The Neurobiology of Tourette Syndrome

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SUMMARY

Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by chronic motor and vocal tics. Although it is a common disorder in childhood, the etiology of Tourette Syndrome has not been fully elucidated yet. Studies, -conducted so far- have revealed differences in neurobiological structures of individuals who suffer from Tourette Syndrome. The objective of this review is to assess etiological and pathophysiological studies in the Tourette Syndrome literature. An electronical search was conducted in PubMed database using the keywords tic disorders, Tourette Syndrome, neurobiology, genetics, neuroimaging and animal models. Research and review studies published between 1985 and 2015, with a selection preference towards recent publications, were reviewed. According to the studies, genetic predisposition hypothesis is considered as a priority. However, a precise genetic disorder associated with Tourette Syndrome has not been found. The evidence from postmortem and neuroimaging studies in heterogenous patient groups and animal studies supports the pathological involvement of cortico-striato-thalamo-cortical (CSTC) circuits in Tourette Syndrome. Consequently, the most emphasized hypothesis in the pathophysiology is the dopaminergic dysfunction in these circuits. Furthermore, these findings of the animal, postmortem and neuroimaging studies have confirmed the neurodevelopmental hypothesis of Tourette Syndrome. In conclusion, more studies are needed to understand the etiology of the disorder. The data obtained from neurobiological studies of the disorder will not only shed light on the way of Tourette Syndrome, but also guide studies on its treatment options.

Keywords: Tic disorders, Tourette Syndrome, neurobiology, genetics, neuroimaging, animal models.

INTRODUCTION

Tourette Syndrome (TS) is a neurodevelopmental disorder of childhood that affects 1 in every 4,000-6,000 children (APA 2013). It is characterized by motor and vocal tics that last at least one year. The phenotypical features of TS range from simple motor tics to highly complicated tics and psychiatric comorbid diseases. Tics typically begin around 4-6 years of age and reach their peak around the ages of 10-12. Tics often decrease throughout puberty, and it has been reported that 1/3 of TS patients stop having tics by early adulthood. Based on its age of onset and course of symptoms, TS can be considered as a developmental disease. TS is frequently seen with other psychiatric diseases, and it has been determined that comorbidities are highly important in determining the prognosis (Bloch and Leckman 2009).

The etiology and the pathophysiology of TS have not been fully elucidated. Therefore, the aim of this study is to present a review of the literature regarding the etiology of TS.

METHODS

PubMed was used to obtain recent research papers and reviews (1985-2015). The keywords used were as follows: Tic disorders, Tourette Syndrome, neurobiology, genetics, neuroimaging and animal models.

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ETIOLOGY

1. Genetic Factors

TS has a complex genetic component and a strong hereditary disposition. First degree relatives of those with TS have a high risk of developing TS and other tic disorders (State 2010). Further, TS has a concordance of 77% in monozygotic twins and 23% in dizygotic twins (Price et al. 1985). Family studies have shown that genetic transmission is not related to one single gene, but rather, TS is caused by the complex transmission of many genetic loci that create a risk for TS and other developmental disorders (O'Rourke et al. 2009). Other recent family studies support the hypothesis that TS, Obsessive Compulsive Disorder (OCD), and Attention Deficit and Hyperactivity Disorder (ADHD), which are commonly seen together, share a common genetic etiology (O'Rourke et al. 2011).

In diseases that are thought to have a complex genetic transmission, the individual differences in a patient's DNA (polymorphisms) are believed to increase the risk of the disease and may cause the disease by a cumulative effect. These DNA polymorphisms are referred to as Single Nucleotide Polymorphisms (SNP) and Copy Number Variants (CNV) (Battaloğlu and Başak 2010). Neurotransmitters are thought to play a key role in the neurobiological pathways of TS, and there has been significant research conducted on candidate genes related to these neurotransmitters. The results of these studies, which had different sample sizes and patient ethnicities, have been inconsistent with regards to neurotransmitter SNPs. However, the majority of these studies do indicate that genes related to *DRD2* (dopamine receptor D2), *MAO-A* (monoamine oxidase-A) and *DAT1* (dopamine transporter-1) may be involved (Paschou 2013). Further, the first of the CNV studies indicated that the *NRXN1* (neurexin 1) and *CTNNA3* (catenin, alpha 3) genes may also be involved (Sundaram et al. 2010). More recently, two CNV studies found evidence that TS is a neurodevelopmental disorder and that its genetic etiology coincides with other neurodevelopmental disorders. The first of these studies (Nag et al. 2013) identified two CNVs in the *NRXN1* and *COL8A1* (collagen, type VIII, alpha 1) genes. Further, this study reported that wide CNVs were seen more often in TS patients with concomitant ADHD and/or OCD when compared with the control groups, just as in other developmental psychopathologies. The second study revealed that wide pathogenic CNVs exist in TS, and that these have also been observed with other developmental psychopathologies (McGrath et al. 2014).

