



Clinical Aspects of Premonitory Urges in Patients with Tourette's Disorder

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Most patients with Tourette's disorder experience an uncomfortable sensory phenomenon called the premonitory urge immediately before experiencing tics. It has been suggested that premonitory urges are associated with comorbidities such as obsessive compulsive disorder, anxiety disorders, and attention-deficit/hyperactivity disorder, although these associations have been inconsistent. Most patients experience tics as a result of the premonitory urges, and after the tics occur, most patients report that the premonitory urges are temporarily relieved. As a consequence, several studies have assessed the premonitory urge and its potential therapeutic utility. Based on the concept that the premonitory urge induces tics, behavioral treatments such as Exposure and Response Prevention and Habit Reversal Therapy have been developed. However, it is still unclear whether habituation, the main mechanism of these therapies, is directly related to their effectiveness. Moreover, the observed effects of pharmacological treatments on premonitory urges have been inconsistent.

Key Words: Behavior therapy; Comorbidity; Drug therapy; Premonitory urge; Tourette disorder.

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INTRODUCTION

A tic is an observable, sudden, rapid, repetitive, and non-rhythmic movement that can occur in any part of the human body. Rapid, repetitive, and non-rhythmic vocalizations are also classified as tics. The onset of tics usually occurs when patients are between 3 and 8 years of age, and its symptoms peak between 10 and 12 years of age. Tic symptoms progressively improve as patients proceed through puberty, and 60–80% of patients show a complete or significant absence of these symptoms by adulthood [1,2].

The diagnostic criteria recently published in the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) suggest that patients with tic symptoms that persist for ≥ 1 year can be diagnosed with persistent motor or vocal tic disorder or Tourette's disorder (TD). Although the main therapies for these disorders are behavioral and pharmacological in nature, evaluating the effectiveness of treatments is extremely difficult because tic symptoms wax and wane.

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Tics have traditionally been considered to be involuntary hyperkinetic movements. However, most TD patients report experiencing an unpleasant and distressing somatosensory event called the premonitory urge immediately before a tic occurs [3].

Several studies have been performed to identify the clinical characteristics of premonitory urges in order to target these urges therapeutically. In this review article, we will provide a comprehensive summary of the findings of previous studies assessing the clinical characteristics of the premonitory urge, the association between the premonitory urge and comorbid psychiatric disorders in TD patients, and therapeutic utilization of the premonitory urge.

CLINICAL CHARACTERISTICS OF THE PREMONITORY URGE

Previous studies have defined the premonitory urge as an occurrence of localized muscle tension. However, few TD patients experience this symptom [4,5]. In contrast, if the premonitory urge is re-defined as an uncomfortable somatic sensation occurring before tics, over 90% of TD patients would

be classified as having these urges [3,4]. Although earlier studies reported a greater frequency of premonitory urges in males compared to females [3], follow-up studies showed no clear differences based on gender [6-8]. In addition, the association between intelligence quotient (IQ) and the severity of the premonitory urge has not been consistently observed in different studies. Woods et al. [9] reported that there was no relationship between IQ and the severity of premonitory urges, while Reese et al. [8] suggested that an increased severity of premonitory urges was correlated with high IQ.

The mean age of pediatric patients reporting symptoms of premonitory urges is 10 years, approximately 3 years after the onset of tics [3]. Although there is no clear explanation for this delay in symptom manifestation, it has been proposed that limitations in the cognitive abilities of pediatric patients might prevent them from correctly expressing or reporting the symptoms of premonitory urges [9]. This hypothesis is further supported by the outcomes of previous studies showing that pediatric patients who are less than 10 years old rarely report having premonitory urges [3], and that premonitory urges are reported more frequently in TD patients as they age [10].

Premonitory urges can manifest anywhere in the human body, and the symptoms can be felt systemically or can be localized. However, the symptoms are frequently experienced in the face, neck, shoulders, arms, palms, or midline abdomen [3,11,12]. A previous study described the premonitory urge as the sensation of an extensive amount of energy in the muscle, joint, or sometimes the skin of the patient. The premonitory urge has also been described as a feeling similar to hiccups, strong or intense feelings, pressure inside the brain or body, or itching [3]. Other studies have described it as an urge to move. Some patients have described this phenomenon as tension, a tickling sensation, pruritus, a feeling that something is just not right, a sense of incompleteness, an impulse to manifest tics, or a feeling that they will be satisfied after the expression of tics [12,13]. Among these descriptions, the “just right” phenomenon is expressed in terms of all sensory perceptions, including visual, tactile, and auditory sensations. The tic appears repeatedly until the patient feels that “something is complete” [13].

