Tourette's syndrome: clinical features, pathophysiology, and therapeutic approaches

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Tourette's syndrome (TS) is a disease which has its onset during childhood and/or adolescence and is often life-long. Although the earliest descriptions of patients with motor and vocal tics were passed down from the ancient Greeks, Gilles de la Tourette was the first person who systematically described nine cases of the disorder that now bears his name, in 1885 when he was a student of Charcot at the Salpétrière hospital in Paris.

Gilles de la Tourette reported a positive family history in several of his nine original TS cases, rasing the question of a genetic origin of the disorder. The etiology of TS, however, was subsequently ascribed to psychogenic causes until the 1950s. This perception began to change in the 1960s, when the beneficial effects of neuroleptic

Tourette's syndrome (TS) is a disorder characterized by simple and complex motor tics, vocal tics, and frequently obsessive-compulsive symptoms. Its onset occurs before the age of 21. Typically, TS shows a waxing and waning course, but a chronification of the tics, even during later life, is often observed. TS mainly occurs in boys, and shows genetic heritability with differing penetrance. The pathological mechanism is still unclear. Neuroanatomical and neuroimaging studies, as well as effective treatment using antipsychotics, suggest that a disturbance of the dopaminergic system in the basal ganglia plays an important role in the pathogenesis of TS. Several possibly causative mechanisms of the disturbed dopaminergic neurotransmission are discussed, with the main emphasis on the—infection-triggered—inflammatory immune process. Extrapyramidal movement disorders are known to occur as a symptom of poststreptococcal disease, such as in Sydenham's chorea. Cases of childhood TS are proposed to be caused by such a post-streptococcal mechanism, being part of a spectrum of childhood neurobehavioral disorders termed pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS). The overlap between TS and PANDAS is discussed, and a critical view of the PANDAS concept is presented. The therapeutic implications of the different pathological mechanisms are described, taking into consideration not only the acute or chronic natures of different infections, but also an autoimmune process. Moreover, therapeutic strategies using typical and atypical antipsychotics, and also experimental therapies such as repetitive transcranial magnetic stimulation and deep brain stimulation, are critically discussed.

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Selected abbreviations and acronyms

ADHD	*attention deficit-hyperactivity disorder*
OCD	*obsessive-compulsive disorder*
PANDAS	*pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection*
TS	*Tourette's syndrome*

drugs on the symptoms of TS began to be recognized. This observation helped to refocus attention from psychogenetic causes to Gilles de la Tourette's view of biological central nervous system mechanisms.

In the following review, an overview of the advances made in the understanding of TS, with a special focus on the role of an infectious and inflammatory process, is provided.

Clinical and epidemiological features of TS

TS is clinically characterized by simple and/or complex motor tics and simple or complex vocal tics *(Tables I and II)*, which cause marked distress or significant impairment in social or other important areas of functioning (*Diagnostic and Statistical Manual of Mental Disorders*. 4th ed *[DSM-IV]* criteria).[1] Sensory tics such as body sensations, eg, cold, heat, heaviness, urging, and touching, which often preceed a motor tic, have been described in a large number of TS patients. In sensory tics, the motor action acts as a response to an internal or external stimulus.[2]

A characteristic of TS is its great variability of symptoms. Motor, vocal, and sensory tics start during childhood/adolescence, and show a waxing and waning course, with exacerbations in periods of emotional stress; however, periods without such obvious symptoms are also typical. Symptoms other than tics such as echolalia and echopraxia, palilalia, coprolalia, mutilations, and disturbed impulse control characteristically often occur, although they are not obligatory for the diagnosis of TS. Furthermore, obsessions and compulsions,[3] cognitive dysfunction, or affective disturbances such as depression or anxiety have frequently been described in these patients.[4,5] An increased comorbidity of TS and obsessive-compulsive disorder (OCD),[3,6,7] mood disorders, and anxiety,[8,9] as well as phobias[10,11] and attention deficit/hyperactivity disorder (ADHD)[12,13] have been reported. Increased substance abuse has been suggested, since the sedative effect of alcohol often improves the tics.[14] However, systematic studies of substance abuse or dependency in TS are lacking.

