

Fits, Tantrums, and Rages in TS and Related Disorders

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Published online: 8 August 2015
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Abstract Tourette syndrome (TS) is a neuropsychiatric disorder of childhood onset characterized by motor and phonic tics. In the majority of cases, psychiatric comorbidity complicates TS, manifesting with a wide range of affective and behavioral disturbances. Aggressive symptoms are relatively common in TS and have adverse impacts on family functioning and quality of life. The etiology of such symptoms may reflect a complex interplay among neurobiological, genetic, and environment factors. This paper provides an update on aggressive symptoms in TS with focus on explosive outbursts or “rages” and self-injurious behaviors. Recent studies highlight the association between aggression and common psychiatric comorbidities as well as the role of psychosocial influences. Aggressive symptoms in TS appear associated with tic severity and certain psychiatric comorbid disorders including attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), and mood disorders. Although still limited, pharmacological and non-pharmacological evidence-based treatments are emerging.

Keywords Tourette syndrome · Explosive outbursts · Rages · Aggressive symptoms · Disruptive behaviors

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder of childhood onset characterized by waxing and waning of motor and phonic tics present for over 1 year [1]. Meta-analyses of population-based prevalence studies estimate TS in 0.52–0.77 % of youth [2–4]. Tic severity appears to peak between ages 10–12 years and often declines significantly by late adolescence, although a minority may experience persistent and disruptive tics into adulthood [5, 6, 7]. Co-occurring psychiatric conditions are extremely common and associated with greater overall morbidity in TS [8–10]. Based on the largest comprehensive study of psychiatric comorbidity in TS to date, the estimated lifetime prevalence of any psychiatric comorbidity in TS is 85.7 % with over half suffering from two or more psychiatric disorders [11••]. Most individuals with TS develop psychiatric symptoms during childhood and meet diagnostic criteria for obsessive–compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD), mood disorders, non-OCD anxiety disorders, and disruptive behaviors also occur with increased frequency [11••].

Aggressive symptoms and problems with anger control appear common in TS and cause considerable morbidity [12–15, 16••]. Results from a large international survey of TS specialists indicated that 37 % of all TS patients reported anger control problems at some point in their life and 25 % reported currently experiencing anger control problems [17]. In a study of 58 Swedish schoolchildren with TS, teachers reported 35 % of the children had major problems with aggression [14]. Parents and teachers reported significantly higher ratings of anger and externalizing problems in a clinical

This article is part of the Topical Collection on *Tourette's Syndrome*

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study of 25 children with TS when compared with that in healthy controls [18•]. Early literature on aggressive symptoms in TS was limited primarily to case series, retrospective studies, and relatively small clinical trials; limitations of recent large epidemiological studies include varying methodologies for assessing and characterizing aggressive symptoms and their severity [19]. Meanwhile, clinicians face the need to better recognize, evaluate, and appropriately treat these common and highly disruptive symptoms in their TS patients. This paper will briefly discuss predatory/non-reactive and non-predatory/impulsive aggression, describe the phenomenology of aggressive symptoms in TS and associated psychiatric disorders, consider known and potential etiologies of such symptoms, and highlight the emerging evidence-base for pharmacological and non-pharmacological treatments of affected individuals.

Pathological Aggression

Some aggressive behaviors occur during normal development in early childhood. “Temper tantrums” are episodes of severe frustration and anger that may involve screaming, falling to the floor, biting, or head banging. These behaviors are most commonly observed in children ages 3–5 years; up to 83.7 % of preschoolers were found to have temper tantrums [20]. Temper tantrums become much less frequent as children mature and develop the ability to inhibit unacceptable impulses and actions [20, 21]. More extreme aggression towards people or animals and severe destruction of property are associated with later development of conduct disorder [22]. Pathologic aggression describes aggressive behaviors that are age inappropriate, inapt for social context, or excessive in intensity, duration, and frequency [23]. Up to 60 % of referrals to outpatient child psychiatric clinics are explicitly for evaluation and treatment of aggression [22, 23].

