Tourette syndrome and the spectrum of neurodevelopmental tic disorders

Sylvain Chouinard, Paul Lespérance, Francois Richer

Centre Hospitalier de l'Université de Montréal

The first description of a tic disorder was made as early as 1825 by Itard who discussed the case of a French noblewoman, the Marquise de Dampierre who displayed involuntary movements and coprolalia. At the end of the XIXth century, french neurologist Georges Gilles de la Tourette described the disorder which now bears his name. In his seminal paper, he described the symptomatology of nine patients with multiple tics, echolalia and coprolalia. Gilles de la Tourette suggested that it was a neurological condition with a hereditary component. Nevertheless, this syndrome was later considered as having a mainly psychogenic origin and it is only since the 1960s, with the use of neuroleptics, that the organic basis of Gilles-de-la-Tourette syndrome (TS) has been reaffirmed. TS is now considered a hereditary neuropsychiatric disorder linked to cortico-striatal brain circuits.

Epidemiology

TS prevalence remains unclear partly because of the lack of biological markers, the wide fluctuation of the symptoms and lack of a consensus regarding a definition of the disorder. According to some studies, it is estimated that between 1 and 3% in the school age population are affected by the syndrome (Horsne et al., 2001). However, because of

the fluctuating nature of the disease and because of the unawareness of the tics, the real prevalence is probably higher. Also, if we consider that chronic motor or vocal tic disorders are manifestations of the TS genes, the actual gene prevalence may be higher than standard estimates.

Phenomenology of Tics

Tics are repetitive and sudden stereotyped movements which often occur in response to a sensation or an urge and often occur in bouts. Tics present themselves in a simple or complex form. Motor tics usually manifest first at the head level and then migrate to the distal parts of the body during evolution. The most frequent motor tics are eye blinking and oro-facial grimaces. Among vocal tics, throat clearing, shouting and simple non-verbal sound are most common. Tics are called complex when they involve several segments or when they appear goal-directed like touching, smelling, hitting, imitating actions (echopraxia) or repeating words (echolalia). Coprolalia, an involuntary verbalization of obscene or scatological words, appears only in a minority of subjects affected by TS and it is often a temporary manifestation (Erenberg et al., 1986).

Tics are often preceded by a localized sensation or by a general discomfort which is relieved by the production of the tic. These premonitory sensations are mainly reported by children over 10, possibly due to a cognitive maturation allowing them to better detect these signs (Banaschewski et al., 2003). Repetitive, intrusive uncomfortable sensations (sensory tics) can also occur independent of externally apparent tics and often in the absence of a verifiable stimulus (Miguel et al., 2000). Sensory tics and premonitory

sensations give a semi-voluntary property to some tics as they feel like they are released by the individual to relieve an itch (Kwak et al., 2003; Woods et al., 2005).

A fundamental characteristic of tics is that they can be voluntarily inhibited during a short moment, but at the expense of an increasing urge to express them. This temporary suppression ability can give the impression that tics are partly voluntary and can then increase the guilt linked to the fact that they cannot be inhibited indefinitely. Like many types of involuntary movements, tics can be reduced by concentration on voluntary tasks which activates fronto-striatal brain circuits. Tics can also be exacerbated by stress and fatigue but the link between small stressful life events and tic exacerbation in the same week does not appear to be simple in most cases (Hoekstra et al., 2004; Lin et al., in press). Another critical feature of tics is their plasticity and suggestibility. New tics can replace old ones within a short period of time, tics can be evoked by discussing them with the patient, and they can be developed through observation of other people's tics (Woods et al., 2001). This plasticity suggests that tics are linked to fluctuations in the activation threshold of circuits controlling fragments of stereotyped movements (Heinz, 1999).

Diagnostic criteria

TS is characterized by the presence of chronic tics appearing before 21 years (Tourette Syndrome Classification Study Group (TSCSG), 1993). According to the criteria of the TSCSG, a TS diagnosis depends on the presence of multiple motor tics and a least one vocal tic with a fluctuating course during at least one year (Leckman et al., 1999). However, this definition may be somewhat arbitrary as for the necessity of a vocal tic, since chronic motor tic disorder (CMTD), a lower-severity variant of TS often show the

same evolution and co-morbidities as TS (Diniz et al., 2006; Saccomani et al., 2005). CMTD should be included in the family of Tourette spectrum disorders (TSD) to insure adequate attention and care for all individuals with primary tic disorders.

Diagnosis is made according to the history and the presence of tics during the exam. There is no diagnostic test and radiological exams are useful only if the presentation is atypical or the neurological exam is abnormal. EEG and evoked potentials measures are usually normal (Drake et al., 1992; Drake et al., 1991). Differential diagnosis includes transient tics, compulsions as well as stereotypies (see Table 1).

Natural history

Transient tics are very frequent among very young children (3-24%) suggesting that cerebral developmental processes associated with transient tics could be involved in TS (Snider et al., 2002). The median age of tic onset in TS patients is 5-7 years but symptoms can appear as early as the first year and 96% of all patients will have symptoms by the age of 11 (Robertson, 2000). Despite the fact that diagnostic criteria have a beginning before the age of 21, rare cases can show tic onset in adulthood (Chouinard and Ford, 2000) .

An irregular evolution is characteristic of the syndrome, with exacerbation periods interspersed with remissions. Tic severity generally peaks between 8 and 15 years (Leckman et al., 1998) and the specific role of puberty or adrenarche in tic reduction is still unclear (Bloch et al., 2005). In the majority of cases, symptoms subside during adolescence and are much less noticeable by adulthood, but a majority of adults still

show some tics even if they are unaware of them (Pappert et al., 2003) and fluctuation of severity throughout life is typical in TS.

TS manifests itself in a large variety of phenotypes. Many affected persons will never consult for this disorder because of the intermittent nature of their symptoms, their ignorance of the syndrome or because of the low impact of symptoms in everyday life. Those who consult usually have more severe symptoms. Individuals with tics alone without associated comorbidities represent a small minority of patients. Children are often brought to consultation for comorbidities such as learning disabilities or behavioural problems such as obsessive-compulsive symptoms, hyperactivity, opposition, conduct disorder, and rage outbursts. It is only when discovering the presence of tics that the professional will associate these symptoms to co-morbidities of TS.

There is increasing evidence that TS is part of a family of Tourette spectrum disorders (TSD), in which variations in the severity of multiple symptoms including among others tics, compulsions or impulsive behaviour can lead to large variations in phenotype. Some may even consider that phenotypes with transient tics and significant behavioural symptoms should be included in the TSD family. An improved classification and characterization of TSD based on endophenotypes should facilitate progress on the etiology and neurobiology of these disorders which is presently impeded by amalgamation of diverse phenotypes.

Obsessive-Compulsive symptoms

Obsessive-compulsive symptoms (OCS) involve sudden, intrusive and repetitive thoughts or desires to act. OCS are frequent in TS, especially among girls. OCS tend to increase in

severity several years after tic severity has peaked (Bloch et al., 2006). Prevalence of OCS in TS has been reported as high as 80% of probands (Gaze et al., 2006), and is increased in relatives of TS patients as are tics in relatives of obsessive-compulsive disorder (OCD) patients (Pauls et al., 1986; Leckman et al., 1999; Chabane et al., 2005; do Rosario-Campos et al., 2005). This suggests that OCS is part of the TS phenotype and that TS and OCD are linked etiologically.

Reports of OCS prevalence vary from 30 % to 80%, which may reflect referral biases or adherence to OCS spectrum vs OCD criteria. Obsessions may be concerns about contamination, safety/harm, unwanted acts of aggression or self harm (impulse-control phobias), thoughts or images of religious and sexual contents, or need for symmetry and exactness (ex: the "just right" phenomenon). Compulsions may be cleaning rituals, checking behaviors, ordering and hoarding behaviors, useless counting or recitation (mental compulsions). Some level of OCS may be a normal developmental process, and was reported as high as 60% in 3 year-old children and even more frequent in children with developmental delays (Evans et al., 2001). Like transient tics, transient compulsions may be a substrate for the development of clinical symptoms in high-susceptiblility individuals.

