SAR Journal of Medical Biochemistry

Abbreviated Key Title: *SAR J Med Biochem*

Home page: https://www.sarmedjournals.com/sjmb

OPEN ACCESS

ISSN 2707-7721 (P)

Review Article

Tourette Syndrome- Disorder Characterized by Tics

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Article History: | Received: 05.02.2020 | Accepted: 14.02.2020 | Published: 28.02.2020 |

Abstract: Tourette syndrome (TS) is a chronic neurodevelopmental disorder characterized by tics: repetitive, involuntary movements and vocalizations. These symptoms can have a significant impact on patients' daily functioning across many domains. Tics tend to be most severe in child and adolescent sufferers, so their presence has the potential to impact a period of life that is both critical for learning and is often associated with the experience of greater social tension and self-consciousness than adulthood. Furthermore, control over tics that lead to physical impairment or self-injurious behaviour is of vital importance in maintaining health and quality of life. There are numerous complicating factors in the prescription of treatment for tics, due to both the side effects associated with alleviating agents and patient characteristics, such as age and comorbid conditions. This review summarizes literature pertaining to the efficacy and safety of both traditionally prescribed and more modern medications. We also discuss the merits of behavioral and surgical techniques and highlight newer emerging treatments. Although treatment response is to some extent variable, there are a number of agents that are clearly useful as first-line treatments for TS. Other interventions may be of most benefit to patients exhibiting refractory tics or more specific symptom profiles.

Keywords: antipsychotics, botulinum toxin, deep brain stimulation, medication, neuroleptics, tics, Tourette syndrome, treatment.

INTRODUCTION

TS is diagnosed according to the presence of multiple motor and one or more phonic tics, which do not have to be present simultaneously. Other tic-related symptoms that may be present include coprophenomena (such as coprolalia: the uttering of obscene language), echophenomena (copying behaviors) and paliphenomena (repetitive behaviors). The majority of individuals with TS exhibit comorbid conditions, the most common of which are obsessive–compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) [Cavanna *et al.*, 2009]. Other behavioral difficulties can include impulse discontrol (e.g. explosive outbursts or conduct disorder), affective dysregulation and sleep disturbances. Moreover, at least a third of patients with TS exhibit tic-related self-injurious behaviors [Robertson *et al.*, 1989] such as head banging and/or self-directed hitting, punching or scratching. Self-injurious behaviors may be integral to TS as they are sometimes even present in mild cases [Robertson and Stern, 2000], and control of these symptoms is clearly of great importance in maintaining physical health. In addition, a significant proportion (perhaps up to 30%) of patients with TS exhibit nonobscene socially inappropriate symptoms (NOSIS). These socially inappropriate symptoms include uncontrollable urges to insult others or behave aggressively, and can sometimes lead to physical confrontation and trouble with the law [Kurlan *et al.*, 1996]. As well as leading to social difficulties, tics and tic-related behavioral symptoms can have a major impact on performance at school and work. Tic severity was a significant independent predictor of QoL, although features of ADHD and OCD were also found to be related. Packer and colleagues studied QoL in a similar TS sample (age range 6–17 years) [Packer, 2005]. In relation to academic performance, 50% of respondents reported that tics had moderate to significant impact, whereas 24% reported a mild impact. Tic-related difficulties included eye, head, neck and arm tics which interfered with reading, and the avoidance of reading aloud or speaking out in class due to vocal tics. The treatment of TS is complicated by the range of symptoms associated with this condition and the variability across individual symptom profiles. TS is now viewed as a neuropsychiatric spectrum disorder in which the tics are commonly associated with attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). For some patients, these behavioral comorbidities can be the major source of disability and should be considered to be important targets for treatment.

