Tourette's Syndrome: A Review from a Developmental Perspective

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ABSTRACT

The object of this review is to summarize some of the recent developments in the understanding of Tourette's Syndrome which can be regarded as the prototype of a developmental psychopathological entity. The review covers the following topics: tics and their developmental course; sensory phenomena related to tics including measurement of these phenomena; pathophysiology of tics and compensatory phenomena and the parallel development of the various psychiatric comorbidities as they emerge over the life span. Finally there is an attempt to summarize the major points and future directions.

BACKGROUND

Tourette's Syndrome (TS) is a prototypical developmental neuropsychiatric disorder that usually begins in childhood, around the age of five or six, involving a variety of motor and sensory phenomena that wax and wane throughout development (1). It encompasses emotional and cognitive aspects of behavior and both influences and is influenced by the environment and life events as the life cycle proceeds. Thus the syndrome comprises physical, psychical as well as social phenomena that evolve in an interactive stepwise fashion, illustrating how motor and emotional development interact. For this reason the study of TS is of immense interest in the study of developmental psychopathology.

TICS

TS is characterized by tics which are sudden, involuntary, repetitive, non-rhythmic movements or vocalizations. Simple motor tics are sudden, fleeting or fragmentary movements such as blinking, grimacing, head jerking, or shoulder shrugs. Complex motor tics consist of several simple motor tics occurring in an orchestrated sequence or semi-purposeful movements, such as touching or tapping; these may also have a more sustained, twisting, and dystonic character (2).

Simple phonic tics consist of simple, unarticulated sounds such as throat clearing, sniffing, grunting, squeaking, or coughing. Complex phonic tics consist of out-of-context syllables, words, phrases or paroxysmal changes of prosody.

Complex tics may involve socially inappropriate or obscene gestures (copropraxia) or utterances (coprolalia), as well as echo phenomena, such as echolalia or echopraxia (repeating others' words or gestures), which exemplify the suggestibility of tics. Infrequently, complex tics may include self-injurious behavior (cheek chewing, eye-poking and self-hitting). Tic complexity, also, generally evolves with age (2).

DEVELOPMENTAL COURSE OF TICS

The severity of tics in TS waxes and wanes throughout the course of the disorder and is characterized by changing symptoms as it follows the child's development. The tics of TS and other tic disorders are highly variable from minute to minute, hour to hour, day to day, week to week, month to month and even year to year. Tic episodes occur in bouts, which in turn also tend to cluster (2). Tic symptoms, however, can be exacerbated by stress, fatigue, extremes of temperature and external stimuli (as with echolalic or echopraxic tics). Intentional movements attenuate tic occurrence over the affected area and intense involvement and concentration in activities tend to dissipate tic symptoms (3).

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Initial sniffing or blinking tics may be mistaken for allergies or eye problems, and it is mainly their waxing and waning and the subsequent appearance of other tics that help make the diagnosis. There is also often an anatomical progression, with head and facial tics being the first to appear and more caudal and more complex tics appearing later. Longitudinal studies of TS have found that the tics of TS typically have an onset around the age of 5-6 years and usually reach their worst ever severity between the ages of 10-12 years (4-6). Approximately one-half to two-thirds of children with TS will experience a substantial decrease or remission of tics during adolescence (2). A small proportion of those who continue to have tics into adulthood suffer from tics that are severe, complex or that cause social embarrassment or self injury (4). A small minority of TS patients experience catastrophic outcomes in adulthood, although these are the exception. Most individuals do not experience either a sustained worsening or improvement of their symptoms after the third decade of life.

Identifying clinical measures that can predict whose tic symptoms will persist into adulthood is an area of great concern for patients and their families, as well as for researchers seeking clues as to the underlying pathophysiology of tics. Among a battery of neuropsychological measures administered to a group of children with TS, age 8-14 years, the Purdue Pegboard, a test of fine motor skills, best predicted tic severity and global psychosocial functioning at follow-up clinical assessment 7.5 years later (7). Poor performance on the Purdue Pegboard and Beery Visual-Motor Integration test (VMI) also predicted worse adult global psychosocial functioning. It has been hypothesized that performance on these tests might serve as an endophenotype as a measure of basal ganglia dysfunction in young TS patients. However, it is probably too optimistic to envisage that simple tests such as these will provide an answer to the very complicated problem of predicting outcome in individual cases.

