

Gilles-de-la-Tourette Syndrome in Childhood: A Comprehensive Review of Molecular, Neurobiological and Genetic Aspects

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ABSTRACT

Tourette syndrome is a neurodevelopmental disorder first described by Georges Gilles de la Tourette in 1885. This syndrome is characterised by repetitive, involuntary movements and vocalisations known as tics. Animals often exhibit repetitive and predictable behaviours. These repetitive actions can be learned and become habits, which can be advantageous from an evolutionary standpoint as they reduce cognitive strain and attentional resources. Repetitive behaviours can also be intentional and conscious, occurring without habit formation, especially in normal child development or certain neuropsychiatric conditions. When these behaviours disrupt social interactions and daily functioning, they may be considered pathological. Conditions such as Gilles de la Tourette syndrome (GTS) can manifest as compulsive, stereotyped, and ritualistic behaviours.

GTS is a congenital disorder of the nervous system and are characterised by involuntary movements and also tic-like vocal or speech expressions. The dopaminergic and serotonergic pathways are believed to play an important role in the development of GTS. The striatum nucleus in the basal ganglia is believed to play a key role in regulating these repetitive behaviors through its connections with various areas of the cortex. However, the specific mechanisms within the striatum, including its organisation, cellular functions, and connections, are still actively researched. At the cellular level, post-mortem studies have found a reduced number of parvalbumin-expressing and cholinergic interneurons. There

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is extensive evidence that the dopaminergic signal transmission in the striatum is disrupted.

This study aims to provide an overview of Gilles de la Tourette syndrome with special focus on molecular aspects, treatment options and recent research with a focus on new targets to treat this rare hereditary disorder in childhood. A multidisciplinary treatment approach is necessary, including drug medication, psychotherapy or deep brain stimulation with focusing on recent research treating this rare disease in childhood sufficiently.

Keywords: Tourette; child treatment; neuropsychiatric; hereditary disorder.

1. INTRODUCTION

The Gilles de la Tourette syndrome is a congenital disorder of the nervous system. Once considered a rarity, Gilles de la Tourette syndrome is now recognised to be a relatively common disorder, which may be associated with considerable psychiatric comorbidity and impaired psychosocial functioning (Schrag & Robertson, 2007; Gunturu et al., 2025). The main features are involuntary movements and also tic-like vocal or speech expressions (Bittmann, 2024). Tics are movements or sounds that appear repetitive, seemingly uncontrollable, out of context, and exaggerated (Zapparoli et al., 2024). Simple motor tics can manifest as eye blinking, nose twitching, head tossing, or grimacing. Examples of simple vocal tics include emitting meaningless sounds, coughing, or imitating animal noises. Complex motor tics in the motor area include imitative grimacing and mimicking the actions of others (Bittmann, 2024). Complex vocal tics are repeating words or blurting out obscene and aggressive expressions. Tics are sometimes difficult to distinguish from spontaneous movements in healthy controls. However, tics occur in a repetitive pattern and appear temporally and situationally misplaced (Kleimaker et al., 2020; Johnson et al., 2023).

Tourette syndrome is classified as a central nervous system movement disorder. Although many patients experience only mild or moderate symptoms, some cases are severe and treatment refractory (Terao et al., 2023; Szejko et al., 2020). Primary tic disorders cannot be cured or causally treated (Bittmann, 2024). Only palliative treatment approaches are available. The name refers to the French neurologist and psychiatrist Georges Gilles de la Tourette, who first described the condition in 1884/1885 at the suggestion of his teacher Jean-Martin Charcot" (Walusinski & Bogousslavsky, 2011). Jean Marc Gaspard Itard had already reported on similar symptoms in one of his patients in 1825 (Itard, 2006). The estimated prevalence in children is 0.3 to 0.9 per cent (Cavanna et al., 2024). In adults, the frequency is significantly lower (Farhat et al., 2023). Differences in frequency in international comparisons are attributed to cultural differences, as the symptoms themselves are similar everywhere and therefore suggest common biological causes. It is diagnosed about three times more often in boys than in girls (Dy-Hollins et al., 2024). Tourette syndrome has specific key symptoms and usually other abnormalities (Bittmann, 2024). The specific appearance varies from patient to patient. Tics are involuntary, rapid, often

