

## Review

# Current Issues in Tourette Syndrome

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In the late 19th century Georges Gilles de la Tourette described nine patients with chronic tic disorders characterized by the presence of involuntary motor and phonic tics.<sup>1</sup> He also noted that these individuals had a variety of comorbid neurobehavioral problems, including obsessive-compulsive behaviors (OCB), anxieties, and phobias. Since the initial description of this disorder, Tourette syndrome (TS) has been considered to be a model neuropsychiatric condition with a complex interaction of biologic and psychologic factors. The goal of this article is to review newer developments in Tourette syndrome by focusing on recent information published within the past 2 to 3 years (notated in Medline). Areas to be covered include the phenomenology of tics, newer tic scales, epidemiology, genetics, neuroimmunology, neurobiology, and treatment. Although advances have been made in each of these areas, it will become clear to the reader that many questions persist and much work remains to be done.

### PHENOMENOLOGY

Tics, the essential component of TS, are readily observed but broadly defined (involuntary, sudden, rapid, repetitive, nonrhythmic, stereotyped) movements or vocalizations. They are manifested in a variety of forms, have different degrees of severity and duration, and no two patients have the same symptoms. Despite these wide guidelines, recent reports continue to document unique presentations. Vomiting and retching have been diagnosed as tics in 10 patients with TS, but it is possible that these symptoms represent a side effect of pharmacotherapy or a coexisting psychiatric disorder.<sup>2</sup> One teenager with numerous typical tics developed anterior-posterior displacement of the external ear, labeled “ear

dyskinesias,” which was briefly suppressible.<sup>3</sup> Sign language tics have occurred in a woman with TS who learned to sign in adulthood<sup>4</sup> and in a prelingually deaf individual who replaced vocal tics with equivalent sign language tics.<sup>5</sup> On the basis of the latter case, it has been suggested that semantics are more important than phonology in the generation of tics.

Several articles have re-emphasized the presence of common, but misdiagnosed, symptoms in TS, such as a chronic persistent cough, eye blinking, ocular tics, tics mimicking asthma, or atopic symptoms and dermatologic manifestations.<sup>6–10</sup> In nine patients with TS, the blink rate was approximately two- to threefold higher at rest than the blink rate of control subjects. Task-specific events were shown to affect eye blinks and ocular tics; eye blinks were increased by watching videos but not by conversation, whereas ocular tics were generally increased while watching amusing videos but decreased during active involvement in conversation.<sup>7</sup> The potential for tics in patients with developmental stuttering has also been emphasized in the literature. An array of non-speech motor behaviors (eye blinking or deviation, head jerks, limb and trunk movements) have often been noted in individuals who stutter, but generally these movements have not been considered to be tics. In a study of 22 children and adults with developmental stuttering, Abwender and colleagues<sup>11</sup> suggested that one half had undiagnosed TS symptoms. Lastly, in a study of tic characteristics, Peterson and Leckman<sup>12</sup> measured intervals between temporarily adjacent tics and showed that tics occur in a “burst-like” fashion with a nonrandom pattern of recurrence. The authors suggest the presence of a “fractal, deterministic, and possibly chaotic process” determining tic activity, that is, regardless of the time interval (minutes, hours, days), a similar bursting intermittency is present.

Overlapping clinical and pathologic features have been suggested to exist between individuals with TS and the restless legs syndrome (RLS). RLS is characterized

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by a desire to move the limbs in association with uncomfortable paresthesias or dysesthesias and is typically worse in the evening and while at rest.<sup>13</sup> The syndrome may appear in childhood, family history is often positive, movements are performed to alleviate preceding sensory symptoms, sleep disturbances are common, a dopamine mechanism has been proposed, and treatment includes the use of dopaminergic agonists. To further investigate similarities between RLS and TS, seven medication-free adults with TS were evaluated for the presence of periodic limb movements in sleep (PLMS), a frequent finding in RLS.<sup>14</sup> Polysomnograms with electromyograms showed that five of seven subjects with TS had periodic leg movements and four of seven had periodic arm movements during sleep. Further comparison studies are expected.

In addition to reports on new and old tic symptoms, several articles have emphasized that there may be a spectrum of movements in patients with TS that are not tics.<sup>15,16</sup> For example, it is always possible that these are drug-induced movements (akathisia, dystonia, chorea, parkinsonism) or those associated with comorbid conditions such as obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), or anti-social behavior. Tic symptoms have been reported as an early expression of Lyme infection<sup>17</sup> and after treatment with lamotrigine<sup>18</sup> or clomipramine.<sup>19</sup> Several factors may assist the clinician in differentiating between tics and other conditions, including subjective perceptions, factors that suppress or exacerbate, suppressibility, variability, presence during sleep, and associated disturbances (hyperactivity or compulsions).<sup>15,20</sup> Clearly, the misinterpretation of symptoms can lead to ineffective and inappropriate management.

Although TS was originally proposed to be a lifelong disorder, its course may be variable, and some patients may have a spontaneous remission or marked improvement independent of the use of tic-suppressing medications. Leckman and colleagues,<sup>21</sup> using a mathematical model to assess the time course of tic severity over the first two decades, have suggested that maximum tic severity occurs between the ages of 8 and 12 years and is then followed by a steady decline in symptoms. Similar to other reports,<sup>22</sup> early tic severity was not found to be a good predictor of later tic severity. The role of puberty in altering tics remains speculative, because the authors did not assess pubertal changes by physical examination.

