Gilles de la Tourette's Syndrome

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ABSTRACT: Tourette's syndrome (TS) is a childhood onset neurological disorder characterized by motor and vocal tics. It may be associated with a number of co-morbidities including attention deficit hyperactivity disorder, obsessive compulsive symptomatology, and behaviour disorders. Prevalence of TS is higher than previously thought, and may be present in up to 2% of the population. Tourette's syndrome has a significant genetic component. Inheritance may involve several mechanisms including autosomal dominant, bilinear, or polygenic mechanisms. Pathophysiology is still unknown, although is thought to involve striatocortical circuits. Treatment begins with modification of the work and home environment. For more severe cases, medications such as tetrabenazine and neuroleptics may be helpful. Treatment of co-morbidities needs to be considered, as these may result in more disability than the tics themselves.

RÉSUMÉ: Le syndrome de Gilles de la Tourette. Le syndrome de Gilles de la Tourette (SGT) est un désordre neurologique commençant dans l'enfance, caractérisé par des tics moteurs et vocaux. Il peut être associé à certaines comorbidités dont le trouble de déficit de l'attention/hyperactivité, une symptomatologie obsessive-compulsive et des troubles du comportement. La prévalence du SGTest plus élevée qu'on ne le pensait et pourrait atteindre 2% de la population. Il existe une composante génétique importante dans le SGT. Le mode d'hérédité peut comporter plusieurs mécanismes, dont des mécanismes autosomiques dominants, biparentaux ou polygéniques. Sa physiopathologie est encore inconnue, mais on pense qu'elle implique les circuits striato-corticaux. Le traitement commence par des modifications de l'environnement au travail et à la maison. Dans les cas plus sévères, des médicaments tels la tétrabénazine et les neuroleptiques peuvent être utiles. Le traitement des comorbidités doit être envisagé parce qu'elles peuvent être plus invalidantes que les tics eux-mêmes.

Gilles de la Tourette's syndrome (TS) is a disorder characterized by multiple chronic motor and vocal tics that wax and wane with time. Though neurologists and psychiatrists of the early 20th century believed TS to have a psychogenic origin, more recent research has resulted in a return to Gilles de la Tourette's initial impression of the disorder as a nonprogressive, hereditary neurological condition.

CLINICAL MANIFESTATIONS

A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization. Motor tics may be experienced in any part of the body and may be simple or complex in nature. A simple motor tic is a simple, nonpurposeful movement of functionally related muscle groups, and may further be subdivided into clonic (eye blinking, shoulder shrugging), tonic (arm stretching), and dystonic (facial grimacing). Complex motor tics are semipurposeful movements, such as touching oneself, other people or objects, jumping, grooming behaviours, or echopraxia. Likewise, vocal tics can be simple (coughing, grunting, sniffing or throat clearing) or complex (repetition of words or phrases out of context, palilalia, echolalia, or coprolalia).[1]

Many patients report uncomfortable feelings or sensations that immediately precede the tic, and are typically temporarily relieved by the movement.[1] These premonitory symptoms may take the form of a somatic sensation localized to a particular part of the body (particularly the palms, shoulders, midline abdomen, and throat).[2] Alternatively, they may be a nonlocalized, or poorly characterized feeling.[2,3] Thus, tics are semi-voluntary, and this is important in differentiating tics from other hyperkinetic movement disorders.

Current criteria for the diagnosis of TS are shown in Table 1.

NATURAL HISTORY

Tourette's syndrome has a childhood onset, with a mean age of onset of six to seven years. Significant variability is seen in

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type of tics, area of onset, and rate of progression.

Most common presentation is with facial twitching (50-70% of patients).[3] Tics typically begin as simple motor, with later development of complex motor tics; simple vocal tics proceed to words and phrases. After onset, there is typically a prepubertal exacerbation, a postpubertal attenuation, and adult stabilization of symptoms.[4] Traditionally, it was thought that TS was a life-long disorder. However, in a retrospective cohort study, 50% of TS patients were asymptomatic by age 18.[5] The adulthood course of TS is generally stable, with 65% of patients not exhibiting any changes in symptomatology over five years.[6] Severity of tics during childhood does not predict the later course of TS.[5]