Aggressive behaviors are classified as proactive/“non-impulsive” or reactive/“impulsive” depending upon key features. Proactive or “non-impulsive” aggression is characterized by aggressive behaviors that are premeditated and performed to attain a specific goal, typically accompanied by low levels of physiological arousal and limited guilt or regret [24, 25]. Reactive aggression or “impulsive aggression” is spontaneous, without obvious intent or organization, usually triggered by acute frustration, and is accompanied by high levels of physiological and emotional arousal [24, 25]. Causes of aggressive symptoms are diverse and may include environmental factors such as prenatal exposure to alcohol, drugs of abuse, and lead poisoning as well as psychosocial factors including poverty, malnutrition, and chaotic home environments [26]. Victims of physical, sexual, or emotional abuse are all at higher risk for symptoms of pathologic aggression [23, 26, 27].

Aggressive symptoms are frequent in other psychiatric conditions including autism spectrum disorder (ASD), ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), alcohol and/or substance abuse disorders, bipolar disorder (BD), intermittent explosive disorder (IED), and the relatively newer DSM-V diagnostic entity “disruptive mood dysregulation disorder” (DMDD) [1]. Impulsive, unpredictable aggressive outbursts are cardinal symptoms of IED and may include verbal tirades or physically aggressive displays that are grossly out of proportion to the preceding precipitant or stressor causing distress, financial or legal consequences, and/or impairment of function. Such outbursts must occur twice a week for at least 3 months [1]. DMDD is also characterized by the onset of severe and recurrent developmentally inappropriate temper outbursts that occur three or more times each week for at least 1 year or more with onset in childhood; these outbursts are also grossly out of proportion in intensity or duration to the situation [1, 28]. However, in contrast to IED, between outbursts children with DMDD experience a persistently irritable or angry mood, most of the day and nearly every day, present in at least two settings (e.g., at home, at school, or with peers), severe in at least one setting, and present for at least one or more years [1]. Increased irritability, disinhibited anger, and aggression can also occur in a number of other movement disorders such as Huntington’s disease or Wilson’s disease and from traumatic brain injury, dementias, or encephalitis [29, 30]. Pediatric acute onset neuropsychiatric syndrome (PANS) characterized by both early onset OCD and tics may manifest with severe anxiety, emotional lability, irritability, highly oppositional behaviors, and aggression ([31]. PANS should be considered in any child with new, abrupt onset of OCD with or without tics symptoms showing aggression, particularly before making a diagnosis of IED or DMDD.

Neurobiology of Aggression

Pathological aggression can result from abnormal development or damage to areas of the brain involved in executive function and affective regulation [32]. The amygdala regulates aggressive behaviors by receiving sensory input from the thalamus and cortex; if an aggressive stimulus is present, the amygdala signals a response through the hypothalamus to the periaqueductal gray [33]. Reduced amygdala volumes, heightened reactivity to socially threatening stimuli, and dysfunction of the limbic prefrontal regions (i.e., orbitofrontal cortex) and of the ventral striatum have all been associated with aggression [25]. The major transmitters involved in the neuroanatomical loops that enable threat assessment and promote appropriate action (i.e., “fight” or “flight”) include dopamine, serotonin, and norepinephrine [23, 25]. Imbalances of these neurotransmitters in the prefrontal cortex, or of

excitatory glutamate and inhibitory gamma-aminobutyric acid in the subcortex, can lead to increased aggression [25, 27]. Increased testosterone levels and low cortisol levels are also associated with aggressive behaviors [23, 33].

Aggressive Symptoms in TS

Aggressive symptoms in TS encompass both non-impulsive and impulsive aggressive behaviors. Both clinically referred TS studies and investigations using community samples report similar highly disruptive aggressive symptoms that are primarily although not exclusively impulsive in nature [5, 16•, 34, 35•]. This paper will highlight the two most commonly clinically encountered aggressive symptoms in TS: explosive outbursts and self-injurious behaviors (SIB). Some individuals with TS also describe urges to make insulting remarks or perform other socially disruptive, inappropriate behaviors [36, 37•]. While the relationship of such behaviors with explosive outbursts remains unclear, these non-obscene socially inappropriate symptoms (referred to by some investigators as “NOSIS”) appear aggressive and may result in legal problems [37•].

