Asian Journal of Pediatric Research

Volume 14, Issue 8, Page 8-17, 2024; Article no.AJPR.120823
ISSN: 2582-2950

Gilles-de-la-Tourette Syndrome in Childhood: Molecular, Neurobiological and Genetic Aspects

Stefan Bittmann [a,b++*]

[a] Department of Pediatrics, Ped Mind Institute (PMI), Hindenburgring 4, D-48599 Gronau, Germany.
[b] Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i8376

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/120823

Review Article

Received: 23/05/2024
Accepted: 25/07/2024
Published: 27/07/2024

ABSTRACT

Animals often exhibit repetitive and predictable behaviors. 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 behaviors can also be intentional and conscious, occurring without habit formation, especially in normal child development or certain neuropsychiatric conditions. When these behaviors 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 behaviors. 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 organization, cellular functions, and connections, are still actively researched. At the cellular level, post-mortem studies have found a reduced number of parvalbumin-expressing and

[++] Head and Visiting Professor;
**Corresponding author: Email: stefanbittmann@gmx.de;*

Cite as: *Bittmann, Stefan. 2024. "Gilles-De-La-Tourette Syndrome in Childhood: Molecular, Neurobiological and Genetic Aspects". Asian Journal of Pediatric Research 14 (8):8-17. https://doi.org/10.9734/ajpr/2024/v14i8376.*

cholinergic interneurons. There is extensive evidence that the dopaminergic signal transmission in the striatum is disrupted. This work focus on 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.

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

1. INTRODUCTION

"The Gilles de la Tourette syndrome is a congenital disorder of the nervous system. The main features are involuntary movements and also tic-like vocal or speech expressions. 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. Complex vocal tics are repeating words or blurting out obscene and aggressive expressions. Tourette syndrome is classified as a central nervous system movement disorder. Primary tic disorders cannot be cured or causally treated. 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" [1]. Jean Marc Gaspard Itard had already reported on similar symptoms in one of his patients in 1825 [2]. The estimated prevalence in children is 0.3 to 0.9 percent [3]. In adults, the frequency is significantly lower [4]. 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 [5]. Tourette syndrome has specific key symptoms and usually other abnormalities. 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 [6-8]. 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 [9-11].

Complex motor tics in the motor area include imitative grimacing and mimicking the actions of others (echopraxia). Self-injurious behavior, 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. "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 [12,13]. 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)" [14,15]. Another common accompanying manifestation is obsessive-compulsive disorder. Other disorders occur, but it is often unclear whether they are not rather aspects of the two main accompanying conditions mentioned above. Those affected suffer mainly from the environment's reaction to their symptoms [16-18]. 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. 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 often 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 and music in two chapters of his books. 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 [19]. “It has also been linked to various human psychiatric disorders such as schizophrenia, bipolar disorder, autism spectrum disorder and Tourette syndrome. 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” [19]. “In a recent 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” [19].

“Immunohistochemical analysis revealed that Reelin does not appear to influence the organization of striatal patch and matrix regions, examined using μ-opioid receptor immunohistochemistry, or the density of medium spiny neurons (MSNs, studied with DARPP-32)” [19]. “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” [19]. “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” [19].

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 [20]. “The study examined how these cytokine levels were related to clinical factors in the TD group” [20]. “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-1β, TNF-α, IL-6, and IL-4 expression, and lower levels of IL-17 compared to healthy controls” [20]. “These

findings suggest that children with TD may have a proinflammatory state that is not influenced by comorbidities or symptom severity" [20]. "Understanding the role of immune system changes in the development of tic disorders could lead to improved treatment options" [20].

"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" [21]. "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 etiology" [21]. "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 behavioral studies of patients with OCD" [21].

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. 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 behaviors 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. Neurons in these pathways release dopamine as a neurotransmitter at their terminals. There are five known dopamine receptor subtypes, categorized 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 adenylate 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" [22].

2.4 Genetic Aspects

"A significant locus on chromosome 5q15 was identified through genome-wide analysis" [23]. "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" [23]. "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" [23].

"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" [24]. "The distal chromosomal breakpoint was identified between the genetic markers D7S515 and D7S522, a region previously associated with GTS" [24]. "Yeast and bacterial artificial chromosome clones spanning the breakpoints were identified using FISH analysis. 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" [24]. "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" [24].

"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" [25]. "Histamine is also

present in various foods. The HDC gene has previously been linked to Tourette Syndrome" [25].