In order to assess the characteristics of premonitory urges, Woods et al. [9] developed the premonitory urge for tics scale (PUTS), and Sutherland Owens et al. [7] developed the University of Sao Paulo Sensory Phenomena Scale. McGuire et al. [14] recently developed the individualized PUTS (I-PUTS), which is quite different from the traditional PUTS in multiple aspects. Unlike the PUTS, which is a self-reporting scale assessing general symptoms of premonitory urges, the I-PUTS is a clinician-rated scale that is used to perform a multi-di-

dimensional assessment of premonitory urges, including the frequency, severity, and specific location of the symptoms. Tics and PMUs experienced by the patient in the past week are simultaneously evaluated. Thus, the I-PUTS is a more specific and detailed examination compared to the PUTS, which can misinterpret sensory phenomena unrelated to tics as premonitory urges. In addition, because the I-PUTS is administered by the clinician, it is more suitable for patients who have high levels of anxiety or are distracted and inattentive.

Many tic disorder patients experience tics that arise from preceding premonitory urges, and most patients experience a reduction in premonitory urges after tic expression [3,15,16]. The reduction in premonitory urges after the manifestation of tics is a phenomenon of negative reinforcement [17,18]. In other words, a tic is not a completely involuntary movement but rather a semi-voluntary movement aimed to relieve the premonitory urges [12]. From these results, one can hypothesize that a premonitory urge of higher severity would induce more severe tics. However, outcomes from previous studies assessing the correlation between the severities of premonitory urges and tics were not consistent [8,9,13,19].

RELATIONSHIPS BETWEEN PREMONITORY URGES AND CO-OCCURRING PSYCHIATRIC DISORDERS IN TOURETTE’S DISORDER

Obsessive compulsive disorder

Many obsessive compulsive disorder (OCD) patients exhibit repetitive actions after sensory phenomena such as premonitory urges, not after obsessive ideation; 65% of OCD patients were reported to experience at least one sensory phenomenon [20]. Also, patients with sensory phenomena had higher rates of comorbid tic disorders than those without sensory phenomena [20,21]. Another study demonstrated that the premonitory urge is associated with obsessive symptoms, and that the severity of the premonitory urge is directly proportional to the severity of obsessive symptoms [19,22]. More specifically, the group of patients with high PUTS scores showed high scores in symmetry, aggression, sexual, and religious dimensions on the Dimensional Yale-Brown Obsessive-Compulsive Scale [22].

Approximately 30–50% of TD patients have comorbid OCD [23]. TD patients with OCD exhibit repetitive, compulsive behavior until they experience a sense of completion [24]. During this process, TD patients are more susceptible to sensory inputs or sensory information such as premonitory urges compared to healthy individuals. If the patient continues to feel uncomfortable, the patient repetitively evaluates sensations including touch, seeing, or hearing. The “just right”

sensation, or a sense of “completeness,” is also sought [24-26]. Previous studies have reported that approximately 30–90% of TD patients experience this “just right” phenomenon [13,27-29].

Furthermore, the frequency of the “just right” phenomenon is higher in patients with both tic disorder and OCD compared to patients with only tic disorder or tic disorder with some obsessive-compulsive symptoms. The latter pertains to patients exhibiting subthreshold OCD symptoms not severe enough to merit a diagnosis with the actual disorder [10,12,13,30]. Based on these observations, premonitory urges can be considered to be compulsive thoughts. However, another study posited that the premonitory urge cannot be considered an obsessive symptom because patients with such urges do not manifest cognitive aspects of anxiety, i.e., the feeling that something bad might happen if the compulsive behavior is not performed. Premonitory urges are also limited to physical discomfort, unlike obsessive symptoms [11].

Anxiety disorders

Aversive experiences resulting from tics, such as pain during tics, bullying by peers, or attracting attention from others, are thought to be associated with premonitory urges [31]. If the patient does not perform tasks that he or she doesn't want to do (i.e., homework or errands) because of tic symptoms, the onset or progression of premonitory urges will be affected [31-34]. In a study of adolescents aged 9 to 17 years old, Rozenman et al. [35] reported that the severity of anxiety and panic symptoms or somatic symptoms assessed using the Screen for Child Anxiety-Related Emotional Disorders-Child Version is associated with the PUTS score.

These results are in agreement with earlier studies that suggested an association between premonitory urges and psychological states (i.e., anxiety, mood symptoms, social withdrawal, and aggression) assessed using the Child Behavior Checklist (CBCL) [9]. However, these findings were limited to patients who were ≥ 11 years old and were not observed in patients ≤ 10 years old. These observations are once again in agreement with previous reports suggesting that pediatric patients who are 10 years or older can better recognize and report the symptoms of premonitory urges that they experience [3].

