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Comorbid Psychiatric Disorders in Tourette Syndrome: Neuropathology and Mental Health Needs for Tourette Syndrome Patients

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Abstract:

Tourette syndrome (TS) is a neurodevelopmental disease that typically starts in childhood or early adolescence. It has become increasingly prevalent in recent years. It is characterized by uncontrollable motor tics and sounds which usually are socially inappropriate. These impulses which cause these movements and sound are repetitive and intrusive for kids, accompanied with a sense of relief after tics. For TS patients, TS is not only a source of physical discomfort but also a significant cause of emotional distress and social impairment. Such anxiety and sensory stimuli would reinforce the urge, which triggers the tics and vocal outbursts. Moreover, TS frequently co-occurs with or evolves into other neurodevelopmental or psychiatric conditions during adolescence, such as obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and anxiety disorders. In many cases, these comorbid conditions can be more impairing than the tics themselves. Although current evidence suggests that the mechanisms of comorbid disorders are similar with TS, their relationship and solution worth more attention and scientific resources. Therefore, the social and mental supports needed by TS patients are greater than previously recognized. While the exact genetic causes of TS remain unclear, research indicates that dysfunction in the dopaminergic system and abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuits are among the key pathophysiological mechanisms. With deeper study in TS, more medication and therapy are found, and hopefully they would become more prevalent and targeted for TS patients in the future to alleviate their internal distress.

Keywords: Tourette Syndrome, Tic Disorders, Attention Deficit Hyperactive Disorder, Obsessive Compulsive Disorder, depression

1. Introduction

Tourette's Syndrome has been known as one of the most common childhood neurodevelopmental and movement disorders. It is also a specific type of tic disorder. Tics are involuntary, rapid and non-rhythmic muscle contractions causing purposeless motor actions [1]. Contractions of respiratory, nasal, and oral muscles would produce sounds (phonic tics), and contractions of wide variety of body muscle groups produce movements (complex motor tics) [1]. According to DSM-5 edition, Tourette's Syndrome (TS) is characterized by rapid, repetitive motor and phonic tics that usually happen in children, sometimes lasting until adolescence [2]. French physician Georges Gilles de la Tourette first described its symptoms in 1885 [3]. TS could affect different parts of the body, such as shoulder jerking, but is most prominent in facial movements such as eye blinking or sniffing [4]. The symptoms of TS also vary from person to person. Coprophenomena, including coprolalia (phonic tics) and copropraxia (in movement), are typical symptoms in TS patients. It refers to involuntarily producing socially unacceptable movement or obscene words. Patients often report that tics usually occur after irresistible sensory impulses, and they would relieve such urge, which are considered rewarding [4]. Then, tics recur, and such process repeats. People may consider tics as a habit due to their repetition, but only children with TS know that this is their source of distraction and inner pain. Since some symptoms such as coprolalia are socially unappreciated, patients face considerable social challenges beyond what is commonly recognized. When the urge to tic arises, patients experience embarrassment and nervousness, and tension or emotional excitement can intensify the tics, making them even more irresistible [4]. However, the intensity of tics fluctuates due to many reasons. The tics would decrease during goal-oriented activities which usually require high concentration and fine motor skills, but the tics become more frequent when patients feel anxious and nervous. Conversely, relaxation helps decreasing the frequency [4,5]. By adulthood, the tics would gradually disappear in most cases.

The epidemiology of TS has shown why people should focus on both children and adults to study this disease. Previous reports show that the prevalence of comorbid disorders was 85.7%. Comorbid disorder refers to two or more related psychiatric conditions happened in a patient. More than 70% of patients experience attention deficit/hyperactivity disorder (ADHD) and around 30% of patients had other psychiatric conditions, including obsessive compulsive disorder (OCD), anxiety, and disruptive behaviors [3,6]. There are also reports proving the increased prevalence of migraine in TS patients compared to people without TS [3]. It seems that TS did not disappear but persisted in different ways in lots of patients in adulthood. There are also differences between TS in males and females. Garcia-Delgar et al. conducted a study of 709 participants with TS to investigate the relation between sex, age and severity of tics in TS patients, and they found that motor tics were more severe in males than in females (males generally scored higher in Yale Global Tic Severity Scale (YGTSS) and Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS) compulsion than females), but female experienced worsened tic in adulthood [7]. Moreover, they proved their hypothesis that males are more severe in externalizing problems including ADHD and autistic spectrum disorder (ASD) while females have higher likelihood in internalizing problems, such as exhibiting more severe emotional disorders or OCD [7].

