Chapter 4
Tourette Syndrome and the Spectrum of Neurodevelopmental Tic Disorders

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This chapter contains video segments that can be found on the accompanying DVD.

Video Segment Content

Case 1: Gilles de la Tourette syndrome: Simple motor tics.
Adult patient demonstrating simple motor tics. The patient has repetitive eye blinking, a very common motor tic.
Case 2: Gilles de la Tourette syndrome: Vocal tics.
This young adult with Gilles de la Tourette syndrome has vocal tics consisting of screams.
Case 3: Gilles de la Tourette syndrome: Coprolalia.
This young patient with Gilles de la Tourette syndrome has coprolalia as one of her vocal tics. The patient also demonstrates copropraxia.
Case 4A: Gilles de la Tourette syndrome: Multiple motor and vocal tics.
This adolescent has severe and medically refractory motor and vocal tics.
Case 4B: Gilles de la Tourette syndrome: Suppressibility and urge.
This is the same patient as in video 4A, demonstrating that despite the severity of the tics the patient is able to suppress them for a short period of time when asked to do so at the beginning of the video. The patient is describing the urge he feels when he tries to suppress his tics. At the end of the video, when the patient is asked to stop suppressing his tics, they become much more frequent and intense.

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O. Suchowersky and C. Comella (eds.), *Hyperkinetic Movement Disorders*,
Current Clinical Neurology, DOI 10.1007/978-1-60327-120-2_4,

The first report of a tic disorder was made as early as in 1825 by Jean Marc Gaspard Itard, a French neurologist. He described the case of a French noblewoman, Marquise de Dampierre, who displayed involuntary movements and coprolalia. At the end of the nineteenth century, Armand Trousseau and Georges Gilles de la Tourette published a more complete description of the disorder [1, 2]. In his paper, Gilles de la Tourette described the symptomatology of 9 patients with multiple tics, echolalia, and coprolalia and suggested that it was a neurological condition with a hereditary component. Nevertheless, this syndrome was later considered to be primarily psychogenic in 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 corticostriatal brain circuits.

Epidemiology

The prevalence of TS remains unclear partly because of the lack of biological markers and the wide symptom fluctuations and partly because of the lack of a consensus regarding the definition of this disorder. According to some studies, it is estimated that between 1 and 3% of the school age population is affected by TS [3]. 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 TS, the condition may be quite frequent.

Phenomenology of Tics

Tics are repetitive, sudden, rapid, nonrhythmic, stereotyped movements which often occur in response to a sensation or an urge and occur in bouts. Tics can be simple or complex. Eye blinking and orofacial grimaces are the most common simple motor tics one can encounter and typically are present at onset of the disorder. With evolution, tics tend to migrate to affect more distal body parts. Among vocal tics, throat clearing, shouting, and simple nonverbal sounds are the most common. Tics are considered complex when they involve several segments or appear goal-directed. Examples include touching, smelling, hitting, imitation of actions (echopraxia), or repetition of words (echolalia). Coprolalia, an involuntary verbalization of obscene or scatological words, is a manifestation of the disorder only in a minority of subjects affected by TS and is often temporary [4].

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 typically reported by children over 10 years of age, possibly because they have achieved a cognitive maturation, allowing them to better describe these symptoms [5]. Repetitive, intrusive, and/or uncomfortable sensations (sensory tics) can also

occur without any externally apparent tics and often in the absence of a verifiable stimulus [6]. Sensory tics and premonitory sensations give a semivoluntary property to some tics; the individual needs to do the tic in order "to relieve an itch" [7, 8].

A fundamental characteristic of tics is that they can be voluntarily inhibited for a short period of time but at the expense of an increasing urge to express them. The suppressibility and the inner sensation caused by the former are probably the most important characteristics to help differentiate tics from other movement disorders such as tremor, dystonia, chorea, or myoclonus.

As with many types of involuntary movements, the amount of tics can be reduced when the individual concentrates on voluntary tasks, presumably increasing activation in frontostriatal brain circuits. Tics can also be exacerbated by stress and fatigue. However, the relationship between small stressful life events and tic exacerbations in the same week is not clear in most cases [9, 10]. Another critical feature of tics is their plasticity and suggestibility. New tics can replace old ones within a short period of time (plasticity), tics can be evoked by discussing them with the patient, and they can be developed through observation of other people's tics (suggestibility) [11]. The plasticity of tics suggests that they are linked to fluctuations in the activation threshold of circuits controlling fragments of stereotyped movements [12].