### TIC RATING SCALES

Because of their wide variability, spontaneous waxing and waning, and ability to be partially volitionally suppressed, tics are difficult to rate with reliability. This

problem is not new, but has been emphasized in several recent studies focusing on tic status during stimulant treatment.<sup>23,24</sup> In particular, investigators questioned a clinician's ability to rank changes in tic severity by counting the number of tics observed during a 2-minute interval. One recent effort to improve an existing protocol includes modification of the scoring for the Rush Video-Based Tic Rating Scale.<sup>25</sup> This 10-minute film protocol includes near and far body views obtained under two conditions, patient relaxed with and without the examiner in the room. The new scoring system provides a 0-4 comparison in five domains (number of body areas, frequency of motor and phonic tics, and severity of motor and phonic tics) plus a total score of overall tic disability. A video-based rating scale is advantageous for several reasons, including the collection of data with the patient in a relaxed setting without direct scrutiny, and the ability for the video to be replayed and validated. To date, a long-awaited standardized Unified Tic Rating Scale is still being field-tested.

In addition to challenges in the measurement of tic severity, until recently there has been no existing instrument to measure the lifetime likelihood of a person having or ever having had TS, which is important information for accurate pedigree linkage analysis. To correct this deficiency, a collaborative group of experts developed the Diagnostic Confidence Index: a questionnaire independent of current severity that provides a graded score of 0 to 100.<sup>26</sup> Several of the more highly weighted diagnostic confidence factors include a history of coprolalia, complex motor or vocal tics, a waxing and waning course, echophenomena, premonitory sensations, an orchestrated sequence, and age of onset.

### EPIDEMIOLOGY

The estimated prevalence of TS has varied from 1 to 10 per 10,000 individuals, in part as a result of selection and attribution bias. To eliminate some of these methodologic problems, Mason and colleagues<sup>27</sup> investigated the prevalence in 13- to 14-year-old students attending a mainstream secondary school in the United Kingdom. Five of 166 pupils were identified as having TS, resulting in a prevalence estimate of 299 per 10,000. Because this study had a small sample size and the identified cases were not reassessed or formally diagnosed by an expert, these results must be interpreted with caution. The study does, however, emphasize that there may be many mild cases with minimal psychopathology. For comparison, Hanna and coworkers<sup>28</sup> in Houston, Texas, found a prevalence rate of definite TS or TS by history in 0.7% of 1142 students in second-, fifth-, and eighth-grade classrooms.

Other prevalence studies have sought to document the co-occurrence of autism and TS. In an extended study of 447 pupils in special schools for autism, a rate of 6.5%, similar to results in smaller studies, exceeds that expected by chance.<sup>29</sup> TS was found to be equally common in children with autism, Asperger syndrome, and autistic spectrum disease, implying that TS is unrelated to the severity of autism. This report is in keeping with previous investigations that have shown children in special school populations have an increased prevalence of TS.<sup>30</sup> Tourette syndrome occurs worldwide, with increasing evidence of common features in all cultures and races. A previous report suggested that the incidence of coprolalia was lower in Japan than in the West.<sup>31</sup> Kano and coworkers,<sup>32</sup> however, in a combined in- and outpatient psychiatric cohort of 64 Japanese patients with TS, identified an incidence of coprolalia of 50%. This discrepancy between studies within the same country emphasizes that ascertainment bias should always be considered in reviewing clinical characteristics.

### GENETICS

Although Georges Gilles la Tourette suggested an inherited nature for TS, the precise pattern of transmission and the identification of the gene remains elusive. Strong support for a genetic disorder is provided by studies of monozygotic twins that show an 86% concordance rate with TS compared with 20% in dizygotic twins.<sup>33,34</sup> Earlier proposals suggesting a sex-influenced autosomal-dominant role of inheritance with variable expressivity as TS, chronic tic disorder, or OCD<sup>35</sup> have been seriously questioned. Other investigators have proposed hypotheses of a single major locus in combination with a multifactorial background, that is, either additional genes or environmental factors.<sup>36</sup>

The search for a genetic site is being actively pursued but, despite several studies, to date no reproducible locus has been identified. In a systematic genome scan of 76 affected sib-pair families with a total of 110 sib-pairs, the multipoint maximum likelihood scores for two regions (4q and 8p) showed a trend but did not reach acceptable statistical significance.<sup>37</sup> Fine point mapping studies are currently in progress and additional families are being collected. One region, chromosome 19p, suggested from a genome scan of multigeneration families,<sup>38</sup> was also positive in the sib-pair study. Nevertheless, in the study by Barr and colleagues,<sup>38</sup> no logarithm of the odds (LOD) score was greater than 2 for any marker. Tourette syndrome has also been diagnosed in three of five patients with a fragile site at 16q22-23.<sup>39</sup> Several variables have been proposed to explain the unsuccessful genome search, including problems defining the phenotype, in-

accurate diagnostic assessment, improper ascertainment methods, and problems with genetic modeling and data analysis.<sup>40,41</sup>