As there is an increasing number of SNPs and CNVs identified for diseases with complex genetic transmission, and because the examination of the whole genome has become possible with advancing technology, the number of genome-wide genetic association studies (GWAS) have rapidly increased. With GWAS, a large number of patient/control samples (>1000) can be analyzed, one million SNPs and CNVs can be tested simultaneously, and genes with little effect can be identified (Battaloğlu and Başak 2010). The first GWAS on TS patients revealed that the *COL27A1* (collagen type XXVII, alpha 1) gene gave the highest signal; however, no variant could be identified that was significant genome-wide. Also, the genes that were significant in previous candidate gene studies were not found to be significant in a subsequent study (Scharf et al. 2013). Another study analyzed the sample cohort of the study by Scharf et al. and the GWAS results of another patient group with OCD, and found a possible common genetic etiology of TS and OCD (Davis et al. 2013). In GWAS studies related to TS, one single gene locus was identified on chromosome 2p (Tourette Syndrome Association International Consortium for Genetics 2007); this was the only gene to reach genome-wide significance. While other studies have identified genes reaching genome-wide significance (Paschou et al. 2014), the mechanism of only one gene was identified (Ercan-Şencicek et al. 2010). It was determined that a premature termination codon (W317X) forms at the risky part of the *HDC* (histamine decarboxylase) gene due to a single rare coding mutation. This mutation causes dysfunction in the *HDC* gene, which is responsible for producing L-histidine decarboxylase, the rate-limiting enzyme in histamine biosynthesis. The relationship between the synthesized mutant protein and TS has also been shown in vitro studies (Castellan Baldan et al. 2014). A recent study re-analyzed the first TS GWAS results, and a relationship was found between TS pathogenesis and the 33 genes that regulate glycolysis and glutamate metabolism, both of which help astrocytes support synaptic function (de Leeuw et al. 2015).

Cytogenetic studies can identify changes that cause chromosomal differences in sick individuals, such as translocation, duplication, or deletion. These studies identified that TS is related to some chromosomal disorders. In one TS case, it was found that the functional defect on the *IMMP2L* (inner mitochondrial membrane protein) gene was due to a de novo duplication on the seventh chromosome (Petek et al. 2001). Four other studies (one familial case and three de novo cases) also identified the 18q22 location (State 2010). Further, in three TS cases, a functional defect was found on the *CNTNAP2* (contactin related protein 2) gene; this was caused by a 2p21-p23 insertion on 7q35-q36, which is associated with other developmental disorders as well as TS (Verkerk et al. 2003). A study involving two families with TS reported that functional defects exist on the *SLITRK1* (SLIT family membrane protein, 1) gene due to a de novo insertion on the 13th chromosome and on the *NLGN4X* (neuroligine 4, X-dependent) gene due to exon 4-6 deletions (Abelson et al. 2005).

2. Environmental Factors

Since neonatal hypoxia was reported to augment the severity of TS tic symptoms, some researchers are of the opinion that environmental factors play just as a great role in the development of TS as do genetic factors. However, this finding could not be repeated in some later studies, and smoking during pregnancy and low birth weight have become the most repeated significant prenatal-perinatal risk factors (Chao et al. 2014). In addition, birth by caesarian section has also been reported to be a risk factor (Cubo et al. 2014). Animal experiments have shown that developmental hypoxia causes interneuronal loss in the cortex (Fagel et al. 2009). Further, post-mortem studies report that environmental factors affect the parvalbumin-expressing neurons in the striatum or cholinergic interneurons. It is believed that the interaction between the genetic and environmental factors play a role in the development of TS (Kataoka et al. 2010).

The exposure to androgens is one of the environmental factors associated with TS development. As TS more commonly occurs in males, researchers hypothesize that androgenic steroids during the androgen-sensitive period of fetal development may play a role in the development of TS (Alexander et al. 2004). Studies have examined the relationship between TS and the consumption of commercially prepared foods and drinks that contain excessive amounts of excitatory amino acids. These studies focused on the effects of excitatory amino acids on both the central nervous system and the sex hormones (Zou et al. 2011), but they found no conclusive link between their consumption and TS.