The neuropathology of TS remains incompletely understood, and the cause of TS is extremely complex. From a genetic perspective, it is considered the result of the impact of the environment on genetically predisposed individuals [3]. There are several wide-accepted models for the pathophysiology of TS. Firstly, there is a decrease in the thickness and size of gray matter in the internal, inferior, and superior frontal sulci in the brain of TS patients, which affects people's cognitive, executive and behavioral functioning. The abnormality in dopamine levels in the cortico-striato-thalamo-cortical (CSTC) circuit and the dysfunctions in GABA pathway and basal ganglia are considered the main causes of the tics [3,6]. Co-occurring disorders make the cure and diagnosis of TS even more challenging.

This review focuses on multiple co-occurring psychiatric disorders in TS patients, including how the symptoms of TS develop into multiple disorders, their correlation, and the similarity in pathology between them. The discussion would start from several popular theories of the neuropathology of TS, then three types of comorbid disorder of TS would be discussed separately. New treatment and medication would also be updated in this review based on their effectiveness and side effects.

2. Neuropathology of TS

One of the most widely accepted theories of TS is that the loss of inhibitory control in the brains of TS patients leads to involuntary movements. The evidence supporting this point includes two inhibitory networks: decreased short intracortical inhibition (SICI) showed by transcranial magnetic stimulation (TMS) and prepulse inhibition (a first small sensory stimulation inhibits a reflex to trigger a second stronger sensory stimulation) [5]. The failure of inhibition happens mainly in the frontal-subcortical motor

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circuit for throat clearing, eye blinking, sniffing etc. [8]. Such loss of inhibition is secondary to abnormal levels of GABA neurons concentrating in regions including thalamus, bilateral ventral striatum, amygdala and right insula [4].

Another mechanism of the tics is the overactivity of dopamine circuitry. Some theories and studies prove developmentally hypofunctional dopamine system results in dopamine receptor hyperactivity [4]. Unlike the tics in general tic disorder, which is purposeless, the tics for TS patients are more purposeful. They are considered as a reward because tics can relieve the impulse repeatedly, and reward is expressed by the release of dopamine. Such repeated pattern becomes a habit, pushing dopamine signal to trigger movement repeatedly to relieve the urge, and dopamine receptors experience overactivity [4]. The research published by Johnson et al. also supports the opinion that the tics represent a continuous and exaggerated motor habit that is reinforced and simultaneously increases dopamine release [4]. This is a loop where aberrant dopamine level increases the execution of learned behaviors, such as tics, with the change of plasticity in cortico-basal ganglia dopamine pathway [4]. The current model of premonitory urge in TS patients proposes that abnormal interoceptive and exteroceptive functioning could generate the urge, which causes action initiation and tics via cortico-basal ganglia sensorimotor system [4]. Moreover, amphetamine, a dopamine releaser, has been proven to lead to a significantly greater widespread activation in various brain regions associated with motor information output, including the striatum [5]. This mechanism results in excessive dopamine release in the brain of TS patients.

Basal ganglia play a key role in the pathophysiology of TS and motor control/inhibition [1,3, 5,6]. One of the reasons is because they are important in control of internal switching mechanisms. People act and react following a certain visual pathway based on advance information on motor sequence, and they complete tasks with normal motor initiation; However, research shows that people with TS have impaired basal ganglia functioning which results in patients abnormally relying on external sensory cues to process and focus on certain information [1]. The dysfunction of basal ganglia and frontal striatum also causes the longer time needed and worse movement preparation exhibited by TS patients to plan movements in the absence of visual cues and advance information [1]. The evidence provided by TMS also shows a shortened cortical silent period and reduced intracortical inhibition in TS and OCD patients, which supports the opinion that such abnormalities is due to the dysfunction in corticobasal ganglia circuits happened in TS and OCD (one of the comorbidities of TS) [1].