Since the onset of TS is before the age of 18 *(DSM-IV)*[1] and often leads to severe psychosocial impairment, children and adolescents suffering from TS are often discriminated against and have disadvantages in terms of psychosocial development. Moreover, the 50% to 60% comorbidity with ADHD or OCD additionally contributes to the impaired development of personality during the critical period. Furthermore, these patients are also more likely to experience academic as well as psychosocial problems, and these conditions may contribute to a chronification of the disorder on the one hand and to the development of personality disorders on the other.

The prevalence of TS is estimated at about 4 to 5 per 10 000 according to the internationally accepted American estimation of prevalence *(DSM-IV)*.[1] Studies relying on stricter methodological criteria describe a prevalence between 0.7 and 5.3 per 10 000.[15,16] Other findings suggest that, especially in males, the prevalence is up to 1% of the population.[17] The male:female ratio for TS is around 4:1.[15]

Delayed diagnosis of TS

The estimated time from onset of the first symptoms of TS to the time the final diagnosis is established is about 5 to 10 years.[18] Since TS is characterized by severe socially

Simple motor tics	Simple vocal tics
Blinking	Throat-clearing
Turning the head	Sniffing
Shrugging	Coughing
Shaking of extremities	Mumbling
Foot-stamping	Flicking
	Whistling
	Grunting
	Snoring
	Barking

Table I. Examples of simple tics.

Complex motor tics	Complex vocal tics
Touching	Imitation of sounds
Lying down flat	Repetition of senseless items
Deep knee bends	Coprolalia
Pushups	Echolalia
Steps backwards	Palilalia
Certain order of steps during walking	Echokinesia
Turning around	

Table II. Examples of complex tics.

disabilitating symptoms, this delay causes additional negative reactions, and leads to significant psychosocial suffering in many cases. Although controlled data are still lacking, there are indications that the course of TS and the patient's capacity to cope with it will be more favorable in cases where TS is diagnosed earlier. The high comorbidity with emotional instability and personality disorders may result at least partly from these problems.

TS: a syndrome of different etiologies and variable phenomenology

Clinically, the symptoms of TS show a broad variability; however, whether this variability corresponds to differences in the outcome as well as to the response to special treatments has not been investigated. Furthermore, different etiological factors may contribute to TS. There is no doubt that genetic factors which have not yet been specified do play a pivotal role. Neurochemical and pharmacological studies suggest a functional hypersensitivity of dopaminergic neurotransmission and a dysfunction of the opiatergic system. Probably, the disturbance of the dopaminergic neurotransmission is the final stage of different pathogenetic pathways. Neurophysiological studies have shown reduced neuronal inhibition within the sensorimotor loop, with good frontocortical compensatory mechanisms.[19] Within a subgroup of TS patients, recurrent or chronic inflammation may lead to a manifestation of tics. Recently, the diagnosis of postinflammatory immune processes after streptococcal infections associated with tics or obsessive-compulsive (OC) symptoms, known as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) has been established in the USA. Furthermore, TS symptomatology can be the result of trauma, of intoxication, or of pharmacological treatment. There is evidence that long-term treatment with classic neuroleptics, as well as treatment of ADHD with stimulants, might increase the risk of tic development in some children.

Differential diagnosis of TS

Due to the high variability of TS symptoms, the diagnosis of TS is often difficult. Since the typical course is one of exacerbations and remissions, typical vocal or motor tics often do not occur during the symptom-free intervals, although these patients still suffer from other—often comorbid—symptoms, hampering the TS diagnosis. Mutilations, obsessive-compulsive (OC) symptoms, or other behavioral "abnormalities" often dominate the clinical symptoms. Moreover, patients suffering from TS often describe their motor and vocal tics as compulsions.[3] Moreover, the suppression of tics for a certain time is a diagnostic feature of TS, especially in situations where the patient's attention is drawn to them (eg, during a medical examination). In particular, typical but awkward symptoms such as coprolalia, copropraxia, or echolalia, are often concealed.