Explosive Outbursts/“Rages”

Explosive outbursts (also referred to as “Rage Attacks”) are severe and recurrent impulsive/reactive episodes of anger. These symptoms are a leading cause of morbidity in TS and have been reported worldwide [12, 17, 38]. Studies using clinically referred samples suggest that approximately 25–70 % of individuals with TS also report problems with uncontrollable anger and, when present, cause significant disruption [16•, 19, 38–44, 45•]. The onset of explosive outbursts in TS typically occurs during childhood and may herald a particularly agonizing period for family and peer relationships, often derailing normal psychosocial development and academic progress. The clinical phenomenology of explosive outbursts in TS has been explored using modified DSM-IV diagnostic criteria for IED [13, 35•, 38, 40]. Approximately 23–40 % of clinically referred TS subjects report distressing behavioral symptoms of this type: sudden unpredictable anger, irritability, temper outbursts, and aggression but due to lack of systematic evaluation, their prevalence and etiology remain unknown [19].

Like IED, explosive outbursts in TS occur with little to no apparent provocation or are grossly out of proportion to the stressor [39]. Common precipitants include being reprimanded or corrected, feeling frustrated by failure to get one’s way, or by confrontation with a change in routine or schedule [13, 38]. Also, like IED, explosive outbursts in TS may result in the physical mutilation and destruction of property or involve devastating verbal assaults on loved ones [39].

Explosive outbursts are sometimes preceded by a mental or sensory urge, almost always accompanied by heightened physiological arousal, typically experienced as uncontrollable and distressing, and frequently accompanied by subsequent shame with remorse [13]. This latter prosocial trait is in contrast to the limited empathy, more pervasive and enduring antisocial activities such as stealing, lying, and serious violations of rules that characterize those with Conduct disorder (CD) [1]. In addition, individuals with explosive outbursts and TS do not usually have a family history of aggressive, violent behaviors, arrests, or legal encounters as is typical with CD. Unlike DMDD, once the explosive episode concludes, there may be a sensation of increased “calm” or even fatigue, although a subset of children with TS and explosive outbursts appear to remain highly irritable [13]. Surveys of explosive outbursts completed by parents of children with TS report that these episodes occur most frequently at home and are most commonly directed towards a parent, usually the child’s mother although less frequently towards siblings, pets, and property [13, 40]. It appears that these episodes are much less likely to occur when the child with TS is at school or in other settings [13, 38].

Current evidence suggests that the etiologies underlying explosive outbursts in TS may be both phenotypically and genotypically diverse, resulting from a variety of psychological, biological, and environmental conditions [11•, 13, 19, 35•, 46].

Self-Injurious Behaviors

Self-injurious behaviors (SIB) comprise symptoms that are deliberate, repetitive infliction of self-harm without suicidal intent. SIB occur in 14–60 % of all patients with TS and have been reported to be correlated with tic severity, high levels of obsessiveness and hostility, and with increasing number of comorbid psychiatric disorders [16•, 17, 47–49]. These self-directed aggressive symptoms include moderate self-injury by repetitive poking, pinching, slapping, biting, or more severe and complex aggressive behaviors directed towards self such as violent head banging, breaking fingers, extracting teeth, or causing facial fractures and may occur in even mild cases of TS [50]. A study examined nearly 300 subjects with TS revealed that mild/moderate SIB correlated with the presence of obsessive–compulsive symptoms (including aggressive obsessions or violent compulsions), with the presence of obsessive–compulsive disorder (OCD), and with the overall number of obsessions. Severe SIB correlated with variables that related to both affect and impulse dysregulation including episodic rages/explosive outbursts and increased risk-taking behaviors [48]. A large survey of clinicians worldwide who treat TS reported rates of SIB as higher in those TS individuals with comorbid ADHD; the age at onset of SIB was found to be 7.4 years in the TS+ADHD group, as compared with 10 years

in the TS–ADHD group [51]. A clinical investigation of rage attacks in Japanese youth with TS found that subjects with aggression were also more likely to engage in self-injurious tics [38].