sudden and sometimes very intense movements that can occur repeatedly in the same way, individually or in series (Hartmann et al., 2024; Morishita et al., 2024; Gao et al., 2024). Vocal, involuntary utterances such as exclamations or noises are also included. The main symptoms are various types of motor and vocal tics, which often first appear in elementary school age and usually fully develop by around age 14. A worsening is often observed during puberty. In some patients, tics decrease between the ages of 16 and 26, but in the majority of affected individuals, the symptoms persist throughout life. Simple motor tics can manifest as eye blinking, nose twitching, head tossing, or grimacing. Examples of simple vocal tics include emitting meaningless sounds, coughing, or imitating animal noises. The diversity of symptoms is large, so each affected individual shows their own appearance, which can also change over time (Zhang et al., 2024; Okun et al., 2024; Liker et al., 2024).

Complex motor tics in the motor area include imitative grimacing and mimicking the actions of others (echopraxia). Self-injurious behaviour, even when repeated in a tic-like manner, is attributed to other, possibly accompanying - disorders. Complex vocal tics are repeating words, echolalia or palilalia, or the known as coprolalia, the outburst of obscene and aggressive expressions. The symptoms can either occur permanently, multiple times a day (mostly in series), or only in stressful situations (Bittmann, 2024). "It is also typical for many affected individuals to be able to suppress their tics over certain periods of time. It has been found that they, compared to healthy individuals, have an overall increased ability to control the initiation of movements (Hollunder et al., 2024; Nieto-Alamilla et al., 2016). This has been attributed to a training effect through tic suppression and corresponding adaptations in the brain. The practice of suppression can therefore be a useful part of therapy. The most common comorbid condition is attention deficit/hyperactivity disorder (ADHD)" (Roessner et al., 2006; Casas et al., 2024). Another common accompanying manifestation is obsessive-compulsive disorder. Other disorders occur, but it is often unclear whether they are rather aspects of the two main accompanying conditions mentioned above. Those affected suffer mainly from the environment's reaction to their symptoms (Schüller et al., 2024; Zhang et al., 2024; Strom et al., 2024). Especially because people with Tourette syndrome have little or no control over their tic symptoms, the abnormalities associated with Tourette syndrome are often interpreted as bad habits. This often leads to feelings of guilt among parents for their supposedly failed upbringing (Bittmann, 2024). As adolescents, those affected encounter a lot of misunderstanding and rejection in public and school, which can in turn lead to an exacerbation of the abnormalities. Adults with Tourette syndrome are often discriminated against and experience restrictions in their professional and personal development. Outsiders often feel personally provoked by the involuntary tics. This is particularly evident in coprolalia and copropraxia and can lead to a worsening of such situations. Tourette patients are usually as capable as their peers and can fully participate in social life, provided there are no severe accompanying conditions. People with Tourette syndrome have a prolonged reaction time for some tasks, which has been associated with their practice in motor control through tic suppression. There are conflicting results regarding motor skills, which have been attributed to possible unconsidered influences of

accompanying disorders. The neurologist and writer Oliver Sacks addresses the relationship between Tourette's and music in two chapters of his books (Bittmann, 2024). The syndrome is impulsive and productive. On the one hand, it can lead to repetitive movements; on the other hand, it can take on an elaborate, phantasmagorical form. People with a phantasmagorical Tourette syndrome, if they manage to make use of it, can exhibit an overflowing and almost uncontrollable creativity. The American composer Tobias Picker, who has Tourette syndrome, is free of tics while composing and playing music. He believed that the tics had found their way into his creative imagination. The English pianist Nick van Bloss sees his Tourette syndrome as energy that he uses and channels when making music. According to Sacks, jazz and rock music are particularly attractive because of their heavy beats and freedom for improvisation.

