Tricky "Ticcy" Case: Tics/Tourette Syndrome with Co-occurring OCD

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Erica Greenberg, Angela Essa, and Jeremiah M. Scharf

Case

Jackson is an 11-year-old left-handed boy who presents to the outpatient clinic with what his parents describe as repetitive movements and sounds that occur throughout the day and that he feels he is "unable to control."

His parents report that, a little over a year ago, Jackson developed repeated eye blinking and sniffing, even though he had no history of seasonal allergies. His movements subsequently changed over time, began to involve his arms and trunk, and appeared more complex in nature. While at first Jackson only had simple head and eye movements, he developed shoulder shrugging, abdominal tensing, and an ordered sequence of movements where he would turn his head to the left, pound his

E. Greenberg
OCD and Related Disorders Program, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
e-mail: egreenberg@partners.org

A. Essa
Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
e-mail: aressa@partners.org

J. M. Scharf (✉)
OCD and Related Disorders Program, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

Division of Movement Disorders, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

Division of Cognitive and Behavioral Neurology, Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA
e-mail: jscharf@partners.org

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fist on the table, and grunt. The sniffing continued, but he also developed repetitive throat clearing, a high-pitched squeak, and saying "I see" in a stereotyped manner. When asked to stop, Jackson told his parents that he couldn't. He described an uncomfortable feeling in his body just before he engaged in the movement or sound and that he "felt like he would explode" if he didn't let them out. These movements and sounds seemed to increase when he was either bored, tired, or very excited and to worsen while watching TV and doing homework and when he was worried about an upcoming event. They also improved when he was on the soccer field. His parents have noticed that the movements often occur in "bouts" and worsen whenever someone asks him about them. Jackson initially could hold in, or suppress, the movements/sounds, but over the last few weeks, they have become constant, occurring in school and causing disruption for him and the class. His parents report that they brought Jackson to the pediatrician 6–8 months ago who diagnosed him with "benign tics." She treated him with various alpha-2 agonists, including short- and long-acting clonidine and guanfacine (total daily dose of 0.4–0.6 mg and 4–6 mg, respectively), but these either made him too sleepy or moody and did not reduce his tics.

Jackson lives at home with both parents and an 8-year-old sister. He is in sixth grade at a local middle school. Regarding family history, mom reports that she has obsessive-compulsive disorder, and dad states that he "probably has ADHD." On further inquiry, they report that Jackson was diagnosed with ADHD at age 5, when his Kindergarten teacher and soccer coach both described a pattern of inability to sit still, difficulty paying attention, and increased impulsivity compared to other children his age. He was started on mixed amphetamine salts with improvement both in sustained attention and impulsivity. He remained on stimulants for 3 years, but his parents stopped them at age 8 after he began to fall off the growth curve due to decreased appetite. In retrospect, his parents realized that shortly after starting stimulants, Jackson developed intermittent "sniffles" for about a month, even though he didn't appear to be sick.

Right before fourth grade, Jackson's family moved to another state. He began to have more difficulty separating from his mother, and when school started, he would cry, have tantrums, and would refuse to leave the car upon drop-off. Additionally, he developed a slew of worries, including how he would perform in school despite having good grades and whether something bad might happen to him or his parents. These worries sometimes made it difficult for him to fall asleep at night. He also developed headaches and stomachaches and would leave class to visit the nurse multiple times a day.

Given Jackson's new symptoms of impairing anxiety, his pediatrician diagnosed him with generalized anxiety disorder and recommended that he work with a psychologist to receive cognitive behavioral therapy (CBT). As these symptoms were causing significant impairment and distress in school and at home, she also recommended starting fluoxetine, a selective serotonin reuptake inhibitor (SSRI). Jackson tolerated 10 mg without significant reduction in symptoms or side effects, but upon increasing to 20 mg, he became "activated." His parents describe that he suddenly

developed excessive energy, was more irritable, angry, and rageful, and had difficulty falling asleep. As a result, his parents stopped the fluoxetine, and these symptoms/side effects subsided. They tried another SSRI, but the same activation symptoms returned. Jackson ultimately worked with his therapist for 6 months, which led to an improvement in his generalized anxiety.