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 [26]. The study found that SLC6A4 expression was increased in GTS individuals compared to controls [26]. 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 [26].

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 [27]. 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* [27]. 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 [27].

A further study aimed to investigate the molecular mechanisms underlying TS in a large group of pediatric patients [28]. The analysis included array-CGH testing to identify copy number variations (CNVs) in the patients. The main objective was to characterize 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 [28]. This comprehensive approach helps in the clinical and molecular profiling of patients for better prognosis and management. 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 [28].

2.5 Functional Neuroimaging Studies

"Functional neuroimaging studies show an *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)" [29]. "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)" [29]. "A recent study included 25 treatment-naive 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 behavioral, emotional abnormalities, somatic complaints, and social competencies were conducted using the Child Behavior 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" [29]. "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" [29].

2.6 Treatment Aspects

Treatment focus on classical drug management including Risperidon, Tiaprid, Sulpirid, Quetiapin, Pimozid, Haloperidol and Aripripazol.

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 [30]. 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) [30]. 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 $p<0.0001$) [30]. 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 [30].

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 minimized 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. 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 [31].

2.9 Psychotherapy (Habit-reversal training)

Habit-reversal training is a well-known additive treatment for Tourette syndrome. Habit reversal training is another effective behavior 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, recognizing responses, early warning processes, and situational awareness training. 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.

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. 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 [32]. In this extensive case series, a new staged procedure called Stereotactic awake basal ganglia electrophysiological recording and stimulation (SABERS) is utilized to assess targets for neuromodulation tailored to each patient's needs (32). 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. The SABERS protocol allowed for personalized 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 [32].

3. DISCUSSION

Tourette syndrome is a rare neurodevelopmental disorder in children, often accompanied by neuropsychiatric disorders such as OCD and ADHD. From genetical viewpoint, a multigenetical 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 HDC gene and a higher SLC6A4 gene expression* in patients with Tourette syndrome [23,25,26,24]. While the exact cause and genetic origin of TS is still unknown, various drug applications have advanced. Mild cases may benefit from psychological and behavioral 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. The pathophysiology of Tourette syndrome remains variable from genetic aspect, with no single point mutation as a clear origin of the disease. This aggravates thinking about curing Tourette syndrome when not knowing clearly what the origin is. From therapeutical aspect, a multifactorial treatment is necessary, dietic, 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 relieving symptoms, that disturb patients life in an extraordinary way. Researchers are well engaged in focussing on the disease, but it is a misconception to think getting a grip on the causes of Tourette syndrome.