Regarding the differential diagnosis of TS *(Table III)*, other tic disorders such as chronic motor tic disorder, which lacks vocal tics, must be excluded. In cases where the disorder starts later than the consensus age of 18 or 21 years, even full-blown TS symptoms cannot be diagnosed as TS *(DSM-IV)*.[1]

Extrapyramidal movement disorders, but also OC symptoms, are known to occur as a symptom of poststreptococcal disease, such as in Sydenham's chorea, for a long time.[20,21] Huntington's disease, today easily diagnosed by molecular genetic methods, is a movement disorder often showing similar phenomena to TS; this differential diagnosis needs to be kept in mind. Pharmacologically induced hyperkinesia, induced by, eg, L-dopa or amphetamine, is an important differential diagnosis, but tardive dyskinesias, caused by antipsychotic therapy, often show similar motor symptoms to tics. Moreover, schizophrenia is often associated with movement abnormalities such as stereotypic movements and motor automatisms, the latter also frequently found in organic brain disorders. This has to be considered as well, particularly since schizophrenia and TS have common pathogenetic features and co-occur in certain cases.[22] Apart from schizophrenia, psychogenic movement disorders are an important psychiatric differential diagnosis in TS.

Neuroacanthocytosis is another group of neuropsychiatric disorders which shows features of TS. Primarily, it is characterized by abnormal erythrocytes in the blood,

Pharmacologically induced hyperkinesias (L-dopa, amphetamine)
Huntington's disease
Sydenham's chorea
Metabolic disturbances (eg, Wilson's disease)
Schizophrenic stereotypes
Tardive dyskinesias
Motor automatisms
Psychogenic movement disorders

Table III. Differential diagnosis of Tourette syndrome.

acanthocythes, which seem to be the result of a hereditary component and represent an impairment of structural proteins of the cellular membrane. The first symptom of neuroacanthocytosis is often an epileptic seizure, but OC symptoms, symptoms of ADHD, or tics are described as manifestations of the condition.[23,24] In some recent studies, in patients primarily presenting with tics, genetic defects belonging to the group of neuroacanthocytosis syndromes, such as chorea-acanthocytosis, have been reported.[25,26]

TS is not only a movement disorder, but a psychiatric disorder

Because of its rich clinical expression and frequent association with comorbid disorders, the spectrum of TS is often not recognized or fully appreciated. As our knowledge about TS expands, however, it is becoming increasingly obvious that TS is not merely a movement disorder, manifested by motor and vocal tics, but a relatively common neurobehavioral complex manifested, in addition to tics, by attention deficit, OC symptoms, lack of impulse control, and a variety of other behavioral symptoms. Since most cases of TS are mild and do not provoke medical diagnosis and treatment, the patients seen in the clinic represent only the tip of the iceberg. Although no valid data exist regarding the frequency of substance abuse, there is no doubt that many persons suffering from TS show a comorbid substance abuse. Alcohol and sedative drugs such as benzodiazepines have a short-term effect on tics and other symptoms of TS, leading to a high prevalence of alcohol abuse, which is estimated at about 30% in our own sample(Muller, unpublished observation). Due to the early onset of tics, many children affected with tics are socially withdrawn; they become outsiders in their families and peer groups. This might promote the development of personality disorders, which have been described in 60% of TS patients.[27] A comorbid depressive syndrome is found in about a quarter of affected persons.[11] Markedly higher is the rate of comorbidity with ADHD, observed in 55% of the TS patients.[28] The comorbidity with OCD appears to be even higher, having been described in 40% to 90% of the patients.[5,29] However, due to the broad overlap of tics, in particular complex tics and OC symptoms, there is some discussion as to whether "specific" compulsions such as symmetry behavior, echophenomena, or touching should be classified as tics or as OC behavior.[3,9]

Neurobiological characteristics of TS

Although TS is a disorder of primarily the dopaminergic system of the basal ganglia, there is no doubt that cortical structures are also involved. The hypothesis of Kurlan,[30] in particular, focuses on disinhibition within the cortical-striatal-thalamic motor loop, including the limbic system. Similar conclusions were drawn by studies using transcranial magnetic stimulation, which show reduced intracortical inhibition in TS patients.[31] We found that disturbed saccadic eye movements are in keeping with the hypothesis of a disturbed activation of the frontal cortex by ascending loops from the basal ganglia.[32] Moreover, the disturbed inhibition of unwanted orientation reactions revealed by antisaccades, as well as the known attention problems, favor a functional impairment of the frontal cortex in TS.

