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TOURETTE'S SYNDROME

Tourette's syndrome (TS) is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette who in 1885 described nine patients with TS symptoms including verbal and motor childhood-onset tics and other behavioral problems including poor impulse control and obsessive-compulsive behaviors. The disease, once believed to be extremely rare, is now considered to be quite

common, affecting approximately 2% percent of the population. The disease afflicts males 5 times more often than females. The onset of TS, as characterized by the emergence of motor and vocal tics, typically emerges between the ages of 3 and 8 with a reduction in these symptoms occurring by age 20.

SYMPTOMS

The hallmarks of TS are the motor and verbal tics. These tics vary in complexity, duration (ranging from 1 year to lifelong), intensity (from mild to severe), and frequency (from rare to constant). Tics are brief movements or sounds that appear unpredictably. They emerge individually or in choreographed clusters and can be expressed either intermittently or continuously for hours. These tics fall into one of several categories: (1) motor tics which can include intense eye blinking, throat clearing, and neck and arm twitching; (2) phonic tics such as repeated utterance of a particular word, shouting (obscenities), or grunting; (3) aggressive phenomenon such as self-injury, hitting, kicking, or biting self or others; and (4) compulsive behaviors that may include hand-washing, door locking, checking and organizing objects, and touching or tapping others and objects.

The motor and phonic symptoms typically wax and wane. This waxing and waning is most likely influenced by ongoing brain developmental changes and environmental influences such as stress. Additionally, medications for TS can also cause changes in the brain that result in corresponding behavioral changes. The repertoire and severity of symptoms of TS patients, therefore, require constant monitoring by the patient and family, as well as by the physician who will adjust the dose and type of medication accordingly. Studies have reported that the highest incidence and severity of tics occur with anticipation or resolution of emotional changes. Consistent with this, stress, anxiety, and fatigue exacerbate tics, and ironically, the very urge and attempt to control the tic can itself lead to additional stress and anxiety. Altogether, the disease and its consequences can often lead to problems in school performance and self-esteem, and also in a variety of social and behavioral problems at school, at home, and in society in general.

GENETICS

Tourette's syndrome has a significant genetic component. Several genes have been identified through family studies, segregation analyses, candidate gene studies, and linkage studies. TS inheritance may involve several mechanisms including autosomal dominant, bilinear, or polygenic mechanisms. Candidate genes for TS pose a genetic susceptibility with such factors as pre- or postnatal stress, and other environmental factors such as viral infections or stress, increasing their likelihood of expression. It is critical therefore to continue studies designed to identify specific gene-environmental interactions. The candidate genes identified thus far appear to be involved in the regulation of brain development and neurochemical signaling. For example, several dopamine (DA) receptor (D1, D2, D4, D5) and noradrenergic receptor (ADRA2a, ADRA2c and DBH) genes and a few serotonin genes have been identified. In conclusion, many candidate genes that pose a susceptibility to developing TS have been identified. The heterogeneity of identified TS genes together with their varying etiologies and environmental interactions make it impossible to provide a single or simple explanation for the etiology of TS. Research progress in this area will lead to a better understanding and predictability of the etiology of TS and improved treatments for these patients.

NEUROBIOLOGY

Numerous neuroanatomical and brain imaging (fMRI, PET, SPECT) studies have identified the prefrontal cortex (PFC)–basal ganglia (BG) circuit as the major system involved in Tourette's syndrome. This circuit is involved primarily in regulating a variety of motor, limbic, and cognitive functions. The dorsal striatum (consisting of the caudate and putamen) of the BG is implicated primarily in motor control and habit formation, whereas the ventral striatum is implicated in compulsivity and addiction. The prefrontal cortex is involved in such higher-order executive decisions as impulse control. Other related areas such as the brain stem, which has been implicated in eye blink reflex, have also been implicated as well as other areas that interact with the PFC-BG circuit including motor, cingulate, temporal, and parietal cortical areas, Broca's area, thalamus, and cerebellum.