4. CONCLUSION

Gilles de la Tourette syndrome in childhood is a therapeutic challenge. From genetic aspect, there seem to be multiple genetic causes and variants of the disease, 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 focussing on recent research treating this rare disease in childhood sufficiently.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declares that NO generative AI technologies such as Large Language Models (Chat GPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Walusinski O, Bogousslavsky J. Georges Gilles de la Tourette (1857-1904). J Neurol. 2011 Jan;258(1):166-7.
   DOI: 10.1007/s00415-010-5800-4. Epub 2010 Oct 27. PMID: 20978906
2. Itard JM. Study of several involuntary functions of the apparatus of movement, gripping, and voice. 1825. Hist Psychiatry. 2006 Sep;17(67 Pt 3):339-51.
   DOI: 10.1177/0957154X0601700308. PMID: 17375450
3. Cavanna AE, Spini L, Ferrari S, Purpura G, Riva A, Nacinovich R, Seri S. Functional tic-like behaviors: From the COVID-19 pandemic to the post-pandemic era. Healthcare (Basel). 2024 May 28;12(11):1106.
   DOI: 10.3390/healthcare12111106. PMID: 38891181; PMCID: PMC11171709
4. Farhat LC, Behling E, Landeros-Weisenberger A, Levine JLS, Macul Ferreira de Barros P, Wang Z, Bloch MH. Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: A systematic review and network meta-analysis. Lancet Child Adolesc Health. 2023 Feb;7(2):112-126.
   DOI: 10.1016/S2352-4642(22)00316-9. Epub 2022 Dec 14. PMID: 36528030
5. Dy-Hollins ME, Chibnik LB, Tracy NA, Osiecki L, Budman CL, Cath DC, Grados MA, King RA, Gholson L, Rouleau GA, Sandor P, Singer HS, Sharma N, Mathews CA, Scharf J. Sex differences in people with tourette syndrome and persistent motor or vocal tic disorder in the tourette association of America international consortium for genetics database. medRxiv [Preprint]. 2024 Jan 9:2024.01.07.24300816.
   DOI: 10.1101/2024.01.07.24300816. PMID: 38260551; PMCID: PMC10802652
6. Hartmann A, Ansquer S, Brefel-Courbon C, Burbaud P, Castrioto A, Czernecki V, Damier P, Deniau E, Drapier S, Jalenques I, Marechal O, Priou T, Spodenkiewicz M, Thobois S, Roubertie A, Witjas T, Anheim M. French guidelines for the diagnosis and management of Tourette syndrome. Rev Neurol (Paris). 2024 May 16:S0035-3787(24)00524-1.
   DOI: 10.1016/j.neurol.2024.04.005. Epub ahead of print. PMID: 38760282
7. Morishita T, Sakai Y, Iida H, Tanaka H, Permana GI, Kobayashi H, Tanaka SC, Abe H. Surgical concepts and long-term outcomes of thalamic deep brain stimulation in patients with severe tourette syndrome: A single-center experience. Neurol Med Chir (Tokyo). 2024 Jun 19.
   DOI: 10.2176/jns-nmc.2023-0254. Epub ahead of print. PMID: 38897940
8. Gao Y, Wang S, Wang A, Fan S, Ge Y, Wang H, Gao D, Wang J, Mao Z, Zhao H, Zhang H, Shi L, Liu H, Zhu G, Yang A, Bai Y, Zhang X, Liu C, Wang Q, Li R, Liang K, Brown KG, Cui Z, Han C, Zhang J, Meng F. Comparison of children and adults in deep brain stimulation for Tourette Syndrome: A large-scale multicenter study of 102 cases with long-term follow-up. BMC Med. 2024 May 30;22(1):218.
   DOI: 10.1186/s12916-024-03432-w. PMID: 38816877; PMCID: PMC11141040
9. Zhang A, Liu T, Xu J, Zhao Q, Wang X, Jiang Z, Liang S, Cui Y, Li Y. Efficacy of deep brain stimulation for Tourette syndrome and its comorbidities: A meta-analysis. Neurotherapeutics. 2024 Apr 29:e00360.
   DOI: 10.1016/j.neurot.2024.e00360. Epub ahead of print. PMID: 38688785
10. Okun MS, Cagle J, Gomez J, Bowers D, Wong J, Foote KD, Gunduz A. Responsive deep brain stimulation for the treatment of Tourette syndrome. Sci Rep. 2024 Mar 18;14(1):6467.
    DOI: 10.1038/s41598-024-57071-5. PMID: 38499664; PMCID: PMC10948908
11. Liker MA, Sanger TD, MacLean JA, Nataraj J, Arguelles E, Krieger M, Robison A, Olaya J. Stereotactic awake basal ganglia electrophysiological recording and stimulation (SABERS): A novel staged procedure for personalized targeting of deep brain stimulation in pediatric movement and neuropsychiatric disorders. J Child Neurol. 2024 Jan;39(1-2):33-44.
    DOI: 10.1177/08830738231224057. Epub 2024 Feb 26. PMID: 38409793
12. Hollunder B, Ostrem JL, Sahin IA, Rajamani N, Oxenford S, Butenko K, Neudorfer C, Reinhardt P, Zvarova P, Polosan M, Akram H, Vissani M, Zhang C, Sun B, Navratil P, Reich MM, Volkmann J, Yeh FC, Baldermann JC, Dembek TA, Visser-Vandewalle V, Alho EJL, Franceschini PR, Nanda P, Finke C, Kühn AA, Dougherty DD, Richardson RM, Bergman H, DeLong MR, Mazzoni A,

Romito LM, Tyagi H, Zrinzo L, Joyce EM, Chabardes S, Starr PA, Li N, Horn A. Mapping dysfunctional circuits in the frontal cortex using deep brain stimulation. Nat Neurosci. 2024 Mar;27(3): 573-586.
DOI: 10.1038/s41593-024-01570-1. Epub 2024 Feb 22. PMID: 38388734; PMCID: PMC10917675

