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Review article

Tourette Syndrome: Update ☆

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Abstract

Tourette Syndrome is a disorder characterized by tics. It typically begins in childhood and often improves in adult life. Tics are best described as voluntary movements made automatically so that volition is not ordinarily appreciated. There is frequently an urge, sometimes in the form of a specific sensory feeling (sensory tic), that precedes the tic. Patients say that they make the tic in order to reduce the urge, although shortly after the tic, the urge recurs. The sensory feeling may arise due to defective sensory habituation. Since tics relieve the urge, this can be considered rewarding, and repetition of this behavior may perpetuate the tic as a habit. Tourette Syndrome affects boys more than girls and is associated with attention deficit hyperactivity disorder and obsessive compulsive disorder. Although Tourette Syndrome often appears to be autosomal recessive in inheritance, it has been difficult to find any abnormal genes. There is a loss of inhibition in these patients and recent studies show abnormalities in brain GABA. Certainly there is also an abnormality in dopamine function and dopamine blocking agents are effective therapy. In severe drug-refractory patients, deep brain stimulation can be effective.
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Keywords: Tic; Urge; Sensory habituation; Habit; Inhibition; Dopamine

1. Introduction

Tourette Syndrome (TS) is a disorder, mainly of childhood, with a prominent manifestation of tics. In DSM-5, an alternate term for TS is Tourette's Disorder. Tics, as formally defined in DSM-5, are "sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations, generally preceded by urge". It should be noted that young children, less than ten years of age, most often do not report urge, and that could be either because there is no urge or it is difficult to describe. There are a number of tic syndromes, and perhaps the most common is provisional tic disorder (previously called transient tic of childhood) where the tics last about one year. In order to qualify for TS, again by DSM-5, there must be multiple motor and vocal tics present at some time with the disorder beginning before age 18 and lasting more than one year, and where the tics are not secondary to a physiological substance or other neurological disorder. There are a number of patients who do not have vocal tics, but are in other ways similar, and, while that disorder would be called persistent tic disorder (previously, chronic motor tic), the disorder is likely the same.

The Tourette International Consortium reported on the characteristics of 6805 patients with TS [1]. The male to female ratio is 4.4–1; the mean age of onset is

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6.4 years. A family history is present in 51.7% of patients. Attention deficit/Hyperactivity Disorder (ADHD) is seen in 55.6%, and obsessive compulsive disorder (OCD) is seen in 54.9%. In terms of clinical course, tics disappear in adult life in approximately half of patients, are improved in 40–45% of cases, and remain in only 5–10% of patients [2,3].

Tics can affect any part of the body, but seem particularly prominent in the face, such as eye blinking. Tics can be either simple or complex movements, but there is no evidence that they are different in type. Vocalizations can be a variety of sounds and words, including coprolalia. The urge, or premonitory phenomenon, can be just an inner tension of wanting to move or can be a specific feeling in a specific part of the body. If in a specific body part, it can be called a sensory tic, and many patients will say that the sensory tic is the main aspect of the disorder, since the movement is made voluntarily to make the sensation go away. Unfortunately, the benefit is only short lasting and the urge or sensory tic builds up shortly again. In a series of 50 patients, sensory tics were localized in face and head in 73%, neck in 66%, shoulders 56%, arms 39%, hands 34%, throat 34%, and other sites less than 30% each [4]. In the same series, character of the urge most frequently, between 80% and 90%, was "urge to move" or "had to do it", whereas more sensory feeling such as "ache", "itching" and "tingling/numbness" were only a little more than 20% each.

While the family history is often positive and a genetic etiology is assumed, finding relevant mutations has been very difficult. It appears that the disorder is complex and multifactorial with some rare Mendelian genes and many risk genes. In the risk gene category, many seem to involve the dopaminergic and serotonergic systems. A recent large genome-wide association study identified the largest signal from rs7868992 on chromosome 9q32 within the gene COL27A1, but the meaning of this is unclear [5]. There is evidence for a mutation in the gene leading to histidine decarboxylase deficiency as a rare stronger influence in causing TS [6].

2. Pathophysiology

In order to determine where the abnormalities are in the brain in patients with TS, there have been many neuroimaging studies. Studies examining brain structure have used a variety of methods, and while they seem reasonable, many studies are not compatible with each other. This might be due to small numbers of subjects, difficulties with the methods, or other factors not determined. As examples, a few of these studies will be noted here. A study of caudate volume in 43 patients studied once before age 14 and again about 7.5 years later showed that caudate volume correlates significantly and inversely with severity of tics (and OCD) in early adulthood [7]. Using voxel based morphometry (VBM), one study showed increased gray matter in the midbrain [8], while another showed increased gray matter in the ventral putamen and left hippocampus [9]. The white matter tracts have also been examined using diffusion tensor imaging (DTI) [10]. Analyzing the data with probabilistic fiber tractography, there were reductions in connectivity between supplementary motor area (SMA) and basal ganglia, as well as in frontal cortico-cortical circuits [11].

Physiological studies have revealed some valuable details about the nature of the disorder. Starting on the sensory side, not only are there frequency sensory tics in the patients, but often they report that sensory stimuli seem particularly bothersome. In a questionnaire study, patients reported that they were very sensitive to stimuli in every modality, sound, light, smell and taste as well as touch [12]. Moreover, the patients noted that faint stimuli might well be more troublesome than more intense stimuli. Following the questionnaire, the investigators did some quantitative sensory testing. They found that sensory thresholds were the same as normal for tactile stimuli on the leg or site of sensory trick and the same for olfactory stimuli. Moreover, the subjective intensity near threshold was similar to normal, despite noting that faint stimuli were generally more bothersome. The interpretation of these data suggests that the problem is not that of simple sensory perception, but might be a deficiency of habituation.

Evaluating the brain activity associated with tic has been done with EEG and neuroimaging techniques. Starting with the EEG, a number of groups have looked specifically for the EEG activity preceding the tic. EEG activity preceding voluntary movement is characterized by a slowly rising negativity for about 1 second, called the Bereitschaftspotential (BP) [13]. The BP has two components, called early and late. The early component arises from both medial and lateral area 6, the SMA and premotor cortex, respectively. The later component, which is more lateralized over the motor cortex contralateral to the moving limb, includes activity of the primary motor cortex. Since many of the patients say the tic is actually voluntary, one might expect a BP preceding the tic. However, the BP may well be fully absent [14] or just consisting of the late component [15]. In a study of 14 patients, 6 had a BP and only 4 of these included the early component [16]. This finding suggests diminished involvement of area 6. Certainly some patients will say that the movement is involuntary, and some will be unsure of whether the tics are voluntary or involuntary. This confusion might arise if the tics are highly automatic and the sense of volition might well be weak.

Functional neuroimaging studies have been particularly revealing. Since tics are discrete events, it is possible to do event-related design functional MRI (fMRI). The BOLD signal is aligned with the tic, similar to