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A Brief Analysis of Manifestation in Tourette Syndrome

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ABSTRACT

Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by psychiatric and neurological symptoms that typically emerges during childhood or adolescence. Individuals with TS experience involuntary movements or sounds known as "tics." These tics can be categorized as simple, like eye blinking or shoulder shrugging, or complex, such as licking or jumping. Coprolalia is the most recognized symptom, involving complex vocal tics that cause involuntary swearing. TS is more commonly observed in boys than in girls. The gene responsible for Tourette syndrome is inherited as a dominant trait. An abnormality in either the dopaminergic or endorphin receptor system within the basal ganglia may be the cause. The primary objective of this article is to examine the developmental characteristics of Tourette syndrome in children and explore potential treatments for the condition in the future. The pathophysiology encompasses the mechanisms involving the direct pathway of the basal ganglia as well as the mechanism of dopamine. This review focuses on the management of Tourette Syndrome through various treatment approaches, including behavioral therapy and the use of pharmacological medications such as neuroleptics.

KEYWORDS: *Tourette Syndrome (TS), Tics, Coprolalia, behavioural therapies, Neuroleptics*

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INTRODUCTION:

Motor tics, sometimes known as vocal tics, are sudden, rapid, repetitive, erratic motor movements, while vocal tics are vocalisations(1). The disease usually first manifests in childhood and can last throughout maturity, affecting people worldwide in all age groups . Tourette syndrome (TS) is a complex neuropsychiatric disorder characterized by a variety of motor and vocal tics (2).Tic disorders usually appear before puberty, especially between the ages of 4 and 6years, with peak severity observed between10and12yearsofage. Patients have options to manage symptoms through pharmacological or nonpharmacological treatments that can be incorporated into daily life(3).The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classified tic disorders into three groups. These groups include.

Tourette syndrome, persistent motor or vocal tic disorders, and episodic tic disorders. People with these disorders experience tics, which are characterized by sudden, non-rhythmic motor movements and repetitive vocalizations**.** These tics are not caused by other disorders and usually precede theurge (4).

Fig.1: Simple Tics

History:
Tourette Syndrome is a hereditary neurological condition that typically starts during childhood or adolescence. It is identified by the occurrence of various physical (motor) tics along with at least one vocal (phonic) tic (5).

Fifteenth century:
The initial documentation of Tourette syndrome is believed to have occurred in the 15th-century publication Mal leusMaleficarum (Hammer of Witches). This book recounts the story of a priest whose involuntary movements and vocalizations were attributed to demonic possession(6)(7).

Nineteenth century:
Jean-Martin Charcot, a prominent French doctor, tasked his pupil and assistant Georges Gilles de la Tourette with examining individuals suffering from movement disorders at the Salpêtrière Hospital. The objective was to establish a separate medical condition apart from hysteria and chorea(8). Charcot and Gilles de la Tourette hypothesized that the "tic illness" they had witnessed constituted an incurable, persistent, and degenerative hereditary ailment(9).

Twentieth century:
In 1965, a significant moment occurred when Arthur K. Shapiro, often referred to as the pioneer of contemporary tic disorder research (10), administered haloperidol to a patient suffering from Tourette's syndrome. The outcome of this treatment was detailed by Shapiro and his wife, Elaine Shapiro, in a publication from 1968, where they also criticized the psychoanalytic approach(11).

Twenty-first century:
Research on the neurophysiology and neuropathology of Tourette's syndrome aims to establish connections between the disorder and specific brain mechanisms. Clinical trials have prioritized the exploration of tic suppression, comorbid conditions, innovative treatment methods like botulinum toxin, and targeted behavioral therapies (12).