Anatomically, researchers found decrease in the thickness of gray matter in the pre- and post-central, inferior, internal, and superior frontal sulci. These regions have been associated with impairments in self-regulation, emotional control, decision-making and increased risk of disorders including ADHD and depression [9]. Neuroimaging studies also show anatomical changes in prefrontal, premotor, and orbitofrontal cortex in the brain with TS and a decreased volume of gray matter accompanying with a large area of white matter [1]. There are also structural changes happening in the brain of TS patients. A decrease in volume of basal ganglia and the asymmetry of the putamen and caudate nucleus are involved in inhibiting and selecting competing motor patterns, and the repeated tic suppression can also cause these structural changes [5]. It creates a vicious circle where the mechanism of tics is further intensified.

In term of premonitory urges, they are intrusive sensation or feeling that drive individuals to seek for relief via certain actions. The most frequently recorded location of premonitory urges are the palms, shoulder and throats [9]. It might also present with multiple comorbid behavioral disorders, such as ADHD and OCD, which explains the diversity of sensation urges and tics. Premonitory urges have been considered to cause more stress than normal tics because they appear semi-voluntary in response to inner impulse [9]. Some researchers proposed that premonitory urges emerge from a hyperactivation of cortical areas, including the insular cortex, supplementary motor area, anterior cingulate cortex, and parietal operculum due to a lack of inhibitory (i.e., GABAergic) interneurons [5]. In addition, frequent activation of amygdala results in excessive dopamine release to the striatum through dopamine pathway, and a large number of neurons in striatum become improperly overactive [5]. This concentration in dorsal striatum would unsuitably stop basal ganglia output neurons from normally functioning in the globus pallidus pars interna and substantia nigra pars reticulata. It in tern leads to the disinhibition of the output neurons in the primary motor cortex and thalamus, which causes overactivated basal ganglia unable to inhibit involuntary movements [5].

3. Comorbid Disorders of TS

3.1 ADHD

In DSM-5, ADHD is described as a neurodevelopmental disorder characterized by a reoccurring pattern of hyperactivity-impulsivity and inattention that becomes disturbing enough to interferes with patients' self-development and daily functioning [2]. The similarity in neuropathology of

ADHD and TS has been proven by previous studies, making it become the most common comorbid disorder among TS patients to affect up to 60%-80% of TS patients [3]. An abnormality in neurotransmitter levels (mainly glutamate and dopamine) accompanying with the asymmetry of globus pallidus is observed in both. Several genes have been implicated in the comorbidity of ADHD in TS patients, such as catechol-O-methyltransferase (COMT) and dopamine receptor D2 (DRD2) [3]. Neurologically, the dysfunction in cortico-striato-thalamo-cortical (CSTC) circuits and abnormal level of dopamine signaling in basal ganglia and prefrontal cortex are two brain networks responsible for motor controlling and behavior regulation, which are also the main causes of the tics in TS and impulsivity in ADHD [3].

For the treatment of ADHD in TS, it is multimodal and complex based on severity and the type of symptoms. In term of medication, stimulants, typical and atypical antipsychotic medications are three main categories of TS treatment [3, 10]. Typical antipsychotics, including haloperidol, fluphenazine and pimozide, are highly effective due to their action as postsynaptic dopamine receptor blockers; however, they remain second-line treatments because of potential side effects, such as extrapyramidal symptoms [10]. Atypical antipsychotics, such as ziprasidone, olanzapine, aripiprazole, and quetiapine, are considered better than typical antipsychotics since a higher affinity for serotonin receptors is exhibited relative to D2 receptors, with generally minimal side effect [10]. More recently, rather than stimulants and alpha-2 agonist, more researchers have recommended aripiprazole, a dopamine agonist, to be the first-line treatment for mild ADHD and TS with minimal side effect [3]. This is a hopeful discovery, and further investigation in this area is waiting to be done in the future.