Given the frequent co-occurrence of obsessive-compulsive disorder (OCD) in children with tic disorders, Jackson was asked further about various OCD symptoms. He describes a need for "symmetry" (if something touches one side of his body, he has to touch the other side) and a need to engage in repeated actions until he feels "just right." For example, he needs to touch his knees together in sets of threes, which sometimes prevents him from leaving the classroom at the end of class. He will also tap and touch objects. Jackson denies having any worries about contamination or dirt and germs or any need to wash his hands repetitively. He endorses no checking of lights or the TV to make sure they are off, though he does state that he will often check in with his mother to make sure he "didn't do something wrong" or to make sure that he "isn't a bad person." Jackson also states that in school he will sometimes need to reread the text or rewrite his essay if the words aren't aligned correctly. He will also feel uncomfortable when he sees odd numbers. Upon asking Jackson whether he ever gets thoughts, ideas, or images that are unwanted, upsetting, and distressing, he appears embarrassed and sheepishly admits that, for the last few months, he has been having the recurrent image of "stabbing his mother" in his head. He insists he doesn't want to do it and would never hurt anyone, but because he keeps having these intrusive thoughts, he worries that he might actually want to harm his mother. These thoughts cause him a great deal of distress, and therefore he has been avoiding any sharp objects or being in a room alone with his mother for the last 2 weeks.

In a separate meeting with Jackson's parents to gather additional history, they describe that, over the last year or so, Jackson has had episodes at least twice a week where he seems to go from "0 to 100" with rage/anger and that when he is in this state, "it's like he's not there" and "there is no reasoning with him." His parents describe that these episodes typically occur after minimal provocations or triggers, such as not getting what he wants, but also on days when his tics or OCD symptoms are bad or while struggling to finish homework. After these episodes, Jackson is always extremely remorseful and feels guilty about his actions.

As part of his assessment, Jackson and his parents together complete two clinician-administered scales. The first is the Yale Global Tic Severity Scale (YGTSS) – a clinician-administered, semi-structured scale that provides tic severity ratings for motor and phonic (vocal) tics separately and assesses tic number, frequency, intensity, complexity, and degree of interference with actions or speech (rated on a scale of 0–50). There is a separate "impairment" score (also rated 0–50), which is used to characterize effects on self-esteem, social life, family life, and school/job functioning. Jackson scores a 35/50

(moderate severity) on the tic severity component and a 30/50 for impairment, with problems in self-esteem, social acceptance (frequent teasing by peers), and school challenges secondary to tics. They also complete the Child Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) – another semi-structured, clinician-administered scale that rates OCD symptom severity in children and adolescents. Obsessions and compulsions are discussed separately, and questions assess time occupied by interference, distress, and resistance against and degree of control over obsessions and compulsions, each rated 0–4 for a total scale of 0–40. Jackson's primary obsessions include ego-dystonic thoughts about stabbing his mother and worrying that he is a bad person. His primary compulsions include checking/reassurance seeking from his parents, engaging in symmetry/"just right" behaviors, and rereading/rewriting his schoolwork. He scores a 24/40, consistent with "severe" OCD.

Diagnostic Impression

Following the interview and assessment scales, Jackson and his parents are told that he meets criteria for multiple diagnoses, including Tourette syndrome (TS), OCD, ADHD, generalized anxiety disorder, and intermittent explosive disorder (IED). However, the expert neuropsychiatrist emphasizes that while these sound like a lot of separate diagnoses, they are now considered to be different aspects of a common developmental susceptibility of overlapping brain circuits associated with TS, rather than entirely independent disorders [1, 2]. The discussion begins by describing TS and how Jackson fulfills criteria for the disorder by having at least two motor tics and one vocal tic for at least a year (starting before age 18). Furthermore, given that TS, OCD, and ADHD all share certain genetic underpinnings, it is not surprising that his mother has OCD and his father has ADHD. The neuropsychiatrist also notes that Jackson's progression of tic symptoms is well-described, in that tics typically begin between ages 5 and 9, often as simple (one muscle group per tic) motor tics in the head/neck region and, by definition, change in frequency and intensity over time and involve other parts of the body usually in a proximal-to-distal fashion with more coordinated or purposeful appearing tics arising later in a subset of children. His parents are relieved to learn that socially inappropriate utterances such as cursing ("coprolalia") are *not* required for the diagnosis and in fact only occur in ~15% of TS patients. The neuropsychiatrist then discusses that the distinction between TS and a persistent tic disorder with only motor or only vocal tics is completely arbitrary and that all tic disorders likely exist on a continuous developmental spectrum. Lastly, Jackson's parents learn that tics tend to peak at an average age of 10–14 and that most children's tics improve in late adolescence/early adulthood, with ~1/3 experiencing minimal/no tics, ~1/3 with mild tics, and ~1/3 or less with moderate or severe tics as adults.

