symptom as a tic after they have been educated about possible symptoms.

The history of patients with long-standing Tourette's syndrome is often confused by use of drugs. Often, drugs have been stopped because they were thought to have been useless or to have caused side-effects. The history of treatments and what they have meant to the child and family can be pieced together during the assessment. Also, the clinician can learn why earlier treatment attempts were not useful.

When a child or adolescent, and his or her parents, is given enough time, over the course of several sessions, to narrate their experiences, sadness, and disappointments, they may feel that their full story has finally been heard, perhaps for the first time, after having seen many doctors. This process of rethinking the past and integrating disparate threads of experience can be therapeutic in its own right, and could help to ease the immediate crisis that led to the consultation. The experience of being understood through the diagnostic process is reassuring. Many patients and families often feel supported, understood, and reassured by hearing a more or less detailed account of our understanding of the pathogenesis and natural history of Tourette's syndrome. Knowledge that their experience is similar to that of other families, and that many of the most puzzling features of the disorder are typical (such as waxing and waning, symptom variation, ability to suppress tic for brief periods, and premonitory urges), can be a great reassurance to families.

**Treatment**

Multimodal treatment for Tourette's syndrome is usually indicated.69 As noted above, this approach includes educational and supportive interventions appropriate for any chronic disease. Panel 2 outlines possible protective factors for the disorder. The various manifestations of the disorder are best treated in the context of a long-term relationship with a clinician who can help the patient, family, and school deal with the changing manifestations of the disorder through the years. Because acute and chronic stress can exacerbate tics, psychotherapeutic attention to difficulties of self-esteem, social coping, family issues, and school adjustment could have non-specific ameliorative effects on tic severity and on attendant anxiety and depression. Local chapters of patients' advocacy organisations, such as the Tourette's Syndrome Association, can have a very supportive role, by putting families of newly diagnosed children in contact with more experienced families. Parents should be encouraged to build on their child's strengths.

Many cases of uncomplicated Tourette's syndrome can be successfully managed with just these interventions, and do not need anti-tic drugs. When patients present with co-existing hyperkinetic disorder, obsessive-compulsive disorder, depression, or two or three of these disorders, it is usually better to treat these comorbid disorders first, since successful treatment of them will often diminish tic severity.

**Anti-tic treatments**

Ideal anti-tic treatments are not presently available. None of the drugs or techniques can be used effectively just when tics are at their worst. Most of the available pharmacological drugs need long-term treatment, and many have potentially serious side-effects. Indeed, for some drugs, it is much easier to begin their use than to stop them. The natural waxing and waning pattern of tics often confirms the results of drug trials. Even without intervention, periods of severe tics will be followed by one of spontaneous waning. Because tic-suppressant drugs generally need several weeks to have their full effect, it is often difficult to distinguish response to a drug from...
spontaneous waning of symptoms. Thus, it is usually best to avoid beginning or increasing drugs as soon as an exacerbation begins.

Two classes of drug are most widely used to control tics associated with Tourette's syndrome: \( \alpha_2 \) adrenergic agonists and neuroleptics. Guanfacine and clonidine are two \( \alpha_2 \) adrenergic agonists originally developed as anti-hypertensives for adults. In low doses, clonidine reduces central noradrenergic activity by stimulation of presynaptic \( \alpha_2 \) adrenergic autoreceptors; guanfacine is believed to act more selectively on postsynaptic \( \alpha_2 \) adrenergic receptors in the prefrontal cortex. Use of these drugs is supported by results of randomised, placebo-controlled, clinical trials. However, this support is not uniform. Although they are generally not as potent as neuroleptics in suppression of tics, guanfacine and clonidine are more benign than neuroleptics in terms of potential short-term and long-term side-effects and are frequently the first choice in previously untreated individuals, especially those with mild-to-moderate symptoms.