Oliver Sacks addressed in his various publications the relationship between Tourette syndrome and the self of the affected person. The syndrome develops an often complicated interweaving with the personality over the course of life. The relationship can be so destructive that some patients hardly find their true identity "in the face of the confusing chaos and the tremendous pressure of impulses." Other patients manage to integrate the syndrome into their personality and "benefit from the rapid pace of thoughts, associations, and ideas that this syndrome brings." The syndrome can lead to "unusual and sometimes astonishing achievements."

2. MOLECULAR ASPECTS

2.1 Protective Effect of Extracellular Matrix Protein Reelin

Reelin, an extracellular matrix protein, is known to play a role in neuronal migration, brain development, and adult plasticity (Pardo et al., 2023). "It has also been linked to various human psychiatric disorders such as schizophrenia, bipolar disorder, autism spectrum disorder and Tourette syndrome (Bittmann, 2024). Studies on heterozygous reeler mice have shown similarities to these disorders, and overexpression of Reelin has been found to offer protection against their manifestation. The specific impact of Reelin on the structure and circuits of the striatal complex, a crucial region for these disorders, especially in cases of altered Reelin expression levels in adulthood, remains unclear" (Pardo et al., 2023). "In a recently published study, conditional gain and loss-of-function mouse models were used to explore how Reelin levels may affect the adult brain's striatal structure and neuronal composition" (Pardo et al., 2023).

"Immunohistochemical analysis revealed that Reelin does not appear to influence the organisation of striatal patch and matrix regions, examined using μ -opioid receptor immunohistochemistry, or the density of medium spiny neurons (MSNs, studied with DARPP-32)" (Pardo et al., 2023). "Researchers observed that overexpression of Reelin resulted in increased numbers of striatal parvalbumin- and cholinergic-interneurons, as well as a slight increase in tyrosine hydroxylase-positive projections" (Pardo et al., 2023). "These findings suggest that elevated

Reelin levels may impact the numbers of striatal interneurons and the density of nigrostriatal dopaminergic projections, potentially contributing to the protective effects of Reelin in cases of Tourette syndrome" (Pardo et al., 2023).

2.2 Role of Interleukins and CSF Oxytocin Levels

The cause of tic disorders is not fully understood, but there is evidence suggesting that the immune system may play a role in the development of these disorders. In an interesting study, an investigation of levels of pro-inflammatory and anti-inflammatory cytokines in children with TD compared to healthy controls were performed (Kutuk et al., 2024). "The study examined how these cytokine levels were related to clinical factors in the TD group" (Kutuk et al., 2024). "A total of 88 children with tic disorders and 111 healthy children participated in this study. Most children with tic disorders had Tourette's disorder (53.4%) or persistent motor tic disorder (44.3%), with a small number diagnosed with persistent vocal tic disorder (2.3%). Our results showed that children with tic disorders had higher levels of IL-1 β , TNF- α , IL-6, and IL-4 expression, and lower levels of IL-17 compared to healthy controls" (Kutuk et al., 2024). "These findings suggest that children with TD may have a proinflammatory state that is not influenced by comorbidities or symptom severity" (Kutuk et al., 2024). "Understanding the role of immune system changes in the development of tic disorders could lead to improved treatment options" (Kutuk et al., 2024).

"The elevated levels of oxytocin in the CSF and the correlation between CSF oxytocin levels and OCD severity suggest a potential role for oxytocin in the neurobiology of a specific subtype of OCD" (Leckman et al., 1994). "These findings highlight the importance of using family genetic data to identify biologically homogeneous groups of patients with OCD, which may have a more consistent aetiology" (Leckman et al., 1994). "Additionally, the differential responsiveness to treatment of tic-related OCD compared to non-tic-related OCD, as shown in emerging pharmacological data, underscores the need to consider tic-relatedness as a variable in biological and behavioural studies of patients with OCD" (Leckman et al., 1994).