Brain morphology of TS

A neuroimaging study in adult TS patients without long-term antipsychotic treatment revealed smaller mean volumes of the caudate, lenticular, and globus pallidus nuclei compared with controls, on both the right and left. Further analyses of basal ganglia asymmetry indices suggest that TS basal ganglia do not have the volumetric asymmetry (left greater than right) seen in normal controls.[33] Similar findings were reported by other researchers studying a group of TS children: statistical comparisons between TS patients, with (n=18) or without (n=19) ADHD, and controls showed significant differences in the volume of the left globus pallidus and in lenticular asymmetry.[34] Interestingly, caudate volumes in children with TS predict the severity of tic and OC symptoms in early adulthood. This study provides compelling evidence that morphologic disturbances of the caudate nucleus within cortico-striatal-thalamo-cortical circuits are central to the persistence of both tics and OC symptoms into adulthood.[35] These findings strongly support the view that TS is related to a basal ganglia dysfunction, although several other brain regions are involved in the pathophysiology of tics as hypothesized by the concept of Kurlan and shown by functional magnetic resonance imaging (MRI).[36] Interestingly, neuroimaging data in TS also show significantly increased white matter lesions in the basal ganglia and other brain regions, a finding that will be discussed in the context of the inflammatory hypothesis of TS.[37]

Genetics of TS

There is evidence for a strong genetic background of TS. It has been demonstrated in twin studies that monozygotic twins are more often concordant for the presence of TS in up to 53% or any tics in up to 77% compared with dizygotic twins (up to 8% concordant for TS and 23% for any tics).[13,14] While it is evident that genetic factors play a profound role, the phenotype may be variable and may not be confined to full-blown TS.

The risk for TS is sex-dependent: 11.5% for brothers of an affected person and 4.8% for sisters.[38] The frequency of TS in first-degree relatives ranges from 9.8% to 15%, according to the study cited.[39,40]

A particular risk gene for TS, however, has not yet been identified. Although large linkage studies have been performed, a genome-wide screen for linkage using 386 markers did not show a limit of detection (LOD) score of more than two,[41] nor did a genome-wide screen based on 110 sib pairs, show significant loci.[42] A sample from a French-Canadian family (127 members, 20 to 40 affected) showed a LOD score greater than three on 11q23.[43] However, the incomplete genetic penetrance, the high variability of the phenotype (symptoms), possible different etiological factors, and several other concomitant factors complicate genetic studies in TS.

TS as an inflammatory disease

Recent studies suggest that an inflammatory process, due to an acute or chronic infection or a postinfectious immune response, may be involved in the pathogenesis of TS.[44]

Although the pathological mechanism in TS is unclear, contribution of an immunological dysfunction or an inflammatory process has been discussed. With regard to research on immune function in TS, most studies have focused on antibody production. Increased antibody production including antiphospholipid[45] and antineural antibodies directed against structures in the basal ganglia[46-50] has been described. Recent research, however, showed conflicting results regarding increased antineural antibodies in the serum of TS.[51-53] D8/17, a surface marker on antibodies producing B-lymphocytes, has been described to be a diagnostic marker in OCD and in tics,[54] but this has not been confirmed.[55] However, increased titers of antiphospholipid antibodies, and increased IgE levels have been described in TS.[45,56,57] In recent years, immunological research in TS has focused on cytokines. In a recent prospective longitudinal study, increased serum levels of the cytokines interleukin (IL)-12 and tumor necrosis factor (TNF)-α in juvenile TS patients were observed.[58] During exacerbations of tics, a further increase in IL-12 and TNF-α was observed, pointing to a relationship between tic severity and proinflammatory cytokines. In OCD, however, decreased levels of TNF-α were described.[59-61] Since OCD and TS show a high rate of comorbidity, a possibly discriminative marker—decreased in OCD and increased in TS—would be very valuable.