Since gene mapping with large kindreds has failed to identify a specific consistent abnormality, efforts have begun to evaluate genetically isolated populations. For example, recent reports describe a genome scan in which DNA samples from patients with TS and unaffected control subjects in a South African Afrikaner population were examined.<sup>42</sup> An additional approach has been to search for a linkage to candidate genes, often those associated with specific synaptic markers. Recent linkage studies, however, have yielded no positive results to dopamine D1-5 receptors<sup>43-46</sup>; glycine alpha 1 subunit (GLRA1), GABA<sub>A</sub> receptor alpha-1, alpha-6, and gamma-2 subunits (GABRA1, GABRA6, GABRG2), GABA<sub>A</sub> receptor beta-1 and alpha-2 subunits (GABARB1, GABARA2), glutamate receptor GLUR1, the alpha adrenergic receptor ADRA1, the beta adrenergic receptor ADRB2, and the glucocorticoid receptor GRL<sup>47</sup>; norepinephrine transporter gene<sup>48</sup>; and catechol-o-methyltransferase.<sup>49</sup> Investigators have also sought to identify associations between TS and other movement disorders. Expanding on suggestions of a relationship between TS and dystonia,<sup>50</sup> a three-generation family in which the two cosegregates (5 with dystonia, 3 with TS/facial tics) have been described.<sup>51</sup> The authors hypothesize that all are carrying a "susceptibility gene," but larger pedigrees will be required to confirm these assertions.

Most segregation analyses for TS consistently suggest that the risk for TS is transmitted in a Mendelian fashion with contributing genes of major effect. In contrast, a recent genetic study, with use of a data modeling computer program, REGTLhunt (modified from S.A.G.E. [Statistical Analysis for Genetic Epidemiology]), available from the Dept. of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH, USA), to evaluate 108 extended families, each obtained through a TS proband, suggests that transmission of TS is not consistent with Mendelian inheritance.<sup>52</sup> This investigation also reported that the association between frequency of TS diagnosis and OCB/OCS was lower than that previously reported. Hence, prior suggestions that TS is not genetic but rather represents a common disorder in the general population<sup>53</sup> have received some scientific validation.

Further complicating our understanding of TS genetics is the issue of the influence of family history on clinical expression. For example, the sex of the transmitting parent (genomic imprinting) may affect the clinical phenotype. Lichter and coworkers<sup>54</sup> suggested that paternal

transmission was associated with increased vocal tics and ADHD, whereas maternal transmission led to greater motor tic complexity and obsessive-compulsive symptoms. This concept is controversial, however, because some investigators found no phenotypic effect associated with paternal transmission and no difference in age of onset.<sup>55,56</sup> Eapen and colleagues<sup>56</sup> did show that maternally transmitted offspring had a significantly earlier age of onset, possibly suggestive of a meiotic event or intrauterine influence. To date, the role of genomic imprinting remains controversial and conflicting reports need to be resolved.

A second issue is that of bilineal transmission, genetic contribution from both sides of the family. In general, a unilineal-inherited pattern implies dominant inheritance, whereas bilineality implies recessive or polygenic transmission patterns. One issue that remains undetermined is what behavior should be considered when assessing for bilineal transmission. For example, studies have reported that the likelihood of both parents of a TS proband having tics is in the range of 6% to 15%, but when other factors (OCB, ADHD, panic attacks, drug or alcohol abuse) are included, the incidence rises to 34% to 41%.<sup>57-59</sup> Several recent studies have provided additional data on the incidence and effect of bilineal transmission. Hanna et al.<sup>28</sup> found that 26% of patients with TS had evidence of bilineality (tics, OCB, or ADHD), more fathers than mothers had tics, and more mothers had OCB. A similar assessment in normal control families showed that features of the TS spectrum were uncommon. Lichter and coworkers<sup>60</sup> showed that patient age, sex, tic severity, and the presence of ADHD were similar in patients with either sporadic or familial TS, both bilineal and unilineal. Patients with familial transmission did have more prominent obsessive-compulsive behaviors and bilineal patients were more likely to exhibit self-injurious behaviors. These studies emphasize that factors other than genetic dose effects, such as genetic heterogeneity, epigenetic factors, and gene-environment interactions, may play an important role in determining tic severity in TS.

In pursuit of assessing the importance of epigenetic risk factors, such as low proband birth weight, nonspecific maternal emotional stress, and severity of mother's nausea and vomiting during the pregnancy, Burd and colleagues<sup>61</sup> performed a univariate analysis of 92 Tourette cases and 466 year- and month-of-birth-matched control subjects. Several risk factors were identified, including the month and trimester that perinatal care began, number of prenatal visits, and the Apgar score at 5 minutes. Further replication of this study from other

clinical settings will be necessary before its significance can be truly assessed.

## NEUROIMMUNOLOGY

A hypothesized role for environmental factors, especially infections, in the presentation or exacerbation of neuropsychiatric diseases, such as tics and OCD, is not a new phenomenon.<sup>62-64</sup> More recently, Swedo and colleagues<sup>65</sup> proposed that central nervous system manifestations of group A  $\beta$ -hemolytic streptococcal infection (GABHS) account for a cohort of children with neurobehavioral symptoms that include tic disorders, OCD, and ADHD (that is, PANDAS; postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infection). Their diagnostic criteria, established in 50 cases recruited from a nationwide search include: the presence of OCD and/or tic disorder; prepubertal age at onset; sudden, "explosive" onset of symptoms and/or a course of sudden exacerbations and remissions; a temporal relationship between symptoms and GABHS; and the presence of neurologic abnormalities, including hyperactivity and choreiform movements. Volumetric magnetic resonance imaging (MRI) analysis in 34 children with PANDAS showed that the average size of the caudate, putamen, and globus pallidus, but not the thalamus or total cerebrum, was significantly greater in the affected group than in 82 healthy children.<sup>66</sup> Based on a proposed association between tics/OCD and GABHS, a double-blind, cross-over trial with 250 mg oral penicillin V was undertaken to attempt to prevent recurrences of PANDAS.<sup>67</sup> No significant change in either obsessive-compulsive or tic symptom severity occurred between the active and placebo phases but, because an acceptable level of streptococcal prophylaxis was not achieved, no firm conclusions were possible.