The psychiatric definition of OCD may differ in several ways from TS-related OCS. Marked distress with the symptoms is imperative for a diagnosis of OCD and may not be present in the context of symmetry/hoarding OCS in TS, the most frequent subtype of symptoms in TS (Goodman et al., 2006). Although developed to evaluate the severity of idiopathic OCD, the Yale-Brown Obsessive-Compulsive Scale (YBOCS) is widely used in TS patients (Goodman et al., 1989). It measures both the intensity and functional

impact of obsessions and compulsions in a combined score. However, more compulsions than obsessions independently of YBOCS score are typical of TS patients and are associated with poorer pharmacologic treatment response (Mataix-Cols et al., 1999).

Tics and compulsions are sometimes on the same clinical spectrum, and distinguishing one from the other may be challenging. The purposefulness of an action and its reduction of anxiety are hallmarks of a compulsion. Touching both legs with a finger may be a complex tic if it seems purposeless. However, the same gesture would be classified as a simple compulsion if done in response to a symmetry/just right obsession. However, such compulsions may predict a better response to neuroleptics than SSRIs, as would be expected of tics (Mataix-Cols et al., 1999). Clear cut premonitory urges may help to support a complex tic, rather than a simple compulsion, but sensory phenomena have also been documented in OCD, especially the child-onset type (Eichsted and Arnold, 2001). Tic-related OCS may be less responsive to medication, but this remains uncertain (Shavitt et al., 2006). Some studies suggest that echophenomena and complex tics are significantly correlated with OCS in TS (Cath, 2001). Whether it is due to true comorbidity between tics and OCS or definition blurriness is still unclear.

In idiopathic OCD, obsessions are intrusive thoughts and worries associated with a need to verify, check or wash, to act in order to relieve the anxiety or emotional distress. Obsessions in Tourette's syndrome are frequently described as vivid, imposed images or brief thoughts of violence or sex that may or may not be associated with distress (Cath, 2001). These mental events have no particular purpose and may thus qualify as impulse-control symptoms or mental tics rather than OCS (Cath et al., 1992).

ADHD and Cognition

Attention deficit hyperactivity disorder (ADHD) is strongly associated with tic disorders in clinical samples (40 to 60% of children with TS). However, ADHD is often the main reason for consultation and among the school age population 2 to 10% of children present a clinically significant ADHD (Swanson et al., 1998). The association between tics and ADHD in community samples is less clear and may depend on the severity of the tic disorder (Peterson et al., 2001; Kurlan et al., 2002; Apter et al., 1993). The etiologic link between ADHD and TS is still unknown but there is little evidence of a genetic link between the two syndromes and an overlap in cerebral substrates is often hypothesized (Stewart et al., 2006). Like TS, ADHD has a significant heritability, it is linked to fronto-striatal brain systems and to dopamine systems, and it is characterized by behavioral impulse control problems.

The disruptive behavior of ADHD associated with hyperactivity, impulsivity, insistence, and excitability has a widespread psychosocial impact, affecting sleep, school performance as well as social and family functioning. The inattentive ADHD subtype may be relatively independent of ADHD with hyperactivity-impulsivity and more linked to lower IQ and learning disabilities. ADHD shares common features with tics and compulsions, including a heightened reactivity to stimuli and a poor inhibition of urges. There appears to be little difference between the ADHD symptoms on non TS patients and those of TS+ADHD patients.

Among TS+ADHD subjects, distractibility, emotional reactivity and impulsivity lead to problems in tasks which require sustained attention or attention to details. Impulsivity in

particular can often make answers and actions more approximate, poorly planned and less adequate in relation to instructions. These problems can lead to academic performance that is inferior to the cognitive potential. Several studies with large and well selected samples have reported normal cognitive functions in people diagnosed with TS especially when they don't present behavioral co-morbidities (Bornstein, 1990). Intelligence measures show a similar distribution to the global population. However, several TS patients can show lower performance IQ due to visuomotor problems especially when ADHD is present (Brookshire et al., 1994; Como, 2001; Schultz et al., 1998). TS+ADHD children are also more inclined to present learning disabilities affecting mathematics and reading. Patients with a more severe TS usually show more cognitive problems than patients suffering from a more simple syndrome (Harris et al., 1995; Schuerholz et al., 1998; Sherman et al., 1998). When cognitive dysfunctions are present, problems are often similar to those produced by frontal or striatal disorders, which affect the executive control of attention and action (Sutherland et al., 1982; Yeates and Bornstein, 1996). However, only a minority of TS patients show clear executive control problems. Response slowing and variability in response speed can be observed in patients with or without ADHD (Harris et al., 1995; Shucard et al., 1997). The learning and the recall of semantic and episodic information are usually adequate in TS. Some learning problems have been reported in probabilistic classification tasks (Keri et al., 2002; Marsh et al., 2004) but not in all sensorimotor learning tasks (Marsh et al., 2005).

Rage outbursts and self-injurious behaviors

Inappropriate aggressive behaviors are frequently encountered in TS patients, mostly in the form of rage outbursts, usually directed at others or objects. Explosive outbursts are seen in up to 50% of clinical TS samples (Kenneth et al., 2000; Richer et al., submitted). Although they may be surrogate events of other comorbidities, such as impulsivity associated with ADHD, oppositional-defiant disorder (ODD) or OCS (frustration over unmet needs), they are sentinel symptoms worth looking for, and represent one of the most challenging clinical situation in many patients. During these outbursts, the patient "looses control" and is usually shameful, when the crisis subsides. In TS, risk factors for rage behavior appear to include obstetric complications as well as tic severity, ADHD symptoms, male gender, and maternal rage outbursts (Richer et al., submitted).

Self-injurious behaviors (SIB) should be distinguished from complex tics (such as fist pounding on the thigh with secondary bruises) or pathological "grooming" behaviors (trichotillomania-hair pulling or skin picking, severe nail biting) (Mathews et al., 2004). Rage outbursts and SIB are also seen in many children with neurodevelopmental problems such as mental retardation, autism spectrum disorders and anoxic encephalopathy (Roberston, 2000).

Anti-social and oppositional behaviors

Although psychosocial, familial and economic settings may be more relevant as a whole to help understand these pathological relational behaviors, antisocial and oppositional behaviors are frequently encountered in TS. Some patients may also show symptoms of anti-social behaviors (conduct disorder in children, anti-social personality disorder in

adults) such as lying, stealing, and fighting. Again, overlap with OCS, ADHD and impulse-control disorder probably play a significant role in these behaviors.

Autistic features and deficits in social abilities

Many patients with autism show various stereotypies, mannerisms, and tics. In children with autism spectrum disorders, tic disorders appear to be common, with a prevalence of 6.5% to 22% (Baron-Cohen et al., 1999; Canitano and Vivanti, 2007). Conversely, a subgroup of TS patients will show concomitant autistic traits and perseverative behaviors, and up to 20% will show significant deficits in social skills. (Freeman et al., 2000). These individuals may be described as socially inept, show very little insight and tend to invest one area of interest to the detriment of other important endeavors which may impact their ability to lead normal lives at home, school or work. An overlap in limbic circuitry or genetic contributions could be involved in the comorbidity between TS and autistic spectrum disorders.

Anxiety and depression

Although anxiety and depression symptoms may be increased in TS (Coffey et al., 2000; Comings and Comings, 1987), the list of possible contributing factors is endless. In TS, anxiety symptoms and psychosocial distress seem particularly relevant since they may predict future tic severity (Lin et al., in press). Of interest, ADHD has been proposed as a risk factor for generalized anxiety disorder (GAD) in adults and may very well share genetic factors.

Sleep disturbances

Sleep studies have repeatedly described insomnia and lighter sleep, complaints of parasomnia (sleep walking, sleep terrors), and agitated sleep in TS. (Kostanecka-Endress et al., 2003). Behaviorally, tics may be seen during sleep. Polysomnographic studies, although not all in agreement, show that tics are rare in slow wave sleep (SWS), and seen mostly in lighter sleep stages or sleep stage changes. Increases in micro-arousals and periodic limbs movements in sleep, suggest NREM sleep instability in TS even without ADHD (Lesperance et al., 2006). Studies on the impact of sleep problems in children are rare. However, a recent study has shown that discrete sleep deprivation may have a profound impact on children's behavior and academic achievement in an experimental design (Fallone et al., 2005). These preliminary data suggest that improving sleep quality of TS patients may improve symptoms and should be part of a comprehensive treatment algorithm.