Although the results of the kynurenine estimations in TS are divergent, depending on interfering factors,[62,63] changes in the kynurenine levels in the sera of TS patients also point to the involvement of the immune system. Kynurenine is the product of activated monocytes/macrophages; changes in kynurenine production take place during inflammatory processes. Moreover, kynurenine and other products of the tryptophan/kynurenine-metabolism are neuroactive proteins, possibly themselves contributing to changes in neurotransmitter metabolism. Moreover, increased levels of the soluble adhesion molecules V-CAM-1 and E-selectin—increased in inflammatory states—were reported in children and adults suffering from TS.[64]

A case report of successful treatment with a cyclo-oxygenase (COX)-2 inhibitor also promotes the view that an inflammatory process is involved in TS.[65]

Inflammation in TS as a result of an infectious or postinfectious process

It has been described that tics appear or are exacerbated in acute Lyme disease,[66] infection with *Mycoplasma pneumoniae*,[67,68] or acute streptococcal infection.[69] Moreover, an association of the common cold with tic disorders has been observed.[63] Improvement or remission of the tics has been associated with antibiotic therapy.[65,66,68] These findings strongly suggest that infectious agents contribute to the pathogenesis of tics and TS.

PANDAS[70,71] has been extensively described during recent years. The main symptoms of PANDAS are motor and vocal tics and OC behavior like that found in TS.[72] Although crossreacting antibodies against the putamen have been observed in PANDAS,[73] the mechanism has not yet been established. TS is proposed to be a part of PANDAS. Increased antibody titers and other features of PANDAS, however, have also been described in adult TS patients,[74,75] while the PANDAS concept is restricted

to children. Antibodies against certain streptococcal M proteins, ie, proteins on the surface of streptococci which are known to be responsible for the virulence and the immune properties of the particular streptococcal strain, are increased in children and adult TS patients. In particular, antibodies against M12 and M19, which are known to crossreact with brain cells, are increased in these patients, while no difference could be detected in other, more frequent M-protein antibody titers.[76] This finding—in addition to others with cross-reacting antibodies—shows that a poststreptococcal autoimmune process is involved in TS. This is the basis for the successful application of immune-modulating therapeutic approaches in TS and PANDAS.[72]

Different types of infectious agents and different stages of infection—eg, acute streptococcal infection[77] and poststreptococcal inflammation,[75] were reported to be associated with TS. The therapy, however, has to take into consideration different therapeutic strategies for acute or chronic infection, or for a postinfectious autoimmune process. Therefore—although there are continuous transitions between these inflammatory states—research should focus on the differentiation and differential therapies of these stages of inflammation.

Anti-inflammatory therapy in TS, eg, use of a COX-2 inhibitor, has also shown positive effects.[65] Altogether, the involvement of inflammatory immunological mechanisms in the pathogenesis of TS, at least in a subgroup of patients, is obvious. A multifactorial pathogenesis has been proposed, with the involvement of an (immuno)genetic predisposition and environmental factors such as infection or postinfectious phenomena. Further research also has to identify markers for the differentiation of inflammation-mediated and other forms of TS.

Recent findings from T2-weighted MRI in patients with TS, but also other syndromes (OCD and ADHD, which show a high prevalence of comorbidity with TS) revealed a significantly higher frequency of cortical and subcortical hyperintensities compared with controls, a finding which is in accordance with an inflammatory process in certain cases of TS.[37]

Shortcomings of the PANDAS concept

The PANDAS concept, however, is limited by several shortcomings. Although this disorder is associated with streptococcal infection, no test for streptococci to support the infection, is required for the diagnosis. An objective parameter supporting the clinical diagnosis (eg, increased antistreptococcal titers) would help to confirm the diagnosis.