The neuropsychiatrist then focuses on OCD and notes that OCD affects 30–50% of children and adolescents with TS. Jackson meets criteria for OCD, since his symptoms take up >1 h a day and cause clinically significant distress/impairment. The

clinician next explains that TS and OCD have overlapping genetic susceptibility and that some of Jackson's OCD symptoms can be described as "tic-related OCD" or "Tourettic OCD," which may be genetically more similar to TS than to OCD without tics [3]. Tic-related OCD tends to have an earlier age of onset than the more common late adolescent/young adult onset for typical OCD and is more male-predominant than adult-onset OCD. While patients with TS can have any of the OC symptoms present in patients with OCD without tics, tic-related OCD may be more likely to include aggressive, sexual, and religious obsessions and symmetry, touching, counting, and "just right" compulsions. It can be difficult to discriminate between a compulsive tic and a complex compulsion in tic-related OCD, but one helpful distinction is that compulsions are often performed to relieve thoughts/feelings of anxiety or disgust, while tics are often performed in response to unpleasant internal sensory phenomena ("premonitory urges"). However, these tic/OCD overlap symptoms typically require treatments targeting both tics and OCD to achieve symptom reduction.

Though not a focus at the initial visit, the neuropsychiatrist also discusses that ~85% of those with TS in a clinical setting have at least one co-occurring neuropsychiatric condition, with ~50% having co-occurring ADHD, 30% having non-OCD anxiety disorders, and ~15% to 30% having co-occurring intermittent explosive disorder (characterized by at least two non-premeditated aggressive outbursts weekly, out of proportion to the trigger, and often associated with distress/remorse) [4].

Neuroanatomy and Pathophysiology

Neuroimaging, neurophysiology, and neuropathologic studies in humans, along with experimental data from nonhuman primates, have implicated dysregulated development and/or functioning of orchestrated circuits between the cerebral cortex, basal ganglia, and thalamus, i.e., cortico-striato-thalamo-cortical (CSTC) loops, in TS pathophysiology (Fig. 3.1) [2]. While the basal ganglia have traditionally been viewed as the "habit system" of the brain, playing a role in goal-directed motor planning as well as storing, selecting, and executing overlearned (automatic) motor plans, they are now understood to comprise limbic and associative domains as well, in which emotional, motivational, and cognitive information is processed to influence movement and behavior. These functional domains are thought to map onto parallel sensorimotor, limbic (emotional), and associative (cognitive) CSTC loops. In this context, the frequent co-occurrence of TS, OCD, and ADHD is thought to arise from a shared developmental dysregulation within these parallel CSTC circuits that results in overactive formation of automatic motor plans (tics), repetitive intrusive thoughts that trigger cognitive and motor rituals (obsessions/compulsions), and difficulty prioritizing intended thoughts as well as filtering unwanted thoughts/movements (inattention and hyperactivity/impulsivity).

Within the sensorimotor basal ganglia, like the corresponding areas of sensorimotor cerebral cortex, there is further organization of motor CSTC circuits to reflect a body map, or "homunculus," ascribing certain regions to control motor plans involving the face, arms, and legs, as well as separating simple and complex