Treatment with these drugs for children and adults is usually started at a low dose and gradually increased. Beginning with a morning dose of 0.025 mg or 0.05 mg of clonidine, additional doses are added every 3–4 h. The size of each dose can be gradually increased to a total dose of 0.2–0.3 mg daily. Although the effect of each individual dose of clonidine wears off after about 3–5 h, the full tic-suppressant effects of the regimen could need 10–12 weeks to be apparent. Guanfacine is longer acting than clonidine, but is given in a similar way, in a range of 0.25–1.0 mg two or three times a day.

The main side-effect of these two drugs in the recommended dose range is sedation, sometimes accompanied by irritability. This unwanted effect may need dose reduction or a change of drug. Reversible cardiac arrhythmias have been rarely reported with clonidine; however, the need for electrocardiographic studies at baseline and as soon as a stable dosage is reached remains controversial. Hypotension has not been a typical drawback in children taking these drugs. If a decision is made to discontinue these drugs, gradual tapering over a week or two is advisable to avoid tic flare-ups or rebound hypertension. Several typical and atypical neuroleptics are frequently used for treatment of Tourette's syndrome, especially in patients with severe tics or whose tic symptoms are unresponsive to \( \alpha_2 \) adrenergic agonists. Efficacy of these drugs is associated with their potency in blockade of postsynaptic dopamine-2 receptors. Pimozide, haloperidol, sulpiride, and tiapride are the most frequently used typical neuroleptics, whereas risperidone and ziprasidone are two atypical neuroleptics with proven tic-suppressant efficacy.

Sulpiride is a substituted benzamide and a selective dopamine-2 antagonist, and has been widely used, especially in Europe. In the only double-blind trial with this drug, George and colleagues undertook a 14-week placebo-controlled crossover study of fluvoxamine versus sulpiride, followed by single-blind combined treatment in 11 patients with comorbid Tourette's syndrome and obsessive-compulsive disorder. Sulpiride monotherapy greatly reduced tics and non-significantly improved obsessive-compulsive symptoms. With neuroleptics, it is best to start with a low daily dose and gradually increase the dose. With sulpiride, the initial dose is 200 mg per day, gradually increasing to 1 g per day.

However, use of high doses of these drugs rarely shows additional improvement in tics, and very often produces bothersome side-effects. Withdrawal from neuroleptics can produce tic exacerbations and dyskinesias that can be delayed in onset by several weeks. Although neuroleptics are widely prescribed for patients with Tourette's syndrome, many patients do not adhere to treatment. The most typical, dose-related side-effects of neuroleptics are sedation or dysphoria. Weight gain is also a drawback with most of these drugs, especially risperidone. Some children taking for adults. In low doses, clonidine reduces more selectively on postsynaptic two is advisable to avoid tic flare-ups or rebound exacerbation begins.

Although atypical neuroleptics are believed to have a low risk of tardive dyskinesia, acute extrapyramidal reactions—eg, torticollis, oculogyric crisis, akathisia—do arise, and they might need anticholinergic drugs. Because of potential QT changes, baseline and follow-up electrocardiography is recommended for risperidone, ziprasidone, and pimozide. It is also essential for the prescribing clinician to be familiar with potential cytochrome P450-related drug reactions, because fatal interactions have arisen with pimozide and erythromycin-related antibiotics.

In accordance with the neuromodulatory role of tonically active neurons in the striatum (figure 4), nicotinic drugs, especially in combination with neuroleptics, have shown some promise in clinical trials. Other drugs with some promise include low doses of pergolide, a mixed D1-D2-D3 dopamine receptor agonist, and locally injected dilute botulinum toxin. Some patients report a striking reduction in premonitory sensory urges after local injections of botulinum toxin. Furthermore, investigators have used several specific behavioural techniques, eg, habit reversal, hypnotherapy, relaxation, and biofeedback techniques, and a growing use of alternative treatments—eg, acupuncture and dietary supplements—has been seen. The most promising of these approaches is habit-reversal training. Azrin and Nunns developed this procedure for treatment of tics and other habits. As originally described, the intervention consists of several inter-related components.