Fig.2: Georges Gilles de la Tourette

Symptoms of TS:

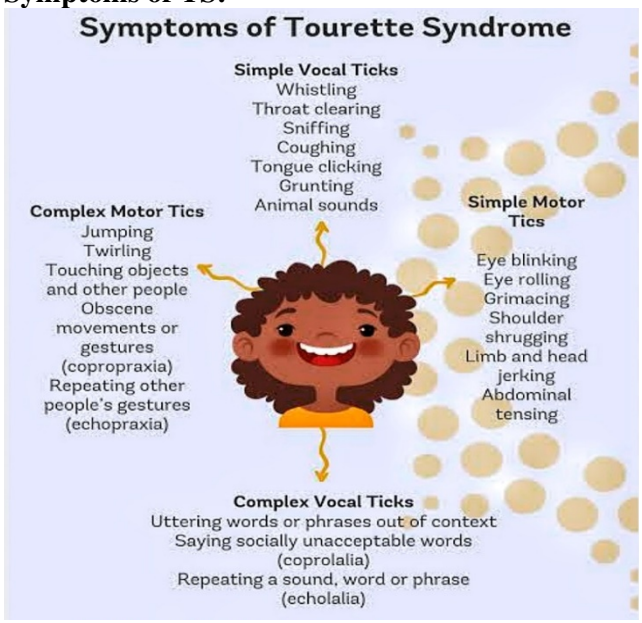

Fig.3: Signs of TS

Classification of tics :
Tics can be categorized as either simple or complex, as Figure 1 illustrates. Simple tics might entail vocal habits like clearing one's throat or physical actions like blinking of the eyes. They are frequently brief, lasting only a few milliseconds. Oftentimes, basic tics include shaking one's head while sighing and holding on for a prolonged period of time, occasionally more than a second Echopraxia, a tic-like repetition of other people's movements, and copropraxia, tics involving appropriate statements, are two examples of complex motor tics. They can include coprolalia (uttering profanities or swear words), echolalia (repeating the last word or phrase heard from others), and palilalia (repeating one's own words or phrases) [13].Individuals may sometimes detect a unique emotion or urge that happens prior to the commencement of a tic, such as an itch before reaching for a scratch. Tics are also more common or severe during stress, excitement, or tiredness. TS and associated tic disorders have no cure, but they can be treated with a mix of therapy and medication [13].

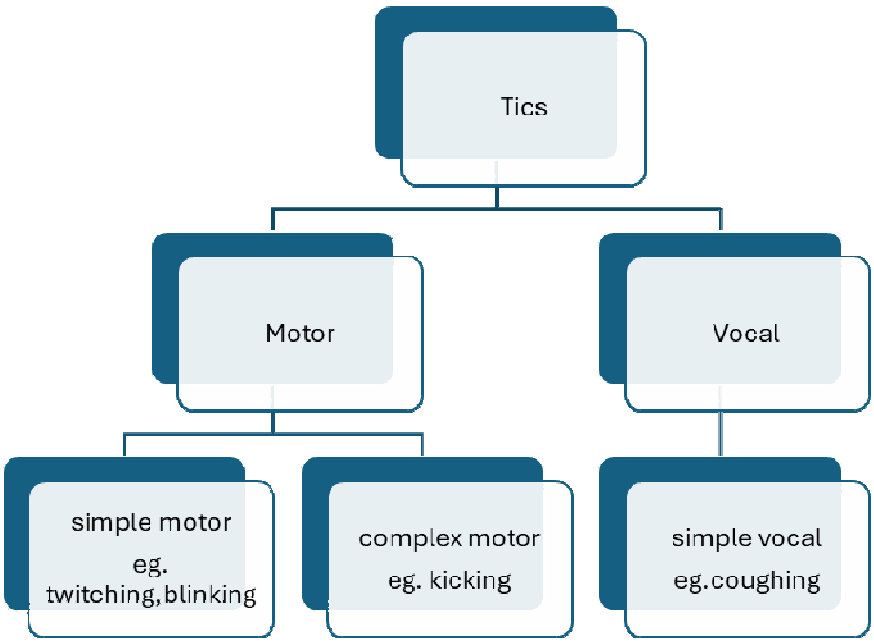

Fig.4: Classification of Tics

Genetics:

In the past year, there have been significant developments in the field of TS genetics, mainly attributed to extensive collaboration. The influence of genetic factors on TS is evident as patients' family members exhibit a higher occurrence of tics, OCD, and ADHD. A noteworthy observation is the elevated prevalence rate among monozygotic twins, whereas dizygotic twins do not display the same pattern (14). The production of histamine, which leads to heightened tic-like behavior, is reliant on the histidine decarboxylase (Hdc) gene. For instance, Hdc mutant mice exhibited excessive grooming (15). The TS gene is most probably passed down as an autosomal dominant trait, although its penetrance is decreased, with around 70% of those inheriting the gene experiencing symptoms. The severity of tics can vary within the same family: some members may show the complete syndrome, while others may only have chronic motor tics, chronic vocal tics, or even transient childhood tics at times. (16) The characteristic is influenced by sex, with a higher frequency of males being affected compared to females. Obsessive-compulsive disorder could be seen as an expression of the TS gene, especially in women. There is also a theory that ADD might be a singular expression of the TS gene (17).

Pathophysiology:

Structural Neuroimaging-

Numerous neuroimaging investigations have been conducted to identify the brain region afflicted in TS patients; however, some of these studies have not found any differences in the white or grey matter [18]. Bloch et al. discovered a substantial and inverse relationship between the severity of tics and caudate volume in early childhood in a prospective longitudinal study [19].

Functional Neuroimaging-

Two patterns were identified by positron emission tomography (PET) and fluorodeoxyglucose (FDG) scans. These patterns include decreased metabolic activity in the orbital frontal cortex and caudate/putamen and increased cerebral activity and bilateral premotor cortex [20]. It was discovered that TS patients had reduced binding in the bilateral thalamus, right insula, bilateral ventral striatum, and bilateral amygdala and increased binding in the bilateral substantia nigra, bilateral striatum, and bilateral thalamus when flumazenil, a GABA receptor agonist, was administered. Cerebellum; Right posterior Cingulate Cortex; Dentate Nuclei. This led to the conclusion that TS patients' brains have inhibitory loss due to involvement of the GABA-ergic system, which results in prompted fast movements [21].

Neurophysiology-

It is believed that in TS patients, the defective inhibitory system in the basal ganglia is unable to prevent undesired signals from getting to the motor cortex (cerebrum). This results in the carrying out of undesirable acts by the sufferer, which is the cause of their tics. Movements are believed to be produced by a combined reaction of failing inhibition in the bas al ganglia and increased activity in the motor pathway [22].While glutamate is excitatory, gamma aminobutyric acid (GABA) is inhibitiory[23].

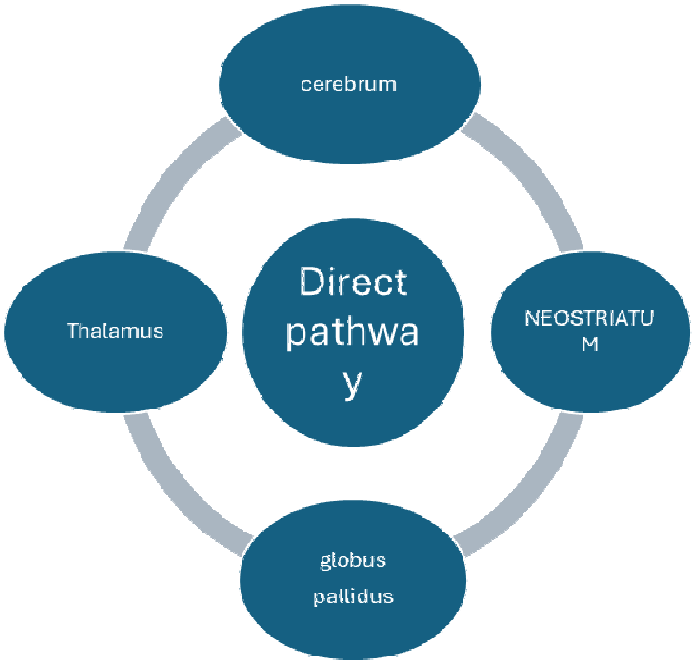

Fig.5:Mechanism of action of basal ganglia via direct pathway.

