



## **Understanding the Pathophysiology of Tourette's Syndrome: A Review**

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### **ABSTRACT**

Tourette's syndrome (TS) is a neuropsychiatric and neurodevelopment disease typified by deterioration of motor and vocal tics which leads to neuropsychiatric symptoms and impaired motor activities manifestation. Several lines of study indicate the interplay of genetic and environmental factors to be involved in this complex neuropsychiatric syndrome. Approximately 1% people are affected worldwide from this syndrome. In this review, a concise outline presented on the classification, its clinical features and neuropsychiatric co-morbidities linked with this syndrome.

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This paper also highlights the neurochemistry, dysfunction of (Cortico-Striato-Thalamo-Cortical) CSTC circuits in TS and an overview on the management approach towards the prevention of TS. Regardless of the major improvements in the understanding of exact cellular and molecular basis of TS, the various evidence indicate that the various neurotransmitter such as dopamine, glutamate, gamma- aminobutyric acid (GABA), serotonin, noradrenergic, cholinergic system, serotonergic system and histaminergic pathways play a major role in pathogenesis of TS. Several research indicates that the dysfunction of CSTS circuits occurred in this complex syndrome These areas of research have contributed to the therapeutic approach towards the management of TS and also provide the basis for future progress of the therapeutic strategies. Thus, tics generated in TS, which affect the social and academic life of patients and disruptive or troubling the family of patients. Patients existing with this syndrome have to face difficulties integrating into social life and coping with day to day basis activities, as a consequence of the syndrome.

**Keywords:** *Tourette's syndrome; GABA; Basal ganglia; Dopamine; Tics; Movement disorders; Pathophysiology; Diagnosis; Management; Neuropsychiatric disorder.*

## ABBREVIATIONS

VMAT : Ventral tegmental area  
 DAT : Dopamine transporter  
 D : Dopamine  
 VS : Ventral striatum  
 HDC : L-histidine decarboxylase  
 5 HIA : 5-hydroxy-indoleacetic  
 TPN : Thalamocortical projection neurons  
 MSN : Medium spiny neurons  
 TANs : Tonically active striatal interneurons  
 VMAT : Vesicular mono amine transporter  
 SNr : substantianigra pars reticulata  
 GPi : globuspallidus internal segment  
 SERT : Serotonin transporter  
 GPe : Globus pallidus external segment  
 TS : Tourette syndrome  
 SN : SubstaniaNigra  
 PC : Pars compacta  
 LC : Locus Coeruleus  
 NS : Noradrenergic System  
 CSF : Corticotrophin-releasing factors  
 PC : Peripheral cortisol

## 1. INTRODUCTION

Tourette's Syndrome (TS) is a neuropsychiatric and neurodevelopment disease described by deterioration of multiple tics; both motor and vocal, which lead to neuropsychiatric symptoms and impair the motor activities manifestation [1]. Several lines of study indicate that interplay of genetic and environmental factors are involved in this complex neuropsychiatric syndrome [2-3]. Approximately 1% of people are affected worldwide from this syndrome. TS is first a movement disorder that occurs mostly in adolescents and most often resolves in adult age. The males are 3-4 times more affected than females in this disease [4]. Tics comprise of

sudden, brief, recurrent, repetitive involuntary movements and also the vocalization which occurs as an interruption of abnormal background of movements which ultimately leads to deterioration of tics in terms of both quality and quantity. The motor tics affect various body parts and vocal tics affect the muscles of body which leads to vocalization [5-6]. The multiple motor and vocal tics are involved in TS during childhood. Despite the major comprehension of specific cellular and molecular foundation of tics generation in TS, the various evidences indicate that the several neurotransmitters such as dopamine, glutamate, GABA, serotonin, noradrenergic, cholinergic system, serotonergic system and histaminergic pathways are involved in pathogenesis of this syndrome [7-15]. These areas of research have contributed to the therapeutic approach towards the management of TS and also provide the basis for future progress of the therapeutic strategies [7].

Multiple types of tics represent the TS and these tics vary in terms of types over time, waves, intensity and frequency, Stress, fatigue, emotional state upset, low birth weight, fetal hypoxia and maternal smoking in pregnancy, tiredness are the exacerbating factors which contribute into the generation of tics which ultimately lead to the cause of TS [16]. Tics generally initiate in the age of 6-8 years and deteriorate in pre-pubertal period and decrease in early adulthood in most cases [17]. Some of the additional deregulated movements (paroxysmal dyskinesia and dystonia) may create misdiagnosis due to overlapping of clinical symptoms of tics with the other movement disorders, neurodegenerative diseases, acute brain lesions, immune mediated conditions and drugs or toxins may be associated with the

secondary tics. TS is also associated with various neuropsychiatric conditions. Physical complications are also linked with the TS which produces myelopathy and vertebral artery dissection leading to stroke caused by violent neck tics of TS [5,18].

Several brain regions and their pathways such as sub cortical nuclei, basal ganglia, caudatus nucleus, ventral striatum limbic pathways, sensorimotor pathways, temporolimbic pathways, orbitofrontal pathways, cingulate cortex, globus pallidus, substantia nigra and ventral nucleus complex are also implicated in TS. The cortico-striato-thalamo-cortical (CSTS) circuits are also linked with this complex syndrome [1,19]. TS is a complex neuropsychiatric disorder, which has a significant influence on the excellence and increased quality of life of both the patients and his/her family. The goal of the paper is to give an overall comprehensive review of Tourette's syndrome with a focus on diagnosis, classification of the tics, its clinical features and neuropsychiatric co-morbidities linked with TS and involvement of multiple neurotransmitters. This paper also discusses the neurochemistry, dysfunction of CSTS circuits in TS and therapeutic approach towards the management of TS. An appropriate diagnosis of this syndrome in early stages is essential to diminish the symptoms of disease and reduce the social burden of the patients suffering from disease [10]. Future investigation should depend upon the understanding the various neurotransmitter involvement in tics generated in TS and also the brain regions involved in TS. A better therapeutic management can be achieved by understanding of the disease mechanism, multiple neurotransmitter involvement and their pathways involved in TS.

