INTRODUCTION

Gilles de la Tourette's Syndrome (TS) was originally described by Jean-Marc Itard in 1825 (1) and was later expanded on by Gilles de la Tourette (2), whom the disorder was named after. The syndrome is probably best known for the minority of cases that express coprolalia (involuntary use of obscene and vulgar language). However, TS is more generally a severe form of a tic disorder, of which coprolalia is a complex vocal tic.

In some respects, research into the understanding of TS has made considerable advances; however, in other respects, the progression has been rather slow. Early investigators, including Gilles de la Tourette, considered TS to be hereditary in origin due to its familial transmission (2,3,4). However, by the beginning of the twentieth century, psychiatrists had changed their emphasis to the psychodynamic aspects of the disorder (5). Tics were thought to be "a coordinated purposive act" that occurred in individuals with "indications of mental instability" (6). The emergence of psychoanalysis lead to new theories such as classifying TS as a narcissistic or anal-sadistic disorder. Unfortunately, psychotherapy, in its many different forms, has not proven to be a successful treatment for the suppression of tics (6).

The most significant advance in the understanding, as well as the treatment, of TS was the introduction of haloperidol as a form of pharmacotherapy in 1961 (7-9). Since this discovery and the establishment that haloperidol acts as a dopamine receptor antagonist (10), there have been no major advances in the understanding of TS. Rather, there have been many small advances in two separate yet connected areas of the syndrome, namely, genetics and neurochemistry. This review will present evidence suggesting both the heritable nature of TS and the likely involvement of dopamine system dysfunction in the pathology of TS. However, before discussing these recent advances in TS, the clinical presentation will be briefly described.

CLINICAL PRESENTATION

TS is a chronic tic disorder characterized by multiple motor tics with at least one vocal tic present at some time during the course of the illness, which distinguishes it from chronic multiple tic (CMT) disorder in which only vocal or only motor tics are seen (11) (see Table 1 for complete Diagnostic and Statistical Manual Fourth Edition (DSM-IV) TS diagnostic criteria). Tics are involuntary, sudden, rapid, brief, repetitive, and stereotyped movements or vocalizations (12) which are enhanced by anxiety, anger, stress and fatigue (6). Motor tics range from simple to complex; simple motor tics involve a single muscle group, causing symptoms such as involuntary eye blinking or shoulder shrugging. Complex motor tics are coordinated patterns of movement, such as touching, jumping or smelling (12). Motor tics can disappear only to be replaced by other tics often in a rostral to caudal progression, e.g., head twitching followed by shoulder...
Two of the most socially distressing motor tics, both of which can be seen in TS, include echopraxia (imitations of movements made by another) or copropraxia (obscene gestures or movements). Vocal tics also range from simple, such as throat clearing, grunting or barking, to complex, such as echolalia (repetition of words or sentences spoken by another) or coprolalia (6). Tics can be suppressed, however, this leads to emotional tension, which can only be relieved by performing the tic. Patients often make an effort to mask the tics by turning them into a seemingly purposeful act, such as following a head twitch by voluntary grooming of the hair (12).

TS affects males approximately three times as often as females (13) and is seen across all ethnic and racial backgrounds with a prevalence of 3 to 5 per 10,000 (13,14). Symptoms can begin at anytime between one and 18 years old (15). The DSM-IV requires that tics begin before 18 and be present for at least one year for a diagnosis of TS (Table 1) (11). However, despite this early onset, the correct diagnosis is often delayed 5 to 11.7 years on average (16, 17). It has been estimated that in approximately 85% of cases the proper diagnosis is made by parents, relatives or friends, with the physician delaying diagnosis until coprolalia appears (12). As mentioned, TS is usually chronic, however, in a few cases, complete remissions have been seen (18). Symptoms are usually more severe in adolescence, for example, 24% of adolescents demonstrate coprolalia while only 4% of adults do. Most importantly, the majority of individuals with TS are able to function normally in society with 98% graduating from high school and 90% obtaining employment (18).

TS is commonly associated with both obsessive compulsive disorder (OCD) and attention deficit disorder (ADD) with or without hyperactivity. As will be discussed later, OCD appears to be genetically linked to TS while ADD may simply increase the likelihood of seeking medical attention. The frequency of OCD in TS patients ranges from low estimates of 45% (19) up to estimates of 63% (20). ADD usually precedes the diagnosis of TS by 2.5 years and is seen in 62% of TS patients (6,18).

When examined using standard neurological exams, TS patients usually do not demonstrate any abnormalities. However, a small number of cases will present mild deficits in motor coordination, reflex symmetry or mirror movements, especially in cases with concurrent ADD (6,12). Furthermore, EEG data on TS patients reveal abnormalities in a slight majority of patients (21). However, this evidence is disputed by some investigators who find a much lower incidence of EEG abnormalities (12). Interestingly, one of the EEG differences noted in TS patients is the lack of pre-movement potential prior to tics, which are usually seen prior to all voluntary movements and can be detected when TS patients voluntarily perform a movement mimicking their tic (21). Finally, while TS patients perform normally on cognitive tests, they generally have greater academic difficulties, reflecting presumably the high incidence of ADD in TS patients (6).

