EDITORIAL

The Pathogenesis of Tourette's Syndrome: Epigenetic Factors Active in Early CNS Development

Tourette's syndrome (TS) is a chronic neuropsychiatric disorder of childhood onset characterized by tics that wax and wane in severity, and an array of behavioral problems that include attention deficit hyperactivity disorder (ADHD) and some forms of obsessive compulsive disorder (OCD). Less well appreciated are the sensorimotor phenomena that frequently accompany tics and obsessive-compulsive behaviors. These experiences include premonitory feelings or urges that are relieved with the performance of the tic, and a need to perform tics or compulsions until they are felt to be "just right."

During the past decade, TS and related conditions have emerged as model disorders for researchers interested in the interaction of genetic, epigenetic (environmental), and neurobiological influences that shape clinical outcomes from health to chronic disability over the life span. Genetic factors clearly play an important role. Twin studies have demonstrated that genetically identical individuals have a high concordance rate for TS and related disorders, ranging from 50% to 90% (Hyde et al 1992). By comparison, the concordance rate for fraternal twins, who share half their genes in common, is substantially lower, in the range of 10% to 25%. Family genetic studies are also consistent with vertical transmission of a putative TS vulnerability gene from one generation to the next, and segregation analyses of these family data suggest that a single major autosomal gene may be at fault (Pauls et al 1991). Genetic linkage studies, however, have thus far failed to identify the chromosomal locus of this putative gene.

Twin studies also provide the strongest evidence for the importance of epigenetic or environmental factors in the pathogenesis of TS. Some genetically identical monozygotic (MZ) twin pairs, for example, are completely discordant for TS. Other pairs of MZ twins are markedly discordant for symptom severity, with one twin having severe symptoms of TS while the cotwin may only have a mild chronic motor tic disorder. Since these individuals are genetically identical, the observed differences in severity cannot be due to genetic influences alone.

Prenatal factors, particularly those that influence intrauterine growth, have been repeatedly implicated in TS. In discordant MZ twin pairs, the more severely affected individual usually has a lower birth weight (Leckman et al 1987). Indeed, Hyde et al (1992) found that the greater the intrapair birth weight difference, the greater was the observed difference in tic severity. Although the mechanisms underlying this association between birth weight and tic severity have not been established, differing degrees of oxygen and nutrient delivery to developing brain structures such as the basal ganglia may play an important role. Other prenatal factors that may influence later tic severity include sex-specific hormones and maternal stress during pregnancy.

Exposure to Sex-Specific Hormonal Factors

Males are more likely to be affected with TS or a related tic disorder than are females. Yet the presumed autosomal dominant inheritance of TS would suggest that male and female offspring should be at equal risk. This observation had led us and others to hypothesize that androgenic steroids acting at key developmental periods may be involved in determining the natural history of TS and related disorders. Given the prepubertal onset of TS and the not-infrequent presentation of tic symptoms in the 2- to 5-yr age range, we have speculated that exposure of the developing brain to normal surges in testosterone and other androgenic steroids early in fetal life may set the stage for the later development and exacerbation of tic symptoms among genetically vulnerable individuals (Peterson et al 1992). These prenatal surges in testosterone, the formation of active metabolites (especially dihydrotestosterone and 17-beta estradiol), and their interaction with selectively distributed nuclear steroid receptors, are likely to influence aspects of neurogenesis, neuronal migration, specification of cellular phenotypes, neurite extension, and synaptic connectivity as well as subsequent periods of programmed cell death, axonal elimination, and synaptic pruning. Many

Presented in part at the Society of Biological Psychiatry 1993 Annual Meeting. This work was supported by NIH grants MH44843, MH00508, NS16648, HD03008, RR00125, RR06022, MH30929, and by the Tourette Syndrome Association. The authors wish to acknowledge the contributions of Drs. Donald Cohen and David Pauls and our many other colleagues at Yale.

0006-3223/93/$06.00

of these effects are enduring and contribute to the development of sexually dimorphic brain regions, structural brain asymmetries, and altered cellular responsiveness to subsequent hormonal challenges months or years later. Evidence of such altered responsivity in TS patients includes anecdotal reports of tic exacerbation during exposure to anabolic steroids and improvement of tic symptoms following the administration of agents that block the androgen receptor (Peterson et al 1992). It is also worth noting that the cellular machinery needed to process gonadal hormones (certain enzymes and receptors) exist in selected regions of the brain throughout the life cycle. For example, the dopamine rich areas of the pars compacta of the substantia nigra and the ventral segmental area contain androgen, but not estrogen, receptors.