**Selection Criteria:** Different authentic, peer reviewed and cited review articles and scientific papers were searched by the authors for writing this current comprehensive review. Various keywords and terms were looked into for drafting this paper such as "Tourette's Syndrome", "GABA", "Basal Ganglia", "Dopamine", "Tics", "Movement Disorders", "Current", "Neuroimaging", "Therapy", "Involuntary movement", "Neuropsychiatric Diseases", "Pathophysiology", "Diagnosis", "Management", "Neurophysiology" and "Neurodevelopmental disorders". The online literature search and survey was conducted by utilizing various platforms and search engines for journals indexed in Google Scholar, Pubmed, Scopus,

Science Direct and various websites of reputed indexed journals. Further, supplementary papers and review papers were scrutinized by investigating the references of explored articles to gather valuable information on pertinent aspects of Tourette syndrome.

## 2. CLASSIFICATION, DIVISION AND DESCRIPTION

Tics are the main clinical characteristic of TS which include both motor tics and sounds (vocals or phonic tics). They represent the simple or coordinated, sequential or repetitive movements, gestures, utterances which stimulate fragments of the normal behavior. Both vocal and motor tics can be further differentiated into a simple or complex presentation. The *simple tics* are fleeting and sudden tics utilizing individual muscles or limited number of few muscle groups. It includes various examples such as darting of eye, twitching of nose, shrugging of shoulder, jerking of head, sniffing and clearing of throat. The *complex tics* include more sequenced, distinct and coordinated patterns of movements involving various muscle groups. It exhibits socially inappropriate behaviors and different examples are repeating or gesturing phrases, facial frowning, arm flapping, stepping, jumping or hopping in a specific manner. The complex multiple tics of motor and vocals lead to paresthesia or discomfort produced by premonitory sensations and these sensations are comforted for a moment after the execution of these complex multiple tics [19].

Many patients generally repeat the specific movements to reduce these tics until they feel good. There is reduction in severity and frequency of tics during the involvement in physical activity, mental activity. These tics disappear in the sleep. Tics can be worrying for the patients in TS, because of the patient's face embarrassment and it also interferes with their social life during interaction with the others people. It's a quite painful and uncomfortable situation for the patients of TS at that moment. TS is the most common disease which is caused by tics that leads to behavior disturbances.

The simple motor tics which represent the short duration generally less than 1 second, brief and sudden behaviors whereas the complex motor tics indicate the long duration, sudden, emerge in purposive manner, stereotyped behavior and movements in the coordinated manner of words or the phrases like add speech pattern in terms

of change of volume, rhythm and rate of speech [19-21]. The classification, division and description of TS are summarized in Fig. 1.

### 3. DIAGNOSIS OF TS

There is no precise technique and blood test available that can identify and diagnose Tourette's syndrome. The diagnosis is generally dependent upon the record of patient history of various signs and symptoms. Tic disorders are diagnosed and recognized employing a vigilant history recording onset of childhood, family history record, identification of wide range of behavioral and motor phenomena and neurological examination. The identification and diagnosis of Tourette's syndrome is done when together vocal and motor tics exist at some span of time during history of patient and remain importunate for more than one year. Also the onset of tic disorder must persist before 18 years of age and tics are not brought by medicines or other substances or persisting other medical disorders. The existence of co morbidities is not an essential prerequisite for diagnosing Tic disorder. Wax and wane in severity, characteristically linked with sensory phenomena, temporarily suppression and character of movements change over time, are the various distinguished characteristics of tics which distinguish them from others movement

disorders. The severity of tics generally peak between 10-12 years of children and most cases symptoms will diminish in the age of adolescence. It is very rare that severity of tics remains present in adolescence [5, 21-23].

The TS diagnosis includes *tics, stereotypies, chorea, dyskinesia, myoclonia, and synkinesis*, among other movements. The *stereotypies* behaviors refer to purposeless, repetitive behaviors and apparently voluntary movements; simple, irregular and random behaviors are involved in *chorea*. Movements of protracted twisting leads to intersperse with extended states of the muscular tensions are involved in *Dyskinesia*. The *myoclonic* movements indicate the simple, brief, shock like contractions of the muscle which leads to influence the individual's muscles or groups of muscles. *Synkinesis* represents the movements of involuntary nature which are linked to precise voluntary action such as opening corner of mouth while closing single eyes.

Differential diagnosis of tics disorders are shown in Fig. 2 [5,21-23]. Thus, tics and their linked comorbidities features can affect quality life of patients, their social and academic involvement, disruptive and troubling the family of patients [21,24]. Various exacerbating factors for the tics are shown in Fig. 3 [5,25-26].

