Case Report: Exacerbation and Provocation of Tics by Imipramine and Sulpiride

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This paper deals with the problem of overlapping clinical effects of neurotropic agents in treating children with complex comorbidity. An 8-year-old boy suffering from a complexity of symptoms such as chronic motor tics, compulsions, phobias, anxious inhibition, and stuttering displayed the totality of Tourette’s syndrome while taking imipramine. Sulpiride also enhanced motor and vocal tics. In the discussion, a review on the neurometabolic mechanisms in tic disease actually known is given, and on drugs proven to precipitate tics, which is the case in a number of neurotropic agents. Psychodynamics and family dynamics are another issue to be regarded independently.

Introduction

Treatment of tic disorder in childhood and adolescence presents special problems to the doctor, especially when it is comorbid with symptoms of hyperactivity, attention deficit (ADHD), phobic and/or obsessive-compulsive disorders (OCD). Drugs that improve one target symptom may exert unfavourable effects on others. Additional complications may arise from the highly, individually variable response of tics to treatment dose.

Case Report

P, a boy aged 8.2 years on admission, had suffered for 3 years from clonic stuttering and various compulsions (e.g. need to touch things, walls and repeatedly ask questions to reassure himself). The family believed his illness was due to witnessing his father’s heart attack. During P’s eighth year tics occurred first in a single group of muscles (head jerks, 7.2 years) and then spread to blinking (7.8 years). A water phobia had been present since 4 years of age (fear of entering a swimming pool). By screaming and causing much trouble P was able to make his family avoid talking about worrying subjects such as illnesses and visits to the dentist. The child was referred to a child psychiatrist because of problems at school, where P was unable to speak up in class.

There was a history of relevant psychiatric disorders in the family: suicide of P’s maternal grandfather, consecutive phobias and stuttering of P’s mother (14 years); cardiac neurosis of P’s father. The family atmosphere was marked by restriction and overprotection.

P’s birth was uncomplicated but he required phototherapy for hyperbilirubinaemia. He suffered from extensive eczema neonatorum. P’s parents felt that he was an extremely lively and restless infant compared to his 2-year older brother. As a result of strong separation anxiety P entered kindergarten late and often refused to attend.

On admission P was physically healthy, also had an adequate developmental and neurological state. EEG basal activity was slightly slow and dysrhythmic. Psychiatric interviews showed up a marked separation anxiety. He would panic when about to use the lift. In personal interactions he was tense, fluttery and would try to avoid engaging in contact or verbal exchanges. He showed poor concentration. He was clearly anxious and tense during IQ testing (WISC IQ 82, Raven IQ 93).

P demonstrated a developmental language delay and a secondary consolidation of stuttering with motor stiffness and accessory movements. Al-

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though the motor quotient (67) was pathologic, P displayed better coordination when he believed he was not being observed.

**Therapy and Development**

Treatment followed a psychotherapeutic course including individual and family sessions along with occupational therapy, milieu therapy and special classes. Tics were markedly reduced and were at times absent for several days at the beginning. At school, anxiety and withdrawal were reduced but tended to recur when P was faced with new situations. Compulsions, stuttering and anxious arousal were more apparent in the presence of his family.

In response to the news that he would soon return to his family, where the dynamics continued to be characterized by anxious avoidance, P withdrew from group activities and became depressed. As a consequence it was decided to give P a pharmacological “back-up” to ease this anxiety and inhibition and to reduce the corresponding compulsions. As anxiety clinically outweighed the inhibition, imipramine was selected for administration (initial dose 20 mg/d, maintenance 30 mg/d).

Initially P appeared tired but was more relaxed. But after 3 days of the maintenance dose there was a striking increase in the incidence of tics and of stuttering. A dysregulation of breathing in the sense of impaired speech fluency was also noted. However in making contacts P became more active and constructively approached his peers with play initiatives: he became more open in verbal exchanges and he made more intensive physical contacts. Nonetheless medication had to be withdrawn after 14 days as the tics had become very intense, frequent and various in nature. Tics were now also vocal and involved the perioral muscles. Four days after withdrawal of the medication the incidence of tics had clearly subsided, yet reappeared in strenuous situations, and he often relapsed into his former social withdrawal and compulsive symptoms.