Aggressive Symptoms in TS and Tic Severity

Recent evidence points to a relationship between aggressive symptoms and tic severity. Phenotype analyses from participants in a large genetic study by Mathews et al. show that mild/moderate and severe SIB correlated with tic severity [48]. A subsequent analysis of 218 TS from this same international cohort demonstrated an association between worsening tic severity, lower age of onset of tic disorder, and increased aggressive behaviors [35]. Robertson et al. also reported a significant association between tic severity and the presence of aggressive behaviors in 578 clinically referred cases of TS [16]. A recent clinical study of 101 clinical patients with TS showed a significant association between tic severity and higher levels of irritability [52]. However, others have failed to find a direct relationship between tic type or severity and aggressive symptoms [38, 40].

Aggressive Symptoms in TS and Co-occurring Psychiatric Disorders

Increased risk for explosive outbursts and other aggressive behaviors in TS appear highly associated with co-occurring psychiatric disorders. Several studies have shown that aggressive behaviors in clinically referred cases of TS closely relate to comorbid OCD, ADHD, and ODD [13, 17, 19, 34, 35, 39, 40, 44, 53]. A recent retrospective clinical study of 92 youth with TS showed elevated behavioral problems including aggression and emotional lability on Child Behavior Checklist (CBCL) when compared with healthy controls, and those with comorbid OCD, ADHD, or combined ADHD+OCD had significantly higher levels of disruptive behaviors than those with TS only [53]. There were no differences in behaviors between subgroups of TS youth with comorbid conditions [53]. Improved recognition and effective treatment of co-occurring psychiatric conditions in TS may reduce overall psychosocial stress, which in turn may reduce tic severity [54]. The net effect may result in improved quality of life and functioning with diminished frequency and intensity of explosive outbursts [35, 41, 55].

Aggression in TS and ADHD

ADHD is the most common co-occurring psychiatric morbidity in TS, typically presenting prior to onset of tics and associated with considerable adverse effects on academic

performance, peer relationships, and overall functioning in TS [53, 56]. Among clinical populations, 60–80 % of TS patients have comorbid ADHD [17, 43, 57], although frequencies are lower (i.e., 17–18 %) in population-based studies [58]. Hischritt et al.'s recent cross-sectional study of prevalence rates in 1374 individuals with TS reported 54.3 % had co-occurring ADHD and that increased rates of comorbid TS and ADHD suggest a shared neurobiological and genetic basis [11]. Some investigators suggest that ADHD symptoms emerging after tic onset may be part of the underlying tic syndrome [59]. Supporting this hypothesis, a factor analysis of 639 patients with TS identified ADHD and impulsivity, coupled with aggressive behaviors, as one of three significant factors that account for 48.5 % of symptomatic variance in TS [44]. It has also been postulated that many of the disinhibited behaviors (including aggression) seen in TS are due to ADHD comorbidity and unrelated to TS per se [16]. Others suggest that until the mechanisms that underlie both ADHD and TS are better clarified, it may be preferable to consider ADHD and TS as “co-occurring” or “co-existing” conditions [60].

Combined ADHD and TS commonly co-occurs with other comorbid disorders including OCD, mood disorders, ODD, and conduct disorders [16, 51, 57]. ADHD is also associated with sleep difficulties, a combination that may further increase risk for aggressive behaviors in TS. A clinical study of children with TS and/or ADHD showed that subjects who had more arousals from sleep were more likely to display conduct disorder, hyperactivity/immaturity, and restless/disorganized behaviors [61].

Disentangling overlapping symptoms from co-occurring multiple categorical psychiatric diagnoses has further complicated our understanding of aggressive symptoms in combined TS and ADHD. Furthermore, clinical phenotypes evolve during development as emphasized by findings from a retrospective study of the long-term clinical course of TS in 100 clinically referred patients who received semi-structured assessments and rating scales of tics, OCD, anxiety, and ADHD were re-assessed after 10 years [6]. This study demonstrated that all patients who presented with TS+ADHD at the onset of treatment showed a different clinical phenotype at 10-year follow-up: 62 % were subsequently classified as TS-only, 35 % as TS+OCD, and 2 % were classified as TS+ADHD+OCD. In the subjects who initially presented with TS+ADHD+OCD, only 14 % showed the same clinical phenotype at 10-year follow-up while the majority no longer displayed ADHD symptoms [6].