PATHOGENESIS

Tourette's is one of a range of tic disorders that can involve transient or chronic tics. The tic can emerge at any age, but it most commonly appears between the ages of 6 and 18 years. During adolescence and early adulthood, the tics will normally become less severe, but in 10 to 15 percent of cases, Tourette's can become worse as the person moves into adulthood. For most people, the frequency and intensity of both minor and major tics tend to fluctuate. Tics may become more frequent and more intense when a person is facing physical, emotional, or mental stress. Most people with Tourette's have normal intelligence and life expectancy. Probably the most accepted current hypothesis regarding the underlying pathophysiology and pathological anatomy of TS is that there is an impairment of cortical inhibition of motor programs that are spontaneously generated in the basal ganglia and expressed as tics. In support of this notion, a repetitive transcranial magnetic stimulation study of patients with TS found reduced excitability of intracortical inhibition (Leckman, J. F., & Cohen, D. J. 1999), suggesting that sensory inputs have an increased ability to stimulate motor outputs. This finding may represent a physiological correlate of the known clinical feature of TS that tics are often linked to premonitory sensations (Leonard, H. L. *et al*., 1992). Volumetric brain MRI studies have identified cortical abnormalities in patients with TS, but structural localizations have been inconsistent, although several MRI studies have reported reduced caudate volumes (Leckman, J. F. *et al*., 1993). Basal ganglia functional disturbances have also been identified in TS. Only a small number of postmortem TS brains have been examined pathologically. Two postmortem brain studies revealed a decrease in parvalbumin positive GABA neurons and cholinergic neurons in the striatum (Leonard, H. L. *et al*., 1992; Pauls, D. L. *et al*., 1981). Further support for a disturbance of GABA neurotransmission comes from a recent positron emission tomography study that found abnormal binding of $GABA_A$ receptor binding in patients with TS compared to normal controls (Pauls, D. L. *et al*., 1994). A variety of studies have reported disturbances in other neurochemical systems, including acetylcholine, glutamate, norepinephrine, histamine, opiates, adenosine and second messenger systems, but there is inadequate information to suggest new rational therapeutic approaches.

TABLE I-Examples of Simple Tics

SIMPLE MOTOR TICS	SIMPLE VOCAL TICS	FOOT-STAMPING	FLICKING
BLINKING	THROAT CLEARING	SNORING	WHISTLING
TURNING THE HEAD	SNIFFING	BARKING	GRUNTING
SHRUGGING	COUGHING	FOOT-STAMPING	FLICKING
SHAKING OF EXTREMITIES	MUMBLING	SNORING	WHISTLING

Neurobiology of Tourette syndrome

Important models have been proposed to account for a widerange of CSPT disorders, based on variations in responses to ''generalized'' or ''epigenetic'' early developmental insults, from neonatal hypoxia to bacterial infections. Despite this departure from the notion of discrete, specific ''lesions'' and circumscribed clinical presentations, the prevailing modelin thesearch for the pathophysiology of TS is perhaps closest to that previously applied to Huntington disease, in which a unique mutation in a single gene causes—by as yet unknown cellular mechanisms—a characteristic disease that leads to a fairly predictable clinical presentation and course. Yet the actual pathophysiology of TS remains quite elusive. The scant tangible evidence of the pathophysiology of TS comes primarily from studies in neuropathology and neuroimaging; supportive evidence comes from other fields of investigation, including neuropsychology and psychophysiology, and from ties between TS and other disorders, such as OCD and ADHD, providing indirect evidence based on what is known about the pathophysiology of these other disorders. The most consistently observed deficits occur on tasks requiring the accurate copy of geometric designs, that is, ''visualmotor integration'' or ''visual-graphic'' ability (Leonard, H. L. *et al*., 1992; Pauls, D. L. *et al*., 1981); somewhat similar deficits are reported in patients with OCD (Pauls, D. L. *et al*., 1994). No compelling evidence links these deficits in TS and OCD with a specific frontal or frontal corticostriatal territory, although visuospatial functions have generally been conceptualized to be regulated by dorsolateral prefrontal cortex and descending cerebrospinal fluid inputs to the head of the caudate nucleus (79). Neurophysiologic studies have documented a reduced cortical silent period after repeated *transcranial magnetic stimulation* (rTMS) in TS (Pauls, D. L. *et al*., 1994). This increased cortical excitability could result from impaired inhibition through disinhibited thalamocortical inputs or through abnormalities intrinsic to cortex, or both. Further support for the role of basal ganglia circuitry in TS comes from anecdotal reports of symptom exacerbation or reduction in patients with tumors within, or transections of, CSPT elements, respectively (American Psychiatric Association. 2000; Leckman, J. F. *et al*., 1993).

Table II-Examples of Complex Tics

COMPLEX MOTOR TICS	COMPLEX VOCAL TICS	PUSHUPS	ECHOLALIA
TOUCHING	IMITATION OF SOUNDS	STEPS BACKWARDS	PALILALIA
LYING DOWN FLAT	REPETITION OF SENSELESS ITEMS	CERTAIN ORDER OF STEPS DURING WALKING	ECHOKINESIA
DEEP KNEE BENDS	COPROLALIA	TURNING AROUND	

TABLE III-Development of Dna Sequencing

PHARMACOLOGICALLY INDUCED HYPERKINESIAS (L-DOPA, AMPHETAMINE)	SCHIZOPHRENIC: STEREOTYPES
HUNTINGTON'S DISEASE	TARDIVE DYSKINESIAS
SYDENHAM'S CHOREA	MOTOR AUTOMATISMS
METABOLIC DISTURBANCES (EG, WILSON'S DISEASE)	PSYCHOGENIC MOVEMENT DISORDERS