Tics must be differentiated from other stereotyped movement disorders including stereotypies, habits, and mannerisms. Stereotypies are involuntary, patterned, purposeless, and repetitive movements that often begin in early infancy. They are generally associated with periods of excitement, stress, or boredom and can be suppressed by distraction. One major difference between a tic and a stereotypy is that most often, stereotypic movements do not change over time. It is important to recognize that stereotypies can occur in normal children even though they have been traditionally described with sensory deficits (such as deafness or blindness), mental retardation, autism, or schizophrenia.

Diagnostic Criteria

TS is characterized by the presence of chronic tics appearing before 21 years [13]. According to the criteria of the Tourette Syndrome Classification Study Group (TSCSG), a diagnosis of TS requires the presence of multiple motor tics and a least one vocal tic, a fluctuating course, and a symptom duration of at least 1 year [14]. 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 shows the same evolution and comorbidities as TS [15, 16]. CMTD should be included in the Tourette spectrum disorders (TSD) to insure adequate attention and care for individuals with primary tic disorders.

Diagnosis is made according to the history and the presence of tics during the interview and examination. There is no diagnostic test; radiological investigations are recommended only if the presentation is atypical or the neurological examination is abnormal. EEG and evoked potentials measures are usually normal [17, 18].

Table 4.1 Differential diagnosis of tic disorders

Primary tic disorders	Transient tic disorder Chronic motor tic Chronic vocal tic Tourette syndrome Adult-onset tic disorder
Secondary tic disorders	Prenatal/perinatal insults • Congenital CNS defects • Birth defects Infections • Postviral encephalitis • HIV infection of CNS • Lyme disease Head trauma Brain tumor Toxin exposure • Carbon monoxide • Gasoline Drugs • Neuroleptics (“tardive tics”) • Levodopa • Opiate withdrawal • Amphetamines • Lamotrigine Genetic disorders • PKAN (pantothenate kinase-associated neurodegeneration) • Wilson disease • Rett syndrome • Huntington disease • Chorea-acanthocytosis Chromosomal abnormalities • XYY • XXY Fragile X syndrome

Adapted from Faridi and Suchowersky [209]

The vast majority of patients will present with an idiopathic tic disorder. In a minority of patients, tics have been associated with a variety of insults to the brain such as head trauma, stroke, neurodegenerative conditions, genetic disorders, or exposure to drugs (Table 4.1). A recent article reported a child presenting, at the age of 11 years, with attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), generalized anxiety, and stimulant-induced tic disorder who developed sinus node dysfunction requiring selective cardiac ablation as well as secondary generalized tonic-clonic seizures. This child was found to have a right temporal lobe tumor with extension to the basal ganglia [19].

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 [20]. The median age of tic onset in TS patients is 5–7 years, but symptoms can appear as early as the first year of life. About 96% of TS patients will have symptoms by the age of 11 years [21]. Despite the fact that diagnostic criteria require that the onset of tics be before the age of 21, rare cases of tics with onset during adulthood have been reported [22].

Irregular periods of exacerbation interspersed with remissions are characteristic of TS. Tic severity generally peaks between 8 and 15 years [23]. The specific role of puberty or adrenarche in tic modification is still unclear [24]. 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 [25]. Fluctuation of severity throughout life is typical.

TS manifests through a large variety of phenotypes. Many affected individuals will never see a physician for this disorder because of the intermittent nature of their symptoms, ignorance of the syndrome, or because of the low impact of symptoms in their everyday life. For those with 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 behavioral problems such as obsessive-compulsive symptoms (OCS), hyperactivity, opposition, conduct disorder, or rage outbursts. It is only when discovering the presence of tics that the professional will associate these symptoms to comorbidities of TS.