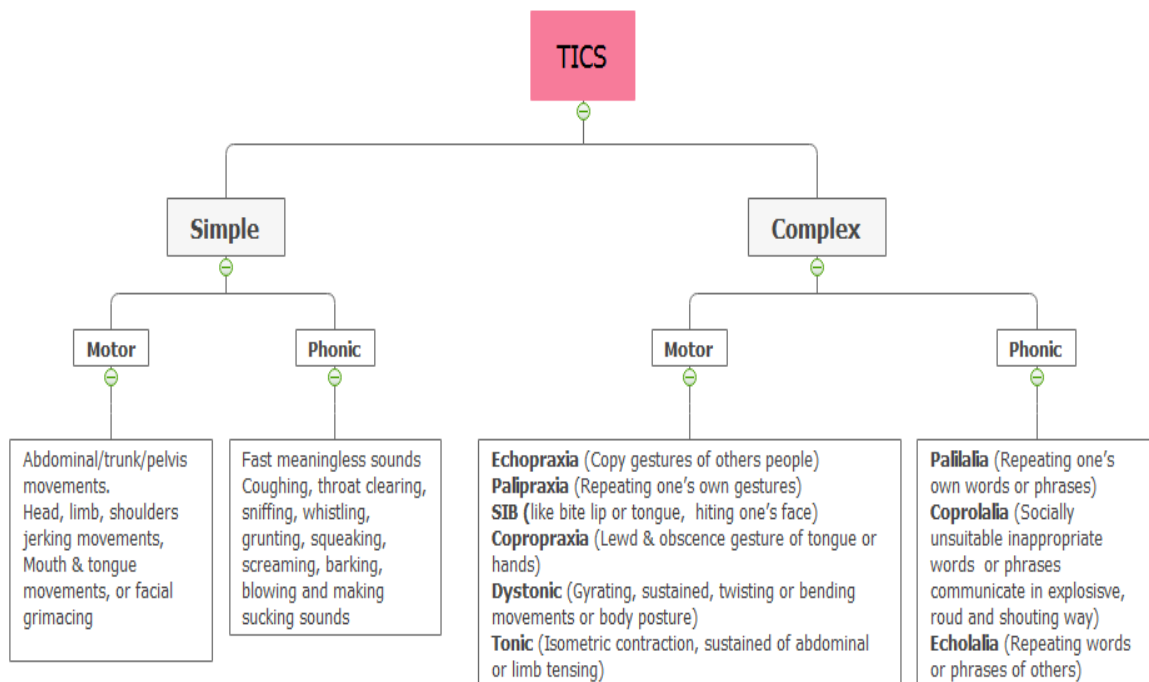
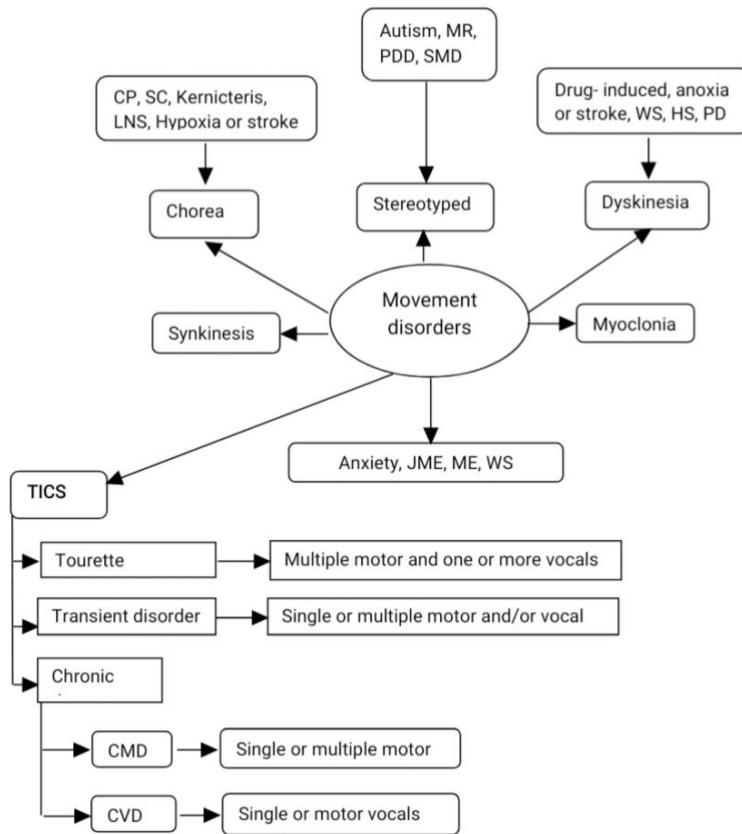
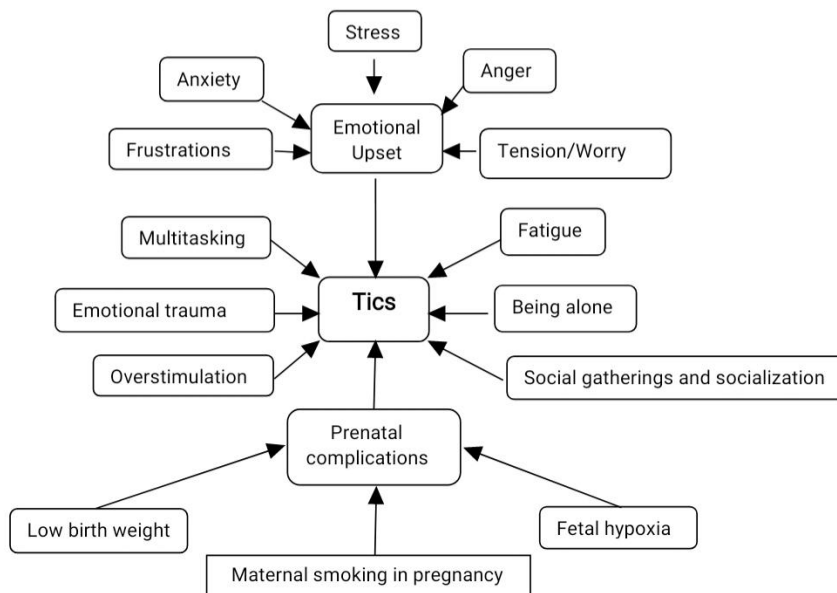


Fig. 1. Classification, division and description of tics in TS



**Fig. 2. Differential diagnosis of tics disorders**

CTS: Chronic Tic disorders; TTD: Transient tics disorders; MR; Mental retardation; PDD: Pervasive developmental disorders; SMD: Stereotyped movement disorders; CP: Cerebral palsy; LNS: Lesh –Nyhan syndrome; WS: Wilson’s disease; HD: Huntington’s disease; PD: Parkinson’s disease; ME: Metabolic Encephalopathies; CMD: Chronic motor disorder; CVD: Chronic vocals disorder; TS: Tourette syndrome; SC: Sydenham’s chorea; JVE: Juvenile myoclonic epilepsy



**Fig. 3. Exacerbating factors for the tics**

Various clinical features consequence to chronic and complex neuropsychiatric features such as obsessive compulsive disorders (OCD), attention deficit hyperactivity disorder (ADHD), impulsive control disorders (ICD), rage attack, depression, sleep issue, learning disabilities, migraine and rare neurological complications [21,27-33]. The comorbidities linked to TS are shown in Table 1.

## 4. PATHOPHYSIOLOGY OF TS

### 4.1 Neurochemistry of TS

Numerous reports of clinical trials, imaging, and individual sample studies have jointly resulted in the theories of neurochemical based abnormalities for TS. The most familiar neurochemical theory of TS is dopaminergic dysfunction, depending originally on the remark that dopamine receptor-blocking drugs known as neuroleptics were most efficient in lessening tics. Although some reports have observed dopamine transporter combining ability abnormality and amplifying cortical and striatal dopamine receptors, no dopaminergic hyperinnervation has been illustrated by Positron Emission Tomography (PET) analysis. Despite the major progress in comprehension of exact cellular and molecular grounds of TS, the various evidences indicate that the various neurotransmitters such as dopamine, glutamate, GABA, serotonin, noradrenergic, cholinergic system, serotonergic system and histaminergic pathways are involved in the pathophysiology of this syndrome [7,11,15,21, 49-51]. These areas of research have contributed to the therapeutic approach towards the management of TS and also have provided the basis for future progress of the therapeutic strategies. Thus, multiple neurotransmitters are implicated in the pathophysiology of TS [7,14-15,21]. The various neurotransmitters functions which are impaired in Tourette's syndrome are summarized in Fig. 4 [10-12].