Moreover, different stages of streptococcal infection might lead to different therapeutic consequences. Although acute and chronic infection with streptococci require antibiotic treatment, a poststreptococcal autoimmune process may respond better to immunomodulatory therapy. A further difficulty for the PANDAS diagnosis might be the heterogeneity of the symptoms, which include not only motor and vocal tics, but also OC symptoms, which often, but not necessarily, co-occur in one child. The restriction of the PANDAS concept to children/adolescents, however, is a further point for discussion. Tics and OC symptoms also often occur in adults. Accordingly, an association between tics and infectious agents in adults has been reported.[67,78] Although it is known that children and adolescents are more vulnerable to certain infections, the association between tics, OC symptoms, and infection is not restricted to this population. Moreover, studies have shown that not only streptococci but also other infectious agents such as *Borellia Burgdorferi* or *Mycoplasma Pneumoniae* are associated with tics, ie, the association of tics and infectious agents is not restricted to streptococci. A broader concept of this association, however, would more fulfill the needs for an infectious concept of TS.

Conventional pharmacotherapeutic concepts of TS

There is no doubt that dopaminergic neurotransmission is involved in the pathophysiology of TS. Dopamine (D_2) receptor blocking agents such as haloperidol or pimozide have been shown to be effective in TS in several studies.[79] Haloperidol showed an efficacy between 78% and 91% in 41 reports over a 14-year period.[4] Many patients, however, discontinue haloperidol due to extrapyramidal side effects, while pimozide showed a superior profile regarding side effects. Pimozide was effective in several double-blind, placebo-controlled studies.[80] There are also reports of effective treatment with drugs such as fluphenazine, penfluridol, trifluoperazine, and flupenthixol.[81]

In the meantime, atypical antipsychotics such as risperidone, which is not only a D_2 receptor antagonist, but also a serotonin $(5\text{-HT})_2$ antagonist, has been shown to be effective in TS.[82,83] Clozapine was observed to be effective against tics,[84] although there have also been negative

results reported.[81] A partial control of tics during therapy with olanzapine at a dose of 5 to 10 mg/day was reported, as well as a reduction in tics in a controlled study (n=4).[85] Ziprasidone, at a dose of 5 to 40 mg/day, was shown to be significantly more effective than placebo in 28 patients (7 to 17 years old) in a double-blind, randomized study, and was well tolerated.[86] It should be noted, however, that the sudden death of a TS patient under therapy with ziprasidone during a clinical trial was reported.[87]

Aripiprazole, a new atypical antipsychotic that acts as a dopaminergic modulator showing mixed dopamine antagonistic and agonistic effects, may take a special position in the therapy of TS. Effective treatment of TS using aripiprazole was reported repeatedly, in contrast to those treated with other antipsychotics, a number of patients showed complete recovery from tics without significant adverse effects.[88-90]

The drug of first choice, for therapy of tics, particularly for children in many European countries, is tiapride, a benzamide derivate, which selectively blocks dopamine in the basal ganglia. Although only double-blind, placebo-controlled studies show beneficial effects on movement disorders and tics,[91,92] tiapride is widely used in countries such as Germany, France, and others. It is one of the few drugs which is prescribed not only in adults, but also in children. In contrast to several antipsychotics, however, no adverse effects on cognitive performance in children have been observed.[92]

However, clonidine, a central α_2-adrenoceptor agonist reducing noradrenergic activity in the central nervous system, has also been reported to be effective in TS, although controversial effects of clonidine in different studies were shown in a dose of 3 to 5 µg/kg body weight.[93,34] Possibly, the beneficial effects of clonidine on behavioral abnormalities are more pronounced than on vocal and motor tics. In general, antipsychotics seem to be more effective compared with clonidine.[95] The effect of clonidine, however, shows that noradrenergic neurotransmission is also involved in TS.