Pathophysiologically, based on a Sydenham's chorea (SC) model, an immune-mediated mechanism involving molecular mimicry has been proposed for PANDAS (that is, antibodies produced against GABHS cross-react with neuronal tissue in specific brain regions). Indirect support for this hypothesis is derived from a study examining the response of patients to two forms of immunotherapy, intravenous immunoglobulin (IVIG) and plasmapheresis (PEX).<sup>68</sup> Twenty-nine children with PANDAS, obtained from a nationwide search, were randomized in a partially double-blind fashion (no sham apheresis) to an IVIG, IVIG placebo (saline), and PEX group. One month after treatment, the severity of obsessive-compulsive symptoms (OCS) were improved by 58% and 45% in the PEX and IVIG groups, respectively, compared with only 3% in the IVIG control. In contrast, tic scores were only improved after PEX treat-

ment, that is, reductions of 49% (PEX), 19% (IVIG), and 12% (IVIG placebo). Improvements in both tics and OCS were sustained for 1 year. Explanations for a lack of therapeutic response in proportion to the rate of antibody removal, how peripheral changes affect events across the blood–brain barrier, and the mechanism by which the immune therapy produces its beneficial response remain elusive. Active immunomodulatory therapy, although potentially promising for the highly selected patient, in my opinion remains in the experimental phase, and all treatments should be part of controlled double-blind protocols.

The documentation of antineuronal antibodies in patients with TS or OCD has provided additional support for a potential immune abnormality.<sup>69,70</sup> In one study, Singer et al.<sup>69</sup> showed that compared with control subjects ( $n = 39$ ), children with TS ( $n = 41$ ) had a significant increase in the mean and median optical density levels of serum antibodies (measured by ELISA) against the putamen, but not the caudate or globus pallidus. Western blot analyses indicated that specific antibodies to caudate/putamen occurred more frequently in TS subjects at 83, 67, and 60 kDa. Trifiletti et al. have confirmed the presence of a specific brain protein at an apparent molecular weight of 83 kDa that is recognized by antibodies in the serum of 80% to 90% of patients with TS or OCD.<sup>70</sup> The importance of using human tissue as the antigenic substrate is emphasized by failure to confirm similar antibody changes with neuroblastoma cells.<sup>71</sup> Development of dyskinesias (paw- and floor-licking, head- and paw-shaking) and phonic utterances has been reported in rodents after the microinfusion of dilute IgG from TS subjects into their striatum.<sup>72</sup>

The existence of PANDAS, however, is not free of controversy.<sup>73</sup> For example, no prospective epidemiologic study has confirmed that an antecedent GABHS infection is specifically associated with either the onset or exacerbation of tic disorders or OCD. Diagnostic criteria established for PANDAS are also potentially confounded by the phenotypic variability commonly associated with tic disorders: a normal fluctuation in the frequency and severity of symptoms; exacerbation of tics by stress, anxiety, fatigue, and illness; the occurrence of “sudden, abrupt” onset and/or recurrence of tics in non-PANDAS subjects<sup>74</sup>; a variable response to pharmacotherapy; and the lack of a precise definition for choreiform movements. Additionally, longitudinal laboratory data, rather than studies that use only a throat culture or only a single antistreptolysin O (ASO) or antideoxyribonuclease B titer, are necessary to confirm the presence of a previous GABHS infection. Evidence to support an

immune-mediated hypothesis for PANDAS also remains mostly circumstantial. For example, the often-cited evidence documenting an antineuronal hypothesis in SC<sup>75</sup> relies on data obtained by use of a potentially inaccurate immunofluorescent antibody methodology. Additionally, despite reported higher antineuronal antibody values in children with neurobehavioral problems and/or movement disorders including tics,<sup>69,76,77</sup> the sensitivity and specificity of these studies remain a major issue and confirmatory longitudinal studies are needed.

## NEUROBIOLOGY

The exact neuroanatomic localization of Tourette syndrome remains unknown. Significant data, however, support the concept that TS is a neurologic disorder associated with frontal–subcortical pathways.<sup>78</sup> In the past, routine noninvasive neuroradiographic studies (computed tomography and MRI) have identified only isolated defects that are considered to be incidental nonspecific findings unrelated to the basic pathology. In two recent publications, localized lesions have been associated with clinical symptoms. One was a 17-year-old boy with TS and comorbid OCD, ADHD, stuttering, and gait disturbance whose scan showed bilateral symmetric globus pallidus lesions<sup>79</sup> and a second was an 11-year-old boy with TS who had multicystic changes predominantly in the gyrus rectus of the left frontal lobe.<sup>80</sup> On the basis of a reduced cortical silent period after suprathreshold stimuli and diminished inhibition of a motor-evoked potential after pain stimuli, transcranial magnetic stimulation studies have suggested decreased inhibition of the motor cortex.<sup>81</sup>