TIC ASSOCIATED SENSORY PHENOMENA

Tics are not purely motor phenomena but also have in many cases an associated sensory and/or cognitive component. These include uncomfortable bodily sensations that "force" the individual to perform the tics, and unexplained internal urges or energies situated from within the body. The discomfort associated with these feelings can cause more distress than the tics themselves. These

mental components also have a developmental trajectory and most children recall first noticing the sensory phenomena beginning around the age of 10 (8), three years after the onset of tics on average.

PREMONITORY URGE AND ITS ASSESSMENT

Most systematic studies suggest that premonitory urge prevalence rates are 77% in patients with TS who are older than 13 years and 93% in a tic disorder sample ranging in age from 8 to 71 years (9).

A scale for urge severity the Premonitory Urge for Tics Scale (PUTS) was developed by Woods et al. (10, 11), comprising nine items designed to measure premonitory urges in children with tics. This questionnaire asks TS patients and their parents the question: "Do you feel a kind of pre-sensation immediately before the tic?" and "Are you able to suppress tics for a while?" Studies with the PUTS have shown that premonitory sensation awareness is a maturational process independent of tic duration and of age of tic onset. This maturational step occurs between 8-10 years and 10-14 years, emphasizing that tic awareness and the ability to suppress tics are correlated and age related (10).

The questionnaire deals with both sensory and mental phenomena. PUTS severity scores are correlated with tic severity as measured by the Yale Global Tic Severity Score (YGTSS), and specifically with complexity, interference and number of tics. Other interesting correlations were found between premonitory urge and Obsessive-Compulsive symptoms (OCS), as measured by the children's version of the Yale Brown Obsessive Compulsive Scale (CYBOCS) total score in older but not younger children. The internal consistency and other psychometric properties of this questionnaire were excellent for older children (>10 years) but poor for those under the age of 10 years, underlining the fact that these urges have a developmental track perhaps relating to cognitive maturation and increasing internal awareness in older children. The ability to quantify these sensory phenomena has facilitated exploration of the links between these sensory phenomena, tic complexity and OCD symptomatology (10).

The maturational awareness of the premonitory urges and the accompanying ability to suppress tics plays an important role in the development of modern psychological treatments for tics. One such treatment, called Habit Reversal Therapy (HRT), is based on teaching the child to become aware of the premonitory urge preced-

ing a tic, recognizing it, and developing a competing response incompatible with performing the tic (12).

PATHOPHYSIOLOGY

Accumulating knowledge on the developmental trajectories of sensory phenomena and suppressibility of tics in TS patients has also shed light on the pathophysiology of TS. It is postulated that the urge to perform motor actions involves sensory motor networks of the brain, specifically the supplementary motor area, as well as activity in the basal ganglia, thalamus, and frontal cortex (13). This hypothesis is derived from functional MRI studies of tic suppression and may be a basis for a better understanding of the neuronal networks involved in TS.

IMAGING STUDIES

An increased overall volume in dorsolateral prefrontal regions in children, but not adults, with TS has been reported. This increase in volume was inversely related to tic severity such that patients with greater prefrontal volumes exhibited decreased tic severity. Volumes of the corpus callosum (CC) are decreased in children with TS, correlate inversely with prefrontal volumes, and are positively related to tic severity. It is likely that these findings of increased prefrontal volumes and decreased CC size represent a compensatory mechanism developed in children with TS in order to facilitate suppression of tics. Larger prefrontal volumes found in children with TS may represent the occurrence of synaptic plasticity associated with the constant need to suppress tics in social contexts. Adults with TS may represent a subsection of the overall TS population who do not generate a plastic, compensatory response in the prefrontal cortex, leading to increased severity of the disorder and its persistence into adulthood. The development of TS is likely to be two-fold, involving an abnormality in basal ganglia output systems in conjunction with an impairment in frontal inhibition of this output. Considerable evidence indicates that the frontal lobes are not fully developed until young adulthood, suggesting that while impaired inhibition of striatal output is responsible for the commonly occurring tics and compulsions found in childhood, development of the frontal cortex in response to overactive striatal output in TS may be a determining feature of the long-term course of the disorder (14).

