Pathophysiology of tics and Tourette syndrome

Abstract  Tics are involuntary movements that can affect one or more muscles producing simple or complex movements. Blink reflex and startle reflex studies disclose an increased excitability of brain-stem interneurons. Analysis of voluntary movement shows that when advance visual information is reduced, patients with tics and Tourette syndrome become progressively slower in completing motor sequences. Sensorimotor integration is abnormally processed. Studies of the contingent negative variation demonstrate abnormalities of movement preparation and the investigation of premotor potentials shows that in some patients tics are not preceded by a normal premotor potential. Magnetic stimulation studies demonstrate an increased excitability of cortical motor cortex. Functional MRI, PET and SPECT studies show abnormal activation of cortical and subcortical areas. Dysfunction of basal ganglia-thalamo-cortical projections affects sensorimotor, language and limbic cortical circuits, and may explain why patients with Tourette syndrome have difficulty in inhibiting unwanted behaviors and impulses.

Key words  tics · Tourette syndrome · motor disturbances

Introduction

Tics are involuntary, brief, rapid and non rhythmic muscle contractions occurring on a background of normal activity and causing purposeless and stereotyped motor actions (motor tics). Contraction of respiratory, laryngeal, oral and nasal musculature may produce sounds (vocal tics). Simple motor tics are repetitive stereotyped jerks involving isolated muscles of the upper parts of the body, particularly the face and neck, producing simple stereotyped movements such as blinking of an eyelid, elevation of eyebrows, a sniff or a brief shrug of a shoulder. Complex motor tics consist of a wide variety of muscle jerks and contractions in different muscle groups organized in sequence and coordinated movements resembling normal motor gestures. Tics are abrupt in onset and occur as discrete, isolated movements that can fluctuate from one part of the body to another. They decrease with distraction, relaxation, or when the subject is engaged in acts that need selective attention, and increase with stress. Many patients are able to exert some voluntary control over their tics. Motor tics can be suppressed by an effort of will or concentration and reappear when the patient is relaxed [21,29].

Tics may be preceded or accompanied by sensory phenomena. The most common sensory phenomena are unusual bodily sensations (tactile, muscular-skeletal or visceral) or an irresistible urge to move. Such uncomfortable sensations, termed ‘sensory tics’ can be distressing and painful [26,28]. Patients often interpret their tics as ‘intentional’ movements directed to relieve ‘involuntary’ sensations, possibly even extra-corporeal (‘phantom tics’) [23].

Motor tics may occur as isolated phenomena. Isolated motor tics are seen in childhood as acute transient
tics. Tics may occasionally persist and are referred to as chronic. Most of these idiopathic motor tics subside before adult life. Children requiring special education may represent a high-risk population for tics.

Motor tics accompanied by vocal tics and speech or behavioral disorders, with an onset between ages of 5 and 15 years, and a tendency to wax and wane in severity over time, fulfill the criteria for a diagnosis of the Gilles de la Tourette syndrome (TS) [21, 29, 38]. Among the behavioral disorders that develop in many patients are obsessive-compulsive disorders and attention deficit hyperactivity disorders, impulsive and self-destructive behavior, sleep abnormalities and alterations in mood and sexual behavior. Sensory tics are more frequently found in patients with TS than in patients with obsessive-compulsive disorders (OCD) [31].

Tics may also develop in the course of a number of neurological diseases, and are classified as secondary tic disorders. These symptomatic tics may complicate encephalitis, stroke, head injury, carbon monoxide poisoning, as well as neuro-acanthocytosis, and a variety of other degenerative neurological conditions. Post-infectious autoimmune mechanisms have recently re-emerged as contributing factors for the pathogenesis of some cases of TS. Drug-induced tics also have been described after treatment with neuroleptics, levodopa and sympathomimetic agents.

Despite detailed clinical descriptions of the phenomenology of tics the pathophysiology of this condition is still largely unknown. Our aim in this article is to review the available information from neurophysiological studies in order to clarify better the pathophysiology of this movement disorder.

Pathophysiology

- **Standard neurophysiological investigations**

Surface electromyographic (EMG) recordings of simple tics reveal short bursts of muscle activity usually lasting less than 200 ms in a single muscle or in co-contracting agonist and antagonist muscles [30]. Complex tics are recorded as various patterns of EMG activity in many muscles organized in the same way as a normal voluntary rapid movement: some recordings may also show prolonged EMG bursts in co-contracting muscles.

Conventional neurophysiological investigation of cortical activity shows normal EEG and evoked potentials in patients with tics [25, 34, 49].

- **Blink rates, trigeminal-facial reflexes and startle reflex**

Another research approach to patients with TS entails quantifying the rate of spontaneous eye blinks and frequency of eye tics [50]. Patients were studied while resting, conversing and watching video. They showed a significantly higher blink rate than controls during rest and video watching, but not during conversation. These findings suggested increased central dopaminergic activity.

Blink-reflex studies have disclosed other defective inhibitory mechanisms, suggesting that the excitability of brainstem interneurons is increased in TS [8, 44]. In particular, patients had an increased duration of the late response of the blink reflex, and most of them had reduced inhibition at paired pulse testing. Some patients, however, can have normal recovery cycles. In all patients, voluntary suppression of tics and blinks reduced the amplitude of the late blink reflex response.

Another finding, possibly related to a state of dopaminergic hyperactivity, is that some patients with tics have exaggerated audiogenic startle responses [17, 46]. This finding fits well with the hypothesis of a patient's inability to suppress unexpected stimuli. Indeed, tics are sometimes difficult to distinguish from disorders of excessive startle or 'hyperekplexia'. One report has described abnormal prepulse inhibition of the startle reflex in TS [48].

- **Movement studies**

Understanding the pathophysiological mechanisms responsible for tics means investigating movements during tics in these patients. Clinical examination shows that tics in TS are purposeful voluntary movements that are well organized and coordinated. This observation is supported by the finding that in a patient with TS goal-directed movement and tics both entailed anticipatory grip adjustments [13]. When a hand-held object is moved, grip and load force are accurately coordinated to stabilize grasp. The patient was requested to move a hand-held object up and down on a “go” signal that appeared after a variable delay and these movements were then compared with tics in the same directions. The patient modulated grip force in phase with movement-induced fluctuations in load equally well during voluntary movements and tics [13]. This study led to the conclusion that tics, like voluntary movements, are well organized and coordinated. Studying grip-load force control in patients with TS executing a precision manipulative task that required rhythmic unimanual or bimanual movements, Serrien et al. [41] reached the opposite conclusion. During unimanual and bimanual movements patients showed abnormally high force ratios, suggest-