INVESTIGATING THE RELATIONSHIP BETWEEN TOURETTE SYNDROME AND SLEEP QUALITY IN CHILDREN: A REVIEW OF PATHOPHYSIOLOGY AND IMPLICATIONS FOR QUALITY OF LIFE

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ABSTRACT

Current research suggests that children with Tourette's Syndrome (TS) experience greater sleep disturbances and lower sleep quality than children without TS. Sleep plays a fundamental role in a child's mental and social-emotional development. It is hypothesized that dysfunctions in neurotransmitter activity, cortico-striato-thalamo-cortical (CSTC) circuits, and the basal ganglia are involved in the pathogenesis of tics that may influence sleep quality. Furthermore, neurotransmitters, such as norepinephrine and dopamine, are hypothesized to contribute to the pathophysiology of TS and its associated sleep disturbances. This review explores the pathophysiology of TS, tic severity, its influences on sleep quality, and the effects on quality of life (QoL) in children with the disorder. Research highlights the impact of disturbed sleep on health outcomes, demonstrating the importance of further research to address these concerns and improve QoL in children with TS. However, there is limited research on the specific mechanisms that influence sleep quality in children with TS.

INTRODUCTION

Tourette Syndrome

TS is a childhood-onset neurodevelopmental disorder characterized by tics, which are sudden, repetitive, and involuntary motor or vocal movements [1]. Tics are categorized as simple and complex. Simple tics are brief and repetitive movements or sounds affecting a limited number of muscle groups, while complex tics involve multiple muscle groups, and can involve a sequence of movements or vocalizations [1]. TS typically emerges between the ages 5-10, and tics may be more pronounced in childhood, often improving in adolescence and early adulthood [2,3]. A systematic review determined that the global prevalence of TS is 0.5% [3]. The CDC reports that 1 out of 162 children (0.6%) have TS, with 44% of children diagnosed with TS in 2016-2017 having moderate to severe tics in the United States [4].

Diagnosis

The current standard of diagnostic criteria for TS and other tic disorders, follow the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR), developed by the American Psychiatric Association [5,6]. Other tic disorders described by the DSM-5-TR are Persistent Motor or Vocal Tic Disorder and Provisional Tic Disorder, whose diagnostic criteria vary from TS in terms of the duration of tics (more than 1 year for TS and Persistent Motor or Vocal Tic Disorder, versus less than 1-year Provisional Tic Disorder). Additionally, TS varies in that diagnosis requires the presence of both motor and vocal tics, whereas other tic disorders diagnose only require motor or vocal tics [5].

TS diagnosis is based on the presence of both motor and vocal tics that occur several times a day (concurrently or non-concurrently) or most days [5]. Tic frequency is not specifically quantified; the DSM-5 states that tics need to occur frequently throughout the day, typically in episodes, daily or intermittently for a duration of at least one year [5]. The tics must have emerged prior to 18 years of age, and tics must not result from medications used to treat another condition [2,5]. TS diagnoses are made by healthcare professionals who assess a child's symptoms and medical history [1,5].

Comorbidities

TS is often comorbid with other conditions, with the most prevalent being attention-deficit hyperactivity disorder (ADHD), anxiety, obsessive-compulsive disorder (OCD), depression, and insomnia [7-9].

Although there is no cure for TS, treatments and therapies can help children manage their tics, and in many cases, improve symptoms over time, particularly during adolescence and early adulthood [10-12]. Pharmacological treatments include Clonidine and Haloperidol, pimozide, and aripiprazole [12]. An emerging therapy that uses habit reversal training (HRT) is Comprehensive Behaviour Intervention of Tics (CBIT) [10]. While treating comorbidities does not eliminate tics, it can also lead to tic reduction, and improve children's relationships with family, friends in school and at home [10]. Individuals will need different treatment plans based on the comorbidities children with TS are diagnosed with [10].

Quality of Life in Tourette Syndrome

QoL refers to an individual's well-being, which encompasses physical health, mental and emotional state, social relationships, and functional abilities [13]. Research indicates that children with TS often experience lower QoL compared to their peers without TS [14-16].