NEURO-PSYCHOLOGY

Although deficient motor inhibition is often considered to be the basic underlying pathology, cognitive and affective development are also liable to be impaired. Thus cognitive inhibitory deficits have been found in a variety of neuropsychological and experimental paradigms, especially in those children with comorbid ADHD and OCD or in those children whose frontal lobes are not fully developed.

Impaired development of affective regulation is also frequently found, with explosive rage attacks and/or self injurious behaviors (SIB) occurring in at least one-fourth of children with TS in some clinical samples. It is likely that developmental dysfunction in orbito-frontal-basal ganglia circuitry contributes in part to the problems of impulsivity and rage attacks, although this hypothesis remains to be proven. The subtle but complex homeostatic influences of development in TS are best summed up in the statement by Stern et al. (14): "Although inhibitory motor deficits in TS might be expected to lead to more general problems with cognitive and social self-regulation, a developmental approach suggests otherwise. In particular, the developmental approach suggests that compensatory processes occurring over time and in response to motor inhibition deficits could work either to offset or to exacerbate cognitive and social self-regulation deficits in persons with TS……. One hypothesis concerning the differentiation of persons for whom symptoms attenuate from those who retain symptoms into adulthood concerns the development of frontal cortical top-down control of motor deficits. Specifically, given the relatively protracted course of the development of the prefrontal cortex and processes of use dependent synaptic plasticity, it is likely that attenuation of the disorder is due to compensatory developmental neurobiological processes.

From a developmental standpoint, it makes sense to also ask whether or not variation in cognitive inhibitory control or impulse inhibition in TS is associated with the unique experiences of the patient during the course of the disorder. Here, it is important to consider the developmental process as it occurs in response to the psychosocial environment in which the individual is situated in addition to constraints imposed by the neurobiological motor deficit. Such an approach can increase understanding of longer-term outcomes and also suggest some potentially efficacious therapies to improve quality of life for patients with TS" (pp. 14-15).

COMORBIDITIES

As development progresses several other neuropsychiatric syndromes develop either prior to, concomitant with or following tic onset. These include attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and other anxiety disorders, learning disability, oppositional defiant disorder including rage attacks, self injurious behavior (SIB) and depression (15). Many late adolescent and adult TS patients regard their behavioral problems (including ADHD and OCD) and learning difficulties as having had an impact on their life function equal or greater to that of the tics themselves. In the natural course of comorbid psychiatric illness in TS, ADHD symptoms are usually present from early childhood and often precede the onset of tic symptoms by several years, whereas OC symptoms more commonly present in later childhood after tics have reached their peak severity, though they may be apparent earlier on (3).

ADHD, as well as irritable or oppositional behavior, is found in at least one-half of clinically referred children and adolescents with TS. It is also not uncommon to see children with ADHD who have developed transient or persistent tics following being started on stimulant medication, posing a sometimes difficult therapeutic dilemma (16). A recent meta-analysis has supported the use of stimulant medications in children with tics (17).

The nature of the association between TS and ADHD is still a matter of debate, but it is clear that youngsters with TS plus comorbid ADHD usually have more adaptive difficulties than those with tics alone (18, 19). In a large international database of 6,805 cases of TS, the prevalence of ADHD in TS was 55%. If a proband was diagnosed with ADHD, a family history of ADHD was much more likely. Comorbid ADHD was associated with earlier diagnosis of TS, great peak tic severity, and an increased male-to-female predominance of 7.3:1 (20).

Moreover, the group with comorbid ADHD has much higher rates of anger control problems, sleep problems, specific learning disability, OCD, oppositional-defiant disorder (ODD), mood disorder, social skill deficits, inappropriate sexual behavior and self-injurious behavior. The greatest behavioral difficulties in subjects with ADHD are associated with the Combined or Hyperactive-Impulsive Subtypes of ADHD. These findings confirm other clinical research indicating the important contribution of ADHD to the behavioral problems often associated with TS. The high rates of comorbidity with ADHD found in clinical samples may be an artifact of referral bias since children with tics only may not require treatment at all (20). However, one epidemiological study suggests an association between tics and ADHD even in a non-referred community child sample (17).