**GENETICS**

Since the inception of TS as a distinct disorder, researchers have suspected that there is a hereditary component to the disorder (2,3,4). However, whether the observed familial transmission was actually due to a genetic predisposition was not known. In the 1970s, the results of a large number of studies examining the transmission of TS supported the notion of a hereditary component. Unfortunately, these studies did not definitively resolve important issues such as mode of transmission (6). It was, however, established that 32% of TS patients have relatives with tics and that 29% of patients with tics, but not full blown TS, have relatives with tics (6).

In the early 1980s, Kidd and Pauls made significant steps in understanding the transmission of TS by confirming four separate conclusions (22,23). First, and very importantly, a statistically significant transmission of CMT disorder with TS was demonstrated (22,23). Accordingly, using a diagnosis of CMT disorder or TS as genetically equivalent, Baron et al. were able to demonstrate that their joint transmission is explained by a single major gene locus model (24). In later studies, Kidd and Pauls were unable to replicate this finding, being unable to exclude any genetic hypotheses as their data fit all statistical models (25).
However, from the original study of Kidd et al., the single locus model gave the best statistical fit to the data (22), which has been validated by several (26-30), but not all (31-32), other studies, making it the best possible explanation of the data.

The second conclusion Kidd and Pauls derived from their initial studies was that TS is transmitted from parent to child (22,23), which had been suggested many times before. However, the mode of transmission has not been consistent across all studies, and both autosomal dominant with reduced penetrance and autosomal recessive with full penetrance have been suggested (29,31). The remaining two conclusions Kidd and Pauls made were that there is a sex difference in the transmission of TS and that this can be considered a threshold phenomenon correlated with genetic loading, which leads to a higher transmission of TS through females than males (22,23) (due to having a higher threshold for developing symptoms, females require a greater genetic load leading to an increased risk for TS in male children of female probands).

The initial studies of Pauls and Kidd, however, are not without problems since they were based on family histories obtained from mailed questionnaires (22,23). Furthermore, in the study by Kidd only one third of questionnaires were returned. These two concerns potentially cause misdiagnosis and self-selection bias, respectively (22). In fact, Pauls and Kidd later demonstrated that direct interview leads to 5.5 times the diagnosis of TS and 1.5 times the diagnosis of CMT disorder compared to obtaining a family history from one person (33). However, despite the potential for false negative TS and CMT disorder diagnosis in the initial study, the conclusions were statistically supported. Furthermore, the initial conclusions were supported by detailed family studies in which every member was interviewed (29,33). The conclusions themselves do not set the work of Pauls and Kidd apart, since most had been suggested previously. However, the statistical methods that were used strengthened the genetic hypothesis of TS since previous studies of hereditary patterns had relied mostly on descriptive analyses of the data, while Pauls and Kidd used carefully applied logistic models.

OCD and ADD are frequently found in patients diagnosed with TS to the extent that OCD and ADD have been proposed to be genetically related to TS (29,34,35). Evidence has accumulated supporting the genetic relationship between OCD and TS, such as increased prevalence of OCD in first degree relatives of TS patients, segregation and linkage of OCD with TS and increased occurrence of vertical transmission of OCD (29,36,37). It has even been proposed that the genetic predisposition can be expressed as either TS or OCD (12,36). However, the link between ADD and TS has not held up to further scrutiny. Using a family study design it was demonstrated that ADD and TS segregate independently indicating they are not genetically related (29, 38).

The final evidence concerning the genetics of TS truly addresses the involvement of genes with minimized environmental confounds by comparing monozygotic and dizygotic twins. While some suggest that monozygotic twins in general will actually have a greater similarity in their environment than dizygotic twins (39), this minor difference in environmental influence does not overly detract from the nearly ideal situation. Using the diagnostic criteria of TS alone, meaning motor and at least one vocal tic, Price et al. demonstrated that 53% of monozygotic and 8% of dizygotic twins were concordant (40). Reanalysis with broader diagnostic criteria that included any tic raised the concordance to 77% and 23% for monozygotic and dizygotic twins, respectively (40). Two important ideas emerge from this study. First, that the greater the genetic similarity between individuals with very similar environments, the greater the concordance for TS. Also, this study suggests that environment does play a role in TS since individuals that are 100% genetically similar are not always concordant. Hyde et al. confirmed these results and took them one step further by demonstrating that phenotypic expression of TS varies with birth weight (41). In monozygotic twins concordant for TS, the more severely affected twin had a lower birth weight in 12 of 13 pairs. This suggests that prenatal events contribute to the non-genetic factors affecting TS expression (41).

