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Review

Environmental factors in Tourette syndrome

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ABSTRACT

Environmental exposures during the prenatal period, perinatal stages, and postnatal life may contribute to onset and course of Tourette syndrome (TS). Pregnancy-related noxious exposures may be more frequent in pregnancies of children who will develop TS, particularly maternal smoking and prenatal life stressors. Lower birth weight and use of forceps at delivery may be associated with tic severity in the offspring; moreover, low birth weight and maternal smoking during pregnancy may affect the risk of co-morbid attention-deficit/hyperactivity and obsessive-compulsive disorders. Group A streptococcal infections as risk-modifier for TS has not been convincingly demonstrated to date, although an interaction with stressors was suggested. The PANDAS hypothesis is currently undergoing a nosological revision. Only limited anecdotal evidence supports a link of TS to other pathogens. Nevertheless, the relationship between infections and TS may be complex. Recent data point to intrinsically altered immune regulation in TS, which might predispose to both infections and autoimmune mechanisms; however, evidence of cell-mediated and antibody-mediated autoimmunity in TS is still insufficient. Psychosocial stress remains the most important contextual factor influencing tic severity, as confirmed by prospective studies. This might in part be related to enhanced reactivity of the stress response in TS patients, the mechanisms of which need to be explored further. New studies on large prospective cohorts of patients of different age and the identification of reliable biomarkers or endophenotypes indicating early, prenatal exposure to environmental insults are needed.

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1. Introduction

The aetiology and pathogenesis of Tourette syndrome (TS) are recognized to be complex and multifactorial. Its strong genetic basis, albeit heterogeneous, is undisputable, but there is also a growing body of evidence supporting the contribution of extra-genetic factors to the onset and natural course of tics and related symptoms, such as obsessive-compulsive symptoms (OCS). The effect of environmental factors upon the disease mechanisms and the clinical presentation of TS may begin *in utero* and during the perinatal period, and continue throughout virtually the whole life span of the patient, across childhood, adolescence and adulthood. Very early noxious exposures, e.g. during pregnancy or as a result of complications at delivery, might exert *organizational effects* upon the development of brain networks relevant to the generation of tics and associated symptoms. The first part of this article will review the available evidence on the role or pre- and perinatal factors upon the risk of developing tic disorders, upon the degree of severity of tics, as well as upon the burden of the most common co-morbid behavioural illnesses observed in TS patients (mainly attention deficit hyperactivity disorder and obsessive-compulsive disorder).

Environmental contingencies during post-natal life could, on the other hand, exert *activational* effects, lead to changes in the activity of tic generating networks, and ultimately affect the phenotype of the tic disorder. Tics can be defined as stereotyped motor responses originating from an abnormal sensitivity to stimuli coming from within the body or from the outside world (Leckman et al., 2006a). With this perspective, tics appear as manifestations of a dysfunctional gating process, which does not allow the subject to filter out irrelevant information coming from sensory systems and different cognitive domains. An additional core feature of tics is represented by their fluctuation in severity. Tics occur in bouts, and may wax and wane over the course of days, weeks and months. Peterson and Leckman (1998) suggested that this temporal pattern follows a fractal dynamics, repeating itself across different time scales, and hypothesized that this could be the effect of specific neuronal firing patterns within crucial brain regions, e.g. the striatum (Leckman et al., 2006b). An alternative, although not mutually exclusive, interpretation for the waxing and waning course of tics is the effect of continuously changing environmental influences. Indeed, tics display a clear liability to contextual changes within the environment (Conelea and Woods, 2008). The second part of this article will evaluate the available evidence on the impact of environmental factors such as stressors or infectious processes upon the clinical course of TS.

2. Pre- and perinatal adverse events

A body of evidence has documented an association between the risk of developing TS and different prenatal and perinatal adverse events (Table 1). Although the precise mechanisms remain undetermined, suboptimal degrees of oxygen and nutrient delivery to developing brain structures such as the basal ganglia and/or early trauma on the brain during crucial periods of development are thought to play an important role.