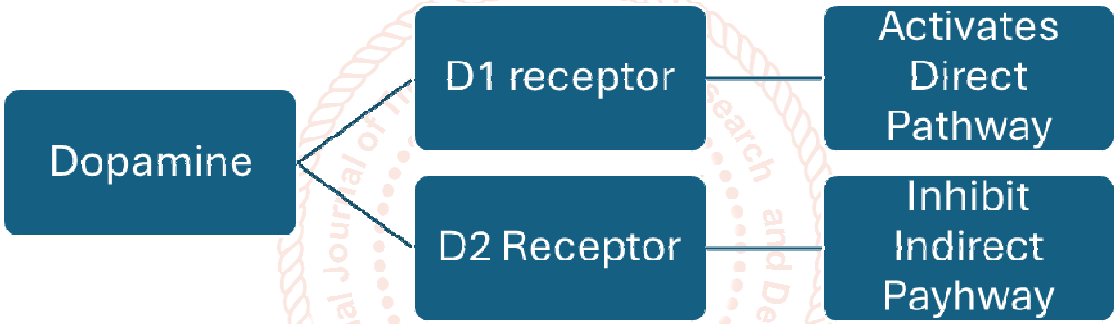

Fig.6: Mechanism of action of dopamine.

Tourette in Children:

Tic disorders impact a significant proportion of children during their developmental years, with prevalence rates ranging from 4% to 18% (24).Tourette's syndrome typically manifests during early childhood, specifically around the age of 6-7 years. Similar to other neurodevelopmental disorders, it is observed to be more prevalent in boys. While Tourette's syndrome was previously considered rare, recent studies conducted in schools have revealed a higher prevalence rate of 1-3% when a broader definition encompassing chronic motor and vocal tics is employed (25). A group of children who experience a sudden onset of tics and obsessive-compulsive disorder have been identified in recent studies. These symptoms are found to be associated with an infection caused by B-haemolytic streptococcal sore throat (26). As children with Tourette Syndrome enter adolescence, the severity of their tics tends to diminish, yet the coexisting disorders may endure and frequently result in heightened functional challenges (27). The onset of motor tics typically occurs between the ages of 4 and 6, preceding the emergence of vocal tics by a few years. In contrast, vocal tics commonly start between 8 and 12 years of age (28). Children with Tourette Syndrome have also been documented to exhibit impairments in procedural memory and habit learning compared to typically developing individuals. This suggests that there may be specific cognitive challenges associated with TS that impact these particular areas of learning and memory (29,30). Numerous epigenetic elements have been linked to the development of TS, such as perinatal injuries, androgen exposure, psychological stress, and autoimmune reactions following infections (31). The main objective for children with TS should be centered on enhancing their abilities in academic environments and social interactions, rather than striving to eradicate their tics. Engagement in physical activities, exploring talents such as playing musical instruments, and practicing good sleep habits are frequently promoted (32). Habit reversal therapy (HRT) has shown promising results in reducing tic severity in children with Tourette syndrome (TS), establishing itself as a leading behavior therapy for this condition (33).

Treatment:

Pschyo education and supportive therapy (PST)-

Age-appropriate explanations for TS and related comorbidities can be given, as well as psychoeducation and supportive therapy (PST) to help lessen misconceptions about TS and perceived stigmas [34]. PST corrects TS misunderstandings and enhances knowledge, according to one meta-analysis [35]. When PST is added to medication, as opposed to medication alone, there is evidence of a further reduction in tics [36]. Accurate information is essential for promoting tics sufferers' well-being. In response to the COVID-19 pandemic, the usage of social media and virtual communication surged, and people—especially teenagers—are increasingly turning to the Internet and these platforms for health-related information [37, 38]. The incidence of explosive onset functional tic-like behaviors may have increased due to social isolation and the need for connection, as well as the increased ingestion of inaccurate information concerning TS from public sources [39].

Behavioral Interventions-

At least one study has demonstrated that behavioral interventions are comparable to pharmacotherapy at reducing tics [40]. Patients are exposed to unpleasant sensations during ERP. Habit reversal therapy (HRT) involves habit control, competing responses, and awareness training. CBIT is an extension of HRT and includes education, relaxation, rewards, and interventions.[41].

Modifications of Existing Behavioral Interventions-

Children with TS between the ages of 9 and 17 were the target population for the initial CBIT trial [42]"The Opposite Game" has been developed as an adaptation of CBIT for kids as young as 5 or 8 years old [43]. Families can now receive instructional HRT training from a DVD at home in addition to in-person CBIT [44].