Tics are remarkably plastic: they not only change in nature and location over time, but they also wax and wane in both severity and frequency. Many patients report that tics are characteristically exacerbated by certain environmental factors, such as anxiety-inducing events (stressful academic situations, moving to a new location, and family arguments), "emotional trauma", fatigue, TV watching, social gatherings, and being alone.[7] Other factors, such as alcohol, relaxation, concentration on an enjoyable task, or reading for pleasure may alleviate symptoms. Unlike other movement disorders, in 20% of patients, tics do not disappear with sleep.[1,7]

DIFFERENTIAL DIAGNOSIS

As there is no pathognomonic sign or "gold standard" diagnostic test associated with TS, the diagnosis is made based on clinical features. Secondary tic disorders and other movement disorders must be ruled out by careful neurological examination and appropriate investigations (see Table 2).

Tics have been found at an increased rate among children with developmental and chromosomal disorders. One study found tics to be present in 6.5% amongst 447 children with pervasive developmental disorders.[8]

Table 1: Diagnostic Criteria for Tourette's Disorder

A. Both multiple motor and one or more vocal tics are present although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)

B. The tics occur frequently throughout a period of more than one year, and during this period there is no tic-free period of more than three consecutive months.

C. The onset is before 18 years of age.

D. Other causes of tics have been ruled out. (see Table 2).

Criteria modified from Marcus and Kurlan[1] and DSM-IV-TR, American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington, DC: American Psychiatric Publishing Inc, 2000

Table 2: Differential Diagnosis of Tics and Tourette's Syndrome

1. transient tics of childhood

2. prenatal/perinatal insults
   - congenital CNS defects
   - birth defects

3. infections / post-infectious
   - post-viral encephalitis
   - HIV infections of CNS
   - Lyme disease
   - pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)

4. head trauma

5. toxin exposure
   - carbon monoxide
   - gasoline

6. drugs
   - neuroleptics ("tardive tics")
   - levodopa
   - opiate withdrawal
   - amphetamines
   - lamotrigine

7. chromosomal abnormalities
   - XYY
   - XXY
   - fragile X syndrome

8. genetic disorders
   - Hallervorden-Spatz disease
   - Wilson's disease
   - hyperekplexias
   - Rett syndrome
   - neuroacanthocytosis

9. autism/Asperger's syndrome

CO-MORBIDITIES

Obsessive-compulsive symptoms and behaviours

Obsessive-compulsive symptoms (OCS) and obsessive-compulsive behaviours (OCB) are strongly associated with TS. Although figures vary in different studies, approximately 40% of TS patients will display these.[7] Obsessive-compulsive symptoms/obsessive-compulsive behaviours are seen more commonly in women and may represent a "forme fruste" of TS.

A number of studies have demonstrated that there is a difference in the nature of obsessions and compulsions experienced in TS patients as compared to patients who have no

tics.[9,10] Patients with TS and OCS/OCB tend to have obsessions centered on symmetry and getting things "just right", in addition to more violent and sexual obsessions. Similarly they reported more touching, counting, and blinking or staring behaviours. Patients with pure obsessive-compulsive disorder (OCD) report more contamination obsessions and washing behaviours. These differences in nature and content of obsessions and compulsions suggests that patients with TS may have a form of OCS/OCB which is phenomenologically and etiologically distinct from that seen in patients with pure OCD.

ADHD

The rate of co-occurrence of attention deficit hyperactivity disorder (ADHD) and TS has been described as being between 8% and 80%.[11] As the majority of these studies are based on a clinically derived sampling of TS patients, referral bias is likely to inflate the reported prevalence rates.[12]

In the largest population based study, 28,037 16- and 17-year-olds entering the Israeli army were screened by a multistage process for TS. Of the 12 patients identified with TS, one was diagnosed with ADHD, giving a prevalence of ADHD in TS of 8.3%, which is not significantly elevated from the population prevalence of 3.9% measured in a subgroup of patients.[12] However, as the authors point out, a retrospective patient-survey based survey is not very sensitive for ADHD.

Despite these equivocal epidemiological findings, it is apparent that TS and ADHD do frequently occur together in those patients who seek medical attention. Observations that ADHD occurs at an increased rate in the probands of patients with TS in some studies, suggests a shared group of genes.[13] Several authors have suggested two forms of ADHD may exist in patients with TS, one which is related to TS and one which is independent.[14] Alternatively, TS and ADHD may be linked to an overlapping set of genes.