**NEUROCHEMISTRY AND ANATOMY**
There have been numerous theories that consider dopaminergic, serotonergic, adrenergic, cholinergic, GABAergic and the opioid systems as potential sites of primary dysfunction in TS (12). However, this discussion will be limited to the dopaminergic system because it represents a clinically successful site for pharmacological intervention and is associated with various neuroanatomical and neurochemical abnormalities seen in TS.

The suggested involvement of dopamine in TS dates back to the discovery that haloperidol, a dopamine receptor antagonist, is an effective treatment for tics (7-9). Since then it has become the standard treatment for TS (6), with improvements seen in 62% to 91% of patients (42). Shapiro et al. conducted the first double-blind placebo controlled study of haloperidol and found haloperidol to be more effective than placebo. Furthermore, they found that haloperidol was even more effective than another commonly used dopamine receptor antagonist, pimozide (42).

Two important facts about haloperidol and pimozide raise questions as to whether their efficacy necessitates a dopamine involvement in TS. The first is that neither is remarkably selective for dopamine receptors, leading to the possibility that their therapeutic activity could be mediated by blockade of another neurotransmitter, such as noradrenaline. Furthermore, haloperidol, which is more clinically efficacious than pimozide, results in greater noradrenergic blockade due to the greater dopamine selectivity of pimozide (43). However, when examined in the plasma, CSF or the brain, noradrenaline metabolites are unchanged in TS patients (44-49), indicating noradrenaline abnormalities are not likely to contribute significantly to TS. Furthermore, although some studies report that clonidine (a presynaptic *2 noradrenergic receptor agonist which reduces noradrenaline release) is an effective treatment of TS (50-53), it was found to be ineffective in reducing motor tics, vocalization or behavioral symptoms in a placebo-controlled crossover study (54). Hence, it is unlikely that either haloperidol or pimozide reduce TS symptoms by interfering with noradrenergic neurotransmission.

The second confounding factor of haloperidol is that it has a potent sedative action, which could lead to a reduction of tics without a direct action on the neural systems involved. Pimozide would not be expected to reduce tics through sedation as much as haloperidol due to its documented lower sedative effect (55). However, a double blind cross-over study comparing haloperidol to pimozide found haloperidol to be significantly more sedative than pimozide, but not significantly different in their capacity to reduce tics, indicating that the sedative action is likely unrelated to tic reduction (56).

Finally, there have been reports of reduction in tics caused by blockade of dopamine synthesis (57,58) as well as the spontaneous appearance of tics following cessation of neuroleptic treatment (chlorpromazine, a dopamine antagonist) which is known to induce a hyperdopaminergic state (59). Therefore, while the clinical efficacy of haloperidol and other dopaminergic antagonist do not necessarily indicate the involvement of dopamine in TS, it does form a well established foundation for this hypothesis.

The dopamine hypothesis of TS has been further confirmed by studies and clinical observations of central nervous system (CNS) stimulants, which are dopamine agonists. Golden originally described the exacerbation and recurrence of symptoms in TS patients who had taken CNS stimulants, in most cases methylphenidate (60). He also described the induction of TS in children after taking methylphenidate for ADD (60,61). An examination of tics in twins and non-twins taking CNS stimulants (methylphenidate in most cases), conducted by Price et al., indicated that there is a correlation between stimulant use and exacerbation of symptoms in TS patients (62), which has been replicated for both cocaine and amphetamine (63,64). It was concluded, however, that stimulants did not cause the emergence of tics in the majority of cases since, in a number of instances, twins were concordant for TS but discordant for use of stimulants (62). Therefore, even though dopamine agonists do not appear to cause TS, the data clearly indicate that they exacerbate symptoms, further implicating dopamine in the expression of TS.
The dopamine system has four major areas of action: the striatal (caudate nucleus and putamen), limbic (cingulate cortex and nucleus accumbens), cortical (prefrontal cortex) and tubero-infundibular (median eminence) areas. Of these sites, only the striatum has been suggested to be altered in TS. Using MRI, it has been demonstrated that the usual asymmetry of the striatum (left greater than right) is reduced, as is the volume of the caudate nucleus in TS patients compared to controls (65,66). Also, in twin pairs concordant for TS, the more severely affected twin had a greater reduction in striatal asymmetry as well as a reduced volume of the caudate nucleus (67). Furthermore, the dopamine hypothesis of TS is strengthened since the only other area in the brain implicated in TS is the globus pallidus, which is the output site of the striatum (65,66), and even this difference has been linked to ADD being present with TS and not TS alone (68).