3.2 OCD

OCD is defined by the reoccurring presence of obsessions (intrusive, unwanted thoughts and urges) and repetitive compulsions (uncontrollable behaviors) which cause distress and adaptive malfunctioning in daily life [2]. The prevalence of OCD ranges from 11%-80% of TS patients [3]. There is a clear correlation between these two disorders; some children initially diagnosed with OCD also present with tics, and repetitive involuntary actions, thoughts, and urges are common features of both OCD and TS [11]. Studies have found the similarities in neuropathology between them. Both disorders exhibit the disruption of the indirect pathway in basal ganglia circuit which leads to repetitive behaviors and obsessions in OCD, and these might become more severe during the course of TS [3]. Moreover, the change in structure of the caudate nucleus, putamen, and thalamus is found in the brain of both OCD and TS patients [11]. MRI studies have revealed the thinning of anterior cingulate cortex accompanying with the abnormal volume and the asymmetry of prefrontal cortex in TS patients, while the abnormalities in anterior cingulate cortex and orbitofrontal cortex are also found in OCD patients [11]. There are multiple models in the treatment of OCD in TS patients, combining cognitive behavioral therapy (CBT) and medication to maximize the effectiveness and minimize the side effect that drugs could bring. Recommended medications currently include atypical antipsychotics such as risperidone combined with selective serotonin reuptake inhibitor (SSRI) [3].

3.3 Depression

According to DSM-5th, depression is characterized by the loss of interest and depressed mood lasting for at least two weeks [2]. Approximately 13%-76% of patients with TS are reported to experience depression, making it one of the most common comorbid behavioral disorders associated with TS [3]. Several research shows that the depression ratings collected from the group of people with TS were significantly higher than the control group without TS, with all individual depressive symptoms reported as more severe and frequent by the TS group, such as the decrease in activity and pleasure which are core symptoms of depression [12,13]. Another group of researchers found that patients experience decreased activity and lower energy which are major indicators of depression [13]. Depression and anxiety are both prominent feature in people with TS, and depression in TS has become a problem due to multiple reasons. Patients with TS might experience deficient cognitive functioning and psychosomatic health problems, which further contribute to depression [13]. The increased severity of depression in TS patients is related to the impairment of social functioning and behavioral control (the ability to initiate, regulate and inhibit the course of action). People with TS have difficulties with verbal fluency, cognitive functioning and the suppression of actions which is related to the abnormality in fronto-striatal circuit, similar with the mechanisms of ADHD and OCD [13]. From psychological perspective, patients face dilemma in social aspect because tics make them harder to integrate and establish contacts with others due to the tics or the anxiety and fear of having tics. Feeling social stigma also leads to this result when children with TS often experience bullying, teasing, receiving nicknames etc. at school [3]. They might be also harder to concentrate on tasks which makes them negatively assess their capability. The treatment of depression in TS patients requires the combina-

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tion of pharmacotherapy and psychological interventions, including psychotherapy [13]. SSRI and tricyclic antidepressants have been reported to be effective in alleviation of depression in TS patients [3]. Another study discovered that the use of dopamine antagonists may increase the risk of depression [13]. Currently, typical antipsychotics are preferred when it comes to treating depression in TS, but the relationship between the severity of depression and dosage of medications is still not fully discovered.

4. Treatment

With the increasing investment in Tourette syndrome research, researchers have made notable progress in its treatment approaches, laying a crucial foundation for finding effective, side-effect-free treatments in the future. This goal is challenging due to the periodic changes of symptoms and the presence of associated comorbidities [13]. According to American Academy of Neurology (AAN), no medication exhibits high credibility and confidence in the efficacy for tic reduction due to the deficit of systematic clinical trials [6]. In pharmacological therapies, current first line medications include atypical neuroleptic antipsychotics (ie, aripiprazole, risperidone), alpha2-adrenergic presynaptic agonists clonidine (Catapres), and, less often, benzodiazepine clonazepam (Klonopin) [6, 8]. Various research show their modest effectiveness by children taking them who became less impulsive, and their ADHD symptoms were alleviated as well [8]. Two larger studies provide firmer evidence supporting the use of clonidine to reduce tics. Both studies show the high effectiveness of clonidine and methylphenidate compared with placebo using Yale Global Tic Severity Scale (YGTSS), and the combination of two drugs also shows significant improvement in tic suppression [13]. Second line medication includes typical antipsychotics, anticonvulsants, antidepressants, Chinese medicine, and neurotoxins [6]. Haloperidol and pimozide (typical antipsychotics) have become widely used anti-tics treatment for TS patients [14]. However, due to the risk of side effects such as movement disorders, researchers switched their interest from typical medications to the effective use of atypical antipsychotics, such as aripiprazole and risperidone [14]. They act as serotonin 5-hydroxytryptamine type-2 receptor antagonists working together with dopamine D-2 receptor antagonism to reduce tics and motor disorders [14]. More rigorous studies are waiting to be done in this area. Moreover, the Food and Drug Administration (FDA) currently has approved only 3 medications (i.e. aripiprazole, haloperidol, pimozide) for the treatment of Tourette syndrome–related tics, which means that there are broader range of clinically used drugs compared to those of widely used [13]. Therefore, despite significant investment in the research of medications for TS, issues concerning their accessibility and safety remain to be adequately considered and addressed.