Restless legs

Restless legs syndrome (RLS) is an urge to move a limb, usually one or both legs, associated with focal dysesthesia, which is increased by rest and reduced by movements, mostly in the evening or at bedtime. We have previously described increased RLS symptoms in children with TS (10%) (Lesperance et al., 2004) independently of ADHD co-morbidity, a reported risk factor for adult RLS (Cortese et al., 2005). We have proposed parallels between premonitory urges, relieved by tics and the dysesthesia/urge to move relieved by simple leg movements or complex motor behaviors (walking, stretching, leg rubbing) typical of RLS. Of interest, low doses of dopamine agonists with

documented efficacy in RLS, may also have anti-tic properties at low doses (Anca et al., 2004; Gilbert et al., 2000).

Etiology

Several studies have confirmed the presence of an important genetic component in TS. Whereas more than 50% of identical twins show a concordance for the TS, less than 10% of fraternal twins are concordant (Price et al., 1985). The data suggest a heritability between 54% and 86%. Studies on TS families indicate that the relative risk in first-degree relatives is 8.3% for TS and 16.3% for chronic tics. Until now, no major vulnerability gene has been identified for TS, but several genes show a significant statistical association with this syndrome. TS is probably a complex trait which involves several genes (Walkup et al., 1996; State et al., 2001).

Because of the high number of identical twins discordant for TS, it is probable that genetic vulnerability factors interact with epigenetic factors affecting gene expression during embryogenesis and environmental factors. Several non-genetic factors are already associated with TS including prenatal and perinatal events, hormones, immune responses and stressors. There is evidence for greater severity in TS twins with perinatal complications compared to the co-twin (Hyde et al., 1992). Perinatal cerebral ischemia significantly increases the risk for tics and ADHD (Whitaker et al., 1997). Also, obstetrical complications were found to contribute to explosive outbursts in TS (Richer et al., submitted).

The much higher prevalence of TS among boys could be linked to a role of steroid hormones (DHEA, sex hormones) in TS (Peterson et al., 1992), although direct evidence

of this contribution is still lacking. Steroid hormones have several effects on cerebral organization during prenatal and postnatal development. Moreover, the high sensitivity of tics to stress suggests that stress hormones (cortisol, noradrenaline) affect the expression of tics. Finally, several data suggest that postinfectious autoimmune responses could contribute to TS, but the evidence is still weak (Singer et al., 1998; Dale, 2005). A related syndrome, called PANDAS (post-infectious autoimmune neuropsychiatric disorders associated with streptococcal infection), was described consequently to a streptococcal infection (Swedo et al., 1998) which consists in a sudden onset of tics or compulsions after a beta-hemolytic streptoccocal infection. Nevertheless, this syndrome remains controversial.

A preliminary model of TS etiology implicates multiple reciprocal interactions between genetic, epigenetic and environmental factors which provoke variable effects on the development of biological systems involved in movement and behavior (see Figure 1). The multiple interactions would be responsible for the important variability of the TS phenotype as well as for temporal fluctuations in the symptoms. TS probably interacts with normal brain development (Kurlan, 1994). Tics, repetitive behaviors, impulsivity and tantrums have a high prevalence in the general population in the first years of life. Susceptibility factors could interact with the neural networks underlying these developmental manifestations to modulate their activation thresholds thus affecting symptom expression in the long term. Genetic, obstetric and hormonal influences can interact during various periods of neural development. One critical period for these interactions is the late prenatal and early post-natal period. This period is characterized by a massive increase in synaptic density (Huttenlocher and Dabolchar, 1997) and this

growth is highly sensitive to ischemia (McDonald and Johnston, 1990 and is modulated by steroids particularly brain estrogen synthesized from androgens (Beyer, 1999). Thus, the first years of life are both a key period for gene-environment interactions and their effects on synaptic development as well as a key period for the expression of non-pathological (developmental) tics, compulsions, echophenomena, opposition, and tantrums. This developmental period should thus be examined further for its role in TS symptom expression.

Neurobiology

No obvious neuropathologic sign is observed during the autopsy of TS patients. However, there is mounting evidence that circuits linking frontal and striatal regions are involved in the syndrome. Lesions of the pallidum and of orbitofrontal cortex have been associated with TS symptoms in case studies (Laplane, 1994; Demirkol et al., 1999; McAbee et al., 1999). MRI volumetric studies show significant differences in the striatum and pallidum of TS patients in comparison with healthy volunteers (Hyde et al., 1995; Peterson et al., 2003; Singer et al., 1993; Kalanithi et al., 2005). Caudate atrophy in childhood appears to be linked to adult tic severity (Bloch et al. 2005). Many volumetric measures have pointed to local atrophy but there is also evidence for local grey matter increases in ventral striatum (Ludolph et al., 2006), thalamus (Lee et al., 2006), and midbrain (Garraux et al., 2006). A reduction of dynorphin in striato-pallidal fibres was also reported (Haber et al., 1986) as well as an imbalance in the distribution of interneurons in striatum and pallidum (Kalanithi et al., 2005) which could suggest that

the functional dynamics of striato-pallidal circuits are altered in TS. However, these findings are still preliminary.

Functional neuroimaging data also point to a dysfunction of fronto-striatal systems in TS. Decreased resting activity has been reported in the basal ganglia, especially in ventral striatum (Braun et al., 1993; Diler et al., 2002; Klieger et al., 1997; Moriarty et al., 1995; Riddle et al., 1992). Changes in functional coupling involving ventral striatum have also been reported (Jeffries et al., 2002). In the orbital frontal cortex, some have found increased activity (Braun et al., 1995; Crespo-Facorro et al., 1999), but others found decreased activity (Braun et al., 1993). In adults, the severity of tics seems to be linked to the metabolism reduction in frontal cortex (Chase et al., 1984). A study observed a cerebral activation synchronized to tic onset in many regions in the sensorimotor, premotor, prefrontal, cingulate and parietal cortex as well as basal ganglia and insula (Stern et al., 2000). Moreover, functional magnetic resonance imaging (fMRI) data suggest that the voluntary suppression of tics affects activity in the striatum, the thalamus and the frontal cortex (Peterson et al., 1998). TS patients can also present a hyperactivation of the sensorimotor and premotor cortex during repetitive voluntary movements (Biswal et al., 1998).

At the neurochemical level, TS may be associated with a dysfunction of dopaminergic modulation of striatal and/or frontal activity. Post-synaptic dopamine receptor binding appears to be normal in TS (Wong et al., 1997). However, presynaptic dopaminergic activity may be abnormally high in TS especially in ventral striatum (Albin et al., 2003; Ernst et al., 1999; Peterson et al., 2001; Serra-Mestres et al., 2004; Singer et al., 2002; Cheon et al., 2004, but see Meyer et al., 1999; Stamenkovic et al., 2001). Several studies

also point to contributions of other neuromodulation systems in TS. For example, there is evidence of a lower serotonin transporter binding in patients with TS, with binding correlating inversely with severity (Muller-Vahl et al., 2005). Noradrenergic as well as neuropeptide systems have also been implicated (Leckman et al., 2003).

Pathophysiological models of TS have emphasized the role of striato-cortical circuits in the selection of voluntary responses and the concurrent inhibition of competing responses (Mink, 2001). Some have also emphasized a possible imbalance in motor and limbic striatal circuits (Groenewegen et al., 2003). In line with the presence of sensory and other subjective phenomena (urges, obsessions) in TS, some have hypothesized that sensorimotor gating deficits may be important in TS although the specific processes have yet to be determined (Swerdlow & Suntherland, 2006).

Subtle neurophysiological anomalies have been observed in TS phenotypes including co-morbidities. Transcranial magnetic resonance studies have shown anomalies in cortical excitability related to hyperactivity in TS such as short-interval cortical inhibition (Gilbert et al., 2004, Orth et al., 2005). These anomalies may also be present in OCD (Greenberg et al., 2000) but it is still unclear whether they affect less severe TS phenotypes without behavioral comorbidities. TS is also associated with sub-clinical anomalies in motor skills, (Sheppard et al., 2000; Serrien et al., 2002), voluntary saccades (Dursun et al., 2000; Nomura et al., 2003), blink reflexes (Tulen et al., 1999; Raffaele et al., 2006) and postural anomalies (Lemay, et al., in press). Some of these anomalies may help identify endophenotypes with some etiological or clinical significance.