Much evidence shows that rates of aggressive behaviors do not differ between subjects with TS and healthy controls, whereas those with comorbid TS+ADHD demonstrate similar rates of aggression as subjects with ADHD alone [56, 62–66]. Children with TS and ADHD show subtle deficits in emotional-processing tasks, particularly of anger, relative to healthy controls and TS-affected children without ADHD

[67]. A clinical study that compared problems with executive functioning in children with ADHD, ASD, and TS relative to healthy controls found increased problems with regulating emotions in children with TS [68•]. A study that compared 80 adults with TS-only to 64 adults with TS+ADHD using clinical interview with standardized ratings revealed more depression, anxiety, and “maladaptive behaviors” including aggression in the TS+ADHD group [69]. Comorbid ADHD has also been associated with increased irritability in adults with TS [52••].

Aggression in TS and Disruptive Behavior Disorders

ODD commonly co-occurs with TS and chronic tic disorders, presumably through its association with ADHD, and may precede development of CD [1, 51]. A worldwide survey of 6805 cases submitted by TS specialists estimated 12.3 % had comorbid ODD or CD [51]. In their large cross-sectional prevalence study, Hirschtritt et al. estimated 29.3 % prevalence of ODD and 3.2 % prevalence of CD in individuals with TS [11••]. A study of 48 clinically referred children with TS and rage attacks that used structured interviews and rating scales revealed 42 % met criteria for ODD [13]. However, it may be important to identify particular dimensions of ODD when examining its association with rage symptoms. In a clinical study of 135 children with TS, ODD was present in 54 %; irritability symptoms of ODD such as temper outbursts were associated with obsessive–compulsive behaviors but not ADHD symptoms [70]. In a study of 578 clinically referred TS cases including both youth and adults, CD was present in 14.5 % and was significantly associated with comorbid ADHD and family history of aggressive behaviors [16••].

Aggression in TS and OCD

Depending upon methodology, estimated rates of obsessive thoughts and compulsive behaviors that reach threshold for clinical diagnosis of OCD range from 20–50 % [11••, 58, 71, 72]. Rates of OCD were 20–22 % in the Avon longitudinal population-based study [58], whereas Hirschtritt et al. reported prevalence rates of 50 % for OCD in TS using cross-sectional structured diagnostic interviews [11••].

In a Japanese study of 53 clinically referred TS patients, severity of obsessive–compulsive symptoms, not impulsivity, was associated with impairments in global functioning and the presence of obsessions involving aggression correlated with worsened global functioning [73•]. Youth with OCD without tics also experience explosive outbursts. Aggressive symptoms in OCD appear context specific: to prevent exposure to a distressing trigger, from exposure to an anxiety-provoking trigger, or as a result of disrupting ritual completion [74••]. These rage attacks, similar to those described in TS, appear to occur unprovoked or “out of the blue,” although the actual

trigger is frequently an unrecognized internal experience/obsession [74••]. Storch et al. found that more than half of the 86 youth with OCD reported experiencing rage attacks [73•]. In this study, youth with OCD and rage attacks displayed elevated OCD symptom severity and greater functional impairment compared to controls. There was a higher incidence of disruptive behavior disorders in those with rage and OCD, but no difference in rates of chronic tic disorders and ADHD [74••].

While most investigators believe explosive outbursts in TS are primarily related to ADHD symptoms, there is also evidence implicating an association with OCD in TS [35•, 40]. It is possible that such discrepancies reflect shared and synergistic processes underlying both OCD and ADHD [75].

Aggression in Mood Disorders and TS

Mood disorders, including major depression and bipolar disorder may be associated with aggressive behavior. Irritability is a common symptom of both, and usually precedes reactive aggression. Rage attacks may signal atypical presentations of a depressive disorder in children or adults [27]. Various depressive symptoms occur in 13–76 % of TS patients attending specialist clinics [57, 71, 76]. Results from Hirschtritt et al. report that 26.1 % of cases met diagnostic criteria for major depressive disorder [11••].