Youth with TS consistently reported the lowest QoL scores compared to other groups, including those with ADHD and mobility limitations, as well as youth without chronic conditions [17]. Another study by Storch et al. indicates that children and youth with more severe tics or comorbid conditions tend to feel less welcome in social spaces, spend less time with friends, and experience more familial conflicts. Children with TS may experience ridicule or social exclusion in school settings due to an inability to complete tasks due to their tics, which may lead to isolation and a hesitance to socialize [14]. This study highlights the challenges faced by youth with TS, particularly in social relationships and academic settings, emphasizing the need for tailored support to enhance their overall well-being [14].

TS can have a significant impact on various aspects of a child's QoL, including sleep [18,19]. Research has shown that sleep is negatively affected in patients with TS, particularly children. Children with TS experience decreased total sleep time, lower sleep efficiency, and an elevated arousal index [18,20,21]. A case-control study published in 2017 reports an incidence rate of sleep disorders of 7.24% in children with TS, compared to 3.53% in children without TS [18]. Sleep disturbances and disorders are highly prevalent in children with TS and are categorized as part of the DSM-5 criteria for sleep disorders, associated with frequent awakenings, arousals, or problems with initiating and returning to sleep [7]. Another study states that 65% of 123 children and young adults, all of whom had TS, experienced sleep disturbances, which ranged from various types including increased sleep disruption and decreased sleep efficiency [22]. Sleep disturbances in children can result in worsened QoL outcomes including impairment in daytime functioning, emotional and behavioral difficulties, and compromised cognitive and academic performance [18, 23-25]. Effective management of sleep problems has been reported to improve tic control and positively impact quality of life in children with TS [7].

Understanding the impact of TS on QoL and sleep quality in children is crucial for providing comprehensive care and interventions that address their holistic well-being and improve their overall outcomes. In this review, we discuss the current literature surrounding TS and the biological mechanisms that contribute to tics. We aim to investigate the relationship between TS and sleep quality in children due to the onset of tics during childhood and youth.

BACKGROUND ON SLEEP

Sleep quality is defined as the holistic assessment of the wellness of an individual's sleep [26-29]. It has four main attributes: sleep latency, duration, efficiency, and wake-after-sleep onset. Multiple factors can influence sleep quality including BMI, circadian rhythm, stress, anxiety, and various neurological disorders, such as TS [26,28]. Typical sleep patterns follow a 'standard' circadian rhythm–the physical, mental, and behavioural changes an organism experiences over a 24-hour cycle [29-31]. Further, light, food intake, social environment, physical activity, etc. can impact this cycle [29-31]. In humans, almost every organ and tissue has its own circadian rhythm which collectively functions in the day and night cycles of life [29,31]. The circadian rhythm is regulated by proteins encoded by many genes that coordinate wakefulness and sleepiness upon activation [29-31]. Variants or malfunctions in these genes can cause abnormalities in an individual's circadian rhythm [29-31]. Additionally, this cycle is regulated by the brain and is composed of a large group of nerve cells that form the suprachiasmatic nucleus (SCN), a structure located in the hypothalamus that controls the production of melatonin based on the amount of light received by the eyes. Melatonin levels, controlled by the pineal gland, typically rise in response to decreased exposure of light to the eyes [31,32]. This elevation in melatonin acts as the onset for the initiation of the sleep phase in the body's circadian rhythm [31,32]. A large majority of sleep disorders are said to be caused by a malfunction in the pathways involved with these proteins and/or nerve networks. Therefore, understanding the role of the body's circadian rhythm, and its regulation processes, is crucial for developing strategies to improve sleep quality [31,32].

Sleep plays a fundamental role in a child's mental and social-emotional development [19,26,33]. The literature shows that poor sleep quality can result in behavioral and emotional consequences such as irritability, fatigue, slowed responses, and daytime dysfunction [29,33]. Negative physical health outcomes can also result from poor sleep quality [26-29,33]. Multiple studies have investigated sleep disorders using the SATED scale; 1) satisfaction/quality, 2) alertness/sleepiness/napping, 3) timing, 4) efficiency/latency, 5) duration [28]. It has been

concluded that an abnormality in any of these areas can be associated with many health outcomes, such as mortality, diabetes, heart disease, and/or impaired neurobehavioral performance [29,33].