Attention-deficit/hyperactivity disorder

The most common comorbid psychiatric condition in TD patients is Attention-deficit hyperactivity disorder (ADHD). The rate of comorbidity is 40–60%, and developmentally, ADHD has an earlier onset compared to TD [36,37]. A previous neuroimaging study hypothesized that severe premoni-

tory urges would cause a poorer attention span in ADHD patients [38]. The authors proposed that because tic suppression requires a high level of attention, the sensitive detection of premonitory urges is essential to suppress tics [38].

However, the association between ADHD symptoms and the severity of premonitory urges evaluated using the PUTS score was inconsistent. Reese et al. [8] reported no association between PUTS scores and ADHD rating scale (ARS) scores. Similarly, Steinberg et al. [19] and Woods et al. [9] also failed to identify any correlation between PUTS scores and ADHD symptoms evaluated using Conner's ADHD rating scale. However, two studies in adult TD patients demonstrated an association between PUTS scores and ADHD symptoms evaluated using the Adult ADHD self-report scale [30,39].

Another study reported an association between behavioral problems such as aggression and premonitory urges. Woods et al. [9] confirmed a positive correlation between aggressive behavior assessed using the CBCL and premonitory urges assessed using the PUTS score in TD patients.

PREMONITORY URGE IN THE TREATMENT OF TOURETTE'S DISORDER

As stated above, the premonitory urge plays an important role in the manifestation of tic symptoms. A previous study demonstrated that 71% of TD patients believe that they would not have tics if their premonitory urges were no longer present [12]. The current behavioral treatment model is based on the theory that tic symptoms are abnormal movements produced to relieve the premonitory urges. This theory assists patients in understanding and treating their symptoms [40]. There are studies suggesting that pharmacological treatments, similar to behavioral treatments, can affect premonitory urges, as well as studies showing an association between premonitory urges and the treatment response rate and prognosis [24,41]. However, these findings require further elucidation.

Behavioral treatments

Behavioral treatment is one of the most effective treatment modalities, with a similar effect size and remarkably fewer side effects compared to pharmacological treatments (Table 1) [42]. Moreover, behavioral treatment becomes more effective as patients grow older and the treatment is administered for a sufficient length of time [42]. The best-studied behavioral treatments are Exposure and Response Prevention (ERP) and Habit Reversal Therapy (HRT), both of which significantly reduce tic symptoms [43]. Active tic suppression, the key mechanism of behavioral treatments, increases the activity of the left inferior frontal gyrus, which is responsible

Table 1. Studies about the effect of behavior therapy on premonitory urge severity

References	Years	Participants	Method	Control/ comparison	Outcome
Hoogduin et al [47]	1997	3 adults & 1 child with TD	ERP, 2-hours 10 sessions	ERP only	3 adults of the 4, PMU habituation both within & between sessions
Himle et al [18]	2007	5 children & adolescents with TD or PTD	ERP, 5 consecutive, 5-min xperimental trials	ERP only	4 of the 5 children demonstrated reliable suppression Of the 4 children who achieved suppression, 3 failed PMU suppression
Verdellen et al [41]	2008	19 adults & child with TD 15 males & 4 females	ERP, 2-hours 10 sessions	ERP only	SUD score of 19 subjects, PMU habituation both within & between sessions
Specht et al [46]	2013	12 children & adolescents with TD or PTD	ERP, 10 min baseline control 3 sessions & 40 min tic suppression 2 sessions	Baseline control	Urge ratings did not show the expected increase during the initial periods of tic suppression, nor a subsequent decline in urge ratings during prolonged, effective tic suppression
Houghton et al [51]	2017	126 youths & 122 adults with TD	CBIT, 10 wks 8 sessions	PST	Adults showed a significant trend of declining PMU severity But results failed to demonstrate that HRT specifically caused changes in PMU severity. Children failed to show any significant changes in PMU severity

CBIT: Comprehensive Behavioral Intervention for Tics, ERP: Exposure and Response Prevention, HRT: Habit Reversal Therapy, PMU: premonitory urge, PST: psychoeducation and supportive psychotherapy, PTD: persistent tic disorder, SUD: Subjective Units of Distress Scale, TD: Tourette's disorder

for top-down motor control [44]. Baym et al. [45] reported a negative correlation between the severity of tic movement and top-down cognitive-motor control tasks.

ERP is one type of suppressive therapy used to prevent tics when the patient experiences premonitory urges. The mechanism by which ERP suppresses tics is most likely via habituation against the premonitory urge. The habituation mechanism allows a gradual reduction in the premonitory urge through the prolonged suppression of tics, although the temporary suppression of tics actually worsens premonitory urge [46]. Two previous studies observed a reduction in the premonitory urge using ERP [41,47]. However, another study showed contradictory results; the patient in this study did not exhibit a reduced premonitory urge despite continuous tic suppression [46].