These relatively high rates of depression in TS may reflect multiple factors, including the considerable burden of living with a chronic and socially stigmatizing disorder. Additionally, major depression in TS appears highly associated with OCD and ADHD [57]. Depression in TS has been associated with increased aggression; a study of 91 adults with TS treated at a specialty clinic, 34.1 % reported aggression towards others and 24.4 % described aggressive behaviors towards property [77]. In this study, aggression correlated with depression scores on the Beck Depression Inventory (BDI) and on the Mood Adjective Checklist (MACL) [77]. Aggressive symptoms may also be a risk factor for suicide. In a recent clinical study of 196 youth with chronic motor tic disorder (CTD), aggressive behaviors were associated with suicidal thoughts or preparatory actions [78].

Medication Treatment of Aggression and TS

The treatment strategy for pharmacological management of aggressive symptoms involves first identifying, prioritizing, and then targeting the primary underlying psychiatric condition(s) associated with aggression. The evidence base for treating aggressive symptoms in TS is generally weak, based primarily on small open-label studies or trials, using varying methodologies, and often combining pediatric and adults study subjects. Haloperidol, pimozide, and now aripiprazole

are the only psychotropic medications with FDA approval for the treatment of tics in TS and have anti-aggression properties [79]. In addition, a variety of other agents including short and long-acting alpha agonists, mixed norepinephrine-serotonin reuptake inhibitors, atypical and typical antipsychotics, and anticonvulsants are used off label to target tics and associated comorbid psychiatric symptoms including aggression [80•].

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are prescribed for treatment of depression, anxiety, or OCD in TS, although their efficacy for targeting aggression in children and adolescents remains unproven [27]. An 8-week open-label study of paroxetine in a clinically heterogeneous cohort of 45 children and adults with TS and explosive outbursts found 76 % reported that rages significantly diminished or were absent on a mean dose of 33 mg/day. Four patients discontinued paroxetine due to exacerbations of rage attacks and one patient experienced a hypomanic episode. No patient in this study met diagnostic criteria for major depression, although the majority of subjects had OCD, ADHD, or both [39]. Larger, randomized placebo-controlled trials are needed to evaluate these preliminary results. Activation, hypomania, and aggression are adverse effects associated with SSRIs that require differentiation from primary aggressive symptoms [81].

Psychostimulants

There is reasonable evidence that stimulant treatment reduces aggression in children with combined TS and ADHD and in those with comorbid ODD [82, 83]. In a double-blind placebo-controlled trial of immediate-release methylphenidate for the treatment of ADHD in 71 children age 6–12 years with TS or CTD), parent and teacher measures of oppositional defiant behavior and interpersonal peer aggression showed marked improvement with methylphenidate immediate release treatment [84]. Further analysis of this study population comparing 31 children + ODD + TS to 26 children with TS without ODD demonstrated that children with ADHD+ODD also showed comparable and significant decreases in teacher- and parent-rated measures of peer aggression when treated with methylphenidate, and teacher-rated aggression decreased at lower dosages than in non-ODD children [85].

Antipsychotics

There is increasing evidence that some atypical antipsychotics may be useful in the treatment of TS-associated rage [86••]. In a retrospective review of risperidone treatment of 49 patients with TS, 28 subjects age 5 to 18 years presented with aggressive behavior at baseline and 22 (78.5 %) showed decreased aggression scores at the end of the treatment period on a mean

dose of 2 mg/day. The most common side effects were weight gain and increased emotional lability [87]. In an 8-week treatment phase trial of olanzapine, 10 children age 7–13 years with TS and a history of aggressive behavior showed significant decreases in aggression as measured by the CBCL [88]. In a 6-week, open-label study of olanzapine in 12 children age 7–14 years with TS, aggression ratings decreased and subjects reported fewer aggressive episodes [89]. ADHD symptoms also showed significant improvements from baseline for both inattention and hyperactive/impulsivity scores [89]. Mean olanzapine dosages in these studies were 14.5 and 11.3 mg/day, respectively, and significant weight gain occurred in both trials. A retrospective observational study of aripiprazole in 37 children and adolescents age 8–18 years with TS demonstrated that explosive outbursts improved in 96 % of subjects who completed the study on a mean daily dose of 11.69 mg. Akathisia, increased mood lability, and increased agitation were primary reasons for discontinuation. Weight gain occurred in 87 % of subjects, with a mean increase of 18 lbs over the study period [41].