A sleep disorder is a condition that disturbs typical sleep patterns [19,33]. Sleep disorders are considered a comorbidity of TS, and the sleep quality of many children with TS can be negatively impacted as a result [19,33]. For instance, difficulties such as fragmented sleep and sleep interfering behaviours may be experienced. Some examples of sleep disorder comorbidities in TS include insomnia (difficulty falling/staying asleep), excessive daytime sleepiness, disorders of arousal (e.g., sleepwalking, sleep talking, sleep terrors, enuresis), persistence of tics during sleep, and the presence of periodic limb movements during sleep [19,33]. Moreover, the increased prevalence of sleep disorders persists after controlling for other known risk factors, such as obesity and co-occurring ADHD, strengthening the correlation between TS and sleep disorders [33]. This comorbidity is important to recognize as sleep disorders may lead to poor associated health outcomes (diabetes, heart disease, impaired neurobehavioral performance, etc.), and impact QoL of children with TS [19,29,33]. Therefore, the high prevalence of sleep disorder comorbidity highlights a need to understand the causes of the correlation between TS and poor sleep quality. By investigating the mechanisms underlying sleep disturbances, the development of more effective strategies for sleep-related issues and the enhancement of overall health outcomes in children with TS may be promoted.

Pathophysiology, Treatment, and Connection to Sleep

TS is a childhood-onset neurodevelopmental disorder characterized by tics, which are sudden, repetitive, and involuntary motor or vocal movements [1]. Tics are categorized as simple and complex. Simple tics are brief and repetitive movements or sounds affecting a limited number of muscle groups, while complex tics involve multiple muscle groups, and can involve a sequence of movements or vocalizations [1]. TS typically emerges between the ages 5-10, and tics may be more pronounced in childhood, often improving in adolescence and early

Neurotransmitter Systems and Activity on REM and NREM Sleep:
Changes within various neurotransmitter systems (including dopaminergic, serotonergic, and noradrenergic systems) are associated with changes in the brain that influence polysomnographic variables that are used to identify sleep abnormalities during rapid eye movement (REM) and non-rapid eye movement (NREM) sleep [34,35]. Polysomnography tests are considered the gold standard to measure sleep architecture, as they reliably document brain activation patterns and other important homeostatic indicators of sleep quality [34]. While REM sleep consists of vivid dreaming, increased brain and heart activity, and rapid eye movement, NREM sleep consists of three stages, where stages one and two involve lighter sleep and stage three involves deep and restorative sleep [34]. Polysomnographic studies in children with TS have found that tics can occur throughout any stage of REM and NREM sleep, which may lead to sleep disruptions and poor sleep quality [34].

Dysfunctions in Neurotransmitter Activity, Basal Ganglia, and CSTC Circuits:
Evidence suggests that excitatory dopamine from the CSTC circuit is linked to the pathogenesis of TS, as excess dopaminergic activity may contribute to the manifestation of tics [36]. Furthermore, dysfunction in the dopaminergic pathways could alter sleep-wake regulation and potentially interfere with one's ability to fall or stay asleep [34]. The dopaminergic ventral tegmental area and nucleus accumbens are dopaminergic brain structures that can modulate the mesopontine brainstem nuclei [7,36]. The mesopontine brainstem nuclei are involved in regulating wakefulness, and the transition between REM and NREM sleep [34,36]. When dopaminergic signalling is dysregulated, its modulating effects on the mesopontine brainstem nuclei can result in poor sleep quality [34]. Moreover, research suggests that unaltered serotonergic firing is associated with sleep maintenance properties, emphasizing the importance of serotonin in maintaining healthy sleep patterns [34,36]. Studies have found that children with TS or sleep disorders may exhibit altered serotonergic firing patterns that lead to decreased serotonergic activity that reduces sleep quality [21,34]. Additionally, it is hypothesized that increased noradrenergic activity is associated with the pathogenesis of tics and is considered a sign of hyperarousal that may also contribute to sleep disturbances by promoting wakefulness [21,34]. However, the specific mechanisms of how serotonin and noradrenaline influence sleep quality in TS is still being researched, as there are conflicting findings on how their activity may be altered in children with TS.