There is increasing evidence that TS is part of a Tourette spectrum of disorders (TSD). In TSD, the severity of the tics and associated comorbidities (obsessive-compulsive symptoms, opposition, ADHD, rage outbursts, etc.) is highly variable. Some may even consider that phenotypes with transient tics and significant behavioral symptoms should be included in the TSD. An improved classification and characterization of TSD based on endophenotypes should facilitate research advancement on the etiology and neurobiology of these disorders

Comorbidities

Obsessive-Compulsive Symptoms

OCS involve sudden, intrusive, and repetitive thoughts or actions. OCS are frequent in TS, especially in females, and tend to increase in severity several years after the tic severity has peaked [26]. Prevalence of OCS is increased in relatives of TS patients, as are tics in relatives of OCD patients [14, 27–30]. This suggests that OCS are part of the TS phenotype and that TS and OCD are linked etiologically.

Reports of OCS prevalence vary from 30 to 80% [27], which may reflect referral biases or adherence to OCS spectrum vs. OCD criteria. Obsessions may be related to contamination, safety/harm, unwanted acts of aggression or self-harm (impulse-control phobias), thoughts or images of religious and sexual contents, and need for symmetry and exactness (e.g., the "just right" phenomenon). Compulsions may consist of cleaning rituals, checking behaviors, ordering and hoarding behaviors, and useless counting or recitation (mental compulsions). Some level of OCS may be a normal developmental process and was reported to be as high as 60% in 3-year-old children and even more in children with developmental delays [31]. Like transient tics, transient compulsions may be a substrate for the development of clinical symptoms in high-susceptibility individuals.

The psychiatric definition of OCD differs 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 and hoarding in TS, the most frequent subtypes of OCS [32]. Although developed to evaluate the severity of idiopathic OCD, the Yale-Brown Obsessive-Compulsive Scale (YBOCS) is widely used in TS patients [33]. It measures both the intensity and functional impact of obsessions and compulsions in a combined score. However, more compulsions than obsessions, independent of YBOCS score, are typical of TS patients and are associated with poorer pharmacologic treatment response [34].

Tics and compulsions can be considered to be on the same clinical spectrum, and distinguishing one from the other may be challenging. The purposefulness of an action and the associated 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 compulsion if done in response to a symmetry/just right obsession. Such compulsions may have a better response to neuroleptics than SSRIs, as would be expected for tics [34]. Clear-cut premonitory urges may help to support categorization of an action as a complex tic, rather than as a compulsion, but sensory phenomena have also been documented in OCD, especially with childhood onset [35]. Tic-related OCS may be less responsive to medication, but this remains uncertain [36]. Some studies suggest that echophenomena and complex tics are significantly correlated with OCS in TS [37]. Whether it is due to true comorbidity between tics and OCS or that these are both part of the same disorder spectrum is still unclear.

In idiopathic OCD, obsessions are intrusive thoughts and worries associated with a need to verify, check, or wash in order to relieve the anxiety or emotional distress. Obsessions in Tourette syndrome are frequently described as vivid, imposed images or brief thoughts of violence or sex that may or may not be associated with distress [37]. These mental events have no particular purpose and may thus qualify as impulse-control symptoms or mental tics rather than OCS [38].

ADHD and Cognition

ADHD is strongly associated with tic disorders in clinical samples; 40–60% of children with TS have a diagnosis of ADHD, and this comorbidity is often the main

reason for seeing a physician. Among the school age population, 2–10% of children present with clinically significant ADHD [39]. The association between tics and ADHD in community samples is less clear and may depend on the severity of the tic disorder [40–42]. The etiologic link between ADHD and TS is still unknown, but there is little evidence of a genetic link between the two syndromes. An overlap in cerebral substrates is often hypothesized [43]. Like TS, ADHD has a significant heritability and is linked to frontostriatal and dopaminergic systems. It is often associated by behavioral impulse control difficulties.

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

Among TS+ADHD subjects, distractibility, emotional reactivity, and impulsivity lead to problems completing tasks requiring sustained attention or attention to details. These symptoms can often result in poorly planned actions and can lead to academic performance that is inferior to the cognitive potential.