On the other hand, there has been a shift from traditional medication towards nonpharmacologic treatment practices. In term of behavioral therapies, following the guideline from AAN, widely acknowledged therapies for TS include comprehensive behavioral intervention (CBIT), habit reversal training (HRT), and exposure and response prevention (ERP) for tics in TS [6]. Currently, HRT has become the most widely applied behavioral therapy for tic disorders like TS [6, 14]. It is based on the idea of replacing tic symptoms with certain competitive behaviors and reinforcing this pattern [15]. It includes various sessions, including awareness training to help detecting early warning signs of tic behaviors, competing response technique etc. [14, 15]. Studies and trials on children and adults have shown significant improvement in tic reduction and behavioral control, which confirmed its effectiveness [14,15]. ERP is another effective therapy for OCD and tic disorders. It is based on the idea that tics become habitual responses to premonitory urges, therefore weakening the connection between them could lead to tic reduction [14]. To be more specific, patients would follow the procedure to tolerate premonitory urges for a long period of time, which is the exposure part, and resisting tics is the response prevention [14]. This pattern would overall help tic reduction in severity and frequency. HRT and ERP are currently designated as first-line behavioral therapy for tic disorders like TS.

For comorbid behavioral disorders of TS, there is cognitive behavioral therapy (CBT) which focuses on replacing unrealistic, compulsive expectations by feasible, structural expectations [5]. For ADHD plus TS, there are CBT and medications such as clonidine and guanfacine [5].

5. Conclusion

This paper has explored the basic symptoms, neurophysiology, associated comorbidities and current first-line treatments for Tourette syndrome. Although every step in this area takes large amount of investment and effort, TS is increasingly understood and interested by researchers as one of the most common neurodevelopmental disorders and movement problems affecting about 1% of population around the world. For now, there are multiple popular theories explaining the pathophysiology of TS. The tics is mainly caused by the dysfunction of inhibitory gate control in the frontal-subcortical motor circuit. It is also related to the dysfunction of basal ganglia and frontal striatum which causes the failure of movement inhibition. Another popular explanation for tics is the overstimulation of do-

pamine circuitry. The tic is the result of all these dysfunctions in the brain of TS patients.

People troubled by motor and phonic tics, involuntary actions, and coprophenomena are likely to experience many comorbid behavioral problems including ADHD, depression and anxiety especially in socializing situation. ADHD has the highest prevalence in TS population, which means that they share lots of in common in pathophysiology. ADHD and OCD are both affected by the abnormal level of neurotransmitters, mainly dopamine. Children with TS often experience bullying and teasing in school, and the lack of understanding and support from parents and teachers may exacerbate the problem. This severely affects children's psychological well-being and social functioning.

Fortunately, more and more researchers have contributed to the study of TS treatment. Currently, first-line medications for tics include aripiprazole, risperidone and clonidine. Second-line medications include haloperidol and pimozide, etc. Nonpharmacologic treatment approaches also widely apply in patients, including CBIT, HRT, ERP, and CBT. Behavioral therapies help to reconstruct the relationship between patients and tics and let patients regain confidence in their well-being.

Continued study is meaningful for deepening people's understanding of TS, helping people identify symptoms for early diagnosis and choosing effective treatment for individuals. Looking ahead, advancements in neuroimaging, genetic technology and computational modeling reinforce people's confidence in a better future for TS patients. While eliminating misunderstanding about TS and tic disorders, study in TS helps people understand the true dilemma and health need of patients, which is important for building a diverse, inclusive society. With increased public awareness and scientific attention, the future provides hope for more interventions and improved quality of life for people with Tourette Syndrome.

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