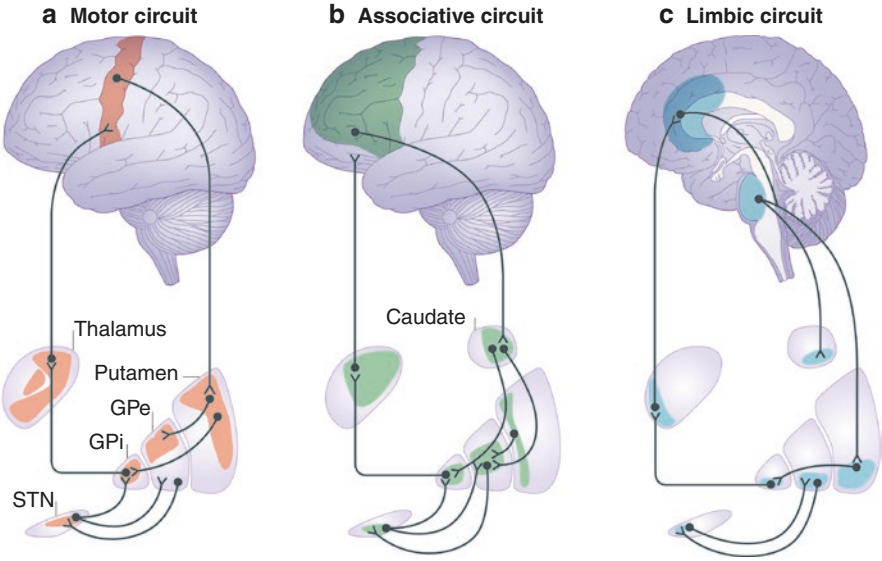

Fig. 3.1 Functional subdivisions of sensorimotor, cognitive/associative, and emotional/limbic cortico-striato-thalamo-cortical (CSTC) circuits. The basal ganglia receive a broad range of descending inputs from across the cerebral cortex (as well as from other subcortical regions) that are processed in parallel, partially overlapping, circuits that project back to the thalamus and subsequently to the frontal cortex. Each of the basal ganglia nuclei – the striatum (caudate, putamen, nucleus accumbens), the globus pallidus externa (GPe) and internal (GPi), and the subthalamic nucleus (STN) – are organized into functionally related subregions that process motor (a, orange), associative/cognitive (b, green), and limbic (c, blue) information that are thought to aid in prioritization, selection, and regulation of movements, thoughts, and emotions. Shared dysregulation in the development and/or maintenance of these parallel CSTC circuits are thought to underlie the frequent co-occurrence of Tourette syndrome, OCD, and ADHD. (Figure reprinted from Jahanshahi et al. [2], and adapted from Rodriguez-Oroz et al. [13], Copyright (2009), with permission from Elsevier)

movements [5]. This somatotopic organization may correspond to clinical observations that tics generally present first in the eyes, head, and neck, with subsequent progression in more severe cases to involve arms and legs, as well as coordinated complex movements.

An additional component of CSTC circuit regulation is the anterior cingulo-insular network (aCIN), also known as the "salience network," which has been identified through functional neuroimaging studies to play a common role in psychiatric illness [6]. The salience network consists of core cortical regions/nodes, including the dorsal anterior cingulate cortex (dACC) and the left and right anterior insula, as well as corresponding non-motor regions of the basal ganglia, ventral tegmental

area (VTA) of the brainstem, and lateral cerebellum (i.e., the structural components of a CSTC circuit). This network is thought to mediate "top-down" processing ("cognitive control") as well as evaluation and prioritization of external and internal sensory and motivational cues, two higher-order processes that are disrupted in most psychiatric disorders. In the case of TS, OCD, and ADHD, the salience network could be conceived as acting (or failing to act) as a brake for lower-order dysregulated CTSC loops and could potentially mediate the frequently observed impairments in impulse control in the most severely affected TS patients.

As noted above, TS, like other neuropsychiatric conditions, is now viewed primarily as a developmental circuit disorder. In this context, neurotransmitter abnormalities in TS likely arise as a secondary result of dysfunctional CTSC circuits. Each of the three major neurotransmitter systems in the basal ganglia – dopaminergic projections from the substantia nigra and VTA to the striatum, excitatory glutamatergic projection neurons from cortex to striatum, as well as inhibitory GABAergic striatal projection neurons and intrinsic striatal interneurons – serves as the basis for the limited number of pharmacological treatments for TS. Typical and atypical neuroleptics acting at postsynaptic striatal projection neurons block the dopamine D2 receptor to slow circuit function; similarly, benzodiazepines act as GABA modulators to boost inhibitory components of CSTC circuits. Recent interest in glutamatergic compounds, such as topiramate for tics as well as memantine, riluzole, and N-acetylcysteine for OCD, have also arisen from observed abnormalities of neurotransmitter function in TS and/or OCD patients. However, the non-specific effects of these medications combined with incomplete knowledge of the primary pathophysiology of the disorder have resulted in high rates of side effects and treatment-refractory cases.

TS and OCD are both highly heritable and have been demonstrated to share a significant portion of genetic risk [1]. Of interest, recent cross-disorder, symptom-driven analyses in TS patients and their relatives suggest that symmetry, ordering/arranging, and counting obsessions/compulsions appear to correlate with aggregated TS genetic (polygenic) risk, while other OCD symptoms correlate best with aggregated OCD polygenic risk [3].