Several studies with large and well-selected samples have reported normal cognitive function in people diagnosed with TS, especially when they do not have associated behavioral comorbidities [44], and intelligence measures show a similar distribution to the global population. However, some TS patients can show lower performance IQ due to visual-motor problems, especially when ADHD is present [45–47]. TS+ADHD children are also more inclined to have learning disabilities affecting mathematics and reading. Patients with more severe TS usually experience more cognitive difficulties compared to patients affected by a less severe syndrome [48–50]. When cognitive dysfunction is present, the observed deficits are often similar to those produced by other frontal or striatal disorders, affecting primarily the executive control of attention and action [51, 52]. Only a minority of TS patients shows clear executive control problems. Response slowing and variability in response speed can be observed in patients with or without ADHD [48, 53]. Learning and recall of semantic and episodic information are usually adequate in TS. Some learning problems have been reported in probabilistic classification tasks [54, 55] but not in all sensorimotor learning tasks [56].

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 other individuals or objects. Explosive outbursts have been reported in up to 50% of clinical TS studies [57]. Although they may be surrogate events of other comorbidities, such as impulsivity

associated with ADHD, oppositional-defiant disorder (ODD), or irritability associated with increased anxiety or OCS (frustration over unmet needs), they are sentinel symptoms worth looking for and represent one of the most challenging clinical situations in many patients. During these outbursts, the patient "loses control" and is usually shameful when the crisis subsides. Risk factors for rage behavior include obstetric complications, tic severity, ADHD symptoms, male gender, and maternal rage outbursts.

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) [58]. SIB is correlated with tic severity and OCS [58]. Rage outbursts and SIB are also seen in many children with neurodevelopmental problems such as mental retardation, autism spectrum disorders, and anoxic encephalopathy [21].

Antisocial and Oppositional Behaviors

Although psychosocial, familial, and economic factors may be more relevant as a whole to help understand these pathological relational behaviors, antisocial and oppositional behaviors are frequently encountered in TS. Oppositional symptoms (argumentation, defiance, irritability, provocation) are predictors of adverse outcomes and are selectively linked to comorbidities such as ADHD and OCS [59]. Some patients may also show symptoms of antisocial behavior (conduct disorder in children, antisocial personality disorder in adults) such as lying, stealing, and fighting. Again, overlap with OCS, ADHD, and impulse-control disorder plays 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 autistic spectrum disorders, tic disorders appear to be common, with a prevalence of 6.5–22% [60, 61]. 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 [62]. 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. These behaviors will impact their ability to lead normal lives at home, school, or work. Predictors of autism in TS include a high number of comorbidities, male gender, and lack of family history of tics [63]. An overlap in the limbic circuitry involved or the influence of common genetic factors may explain the comorbidity between TS and autistic spectrum disorders.

Anxiety and Depression

Although anxiety and depression symptoms may be increased in TS [64, 65], the list of possible contributing factors is endless. In TS, anxiety symptoms and psychosocial distress may predict future tic severity [10]. Of interest, ADHD has been proposed as a risk factor for generalized anxiety disorder (GAD) in adults and may very well share genetic factors with these conditions.

Sleep Disturbances

Sleep studies in TS patients have revealed insomnia and lighter sleep, complaints of parasomnia (sleep walking, sleep terrors), and agitated sleep [66]. Behaviorally, tics may be seen during sleep. Polysomnographic studies, although not unanimous, show that tics are rare in slow wave sleep (SWS) and seen mostly in lighter sleep stages or sleep stage changes. Increases in microarousals and periodic limb movements in sleep suggest NREM sleep instability in TS even without ADHD [67]. 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 [68]. 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

In restless legs syndrome (RLS), patients have an urge to move a limb, usually one or both legs, associated with focal dysesthesia. These symptoms are typically increased by rest and reduced by movement, occurring mostly in the evening or at bedtime. We have previously described increased RLS symptoms in children with TS [69] independent of ADHD comorbidity, which is a reported risk factor for adult RLS [70]. 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 have a documented efficacy in RLS but may also have anti-tic properties [71, 72].

Etiology

In his first description of the syndrome, Gilles de la Tourette reported that the disorder was familial [1]. Since then, studies have confirmed the presence of an important genetic component in the causality of TS, with a recent review article

summarizing the knowledge on this rapidly evolving topic [73]. Twins studies have shown that more than 50% of identical twins show a concordance for the diagnosis of TS, as compared to less than 10% of fraternal twins [74]. The concordance rate for monozygotic twins was found to be between 94 and 100% when TS or other tic disorders are considered [75, 76]. These data suggest 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. In linkage studies, the strongest evidence was observed for a locus on chromosome 2: 2p23.2 [77]. Studies of chromosomal rearrangements in TS patients have suggested four regions to be associated with TS: 7q22-q31, 8q13-q22, 17p11, and 18q22 [78–87].