Other Medications

Adjunctive anticonvulsant treatment with valproate showed efficacy in treating aggression in children with ADHD and disruptive behavior disorders who are partial responders to stimulant treatment [90]. Although treatment with valproate has demonstrated some efficacy in reducing tic symptoms, it is not recommended for routine use in children [91]. In placebo-controlled studies, lithium has demonstrated efficacy in treating conduct disorder and severe aggression [27, 92]. Augmentation of stimulants with risperidone has also demonstrated efficacy in reducing aggression, ADHD, and ODD symptoms in the recent Treatment of Severe Childhood Aggression Study [93•].

Psychosocial Factors of TS and Aggression

Environmental and psychological impacts associated with TS and tic disorders may have more adverse effects on quality of life than tics [94, 95]. People with TS often struggle with academic, social, familial, and occupational competence [96]. Longitudinal studies show that emotional problems and problems with peer relationships tend to increase over time in children with TS [97].

Environmental factors such as harsh parenting, marital discord, and low socioeconomic status contribute to further impairment in TS [96, 98, 99]. Parents of children with TS interviewed by the 2007 National Survey of Children's Health reported greater parental aggravation [100, 101]. Parental aggravation associated with their child's comorbid psychiatric problems was also strongly linked with conduct problems

and ASD [10, 101]. Increased parental aggravation is of clinical concern in TS, since childhood aggression has been associated with non-responsive, coercive, and unaffectionate parenting [99]. Disruption of the parent–child relationship in TS from parental aggravation and stress may possibly account for why adults with TS demonstrate higher levels of insecure attachment, anger, and hostility than healthy controls [102]. Of note, parents who reported feeling more bothered by their children exhibiting tic and rage symptoms were also more likely to punish their affected child [103]. When parents engage in conflict avoidance, failure to set limits, or harsh authoritative parenting, there may be inadvertent reinforcement of aggressive symptoms in children [104]. Family accommodation to rage attacks prompted by OCD symptoms also appears to reinforce these behaviors [105]; it is highly likely that such family accommodation to explosive outbursts in TS has a similar effect.

The negative consequences of aggressive behaviors apparently are not limited to parental involvement since children exhibiting disruptive behaviors are also commonly rejected by peers [99]. The results of such social rejection can in turn adversely influence a child's emotional regulation and social perceptions [106]. An aggression-prone child's disposition relative to their experiences with their family, peers, and community can generate maladaptive non-verbal conflict resolution, in turn, reinforcing unproductive cognitions [99]. Results from the Tourette syndrome impact survey of 211 parent–child dyads age 10–17 years show 26 % reported peer victimization that was more likely in those with co-occurring psychiatric diagnosis. Victims of bullying had higher anxiety and depressive symptoms, lower quality of life, and more explosive outbursts [107].

A child's ability to accurately perceive and process external stimuli influence behavior and overall symptom severity [99]. Maladaptive cognitions or problems processing external stimuli are associated with ADHD and OCD [72, 99, 108]. Children with TS+ADHD show subtle impairments on tasks measuring emotional processing compared to healthy controls or to children with TS only, especially when processing anger items [67]. Aggression-prone children suffering from ODD or other disruptive behaviors also experience cognitive deficits that contribute to maladaptive functioning [16•, 109–111].

Co-occurring psychiatric conditions in TS contribute an even greater risk of impairment with higher levels of behavior problems and a lower quality of life [16•, 94, 112]. Children and adolescents with TS and OCD report greater psychological stress levels than healthy controls and show increased tic severity [113]. A clinical study of 60 youth aged 7–17 years with TS or CTD interviewed to assess major and minor

negative and positive life events, tic severity, and comorbid disorders demonstrated a significant association between quantity of major negative life events and higher aggression scores on the Overt Aggression Scale [113]. Adult patients with TS also reported worse quality of life compared to the general population in association with ADHD, OCD, and tic severity [16•, 69].