Treatment Strategies

In children and adolescents with TS, it is often the co-occurring conditions (e.g., OCD and ADHD) that cause the most impairment and more frequently require treatment compared to the tics themselves. That said, one often chooses to treat tics when they cause physical pain, social/functional/educational problems, and/or psychological distress. There are no disease-modifying treatments or cures for tics, and so behavioral and pharmacological treatment interventions are aimed at symptom reduction. Given the natural waxing and waning of tic severity and frequency, determining

treatment effectiveness can be challenging. There are only three medications that have US Food and Drug Administration (FDA) labeled indications for tics – haloperidol, pimozide, and aripiprazole. Thus, most pharmacological treatments are off-label [7].

Pharmacological treatment for tics should be conceptualized in three tiers, with each tier corresponding with increased efficacy but also a significant increase in side-effect risk.

Alpha-2 adrenergic receptor agonists (clonidine and guanfacine) represent first-tier treatments and are typically used for mild-to-moderate tics, especially with co-occurring ADHD. Unlike the common off-label use of nightly clonidine for sleep, alpha-2 agonists require at least twice daily dosing (or extended release formulations) to suppress tics. Atypical antipsychotics (specifically those with higher dopamine D2 receptor (D2R) potency such as risperidone, ziprasidone, and aripiprazole) are second-tier agents. The third tier is characterized by the typical antipsychotics with the highest D2R potency, specifically haloperidol, fluphenazine, and pimozide. These medications are typically quite effective, though are often not tolerated due to adverse effects.

Some specialists prefer to use tetrabenazine, a presynaptic vesicular monoamine transporter (VMAT2) inhibitor, as a second-tier alternative to atypical neuroleptics with little/no risk of tardive dyskinesia, though at higher doses this medication can cause significant sedation, weight gain, and parkinsonism and can precipitate depression in ~25% of patients. Other pharmacological agents have been trialed with mixed or limited efficacy including topiramate, benzodiazepines, baclofen, and cannabinoids.

The primary behavioral treatment for tics is Comprehensive Behavioral Intervention for Tics (CBIT) and involves habit reversal therapy (HRT) and function-based interventions, in addition to psychoeducation, parent training, and relaxation training. HRT is designed to help the patient develop an awareness of their tics (identify the premonitory urge) and then engage in a competing response that is incompatible with the tic (e.g. tensing shoulders for a shoulder-shrugging tic). Function-based interventions involve understanding and then modifying the contextual factors that may lead to increased tics. CBIT has been demonstrated in multicenter randomized controlled trials to be effective in both children/adolescents and adults, with a treatment effect comparable to that of atypical antipsychotics [8].

Pediatric OCD can be effectively treated with behavioral and pharmacological treatment interventions as well. The gold-standard behavioral treatment for OCD is a subtype of CBT called exposure and response prevention (ERP). In ERP, the patient is exposed to symptom-specific stimuli to provoke their obsessions and accompanying distress/anxiety and is then prevented from engaging in the associated compulsion/avoidance behavior. Serotonergic agents are currently the most effective pharmacological treatment for OCD, with selective serotonin reuptake inhibitors (SSRIs) being comparably effective and the gold standard first-line treatment. Clomipramine is superior to SSRIs in terms of OCD symptom reduction but has prominent side effects/increased risk of toxicity and thus is not used as first-line treatment. A landmark study (the Pediatric OCD Treatment Study) in 2004 demonstrated that for youth with at least moderate OCD, the combination of medication

(sertraline) and therapy (CBT) was superior to either medication or therapy alone, which were both superior to placebo [9]. Clinicians who specialize in treating OCD and tic-related OCD often find that these patients require doses of SSRIs at the upper end of approved ranges. Interestingly, multiple studies have demonstrated that tic-related OCD tends to be less responsive to SSRIs compared to OCD without tics. Meta-analyses in adults with tic-related OCD demonstrate that augmenting with antipsychotics, specifically risperidone, aripiprazole, and haloperidol, improves treatment response compared to augmenting with placebo. Thus, a similar approach is often used in children/adolescents who haven't responded to a combination of SSRIs and CBT [10].