The inheritance of TS is thought to be complex and probably involves several genes [88, 89]. However, candidate gene studies have not revealed any unequivocal susceptibility gene so far [73]. Because of the high number of identical twins discordant for TS, it is probable that genetic vulnerability factors interact with environmental and epigenetic factors affecting gene expression during embryogenesis. Several nongenetic factors have already been associated with the development or severity of TS, including a variety of prenatal and perinatal events, hormones, immune responses, and stressors. There is evidence for greater severity in the TS twin with perinatal complications compared to the co-twin [76]. Perinatal cerebral ischemia significantly increases the risk for tics and ADHD [90]. Also, obstetrical complications were found to contribute to explosive outbursts in TS.

The much higher prevalence of TS among boys raises the hypothesis that steroid hormones (DHEA, sex hormones) play a role in the pathogenesis of TS [91]. However, direct evidence of this 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) may affect the expression of tics.

Finally, postinfectious autoimmune responses could contribute to TS [92, 93] as recent evidence suggests an elevated expression of genes linked to chronic inflammation in the basal ganglia of TS patients [94]. A related syndrome, called PANDAS (postinfectious autoimmune neuropsychiatric disorders associated with streptococcal infection), was first described in 1998 by Swedo et al. [95]. They proposed the term PANDAS to define prepubertal onset of OCS, TS, or tic disorder with abrupt exacerbation following infection. However, this entity remains controversial, and since the first description, considerable debate persists regarding the diagnosis and treatment [96–100].

A preliminary model of TS pathogenesis relies on multiple reciprocal interactions between genetic, epigenetic, and environmental factors leading to variable effects on the development of biological systems involved in movement and behavior (see Fig. 4.1). Multiple interactions would explain the variability of the TS phenotype as well as the fluctuations of symptoms [101]. 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

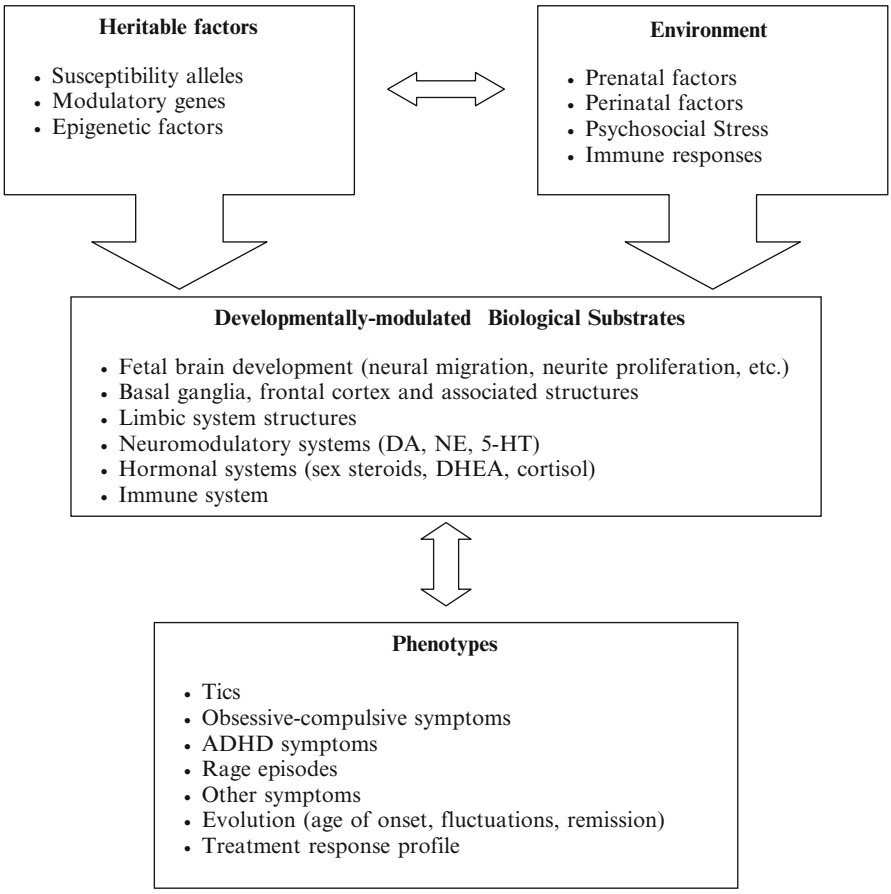

Fig. 4.1 Pathogenesis of TS (adapted from Leckman & Cohen [14])