HRT is a treatment modality that utilizes competing responses so that the patient does not exhibit tics when he or she feels the premonitory urge. HRT is also the core modality of Comprehensive Behavior Intervention for Tics (CBIT). The effectiveness of CBIT has been confirmed in multiple large-scale studies in pediatric and adult TD patients [48,49]. In adult TD patients, a relationship between CBIT and activation of the left inferior frontal gyrus of the brain has been suggested [50].

A recent study assessed the effectiveness of CBIT against

premonitory urges [51]. The degree of reduction of premonitory urges was greater in the group that responded to CBIT compared to the group that did not. The authors demonstrated a reduction in the premonitory urge in adult patients; however, they did not observe this result in pediatric patients [51]. There was no difference between the group that responded to CBIT and the group that received supportive psychotherapy. Further, the authors could not conclude that the reduction in the premonitory urge led to the reduction in tic movements [51].

Pharmacological treatments

Very few studies have assessed the effect of pharmacological treatments on premonitory urges (Table 2). Treatment with botulinum toxin was effective not only against motor tics but also against vocal tics, and its effective reduction of premonitory urges should also be highlighted [52-55]. However, there are also studies reporting no changes in premonitory urges despite improvement of tic symptoms [56,57]. It is thus unclear whether or not botulinum toxin reduces premonitory urges and reduces tic symptoms as a result.

In a previous study, the selective dopamine receptor DR₁ antagonist ecopipam was shown to be effective in relieving tic symptoms, but this agent did not reduce premonitory urges [58]. Another study on topiramate, which is known to act on

Table 2. Studies about the effect of pharmacological treatments on PMU severity

References	Years	Participants	Medication (number)	Dose	Response of PMU	Complications (number or %)
Scott et al [53]	1996	A 13 year old boy	Botulinum toxin I.M. in vocal cord	30 U	Decreased markedly	Hypophonia
Salloway et al [57]	1996	A 28 year old male	Botulinum toxin I.M. in vocal cord	Initial dose 1.25 U per side 3.75 U every 3 months	Not specified	Hypophonia
Trimble et al [56]	1998	A 34 year old male	Botulinum toxin I.M. in vocal cord	3.75 mouse unit per side	Not specified	Hypophonia
Kwak et al [54]	2000	30 males & 5 females 23.3±15.5 (8–69) year old	Botulinum toxin I.M. in cervical (17), upper face (14), lower face (7), vocal cord (4), other (3)	119.9±70.1 U per visit total dose 502.1±779.4 U	Decreased markedly	Mild neck weakness (4) Transient ptosis (2) Mild dysphagia (2) Hypophonia (1) etc
Jankovic et al [59]	2010	26 males & 3 females 16.5±9.89 (7–65) year old	Topiramate p.o.	Initial dose 25 mg Titration depending on tolerance to 200 mg Mean dose 118 mg	YGTSS: 14.29±10.47 at baseline → 5.00±9.88 at visit 5 PMU CGI improved	Headache (3) Diarrhea (3) Abdominal pain (2) Drowsiness (2) etc
Gilbert et al [58]	2014	15 males & 3 females 36.2 (18–63) year old	Ecopipam p.o.	1–2 wks 50 mg daily 3–8 wks 100 mg daily	YGTSS: 30.6 at baseline → 25.3 at 8 wks there was no significant change in PMU	Sedation (39%) Fatigue (33%) Insomnia (33%) Somnolence (28%) etc

CGI: Clinical Global Improvement, PMU: premonitory urge, YGTSS: Yale Global Tic Severity Scale

the GABA system or the glutamate receptor, showed that the drug effectively reduced both tic symptoms and premonitory urges in patients with TD [59]. However, very few studies have assessed the effects of commonly used drugs such as antipsychotic drugs and $\alpha 2$ agonists on the premonitory urge.

CONCLUSION

The premonitory urge is a type of sensory phenomenon preceding tic movements, and it may be the causal phenomenon that enables persistent tic movements. In addition, the premonitory urge is clinically significant because the majority of TD patients experience it. Previous studies have demonstrated that the premonitory urge is associated with anxiety, OCD, and ADHD. However, it is still unknown whether the severity of the premonitory urge is directly proportional to the severity of these comorbidities. Although behavioral and pharmacological treatments are available and are commonly used to treat TD, these therapies only partially reduce the premonitory urge and their effectiveness is inconsistent.

Furthermore, the mechanisms of action of these treatments remain largely unknown. These findings indicate a complex correlation between the premonitory urge and tic movements. In summary, although treating patients with TD requires understanding the associations between the premonitory urge and tics or frequently occurring comorbid psychiatric conditions, these associations have not yet been clearly elucidated.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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