2.1. The effect of pregnancy- and delivery-related complications upon the risk of developing tic disorders in the offspring

A pioneering, well designed early study was the work of Pasamanick and Kawi (1956), who studied the hospital obstetric records of a cohort of 83 children diagnosed as 'tiqueurs' at Johns Hopkins Hospital, Baltimore, and compared these with the obstetric record of the next birth reported from the same place of birth, matched by race, sex, socioeconomic status, and maternal age group. A total of 21 birth complications occurred among the infants who would later develop tics in contrast to ten in the controls. The percentage of mothers of children with tics with one or more complications was 33.3%, as compared with 17.6% for the controls; the percentage of those with two or more complications in the tic group was 7.8% versus only 2% within the healthy controls.

A subsequent study compared birth hospital records of 92 patients with TS with those of 460 controls (five for each patient) matched by sex, year, and month of birth (Burd et al., 1999). Mothers of children who later developed TS tended to seek prenatal care earlier than controls' mothers, and also had more prenatal visits. Moreover, children with a later diagnosis of TS had older fathers. These authors explained the higher number and earlier onset of prenatal care visits as an indication of a pregnancy with early problems apparent to both the mother and her doctor. This, coupled with the patients' lower Apgar scores, confirms the association between problems originating during pregnancy and the development of TS in the offspring.

In a further Italian case-control study (Saccomani et al., 2005) involving 48 referred children with TS, 48 with other chronic tic disorders and 30 healthy control children, the authors found considerably more pre- or perinatal complications (based on parents' report), both in children with TS (54%) and in those with other chronic tic disorders (50%) than among controls (6%). A more recent case-control study (Motlagh et al., 2010) involving 45 individuals with TS only, 52 individuals with attention deficit/hyperactivity disorder (ADHD) only, 60 individuals with TS plus ADHD and 65 unaffected control children investigated the potential role of four specific pre- and perinatal risk factors, based on maternal report date: (1) heavy maternal smoking (>10 cigarettes per day at any point during pregnancy); (2) high levels of maternal stress (across a range of areas including home environment, parental interpersonal relationship, availability of emotional support, parental employment, family financial status, parents' physical health, and pending legal issues; (3) low birth weight (<2500 g); (4) acute hypoxic–ischemic events (based on the presence of delivery or neonatal complications). The rate of heavy maternal smoking in the group of children with TS plus ADHD (11.6%) was elevated compared to healthy controls (1.6%) at a trend level of significance, whereas the rate of heavy smoking during pregnancy in patients with TS only was intermediate (6.6%). Similarly, severe maternal psychosocial stress was judged to be 2.5 times more frequent during the pregnancy of children who would have later developed TS (22% for future TS only patients, and 20% for future TS plus ADHD patients) than during that of healthy controls (8.1%). However, neither the proportion of low birth weight nor that of at least one delivery or neonatal complication differed between children with TS and healthy controls.

There is some indication that, during the fetal period, the male brain may be more vulnerable to the influence of pre- and perinatal insults than the female brain. It is an interesting finding that significantly more males than females with TS reported a history of birth complications both in a cohort of 91 consecutive adult TS subjects from a UK clinic (Eapen et al., 2004) and in a cohort of 60 patients with TS at the Yale Child Study Center (Santangelo et al., 1994). In the latter cohort, the history of delivery complications experienced by mothers of boys with TS was 9 times more frequent than that of mothers of girls with TS, largely due to more frequent forceps deliveries.

Perinatal adversities are not only more prevalent in children with TS, but are also associated with increased tic severity in affected individuals. In an important study involving 16 pairs of monozygotic twins in whom at least one twin had TS, 13 pairs had differing birth weights and the twin with lower weight at birth had a higher tic severity score in 12 of these 13 pairs (Hyde et al.,