In parallel to the accumulating evidence for a role of fronto-striatal brain circuits in the pathophysiology of TS, other evidence has implicated the same systems in ADHD and

OCS (Sherman et al., 1998). TS and its co-morbidities thus represent a model for fronto-striatal neurodevelopmental disorders and any progress on the pathophysiology of TS can have a wide impact in the clinical neurosciences.

Treatment

The first therapeutic approach in TS is education and demystification of the symptoms. People in frequent contact with the child should be informed about tics, fluctuations and possible co-morbidities. It is important to remind people that it is useless to constantly ask the child to try to control his/her tics. Such requests create tension which can exacerbate the symptoms. The goal must be to improve the tolerance of the symptoms and some special measures can be used in doing so ex: decreasing stressful or embarrassing situations, organising private evaluations. Following a complete evaluation, the treatment of tics or comorbidities should be prioritized according to the impairment caused by each problem. Physicians considering pharmacological treatments should be aware of the fluctuating nature of tics and the effect of comorbidities on outcome.

Treatment of tics

The vast majority of affected people will not require any pharmacologic treatment for the tics. On the other hand, if tics have a functional interference, cause pain or induced social difficulties, a medical treatment should be considered.

Dopamine modulating agents

Traditionally dopamine-blocking medications have been the first line treatment for tics disorders and are the class of agents with the most compelling evidence for effectiveness

in double-blind controlled studies. The most three studied agents are haloperidol, pimozide and risperidone (Gibert, 2006).

Because of their presumed lower long term side effects profile, atypical neuroleptics such as risperidone 0.5 to 4 mg (Bruun and Budman, 1996; Scahill et al., 2003) or olanzapine 2.5 to 10 mg will be privileged. The risk of long term side effects especially tardive syndrome in people with Tourette's syndrome is unknown, and these agents should be kept at the lowest dose possible and an attempt at tapering off those drugs should be made periodically. The role of other atypical neuroleptics such as quetiapine (Mukaddes and Abali, 2003; Schaller and Behar, 2002) still need to be studied in larger studies.

Tetrabenazine 12.5 mg at increasing doses with a maximum of 25 mg TID is a monoamine depletor which operates mainly by inhibiting dopamine liberation. This drug may be efficient for the treatment of tics and unlike neuroleptics, doesn't pose any major long term risk at lower doses (Jankovic et al., 1984). The exact role of Tetrabenazine in the therapeutic arsenal of tics however needs to be studied with good prospective studies. Also, this drug has a potential of inducing depression and parkinsonism at high dose

Alpha-2 adrenergic agonists

Because of contradictory results, the role of alpha2-adrenergic agents clonidine and guanfacine in the treatment of tics is debatable. However, in practice, because of a better side effect profile and no long term potential risk; it is often a first line treatment option especially in patients with co-morbid symptoms of ADHD (Leckman et al., 1991; Scahill et al., 2001 ; Tourette Syndrome Study Group, 2002; Goetz et al., 1987; Singer et al., 1995; Shapiro and Shapiro, 1984).

Other agents

Numerous other agents have been studied for the control of tics. However, it is difficult to derive any strong conclusion since most of the studies have been either open-label studies or double-blind studies with few patients and that have not been replicated. These agents are flunarizine (Micheli et al., 1990), naloxone (Sandyk, 1985), delta-9-tetrahydrocannabinol (Muller-Vahl et al., 1999) baclofen (Awaad, 1999; Singer et al., 2001), Ondansetron (Toren et al., 2005), levetiracetam (Awaad et al., 2005) and dopamine agonists (Gilbert et al., 2003). Although sometimes used in children and adults, there has been no controlled study of the efficacy of benzodiazepines in the treatment of tics (Gonce and Barbeau, 1977). Botox has also been suggested as an alternative treatment for vocal and localized motor tics (Marras et al., 2001; Vincent, 2006).

Behavior therapy

There is strong evidence from randomized controlled trials to support the use of behavior therapy, specifically habit reversal training, as an alternative or adjunct treatment in Tourette syndrome. (Himle et al., 2006; O'Connor et al., 2001; Deckersbach et al., 2006; Wilhelm et al., 2003). However, this often requires an important investment of time and the long term effects of these interventions are still unknown.

Neurosurgical treatment:

Multiple neurosurgical target sites including the frontal lobe bimedial frontal leucotomy and prefrontal lobotomy, limbic system anterior cingulotomy and limbic leucotomy, have been tried in patients with severe tics with some results. None of these procedure have

however been studied in a large control-case studies (Temel and Visser-Vandewalle, 2004). More recently, because of lower side effects profile and potential access to deeper region, deep brain stimulation has been advocated as an alternative surgical treatment for cases with severe uncontrolled tics (Vandewalle et al., 1999; Shahed et al., 2007). A recent review has shown this procedure to be highly effective in select cases. (Neimat et al., 2006). Nevertheless, to fully understand the role of brain stimulation in TS will involve developing more complete pathophysiological models and completing larger trials to specify what sites and approaches work best for different phenotypes.

Treatment of anxiety/depression and OCS

Even if tic reduction is the initial goal for the family, the school or the patient, targeting co-morbid conditions may prove to be more beneficial, overall. For OCS, behavior therapy such as exposure and response prevention has clearly shown to be effective (Hembree et al., 2003). When anxiety is present at high levels, SSRIs (such as s-citalopram, fluoxetine, sertraline, etc.) or SNRIs (venlafaxine, duloxetine) should be tried. Starting at a very low dose may help to prevent paradoxical agitation at the onset of treatment, followed by adequate up-titration. It may reduce anxiety and irritability, and indirectly tic severity. Low dose benzodiazepines (such as clonazepam 0.25-0.5 BID) may also reduce both anxiety, and tic severity, but impulse-control symptoms should be closely monitored, since they may be exacerbated with such compounds (Dietch and Jennings, 1988). For depression, several consensus guidelines have been published, where SSRIs or SNRIs are usual first line treatments (APA, 2000), but in children only fluoxetine has clearly shown separation from placebo (Emslie et al., 2002). SSRIs and

SNRIs have been studied in idiopathic OCD where, as stated before, distress, doubt and anxiety are significantly more intense than in Tourette-related OCS. In fact, hoarding/symmetry OCS, mostly seen in TS, are predictive of poorer treatment response to SSRIs (Shavitt et al., 2006). Nevertheless, they should be tried, with the usual caveats of a possible increase in suicidal ideation, especially in children. Atypical neuroleptics may be beneficial in OCS, alone or in combination with SSRIs , especially in the TS hoarding-just right subtype: as stated before such compulsions may be predictors of response to neuroleptics rather than SSRIs, as would be expected of tics (Mataix-Cols et al., 1999).

Treatment of impulse-control problems

Familial intervention should be tried first when facing a difficult situation of impulse-control in TS patients. Pharmacological interventions may be necessary, but efficacy and safety data in children are scant (Ipser and Stein, 2006). For rage outbursts and SIB, atypical neuroleptics may be considered, with regular monitoring of potential tardive motor complications and metabolic syndrome.

Treatment of anti-social behavior, oppositional behavior and ADHD

Again, social and familial interventions are key for patients showing relational behavioral problems like anti-social and severe oppositional behaviors. If, as suggested before, oppositional behaviors are intertwined with OCS, the logical step is to start with the OCS algorithm. If suspecting co-morbid ADHD, then ADHD treatment may be beneficial.

A consensus ADHD algorithm for Tourette's patients has been recently published and suggests starting with psychostimulants (methylphenidate or amphetamines, preferably long-acting) followed by atomoxetine and clonidine/guanfacine (Pliszka et al., 2006). Slow-release or extended-release bupropion may also help in ADHD. Although tic severity may increase with psychostimulants, a Tourette study group study has actually documented, on average, less tics on psychostimulants than placebo (Kurlan et al., 2002).