Virtual Tele- behavioural Interventions-

Amidst the COVID-19 pandemic, which hastened the extensive adoption of telehealth, adaptable approaches to CBIT delivery have assumed heightened significance. Analogous reductions in the severity of tics have been observed when behavioral interventions are administered virtually [45–47].

Pharmacologic Interventions-

Despite the fact that pharmacotherapy is frequently used to treat TS, surprisingly few large, carefully controlled studies have been done to determine the efficacy of medications in TS [48].

While there are many different types of drugs available for treating TS, only three of them have FDA approval at this time: aripiprazole (ages 6–18), pimozide (>12 years old), and haloperidol (>3 years old) [48].

Alpha-2-adrenergic Agonists-

Alpha-2-adrenergic agonists are frequently prescribed as first-line pharmacotherapy due to their comparatively safer side effect profile. These drugs have the potential to inhibit the sympathetic nervous system [49]. As a result, clonidine is advised with a moderate level of confidence in the evidence, while guanfacine is advised with a low level of confidence [50] In clinical practice, guanfacine is frequently preferred over clonidine due to its specificity for alpha-2 receptors, which may make it less sedating than clonidine [51].

GABAergic Medications and Anticonvulsant-

Medication that acts on GABA receptors or influences GABA concentrations has been investigated for use in the treatment of TS since malfunctioning GABA pathways may be part of the underlying etiology of TS [52]. In a double-blind, placebo-controlled trial, opiramate, a broad-spectrum antiepileptic, significantly decreased tics when compared to placebo [53], and a retrospective analysis produced comparable findings [54].

VMAT2 Inhibitors-

The vesicular monoamine transporter-2 (VMAT-2) is responsible for the movement of biogenic amines, such as dopamine. Presynaptic dopamine depletion is how VMAT2 inhibitors function [51]. Tetra benazine has decreased tics in open-label trials [55, 56]. An isomer of tetra benazine with a longer half-life and a lower chance of adverse effects is called deutetrabenazine [57].

Cannabiods-

Tetrahydrocannabinol (THC), which is psychoactive, and cannabidiol (CBD), which is not psychoactive, are the two primary forms of cannabinoids. [37] A synthetic form of THC is called dronabinol, while nabiximol is a combination of THC and CBD [48]. According to a Cochrane study, there is insufficient data to conclude whether or not cannabis is a useful treatment for TS [58]. Dry mouth, nausea/vomiting, headache, exhaustion, confusion, and anxiety are some of the side effects [59] .According to a recent poll, people who have independently used cannabis with high THC content as a treatment for TS prefer it over dronabinol or nabiximols [60]. There are numerous trials that are still in progress. To find out if a certain composition might have greater safety and

efficacy, an RCT comparing placebo and various ratios of THC and CBD was planned; however, the study was stopped due to delayed recruitment (NCT03247244). A study has been registered that compares a 1:1 ratio of THC and CBD compound to an inert oil; the results are not yet accessible (ACTRN12618000545268). In a similar vein, the CANNA-TICS program intends to evaluate nabiximol against a placebo [61].

Botulinum Toxin Injections-

The injection-injected muscle temporarily relaxes as a result of botulinum toxin's inhibition of acetylcholine release at the neuromuscular junction [57•]. Onabotulinumtoxin A injections are likely more likely to lessen tic severity than placebo, according to a meta-analysis of TS therapies [62].

Peripheral Nerve Stimulation-

According to case studies of individuals receiving vagal nerve stimulation (VNS) for unrelated conditions, activating the VNS also reduced tics [63, 64]. Though its exact mechanism of action is yet unknown, VNS may influence tics by lowering the "signal-to-noise ratio," which is thought to aid in distinguishing between background noise and the proper motor impulses [65]. Additionally, it is well recognized that some frequency ranges, including alpha or mu (8–14 Hz) and beta (15–30 Hz), are linked to the inhibition of movement. Therefore, stimulating these cortical oscillations may A recent study found that delivering rhythmic pulses at a frequency of 12 Hz to the median nerve induced mu-band oscillations in the brain, which in turn significantly reduced the frequency and severity of tics as well as the drive to tic [66].

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