## Morphology

Direct evidence for pathophysiological involvement of frontal–subcortical circuits in TS is, in part, derived from volumetric MRI studies. Several structural studies have reported that either the caudate or the lenticular nuclei are abnormal in volume or asymmetry compared with control subjects.<sup>82–84</sup> Because TS is more common in boys than in girls by a ratio of at least 3:1, most research has focused on male subjects, thereby limiting our knowledge of TS in girls. Using methodologies that previously identified structural abnormalities in young male TS patients, Zimmerman et al.<sup>85</sup> showed that basal ganglia volume and asymmetry differences did not distinguish girls with TS from matched control subjects. Similarly, the corpus callosum has been previously shown in MRI studies to be abnormal in individuals with TS, predominantly males.<sup>83,86,87</sup> Once again, a study designed to examine whether abnormalities in corpus callosum morphology were also present in girls with TS failed to show

a significant difference.<sup>88</sup> The aforementioned studies do not imply that the findings in males with TS were invalid, but rather point out that there are gender differences in the neurobiologic manifestations of TS.

### fMRI

Preliminary functional MRI studies have suggested that the pathogenesis of tics involves neuronal activity within subcortical neuronal circuits. Peterson et al.<sup>89</sup> compared images acquired during periods of voluntary tic suppression with those acquired when subjects were allowed spontaneous expression of their tics. Significant changes in signal intensity were seen in the basal ganglia and thalamus as well as in connected cortical regions. The magnitude of regional signal change in the basal ganglia and thalamus correlated inversely with tic severity. To determine whether an abnormal organization of motor functions could be detected in patients with TS, Biswal et al.<sup>90</sup> studied activation of the sensorimotor cortex during a standard motor task paradigm. Functional MRI imaging of five patients with TS during finger tapping showed an increased area of cerebral activation in both sensorimotor cortex and supplementary motor area compared with healthy subjects. Their data support the suggestion that frontal-subcortical pathways contribute to the pathogenesis of TS. Additional studies designed to use fMRI to understand the mechanism of TS by direct imaging are currently in progress.

### Neurotransmitter Abnormalities

The distribution of classic neurotransmitters within the frontal-subcortical circuits raises the possibility that a variety of transmitters may be involved in the pathobiology of TS. Thus, dopaminergic and serotonergic systems have been studied extensively. Dopaminergic hypotheses have included abnormalities of both pre- and postsynaptic function. For example, it has been proposed that TS is the result of supersensitive postsynaptic dopamine receptors (that is, increased number or affinity), dopamine hyperinnervation, abnormal presynaptic function, or an excessive phasic release of dopamine. Despite the aforementioned hypotheses, some investigators have emphasized that abnormalities of dopamine fail to explain many clinical and laboratory observations, including the description of unchanged tics in four adults who developed parkinsonism and received treatment with L-dopa.<sup>91</sup>

### Dopamine

*Postsynaptic Dopamine Receptors.* Limited studies of D1 and D2 receptor binding in postmortem striatal tissue show trends but no significant differences between TS

and control membranes.<sup>92</sup> Overall, studies of D2 dopamine receptors by PET and SPECT techniques have not consistently shown significant differences between patients with TS and control subjects. Nevertheless, several studies have supported the hypothesis that the dopamine receptor is involved in the neurobiology of TS. In five sets of identical twins, increased binding of [<sup>123</sup>I]iodobenzamide (<sup>123</sup>I-IBZM) was observed in the head of the caudate nucleus in association with increased tic severity.<sup>93</sup> Although no significant <sup>123</sup>I-IBZM binding differences were found between unmedicated patients with TS and control subjects, patients with TS with advanced stages of the disorder did have reduced relative binding in the striatum compared with subjects in earlier stages.<sup>94</sup> Lastly, a PET study with a spiperone derivative, 3-N [<sup>11</sup>C] methylspiperone, and a two PET scan technique to measure receptor density (B<sub>MAX</sub>), demonstrated levels beyond the 95th percentile prediction limit (normal regressed against age) in four of 20 subjects.<sup>95</sup> In this same group of 20 patients, multiple linear regression analyses revealed a trend between the severity of vocal tics and B<sub>MAX</sub> values.

*Dopamine Hyperinnervation.* Attempts to provide support for a postulated dopamine hyperinnervation hypothesis by PET or SPECT binding have resulted in contradictory reports. For example, several small studies with [<sup>123</sup>I]β-CIT SPECT have shown striatal dopamine transporter binding to be higher in affected subjects than in control subjects.<sup>96</sup> In contrast, other investigators using similar techniques in 10 adult patients with TS have shown no difference in the mean β-CIT binding compared with control subjects.<sup>97</sup> Studies evaluating dorsal striatal dopaminergic innervation by use of in vivo measures of vesicular monoamine transporter type 2 (VMAT2) binding with the ligand (+)-alpha-[<sup>11</sup>C] dihydrotetrabenazine showed no differences between eight subjects with TS and 22 age-compatible normal control subjects.<sup>98</sup> These results do not support the concept of increased striatal innervation, but do not exclude an abnormality in the regulation of dopamine release or reuptake.

