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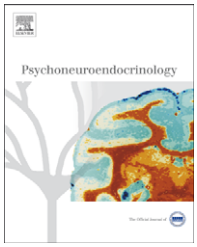

Examining cortisol rhythmicity and responsivity to stress in children with Tourette syndrome

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Summary
Background: Tourette syndrome (TS) is characterized by motor and vocal tics, which are often exacerbated by stress. The hypothalamic–pituitary–adrenocortical (HPA) axis, a major stress response system is thus of interest for understanding TS.
Methods: Diurnal cortisol rhythms were estimated in medication-free children 7–13 years with TS ($N = 20$) and healthy age-matched controls ($N = 16$). Salivary samples were collected on 3 consecutive days from the home. HPA responsivity was assessed by examining cortisol in response to a mock and real MRI scan.
Results: The results of diurnal rhythmicity revealed a trend showing marginally lower evening cortisol for the TS group. By contrast, the TS group had higher cortisol levels in response to the stressor. There were strong, negative correlations between evening cortisol and tic severity as well as diurnal cortisol and anxiety.
Conclusions: The children with TS showed increased cortisol in response to the MRI environment, supporting a model of enhanced HPA responsivity. The lower evening cortisol may be the result of chronic daily stress. Alternatively, the negative associations between cortisol and reported anxiety and tics may reflect biologically based anxiolytic properties of tic expression. Taken together, the results clearly implicate involvement of the HPA axis in the neuropathology of TS.

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1. Introduction

Gilles de la Tourette syndrome (TS) is a complex, highly heritable neurodevelopmental disorder characterized by the expression of motor and phonic tics. The diagnostic criteria require the expression of tics defined as sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements and vocalizations (APA, 1994). TS usually has a childhood onset with waxing and waning symptoms and response to medication over the course of development (Surwillo et al., 1978). Many individuals present with a mild-to-moderate symptom profile that is treated with education, behavioral techniques, and follow-up (Coffey et al., 1994). Patients with more severe symptoms often require treatment that may involve pharmacotherapeutic intervention and cognitive–behavioral therapy. TS is often accompanied by a range of co-occurring symptoms, including inattention, impulsivity, and impaired executive function (Bruun and Budman, 1992). There is also a high preponderance of symptoms of obsessive–compulsive disorder (OCD) in TS (McElroy et al., 1994; Steingard and Dillon-Stout, 1992; Swedo and Leonard, 1994). Further, anxiety disorders are often comorbid with TS and may be related to tic severity (Coffey et al., 1992).

It is commonly reported that stress-related fluctuations in symptom severity occur in all phases of TS illness (Peterson, 1996), often in response to fatigue, emotional trauma, anxiety, or stress (Shapiro et al., 1988). Premonitory urges are a sensory phenomenon that often precede motor tics (Banaschewski et al., 2003; Cohen and Leckman, 1992; Jankovic, 1997; Kwak et al., 2003; Leckman and Peterson, 1993; Woods et al., 2005), such that patients frequently describe their tics as voluntary and intentionally produced, as a way of relieving unpleasant involuntary premonitory sensations. Voluntary tic suppression can result in a buildup of tension that some claim leads to a paradoxical rebound or outburst of tics (Bliss, 1980; Jankovic, 1997). However, some studies involving behavioral observation methods (Himle and Woods, 2005; Meidinger et al., 2005; Woods et al., 2007) and intervention techniques (Verdellen et al., 2004) do not support the presence of a rebound effect.

A diathesis stress model proposed by Leckman et al. (1984) suggested that TS is the product of a genetic predisposition coupled with unknown environmental factors occurring at a vulnerable stage of development. An example of an environmental trigger is pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) that arise after exposure to streptococcal (group A beta-hemolytic streptococcal [GABHS]) infections (Mell et al., 2005; Swedo et al., 1998; Trifiletti and Packard, 1999). However, other research does not support the notion that PANDAS and TS are the result of autoantibody exposure (Harris and Singer, 2006; Kurlan, 1998; Loiselle et al., 2004; Singer et al., 2005).

Aside from these specific etiological factors, anxiety and stress-related symptoms are consistently and intimately involved in both the maintenance and exacerbation of tics (Lombroso et al., 1991; Peterson, 1996). Given this strong relationship between symptoms and stress-related reactivity, the hypothalamic–pituitary–adrenocortical (HPA) axis is of interest in the study of TS.

Regulation of the HPA axis involves three interrelated processes: the maintenance of a diurnal rhythm, activation in response to challenge or threat (stress response), and the restoration of basal activity via negative feedback mechanisms. One or more of these processes could be affected in TS. Additionally, the consistency of the diurnal rhythm has been considered an important factor in some neuropsychiatric disorders (Corbett et al., 2008; Yehuda et al., 1996).

Cortisol, the primary glucocorticoid in humans, is a principal homeostatic regulator. Its secretion follows a circadian rhythm, with high concentrations in the morning and a decline throughout the day, with the lowest levels in the evening and at night. This pattern is already well-developed by the third month of infancy (Price et al., 1983; Vermes et al., 1980). It has been suggested that individual differences in cortisol secretion, especially in the morning, may be an important variable for typically developing children (Bartels et al., 2003) as well as children with neuropathology, such as autism (Corbett et al., 2006; Corbett et al., 2008).

Arguably, the best-studied aspect of the HPA axis pertains to the response to stress, and one of the most widely used biological markers of stress is an increased concentration of circulating cortisol secreted by the adrenal gland. The stress response is initiated by the release of corticotrophin releasing hormone (CRH) from the hypothalamus, which in turn stimulates the synthesis and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which ultimately stimulates release of glucocorticoids, including cortisol, from the adrenal gland. Elevation in cortisol secretion occurs in response to novel, threatening, and unpredictable situations (Gunnar and Donzella, 2002; Hennessey and Levine, 1979).

Despite the observation that tics associated with TS may be exacerbated by stress (Lombroso et al., 1991; Peterson, 1996), there has been a dearth of research exploring the HPA axis in TS (Chappell et al., 1994; Sandyk, 1988; Sandyk and Bamford, 1988; Young et al., 1981), and no such work in children, who are typically most strongly affected by TS.

An early case study of a patient with TS with midbrain involvement showed a normal endocrine evaluation, which included plasma cortisol (Sandyk, 1988). A report of six TS patients evidenced a significant rise in plasma cortisol secretion in response to naloxone challenge (Sandyk and Bamford, 1988). The investigators hypothesized that noradrenergic locus coeruleus receptors involved in the release of corticotropic releasing factor are hypersensitive in response to chronic and excessive opiod-noradrenergic activity in TS (Sandyk and Bamford, 1988). However, given the lack of a direct comparison to control participants, this hypothesis awaits further investigation.

Another study (Chappell et al., 1994) examined the stressful effects of lumbar puncture on plasma ACTH and cortisol, urinary catecholamines, and self- and clinician ratings of anxiety in 13 medication-free TS patients and 10 normal controls, ages 17–41 years. The TS patients secreted significantly more ACTH than the control subjects following lumbar puncture, as manifested by greater mean and peak ACTH levels. Using a similar protocol, adult patients with TS showed elevated corticotrophin-releasing factor (CRF) in response to lumbar puncture when compared to individuals with OCD and normal control subjects (Chappell et al.,