In one study which looked at the phenomenology of ADHD in patients with and without TS, no significant differences were found in the frequency of various co-morbidities between the different groups, with the exception of an increased rate of OCD in the ADHD + TS group compared to the ADHD group.[9] This suggests that, aside from OCD, many of the psychopathologies associated with TS may actually be secondary to the co-morbidity with ADHD, and are often subjectively the most important source of difficulty.[15]

Other

A variety of other behaviours and abnormalities have been reported to be present in a higher than expected frequency in TS. These include: anxiety disorders, phobias, depression, and oppositional defiant behaviour.[16] The nature of these associations is still unclear, but is thought to reflect shared neurobiological circuits. Recently, associations between restless leg syndrome and TS,[17] and stuttering and TS[18] have been suggested.

Psychosocial

Children with TS are often found to have difficulties at school, such as grade retention or special education classroom placement. In addition, up to one third may be diagnosed with learning disabilities. These difficulties seem to be related more to co-morbid ADHD than the tic symptoms of TS.[19]

Children with TS have also been found to have increased problems with peer relationships and social functioning.[20,21] Again, co-morbid ADHD appears to be a more significant factor than tic severity. Interestingly, children with TS do not have increased self-consciousness or decreased self-concept in the absence of co-morbidities.[22] However, a study of how children view peers with symptoms of TS found that a symptomatic TS patient, presented on video-cassette, was rated less positively than a non-TS child.[23] Problems forming peer and romantic relationships have also been reported in adult patients with TS.[24]

PREVALENCE

Tourette's syndrome is found in all ethnic and racial groups although the exact prevalence is unknown due to misdiagnosis, under reporting, and few large epidemiological studies. In a large screening study of 28,037 16- and 17-year-olds entering the Israel Defense Force, an overall rate of TS was found to be 4.3 per 10,000 (4.9/10,000 in males and 3.1/10,000 for females).[12] Another large study of 4,500 children aged 9, 11, and 13 years of age in the south-eastern USA found a prevalence of 10 per 10,000.[25] A more recent observational study of 13- and 14-year-olds in the school environment, found a prevalence of tics of 18.7%, and TS of 1.85%.[26] As symptoms were mild in a number of these children, the diagnosis went unrecognized.

Thus, it appears that TS is more common than previously recognized, with milder cases of TS remaining undiagnosed. If chronic motor or vocal tic disorder, and OCS/OCB are considered to be manifestations of the TS gene, the prevalence is even higher.

PATHOPHYSIOLOGY

Genetics

Numerous family studies have demonstrated that TS is inherited, and first-degree relatives of a proband have an increased risk of TS. In addition, increased rates of chronic tics and transient tics are also observed in the relatives of TS probands, suggesting these are an alternate expression of TS. In twin studies, 8% of dizygotic twins were concordant for TS, while 53% of monozygotic twins were concordant.[27] Seventy-seven percent of monozygotic twins were concordant when analyses were extended to include any tic disorder in the proband's twin, as compared to 22% concordance in dizygotic twins. The incomplete concordance suggests that other factors also influence the phenotypic expression of the TS genotype.

Segregation analysis initially suggested that the major locus for TS was transmitted in a Mendelian, autosomal dominant fashion, with variable penetrance. However, with the failure of linkage studies to uncover any candidate loci for TS, this model has been re-examined. Recent studies have found that an intermediate model of inheritance best accounts for the phenotypic segregation.[28] Walkup et al[29] found evidence for a mixed model of inheritance in their complex segregation analysis of 53 different TS probands and their first degree relatives. In this model, a single major locus and an undefined nongenetic multifactorial background account for TS transmission. About 40% of the phenotypic variance observed was accounted for by this multifactorial background. However, the complex segregation analysis performed by Seuchter et al[30]

on the families of 105 TS probands found that TS inheritance cannot be explained by any model of Mendelian inheritance.[30]