*Presynaptic DA Abnormality.* A third broad proposal implicates a presynaptic dopamine abnormality involving dopa decarboxylase activity. In a PET study, 11 adolescents with TS accumulated [<sup>18</sup>F] fluorodopa at a level 25% higher in the left caudate nucleus and 53% higher in the right midbrain compared with levels in control subjects.<sup>99</sup> The authors suggest that an up-regulation of dopa decarboxylase activity could explain these alterations and that the process reflects deficits in a variety of functional elements of the dopamine system. Nevertheless, a previous study of imaging with [<sup>18</sup>F] fluorodopa showed

no abnormality in presynaptic dopamine function in 10 patients with TS compared with normal subjects.<sup>100</sup> An additional presynaptic hypothesis suggests an abnormal phasic dopamine release from the presynaptic terminal.<sup>101</sup>

### Serotonin

A  $\beta$ -CIT SPECT binding study has reported a negative correlation between overall tic severity and binding in the midbrain (serotonergic) and thalamus (serotonin or noradrenergic).<sup>97</sup> There was no overall reduction in serotonin transporter density in patients with TS. The authors suggest that serotonergic transmission is a modifying, but not causal, factor in the pathogenesis of tics.

In summary, available data have not confirmed a definite, consistent abnormality of synaptic neurotransmission. Although this author continues to think the dopaminergic system has an important role, it is likely that other systems may also be involved, possibly through a common membrane or channel abnormality.

## TREATMENT

The decision to treat an individual patient should be based on an initial comprehensive evaluation, including analysis of tics, documentation of comorbid conditions, assessment of problem severity, and determination of resulting impairment. It is essential that an individual with TS be carefully examined for comorbid features and the treatment of various symptoms should be prioritized. Treatment must be individualized with respect to functional impairments of tics and/or comorbid illnesses, sources of support, capacities for coping, and challenges associated with various stages of development.<sup>102</sup> It has been emphasized that behavioral problems are often associated with comorbid ADHD or OCD rather than with tic severity.<sup>103</sup>

### Tics

Drug therapy for tics is reserved for patients with tics that are functionally disabling, because none of the available pharmacotherapies for tics is curative and all are associated with potential side effects. A variety of non-pharmacologic behavioral treatments (conditioning, techniques, relaxation training, biofeedback, hypnosis) have been proposed as alternative therapeutic approaches, but few have been adequately evaluated. Bergin and colleagues<sup>104</sup> reported a study of 16 patients who were randomized and stratified according to initial tic severity into either a relaxation therapy or minimal therapy (control) group. At the end of a 6-week training period, tics showed greater improvement in the relaxation treatment group, but values failed to reach statistical significance. At a 3-month evaluation, no differences

between therapy groups were apparent. Thus, on the basis of this pilot study, relaxation therapy appears to have a limited role in the treatment of tics in TS.

Traditional Chinese medicine, acupuncture, has been suggested for tic suppression,<sup>105</sup> although it has not received much attention in the scientific literature. Electroconvulsive therapy has been reported in a single case.<sup>106</sup> Lastly, thalamic deep brain stimulation, a modern stereotactic treatment proposed for use in other movement disorders, has been suggested as a potential therapy for the control of tics.<sup>107</sup> While this technique has several advantages over other neurosurgical approaches (for example, lack of permanent complications often associated with lesioning procedures, access to less surgically "accessible" brain regions, and simultaneous bilateral stimulation), pending determination of patient selection criteria and the outcome of carefully controlled clinical trials, a cautious approach is recommended.

### Pharmacotherapy

Neuroleptics that block D2 dopamine receptors such as pimozide and haloperidol are generally considered the most effective tic-suppressing agents. A double-blind, 24-week, placebo-controlled cross-over study of 22 children and adolescents compared the efficacy and safety of pimozide and haloperidol.<sup>108</sup> The authors suggest that at equivalent doses pimozide was a more effective tic suppressor and had fewer serious side effects (depression and separation anxiety) and extrapyramidal symptoms. Alternative selective D2 antagonists not available in the United States but used in Europe include sulpiride and tiapride. The appropriate duration of neuroleptic treatment has been partially addressed in a prospective, randomized pilot of patients with TS who had achieved a medication-induced stable level of tic control.<sup>109</sup> Long-term treatment with pimozide was more effective in controlling the course of tics than pimozide used solely to treat an exacerbation. A regional cerebral perfusion study with technetium-99m HMPAO has shown that neuroleptics increase perfusion to orbital and anterior medial regions of frontal lobes and the left medial temporal cortex.<sup>110</sup> The authors propose that treatment decreases dopaminergic hyperactivity, leading to improvement of clinical symptoms and reperfusion of some previously hypoperfused regions.

Smaller studies or case reports have been published on the use of several atypical neuroleptic agents for tic suppression. These newer antipsychotics (risperidone, olanzapine, ziprasidone, clozapine) are all characterized by having a relatively greater affinity for 5-HT<sub>2</sub> receptors than for D2 receptors. Risperidone has been evaluated in several preliminary studies<sup>111,112</sup> and in a larger cohort

of 38 patients with TS.<sup>113</sup> The results of the latter open-label, 1-month clinical trial showed that 58% improved, 18% had no change, 3% had documented worsening of tics, and 21% did not complete the study because of side effects. Other investigators have suggested that risperidone may be most beneficial in patients having a comorbid obsessive-compulsive disorder.<sup>114,115</sup> Olanzapine has also been shown to produce partial control of tic symptoms. For example, four boys, aged 9 to 16 years, with refractory tics improved after treatment with this medication.<sup>116,117</sup> A similar positive response with olanzapine was reported in an open-label study of 12 patients with severe tics.<sup>118</sup> Side effects included weight gain and mild sedation. Treatment with ziprasidone was significantly more effective than placebo in suppressing tic symptoms in 28 patients with TS, ages 7 to 17, randomly assigned to treatment groups.<sup>119</sup> Although ziprasidone was well-tolerated, additional studies are indicated for a fuller evaluation of safety and efficacy. The combination of 5-HT<sub>2</sub> and D<sub>2</sub> receptor antagonists is not always successful, because the responsiveness of tics to treatment with clozapine has been inconsistent.<sup>120,121</sup>