thresholds, thus affecting symptom expression over time. Genetic, obstetric, and hormonal influences could interact during various periods of neural development, particularly during the critical time of the late prenatal and early postnatal periods, as there is a massive increase in synaptic density [102] and is characterized by an important vulnerability to ischemia [103]. Brain development is modulated by steroids, particularly brain estrogen synthesized from androgens [104]. 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 behaviors, and tantrums.

Neurobiology

No obvious neuropathological abnormality is found in the autopsied brains 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 [105–107]. MRI volumetric studies show significant differences in the striatum and pallidum of TS patients in comparison with healthy volunteers [108–111]. Caudate atrophy in childhood appears to be linked to adult tic severity [24]. Volumetric measures have pointed to local basal ganglia atrophy, but there is also evidence for local grey matter increase in the ventral striatum [112], thalamus [113], and midbrain [114]. Postmortem analyses have shown a reduction of dynorphin in striatopallidal fibers [115], an imbalance in the distribution of interneurons in the striatum and pallidum [111], and a reduction in striatal cholinergic interneurons [116], suggesting that the functional dynamics of striatopallidal circuits are altered in TS. However, these findings are still preliminary.

Functional neuroimaging data point to a dysfunction of frontostriatal systems in TS [117]. Decreased activity at rest has been reported in the basal ganglia, especially in the ventral striatum [118–122]. Changes in functional coupling involving the ventral striatum have also been reported [123]. In the orbitofrontal cortex, some authors have found increased activity [124, 125], whereas others found decreased activity [118]. In adults, the severity of tics seems to be associated with a reduction of the metabolism in the frontal cortex [126]. Stern et al. [127] showed that a cerebral activation of many regions of the brain (sensorimotor, premotor, prefrontal, cingulate and parietal cortex, basal ganglia, and insula) was synchronized to tic onset [127]. Moreover, functional magnetic resonance imaging (fMRI) data suggest that the voluntary suppression of tics affects activity in the striatum, thalamus, and frontal cortex [128]. TS patients have been shown to have a hyperactivation of the sensorimotor and premotor cortex during repetitive voluntary movements [129].

At the neurochemical level, TS may be associated with a dysfunction of dopaminergic modulation of striatal and/or frontal activity. Postsynaptic dopamine receptor binding appears to be normal [130, 131]. However, presynaptic dopaminergic activity may be abnormally high, especially in the ventral striatum [40, 132–138]. Several studies point to contributions of other neuromodulatory systems in TS. Some authors have shown lower serotonin transporter binding, with binding correlating inversely with the severity of TS [139]. On the other hand, a study performed by Haugbol et al. [140] showed increased striatal 5-HT2A binding and upregulation of the 5-HT2A system in patients with TS [140]. Noradrenergic as well as other neuropeptide systems have also been implicated [141].

Pathophysiological models of TS have emphasized the role of striatocortical circuits in the selection of voluntary responses and the concurrent inhibition of competing responses [142]. Some have also emphasized a possible imbalance in motor and limbic-striatal circuits [143]. In line with the presence of sensory and other subjective phenomena (urges, obsessions), it has been hypothesized that

sensorimotor gating deficits may be important in TS although the specific processes involved have yet to be determined [144].