13. Nieto-Alamilla G, Márquez-Gómez R, García-Gálvez AM, Morales-Figueroa GE, Arias-Montaño JA. The histamine H3 receptor: Structure, pharmacology, and function. Mol Pharmacol. 2016 Nov;90(5):649-673.
DOI: 10.1124/mol.116.104752. Epub 2016 Aug 25. PMID: 27563055
14. Roessner V, Banaschewski T, Rothenberger A. Neuropsychologie bei ADHS und Ticstörungen-- eine Follow-up-Untersuchung [Neuropsychological performance in ADHD and tic-disorders: A prospective 1-year follow-up]. Prax Kinderpsychol Kinderpsychiatr. 2006;55(5):314-27. German. PMID: 16869479.
15. Casas G, García Santana C, Cote Martínez D. Trastorno por déficit de atención/hiperactividad (TDAH) y trastorno de Tourette (TT): entre la comorbilidad y el diagnóstico diferencial [Attention deficit/hyperactivity disorder (ADHD) and Tourette disorder (TD): between comorbidity and differential diagnosis]. Medicina (B Aires). 2024 Mar;84 Suppl 1:20-25. Spanish. PMID: 38350620.
16. Schüller T, Huys D, Kohl S, Visser-Vandewalle V, Dembek TA, Kuhn J, Baldermann JC, Smith EE. Thalamic deep brain stimulation for tourette syndrome increases cortical beta activity. Brain Stimul. 2024 Mar-Apr;17(2):197-201.
DOI: 10.1016/j.brs.2024.01.011. Epub 2024 Feb 8. PMID: 38341176
17. Zhang A, Liu T, Xu J, Zhao Q, Wang X, Jiang Z, Liang S, Cui Y, Li Y. Treatment refractory Tourette syndrome in adolescents: Assessment and application of deep brain stimulation. Asian J Psychiatr. 2024 Apr;94:103948.
DOI: 10.1016/j.ajp.2024.103948. Epub 2024 Feb 4. PMID: 38335642
18. Strom NI, Gerring ZF, Galimberti M, Yu D, Halvorsen MW, Abdellaoui A, Rodriguez-Fontenla C, et al. Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci. medRxiv [Preprint]. 2024 Mar 13:2024.03.13.24304161.
DOI: 10.1101/2024.03.13.24304161. PMID: 38712091; PMCID: PMC11071577
19. Pardo M, Gregorio S, Montalban E, Pujadas L, Elias-Tersa A, Masachs N, Vílchez-Acosta A, Parent A, Auladell C, Girault JA, Vila M, Nairn AC, Manso Y, Soriano E. Adult-specific reelin expression alters striatal neuronal organization: implications for neuropsychiatric disorders. Front Cell Neurosci. 2023 Apr 20;17:1143319.
DOI: 10.3389/fncel.2023.1143319. PMID: 37153634; PMCID: PMC10157100
20. Kutuk MO, Tufan AE, Kilicaslan F, Gokcen C, Aksu GG, Yektas C, Kandemir H, Celik F, Mutluer T, Buber A, Karadag M, Coban N, Coskun S, Hangul Z, Altintas E, Acikbas U, Giray A, Aka Y, Basturk B, Kutuk O. Cytokine expression profiles in children and adolescents with tic disorders. Sci Rep. 2024 Jul 2;14(1):15101.
DOI: 10.1038/s41598-024-62121-z. PMID: 38956051; PMCID: PMC11219894
21. Leckman JF, Goodman WK, North WG, Chappell PB, Price LH, Pauls DL, Anderson GM, Riddle MA, McSwiggan-Hardin M, McDougle CJ, et al. Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. Comparison with Tourette's syndrome and healthy controls. Arch Gen Psychiatry. 1994 Oct;51(10):782-92.
DOI: 10.1001/archpsyc.1994.03950100030003. PMID: 7524462
22. The MICAD Research Team. 4-[^{18}F]Fluoro-l-*m*-tyrosine. 2006 Oct 11 [updated 2006 Nov 9]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for biotechnology information (US); 2004–2013. PMID: 20641732.
23. Tsetsos F, Topaloudi A, Jain P, Yang Z, Yu D, Kolovos P, Tumer Z, Rizzo R, Hartmann A, Depienne C, Worbe Y, Müller-Vahl KR, Cath DC, Boomsma DI, Wolanczyk T, Zekanowski C, Barta C, Nemoda Z, Tarnok Z, Padmanabhuni SS, Buxbaum JD, Grice D, Glennon J, Stefansson H, Hengerer B, Yannaki E, Stamatoyannopoulos JA, Benaroya-Milshtein N, Cardona F, Hedderly T, Heyman I, Huyser C, Mir P, Morer A, Mueller N, Munchau A, Plessen KJ, Porcelli C, Roessner V, Walitza S, Schrag A, Martino D; PGC TS Working