Bilineal transmission – genetic contribution from both mother and father contributing to disease – has also been proposed to occur in TS. The frequency of both parents being affected was higher in the group of more severely affected probands.[31] A study of a single, large family with TS suggests that TS patients with bilineal transmission have more tics, more severe types of tics, and an earlier age of onset of tics.[32] Patients with bilineal transmission also have an increased severity of OCS/OCB and are more likely to exhibit self-injurious behaviours as compared to patients with unilineal transmission or sporadic TS.[33]

The phenotypic expression of TS may be altered by the gender of the parent who transmits the TS traits: increased vocal tics and ADHD may be present in patients with paternal transmission, and increased motor tic complexity and OCS in patients with maternal transmission;[34] another demonstrated an earlier age of onset in maternally transmitted TS.[35] One study did not find any genomic imprinting effects on phenotype or age of onset of TS.[36] This issue remains unresolved.

Thus far, no reproducibly genetic locus has been identified in TS. Several explanations are possible for this failure. Difficulties in defining the full phenotype of TS reduce the power of any genetic study. Should chronic tic disorders and OCS/OCB (particularly in women) be considered as expressions of the TS gene? In addition, the lack of a confirmed model of inheritance of TS may result in the use of either incorrect models, or non-parametric analysis.

In the absence of any identified linkages from genomic techniques, many specific genes, suggested by pathophysiologic models of TS, have been studied. Linkage to the dopamine receptor genes (DRD1, DRD2, DRD3, DRD4, DRD5) has been consistently excluded.[37] Genes for other proteins involved in the metabolism of dopamine (including tyrosine hydroxylase, dopamine beta hydroxylase, tyrosinase 46, and the dopamine transporter) have been excluded, as have genes in other neurotransmitter systems.

NEUROIMAGING

Structural neuroimaging

Although general neuroimaging and neuropathological examination of TS brains is normal, morphological abnormalities have been reported in volumetric MRI studies. A loss or reversal of the normal asymmetries of the putamen and lenticular nucleus can be seen.[38] In addition, TS patients who also had ADHD had a smaller left globus pallidus than pure TS patients.[39] In twins with TS, the right caudate nucleus was significantly smaller in the more severely affected twin of the pair.[40] However, the finding of decreased globus pallidus asymmetry in TS patients with ADHD was expanded to demonstrate that pure ADHD patients also displayed these changes, and TS+ADHD patients could not be differentiated from pure ADHD patients on the basis of these findings. Corpus callosum changes have been reported in additional studies: one study of children with TS described an increase in cross-sectional area,[41] while another study of adults described a decrease in total corpus callosum area in TS patients.[42] The significance of these differences in findings is not clear, though

it does appear that corpus callosum morphology, and hence interhemispheric connectivity, is altered in TS. As most of the patients in these studies were male, 19 girls with TS or TS+ADHD were studied. No differences in corpus callosum morphology or basal ganglia asymmetries were described in this group compared to controls.[43,44] This may indicate a gender effect in the pathophysiology of TS, a gender effect in normal brain development which masks the TS effects in girls, or may simply be a result of insufficient power (both studies are smaller than the studies, by the same group, that identified differences in the predominantly male TS groups).

Functional neuroimaging

In additional to structural neuroimaging studies, a number of imaging techniques have been used to allow insight into brain function. Perfusion studies using technetium-99m d,l-hexamethyl propyleneamine oxime (HMPAO) which is a marker for blood flow detected by single photon emission tomography (SPET), have detected hypoperfusion in various areas of the brain in patients with TS, including the left basal ganglia, particularly the left caudate nucleus and left lentiform nucleus, the right basal ganglia, anterior cingulate cortex, the left dorsolateral prefrontal cortex, and the orbital and anterior medial regions of both frontal lobes as well as both temporal lobes.[45-47] One study re-assessed the TS patient group after neuroleptic treatment and found that, with treatment, perfusion was increased in both of these frontal lobe regions, as well as in the left medial temporal lobe.[48]

Using F-18 fluoro-deoxyglucose PET scans to map glucose metabolism in patients with TS and controls, decreased activity in the prefrontal cortices (particularly the orbitofrontal, inferior insular, and parahippocampal regions) and the striatum was found, suggesting an abnormal functional relationship between the striatum and cortex.[49] Further study by this group attempted to correlate metabolism changes with behavioural features of TS, including OCS/OBC, impulsivity, coprolalia, self-injurious behaviour, echophenomena, depression, and attentional and visuospatial dysfunction measures. Though the study was relatively small given the many factors it wished to study, all of these behaviours were found to be associated with an increase in activity in the orbitofrontal cortex.[50]