Treatment of RLS and Sleep disturbances

TS patients with RLS, if severe enough, may seek specific treatment. Dopamine agonists are particularly effective (Chahine and Chemali, 2006). Levodopa may be considered, but augmentation and morning rebound will develop in more than 50% of patients (Paulus and Trenkwalder, 2006). Clonazepam is helpful for light to moderate nighttime RLS associated with insomnia. Gabapentine has shown some effects and opiates are effective for refractory patients (see Vignatelli et al., for treatment guidelines, 2006).

Many drugs used for tic reduction will show hypnotic or sedative properties, such as atypical neuroleptics, clonazepam, baclofen and clonidine/guanfacine. On the other hand, psychostimulants and antidepressants, especially SSRIs and SNRIs, may reduce sleep continuity or cause insomnia. Benzodiazepines typically reduce the severity of NREM sleep parasomnias, sometimes encountered in TS children. Finally, in children with developmental delays, melatonin has been shown to stabilize sleep and may be tried, especially in patients with sleep patterns suggestive of phase-delay or free-running sleep/wake cycles (Armour and Paton, 2004).

References

Albin RL, Koeppe RA, Bohnen NI, Nichols TE, Meyer P, Wernette K, Minoshima S, Kilbourn MR, Frey KA. Increased ventral striatal monoaminergic innervation in Tourette syndrome. Neurology. 2003; 61: 310-315.

American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry. 2000; 157: 1-45.

Anca MH, Nir Giladi MD, Amos D, Korczyn MD. Ropinirole in Gilles de la Tourette syndrome. Neurology. 2004; 62:1626-1627.

Apter A, Pauls DL, Bleich A, Zohar AH, Kron S, Ratzoni G, Dycian A, Kotler M, Weizman A, Gadot N, et al. An epidemiologic study of Gilles de la Tourette's syndrome in Israel. Arch Gen Psychiatry. 1993; 50: 734-738.

Armour D, Paton C. Melatonin in the treatment of insomnia in children and adolescents. Psychiatr Bull. 2004; 28: 222-224.

Awaad Y. Tics in Tourette's syndrome: new treatment options. J Child Neurol. 1999; 14: 316-319.

Awaad Y, Michon AM, Minarik S. Use of levetiracetam to treat tics in children and adolescents with Tourette syndrome. Mov Disord. 2005; 20: 714-718.

Banaschewski T, Woerner W, Rothenberger A. Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. Dev Med Child Neurol. 2003; 45: 700-703.

Baron-Cohen S, Scahill VL, Izaguirre J, Hornsey H, Robertson MM. The prevalence of Gilles de la Tourette syndrome in children and adolescents with autism: a large scale study. Psychol Med. 1999;29:1151-1159.

Beyer C. Estrogen and the developing mammalian brain. Anat Embryol 1999; 199: 379-390.

Biswal B, Ulmer JL, Krippendorf RL, Harsch HH, Daniels DL, Hyde JS, Haughton VM. Abnormal cerebral activation associated with a motor task in Tourette syndrome. AJNR. AJNR Am J Neuroradiol. 1998; 19: 1509-1512.

Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. Neurology. 2005; 65: 1253-1258.

Bloch MH, Sukhodolsky DG, Leckman JF, Schultz RT. Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. J Child Psychol Psychiatry. 2006; 47: 551-559.

Bornstein RA. Neuropsychological performance in children with Tourette's syndrome. Psychiatry Res. 1990; 33: 73-81.

Braun AR, Stoetter B, Randolph C, Hsiao JK, Vladar K, Gernert J, Carson RE, Herscovitch P, Chase TN. The functional neuroanatomy of Tourette's syndrome:

an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. Neuropsychopharm 1993; 9: 277-291.

Braun AR, Randolph C, Stoetter B, Mohr E, Cox C, Vladar K, Sexton R, Carson RE, Herscovitch P, Chase TN. The functional neuroanatomy of Tourette's syndrome: an FDG-PET Study. II: Relationships between regional cerebral metabolism and associated behavioral and cognitive features of the illness. Neuropsychopharmacology. 1995; 13: 151-168.

Brookshire BL, Butler IJ, Ewing-Cobbs L, Fletcher JM. Neuropsychological characteristics of children with Tourette syndrome: evidence for a nonverbal learning disability? J Clin Exp Neuropsychol. 1994; 16: 289-302.

Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. J Clin Psychiatry. 1996; 57: 29-31.

Canitano R, Vivanti G. Tics and Tourette syndrome in autism spectrum disorders. Autism. 2007;11:19-28.

Cath DC, Van de Wetering BJ, Van Woerkom TC, Hoogduin CA, Roos RA, Rooijmans HG. Mental play in Gilles de la Tourette's syndrome and obsessive-compulsive disorder. Br J Psychiatry. 1992; 161: 542-545.

Cath DC. Repetitive behaviors in Tourette's syndrome and OCD with and without tics: what are the differences? Psychiatry Res. 2001; 101:171-185.

Chabane N, Delorme R, Millet B, Mouren MC, Leboyer M, Pauls D. Early-onset obsessive-compulsive disorder: a subgroup with a specific clinical and familial pattern? J Child Psychol Psychiatry. 2005; 46: 881-887.

Chahine LM, Chemali ZN. Restless legs syndrome: a review. CNS Spectr. 2006; 11: 511-520.

Chase TN, Foster NL, Fedio P, Brooks R, Mansi L, Kessler R, Di Chiro G. Gilles de la tourette syndrome: studies with the fluorine-18-labeled fluorodeoxyglucose positron emission tomographic method. Ann Neurol. 1984; 15 Suppl: S175.

Cheon KA, Ryu YH, Namkoong K, Kim CH, Kim JJ, Lee JD. Dopamine transporter density of the basal ganglia assessed with [123I]IPT SPECT in drug-naïve children with Tourette's disorder. Psychiatry Res. 2004; 130: 85-95.

Chouinard S, Ford B. Adult onset tic disorders. J Neurol Neurosurg Psychiatry. 2000; 68: 738-743.

Coffey BJ, Biederman J, Smoller JW, Geller DA, Sarin P, Schwartz S, Kim GS. Anxiety disorders and tic severity in juveniles with Tourette's disorder. J Am Acad Child Adolesc Psych. 2000; 39 :562-568.

Comings BG, Comings DE. A controlled study of Tourette syndrome. V. Depression and mania. Am J Hum Genet. 1987; 41: 804–821.

Como PG. Neuropsychological function in Tourette syndrome. Adv Neurol. 2001; 85: 103-111.

Cortese S, Konofal E, Lecendreux M, et al. Restless legs syndrome and attention-deficit/hyperactivity disorder: a review of the literature. Sleep. 2005; 28: 1007-1013.

Crespo-Facorro B, Cabranes JA, Lopez-Ibor Alcocer MI, Paya B, Fernandez Perez C, Encinas M, Ayuso Mateos JL, Lopez-Ibor JJ Jr. Regional cerebral blood flow in obsessive-compulsive patients with and without a chronic tic disorder. A SPECT study. Eur Arch Psychiatry Clin Neurosci. 1999; 249: 156-161.

Dale RC. Post-streptococcal autoimmune disorders of the central nervous system. Dev Med Child Neurol. 2005; 47: 785-791.

Deckersbach T, Rauch S, Buhlmann U, Wilhelm S. Habit reversal versus supportive psychotherapy in Tourette's disorder: A randomized controlled trial and predictors of treatment response. Behav Res Ther. 2006; 44: 1079-1090.

Demirkol A, Erdem H, Inan L, Yigit A, Guney M. Bilateral globus pallidus lesions in a patient with Tourette syndrome and related disorders. Biol Psychiatry. 1999; 46: 863-867.

Dietch JT, Jennings RK. Aggressive dyscontrol in patients treated with benzodiazepines. J Clin Psychiatry. 1988; 49: 184-188.

Diler RS, Reyhanli M, Toros F, Kibar M, Avci A. Tc-99m-ECD SPECT brain imaging in children with Tourette's syndrome. Yonsei Med J. 2002; 43: 403-410.

Diniz JB, Rosario-Campos MC, Hounie AG, Curi M, Shavitt RG, Lopes AC, Miguel EC. Chronic tics and Tourette syndrome in patients with obsessive-compulsive disorder. J Psychiatr Res. 2006; 40; 487-493.

do Rosario-Campos MC, Leckman JF, Curi M, Quatrano S, Katsovitch L, Miguel EC, Pauls DL. A family study of early-onset obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet. 2005; 136: 92-97.