#### 4.1.1 Dopamine pathways

Dopaminergic pathways are implicated in various movement disorders and also associated with the tics generated in TS. Inputs from ascending D pathways starting in the pars compacta (PC) of the substantia nigra (SN) participate in managing the output from the striatum. Dopaminergic fibres arise from ventral tegmental area (VTA) in frontal regions which directly regulate excitability of pyramidal cell and also indirectly regulate through synapses on the interneurons. The glutaminergic

system input to the striatum which inhibit the projection of medium spiny neuron (MSN) through direct pathways on D1 R and through the indirect pathways on D2 R. The binding of vesicular monoamine transporter (VMAT) is increased in TS. The dopamine receptor (DR) binding potential decreases subcortically and cortically and thus cortical dopamine may be significant in tics generation in TS. Increase of dopamine active transporter (DAT) binding in the neostriatum & increase of D 1 & D 2 release in the ventral striatum (VS). The extra striatal D2 receptors decreased in thalamus and cortex. The various D antagonists are utilized for suppression of designated or specified the participation of DR tics generated in TS [12,49,52-54].

#### 4.1.2 Noradrenergic system

Noradrenergic system indirectly affected the central D system through projections close to regions of VTA. The mechanism of NS is linked with pathogenesis of TS and the beneficial effect of  $\alpha_2$ -adrenergic agonist of clonidine in patients of TS. This system involves a mechanism through a stressor which affects the tics severity. The elevated levels in the Corticotrophin-releasing factors (CSF) and PC is observed in TS [10,45].

#### 4.1.3 Histaminergic system

Histamine is signaling molecule of CNS which is thought to regulate wakefulness, attention of body. Histamine regulates both the dopamine and serotonin. The H1 and H2 receptors present on medium spiny neurons (MSN) in striatum. The relative loss of functions of L-histidine decarboxylase (L-HDC) is basis of therapeutic approach towards the TS and it is synthesized through histidine via LHD [13,55].

#### 4.1.4 Serotonergic system

Ascending the projection of serotonin system in the dorsal raphe is implicated in the pathogenesis of TS. The serotonin, tryptophan and 5HIA levels are decreased in basal ganglia and dorsal raphe. There are decreased serum levels and cerebrospinal fluid (CSF) serotonin and tryptophan which represent that serotonin implicated in TS and Serotonin transporter (SERT) binding potential is decreased in disease. The serotonergic neurotransmission abnormalities play a significant role in pathogenesis of TS [52,56-57].

**Table 1. Comorbidities associated with the TS**

<b>Disease</b>	<b>Comorbidities with the TS</b>	<b>Ref.</b>
ADHD	ADHD is a complex neurobiological disorder which caused the inattention and hyperactivity/impulsivity and it is the most prevalent comorbidity in the TS patients, varying between 60 and 80 %. ADHD symptoms precede the onset of tics by 2–3 years and commence around the age of 3–5 years. The pathogenesis of ADHD in TS patients is complex and includes environmental, genetic, and neurobiological factors. Abnormal level of dopamine and glutamate along with loss of normal globus pallidus symmetry. Multiple genes such as COMT, DRD2, MAOA, SLC6A4, MOBP, DRD1 and FASD2 have been implicated in pathogenesis of ADHD in TS patients.	[34-39].
OCD	The occurrence of OCD varies from 11 to 80 % of patients with TS and the precise etiology of OCD in TS patients is unknown; however, studies have proposed an association of the basal ganglia circuit, particularly disruption of the indirect pathway ensuing in repetitive behaviors and thoughts. OCD indications have been accounted to happen any time throughout the course of TS. Fascinatingly, compulsive indications were more common than obsessions if OCD is the presenting indication in TS patients.	[30,40-41]
ICD	The associated comorbidities with the OCD and ADHD which leads to rage attack, in appropriate sexual activity, SIB, discipline problem and sleep issues and others ICD. ICD fail to control the impulse, temptation, derive which is harmful to others or one's self. It is estimated that 23% to 40% patients of TS reported the disinhibited behaviors of ICD, which are associated with the tics which leads to irritability, sudden anger, temper outbursts, aggressive behavior. SIB which comprise of body punching or slapping, head banging and scratching the body parts.	[5]
Rage Attacks	20% to 75% of patients of TS have episodic behavioral outburst and anger issues. There has been a chiefly enhanced prevalence of impulse control disorder (particularly intermittent explosive disorder) in adult TS patients.	[42-43]
Depression	According to various study, 13% to 76% of patients suffering from TS have representing the depressive indications. The method of growth of depression is multifactorial counting a psychological response to significantly hindering condition and related social stigma, multiple neurotransmitter abnormalities and potential side effect of medications usually employed to manage tics (particularly neuroleptics).	[44]
Sleep Issues	12 % to 60% of patients with TS have showed the numerous sleep problems including sleep issues or difficulty in sleeping, REM (nightmares), NREM sleep disorders (somnambulism, night terrors), trouble initiating sleep and restlessness.	[45]
RNC	TS can hardly be related with more critical complications which comprise cervical disk herniation, cervical myelopathy, compressive neuropathy and stroke.	[46-48]

ADHD: Attention deficit hyperactivity disorder; COMT : catechol-O-methyltransferase, DRD2: dopamine receptor D2 ; MAOA: monoamine oxidase A, SLC6A4: solute carrier family 6, member 4; MOBP: myelin associated oligodendrocyte basic protein; DRD1: dopamine receptor D1; FASD2: fatty acid desaturase 2 ; RNC: Rare Neurological complications; OCD: Obsessive compulsive disorders; ICD: Impulsive control disorders

#### 4.1.5 Excitatory amino acid system

The excitatory neurotransmitter, namely glutamate is discharged due to depolarization by corticosubthalamic, corticostraital, sub-thalamic, and thalamocortical projection neurons (TPN). The relative balance between the glutamatergic pathways and GABAergic pathways is involved in main factors producing the tics. Glutamate is an excitatory neurotransmitter of CNS which takes part in cortico-basal ganglia-thalamo-cortical circuit and glutamate is also connected with the dopaminergic transmission. The amounts of glutamate are decreased in substantia nigra pars reticulata (SNr), globus pallidus internal segment (Gpi) and Globus pallidus external segment (Gpe) [12,58-61].