Clinically effective pharmacological interventions (e.g., haloperidol, pimozide) and neuroanatomical studies suggest that the dopaminergic system is involved in TS. The question remains as to whether abnormalities in the dopamine system can be found in vivo or post mortem in TS brains. Indeed, abnormalities in dopaminergic tone are one of the most reliable findings in TS. Singer et al. demonstrated that dopamine uptake was increased by 37% in the caudate nucleus and 50% in the putamen in post mortem tissue from TS patients compared to controls (69). More recently, dopamine uptake sites were characterized in vivo in TS patients. These studies lead to the similar conclusion that striatal dopamine uptake sites are increased in TS patients, which could be an attempt to compensate for an overactive dopamine system (70,71). Reports on dopamine receptor levels in TS patients have shown no changes compared to controls (69,72). However, Wolf et al. demonstrated that dopamine D2 receptors are increased in the more severely affected twin of concordant pairs (73) (Table 2). By choosing concordant monozygotic twins they were able to obtain perfect genetic matching of pairs, thereby reducing the normal genetic variability in receptor levels. The remaining variable in the study, symptom severity, strongly correlated with the dopamine D2 receptor levels (73).

Alterations in the dopamine system have been well established. However, it is still uncertain whether they represent a primary pathology or a secondary change caused by an unknown primary deficit. One test of the hypothesis that an altered dopamine system is critical in TS pathology is whether dopamine can account for the behavioral profile. As mentioned, alterations in dopamine neurotransmission can produce or ameliorate tics depending on use of either agonists or antagonists, respectively. Furthermore, it is well established that dopamine in the basal ganglia contributes significantly to the initiation of movements (74). However, although this suggests that an altered dopamine system likely contributes to TS symptomatology, it cannot confirm that dopamine alterations are the primary cause of TS.

The second most important behaviors noted in TS are obsessions and compulsions, since they are observed in up to 69% of TS patients (18) and are most likely genetically linked to TS (36,37). Serotonin reuptake inhibitors are the first-line treatment for OCD; however, the dopamine system has been implicated in the disorder and dopamine antagonists have been shown to be an effective treatment for OCD, especially in patients with concurrent tics (75-77). The final set of symptoms in TS patients, such as learning deficits and sleep disorders, while not directly linked to dopamine, can be produced by the other dopamine-induced behaviors. Therefore, functionally, the dopamine system is in a prime location to be the primary pathology in TS.

In order to directly examine this possibility, several studies have examined the genetic linkage of TS to different dopamine receptors and dopamine synthesis enzymes. These studies have suggested that dopamine D1, D2, D3, D4 and D5 receptors genes, as well as dopamine beta hydroxylase, tyrosinase and tyrosine hydroxylase genes, are not associated with TS (78-82). Recently, however, the dopamine D4 receptor gene (83) and a combined effect of dopamine D2 receptor, dopamine beta hydroxylase and dopamine transporter genes have been linked to TS (32), leaving the possibility that dopamine could be directly affected or that an unknown gene controlling the development of the striatum could be affected in TS.

**FINAL REMARKS**
Since characterized by Gilles de la Tourette, the understanding of TS has made considerable progress. The clinical efficacy of the dopamine receptor antagonist haloperidol and the establishment of a familial transmission of TS were fundamental findings which have influenced the direction of most subsequent research. In recent years, advances in the understanding of TS have again been made with the use of twin studies, genetic linkage and in vivo brain imaging. These studies have confirmed the involvement of dopamine abnormalities in TS pathology. Furthermore, it has been confirmed that the transmission of TS is genetic and, most interestingly, that the expression of the TS phenotype can be influenced by environmental factors. While TS pathology is as of yet imperfectly understood, TS is undeniably a genetically transmitted disorder with a dysfunction in the dopamine system that offers a clear route of treatment. It is expected that a more precise understanding of the genetic etiology and the nature of the dopamine dysfunction in TS will lead to a more refined and effective pharmacological treatment.

REFERENCES

1. Itard JMG. Memoire sur quelques fonction involontaires des appareils de la locomotion de la prehension et de la voix. Archives of General Medicine 8: 385; 1825.


81. Brett PM, Curtis D, Robertson MM, et al. The genetic susceptibility to Gilles de la Tourette syndrome in
a large multiple affected British kindred linkage analysis excludes a role for the genes coding for dopamine D1, D2, D3, D4, D5 receptors, dopamine beta hydroxyase, tyrosinase and tyrosine hydroxylase. Biological Psychiatry 37(8): 533-540; 1995.


---

**BIOGRAPHY**

**Graham Wood** received a B.Sc. in Biochemistry from McMaster University (Hamilton, Ontario, Canada) in 1994. He is currently working towards his Ph.D. in Neurological Sciences from the Department of Neurology and Neurosurgery, McGill University (Montreal, Quebec, Canada), where he is studying an animal model of schizophrenia.

Copyright © 1997 by MJM