Another environmental factor that is thought to affect the etiology of TS is the temperature regulation defect of the hypothalamus (Kessler 2004). In the literature, environmental and body temperature changes were shown to temporarily increase tics. This increase in tics was related to increased sweating via dopamine-related pathways in the hypothalamus (Scahill et al. 2001).

In recent years, postinfectious autoimmunity has been the most commonly discussed environmental factor. Prepubertal children presenting with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) also present with tics, OCD symptoms, and/or chorea following A group Beta Hemolytic Streptococcus (AGBHS) pharyngitis. The antisteptococcal immune response can be shown serologically during the illness phase of AGBHS. It has been hypothesized that AGBHS can cause neuropsychiatric symptoms through autoimmunity pathways in genetically-prone individuals (Mell et al. 2005). While there are published studies supporting this hypothesis (Cengel Kültür et al. 2009), there are others reporting that there is no relationship between AGBHS infections and PANDAS (Leckman et al. 2011). It has been reported that individuals with TS have more frequent AGBHS infections and have increased antistreptolysin-O (ASO) levels (Martino et al. 2011). More recently, researchers have detected dysgammaglobuliemia and lower immunoglobulin G3 (IGG3) levels in cases following AGBHS infection; the authors surmised that this finding may have lead to autoimmunity (Bos-Veneman et al. 2011). Case reports have shown that Borrelia burgdoferi, Mycoplasma pneumonia, Chlamydia pneumoniae, Toxoplasma gondii, HIV and other infectious causes, such as viruses causing the common cold, may also play a role (Hoekstra et al. 2013).

It has been reported that TS cases have very different immune responses. One study showed that there are pathological IgG oligoclonal bands in the cerebrospinal fluid of TS patients, which is thought to indicate B-cell immune response-related damage in the blood-brain barrier (Wenzel et al. 2011). In addition, there are decreased levels of T cell regulators in patients with TS, which supports the hypothesis of T cell-mediated autoimmunity (Kawikova et al. 2007). Further, TS patients had higher levels of interleukin 12 (IL-12) and tumor necrosis factor alpha (TNF alpha) at the start of symptoms and during their exacerbation when compared with a control group; further, the authors hypothesized that an excessive cell mediated immune response was responsible for the development of TS (Leckman et al. 2005). In a postmortem study, the brains of four TS patients had increased IL-2 and expressed chemotactic factor (Morer et al. 2010). Other studies have shown changes in natural killer cell functions and viral response regulators (Lit et al. 2009), as well as microglia functions (Chen et al. 2010). Candidate autoantibodies related to pathogenic autoantibodies have been found, but the relationship between these and TS has not yet been elucidated (Hoekstra et al. 2013).

Psychosocial stress is another important factor in the etiology of TS. One study showed that negative life events increased the severity of tics in adults, but not in children (Hoekstra et al. 2004). A longitudinal study revealed that current psychosocial stress increases tic severity in the short term, while past stress affects depression symptoms, but not OCD and tics (Lin et al. 2007). In another study from the same group, AGBHS infections were shown to increase the predictive power of current psychosocial stress on the severity of tics and OCD symptoms (Lin et al. 2010).

PATHOPHYSIOLOGY

1. Findings From Animal Studies

The etiological factors associated with TS have been studied with animal models. Valuable information has been gained from animal models created with interventions imitating genetic, environmental, pharmacological, and immunological effects.

a) Examples of genetic models

The D1CT-7 transgenic rat model was created by fusion of the cholera toxin a1 subunit with the dopamine D1 receptor promoter area. The D1CT-7 transgenic rat is an ideal model in terms of imitating the behavioral symptoms of TS and assessing response to pharmacological agents. In these rats, compulsive behavior and extremity-head jerks were observed starting from the 16th postnatal day, and the jerk movements were observed to subside with clonidine and DRD2 antagonists (Nordstrom and Burton 2002). However, because the genetic alteration created in this model is not observed in humans, the structural validity of the model (i.e. the model's ability to mimic the pathogenic mechanism of the etiological agent) is still in question (Swerdlow and Sutherland 2005).

The expression of the dopamine transporter (DAT) in the striatal dopaminergic neurons is decreased in DAT-knock down rats. The main role of DAT is to ensure dopamine uptake, and therefore, the extracellular dopamine levels of these rats are 170% of the normal value. Excessive activity and stereotypical movements have been observed in these animals (Zhuang et al. 2001). However, this model is considered to be a better model for the OCD symptoms in TS than it is for tics (Berridge et al. 2005).