#### 4.1.6 Inhibitory amino acid systems

GABA constitutes the main segments of CSTC loops. These incorporate GABAergic medium spiny neuron (MSN) projections of the striatum that propel to the inner segment of the GP and the SNr inside the "direct pathway." GABAergic neurons are also available in the "indirect pathway" which communicate information from striatum to an external segment of the GP and finally to the internal segment of GP. GABA is an inhibitory neurotransmitter of MSN located in the striatum and interneurons in the cortex and striatum. Reductions of short interval intracortical inhibition and increased cell density in Gpi along with increased GABAergic interneurons in caudate and putamen [12,15,23,50, 59-62].

#### 4.1.7 Cholinergic system

The cholinergic tonically active striatal interneurons (TANs) in striatum are implicated in the management of striatal response due to interactions with central dopaminergic and GABAergic neurons. In addition, cholinergic projections from the basal forebrain are located all through the cortex and inside crucial structures of the basal ganglia, midbrain comprise of internal segment of the GP, SNr and the LC (locus coeruleus). Acetylcholine (Ach) produced by TAN and Ach is combined to the muscarinic and nicotinic receptors which ultimately lead to modulate the medium spiny projection (MSP) neurons of output in striatum. The level of choline acetyltransferase in striatum is decreased in patients of TS [8, 15, 63].

#### 4.2 CSTC circuits and TS

Although the main cause of this syndrome is unknown, several studies reported that this syndrome involves the dysfunction of cognitive neuronal circuits between specific areas of brain [4,64]. Most of the studies indicate the association of Cortico-striatal thalamo-cortical (CSTC) circuits in the pathogenesis of TS [7,21,65]. CSTC circuits concerned to various behavioral, emotional and cognitive functions are impaired in the TS [65]. CSTC circuits include the motor, sensorimotor, association and inhibitory neuronal circuits which are linked to the basal ganglia. This circuit is implicated in several emotional and cognitive processes like decision making, rewards based learning and goal directed behavior in response to significant stimuli. The motor functions are namely suitable action selection and execution, habit learning, action inhibitor and impulse control which are involved in CSTC circuits. The direct loop is believed to stimulate the cortex which leads to action implementation. The indirect pathways inhibit the direct pathways which ultimately discontinue the impulsive behavior. The balance in between direct and indirect pathways is important for the motor behavior and proper choice of adaptive action. The hyperactivity in exact domain and throughout CSTC circuits is thought to be involved in tics generation in TS [21,28,65-67]. CSTC circuits are comprised of multiple, parallel circuits that receive the signals from the cerebral cortex to subcortex and then gain back projection to cortex regions of the brain. This component such as initiating from the cerebral cortex and projecting reverse to sensorimotor, orbitofrontal along with associated cortices and it is also associated with the limbic system. The mediofrontal prefrontal (anterior cingulate, orbital frontal cortex), sensorimotor cortex (SMC) and associated cortex, motor, premotor, prefrontal cortex and basal ganglia of globus pallidus, substantia nigra pars reticulata of cerebral cortex are dysregulated in TS. Brain regions abnormality of striatum leads to increased inhibition of globus pallidus interna (GPI), disinhibition of thalamus and rotated cortical neurons and ultimately generated tics [61,66-70]

There is excess excitations or diminished inhibition and the disruptions in the various brain regions such as frontal cortex, striatum, thalamus and also impaired regulation of the neurotransmitters such as GABA, glutamate, dopaminergic and cholinergic in the circuits.



Excitatory glutamate connection, GABA-ergic connections are elevated in supplementary motor area and reduction in primary-sensorimotor cortex [1,11,19]. Some of the studies indicated the evidence for the metabolic abnormalities of neurotransmitters (dopamine and serotonin) in the basal ganglia [71]. The decrease in basal ganglia volume and alterations in white matter and cerebellar morphology leads to more diffuse changes in brain structures of TS [72-74]. The density of pre synaptic dopamine transporter increases and postsynaptic D2 receptors lead to abnormal regulations of the dopamine release and uptake in TS. The levels of serotonin are low in the brain stem and glutamate levels also decrease in the globus pallidus [7, 59,75-77]. Inability to control motor, impulse, complex vocal tics and premonitory urges leads to sensitively charged words in TS. The altered motor control processing in TS resulted from dysfunction of the motor cortex, brainstem and basal ganglia which leads to abnormal brain plasticity [22]. GABA-A receptor binding decreased in the ventral striatum, thalamus, globus pallidus, amygdala, right insula and also increase the binding in the right posterior cingulate cortex, bilateral cerebellum, bilateral substantia nigra[3]. Several studies reported that the tics related changes in neuronal activity in various brain regions of striatum, cortex, thalamus, GPi, Gpe and SNr and there is increased neuronal activity related phasic modulations of tics in GP neurons and decrease the firing rates of Gpi[27].

The basal ganglia have two primary signal projections such as GABAergic striatum which are categorized into caudate, putamen and nucleus accumbens and the glutamatergic subthalamic nucleus. These brain regions projected the excitatory glutamatergic input signals from the cerebral cortex and thalamus and projected signals output to globus pallidus interna (Gpi) and substantia nigra para reticulata (SNr). The above said projection is concerned by direct and indirect pathways via globus pallidus externus (Gpe). The action of basal ganglia is regulated by dopaminergic input from substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) directed to the striatum. The GPi/SNr back projection to the frontal cortex of brain regions through inhibitory output to thalamus and the thalamus has excitatory connectivity to the cerebral cortex [27,69-70]. Input to the basal ganglia is projected output to cortical areas which are associated with motor, associative, executive and limbic functions [27]. CSTC associated with the frontal cortex to subcortical structures

perform a role in understanding the neurobiology of TS. It was believed that basal ganglia change the cortical excitability by the mechanism of direct pathways including the signals projection of striatum to Gpi and from the striatum to Gpe to subthalamic nuclei through indirect signals projection pathways. The increased cortical excitability leads to hyperkinetic disorders because reduction of excitatory effects of direct pathways also increase the inhibitory effect of indirect pathways [69,78-80]. There is cortical thinning in frontal, parietal lobes, sensorimotor cortex and the degree of thinning of the cortical which represents the severity of tics [65,81-84]. There is reduced metabolic action in striatum and orbitofrontal cortex along with increase in metabolic activity in cerebellum and prefrontal cortex. Several brain regions such as supplementary motor area, ventral primary motor cortex, sensorimotor cortex, parietal operculum activate the tics. The anterior cingulate cortex, putamen, amygdala and insula and cerebellum is also implicated in tics during tics onsets, the brain regions such as thalamus, central operculum and primary motor and somatosensory cortex were stimulated [65,76]. The affected brain regions of CSTC circuit dysfunctions in TS are shown in Fig. -5 [4, 10, 21,27, 50, 65, 78, 82-84].