Maternal Stress during Pregnancy

Circumstantial evidence suggests that psychological maternal stress during pregnancy may influence the later severity of tic disorders. Specifically, ratings of maternal emotional stress during pregnancy have been found to be associated with later tic severity (Leckman et al 1990). In addition, some behavioral, neuroendocrine, and neurochemical characteristics of TS patients parallel those seen in adult animals who have previously been exposed to high levels of maternal stress in utero.

In animal studies, prenatally stressed rats later show increased behavioral vulnerability to stressful stimuli as adults, in addition to having region-specific changes in biogenic amine concentrations and altered cerebral asymmetries. For example, heightened stress responsivity, a loss in directional bias in amphetamine-induced rotations, and permanent changes in striatal dopaminergic asymmetrics (due to a reduction in the rate of dopamine turnover in the left striatum) have been observed in the offspring of mothers exposed to randomly applied noise and light stress throughout pregnancy. Stress-related fluctuations in symptom severity are common in TS, and patients often report that their tics are worsened by anxiety, emotional trauma, and fatigue. The absence of a directional turning preference in TS subjects has also been observed. Using MRI techniques, we and others have reported reductions in the volume of left lenticular nucleus and a loss of normal asymmetry in this structure in TS patients (Peterson et al 1993). These findings are also consistent with reduced blood flow in the left globus pallidus using single photon emission computerized tomography (SPECT) (Riddle et al 1992).

Animal studies of maternal stress during pregnancy also report alterations in the development of noradrenergic, serotonergic, and opioid systems. Other investigators have reported significantly higher levels of plasma adrenocorticotropin (ACTH) and corticosterone in the prenatally stressed animals. Similarly, we have found that a significant portion of TS patients show a heightened responsivity to stressful stimuli—with elevations in plasma ACTH and urinary norepinephrine (NE) excretion observed in anticipation of a lumbar puncture to collect CSP; CSP levels of NE and corticotrophin releasing factor (CRF) were also elevated in TS patients compared to healthy controls, and the level of CSF NE was found to correlate with current motor tic severity (Chappell et al submitted). Dopaminergic, serotonergic, and endogenous opioid systems have also been repeatedly implicated in the pathobiology of TS.

In summary, maternal stress during pregnancy may be an important mediator of the TS phenotype later in life. If severe, these stresses are likely to have enduring effects on the activity of monoaminergic systems and the hypothalamic-pituitary-adrenal (HPA) axis, as well as alter the development and extent of CNS lateralization.

Alterations in Cerebral Asymmetries Implicate Early CNS Events

There is a substantial body of data that implicates the basal ganglia and related cortical and thalamic structures in the pathobiology of TS. These data include the ameliorative effect of certain neurosurgical procedures that lesion thalamic nuclei or that isolate regions of the prefrontal cortex from their thalamic inputs. Functional neuroimaging studies have shown a reversal of the normal pattern of subcortical and cortical activity so that TS patients are characterized by decreased metabolic rates in the striatum and ventral cortical regions, and by increased metabolic rates in the somatosensory and supplementary motor cortices. These results are consistent with available SPECT and volumetric studies of basal ganglia.

MRI studies offer the most compelling evidence that early events in brain development influence the course of TS. The loss of normal asymmetries in the basal ganglia in both children and adults with TS point to early events involved with either the proliferation of neuronal precursors before the last mitotic division, or with somewhat later events involved with developmental regulated cell death. We have also found substantial reductions in the midsagittal area of the TS corpus callosum (CC) (Peterson et al submitted). Given the dramatic changes in the total number of axons in the CC during midgestation through the first months of postnatal life, it seems reasonable to suspect that events during this period could have a profound effect on the eventual expression of the TS phenotype in vulnerable individuals. The CC findings also suggest that the altered structural lateralization in TS is not confined to the basal ganglia, but may reflect a more global process affecting other telencephalic regions. It is

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also possible that subsequent developmental events—such as the myelination of the CC fibers that begins in the early latency years of childhood—could influence the course of TS by speeding up the existing callosal connections.

Building on the advances of the past decade and the synergistic potential among the various areas of active research, substantial progress can be anticipated in the identification of risk and protective factors that mediate the expression of the TS genotype. Advances in related fields of developmental neurobiology may also clarify the mechanisms by which these risk and protective factors operate.

The prospects for being able to identify specific or nonspecific risk and/or protective factors will be greatly enhanced when the TS vulnerability gene has been mapped. By selecting biologically homogenous high-risk carriers, investigators will be able to control for a significant portion of the biological variance so that detecting effects of a risk or protective factor will be more readily accomplished. Characterization of the putative TS vulnerability gene may also permit the development of transgenic animal models in which to study the gene environment interactions that are central to the pathobiology of TS. The successful identification of risk and/or protective factors, including the vulnerability gene(s), is likely to lead directly to early interventions that will limit, if not prevent, the emergence of clinically significant forms of TS.

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*A complete set of references will be supplied by the authors upon request.