Four components focus on increasing patient's awareness of their tic behaviour. The first component is response description, in which the patient is trained to describe tic occurrences in detail and to re-enact tic movements while looking in a mirror. The second one is response detection, in which the therapist points out each tic as soon as it takes place. The third includes practices aimed at helping the patient to identify the earliest signs of tic occurrence. The fourth is functional analysis, to identify situations in which tics are most likely to happen. A fifth component comprises competing response practice, which teaches individuals to produce incompatible physical responses dependent upon the urge to perform a tic. Individuals are instructed to isometrically contract tic-opposing muscles for 1–3 min, or until the urge to tic has passed. Other components include ones used to increase and sustain motivation and adherence, as well as one aimed at generalisation training. This intervention may be useful for some individuals, but systematic clinical trials have not been done.

Treatment of hyperkinetic disorder in children with tics

Treatment of hyperkinetic disorder in patients with a personal history of tics is common, complex, and controversial. In addition to classroom interventions—eg, small classes, close monitoring, assigned seat at the front of the classroom, assignment of a teacher's aide, and other accommodations—and behavioural interventions at home (eg, parents' management training and behavioural management are often very important, especially when the

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child manifests disruptive behaviour), clinicians typically find drugs to be helpful in treatment of this disorder. Psychostimulants, such as methylphenidate, dexamfetamine, and related drugs are the most effective agents for uncomplicated hyperkinetic disorder. Although these drugs could be used with impunity in some individuals with tics, in a few cases, they can precipitate de-novo tics or exacerbate pre-existing tics in some individuals with Tourette’s syndrome. As a result, many clinicians will begin with clonidine or guanfacine, which, although not as potent as the stimulants, seem to be less prone to exacerbation of tics. Researchers in one large-scale, double-blind, clinical trial reported that the combination of clonidine and methylphenidate was most efficacious in treatment of children with both attention-deficit hyperactivity disorder and chronic tics.  

Treatment of tic-related obsessive-compulsive disorder

Specific cognitive behavioural techniques (eg, exposure and response prevention training) might be useful for selected patients with Tourette’s syndrome who present with obsessive-compulsive disorder. Serotonin reuptake inhibitors are usually useful in treatment of symptoms of this disorder, but might not produce a complete therapeutic response. Augmentation with a low dose of a neuroleptic might increase the anti-obsessional efficacy of these drugs. At higher dosages, the serotonin reuptake inhibitors might occasionally precipitate or exacerbate tics.

PANDAS interventions

Although some cases of Tourette’s syndrome have been proposed to be a sequel of GABHS infections, this connection remains controversial, and is likely to be a contributing mechanism in only a few people with the syndrome. Antibiotic prophylaxis and arduous investigational interventions, such as plasma exchange or intravenous immunoglobulins, have been successfully used in a few patients with exacerbations after streptococcal infection.  

Future prospects

Present ideas about Tourette’s syndrome have been shaped by advances in the neurosciences and our emerging understanding of the role of the basal ganglia in learning and habit formation. Although evidence that the same mechanisms have a role in habit formation and tics is circumstantial, progress has set the stage for a major advance in our understanding of this disorder. Continued success in these areas will lead to molecular insights into functioning of neural networks, complexities of information transfer, and targeting of specific circuits for more intensive study. Diagnostic, treatment, and prognostic advances can also be anticipated.

The identification of susceptibility genes in Tourette’s syndrome will doubtless point us in new therapeutic directions, as will characterisation of possible autoimmune mechanisms active in the PANDAS subgroup of patients. In view of this potential, Tourette’s syndrome can be deemed a model disorder in which to study the dynamic interplay of genetic vulnerabilities, environmental events, and neurobiological systems active during early brain development. Research paradigms used in these studies, and many of the empirical findings resulting from them, will probably be relevant to other chronic disorders of childhood onset and will also advance our understanding of normal development.

References


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