Several fMRI studies have to date been performed in the study of TS. A small study of five TS patients and five normal controls evaluated activation of the sensorimotor cortex during the execution of a motor task (finger tapping). It was found that the supplemental motor cortex was activated to a greater extent in TS patients, suggesting that motor pathways may be organized differently in TS.[51]

Two fMRI studies, rather than comparing "baseline" brain activity levels to normal controls, sought to quantify changes associated with the clinical hallmarks of TS: motor and vocal tics. The first of these examined brain activity when the patient suppressed the urge to have a tic. A significant bilateral decrease in activity of the globus pallidus and putamen, as well as the midbody of each hemithalamus, was observed with tic suppression, while increased activity was seen in the right caudate nucleus. In the cortex, decreased activity was seen in the right posterior cingulate gyrus, the left hippocampus and parahippocampus, the cuneus bilaterally, the left sensorimotor

cortex, and the left inferior parietal region, while increased activity was observed in the right midfrontal cortex, the right midtemporal gyrus, the superior temporal gyrus bilaterally, the right anterior cingulate gyrus, and both inferior occipital regions.[52] The regions activated during tic suppression are compatible with the regions of the brain involved in a neural circuit that plays a role in inhibition of unwanted impulses. This circuit consists of the prefrontal, parietal, temporal, and cingulate cortices, and is modulated by basal ganglia and thalamic activity. Differences were seen in the activation patterns of men and women, reinforcing the gender effect observed in structural imaging studies, discussed above.

Another fMRI study examined cerebral blood flow in patients who were not required to suppress their tics, and who were monitored for the presence of tics during a scan.[53] This study found that several different areas of the brain had abnormal signal with tic occurrence, including the primary motor and Broca's areas, corresponding to motor or vocal tics, respectively. Striatal activity was noted, confirming the role of the basal ganglia. Involvement of the motor, dorsolateral prefrontal, and anterior cingulate areas of the cortex, was suggested by the activation patterns observed in the study. In addition, the midbrain tegmentum, thought to be involved in the modulation of these circuits, was also activated.

The medial premotor cortex is thought to be associated with initializing self-generated movements (i.e., movements not made in response to an external cue), while the lateral premotor cortex is associated with externally cued voluntary movements. The activation of both systems in this study suggests that both systems are involved in the generation of the "unvoluntary" tics of TS. Involvement of the lateral prefrontal cortex may reflect the uncomfortable somatic sensation which sometimes precedes tics, suggesting that these sensations may act in the same manner as an external cue for movement. The anterior cingulate cortex, also found to be activated, is important in the generation of motor actions in response to internal states.

THERAPY

Psychosocial

Foremost in the treatment of TS is education of the patient and family. An explanation of the symptoms, including tics, obsessions, and compulsions allows for an appreciation that these are not voluntary or psychiatric behaviours. Frequently, the individual will suppress the tics throughout most of the day, only to exhibit many tics when he/she returns home from school or work. The family needs to understand that it is necessary for the person to "release" the tics. Particular times of the year may be more stressful than others, e.g., starting school, and will lead to an increase in tics. Education of teachers, (or coworkers in adulthood) is also important. Ongoing psychological counselling may be necessary to provide support for both the affected individual and family as well as helping the TS patient deal with unwanted behaviours such as conduct abnormalities and anger outbursts.

Various specific psychological therapies such as relaxation therapy,[54] habit reduction techniques and habit reversal therapy[55] for the symptoms of Tourette's disorder have been described. However, the literature is limited to anecdotal descriptions involving four or fewer patients and none have been definitively shown to be effective.

Pharmacological

Individuals with mild TS usually do not require medical therapy. When more severe symptoms are present, pharmacological therapy remains the cornerstone, and therapy should be individualized to treat the most distressing symptom(s) (see Table 3).