The overriding problem in TS appears to be the overactivity of motor and motivational/reinforcement systems with an inability of the prefrontal cortex to override or inhibit those related behaviors. TS patients, like patients with prefrontal damage, reveal poor performance on impulsivity control tasks. A functional neuroimaging study revealed an increase

in neural activity in the prefrontal and caudate nucleus and a decrease in the motor-related putamen and globus pallidus in a tick suppression task. Performance on tasks requiring other higher-order functions such as learning and memory, however, remained normal in TS patients.

Examination of the specific neuroanatomical abnormality of the prefrontal-BG circuit has revealed a decrease in the volume of these brain areas in TS patients. It remains unclear, however, as to whether these brain differences are necessarily due to damage or due to compensatory mechanisms. The compensatory nature of the brain further suggests that these individuals may develop alternative cognitive and behavioral strengths that are not dependent on the damaged brain areas. Special efforts should be made by the family, educators, and physicians to help the patient identify such strengths and talents.

Detailed synaptic and receptor microcircuitry abnormalities within the PFC-BG circuits, however, have not been fully explored. The identification of specific cellular and biochemical circuits will help to improve site-specific targeted treatments for this disorder. For example, striatal cholinergic neurons of the striatum are known to signal reward and in turn influence motor signaling as well as incoming prefrontal cortical signals. Dr. Alcantara's work has implicated these neurons and their corresponding dopamine D2 receptors to play a key role in the development of drug abuse and possibly in the treatments designed to treat addiction. Further investigations should examine whether these cholinergic neurons are also critical for motor and impulse control in TS patients.

TS patients express comorbidity with two other PFC-BG related disorders: obsessive-compulsive disorder (OCD) and attention-deficit-hyperactivity disorder (ADHD; which involves increased inattention, hyperactivity, and impulsivity). TS patients also have a high incidence of depression, anxiety, and aggression. Additionally, family members of TS patients show a higher than normal incidence for OCD, ADHD, drug or alcohol dependency, depression, anxiety, eating disorders, and panic disorders, all of which share a common neuroanatomical and biochemical basis with TS.

NEUROTRANSMITTER SYSTEMS

Two neurotransmitter systems most likely affected by TS are the dopaminergic and norepinephrine systems. The dopamine system, central to the PFC-BG circuit, is suggested to be hypofunctional, further implicating the supersensitivity of dopamine D2 receptors and therefore requiring drugs that block these receptors. The norepinephrine (NE) system originating in the brain stem influences motivation, attention, and arousal in the PFC-BG circuit and is also suggested to be hypofunctional, requiring the use of adrenergic (NE) receptor agonists.

TREATMENTS

Pharmacological Treatments

Two classes of antipsychotic drugs that target the DA and NE systems are most widely used. These include the neuroleptics, including fluphenazine, haloperidol, pimozide, sulpiride, and tiapride, which are effective in reducing the symptoms of TS (side effects include sedation or dysphoria). Additionally the alpha2 adrenergic agonists such as clonidine, desipramine, guanfacine, and risperidone often show benefit (side effects include sedation and irritability).

Behavioral Treatments

Behavioral treatment or combined behavioral treatment with drugs is the most effective in treating the symptoms of TS. Cognitive behavior therapy (CBT) is the main behavioral treatment of choice. CBT includes habit reversal, which is the most promising treatment consisting of awareness training, self-monitoring, relaxation training, competing response training, and contingency management. Also hypnotherapy, biofeedback, conductual therapies, acupuncture, electroconvulsive therapy, meditation, and surgery have been employed. Surgery, however, is the most invasive and can lead to subsequent brain circuit deterioration. Both drug and behavioral treatments can target and modify the affected brain areas and related receptor and synaptic microcircuits. These treatments thereby show much promise for the successful long-term treatment of TS. Continued research in the areas of TS and improved animal models should continue to shed light on our understanding of the etiology of TS and the development of improved site-specific targeted behavioral and pharmacological treatments for Tourette's syndrome.

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Further Readings and References

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