## 5. MANAGEMENT OF TOURETTE SYNDROME

Numerous approaches are employed in clinical management of children and adults suffering from tic disorders. Pharmacological medications are divided in three classes namely non-dopaminergic agents, drugs which function through blockade of dopaminergic receptors and agents that are Vesicular Monoamine Transporter-2 (VMAT2) inhibitors. These three categories of agents are described in Table 2 [85]. An enormous amount of data is available for antipsychotic medications namely typical and atypical antipsychotics, even though their usage in children and adults is restricted owing to their potential side effects [86]. Complementary and alternative medicines (CAM) namely acupuncture technique, behavioral therapy, nutritional changes, lifestyle modifications and herbal medications utilized for management of Tourette's syndrome are enlisted in Table 3 [87]. CAM are generally recommended along with pharmacological therapies for treatment of tic disorder patients thereby ensuring better outlook by exhibiting more control on their symptoms that exacerbate tics.

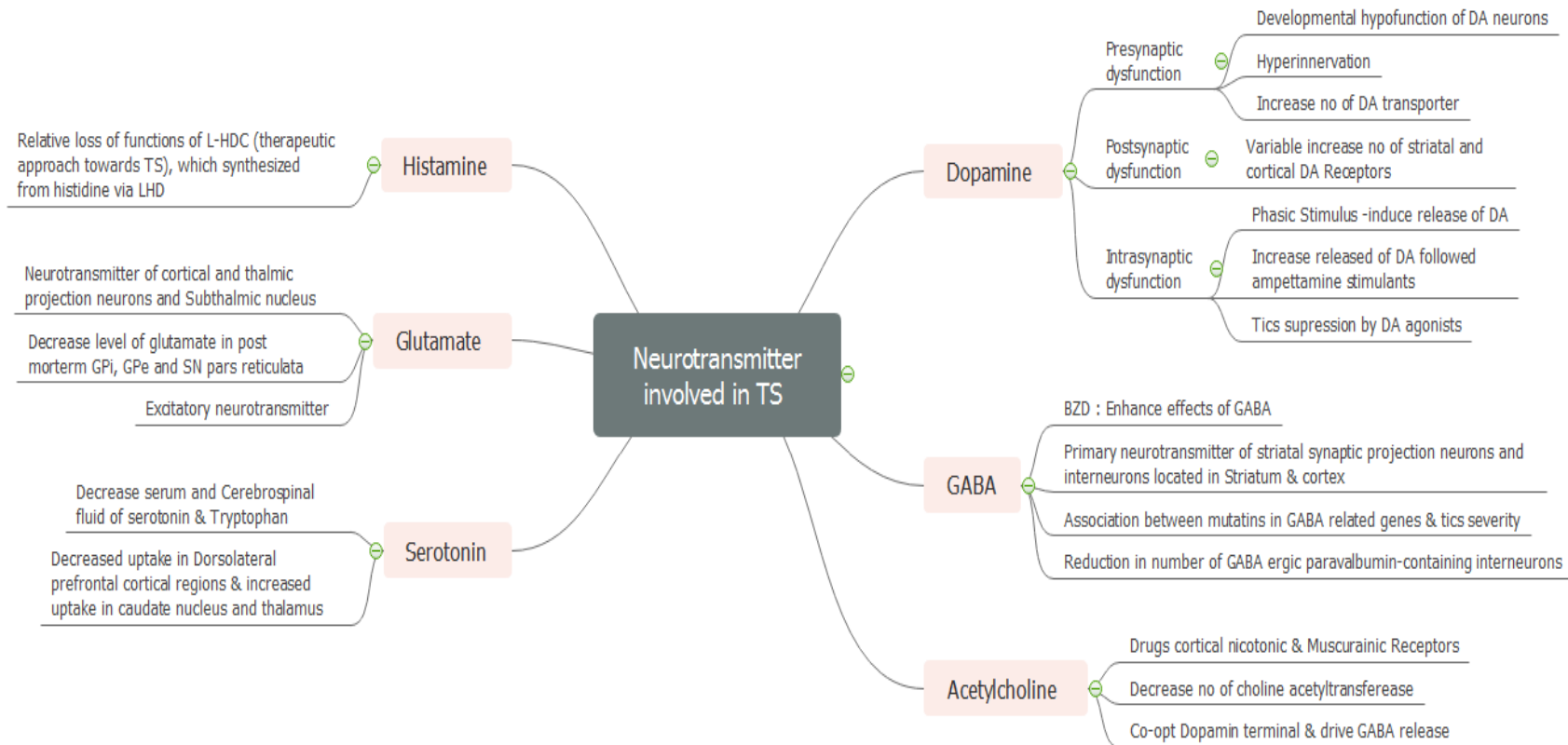
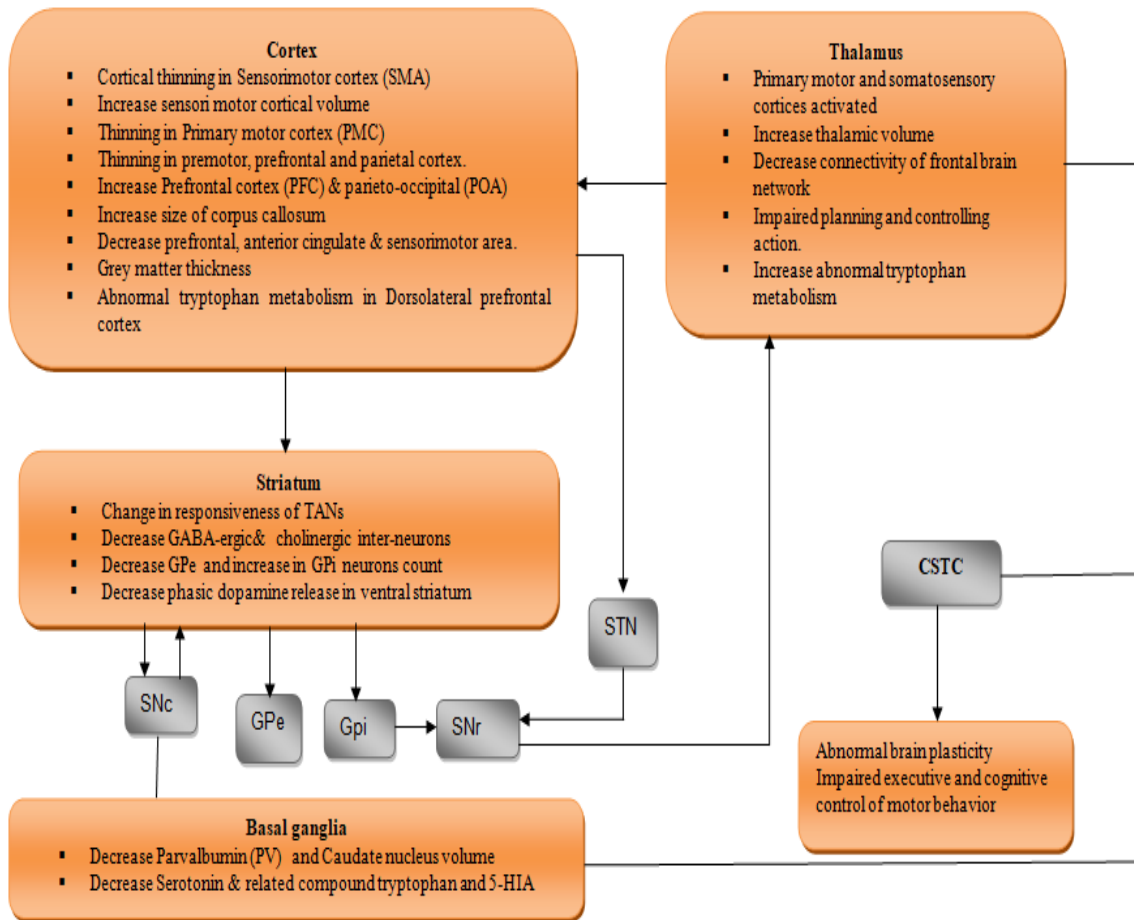