About 50% of patients with TS also have symptoms of *obsessive compulsive disorder* (OCD) and genetic studies raise the possibility of a shared genetic vulnerability common to both disorders (21). OCD usually appears a few years later than the tics. Although patients with TS may manifest the usual harm-avoidant obsessions and compulsions found in other OCD patients without tics, concerns about symmetry, ordering and exactness, as well as intrusive aggressive, sexual or religious images, appear to be more common in tic-related OCD.

TS-related compulsions are often driven by the need to get some appearance or physical sensation "just right." In this subgroup of patients with OCD and tics, compulsions are sometimes performed in response to intrusive experiences or feelings such as urges, tactile sensations or a sense of incompleteness rather than obsessions or harm-avoidance (22). Compared to non-tic-related OCD, tic related OCD is characterized by earlier age of onset, predominantly affects males, and has a distinct pattern of treatment response (23, 24). Patients with TS plus OCD also present with higher rates of ADHD, social phobia, trichotillomania, and body dysmorphic disorder, suggesting that a subtype of OCD that is etiologically linked to TS has an earlier onset than OCD without tics (25).

A variety of studies suggest that, compared to later onset OCD, early onset OCD (before the age of 10) is a distinctive subtype of OCD associated with a greater likelihood of tics, a preponderance of compulsions (rather than obsessions) (as indicated by higher scores on the compulsion subscale of the CY-BOCS [23]), an increased family loading for OCD, male preponderance, and a poorer response to SSRIs (26). A new rating scale, the Dimensional Yale-Brown Obsessive-Compulsive Scale (CY–BOCS), measures the presence and severity of OCD symptoms within six thematically related dimensions and has helped elucidate the distinctive features of tic-related OCD. In addition, tic-related OCD is significantly less responsive to pharmacological therapy with SRIs than non-tic-related OCD and appears to be more responsive to augmentation with antipsychotic agents. Tic-related OCD also responds less well to psychological therapies than does non-tic-related OCD (3).

Youngsters with TS may be prone to comorbid *depression* or *anxiety* as they grow older for a variety

of reasons. The constant barrage of tics and premonitory urges, as well as the frequently comorbid ADHD, OCD and learning difficulties, can induce feelings of hopelessness and learned helplessness in children. Like children with ADHD uncomplicated by tics, children with comorbid TS and ADHD experience greater academic and social difficulties with deleterious effects on their self-esteem (27). The behavioral and learning difficulties that many of these children experience tend to induce stressful life events such as school failure or social rejection that increase the likelihood of developing depression. Furthermore, the various medications used in treating TS, OCD, and/or ADHD can all cause sedation, dysphoria or increased anxiety as unintended side effects. On a constitutional level, TS appears to be associated with increased autonomic lability and sensitivity to stress (26), and there is evidence that some other basal ganglia disorders (such as Parkinson's disease) may confer a vulnerability to depression even prior to the onset of movement symptoms.

CONCLUSIONS AND FUTURE DIRECTIONS

TS remains a prototypical model for studying developmental neuro-psychopathology and as such has an interest far beyond the clinical implications for the specific symptoms. Prospective longitudinal research beginning in early childhood in TS patients will surely contribute to the understanding of the relationships between brain structure, brain function, behavior, and environment - the very essence of developmental psychopathology. Thus the timing of the tic onset, the fractal nature of the tic episodes and the attenuation of symptoms in some but not all patients remain unsolved dilemmas. Are there basic oscillatory rhythmic disturbances that have their origin in neuro-developmental processes, and do patients march to a "drumbeat" that sets them apart (28)? Not considered in this review but of interest is the role of immunological processes. How do these fit in with brain development? New exciting methodologies in brain research and genetics enable us to be optimistic about finding the answers to some of these intriguing questions in the near future.

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