Genetics of Tourette syndrome

TS may be the most clearly inheritable common neuropsychiatric disorder. First-degree relatives of TS probands appear to be 20 to 150 times more likely to develop TS, compared with unrelated persons (Müller, N. *et al*., 1997). Concordance rates for TS among monozygotic twins approach 90%, if the phenotypic boundaries include chronic motor or vocal tics, versus 10% to 25% concordance for dizygotic twins, across the same boundaries (Shapiro, A. K. *et al*., 1988). The mode of inheritance remains elusive, even after more than 15 years of studies. Some segregation analyses have supported transmission through an incompletely penetrant autosomal dominant major locus (Pauls, D. L. *et al*., 1994; Leonard, H. L. *et al*.,1992), but in other studies, more complex models could not be excluded (Pauls, D. L. *et al*.,1981).

Environmental Factors

Evidence of nongenetic environmental factors in the genesis of TS supports an interactive role for at least three sets of environmental factors: adverse prenatal and perinatal events, acute and chronic psychosocial stressors, and postinfectious autoimmune mechanisms. Retrospective studies have identified an association between adverse events during the prenatal and perinatal period and an increased risk for the development of TS. Although the strongest evidence points to chronic mechanismsthat influence the supply of nutrients by the placenta (Leonard, H. L. *et al*., 1992; Pauls, D. L. *et al*., 1994), other risk factors have been proposed including severe nausea and vomiting during the first trimester, severe maternal stress during pregnancy, exposure to high levels of androgenic steroids, and chronic or acute hypoxic and ischemic injury (Pauls, D. L. *et al*., 1994). Although no specific mechanism is known to connect these early life events and the development of TS, preclinical studies have shown that various neural insults during the prenatal and perinatal period result in the delayed emergence of pathology within interconnected CSPT circuitry and in specific behavioral abnormalities that are also manifested by individuals with TS, such as reductions in sensorimotor gating of the startle reflex (American Psychiatric Association. 2000; Leckman, J. F. *et al*., *et al*., 1993). These early insults may also set the stage for a heightened stress response in adulthood and altered immune function (Comings, D. E., & Comings, B. G. 1987).

Conventional Pharmacotherapeutic Concepts

There is no doubt that dopaminergic neurotransmission is involved in the pathophysiology of TS. Dopamine (D2) receptor blocking agents such as haloperidol or pimozide have been shown to be effective in TS in several studies (Pitman, R. K. *et al*., 1987). Haloperidol showed an efficacy between 78% and 91% in 41 reports over a 14-year period (Shapiro, A. K. *et al*., 1988). Many patients, however, discontinue haloperidol due to extrapyramidal side effects, while pimozide showed a superior profile regarding side effects. Pimozide was effective in several doubleblind, placebo-controlled studies (Pauls, D. L. *et al*., 1994). There are also reports of effective treatment with drugs such as fluphenazine, penfluridol, trifluoperazine, and flupenthixol (Pauls, D. L. *et al*., 1994). 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 (Leckman, J. F. *et al*., 1993; Müller, N. *et al*., 1997). Clozapine was observed to be effective against tics, (Shapiro, A. K. *et al*., 1988) although there have also been negative results reported (Pauls, D. L. *et al*., 1994; American Psychiatric Association. 2000). 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) (Leckman, J. F., & Cohen, D. J. 1999). 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 (Leonard, H.

L. *et al*., 1992). It should be noted, however, that the sudden death of a TS patient under therapy with ziprasidone during a clinical trial was reported (Pauls, D. L. *et al*., 1981). 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 (Pauls, D. L. *et al*., 1994; Pitman, R. K. *et al*., 1987).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, (Pitman, R. K.,. *et al*., 1987) 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 (Leckman, J. F. *et al*., 1993). However, clonidine, a central a2-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 pg/kg body weight (Müller, N. *et al*., 1997; Shapiro, A. K. *et al*., 1988) 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 (Leckman, J. F., & Cohen, D. J. 1999). The effect of clonidine, however, shows that noradrenergic neurotransmission is also involved in TS.

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.

Immunomodulatory and Anti-Inflammatory Therapies

Effective treatment with immunomodulatory substances or techniques have been described repeatedly.[7] 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.

Electroconvulsive Therapy

Single case reports describe therapeutic effects of electroconvulsive therapy (ECT) on motor tics, vocal tics, and OC behavior.

Deep Brain Stimulation

During recent years, surgical deep brain stimulation, known to be effective In Parkinson's disease and certain dystonlc 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.

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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