Drake ME Jr, Hietter SA, Bogner JE, Andrews JM. Cassette EEG sleep recordings in Gilles de la Tourette syndrome. Clin Electroencephalogr. 1992; 23: 142-146.

Drake ME Jr, Hietter SA, Padamadan H, Bogner JE. Computerized EEG frequency analysis in Gilles de la Tourette syndrome. Clin Electroencephalogr. 1991; 22: 250-253.

Dursun SM, Burke JG, Reveley MA. Antisaccade eye movement abnormalities in Tourette syndrome: evidence for cortico-striatal network dysfunction? J Psychopharmacol. 2000; 14: 37-39.

Eichstedt JA, Arnold SL. Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? Clin Psychol Rev. 2001; 21: 137-157.

Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002; 41: 1205-1215.

Erenberg G, Cruse RP, Rothner AD. Tourette syndrome an analysis of 200 pediatric and adolescent cases. Cleveland Clinic Quart. 1986; 53:127-131.

Ernst M, Zametkin AJ, Jons PH, Matochik JA, Pascualvaca D, Cohen RM. High presynaptic dopaminergic activity in children with Tourette's disorder. J Am Acad Child Adolesc Psychiatry. 1999: 38: 86-94.

Evans DW, Elliot JM, Packard MG. Visual Organization and Perceptual Closure Are Related to Compulsive-like Behavior in Typically Developing Children. Merrill-Palmer Quarterly. 2001; 47: 323-335.

Fallone G, Acebo C, Seifer R, Carskadon MA. Experimental restriction of sleep opportunity in children: effects on teacher ratings. Sleep. 2005; 28: 1561-1567.

Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol. 2000; 42: 436-447.

Garraux G, Goldfine A, Bohlhalter S, Lerner A, Hanakawa T, Hallett M. Increased midbrain gray matter in Tourette's syndrome. Ann Neurol. 2006; 59: 381-385.

Gaze C, Kepley HO, Walkup JT. Co-occuring Psychiatric disorders in Children and Adolescents with Tourette syndrome. J Child Neurol. 2006; 21: 657-664.

Gilbert D. Treatment of children and adolescents with tics and Tourette syndrome. J Child Neurol. 2006; 21: 690-700.

Gilbert DL, Sethuraman G, Sine L, Peters S, Sallee FR. Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial. Neurology. 2000; 54: 1310-1315.

Gilbert DL, Dure L, Sethuraman G, Raab D, Lane J, Sallee FR. Tic reduction with pergolide in a randomized controlled trial in children. Neurology. 2003; 60: 606-611.

Gilbert DL, Bansal AS, Sethuraman G, et al: Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. Mov Disord 2004; 19: 416-425

Goetz CG, Tanner CM, Wilson RS, Carroll VS, Como PG, Shannon KM. Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. Ann Neurol. 1987; 21: 307-310.

Gonce M, Barbeau A. Seven cases of Gilles de la Tourette's syndrome: partial relief with clonazepam: a pilot study. Can J Neurol Sci. 1977; 4: 279-283.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive-Compulsive Scale. I. Development, use, reliability. Arch Gen Psychiatry. 1989; 46: 1006-1011.

Goodman WK, Storch EA, Geffken GR, Murphy TK. Obsessive-compulsive disorder in Tourette syndrome. J Child Neurol. 2006; 21: 704-714.

Greenberg BD, Ziemann U, Cora-Locatelli G, Harmon A, Murphy DL, Keel JC, Wassermann EM. Altered cortical excitability in obsessive-compulsive disorder. Neurology. 2000; 54: 142-147.

Groenewegen HJ, van den Heuvel OA, Cath DC, Voorn P, Veltman DJ. Does an imbalance between the dorsal and ventral striatopallidal systems play a role in Tourette's syndrome? A neuronal circuit approach. Brain Dev. 2003;25 Suppl 1:S3-S14.

Haber SN, Kowall NW, Vonsattel JP, Bird ED, Richardson EP Jr. Gilles de la Tourette's syndrome. A postmortem neuropathological and immunohistochemical study. J Neurol Sci. 1986; 75: 225-241.

Harris EL, Schuerholz LJ, Singer HS, Reader MJ, Brown JE, Cox C, Mohr J, Chase GA, Denckla MB. Executive function in children with Tourette syndrome and/or attention deficit hyperactivity disorder. J Int Neuropsychol Soc. 1995; 1: 511-516.

Heinz A. Neurobiological and anthropological aspects of compulsions and rituals. Pharmacopsychiatry. 1999; 32: 223-229.

Hembree EA, Riggs DS, Kozak MJ, Franklin ME, Foa EB. Long-term efficacy of exposure and ritual prevention therapy and serotonergic medications for obsessive-compulsive disorder. CNS Spectr. 2003; 8: 363-371, 381.

Himle MB, Woods DW, Piacentini JC, Walkup JT. Brief review of habit reversal training for Tourette syndrome. J Child Neurol. 2006; 21: 719-725.

Hoekstra PJ, Steenhuis MP, Kallenberg CG, Minderaa RB. Association of small life events with self reports of tic severity in pediatric and adult tic disorder patients: a prospective longitudinal study. J Clin Psychiatry. 2004; 65: 426-31.

Hornse H, Banerjee S, Zeitlin H, Robertson M. The prevalence of Tourette syndrome in 13-14-year-olds in mainstream schools. J Child Psychol Psychiatry. 2001; 42: 1035-1039.

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997; 387: 167-178.

Hyde TM, Aaronson BA, Randolph C, Rickler KC, Weinberger DR. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette's syndrome in monozygotic twins. Neurology. 1992: 42: 652-658.

Hyde TM, Stacey ME, Coppola R, Handel SF, Rickler KC, Weinberger DR. Cerebral morphometric abnormalities in Tourette's syndrome: a quantitative MRI study of monozygotic twins. Neurology. 1995; 45: 1176-1182.

Ipser J, Stein DJ. Systematic review of pharmacotherapy of disruptive behavior disorders in children and adolescents. Psychopharmacology. 2006; Sep 16.

Jankovic J, Glaze DG, Frost JD Jr. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology. 1984; 34: 688-692.

Jeffries KJ, Schooler C, Schoenbach C, Herscovitch P, Chase TN, Braun AR. The functional neuroanatomy of Tourette's syndrome: an FDG PET study III:

functional coupling of regional cerebral metabolic rates. Neuropsychopharmacology. 2002; 27: 92-104.

Kalanithi PS, Zheng W, Kataoka Y, DiFiglia M, Grantz H, Saper CB, Schwartz ML, Leckman JF, Vaccarino FM. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. Proc Natl Acad Sci U S A. 2005;102:13307-13312.

Kenneth S, Lesser M, Olson M. Explosive Outbursts in children with Tourette's Disorder. J Am Acad Child Adolesc Psychiatry 2000; 39: 1270-1276.

Keri S, Szlobodnyik C, Benedek G, Janka Z, Gadoros J. Probabilistic classification learning in Tourette syndrome. Neuropsychologia. 2002; 40: 1356-1362.

Klieger PS, Fett KA, Dimitsopulos T, Kurlan R. Asymmetry of basal ganglia perfusion in Tourette's syndrome shown by technetium-99-HMPAO SPECT. J Nucl Med. 1997; 38: 188-191.

Kostanecka-Endress T, Banaschewski T, Kinkelbur J, Wullner I, Lichtblau S, Cohrs S, Ruther E, Woerner W, Hajak G, Rothenberger A. Disturbed sleep in children with Tourette syndrome: a polysomnographic study. J Psychosom Res. 2003; 55: 23-29.

Kurlan R. Hypothesis II: Tourette's syndrome is part of a clinical spectrum that includes normal brain development. Arch Neurol. 1994; 51: 1145-1150.

Kurlan R, Como PG, Miller B, Palumbo D, Deeley C, Andresen EM, Eapen S, McDermott MP. The behavioral spectrum of tic disorders: a community-based study. Neurology. 2002; 59: 414-420.

Kwak C, Dat Vuong K, Jankovic J. Premonitory sensory phenomenon in Tourette's syndrome. Mov Disord. 2003; 18: 1530-1533.