For ADHD, several studies have now shown that stimulants are safe, well-tolerated, and effective in treating ADHD regardless of whether there is a co-occurring tic disorder. In 2002, the Tourette Syndrome Study Group evaluated the effect of methylphenidate (MPH), clonidine (CLON), clonidine and methylphenidate (COMB), or placebo on ADHD and tic symptoms in youth with ADHD and either TS or chronic tics (CT) [11]. They demonstrated that all three treatment groups were more effective for treating ADHD than placebo (MPH better for inattentive symptoms, CLON better for hyperactive/impulsive symptoms). Somewhat surprisingly, all three treatments *were also more effective in reducing tics* (COMB > CLON > MPH > placebo); transient tic worsening was observed in ~20% of all groups, including placebo. A meta-analysis in 2015 also concluded that stimulants were well-tolerated in youth with TS and that there was no significant association between new onset or worsening of tics and stimulant use [12]. Of note, at least one study has shown that amphetamine-based stimulants may lead to worse tic symptoms.

Case Follow-Up

After the initial meeting, Jackson is referred to a local psychologist who specializes in behavioral therapy for OCD (ERP) and tics (CBIT/HRT). However, given the severity of his symptoms and ongoing distress, his neuropsychiatrist also recommends that he simultaneously restart medication. Jackson's parents were not interested in starting an alpha-2 agonist or SSRI, given these medications' previous lack of response/adverse effects. Therefore, they are informed about the pros/cons and risks/benefits of starting an atypical antipsychotic (especially weight gain and potential metabolic sequelae). He is started on risperidone 0.5 mg first nightly and then twice a day, to target tics. Jackson notices almost immediate improvement in his simple tics and some of his complex tics; however, he continues to suffer from OCD, including his need for symmetry and ongoing "just right" compulsions. Given that SSRI-induced activation symptoms tend to be age-dependent and risperidone has mood-stabilizing qualities that might mitigate an SSRI-induced activation response, his parents agree to a very slow titration of sertraline, and the combination of SSRI, atypical antipsychotic, and behavioral therapy is ultimately very helpful. Two years later, with combined medication and behavioral therapy, Jackson's tics, OCD, and anxiety symptoms are all markedly improved, though he continues to have problems with inattention, distractibility,

and organization, particularly now that he has to change classrooms and keep track of his homework assignments himself in middle school. His neuropsychiatrist refers him for neuropsychological testing, which shows a high average IQ, ADHD combined subtype, and a specific learning disorder (seen in 20–30% of youth with TS). With these results, his parents work with his school to develop an Individualized Education Plan (IEP) to better support Jackson. Additionally, they are reminded that there is no longer a contraindication to using stimulants in those with TS and that he may have a better response to methylphenidate-based stimulants than to the mixed amphetamine salt stimulants he had tried in the past.

Lessons Learned About Neuropsychiatry

1. Tics are not *caused* by anxiety – the phrase "nervous tic" is an erroneous assumption that correlation is the same as causation. Through understanding that tics and OCD arise from abnormal development of parallel CSTC circuits that incorporate both internal mood states and the external environment, the neuropsychiatrist understands the biological basis and causes of tics and OCD, as well as the many triggers that cause symptom exacerbation.
2. While tics may be the reason parents bring children for consultation, co-occurring "hidden" neuropsychiatric disorders often cause greater impairment. In addition, since mood/anxiety symptoms and psychosocial dysfunction can exacerbate tics, treating the whole patient (and family) is often necessary for treatment-refractory TS.

Clinical Pearls

- Thirty to fifty percent of youth with TS have co-occurring OCD. For children and adolescents with tic-related OCD whose OCD symptoms don't respond to SSRI monotherapy, it may be beneficial to augment with antipsychotic treatment.
- "Tourettic" OCD appears to have a distinct phenotypic profile with younger age of OCD symptom onset, aggressive/taboo obsessions, and "just right," symmetry, and counting compulsions. Its genetic architecture appears to be more similar to TS than to OCD without tics.
- Differentiating between complex tics and compulsions in tic-related OCD can be challenging and often represents an overlap of both disorders. In general, compulsions are driven by the need to eradicate or avoid thoughts/feelings of anxiety or disgust, and tics are driven by uncomfortable internal sensory phenomena (premonitory urges).
- Stimulants are no longer absolutely contraindicated for treating youth with TS and co-occurring ADHD (especially methylphenidate-based stimulants). Stimulants are least likely to exacerbate tics when started at subthreshold doses and increased slowly, either alone or combined with alpha-2 agonists.

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