Neuroimaging studies have indicated that dysfunction in the basal ganglia and CSTC circuits seen in children with TS may cause abnormal transmission of neural signals to premotor cortices through thalamocortical activation, prompting involuntary sensory urges and the occurrence of tics [34]. It is postulated that during consciousness, the prefrontal cortex compensates by modulating misguided basal ganglia signals to suppress the occurrence of tics [34]. However, during REM and NREM sleep, the activation of the prefrontal cortex is diminished, which can result in aberrant activity in the basal ganglia and disrupt the normal functioning of CSTC circuits [34]. Thus, abnormal basal ganglia signalling and impaired CSTC circuits may lead to increased tic expression and reduced quality of sleep. Given that there are limited neuroimaging studies available that investigate the interplay of the basal ganglia and CSTC circuits on tic expression during sleep, further research is required to confirm this relationship.

Application of Pathophysiology in TS and Sleep Disorders:

To provide an application of the connection between the pathophysiology of TS and its relation to sleep disorders, this section will investigate the use of Clonidine, an alpha2 agonist that is used to treat both tic disorders and sleep disorders [37]. While Clonidine's intended use per Health Canada is primarily for the treatment of hypertension, it is still commonly utilized for children and adolescents in the management of tic symptoms as an off-label intervention [37]. Clonidine functions primarily by affecting the activity of norepinephrine, a neurotransmitter part of the sympathetic nervous system [38]. During sleep, norepinephrine originates in the upper brainstem and plays a role in our brain's arousal system that leads to wakefulness, according to the Institute of Medicine (US) Committee on Sleep Medicine and Research [39]. This norepinephrine release is associated specifically with a secondary pathway that involves flow to the hypothalamus, where it receives inputs from nerve cells that then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and gamma-aminobutyric acid. Ultimately, all these inputs enter the cerebral cortex, where they diffusely activate the nerve cells and prepare them for the interpretation and analysis of incoming sensory information [39]. A review on current treatments for TS highlights that Clonidine acts on the $\alpha 2$ adrenergic receptors located in the locus coeruleus within the brain stem. This limits the release and turnover of norepinephrine, resulting in a reduced sympathetic outflow from the CNS and lessening the number of tics [40]. Clonidine has also been shown to impact other neurotransmitters, with dopamine being a significant player that can be affected. In a study conducted by Yoshida et al., Clonidine was shown to significantly decrease the concentration of dopamine in the nucleus accumbens of rats [41]. This decreased release may lead to a dysfunction in the role of dopamine, which is concurrent with literature on dopamine's impact on a circadian rhythm [42]. The pathophysiology of sleep disorders in children with TS remains very complex. Additional literature also points to dopaminergic dysfunction as a potential cause [7]. This has been supplemented with a more epigenetic based approach to understanding the pathophysiology of the impact of TS on sleep, with various imaging techniques such as positron emission tomography or magnetic resonance spectroscopy utilized to implicate other neurotransmitters [7].

IMPLICATIONS ON CHILD DEVELOPMENT

Quality of Life (QoL)

QoL is suggested to be negatively affected in children with TS.