Furthermore, the differentiation and characterization of subgroups may lead to different therapeutic strategies, for example, early antibiotic treatment in cases in which tics are the result of infection may help to prevent progression to chronic stages which otherwise have to be treated with neuroleptics. Therapy with immunoglobulin IV and plasmapheresis as immunomodulatory treatment strategies are currently the objective of therapeutic trials.[72] Treatment with cannabinoids, in particular 19-tetrahydrocannabinol, has shown beneficial effects in single cases, but a randomized, double-blind study failed to show convincing effects.[96]

Behavior therapy

Until the introduction of haloperidol, TS was thought to be a psychogenic syndrome; psychoanalytic therapeutic concepts were very common and widely practiced. This concept totally changed during recent decades. However, supportive psychotherapy and training in coping strategies, supported by concepts of self-help care, are known to be very important, in particular in such a chronic and socially isolating disease. Although tics and other symptoms can not be influenced decisively, behavior-therapy techniques, including progressive muscle relaxation as well as learning and training of alternative behavior, can reduce the tic intensity and frequency. This technique of habit reversal is based on the identification of tic-preceding sensations (premonitory urges).[97]

Experimental therapeutic approaches in TS

Immunomodulatory and anti-inflammatory therapies

For children with PANDAS, effective treatment with immunomodulatory substances or techniques have been described repeatedly.[72] These therapies include IV immunoglobulin G (IgG) and plasmapheresis, the latter showing even better results than IV IgG. Keeping in mind the critical view of PANDAS, these immunomodulatory therapies might also reveal favorable effects in TS patients not fulfilling PANDAS criteria. Effective IV IgG therapy has been described in TS.[98]

In the case of an acute or possibly also a chronic infection associated with tics, the TS symptoms including motor and vocal tics are cured by antibiotics. This has been reported for infection with *Lyme-Borreliosis*,[66] *Mycoplasma Pneumoniae*,[99] and streptococci.[69,77]

In a retrospective, open-label study in 34 TS patients, the effects and predicting variables for therapeutic effects of IV IgG versus antibiotics were evaluated. It was observed that increased antistreptococcal titer of antiDNase predicted better effects of antibiotics, and increased antichlamydial titers better effects of IV IgG. Around 60% of the total sample showed a therapeutic response to either immunomodulatory treatment.[100] These interesting, but very preliminary, results require further controlled studies.

Moreover, anti-inflammatory treatment with the COX-2 inhibitor celecoxib was described to be effective in TS in a single case,[65] a result also requiring further examination.

Repetitive trancranial magnetic stimulation

A small, open-label study using repetitive trancranial magnetic stimulation (rTMS) over the supplementary motor area of 10 TS patients showed clinically significant improvement of TS and accompanying OCD symptoms, with benefits lasting up to 3 months in almost two thirds of the patients.[101] Other studies, however, failed to bring about improvement using another application of rTMS,[102] while in a crossover trial using high-frequency stimulation of the left prefrontal cortex, a significant improvement of the tics was observed.[103] At this stage of knowledge, further studies have to be performed in order to optimize the localization, the technique, and the number of rTMS-applications, and the sustainability of the effects. RTMS seems a promising method, although it requires elaborate and costly equipment, because it shows only marginal side effects.

Electroconvulsive therapy

Single case reports describe therapeutic effects of electroconvulsive therapy (ECT) on motor tics, vocal tics, and OC behavior.[104,105] Maintenance ECT therapy (one treatment every 4 to 6 weeks) was reported to be effective in a therapy-resistant case of TS.[106] Those reports reveal that ECT is a therapeutic option in treatment-resistant cases of TS.

Deep brain stimulation

During recent years, surgical deep brain stimulation, known to be effective in Parkinson's disease and certain dystonic syndromes, has been increasingly performed in treatment-resistant cases of TS. Stimulation electrodes were placed in various locations. Bilateral stimulation of the thalamus showed moderate improvement of the tics in five cases.[107,108] Bilateral stimulation of the globus pallidus internus showed good and very good results in two cases,[109,110] while bilateral stimulation of the nucleus accumbens revealed moderate improvement of tics and OC symptoms.[111,112]

Conclusion

Although important progress in our knowledge about TS has been made during the last few decades, this syndrome is still poorly understood. The pathophysiology is unknown, but therapeutic strategies are more and more successful. During recent years, the role of inflammation, due to infection associated with a dysfunction of the immune system, has come more into the focus of interest. In addition to a broad spectrum of promising new experimental therapeutic approaches, future research will put emphasis on the role of inflammation, on the differentiation and differential therapies of these stages of inflammation, and on the identification of markers for the differentiation of inflammation-mediated and other forms of TS, because TS is a syndrome of different etiologies and variable phenomenology. ❑