Dopamine modulation drugs

Typical neuroleptics such as haloperidol and pimozide were the standard medications used for treatment of tics in the past.[56,57] Due to concern about side effects and the development of newer drugs, these have been replaced by the atypical neuroleptics.[57]

Risperidone has been found to be effective against symptoms of TS in several open label trials.[58,59] In recent double blind trials, risperidone showed evidence of significant tic reduction.[60,61] Reported side effects included sedation, weight gain, constipation, erectile dysfunction, and increased pigmentation.

Olanzapine has been found to be effective in a six-week open-label study of adults with TS.[62] Tetrabenazine, a dopamine depleting agent, should also be considered particularly in milder cases.[63] Side effects include drowsiness, depression and weight gain.

Dopamine agonists

At low doses, pergolide has been found to be effective in the treatment of TS in a recent double-blind, randomized, cross-over

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Table 3: Treatment of Tourette's Syndrome

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1. Education and counselling

2. Modification of home/school/work environment

3. Tics
   - clonidine
   - tetrabenazine
   - risperidone
   - other typical and atypical neuroleptics
   - pergolide
   - delta-9-tetrahydrocannabinol
   - nicotine
   - baclofen

4. Obsessive-compulsive behaviour
   - fluoxetine, other selective serotonin reuptake inhibitors
   - clomipramine/imipramine

5. Hyperactivity/ADHD
   - clonidine
   - methylphenidate and related meds
   - desipramine

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trial of 24 children and adolescents.[64] No significant adverse effects were identified in any patients in this study. The reason for its activity at low doses is not known, but may be due to the preferential activation of D_1 auto-receptors, which causes a decrease in dopamine release.

Others

A variety of other drugs including flunarizine,[65] naloxone,[66] opiates, delta-9-tetrahydrocannabinol,[67] and baclofen have been reported to be beneficial in controlling tics in small uncontrolled open label trials. Nicotine, added to a neuroleptic, may improve tic control.[68] Occasionally, a short course of a benzodiazipine is required if the tics become severe in a stressful situation, and/or cause self-mutilatory behaviour.

All of the above medications should be used for as short a time as possible. Although long-term use may be necessary in more severe patients, many individuals will improve after several months or years of therapy, and the medication can slowly be tapered.

TREATMENT OF CO-MORBID CONDITIONS IN TOURETTE'S DISORDER

ADHD

The most commonly accepted treatment for ADHD involves the use of stimulant drugs, particularly methylphenidate and dexamphetamine, which markedly improve concentration and hyperactivity. Early reports indicated that these drugs may "unmask" tic symptoms. However, recent studies have shown that use of either stimulant had no statistically significant effects on tic severity; all patients had an improvement in ADHD symptoms in the classroom.[69-71]

Attention deficit hyperactivity disorder symptoms are often reported to be, subjectively, the most disabling symptoms of the TS+ADHD clinical picture. Given the demonstrated ability of stimulant drugs to control these symptoms with no overall exacerbation or unmasking of tics at low doses, use of stimulants is not contra-indicated in patients with TS.

In addition to the use of stimulants, some control of ADHD symptoms has been reported with the $_2$-adrenoreceptor agonist, clonidine.[71] This compound has also been reported to be effective against tic symptoms of TS. In her recent review, Robertson[7] concludes that clonidine is a reasonable first-line agent in the treatment of TS with co-morbid ADHD. Desipramine has also been shown to be effective in controlling both tics and ADHD.[72]

Obsessive-compulsive symptoms and behaviours

Aside from behavioural therapy, selective serotonin re-uptake inhibitors are a mainstay of treatment of obsessive-compulsive symptoms. The benefit of fluoxetine has been confirmed in a double-blind, placebo-controlled cross-over study, with a significant improvement in measures of obsessive-compulsive symptoms; no effect was observed on tic severity.[73]

CONCLUSION

Tourette's disorder is a complex and fascinating genetic neurological disorder with psychiatric co-morbidities. Beyond the basic diagnostic requirement of motor and phonic tics,

significant co-morbidities may be present in patients with TS, and often result in the most subjectively disabling part of the clinical picture. Active research into the etiologic basis of Tourette's disorder has made significant advances, though a unified theory linking genetic and neurobiologic findings with the observed symptoms is still lacking. In addition, the etiologic relationship of the co-morbidities of TS has not yet been elucidated. In the meantime, treatment strategies for TS and its co-morbidities are improving with newer agents providing well-tolerated relief to most patients.

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