2.3 Neurobiological Aspects

The basal ganglia, especially the striatum, have been identified as the central site of the disorders. The core areas of the nucleus caudatus and putamen, located in the latter, are reduced in size in affected individuals (Bittmann, 2024). Imaging techniques have shown that their activity correlates with the frequency of tics. At the cellular level, post-mortem studies have found a reduced number of parvalbumin-expressing and cholinergic interneurons. Furthermore, there is extensive evidence that the dopaminergic signal transmission in the striatum is disrupted. "Dopamine is a crucial neurotransmitter that plays a key role in regulating human movement, motivation, and cognition. It is also involved in behaviours related to reward, reinforcement, and addiction. The central nervous system contains four main dopaminergic pathways. Two pathways originating in the ventral tegmental area project to the cortex and limbic area, a third pathway

projects from the hypothalamus to the pituitary gland, and a fourth pathway projects from the substantia nigra to the striatum (Bittmann, 2024). Neurons in these pathways release dopamine as a neurotransmitter at their terminals. There are five known dopamine receptor subtypes, categorised as D1-like or D2-like. D1-like receptor subtypes (D1 and D5) activate adenylyl cyclase through coupling with the Gs protein, while D2-like subtypes (D2, D3, and D4) inhibit adenylyl cyclase through coupling with G proteins. Dysregulation of the dopaminergic system can lead to various pathological conditions such as Parkinson's disease, schizophrenia, Huntington's disease, depression and Gilles de la Tourette syndrome" (The MICAD Research Team, 2006).

2.4 Genetic Aspects

"A significant locus on chromosome 5q15 was identified through genome-wide analysis" (Tsetsos et al., 2024). "Further analysis involving expression quantitative trait locus, Hi-C data, and genome-wide association study data pointed to the NR2F1 gene and related long noncoding RNAs within this locus" (Tsetsos et al., 2024). "Heritability analysis showed enrichment in brain tissue histone marks, and polygenic risk scoring of brain volume data revealed associations with right and left thalamus volumes and right putamen volume" (Tsetsos et al., 2024).

"A male patient with GTS and other anomalies was found to have a de novo duplication of the long arm of chromosome 7 [46, XY, dup (7) (q22.1-q31.1)], which was determined to be inverted" (Petek et al., 2001). "The distal chromosomal breakpoint was identified between the genetic markers D7S515 and D7S522, a region previously associated with GTS" (Petek et al., 2001). "Yeast and bacterial artificial chromosome clones spanning the breakpoints were identified using FISH analysis (Bittmann, 2024). Further analysis revealed a 6.5-kb SacI junction fragment in the patient's genomic DNA, with two breaks in 7q31 within a 500 kb region. The IMMP2L gene, encoding the human homologue of the yeast mitochondrial inner membrane peptidase subunit 2, was disrupted by the breakpoint in the duplicated fragment and the insertion site in 7q31" (Petek et al., 2001). "The cDNA of the human IMMP2L gene was cloned, revealing a transcript with six exons spanning 860 kb. The potential role of IMMP2L and other candidate genes in the chromosomal rearrangement region, such as NRCAM, Leu-Rch Rep, and Reelin, is discussed. The 7q31 breakpoint interval has also been implicated in other neuropsychiatric disorders with clinical similarities to GTS, including autism and speech-language disorder" (Petek et al., 2001).

"The role of the histaminergic system (HS) in neuropsychiatric diseases is not well-documented, and few studies have reported patients with various neuropsychiatric conditions having disruptions in genes related to the HS. In humans, histamine is produced from histidine by the enzyme histidine decarboxylase encoded by the HDC gene (OMIM*142704), which is the only enzyme in our body capable of producing histamine from histidine" (Lintas et al.,

2022). "Histamine is also present in various foods. The HDC gene has previously been linked to Tourette Syndrome" (Lintas et al., 2022).

Individuals with Gilles de la Tourette syndrome (GTS) exhibit motor and vocal tics and often have comorbid conditions such as obsessive-compulsive disorder (OCD) and attention deficit-hyperactivity disorder (ADHD). The dopaminergic and serotonergic pathways are believed to play a role in the development of GTS. One recent study aimed to investigate the expression of the serotonin transporter (SERT) gene (SLC6A4) in GTS individuals compared to healthy controls and its association with genetic variants (including the 5-HTTLPR, rs25531, and rs25532 variants, and the Ile425Val variant) and promoter methylation of SLC6A4 (Hildonen et al., 2021). The study found that SLC6A4 expression was increased in GTS individuals compared to controls (Hildonen et al., 2021). While no specific genotype, allele, or haplotype was more common in GTS individuals, the LAC/LAC genotype of the 5-HTTLPR/rs25531/rs25532 haplotype was associated with higher SLC6A4 mRNA expression levels in GTS individuals (Hildonen et al., 2021).