Subtle neurophysiological anomalies have been observed in TS. Transcranial magnetic resonance studies have shown abnormalities in cortical excitability related to hyperactivity in TS such as short-interval cortical inhibition [145, 146]. These abnormalities may also be present in OCD [147], but it is still unclear whether they are present in less severe TS phenotypes (without behavioral comorbidities). TS is also associated with subclinical anomalies in motor skills [148, 149], voluntary saccades [150, 151], blink reflexes [152, 153], and postural control [154]. Some of these anomalies may eventually help identify endophenotypes. In parallel to the accumulating evidence for a role of frontostriatal brain circuits in the pathophysiology of TS, the same systems have been implicated in ADHD and OCS [155]. TS and its comorbidities thus represent a model for frontostriatal neurodevelopmental disorders.

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 comorbidities. It is important to remind parents and teachers 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. Special measures can be used in helping the child deal with the tics, such as decreasing stressful or embarrassing situations and organizing 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 individuals will not require any pharmacological treatment for the tics. On the other hand, if tics are causing a functional interference, pain, or social difficulties, a medical treatment should be considered.

Dopamine-Modulating Agents

Traditionally, dopamine-blocking medications have been the first-line treatment for tic disorders. This class of agents has the most compelling evidence for effectiveness

in double-blind controlled studies, with the three most studied agents being haloperidol, pimozide, and risperidone [156].

Because of their presumed lower long-term side effects profile, atypical neuroleptics such as risperidone 0.5–4 mg [157, 158] or olanzapine 2.5–10 mg should be considered for treatment of tics prior to use of the typical antipsychotics. As the risk of long-term side effects (especially tardive syndrome) in patients with TS is unknown, doses should be kept as low as possible, and tapering off these medications should be attempted periodically. A recent study looking at the side effects of antipsychotic medication in patients with TS [159] followed 73 children for a mean duration of 39.6 months and found that 45% developed lipid abnormalities and 49% developed abnormal BMI (body mass index) percentiles. Only 3 patients (4%) developed acute neurological complications: one patient developed akathisia on haloperidol, and the two other patients developed acute dystonic reactions on haloperidol and risperidone. No cases of tardive dyskinesia were reported, but the follow-up was relatively short. The role of other atypical neuroleptics such as quetiapine [160, 161] is still unknown.

Tetrabenazine, a monoamine depletor which operates mainly by depleting presynaptic dopamine, reduces dopamine release in the synaptic cleft. In adult patients, a starting dose of 12.5 mg is recommended, with gradual dose increments until efficacy or the maximum dose of 25 mg t.i.d. is reached. This medication may be efficient for the treatment of tics and, unlike neuroleptics, is not associated with any major long-term risk if given at low doses [162]. However, this drug has the potential to induce depression and, at high doses, parkinsonism. The exact role of tetrabenazine in the therapeutic arsenal of tics, however, needs to be studied prospectively.

Alpha-2 Adrenergic Agonists

Because of contradictory results, the role of alpha-2 adrenergic agents (clonidine and guanfacine) in the treatment of tics is debatable. However, in practice, because of a low side effects profile and the absence of long-term potential risk, it is often a first-line treatment option, especially in patients with comorbid symptoms of ADHD [163–168].

Other Agents

Numerous other agents have been studied for the control of tics. However, it is difficult to draw any definite conclusions since most of these have been either open-label, small sample size, and/or have not been replicated. These agents include flunarizine [169], naloxone [170], delta-9-tetrahydrocannabinol [171], baclofen

[172, 173], ondansetron [174], levetiracetam [175–177], and dopamine agonists [178]. Although sometimes used in children and adults, there have been no controlled studies of the efficacy of benzodiazepines in the treatment of tics [179]. Botox has also been suggested as an alternative treatment for vocal and localized motor tics [180–182].

Behavior Therapy

There is strong evidence from randomized controlled trials to support the use of behavioral therapy (habit reversal training) as an alternative or adjunct treatment in TS [183–186]. However, this often requires a significant investment of time, and the long-term benefits of these interventions are still unknown [187].