Research has shown that there is a genetic alteration in the histidine decarboxylase enzyme, which plays an important role in histaminergic signaling, in those with familial TS (Ercan-Şençiçek et al. 2010). Therefore, HDC-knock out mutant rats were created by inactivation of *Hdc* (histamine decarboxylase) genes in order to mimic histidine decarboxylase deficiency. Spontaneous stereotypes are not observed in these rats; however, they do have increased dopamine levels in the striatum, which is similar to what is seen in patients with TS. These increased levels of dopamine cause an increase in stereotypes induced with amphetamines (Castellan Baldan et al. 2014). Based on this data, it has been argued that histamine has more of a modulator effect than a direct effect on the development of TS (Ellender et al. 2011).

There is a known relationship between *NLGN4* (neuroligine-4) and TS. Since it is also known that neuroligine has a modulating effect on postsynaptic cell adhesion, synaptic plasticity, and dopaminergic transmission as well as a role in the etiology of autism, *NLGN3* (neuroligine-3) mutant rats were created (Ju et al. 2014). These rats exhibit increased repetitive movements, which are thought to be caused by the selective dysfunction of synaptic inhibition of medium spiny neurons carrying dopamine D1 receptors (Rothwell et al. 2014).

Some other genetic animal models created by inspiration from candidate genes in human studies include MAO-knock out models (no expression of the monoamine oxidase gene), hypomorphic rats (Bortolato et al. 2011), *CNTNAP2* (contactin related protein) mutant rats (Penagarikano et al. 2011), and *SLITRK1* (SLIT family membrane protein, 1) mutant rats (Katayama et al. 2010).

b) Environmental etiology models

Studies have shown a causative relationship between obstetric complications (Boksa 2004), maternal smoking, and many developmental disorders. However, the specific use of animal models based on imitating the same pathophysiology for modeling the etiology of Tourette Syndrome is still controversial (Yochum et al. 2014)

c) Pharmacological models

Tic-like movements in rodents can be created by the administration of psychostimulants, as they increase dopaminergic transmission; this model has been used to show the relationship between the basal ganglia (BG), tics, and stereotypic behaviors (Canales and Graybiel 2000). As expected, agents that inhibit dopamine receptors have been shown to alleviate symptoms seen in these models (Gilbert et al. 2013). The gamma aminobutiric acid A receptor (GABA-A) antagonist, bicuculline, was used in cynomolgus type macaque monkeys to cause local disinhibition in the putamen, therefore creating motor tics in the facial area (McCairn et al. 2009). This study demonstrated a relationship between tics and dopamine, which is secreted due to local action potential.

Administration of serotonin receptor (5HT2A) agonist 2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) was reported to cause head jerk movements in rats (Dursun and Handley 1996), while antipsychotic agents alleviated these symptoms (Kohnomi et al. 2008). Further, an alpha 1 adrenergic receptor agonist, sirazoline, was shown to cause prepulse inhibition deficiency and stereotypic movements due to activation in D1 and D2 dopamine receptors in the nucleus accumbens in rats; these symptoms were decreased with clonidine (Swerdlow et al. 2006). The sirazoline model, which is not specific to TS, was deemed appropriate for use in TS models because prepulse inhibition is responsible for sensorimotor gating; defects in sensorimotor gating may cause tics (Swerdlow and Sutherland 2006).

d) Autoimmune models

Results related to autoimmune models created by administering passive antibodies to the striatum of the rodent are controversial. While some studies show that episodic stereotypic movements increase in animals with antibodies obtained from TS patient serum (Liu et al. 2008), other studies could not replicate these results (Singer et al. 2005). In another autoimmune model, rats are immunized with AGBHS to form autoantibodies. A study using this model showed a relationship between autoantibodies against the cerebellum, globus pallidus, and thalamus of the rat and behavioral anomalies and IgG accumulation sites in the cerebellar nuclei (Hoffman et al. 2004).

2. Findings Obtained From Imaging Studies

a) Anatomical studies

The general consensus from anatomical studies is that neural development is impaired and other structural defects signify abnormal brain growth in TS, just as in other neurodevelopmental disorders.

i) Cortex

There is strong evidence suggesting the existence of a primary dysfunction. Literature shows that structural changes in the cortexes of TS patients are related to TS symptoms. However, there are also a small number of studies reporting otherwise.