Preliminary neuroimaging studies suggest that during NREM sleep in TD, there is increased activity in the premotor cortex and decreased activity in the prefrontal cortex. The *circadian rhythm of striatal dopamine* is influenced by the suprachiasmatic nucleus through various molecular mechanisms. Dopamine receptors play a role in regulating circadian function and the expression of circadian genes in the striatum (Ricketts et al., 2023). The connection between TD and restless legs syndrome and periodic limb movements suggests a common underlying pathophysiology involving iron deficiency and variations in the *BTDB9 gene* (Ricketts et al., 2023). Mutations in the L-Histidine Decarboxylase gene in TD point to the potential involvement of the histaminergic system, which is known to play a role in arousal (Ricketts et al., 2023).

A further study aimed to investigate the molecular mechanisms underlying TS in a large group of pediatric patients (Saia et al., 2023). The analysis included array-CGH testing to identify copy number variations (CNVs) in the patients. The main objective was to characterise the neurobehavioral features of patients with or without pathogenic CNVs and compare these findings with those reported in the literature on neuropsychiatric disorders, including TS (Saia et al., 2023). This comprehensive approach helps in the clinical and molecular profiling of patients for better prognosis and management (Bittmann, 2024). The study found that rare deletions and duplications affecting genes involved in neurodevelopment were more common in children with tics and other conditions. Approximately 12% of the patients in the cohort had *potentially causative CNVs*, consistent with previous research (Saia et al., 2023).

2.5 Functional Neuroimaging Studies

"Functional neuroimaging studies show a *disinhibition of the cortico-striatal-thalamo- cortical circuit*, while structural imaging studies present conflicting results, with some indicating smaller volumes of the caudate nucleus (CN) in

children with Gilles de la Tourette syndrome (TS)” (Walter et al., 2024). “A recent interesting study aimed to investigate whether transcranial sonography (TCS) can detect alterations in the raphe nuclei, substantia nigra, lenticular nucleus (LN), or CN in children with Tic disorder or TS (TIC/TS)” (Walter et al., 2024). “A recent study included 25 treatment-naïve children (average age: 12.2 ± 2.5 years) diagnosed with Tic disorder or TS based on DSM-V criteria (10 subjects), without any other psychiatric or neurological diagnoses, and 25 age- and sex- matched healthy controls (average age: 12.17 ± 2.57 years). Parental assessments of behavioural, emotional abnormalities, somatic complaints, and social competencies were conducted using the Child Behaviour Check List (CBCL/4-18R). TCS of deep brain structures was performed through the preauricular acoustic bone windows using a 2.5- MHz phased-array ultrasound system. Fisher's exact test and Mann-Whitney U test were used for comparisons between TIC/TS patients and healthy controls. The TIC/TS group showed a higher prevalence of hyperechogenic area in the left CN compared to the control group” (Walter et al., 2024). “TIC/TS patients with hyperechogenic CN exhibited more thought- and obsessive-compulsive problems. The study identified pathological structural changes in the CN, a higher prevalence in TIC/TS patients compared to healthy controls, and its association with comorbid thought problems. Future research should investigate the underlying molecular mechanisms, potentially related to disrupted iron metabolism” (Walter et al., 2024).

2.6 Treatment Aspects

Treatment focuses on classical drug management, including Risperidon, Tiaprid, Sulpirid, Quetiapin, Pimozid, Haloperidol and Aripiprazol.