Group; TSAICG; TSGeneSEE Initiative; EMTICS Collaborative Group; TS-EUROTRAIN Network; TIC Genetics Collaborative Group; Tischfield JA, Heiman GA, Willsey AJ, Dietrich A, Davis LK, Crowley JJ, Mathews CA, Scharf JM, Georgitsi M, Hoekstra PJ, Paschou P. Genome-wide association study points to novel locus for gilles de la tourette syndrome. Biol Psychiatry. 2024 Jul 15;96(2):114-124.
DOI: 10.1016/j.biopsych.2023.01.023. Epub 2023 Feb 2. PMID: 36738982; PMCID: PMC10783199

24. Petek E, Windpassinger C, Vincent JB, Cheung J, Boright AP, Scherer SW, Kroisel PM, Wagner K. Disruption of a novel gene (IMMP2L) by a breakpoint in 7q31 associated with Tourette syndrome. Am J Hum Genet. 2001 Apr;68(4):848-58.
DOI: 10.1086/319523. Epub 2001 Mar 9. PMID: 11254443; PMCID: PMC1275638

25. Lintas C, Sacco R, Azzarà A, Cassano I, Laino L, Grammatico P, Gurrieri F. Genetic dysruption of the histaminergic pathways: A novel deletion at the 15q21.2 *locus* associated with variable expressivity of neuropsychiatric disorders. Genes (Basel). 2022 Sep 20;13(10):1685.
DOI: 10.3390/genes13101685. PMID: 36292569; PMCID: PMC9602325

26. Hildonen M, Levy AM, Dahl C, Bjerregaard VA, Birk Møller L, Guldberg P, Debes NM, Tümer Z. Elevated expression of *SLC6A4* encoding the serotonin transporter (SERT) in gilles de la tourette syndrome. Genes (Basel). 2021 Jan 12;12(1):86.
DOI: 10.3390/genes12010086. PMID: 33445578; PMCID: PMC7827645

27. Ricketts EJ, Swisher V, Greene DJ, Silverman D, Nofzinger EA, Colwell CS. Sleep disturbance in tourette's disorder: Potential underlying mechanisms. Curr Sleep Med Rep. 2023 Mar;9(1):10-22.
DOI: 10.1007/s40675-022-00242-5. Epub 2023 Jan 23. PMID: 37636897; PMCID: PMC10457082

28. Saia F, Prato A, Saccuzzo L, Madia F, Barone R, Fichera M, Rizzo R. Copy number variations in children with tourette syndrome: Systematic investigation in a clinical setting. Genes (Basel). 2023 Feb 15;14(2):500.
DOI: 10.3390/genes14020500. PMID: 36833427; PMCID: PMC9956985

29. Walter U, Buchmann J, Sülldorf A, Dück A, Russnak A, Hässler F, Berger C. Transcranial sonography of subcortical structures in tic/tourette disorder. J Psychiatr Res. 2024 May 30;176:18-22.
DOI: 10.1016/j.jpsychires.2024.05.058. Epub ahead of print. PMID: 38830296

30. Chen Y, Ke Z, Ouyang Y, Han Y, Liang D, Gao X, He J, Du Y. Clonidine patch for tourette syndrome with attention-deficit/hyperactivity disorder. Psychiatry Investig. 2024 Apr;21(4):387-395.
DOI: 10.30773/pi.2023.0262. Epub 2024 Apr 23. PMID: 38695046; PMCID: PMC11065525

31. Zhao Q, Hu Y, Yan Y, Song X, Yu J, Wang W, Zhou S, Su X, Bloch MH, Leckman JF, Chen Y, Sun H. The effects of shaoma zhijing granules and its main components on Tourette syndrome. Phytomedicine. 2024 Jul;129:155686.
DOI: 10.1016/j.phymed.2024.155686. Epub 2024 Apr 26. PMID: 38759346

32. Liker MA, Sanger TD, MacLean JA, et al. Stereotactic awake basal ganglia electrophysiological recording and stimulation (SABERS): A novel staged procedure for personalized targeting of deep brain stimulation in pediatric movement and neuropsychiatric disorders. Journal of Child Neurology. 2024;39(1-2):33-44.
DOI: 10.1177/08830738231224057

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/120823