While some studies show loss of total brain volume, as well as loss of volume in the cortex/parts of the cortex in TS patients (Hong et al. 2002), another study showed that there is no change in brain morphology in a pediatric patient group (Roessner et al. 2009). A magnetic resonance imaging (MRI) analysis conducted on children with TS revealed that the volumes of the dorsal prefrontal and parieto-occipital areas were larger, while the volume of the inferior occipital area was smaller, than those of a control group. One study showed that the decreasing difference in prefrontal volumes with advancing age was associated with increased prefrontal control over tics (Peterson et al. 2001). A study evaluating male TS patients who were not receiving treatments and did not have concomitant diseases showed that there were changes in the prefrontal, frontal, sensorimotor and anterior cingulate areas (Müller-Vahl et al. 2009). Further, there was a relationship between thinning in the sensorimotor cortex and an increase in the severity of tics (Sowell et al. 2008). In accordance with that study, Fahim et al. (2009) reported thinning of the pre and postcentral gyri in children with TS. They also reported that there was more cortical thinning in males than in females, and that thinning increased with age. Another study conducted on adults revealed that the severity of sensory perception before tics was related to an increase in sensorimotor cortex volume. It was emphasized that cortical thinning and volume changes in at least the motor, frontal and parietal cortexes are seen during childhood, and that these changes could continue until adulthood (Draganski et al. 2010). Another study reported a relationship between the location of cortical thinning and clinical symptoms in TS phenotypes (Worbe et al. 2010), while a more recent study determined that there was a decrease in the depths of the superior, inferior, and internal frontal sulci and the pre and postcentral gyri as well as in the grey matter thickness of TS patients. The same study reported a relationship between tic severity and sulcus changes in the sensorimotor, temporal, dorsolateral prefrontal and middle cingulate cortical areas; further, patients with additional OCD symptoms also had sulcus changes in the olfactory, temporal and insular sulci. In summary, these aforementioned structural changes in the brain sulci suggest a relationship between TS and abnormal brain development (Muellner et al. 2015).

There is also evidence suggesting that there are changes in the subcortical white matter and right frontal areas in TS (Kates et al. 2002). Diffusion Tensor Imaging (DTI) has been used to identify microstructural changes in the corpus callosum and white matter (Jackson et al. 2011). However, other studies found no difference between the white and grey matter of children with TS who were not receiving any treatment and a control group, independent of concomitant diseases and age (Jeppesen et al. 2014). Abnormalities relating to interhemispheric connections have been associated with volume changes in the corpus callosum (Cavanna et al. 2010, Roessner et al. 2011). In addition, Transcranial Magnetic Stimulation (TMS) and DTI have shown abnormal structural and functional connections between the right and left hand motor areas (Margolis et al. 2006, Baumer et al. 2010). In another study with adult TS patients, DTI showed that there were connection deficits in the circuits between the cortex and the basal ganglia (the area shown to be related with tics) and between the cortical areas of the frontal lobe (performs executive functions). An inverse relationship has been identified between tic severity and structural differences in these areas, which cause the connection deficit. These findings support the brain immaturity hypothesis in TS etiology (Cheng et al. 2014). Further, in a study done on a group of adult patients without concomitant diseases who were not receiving any treatment, DTI demonstrated microstructural white matter changes (cause a disconnection in the prefrontal area as well as thalamus and putamen) and structural changes in the cingulate gyrus (thought to be associated with compensation) (Müller Vahl et al. 2014).

ii) Subcortical Structures

The findings regarding subcortical structures in TS patients are very controversial. While the proven volume losses may signify a functional disorder in the related area, some hypothesize that these losses may also indicate a connection network disorder related to the area.

Some studies show no changes in the subcortical structures in TS, such as in the BG and thalamus (Wang et al. 2007). One study reported a volume increase in the left hemithalamus (Lee et al. 2006), while in another, the findings comprise bilateral loss of volume in thalamus and microstructural changes with DTI (Makki et al. 2008). In an MRI study, which had a large sample size and well-controlled confounding factors, a volume loss of 5% was identified in the thalamus (Miller et al. 2010). Loss of volume in the caudate nucleus has been shown repeatedly in studies focusing on the BG (Bloch et al. 2005, Makki et al. 2008). In a longitudinal study, an inverse relationship was detected between the volumes of caudate nuclei of TS patients and symptoms of TS and OCD (Bloch et al. 2005).