Concerning the aspect of Tourette and ADHD, a clonidine adhesive patch was found to be safe and effective in reducing tic symptoms in TS patients with comorbid ADHD and may also be beneficial in controlling ADHD symptoms (Chen et al., 2024). In a recent study, a total of 127 TS patients with comorbid ADHD were included in a subgroup analysis, divided into 2.0 mg/week ($n=35$), 1.5 mg/week ($n=27$), 1.0 mg/week ($n=36$), and placebo groups ($n=29$) (Chen et al., 2024). The TD effective rate at week 8 for the 2.0 mg, 1.5 mg, and 1.0 mg groups was significantly higher than that in the placebo group (85.7%, 81.5%, and 86.1% vs. 20.7%, all $p<0.0001$) (Chen et al., 2024). All groups showed significant improvements in SNAP-IV total scale scores compared to baseline ($p=0.0004$), with treatment groups showing a trend towards better performance at week 8 compared to the placebo group, although without statistical significance (22.1 ± 15.41 , 21.3 ± 11.96 , and 21.2 ± 12.48 vs. 26.0 ± 13.37 , $p=0.3385$). Nine adverse reactions were reported, all of which resolved spontaneously without additional medication (Chen et al., 2024).

2.7 Drugs in Research

SCI-110 combines Dronabinol, an FDA-approved synthetic form of THC, with the endocannabinoid palmitoylethanolamide (PEA). This combination is designed to target cannabinoid receptors in the central nervous system and prevent the

breakdown of endocannabinoids, enhancing the absorption of THC. The expected benefits of SCI-110 include improved oral administration efficiency, reduced dosage requirements, and minimised side effects and adverse events. SCI-110 is currently being investigated for the treatment of Tourette syndrome (TS), obstructive sleep apnea, and Alzheimer's disease-related agitation (Bittmann, 2024). Newly released data from an investigator-initiated phase 2 trial revealed that SCI-110, a cannabinoid-focused agent, successfully achieved its primary goal of tolerability and significantly improved agitation in patients with Alzheimer's disease (AD) and agitation. The trial, which was single-arm and open-label, included 18 participants with AD and agitation who were treated with SCI-110 twice daily for 32 days, followed by a 7-day post-treatment period. SCI-110 is a unique combination of Dronabinol, an FDA-approved synthetic form of delta-9-tetrahydrocannabinol, and CannAmide, SciSparc's proprietary formulation of palmitoylethanolamide. At the end of the 39-day trial period, the primary endpoints of tolerability and treatment-related adverse events were successfully met, with no dropouts due to poor tolerability and no adverse events related to treatment. The trial achieved its secondary endpoint of a reduction in the Cohen-Mansfield Agitation Inventory (CMAI) total score, a measure of agitation in dementia patients. Out of the 15 individuals who received SCI-110 at doses ranging from 7.5 mg to 12.5 mg per day for at least 2 consecutive times during the trial, 13 showed improvement in agitation without requiring rescue medication to manage their symptoms.

2.8 Shaoma-Zhijing Granules

The available evidence indicates that the SMZJG's components likely exert their mechanisms in treating TS by regulating the dopaminergic pathway system, neurotransmitter imbalances, reducing neuroinflammation, promoting the repair of nerve damage and improving sleep disorders (Zhao et al., 2024).

2.9 Psychotherapy (Habit-reversal training)

Habit-reversal training is a well-known additive treatment for Tourette syndrome. Habit reversal training is another effective behaviour therapy method that is widely studied. It focuses on increasing children's self-awareness of tic attacks through various techniques, such as describing tic responses, recognising responses, early warning processes, and situational awareness training (Bittmann, 2024). The goal is to teach children to use competing actions to interrupt or suppress tic attacks. Habit reversal training may also incorporate relaxation techniques, habit management, and general training. Numerous studies have demonstrated that habit reversal training, with or without medication, can effectively reduce motor and vocal tics in adults and children with TS. However, the widespread implementation of habit reversal training is limited by the need for informed consent from families, a shortage of trained therapists, and insufficient insurance coverage (Bittmann, 2024).