Pergolide, a mixed D<sub>1</sub>/D<sub>2</sub>/D<sub>3</sub> dopamine receptor agonist, is typically used in the treatment of Parkinson's disease. Despite concerns that a postsynaptic agonist might exacerbate tics, several studies have suggested that tics are actually improved. In an initial open-label clinical trial, pergolide at dosages of 0.1 to 0.3 mg per day decreased tics in 24 of 32 children by more than 50% from baseline.<sup>122</sup> The presence of restless legs syndrome was highly associated with a positive response. In a double-blind, placebo-controlled, 6-week treatment cross-over study in 24 children, pergolide treatment was associated with significantly lower tic severity scores.<sup>123</sup> The treatment dose of pergolide, 0.15 to 0.3 mg per day, is approximately one tenth the typical dose for treating Parkinson's disease. Side effects were mild and electrocardiograms showed no difference from control. The mechanism of action of low-dose pergolide is unknown, but it is speculated to involve presynaptic rather than postsynaptic striatal or cortical dopamine receptors. Apparently not all DA agonists produce similar therapeutic effects, because talipexole treatment of adults with TS failed to improve tics.<sup>124</sup>

A variety of nondopaminergic therapies have been proposed for the treatment of tic disorders but few have been adequately evaluated. Because cannabinoid receptors are densely located within the basal ganglia (globus pallidus and substantia nigra pars reticulata), a possible role in the control of movement disorders has been hypothesized. Suggestive benefit in TS is based on the results of interviews of 17 patients with TS who described

prior use of marijuana; 14 of 17 reported a reduction of tics.<sup>125</sup> A single uncontrolled, open clinical trial supports a beneficial response of TS to delta-9-tetrahydrocannabinol, the major psychoactive ingredient of marijuana.<sup>126</sup> Prospective, controlled trials, which would presumably be heavily subscribed, are clearly indicated. Evidence suggesting a hormonal influence in TS (for example, a strong sex specificity with males > females and knowledge that sex steroids affect gene expression and neuronal functioning) has led to trials of antiandrogens in the treatment of this disorder. In a double-blind, placebo-controlled, cross-over trial with flutamide, a nonsteroidal androgen receptor antagonist, there was a modest, short-lived reduction in motor (not vocal) tics in 13 adult subjects with TS (10 men and three women).<sup>127</sup> The limited tic improvement and the potential serious side effect of hepatic necrosis suggest that flutamide should probably not be used in the treatment of TS.

Nicotine has a variety of potential mechanisms of action in the central nervous system, including a direct action on cholinergic receptors or an indirect action through interaction with dopaminergic, serotonergic, or noradrenergic systems.<sup>128</sup> Reports have suggested improved tic control when nicotine gum or a skin patch is used in conjunction with a neuroleptic drug.<sup>129-131</sup> Despite these open-labeled reports, side effects of nausea and the addictive potential of nicotine makes any putative benefit from this compound socially undesirable. Mecamylamine, a nicotinic acetylcholine receptor antagonist, has also been reported to reduce tics in 11 of 13 patients with TS.<sup>132</sup> A multisite, double-blind control study has been initiated.

Two children treated with donepezil, a noncompetitive inhibitor of acetylcholinesterase, showed tic improvement.<sup>133</sup> A 20-year-old with TS and neuroleptic-induced tardive dystonia had improvement of dystonic movements, motor tics, and coprolalia after treatment with reserpine.<sup>134</sup> Baclofen, which contains both GABA and phenylethylamine moieties, is postulated to act by altering inhibitory neurotransmission. In an open-label study of this medication containing 264 patients, 95% reported a significant decrease in the severity of motor and vocal tics.<sup>135</sup> The most common side effects were sedation and drowsiness. These outstanding results are surprising and need to be confirmed, because only small amounts of baclofen cross the blood-brain barrier. Lastly, botulinum toxin has been successfully used in treating both motor and vocal tics.<sup>135,136</sup>

In view of proposed serotonergic hypotheses for TS (presence of OCD and abnormalities in SPECT studies), several investigators have evaluated the effect of medi-

cations directed at serotonin mechanisms, including meta-chlorophenylpiperazine (m-CPP) and ondansetron. In 12 medication-free patients with TS, a single dose treatment of m-CPP, a selective 5-HT<sub>2c</sub> agonist, had no effect on tics.<sup>137</sup> In contrast, in an open-label trial, six of seven children who received ketanserin, a 5-HT<sub>2</sub> antagonist and  $\alpha$ -adrenergic agonist, showed improvement of tics within a few days.<sup>138</sup> Ondansetron, a selective 5-HT<sub>3</sub> antagonist, was used in six patients resistant to haloperidol in a 3-week open-label trial; two improved, two had a probable response, and two did not improve.<sup>139</sup> Therapeutic trials with several selective serotonin reuptake inhibitors (SSRIs) have produced variable results. A double-blind, placebo-controlled cross-over trial of fluoxetine monotherapy did not result in improvement of tics after 8 weeks of treatment in 14 subjects with TS.<sup>140</sup> In small, open-label 8-week trials with citalopram and fluvoxamine (three subjects in each group), only the former produced a significant improvement in motor and vocal tic symptomatology over time.<sup>141</sup>

In summary, despite the plethora of agents used to treat TS, substantive conclusions cannot be made because most studies have included few patients.