iii) Findings Related to Other Parts of the Brain

It is well-known that dopamine-related lesions cause tics. Therefore, the grey matter of the midbrain and periaquaductal grey matter were thought to play a role in TS etiology. This hypothesis was supported by one study that showed an increase in the grey matter of the midbrain via the voxel based morphometry (VBM) technique (Garraux et al. 2006). In another study, MRI was used to identify the wide perivascular spaces in the midbrain, which are thought to be related with stereotypic behavior (Da´vila et al. 2010). Further, another study showed evidence of volume loss in the cerebellum and lobules VI, VIIB, VIIIA, as well as grey matter crus I, indicating that there is a defect in the corticocerebellar circuits (Tobe et al. 2010). On the other hand, one study reported no changes in the cerebellar volume in children (Hong et al. 2002). The volume changes in the hippocampus and amygdala, as documented with MRI (Peterson et al. 2007), and the diffusion difference shown by DTI (Neuner et al. 2011) lead one to question whether the limbic system plays a role in the etiology of TS. However, the role of the limbic system was supported by the detection of smaller volumes of the hippocampus and amygdala in adults compared to children, which were associated with resistant tics (Peterson et al. 2007).

Based on the aforementioned research, the neuroanatomical structures associated with TS appear to be the basal ganglia, prefrontal cortex (PFC), and the Cortico-Striato-Thalamo-Cortical circuits (CSTC) that comprise these units. The CSTC parallel circuits connect the frontal cortex and the subcortical structures, and have played an important role in the comprehension of TS and concomitant developmental diseases. In classical movement disorder models, the cortical excitability of the BG has been altered to prove that the BG plays a role in behavior. Further, it has been shown that the BG exerts this effect via the direct pathway of the globus pallidus interna (Gpi) or via the multisynaptic indirect pathway through the globus pallidus externa (GPe) and subthalamic nuclei (STN) (Mink 2003). According to this model, hyperkinetic disorders are caused by decreased BG inhibitor output and increased cortical excitability. However, this hypothesis has failed to sufficiently explain the uniqueness of tics, and BG is thought to have a role in movement selection, making some movements easier while suppressing other competing motor movements (Mink 2003). According to this opinion, tics are caused by the disinhibiton and excessive excitation effects of a group of neurons, which display inhibition through the GPi in the striatum (Albin and Mink 2006).

b) Functional studies

i) Functional Magnetic Resonance Imaging (fMRI) Studies

fMRI has been used to show that there is increased motor activity in the supplemental motor area and in the primary motor cortex during tics (Hampson et al. 2009); this technique has also been used to show that activity begins in the brain areas associated with cognitive control, even before the start of a tic (Bohlhalter et al. 2006). The brain activity of adults with TS during spontaneous tics and induced tics were compared, and it was found that during spontaneous tics, there was excessive motor activity in the related areas and decreased activity in the areas that control the task (Wang et al. 2011). In another study, children and adults were asked to suppress the blinking tic, and it was seen that the activity in the frontal cortex and striatum were higher in TS patients when compared to healthy individuals (Mazzone et al. 2010). Serrien et al. (2002) showed that the secondary motor areas are active in adult TS patients, even in those without tics, and that the activity of these areas is not suppressed during a motor task.

PFC and BG are believed to have equal importance in the formation of tics. The voluntary suppressability of tics prove that this area (PFC) controls the automatic functions of the BG. The efferent neurons stemming from the cortex extend into the dendrites of the medium spiny neurons (MSN) and to the striosome and matrix (structurally similar but neurochemically different areas in the striatum). These areas differentiate according to the received cortical input. Neurons extending into the striosomal MSN receive both limbic and prelimbic input, while the neurons in the matrix that extend into the MSN receive input from the ipsilateral motor and sensorimotor cortex, as well as the contralateral primary motor cortex (Leckman et al. 2010). Therefore, the cortical sensory stimuli may affect some of the MSN's response in the striatum. Normally, the metabolic activity of the MSNs in the matrix is higher than it is in the striatum. However, once this balance is altered for any reason, the likelihood of tics is increased (Canales and Graybiel 2000). In summary, changes in the striatal matrix-striosome balance are thought to be related to the occurrence of tics (Leckman 2002).

When TS patients were compared with a control group, it was seen that TS patients had more functional organization disorder in the cortico-basal ganglion network, their networks were shorter (caused by a lack of connection to some basic anatomic areas), and they had fewer functional connections, albeit those that existed had greater strength. A relationship was also established between the tic severity and functional abnormalities in the cortico-basal ganglion networks of the premotor, sensorimotor, parietal and cingulate cortex, and the medial thalamus. The complexity of tics was determined to be related to the functional abnormalities in the supplemental networks in the sensory motor area, insula and putamen. The severity of concomitant OCD symptoms was associated with functional changes in the orbitofrontal and prefrontal dorsolateral cortexes. Results of this study lead the authors to hypothesize that the functional deficits in the cortico-basal