2.10 Thalamic Deep Brain Stimulation

Deep brain stimulation (DBS) of the thalamus is a safe and effective treatment for various diseases. The primary use of thalamic DBS is for Tourette syndrome. DBS offers advantages over thalamotomy, such as reversibility, the ability to adjust stimulation settings for optimal results and minimal side effects, safe bilateral procedures, and a lower risk of cognitive issues post-surgery (Bittmann, 2024). The most common target for DBS in ET is the ventralis intermedius (VIM) of the thalamus, with the ideal electrode placement at the anterior VIM margin. Other conditions that may benefit from thalamic DBS include non-ET tremor, obsessive-compulsive disorder, neuropathic pain, traumatic brain injury and drug-resistant epilepsy.

2.11 Stereotactic Awake Basal Ganglia Electrophysiological Recording and Stimulation (SABERS)

Deep brain stimulation (DBS) target selection has traditionally relied on clinical experience, but inconsistent outcomes have limited its use in patients with diverse or rare disorders (Liker et al., 2024). In this extensive case series, a new staged procedure called Stereotactic awake basal ganglia electrophysiological recording and stimulation (SABERS) is utilised to assess targets for neuromodulation tailored to each patient's needs (Liker et al., 2024). Thirty children and young adults underwent DBS target evaluation using SABERS, involving testing with temporary depth electrodes over 5-7 days in a neuromodulation monitoring unit. Results guided the decision for permanent DBS implantation and target selection. Postoperative evaluation at 3-6 months using the Burke-Fahn-Marsden dystonia rating scale and Barry-Albright dystonia scale showed significant improvement (Bittmann, 2024). The SABERS protocol allowed for personalised modulation of neurologic deficits in a diverse population, including those with primary dystonia, secondary dystonia, and Tourette syndrome. Most subjects received 4 permanent DBS leads, with no significant adverse events reported. The use of SABERS in the neuromodulation monitoring unit proved feasible and beneficial, expanding the application of functional neurosurgery to identify effective stimulation targets in various brain disorders. This innovative technique supports the prediction of optimal stimulation targets in a wide range of brain function disorders, especially in Tourette syndrome (Liker et al., 2024).

3. DISCUSSION

Tourette syndrome is a rare neurodevelopmental disorder in children, often accompanied by neuropsychiatric disorders such as OCD and ADHD. From genetic viewpoint, a multigenetic origin must be supposed. Different studies revealed different genetic findings in patients with Tourette syndrome, especially *the locus on chromosome 5q15, a de novo duplication of the long arm of chromosome 7; a breakpoint in the duplicated fragment and the insertion site in 7q31; changes in the HDC gene and a higher SLC6A4 gene expression in patients with Tourette syndrome* (Tsetsos et al., 2024; Lintas et al., 2022;

Hildonen et al., 2021; Petek et al., 2001). While the exact cause and genetic origin of TS are still unknown, various drug applications have advanced. Mild cases may benefit from psychological and behavioural interventions, including habit reversal training. Many children require medication to manage tics and related symptoms. This means medication over many years with side effects, without curing the patient, but relieving his symptoms. Research must focus on better targets to cure the disease. But cure means knowing the origin exactly, then thinking about adequate therapy, here especially genetic approaches to cure the disease very early (Bittmann, 2024). The pathophysiology of Tourette syndrome remains variable from a genetic aspect, with no single point mutation as a clear origin of the disease. This aggravates thinking about curing Tourette syndrome when not know clearly what the origin is. From therapeutic aspect, a multifactorial treatment is necessary, dietary, by medication, traditional medicine, behavioral treatment with psychotherapy, deep brain stimulation of the thalamus and, nevertheless, recent research on stereotactic awake basal ganglia stimulation. But all these attempts do not cure the patient. They don't cure, but they can help relieve symptoms that disturb patients lives in an extraordinary way. Researchers are well-engaged in focusing on the disease, but it is a misconception to think that getting a grip on the causes of Tourette syndrome.

4. CONCLUSION

Gilles de la Tourette syndrome in childhood is a therapeutic challenge (Bittmann, 2024). From a genetic aspect, there seem to be multiple genetic causes and variants of the disease, so that a one-time gene therapy approach seems to be forgettable. A multidisciplinary treatment approach is necessary, including drug medication, psychotherapy or deep brain stimulation with focusing on recent research treating this rare disease in childhood sufficiently.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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