Non-pharmacological Interventions

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) has strong evidence supporting its application for treating TD and the co-occurring psychiatric disorder symptoms [114, 115]. CBT functions on the premise of decreasing specific behaviors through re-education and re-learning of behavioral patterns [116]. It aims to target the tic symptoms and provide the individual with coping strategies to modify the impact of environmental factors [112]. Habit reversal therapy (HRT) is the widely accepted component CBT that integrates and implements awareness training, competing response training as well as self-monitoring, relaxation training, and contingency management as its core therapeutic principles. Awareness training teaches how to detect premonitory urges while competing response training promotes engaging in physically incompatible behaviors to prevent re-occurring tics [95, 111, 112]. Contingency management involves systematic use of reinforcements or a rewards system to promote treatment compliance and adherence [95]. CBT techniques such as external positive and negative reinforcement has been seen to impact targeted tic symptoms while providing coping and problem-solving skills beneficial in maintaining daily routines and stress reduction [112]. Individuals with ADHD and TS may not respond as well to behavioral treatment, as ADHD symptoms may impede their ability to participate in therapy [60•].

Anger control training (ACT) is a cognitive behavioral treatment that teaches children to use cognitive and behavioral coping skills to manage anger. Its efficacy for reducing disruptive behavior in children and adolescents with TS was demonstrated [55, 117]. In a study where 26 children age 11–16 years with TS and high levels of disruptive behavior were randomized to anger control training or treatment as usual (TAU), disruptive behavior rating scale score decreased by 52 % in the ACT group as compared to 11 % in TAU; improvements were maintained at 3-month follow-up [55]. However, while 65 % of subjects in this study had explosive outbursts, only two subjects reported physical injury or destruction of property, and average scores for delinquent behavior were in the normal range [55]. The authors note that

application of ACT may be limited by co-occurring psychiatric illness and may be less effective for more severe aggressive behaviors.

Parenting Skills Training

Parent management training is an effective behavioral treatment for children with disruptive behavior disorders, consisting of 10 sessions, which improve parental understanding of disruptive behaviors and teach strategies for improving children's compliance [95, 104, 117]. A study of 24 children with tic disorders ages 6–12 years with moderate disruptive behavior who were randomized to 10 sessions of structured parent management training or treatment as usual showed parent-rated disruptive behavior rating scale scores decreased by 51 % in the parent management training group vs. 19 % in the treatment as usual group. Parent management training demonstrated an effect size of 0.96 on disruptive behaviors, which approximates the effect size demonstrated in children with ODD [104]. Behavioral reinforcement at home is essential to treatment compliance. This requires active parental involvement in treatment parameters and increasing parental awareness through psychoeducation [100, 104, 112, 118]. Parents need to be encouraged to hold realistic goals and appropriate expectations for their child with TS [99]. It has been shown that providing parents and other primary caregivers with support and resources reduces parental anxiety related to their child's tic and associated psychiatric symptoms [16•, 112].

Conclusion

Aggression symptoms are very common in TS that is complicated by psychiatric comorbidities. When present, these symptoms cause considerable morbidity with significant negative consequences for both individual and family. Current evidence suggests that tic severity and psychiatric comorbidity are associated with aggressive symptoms in TS. However, it is likely that aggressive symptoms result from a complex interplay of environmental, genetic, neurocognitive, and neuropsychiatric factors. Larger, more rigorously designed clinical studies are necessary to identify specific risk factors and to help untangle overlapping symptoms of psychiatric comorbidity and potential short and longer-term medication side effect with behavioral toxicity. There is good evidence for efficacy of some non-pharmacological treatments but evidence for current psychotropic medication interventions remains limited and requires further investigation.

Compliance with Ethics Guidelines

Conflict of Interest Cathy L. Budman is a speaker for the National Tourette Syndrome Association–Center for Disease Control (CDC) Partnership and receives funding to conduct clinical trials from the following pharmaceutical companies: Psyadon, Otsuka Pharmaceutical, AstraZeneca, Auspex, and Synchronuron Inc.

Miri Rosen and Sana Shad declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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