In addition to the manifestation of tics in TS, it is known that additional emotional and behavioural difficulties can arise, including issues relating to impulse control as well as OCD and ADHD comorbidities [43-47]. Research suggests that poorer QoL was associated with increased tic symptom severity, ADHD diagnosis, and obsessive-compulsive behaviours [48]. In a study that compared the QoL of children aged 10 to 17 years with TS, epilepsy, and those without diagnosed medical conditions, researchers found significant differences in various QoL contextual items [49]. Specifically, the findings indicated that children with TS experienced a reduced QoL compared to those in the healthy control group. Using the Youth QoL instrument-research version scale, children with TS demonstrated hindered involvement in social activities due to TS, less involvement in house chores, reduced communication with adults about important personal issues, and lower overall levels of participation, a fundamental principle in QoL outcomes. There were also increases in reported externalizing and internalizing behavioural problems including lower self-esteem and increased impulsivity. TS patients reported greater tic severity exhibited significantly lower scores than controls for the QoL contextual items and relationship domains, signifying a positive correlation between tic severity and reduced QoL. Another study that included qualitative measures of interviews yielded similar results, coding qualitative themes across the TS group such as "Tourette syndrome can be distressing and disabling," "needing to control tics," and "struggling to fit into society's expectations of normal behaviour" [48]. Per these findings, it can be understood that tic severity plays a large role in the QoL, and emotional/behavioural challenges faced by children with TS.

Daytime Functioning

Another study examined the relationship between sleep, daytime functioning (defined by competencies at school, activities, and social interactions), and tic severity in children with TS [24]. The study utilized actigraphy and parent reported QoL measures to assess sleep quality and its effects on QoL. The aim was to assess objective sleep parameters and potential links between sleep and daytime functioning in children with and without TS. The primary sleep measure used in the study, actigraphy, is a common non-invasive method to objectively assess sleep behaviour by utilizing a wrist-worn accelerometer to record continuous movement and activity [50]. Its non-invasive nature and ability to provide long-term monitoring make actigraphy particularly suitable for pediatric sleep research. This is especially beneficial for children who might find other monitoring methods uncomfortable or disruptive, or for those who require ongoing tracking of sleep patterns, such as children with TS or other conditions affecting sleep [51]. Via parent-reported measures, it was shown that children with TS displayed significantly greater behavioural manifestations of executive difficulties including working memory, inhibition, and attention, in comparison to controls. A measure called the Flanker

task was used to assess inhibitory control in the children. There were associations between the previous night's actual sleep time and next-day accuracy on this task, wherein children with shorter sleep durations and more disturbances the previous night made more errors across its incongruent trials. This finding is consistent with prior research demonstrating the relationship between nightly sleep quality and inhibition tasks and overall functioning, emphasizing the importance of sleep in the cognitive functioning of children [52-54]. For that reason, it is crucial to further investigate sleep quality in children with TS to improve daytime functioning and tic severity through sleep-targeted interventions in terms of healthcare services, educational plans, and family support systems.

DISCUSSION

Emerging evidence suggests that children with TS are at a higher risk for sleep disruptions and sleep disorders [7,18,22,23]. This can be explained by the presence of tics during sleep and challenges with sleep onset in children. Several studies suggest that altered dopaminergic, serotonergic, and noradrenergic systems are associated with sleep abnormalities; however, the specific mechanisms of these neurotransmitters in influencing sleep disturbances in children with TS are not well-understood [34,35]. Furthermore, it is hypothesized that the basal ganglia and CSTC circuits play a major role in the occurrence of tics during rapid REM and NREM sleep [34]. Considering the significance of sleep for children's daily functioning, it is essential to assess sleep in the clinical management of TS. Implementing interventions for affected patients that target sleep can potentially alleviate symptoms and improve overall health outcomes. The studies reviewed in this article demonstrate the feasibility of actigraphy as a minimally invasive objective measure in assessing sleep onset in children, which can be leveraged to a greater extent to further investigate the impact of tics on sleep quality in TS [50,51]. Tic severity typically peaks during childhood, and it is therefore important that studies investigating the impact of TS involve pediatric populations wherein symptoms are most severe, and management can prove most crucial to child development outcomes [2,3].

CONCLUSION

This review explores the neurobiology of tic severity in TS and its influences on sleep quality and QoL in children. Considering the gaps in existing literature, the studies used in this review highlight that the pathophysiology of tics observed in TS may lead to poor sleep quality and negatively influence QoL. However, further research is needed to understand the variables to enhance treatment strategies, improve health outcomes, and foster educational advancements to enhance the QoL for children with TS.

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