Laplane D. [Obsessive-compulsive disorders caused by basal ganglia diseases]. Rev Neurol (Paris). 1994; 150: 594-598.

Leckman JF. In search of the pathophysiology of Tourette syndrome. In MA Bedard, Y Agid, S Chouinard, S Fahn, AD Korczyn, P Lesperance Eds, Mental and behavioral dysfunction in movement disorders. 2003; Totowa: Humana Press, 467-476.

Leckman JF, Hardin MT, Riddle MA, Stevenson J, Ort SI, Cohen DJ. Clonidine treatment of Tourette's syndrome. Arch Gen Psychiatry. 1991; 48: 324-328.

Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, Kim YS, Peterson BS. Course of tic severity in Tourette's syndrome: the first two decades. Pediatrics. 1998; 102:14-19.

Leckman JF, King RA, Cohen DJ. Tics and tic disorders. In JF Leckman, DJ Cohen Eds, Tourette's syndrome - Tics, obsessions, compulsions: Developmental psychopathology and clinical care. 1999; New York: Wiley Sons, 23-42.

Lee JS, Yoo SS, Cho SY, Ock SM, Lim MK, Panych LP. Abnormal thalamic volume in treatment-naive boys with Tourette syndrome. Acta Psychiatr Scand. 2006; 113: 64-67.

Lemay M, Termoz N, Lesperance P, Chouinard S, Richer F. Postural control anomalies in children with Tourette syndrome. Exp Brain Res. (in press).

Lesperance P, Djerroud N, Diaz Anzaldua A, Rouleau GA, Chouinard S, Richer F, Montreal Tourette Study Group. Restless legs in Tourette syndrome. Mov Disord. 2004; 19: 1084-1087.

Lesperance P, Robert M, Desjardins M, Sforza E, Richer F. Arousal instability in Tourette Syndrome. J Psychiatr Clin Neurosciences. 2006; 18: 278.

Lin H, Katsovich L, Ghebremichael M, Findley DB, Grantz H, Lombroso PJ, King RA, Zhang H, Leckman JF, Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. J Child Psychol Psychiatry. (In press).

Ludolph AG, Juengling FD, Libal G, Ludolph AC, Fegert JM, Kassubek J. Grey-matter abnormalities in boys with Tourette syndrome: magnetic resonance imaging study using optimised voxel-based morphometry. Br J Psychiatry. 2006; 188: 484-485.

Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology. 2001; 56: 605-610.

Marsh R, Alexander GM, Packard MG, Zhu H, Wingard JC, Quackenbush G, Peterson BS. Habit learning in Tourette syndrome: a translational neuroscience approach to a developmental psychopathology. Arch Gen Psychiatry. 2004; 61: 1259-1268.

Marsh R, Alexander GM, Packard MG, Zhu H, Peterson BS. Perceptual-motor skill learning in Gilles de la Tourette syndrome. Evidence for multiple procedural learning and memory systems. Neuropsychologia. 2005; 43: 1456-1465.

Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry. 1999; 156: 1409-1416.

Mathews CA, Waller J, Glidden D, Lowe TL, Herrera LD, Budman CL, Erenberg G, Naarden A, Bruun RD, Freimer NB, Reus VI. Self injurious behaviour in Tourette syndrome: correlates with impulsivity and impulse control. J Neurol Neurosurg Psychiatry. 2004; 75: 1149-1155.

McAbee GN, Wark JE, Manning A. Tourette syndrome associated with unilateral cystic changes in the gyrus rectus. Pediatr Neurol. 1999; 20: 322-324.

McDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Brain Res Rev.1990; 15: 41-70.

Meyer P, Bohnen NI, Minoshima S, Koeppe RA, Wernette K, Kilbourn MR, Kuhl DE, Frey KA, Albin RL. Striatal presynaptic monoaminergic vesicles are not increased in Tourette's syndrome. Neurology. 1999; 53: 371-374.

Micheli F, Gatto M, Lekhuniec E, Mangone C, Fernandez Pardal M, Pikielny R, Casa Parera I. Treatment of Tourette syndrome with calcium antagonists. Clin Neuropharm. 1990; 13: 77-83.

Miguel EC, do Rosario-Campos MC, Prado HS, do Valle R, Rauch SL, Coffey BJ, Baer L, Savage CR, O'Sullivan RL, Jenike MA, Leckman JF. Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder. J Clin Psychiatry. 2000; 61: 150-156.

Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. Pediatric Neurology 2001;25:190-198.

Moriarty J, Costa DC, Schmitz B, Trimble MR, Ell PJ, Robertson MM. Brain perfusion abnormalities in Gilles de la Tourette's syndrome. Br J Psychiatry. 1995; 167: 249-254.

Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. J Child Adolesc Psychopharmacol. 2003; 13: 295-299.

Muller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. Am J Psychiatry. 1999; 156: 495.

Muller-Vahl KR, Meyer GJ, Knapp WH, Emrich HM, Gielow P, Brucke T, Berding G. Serotonin transporter binding in Tourette Syndrome. Neurosci Lett. 2005; 385: 120-125.

Neimat JS, Patil PG, Lozano AM. Novel surgical therapies for Tourette syndrome. J Child Neurol. 2006; 21: 715-718.

Nomura Y, Fukuda H, Terao Y, Hikosaka O, Segawa M. Abnormalities of voluntary saccades in Gilles de la Tourette's syndrome: pathophysiological consideration. Brain Dev. 2003; 25 Suppl 1: S48-54.

O'Connor KP, Brault M, Robillard S, Loiselle J, Borgeat F, Stip E. Evaluation of a cognitive-behavioural program for the management of chronic tic and habit disorders. Behav Res Ther. 2001; 39: 667-681.

Orth M, Amann B, Robertson MM, Rothwell JC. Excitability of motor cortex inhibitory circuits in Tourette syndrome before and after single dose nicotine. Brain. 2005; 128(Pt 6): 1292-1300. Pas dans le texte.

Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology. 2003; 61: 936-940.

Paulus W, Trenkwalder C. Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome. Lancet Neurol. 2006; 5: 878-886.

Pauls DL, Towbin KE, Leckman JF, Zahner GE and Cohen DJ . Gilles de la Tourette's syndrome and obsessive-compulsive disorder. Evidence supporting a genetic relationship. Arch Gen Psychiatry. 1986; 43: 1180-1182.

Peterson BS, Leckman JF, Scahill L, Naftolin F, Keefe D, Charest NJ, Cohen DJ. Steroid hormones and CNS sexual dimorphisms modulate symptom expression in Tourette's syndrome. Psychoneuroendocrinology. 1992; 17: 553-563.

Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. J Am Acad Child Adolesc Psychiatry. 2001; 40: 685-695.

Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch Gen Psychiatry. 1998; 55: 326-333.

Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, King RA, Leckman JF, Staib L. Basal ganglia volumes in patients with Gilles de la Tourette syndrome. Arch Gen Psychiatry. 2003; 60: 415-424.

Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M. The texas children's medication algorithm project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006; 45: 642-657.

Price RA, Kidd KK, Cohen DJ, Pauls DL, Leckman JF. A twin study of Tourette syndrome. Arch Gen Psychiatry. 1985; 42: 815-820.

Raffaele R, Rampello L, Vecchio I, Alvano A, Rizzo R, Pavone P, Maci T, Perciavalle V. Blink reflex abnormalities in children with Tourette syndrome. Eur J Neurol. 2006; 13: 869-873.

Richer F, Lesperance P, Rouleau GA, Chouinard S. Prenatal factors modulate behavioral symptoms in Tourette syndrome. (submitted).

Riddle MA, Rasmusson AM, Woods SW, Hoffer PB. SPECT imaging of cerebral blood flow in Tourette syndrome. Adv Neurol. 1992; 58: 207-211.

Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. Brain. 2000; 123: 425-462.

Saccomani L, Fabiana V, Manuela B, Giambattista R. Tourette syndrome and chronic tics in a sample of children and adolescents. Brain Dev. 2005; 27: 349-352.

Sandyk R. The effects of naloxone in Tourette's syndrome. Ann Neurol. 1985; 18: 367-368.

Scahill LD, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AF, Cohen DJ, Leckman JF. Guanfacine in the treatment of children with tic disorders and ADHD: a placebo-controlled study. Am J Psychiatry 2001; 158: 1067-1074.

Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology. 2003; 60: 1130-1135.

Schaller JL, Behar D. Quetiapine treatment of adolescent and child tic disorders: two case reports. Eur Child Adolesc Psychiatry. 2002; 11: 196-197.

Schuerholz LJ, Singer HS, Denckla MB. Gender study of neuropsychological and neuromotor function in children with Tourette syndrome with and without attention-deficit hyperactivity disorder. J Child Neurol. 1998; 13: 277-282.

Schultz RT, Carter AS, Gladstone M, Scahill L, Leckman JF, Peterson BS, Zhang H, Cohen DJ, Pauls D. Visual-motor integration functioning in children with Tourette syndrome. Neuropsychology. 1998; 12: 134-145.

Serra-Mestres J, Ring HA, Costa DC, Gacinovic S, Walker Z, Lees AJ, Robertson MM, Trimble MR. Dopamine transporter binding in Gilles de la Tourette syndrome: a [123I]FP-CIT/SPECT study. Acta Psychiatr Scand. 2004; 109: 140-146.

Serrien DJ, Nirkko AC, Loher TJ, Lovblad KO, Burgunder JM, Wiesendanger M. Movement control of manipulative tasks in patients with Gilles de la Tourette syndrome. Brain. 2002; 125: 290-300.

Shahed J, Poysky J, Kenney C, Simpson R, Jankovic J. GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. Neurology. 2007; 68:159-160.

Shapiro AK, Shapiro E. Controlled study of pimozide vs placebo in Tourette's syndrome. J Am Acad Child Psychiatry. 1984; 23: 161-173.

Shavitt RG, Belotto C, Curi M, Hounie AG, Rosario-Campos MC, Diniz JB, Ferrao YA, Pato MT, Miguel EC. Clinical features associated with treatment response in obsessive-compulsive disorder. Compr Psychiatry. 2006; 47: 276-281.

Sheppard DM, Bradshaw JL, Georgiou N, Bradshaw JA, Lee P. Movement sequencing in children with Tourette's syndrome and attention deficit hyperactivity disorder. Mov Disord. 2000; 15: 1184-93.

Sherman EM, Shepard L, Joschko M, Freeman RD. Sustained attention and impulsivity in children with Tourette syndrome: comorbidity and confounds. J Clin Exp Neuropsychol. 1998; 20: 644-657.

Shucard DW, Benedict RH, Tekok-Kilic A, Lichter DG. Slowed reaction time during a continuous performance test in children with Tourette's syndrome. Neuropsychology. 1997; 11: 147-155.

Singer HS, Brown J, Quaskey S, Rosenberg LA, Mellits ED, Denckla MB. The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. Pediatrics. 1995; 95: 74-81.

Singer HS, Giuliano JD, Hansen BH, Hallett JJ, Laurino JP, Benson M, Kiessling LS. Antibodies against human putamen in children with Tourette syndrome. Neurology. 1998; 50: 1618-1624.

Singer HS, Reiss AL, Brown JE, Aylward EH, Shih B, Chee E, Harris EL, Reader MJ, Chase GA, Bryan RN, et al. Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology. 1993; 43: 950-956.

Singer HS, Wendlandt J, Krieger M, Giuliano J. Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. Neurology. 2001; 56: 599-604.

Singer HS, Szymanski S, Giuliano J, Yokoi F, Dogan AS, Brasic JR, Zhou Y, Grace AA, Wong DF. Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. Am J Psychiatry. 2002; 159: 1329-1336.

Snider LA, Seligman LD, Ketchen BR, Levitt SJ, Bates LR, Garvey MA, Swedo SE. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. Pediatrics. 2002;110 :331-336.

Stamenkovic M, Schindler SD, Asenbaum S, Neumeister A, Willeit M, Willinger U, de Zwaan M, Riederer F, Aschauer HN, Kasper S. No change in striatal dopamine re-uptake site density in psychotropic drug naïve and in currently treated Tourette's disorder patients: a [(123)]-beta-CIT SPECT study. Eur Neuropsychopharmacol. 2001; 11: 69-74.

State MW, Pauls DL, Leckman JF. Tourette's syndrome and related disorders. Child Adolesc Psychiatr Clin N Am. 2001; 10: 317-331.

Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, Frith CD, Frackowiak RS, Dolan RJ. A functional neuroanatomy of tics in Tourette syndrome. Arch Gen Psychiatry. 2000; 57: 741-748.

Stewart SE, Illmann C, Geller DA, Leckman JF, King R, Pauls DL. A controlled family study of attention-deficit/hyperactivity disorder and Tourette's disorder. J Am Acad Child Adolesc Psychiatry. 2006; 45: 1354-62.

Sutherland RJ, Kolb B, Schoel WM, Whishaw IQ, Davies D. Neuropsychological assessment of children and adults with Tourette syndrome: a comparison with learning disabilities and schizophrenia. Adv Neurol. 1982; 35: 311-322.

Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJ, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet. 1998; 351: 429-433.

Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998; 155: 264-271.

Temel Y, Visser-Vandewalle V. Surgery in Tourette syndrome. Mov Disord. 2004; 19: 3-14.

Toren P, Weizman A, Ratner S, Cohen D, Laor N. Ondansetron treatment in Tourette's disorder: A 3-week, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2005; 66: 499-503.

Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. The Tourette Syndrome Classification Study Group. Arch Neurol. 1993; 50: 1013-1016.

Tourette Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002; 58: 527-536.

Tulen JHM, Azzolini M, de Vries, JA, Groeneveld WH, Passchier J, van de Wetering BJM. Quantitative study of spontaneous eye blinks and eye tics in Gilles de la Tourette`s syndrome. J Neurol Neurosurg Psychiat. 1999;67:800-802.

Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet. 1999; 353: 724.

Vignatelli L, Billiard M, Clarenbach P, Garcia-Borreguero D, Kaynak D, Liesiene V, Trenkwalder C, Montagna P. EFNS Task Force. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. Eur J Neurol. 2006; 13:1049-1065.

Vincent DA jr. Botulinum Toxin in the Management of Laryngeal Tics. J Voice. 2006; Oct 20 [Epub].

Walkup JT, LaBuda MC, Singer HS, Brown J, Riddle MA, Hurko O. Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. Am J Hum Genet. 1996; 59: 684-693.

Whitaker AH, Van Rossem R, Feldman JF, Schonfeld IS, Pinto-Martin JA, Tore C, Shaffer D, Paneth N. Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. Arch Gen Psychiatry. 1997; 54: 847-856.

Wilhelm S, Deckersbach T, Coffey BJ, Bohne A, Peterson AL, Baer L. Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial. Am J Psychiatry 2003; 160: 1175-1177.

Wong DF, Singer HS, Brandt J, Shaya E, Chen C, Brown J, Kimball AW, Gjedde A, Dannals RF, Ravert HT, Wilson PD, Wagner HN Jr. D2-like dopamine receptor density in Tourette syndrome measured by PET. J Nucl Med. 1997; 38: 1243-1247.

Woods DW, Watson TS, Wolfe E, Twohig MP, Friman PC. Analyzing the influence of tic-related talk on vocal and motor tics in children with Tourette's syndrome. J Appl Behav Anal. 2001; 34: 353-356.

Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. J Dev Behav Pediatr. 2005; 26: 397-403.

Yeates KO, Bornstein RA. Neuropsychological correlates of learning disability subtypes in children with Tourette's syndrome. J Int Neuropsychol Soc. 1996; 2: 375-382.

Table 1: Differential Diagnosis of Tics and Tourette Syndrome

Diagnosis	Type
Transient tics of childhood	
Childhood onset stereotypies	
Autism spectrum disorders	
Prenatal/perinatal insults	Congenital CNS defects Birth defects
Infections	Post-viral encephalitis HIV infections of CNS Lyme disease
Head trauma	
Toxin exposure	Carbon monoxide Gasoline
Drugs	Neuroleptics ("tardive tics") Levodopa Opiate withdrawal Amphetamines Lamotrigine
Chromosomal abnormalities	XYY, XXY, Fragile X syndrome
Genetic disorders	Hallervorden - Spatz disease Wilson's disease Hyperekplexias Rett syndrome Huntington’s disease Neuroacanthocytosis

Figure 1. Pathogenesis of TS