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Review

The role of immune mechanisms in Tourette syndrome

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ABSTRACT

Tourette syndrome (TS) is a childhood-onset tic disorder associated with abnormal development of brain networks involved in the sensory and motor processing. An involvement of immune mechanisms in its pathophysiology has been proposed. Animal models based on active immunization with bacterial or viral mimics, direct injection of cytokines or patients' serum anti-neuronal antibodies, and transgenic approaches replicated stereotyped behaviors observed in human TS. A crucial role of microglia in the neural-immune crosstalk within TS and related disorders has been proposed by animal models and confirmed by recent *post mortem* studies. With analogy to autism, genetic and early life environmental factors could foster the involvement of immune mechanisms to the abnormal developmental trajectories postulated in TS, as well as lead to systemic immune dysregulation in this condition. Clinical studies demonstrate an association between TS and immune responses to pathogens like group A Streptococcus (GAS), although their role as risk-modifiers is still undefined. Overactivity of immune responses at a systemic level is suggested by clinical studies exploring cytokine and immunoglobulin levels, immune cell subpopulations, and gene expression profiling of peripheral lymphocytes. The involvement of autoantibodies, on the other hand, remains uncertain and warrants more work using live cell-based approaches. Overall, a body of evidence supports the hypothesis that disease mechanisms in TS, like other neurodevelopmental illnesses (e.g. autism), may involve dysfunctional neural-immune cross-talk, ultimately leading to altered maturation of brain pathways controlling different behavioral domains and, possibly, differences in organising immune and stress responses.

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1. Introduction

Tourette syndrome (TS) is a neurodevelopmental tic disorder with an estimated prevalence of 3–8/1000 in the 6–18 age range and a 3–4/1 male/female ratio. Tics consist of repetitive, unwanted, non goal-directed muscle contractions involving discrete muscle groups, which are associated with preceding sensory phenomena (urges), and are variably suppressible by volition. In TS, the onset of tics occurs between age 4 and 13 in up to 95% of cases. Severity may increase over time, peaking around puberty, with tics manifesting a progressive rostro-caudal anatomic spread (Leckman, 2002). Tics usually fluctuate in severity, persisting into adulthood in 30–40% of cases. TS is currently viewed as a spectrum, encompassing other stereotyped behaviors, e.g. echophenomena, coprophenomena and socially inappropriate remarks or gestures. Up to 90% of TS patients fulfill diagnostic criteria for comorbid psychiatric disorders, including obsessive compulsive disorder (OCD), attention deficit and hyperactivity disorder (ADHD), mood/anxiety disorders, and impulse control disorders (Cohen et al., 2013).

TS is associated with developmental abnormalities of cortico-subcortical and intracortical networks that are responsible for the selection and inhibition of motor output and sensory input. Tics may result from defective striatal inhibition of undesired motor patterns via loss of inhibition of motor cortical neurons (Mink, 2001; Wang et al., 2011). Decreased volume of the caudate nucleus, cortical thinning of primary sensory and motor cortices, and age-related slowing of fronto-striatal and fronto-parietal pathway maturation support the network scale of TS pathophysiology (Bloch et al., 2005; Worbe et al., 2012a). Nuclear imaging studies showed that these network abnormalities are associated with an increased dopaminergic tone, as well as abnormal GABAergic and other monoaminergic (noradrenaline, histamine, serotonine) transmission within striatal, thalamic, insular and cerebellar regions (Buse et al., 2013). Primate models using bicuculline, a GABA-receptor antagonist, confirm a link between tic-like movements, hyperactivity, stereotyped behaviors similar to human compulsive behaviors, and the different networks (sensorimotor, associative, limbic) of cortico-subcortical circuits (Worbe et al., 2012b; Bronfeld et al., 2013). The complexity of disease mechanisms in TS is reflected by the breadth of therapeutic strategies used in this condition, which include pharmacological treatment acting mainly on dopaminergic and noradrenergic transmission, reshaping of behavioral patterns using behavioral therapy, and direct modulation of affected pathways using deep brain stimulation.

The etiology of TS is complex, with polygenic contribution and potential involvement of environmental factors. Genome-wide association, rare variant, linkage analysis and copy number variant studies highlighted a role for genes involved in neural transmission (e.g. *HDC* gene associated with histaminergic transmission) or synaptic development (e.g. *SLITRK1* gene), but the variants so far identified may be relevant only to a small minority of cases. Importantly, copy number variant analyses support the existence of genetic commonalities between TS and other neurodevelopmental disorders (Fernandez et al., 2012), including autistic spectrum disorders (ASD). Amongst environmental factors, pre- or perinatal adversities, such as maternal smoking and life stressors during pregnancy or lower birth weight, might influence risk and severity of TS and comorbid ADHD and OCD in the offspring (Hoekstra et al., 2012). A relationship between immune responses and the neurodevelopmental abnormalities underlying tics and related symptoms has been hypothesized and investigated over the last two decades with different approaches. For example, it has been suggested that potent immunogenic triggers such as group A streptococcal (GAS) or other infections influence the risk of developing TS and/or predict its fluctuating severity. On the other hand, in analogy to autism, immune mechanisms could mediate developmental changes underlying the behavioral anomalies of TS.

This review article explores the link between immunity and TS, summarizing studies focusing on immune-related genetic and environmental factors, research on brain and systemic immune activation in this condition, immune-mediated animal models, with a final comment on the potential similarities in the role of immune mechanisms between TS and other neurodevelopmental disorders, primarily autism.