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Short communications

Tourette syndrome: successful treatment with clonidine and oxycodone

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Summary. A 15-year-old boy with Tourette's syndrome exhibited severe involuntary self-mutilatory behavior. While clonidine effectively controlled the motor and phonic tics, it failed to ameliorate the self-mutilatory behavior. Administration of oxycodone (50 mg/day) combined with clonidine produced a dramatic reduction in the frequency and severity of the self-mutilatory acts within 12 h. This report indicates that disturbances in the functional interplay between the noradrenergic and opiatergic systems may be important in the pathophysiology of Tourette's syndrome.

Key words: Tourette's syndrome – Self-mutilatory behavior – Clonidine – Oxycodone

Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterized by multiple involuntary and repetitive motor and phonic tics and a large number of psychological and behavioral symptoms and signs. The pathophysiology of TS is poorly understood and therapeutic strategies aiming at influencing one or the other neuropsychiatric symptoms have had only partial success [7]. Haloperidol has been reported to benefit about 80% of cases [2], suggesting that hyperactivity of the dopaminergic system may be one of the major contributory neurochemical abnormalities in TS. However, administration of haloperidol is usually limited owing to the potential development of severe and undesirable side effects [5, 7]. Evidence has lately accumulated to indicate that clonidine (an alpha$_2$-adrenoreceptor agonist) may be efficacious in the management of TS in a subgroup of patients [4]. Moreover, we have recently suggested a role for the endogenous opioids in the pathophysiology of TS [3, 8–10]. Whether abnormalities of the endogenous opioids are intrinsic to the disease process remains, however, unknown. The following report adds further support to the role of the endogenous opioids in TS and suggests that disturbances in the functional interplay between noradrenergic and opiatergic systems, possibly at the locus coeruleus (LC) level, may be crucial in the pathogenesis of TS.

Case report

A 15-year-old boy was seen for evaluation and management of a progressive tic disorder associated with behavioral abnormalities that began at the age of 6 years. His early psycho motor development was normal until the age of 6, when he became hyperactive and distractible and showed impaired attention and emotional lability. At that stage he was diagnosed to have "attention deficit disorder" with hyperactivity. Over the following 2 years his behavior progressively worsened. Furthermore, he developed uncontrollable motor tics involving his face, head and shoulders. These were aggravated by stress and emotional upset and disappeared during sleep. At the age of 9 he developed phonic tics that included explosive animal-like noises and the use of obscene language. Over the past 3 years his condition has further deteriorated, involving frequent episodes of temper tantrums, involuntary self-aggressive behavior and a suicide attempt. He was placed in a special school, but his condition remained unchanged despite extensive psychological and pharmacological therapy.

The patient's family history was negative for both neurological and psychiatric disorders. On examination he showed marked hyperactivity and lack of concentration. His affect was labile and he appeared depressed. Barking noises, obscenities, obsessive touching and involuntary hand hitting occurred at a frequency of 8–12/h. As a result of his hand hitting, he had severely bruised his face and eyes. When asked to stop the hitting acts, he reported that he was "forced" to hit his face hard enough to feel pain before he could inhibit the impulse to tic. Indeed, the involuntary self-injuring acts appeared to have diminished the number of the motor tics. Moreover, these acts became more frequent after exacerbation of the motor and phonic tics. He appeared to have had a high tolerance for pain, since self-hitting did not produce excessive discomfort.

A trial with haloperidol (up to 6 mg/day) produced only slight improvement in motor (20–30 tics/5 min) and phonic (10–15 tics/5 min) tics and behavior and was discontinued owing to the development of dystonic movements. A trial with clonidine (0.05 mg twice daily) produced a more marked reduction of the motor (8–12 tics/5 min) and phonic (6–8 tics/5 min) tics within 72 h of administration. In addition, his behavior improved noticeably. Following 3 weeks on clonidine he was less hyperactive and aggressive and there was a noticeable improvement in his mood and sleep. However, clonidine produced no change in the patient's involuntary self-injuring acts and restraining the patient in an institute was considered. Since the patient appeared to be insensitive to external acute pain, he was given oxycodone (50 mg/day), which was added to clonidine. This has produced marked reduction in both the number and severity of the involuntary self-hitting (1–2/h) within 12 h of administration. Furthermore, oxycodone ap-

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peared to have reduced slightly the frequency of the phonic tics (2–5 tics/5 min). Attempts to discontinue or replace oxycodone with placebo resulted in rapid exacerbation of the phonic tics and self-injuring acts. The effects of oxycodone remained unchanged during a 6-month period.

Discussion

Although the pathophysiology of TS is poorly understood, pharmacological studies have indicated a role for both dopaminergic and noradrenergic systems [5]. Involvement of the former was suggested by the beneficial effect of dopamine blocking agents (e.g. haloperidol, pimozide) in the majority of TS patients [2]. The favorable response of some patients to clonidine [2] implicates hypoactivity of the noradrenergic system in TS. Clonidine, an alpha-adrenoreceptor agonist, has been shown to act centrally by inhibiting LC neurones [6]. The activity of the noradrenergic LC neurones has also been shown to be under opioid control [6]. LC neurones are inhibited by both local and systemic administration of opiates and opioids [6]. The effects of opiates on LC neurones have been shown to be reversed by naloxone [6]. On the other hand, naloxone does not antagonize the effects of clonidine on LC neurones [1], suggesting that opiates and clonidine act via independent receptors within the LC to produce similar depressant effects on net LC activity.

Our patient failed to benefit from haloperidol, but administration of clonidine produced marked amelioration of symptoms. Clonidine had no effect, however, on the patient's involuntary self-injuring acts. Since induction of pain by the patient appeared to inhibit motor tics, it appeared that underactivity of the opioid system played a role in the disease process. Indeed, enhancement of opioid activity with oxycodone abolished the patient's impulse to self-injury. From a pharmacological viewpoint, it is thus evident that this patient's underlying transmitter imbalance involved a combination of noradrenergic hypoactivity and opioid system underactivity. Thus this report adds further support to indicate that abnormalities in the functional interplay between the noradrenergic and opiatergic systems at the LC level may be of major importance in the pathophysiology of TS.

Furthermore, since administration of naloxone (an opioid antagonist) was reported in one case to ameliorate symptoms of TS [9], it appears that both over- and underactivity of this system may prevail in subjects with TS. This observation supports the clinical evidence that there are subgroups of Tourette patients within the Tourette group.

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