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 variable results. None of these procedures have been studied in large controlled or case-control studies [188]. More recently, because of the lower side effects profile and potential access to deeper regions, deep brain stimulation has been advocated as an alternative surgical treatment for cases with severe uncontrolled tics [189, 190]. A recent review has shown this procedure to be highly effective in selected cases [191]. Porta et al. [192] reported the evolution of 15 patients with refractory TS who underwent bilateral thalamic DBS implantation over a 24-month period. They concluded to a significant improvement of the tics, OCS, anxious and depressive symptoms, as well as subjective perception of social functioning/quality of life [192]. In a recent article looking at the long-term outcome of 2 patients after thalamic DBS for TS [193], the authors reported sustained efficacy with prolonged tic reduction (6 and 10 years). However, one of the patients developed some tolerance with a slight reduction of efficacy over time. Larger studies are required to better understand the long-term outcome of TS patients treated with DBS. For OCD with or without tics, other targets, such as the ventral striatum/ventral capsule region (near the nucleus accumbens) and subthalamic nucleus, have been used [194, 195]. Personalized DBS targets taking into account comorbidity may yield better overall results in the future. Nevertheless, to fully understand the role of brain stimulation in TS, the scientific community will need to develop more complete pathophysiological models of the disorder and design larger trials to specify what sites and approaches work best for the 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 comorbid conditions may prove to be more beneficial overall. For OCS, behavioral therapy such as exposure and response prevention has clearly shown to be effective [196]. When significant anxiety is present, SSRIs (such as s-citalopram, fluoxetine, and sertraline) or SNRIs (venlafaxine, duloxetine) should be tried. Starting at a very low dose may help prevent paradoxical agitation at the onset of treatment. Use of SSRIs may reduce anxiety, irritability, and indirectly, tic severity. Low-dose benzodiazepines (such as clonazepam 0.25–0.5 b.i.d.) may also reduce both anxiety and tic severity, but impulse-control symptoms should be closely monitored, since they may be exacerbated [197].

For treatment of depression, several consensus guidelines have been published, with SSRIs or SNRIs being the first-line treatments [198]. However, in children, only fluoxetine has clearly been shown to be superior to placebo [199]. SSRIs and SNRIs have been studied in idiopathic OCD where, as stated before, distress, doubt, and anxiety are significantly more intense than in TS-related OCS. In fact, hoarding and symmetry in OCS, mostly seen in TS, are predictive of poorer treatment response to SSRIs [36]. 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 a good response to neuroleptics rather than SSRIs, as would be expected of tics [34].

Treatment of Impulse-Control Problems

Familial intervention should be tried first when facing impulse-control difficulties in TS patients. Pharmacological interventions may be necessary, but efficacy and safety data in children are scant [200]. For rage outbursts and SIB, atypical neuroleptics may be considered, with regular monitoring of potential tardive motor complications and metabolic syndrome.

Treatment of Antisocial Behavior, Oppositional Behavior, and ADHD

Social and familial interventions are key for patients showing relational behavioral problems like antisocial 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 comorbid ADHD is present, ADHD treatment may be beneficial.

A consensus ADHD algorithm for TS patients has been recently published and suggests starting with psychostimulants (methylphenidate or amphetamines, preferably long-acting) followed by atomoxetine and clonidine/guanfacine [201]. Slow-release or extended-release bupropion may also be helpful in ADHD. Although tic severity may increase with psychostimulants, one study has documented, on average, less tics after starting psychostimulants as compared to placebo [41].

A recent meta-analysis regarding the treatment of ADHD in patients with comorbid tic disorders has concluded that stimulants seem to offer the greatest and most immediate improvement of ADHD symptoms, without any clear worsening of the tics. Secondly, use of alpha-2 agonists offers the best combined improvement of both tic and ADHD symptoms. Finally, atomoxetine and desipramine offer additional potential benefits for the treatment of ADHD in this group of patients [202].

Treatment of RLS and Sleep Disturbances

TS patients with RLS, if severe enough, may seek specific treatment. Dopamine agonists are particularly effective [203]. Levodopa may be considered, but augmentation and morning rebound will develop in more than 50% of patients [204]. Clonazepam is helpful for light to moderate nighttime RLS associated with insomnia. Gabapentin has shown some effects; opiates are effective for refractory patients (see [205] for treatment guidelines).

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 delay, 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 [206].

Conclusion

TS is a common lifelong disorder, characterized by multiple motor and vocal tics. It is frequently associated with a variety of comorbidities such as ADHD, OCS, behavioral problems, and sleep disorders. Although thought to have a significant genetic predisposition, etiology and pathophysiology remain unclear. Treatment is aimed at improving the most significant symptoms, using a multidisciplinary approach and a variety of medications in more severe cases.

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