### ADHD

Although psychostimulant medications are generally regarded as the treatment of choice for ADHD, their use in children with TS has been controversial. Because of early reports suggesting that stimulant medications were associated with a potential to provoke or intensify tics and that tics might persist even when the medication was withdrawn,<sup>142-144</sup> some clinicians discourage the use of stimulant medications in patients with tics or even a family history of tic disorders.<sup>145</sup> In contrast, other investigators have countered that patients receiving stimulants did not have a clinically significant worsening of tics or that exacerbations occurred only with lower (starting)<sup>146</sup> or higher doses of medication.<sup>143</sup> Investigators also suggested that methylphenidate (MPH) was better tolerated than dextroamphetamine (DEX); MPH exacerbations diminished with time even with continued administration, whereas fewer DEX exacerbations diminished over the long term.<sup>143</sup>

Several new reports have provided additional information pertaining to the ongoing question of the role of stimulants in worsening tic disorders. To assess the issue of inconsistent prevalence estimates, which range from 1.6% to 60%,<sup>147,148</sup> Law and Schacher<sup>149</sup> performed a 1-year prospective study in 90 children with ADHD with/without mild-moderate tics (not severe tics or TS). Seventy-two subjects received MPH (average dose of 0.5 mg/kg twice a day) and 18 received a placebo. The ap-

pearance of clinically significant tics was not more frequent, either as an initial appearance (20% vs 16%) or an exacerbation of preexisting tics (33% vs 33%), in the MPH-treated compared with the placebo cohort. Forty percent of the tics appeared after 4 or more months of MPH treatment and 3% developed Tourette-like symptoms. The study was limited by its sample size and results do not address populations using higher dosages. Gadow and coworkers<sup>24</sup> evaluated 34 prepubertal children with ADHD plus a chronic multiple tic disorder who were receiving treatment with MPH over a 2-year period. Expressed as grouped data, most ratings of tic severity were unchanged, except for a significantly increased 2-minute physician motor tic count. Data plots for individual children did show considerable fluctuations in the frequency and severity of tics. The authors think individual tic variations occur naturally and suggest that such variations explain some of the reported tic exacerbations in children with preexisting tics. Lastly, the temporary withdrawal of long-term stimulant medication from 19 subjects with ADHD and tics (switched to placebo under double-blind conditions for 2 weeks) did not appear to affect group data of tic frequency or severity.<sup>23</sup> These latter results do, however, differ from a study of five prepubertal boys who had a meaningful reduction in tic status after the withdrawal of long-term MPH treatment.<sup>150</sup>

In summary, there is strong evidence that stimulants are beneficial for ADHD symptoms in children who also have a tic disorder. For most children receiving low-moderate doses of MPH (less information is available for other stimulant medications), there appears to be no clinically significant effect on tics, that is, tics may fluctuate but not require pharmacologic adjustments; lastly, because stimulant medications are not tolerated by all individuals with tics and the possibility exists for tic exacerbation in individual cases, prudent follow up is appropriate.

Alternative medications suggested for the treatment of ADHD symptoms in children with TS include clonidine, guanfacine,<sup>151</sup> desipramine,<sup>152</sup> deprenyl,<sup>153</sup> and nortriptyline. A meta-analysis of clonidine for symptoms of ADHD in children and adolescents (based on 11 reports) showed a moderate effect size.<sup>154</sup> The results of a large multicenter, double-blind treatment study comparing the effects of clonidine, MPH, clonidine plus MPH, and placebo are expected in the near future.

### CONCLUSIONS

Despite its long history, the phenomenology of Tourette syndrome continues to evolve with the addition of new symptoms, clarification of tic diagnoses, and a bet-

ter understanding of the longitudinal course of this disorder. Tic rating scales are becoming more precise, but the intrinsic variability of motor and vocal tics continues to make it difficult to rate these symptoms with reliability. Once considered to be a rare disorder, newer studies show a higher prevalence in both normal and autistic-spectrum populations. The search for a specific gene has intensified, but to date a major breakthrough has remained elusive. Genetic heterogeneity and issues such as genomic imprinting and bilineal transmission are further complicating factors. The potential role of environmental influences, especially infection, and autoimmune contributions to the etiology of tics has gained widespread interest. Brain imaging has provided new information on neuroanatomic abnormalities, areas of enhanced cerebral activation, and potential neurotransmitter abnormalities. Nevertheless, there remains no compelling neurobiologic hypothesis. Therapeutically, traditional neuroleptics represent standard treatment but there is expanding interest in both atypical neuroleptics and nonneuroleptic medications. Although multiple pharmaceutical agents are discussed, most have not been adequately evaluated in randomized, controlled trials. Lastly, there is accumulating evidence supporting the routine use of stimulants for the treatment of ADHD symptoms in individuals with tic disorders. This author remains optimistic that discoveries in the near future will dramatically increase our understanding of this unique and intriguing disorder.

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