Fig. 4. Neurotransmitter and Tourette's syndrome



**Fig. 5. CSTS circuits and TS**

STN: Subthalamic nucleus ; DA: Dopamine ; HIA: Hydroxy-indoleacetic acid; SNc, Substantia Nigra pars compacta ; GABA: Gamma-aminobutyric acid ; Ach: Acetylcholine; GPi : Globus pallidus internal segment; SNr, : Substantianigra pars reticulata; GPe: Globus pallidus external segment;; SP: Substance PVA/VL : Ventral anterior/ ventral lateral nuclei; TANs: Tonicly active striatal interneurons; CSTC: Cortico-striatal-thalamo-cortical

**5.1 Controversy of Neurochemistry of TS**

Structural and functional neuroimaging will however be critical for elucidating the understanding of this circuit disorder. Neuroimaging may offer the intriguing possibility of parsing individual clinical manifestations into specific causative brain regions, and early-onset longitudinal studies can provide insight into the role of brain development in the manifestations and the natural history of TS. Moreover, neuroimaging can allow the study of response to various treatments. Various studies reported on clinical drug trials, imaging and analysis of human samples have jointly consequences to the hypothesis of neurotransmitter dysfunctions in TS. Dopaminergic abnormalities are mainly general neurochemical hypotheses, based

initially on the finding that neuroleptics drugs (dopamine receptor-blocking drugs) were mainly valuable drugs in reducing the tics. Some other studies indicated that abnormalities of dopamine transporter binding capacity and also increases of cortical and striatal dopamine receptors, no dopaminergic hyperinnervation has been demonstrated by PET studies. Dopamine is no longer considered the exclusive neurotransmitter involved in TS. Various studies target serotonergic neurotransmission mechanism pathways involved as significantly in the pathophysiology of TS. Some of others hypotheses indicate that imbalances in various neurotransmitters such as noradrenergic, glutamatergic, serotonergic, opioid, cholinergic, and GABA-ergic systems involved in pathophysiology of TS [10,121-125].

**Table 2. Pharmacological management of tourette syndrome**

<b>S.No.</b>	<b>Category</b>	<b>Name of drug candidates</b>	<b>Mechanism of action</b>	<b>References</b>
1.	Non-dopaminergic agents	Clonidine	$\alpha$ -2 adrenergic receptor agonist	[88]
2.	Non-dopaminergic agents	Guanfacine	$\alpha$ -2 adrenergic receptor agonist	[89]
3.	Non-dopaminergic Agents	Baclofen	GABAB receptor agonist	[90]
4.	Non-dopaminergic Agents	Topiramate	GABAergic and blocks AMPA kainate receptors	[91]
5.	Non-dopaminergic Agents	Botulinum Toxin A	Inhibits acetylcholine release	[92]
6.	Typical Antipsychotics	Pimozide	Dopamine receptor blocker	[93]
7.	Typical Antipsychotics	Haloperidol	Dopamine receptor blocker	[94]
8.	Typical Antipsychotics	Fluphenazine	D1 and D2 receptor blocker	[95]
9.	Atypical Antipsychotics	Aripiprazole	Partial D2, D3, and D4 receptor agonist & Partial 5-HT1A and 5-HT2C receptor agonist	[96]
10.	Atypical Antipsychotics	Risperidone	At low dosage 5-HT2 receptor antagonist and at high doses functions as a D2 antagonist	[97]
11.	Atypical Antipsychotics	Olanzapine	Antagonist of D1, D2, D3, D4, 5-HT2A, 5-HT2C, H1 and muscarinic receptors	[98]
12.	Atypical Antipsychotics	Ziprasidone	Low affinity for D2 receptors, Moderate affinity for M1 and H1 receptors and High affinity for 5HT2A, 5HT1A, and 5HT2C receptors	[99]
13.	Benzamides	Tiapride, Sulpiride and Amisulpride	Highly specific D2-blocking agents	[100-101]
14.	Vesicular Monoamine Transporter-2 Inhibitors	Tetrabenazine, Deutetabenazine, Valbenazine	VMAT2 inhibitor thereby preventing translocation of neurotransmitter monoamines from the cytoplasm into the synaptic vesicles	[102-104]