ganglion network cause a disruption in brain development, which was expressed as functional immaturity (Worbe et al. 2012). Worbe et al. also identified white matter anomalies in the neuronal pathways between the cerebral cortex, BG, and thalamus (2015). They showed that the striatum and thalamus strengthened the connection on the primary and sensorial cortex, paracentral lobule, and helper motor and sensory cortexes. Further, they showed that this strengthened connection was associated with tic severity, which was independent of age, therapeutic drug usage, or gender. Findings pointing to axonal microstructural anomalies in the white matter of the corticostriatal pathways of TS patients were also determined, although these were more prominently seen in females. The authors hypothesized that these white matter changes were caused by abnormal brain development. In contrast to the study by Worbe et al. (2015), other studies focus their attention on the difference in brain functionality; for example, Debes et al. (2011) reported no cortical differences in TS patients and a control group during executive function tests.

Another study found a relationship between the activity in the substantia nigra, the ventral tegmentum, and tic severity, pointing to the role of the dopamine system in TS etiology; this study also noted a relationship between tic severity and cognitive performance, as well as between concomitant ADHD and OCD symptoms (Baym et al. 2008). fMRI studies with large samples reported age-related anomalies in the frontostriatal and frontoparietal connections; these authors surmised that TS patients do not follow the normal maturation processes (Marsh et al. 2007, Church et al. 2009). Taken together, these results strengthen the hypothesis that TS is a developmental disorder.

While changes in the BG, PFC and CSTC circuits are related to many neurotransmitter systems, dopaminergic dysfunction draws the most attention from researchers (Gilbert et al. 2006). This hypothesis was supported by imaging studies (Liu et al. 2010) and postmortem studies (Yoon et al. 2007) showing an inhibitory role of dopamine antagonists and the inducing effects of dopamine agonists on tics. More recent studies have suggested that problems in dopaminergic transmission, which cause tics, are related to the regulation of tonic and phasic dopamine release in the BG. It has been reported that the dopamine transporter is overactive, and also that there exists a phasic dopamine release which responds excessively to stimuli in individuals with tics (Buse et al. 2013). The hypothesis related to this tonic-phasic release applies to the cortex or the striatum. Although many neurotransmitter-related studies focus on the striatum, decreased cortical receptor binding potentials and positron emission tomography (PET) findings show increased dopamine release and postmortem cortical dopaminergic system problems, which indicate that the dopaminergic transmission defect is outside the striatum (Steeves et al. 2010, Yoon et al. 2007).

ii) Transcranial Magnetic Stimulation (TMS) Studies

TMS has been used to examine the defect in the inhibitor control of CSTC circuits. One study found that while the motor threshold levels were normal in TS patients, their short interval cortical inhibition decreased and they had a shortened cortical silent period (Ziemann et al. 1997). In another study conducted on children, the cortical silent period was found shortened similar to adults, but data relating to decreased cortical inhibition could not be repeated (Moll et al. 1999). A study conducted on patients of different ages reported a relationship between decreased intracortical inhibition and tic severity. Also, that same study found a relationship between decreased intracortical inhibition and severity of ADHD symptoms; this relationship was reported to be stronger than that with tic severity (Gilbert et al. 2004). Short interval intracortical inhibition is among the paired-pulse measures; during this process, the response is suppressed by a test stimulus given between 1-6 milliseconds along with a conditioning stimulus. It is thought to represent GABA-A mediated cortical synaptic inhibition. The cortical silent period is the time during which electromyography (EMG) activity is suppressed following a stimulus to the contralateral motor cortex of a voluntarily contracted muscle. This period was reported to show GABA-B receptor mediated inhibitor activity (Yıldız et al. 2015). Recent studies have shown that TS patients have abnormal cortical and brainstem synaptic plasticity, which emphasize abnormal brain growth (Suppa et al. 2011). Findings from another study regarding abnormal cortical supplementary area plasticity have drawn attention as areas for further research (Martin-Rodriguez et al. 2015). In that study, abnormal plasticity was used to represent the indifference in inhibitory or excitatory activity of the motor evoked potentials, despite repetitive excitation of these brain areas.

iii) Positron Emission Tomography (PET) Studies

PET studies have revealed activation in the PFC, premotor and primary motor cortex, anterior cingulated cortex, putamen, and caudate nuclei (Stern et al. 2000). Further, some PET studies have shown decreased activities in the striatum and thalamus, as well as changes in local blood flow due to increased activity in the sensorimotor cortex (Braun et al. 1993). Yet, other studies examining the GABAergic system deficits reported a decrease in bilateral GABA-A receptor binding in the bilateral ventral striatum, globus pallidus, amygdala and right insula, but an increase in the bilateral substantia nigra, left periaquaductal grey matter, right posterior cingulate cortex and bilateral cerebellum; these data support the BG and thalamus disinhibition hypothesis (Lerner et al. 2012) in TS.