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Síndrome de la Tourette: características clínicas, fisiopatología y aproximaciones terapéuticas

El síndrome de la Tourette (ST) es un trastorno caracterizado por tics motores simples y complejos, tics vocales y frecuentemente síntomas obsesivo-compulsivos. Se presenta antes de los 21 años. Típicamente el ST muestra un curso con fluctuaciones, pero con frecuencia se observa una cronificación de los tics, aun durante las últimas etapas de la vida. El ST se presenta de preferencia en niños varones y muestra una herencia genética con penetrancia variable. El mecanismo patológico aun no está aclarado. Los estudios neuroanatómicos y de neuroimágenes, al igual que el tratamiento efectivo con neurolépticos sugiere que una alteración del sistema dopaminérgico en los ganglios basales tiene un papel importante en su patogénesis. Se discuten algunos posibles mecanismos causales del trastorno de la neurotransmisión dopaminérgica, con un principal énfasis en el proceso inflamatorio inmune gatillado por la infección. Se sabe que los trastornos de los movimientos extrapiramidales ocurren como síntoma de enfermedades estreptocócicas, como en el corea de Sydenham. Se ha propuesto que algunos casos de ST en la niñez sean causados por tal mecanismo postestreptocócico, siendo parte del espectro de trastornos neuroconductuales de la niñez llamado PANDAS (trastorno neuropsiquiátrico pediátrico autoinmune asociado con enfermedad estreptocócica). Se discute la sobreposición entre ST y PANDAS y se presenta una visión crítica del concepto de PANDAS. Se describen las repercusiones terapéuticas de los diferentes mecanismos patológicos, tomando en consideración no sólo la naturaleza aguda o crónica de las diferentes infecciones, sino también un proceso autoinmune. Además se discuten críticamente las estrategias terapéuticas que utilizan antipsicóticos típicos y atípicos como también terapias experimentales como la estimulación magnética transcraneal repetitiva y la estimulación cerebral profunda.

Syndrome de Gilles de la Tourette : tableau clinique, physiopathologie et approches thérapeutiques

Le syndrome de Gilles de la Tourette (SGT) est une maladie caractérisée par des tics moteurs simples et complexes et par des symptômes obsessionnels-compulsifs fréquents. Il débute avant l'âge de 21 ans. Le SGT suit habituellement une évolution croissante puis décroissante, mais une chronicisation des tics, même à l'âge adulte, est fréquente. Le SGT se rencontre principalement chez les garçons, avec une héritabilité génétique à pénétrance variable. Le mécanisme pathologique reste encore obscur. Les études de neuroanatomie et de neuro-imagerie, ainsi que l'efficacité des traitements utilisant des antipsychotiques, suggèrent qu'un trouble du système dopaminergique dans les ganglions de la base joue un rôle important dans la pathogénie du SGT. Plusieurs mécanismes éventuellement responsables de la perturbation de la neurotransmission dopaminergique sont envisagés, le principal étant un processus immunitaire inflammatoire activé par l'infection. On sait depuis longtemps que des mouvements anormaux extrapyramidaux se présentent comme des symptômes de maladie post-streptococcique, comme dans la chorée de Sydenham. Certains cas de SGT juvéniles seraient peut-être provoqués par un tel mécanisme post-streptococcique, appartenant à l'éventail des troubles neurocomportementaux de l'enfance appelé trouble neuropsychiatrique auto-immun pédiatrique associé à une infection streptococcique (PANDAS). Le chevauchement entre le SGT et le PANDAS est débattu et le concept de PANDAS est présenté dans l'article. Les implications thérapeutiques des différents mécanismes pathologiques sont décrites en prenant en compte non seulement la nature aiguë ou chronique des différentes infections, mais aussi l'existence d'un processus auto-immun. Les stratégies thérapeutiques utilisant des antipsychotiques typiques et atypiques ainsi que les traitements expérimentaux tels que la stimulation magnétique transcrânienne répétitive et la stimulation cérébrale profonde, sont de plus revus de manière critique.

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