**Table 3. Complementary and alternative medicines (CAM) for cure of tourette syndrome**

S.No.	Name of Therapy	Description	Ref.
1.	Acupuncture	<i>Controls abnormal functioning of brain</i> in individuals suffering from tic disorders. <i>Stabbing/ piercing of fine needles into acupoints</i> as per traditional medicine theory. Effective adjuvant therapy in lessening tic indications.	[105 - 106]
2.	Behavioral Therapy	<b>Habit Reversal Training (HRT):</b> It incorporates tricks which assist the patient in reversing the activity of tics, decreases stress and educates individuals having TS various ways to handle their tics for e.g. an individual may decide to smile when a tic to scowl is activated. <b>Cognitive Behavioral Therapy:</b> This remedy can aid the patient in identifying factors that activate tics. This therapy can be useful for individuals who are facing trouble in socializing. <b>Comprehensive Behavioral Intervention for Tics (CBIT):</b> In this treatment, an experienced therapist will work along with a child or an adult for better understanding of types of tic an individual is suffering from and situations in which tics are at their nastiest. <b>Psychoeducation and teaching public about TS</b> lessens teasing and employs better awareness of tic symptoms and provides social support. <b>Parent training</b> ensures better recognition of behavioral issues of their child and adoption of precise parenting skills.	[107 - 108]
3.	Nutritional Changes	<i>Administering food items and supplements rich in magnesium and vitamin B6</i> namely leafy vegetables, fruits, nuts, whole grains and fish for controlling motor and vocal tics and easing anxiety. <i>Consuming omega-3 fatty acids</i> by children and adults for managing psychological distress and tic impairment. <i>Taking casein free diet and avoiding allergic food items</i> namely dairy products assists in reducing reoccurrence of tics. <i>Consuming gluten free diet</i> helps in lessening motor tics and behavioral issues. <i>Avoiding refined sugar, soda in cola drinks and caffeine</i> in coffee and black tea due to their influence on dopamine levels in brain and also controls gastrointestinal distress.	[109 - 111]
4.	Lifestyle Management	Lifestyle alterations along with indulging in <i>relaxation exercises</i> namely <i>yoga, meditation, visual imaginary, deep breathing</i> , etc. assist in soothing and calming down the triggered patient thereby aids in diminishing intensity and frequency of tics. Relaxation exercises help in alleviating stress that can aggravate tics and ensures better control on your mind and body.	[112 - 115]
5.	Herbal Medications	Herbal medications of Planet Ayurveda are generally harmless to utilize and can be safely employed. <b>Ashwagandha</b> ( <i>Withania somnifera</i> , family Solanaceae) is employed for assuaging body ache, fatigue, induces sleep and diminishes stress, depression and anxiety. <b>Brahmi</b> ( <i>Bacopa monneiri</i> , family Plantaginaceae) is potent	[116 - 120]

S.No.	Name of Therapy	Description	Ref.
		<p>nervine tonic and effective anti-anxiety agent. It is also employed for enhancing learning capability, retention power and lessening stress.</p> <p><b>Gotu kola</b> (<i>Centella asiatica</i>, family Apiaceae) is utilized for enhancing memory and managing acidity that happens due to depression. It aids in calming down nervous system and ensures stress management.</p> <p><b>Jatamansi</b> (<i>Nardostachysjatamansi</i>, family Caprifoliaceae) is cooling herb for controlling resentment, vengeance, negative perceptions and keeps mind cool by inducing sleep.</p> <p><b>Tagar</b> (<i>Valerianawallichii</i>, family Valerianaceae) possess stress breaking characteristics and employed for fighting anxiety and overactive mind.</p>	

## 5.2 Future Insight of TS

There is an abundance of future directions for research in the TS field. Towards the therapeutic measures of the clinical side, it will be essential to understand premonitory urges in a better way, characterize variations in TS phenotypes, and also to better diagnose or characterize the various comorbidities associated with TS. According to studies, gene discovery will be applied to larger cohorts, which more effectively separate different clinical and genetic phenotypes of TS. More electrophysiological studies will be needed, especially in human patients performing intraoperative tasks, or through advanced DBS devices capable of recording brain signals and correlating them to awake human behavior. The manifestations of TS, which are paroxysmal, present a unique opportunity to develop responsive closed loop neurotechnologies designed to suppress tics. All of these approaches should be conducted with the goal of developing new and improved therapies to improve the quality of life for those suffering from TS. A critical step in TS treatment is to provide education to the patient, caregivers, and peers about the condition. This is important in establishing appropriate expectations and optimal treatment strategies and in creating more informed relationships. A common strategy is to tailor therapy to address the symptoms (tics or comorbidities associated with syndrome), which are likely contributing to impairing daily basis functioning and leads to impacting quality of life. Treatment of TS comorbidities may diminish tic severity. Following family education, behavioral and pharmacological approaches may be addressed. Occasional medication refractory cases may lead to discussion of surgical treatment strategies. If easily accessible,

behavioral therapy such as Comprehensive Behavioral Intervention for Tic Disorders (CBIT), which may include habit reversal training (HRT), can be offered to the patients as a first line of treatment. The aim of such a behavioral approach is to facilitate control of tics by disrupting the pattern of premonitory urges and the relief sensation that follows the execution of some tics. Looking to the future, there is a dire need for increased knowledge, awareness, and specialist care for both children and adults with TS [10].

## 6. CONCLUSION

Tourette's syndrome is a chronic form of neuropsychiatric disorder which comprises abnormal motor and phonic tics. This syndrome usually begins in childhood and may collapse or continue into adulthood. In past decades, the widespread study of pathogenesis of TS is not understood clearly. It is necessary to understand the connections of tics which are linked with several neuropsychiatric comorbidities and it is compulsory to clarify the various factors, which can produce or amend behaviors of tics. It is believed that the various neurotransmitters contribute in the message transmission mainly by CSTC circuits. Through proper understanding the pathogenesis of tics and their associated conditions to others disorders can be the basis for effective therapeutic approach of tics in TS. Thus, tics generated in TS, which affect the social and academic life of patients and disruptive or troubling the family of patients. Patients existing with this syndrome have to face difficulties integrating into social life and coping with day to day basis activities, as a consequence of the syndrome. Glancing to the future, there is an extreme urge for enhanced

comprehension, consciousness, and expert attention for both children and adults suffering from TS.

## CONSENT

It is not applicable.

## ETICAL APPROVAL

Authors hereby submit that there are no ethical issues in drafting this manuscript. Authors have not performed any studies on animals or human subjects for writing this review paper.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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