Postmortem studies have revealed the loss of GABAergic and cholinergic interneurons in tic etiology (Kalanithi et al. 2005, Kataoka et al. 2010). These striatal interneurons are thought

to have a modulating effect on dopamine signaling; further, it is hypothesized that the decrease in inhibition contributes to the disinhibition of dopaminergic transmission (Ellender et al. 2011).

Glutamate may be important in TS etiology as it plays a role in CSTC pathways and has been linked to the dopaminergic system (Harris and Singer 2006). The role of glutamate in TS development is strengthened by evidence obtained from genetic studies (Tourette Syndrome Association International Consortium for Genetics 2007, Adamczyk et al. 2010) and because there are decreased glutamate levels in the globus pallidus and the substantia nigra (Anderson et al. 1992).

Because TS has various clinical appearances, the disease was thought to be caused by more than one neurotransmitter system or by dysfunction of a secondary messenger system (Singer and Minzer 2003). There are differences in the modulator effect of serotonin, as there are decreased serotonin transporter levels and increased levels of serotonin 2a receptor binding (Wong et al. 2008). Further, PET studies have revealed anomalies in tryptophan metabolism in the cortical and subcortical areas (Behen et al. 2007). Taken together, the results of studies determining the contribution of serotonin and norepinephrine to tic development are controversial; these neurotransmitters are more clearly associated with concomitant conditions (Udvardi et al. 2013).

Based on these aforementioned studies, it can be argued that TS is a disease that affects all neurotransmitter systems. It has been hypothesized that the etiology of TS involves a secondary messenger system, such as cyclic adenosine monophosphate (cAMP); this hypothesis is supported by data showing decreased cAMP levels in areas of the brain (Singer et al. 1991). However, this finding could not be repeated in later studies (Singer et al. 1995).

CONCLUSION

Many years of TS research have yielded very little information regarding its etiology. Although the pathogenesis of TS has not been fully elucidated, the most substantial evidence points to the role of the dopaminergic transmission defect in CSTC circuits. While the activation of these pathways (shown by functional imaging studies) and anatomical differences in neural structures (shown by MRI studies) may play a direct role in the occurrence of tics, they are also thought to be related to the balancing of neural activities that occur during tics. That postmortem studies have shown a loss of a selected group of interneurons in the caudate nucleus and putamen has strengthened the hypothesis that tics occur with increased excitability due to decreased inhibition. Functional neuroimaging, postmortem, genetic and animal studies conducted to determine the etiology of TS point to the involvement of the dopaminergic system and its controller neurotransmitter systems. It is now known that there are differences regarding the transport, release and activity of dopamine in individuals with TS (Buse et al. 2013).

Longitudinal studies have shown that there is thinning in the cortical and subcortical structures with age, which supports that the disease is neurodevelopmental (Felling et Singer 2011). The opinion that the structural changes to the neural system caused by environmental factors cause TS in those with a genetic predisposition has recently gained more support (Kalanithi et al. 2005, Kataoka et al. 2010).

Genetic studies related to TS have distracted researchers from the classical autosomal dominant single gene transmission hypothesis, and lead them to the idea of a complex genetic transmission that emerges with the interaction of risky alleles. Technical advances have accelerated the number of wide sample GWAS and rare variant studies. The most therapeutically hopeful finding among these is that there is a defect in histamine synthesis, which was shown by genetic studies and in vivo animal studies (Ercan-Sencicek et al. 2010, Castellan Baldan et al. 2014). This development has led to clinical drug studies regarding histamine agonists.

There are limitations in studies researching the etiology of TS, including the use of heterogeneous patient groups in terms of age and clinical symptoms, small sample sizes, and drug use during the studies. Further, there are questions as to the structural validity of animal models, which may have prevented clear results. More multidisciplinary studies are needed that include risky individuals or homogenous patient groups and that comprise versatile evaluations. Future studies should be longitudinal, in parallel with the development of neurodevelopmental disorders, and comprise epigenetic changes. Further, these studies must be validated by animal studies and studies at the cellular level. Evidence regarding the neurobiology of TS will guide future studies regarding treatment options for this disease, which markedly disrupts quality of life.

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