A second trial of pharmacotherapy was then initiated, this time with the atypical neuroleptic sulpiride (initial dose 3 x 25 mg/d raised over 12 days to 3 x 75 mg/d or 7 mg/kg). This treatment was expected to reduce the incidence of tics, increase adaptive behaviour and improve P’s state of mind. Over the first ten days there was a marked improvement with both stuttering and tic symptoms. On the tenth day, coincident with one of the weekly parental visits, tics increased once more. This continued until 2 days after reaching the target dose (14th day of treatment). There were now motor and vocal tics. P would shrug his shoulders and beat his head against the wall or desk rendering teaching efforts at school almost impossible. There was no arrest to the symptoms even during relaxed walks outside the clinic. P became increasingly depressed. Medication was withdrawn after 17 days’ treatment. The parents did not consent to the use of further medication such as tiapride. Two days later the tic symptoms were markedly diminished.

**Further Comments on the Background of the Course of Illness**

During the medication period P was prepared for leaving the ward. He began to show distinct signs of developmental progress, such as an increase of autonomy, more openness and the ability to make his point with others. He developed certain aggressive traits and became able to tackle questions of the family hierarchy, of his dominating the family and the family’s taboo theme of sexuality. In individual therapy predominant themes included aggression and the fear of losing control.

P presented again with massive motor and vocal tics 8 weeks after discharge. He explained that he felt that tics reduced his fears. He felt oppressed by several requirements from school and his parents’ urging him to visit a sport club. Two weeks later he was free of tics but showed increased anxiety and compulsive traits. At home or at school tics were now infrequent enough to be considered non-intrusive and to be causing P little trouble. In the family he had assumed a dominating, controlling role. Outpatient treatment was then discontinued by the family.

**Discussion**

Treatment of chronic motor tic disorder (ICD-10: F95.1/DSM-III-R: 307.22) or Tourette’s syndrome (TS) (F95.2/307.23) can raise many problems when, as is often the case, other neuropsychiatric symptoms are present. More than 50% of tic patients may also exhibit ADHD (Shapiro & Shapiro, 1981; Comings, 1987; Shapiro et al., 1988) and comorbidity of compulsions and tics has
been frequently reported (Pauls et al., 1986; see also below).

The discussion will centre on the following four issues: 1. Family history and genetics; 2. Perinatal risk factors; 3. Comorbidity with compulsions, phobias and stuttering; 4. Provocation of tics by sulpiride and imipramine.

**Family History**

P’s mother’s phobias and stuttering could be seen as a different manifestation of the TS/OCD gene and thus a precursor in family history (Pauls & Leckman, 1986; Comings, 1987). An autosomal-dominant mode of inheritance for chronic multiple tics and their shared expression with OCD is suggested by segregation analyses among first-degree relatives of TS patients (Pauls & Leckman, 1986; Comings, 1987; Curtis et al., 1992). Taking the spectrum of possible manifestations (ADHD, OCD, multiple tics, TS), Pauls and Leckman (1986) estimate the genetic penetrance to be 1.00 in males and 0.7 in females. Epidemiologic findings stated TS among 1 in 95 male school students (Comings et al., 1990).

Alternatively, OCD symptoms and tics may be thought of as a traditional family mechanism of coping with unwanted or forbidden impulses, especially in rigid, domineering and over-protective forms of upbringing, as was seen in our case (Eggers, 1982, 1984a; Bunk et al., 1988). Learning to control the acting-out of impulses and motor control takes place during the same phase of development. Following Comings’ theory (1987) of a limbic disinhibition with a consequent increase of motor, sexual and anger impulses in genetically vulnerable subjects, tic and OCD behaviour might very well form strategies to control these impulses.

However, models based exclusively on the biological or psychodynamic aspects of a particular case are seldom sufficient to explain psychopathology in childhood. It is likely that genetic, interrelational and psychological factors mutually interact and that the so-called waxing and waning of the clinical picture is expressing some of these dynamic processes.

**Perinatal Risk Factors**

An increased incidence of perinatal complications is reported from both OCD and tic patients (e.g. Leckman et al., 1990), though not confirmed by Shapiro et al. (1988). In patient P it is conceivable that the postnatal hyperbilirubinaemia could have had a negative influence on the development of the basal ganglia. Impaired basal ganglia function has been reported from patients with OCD or tic disorders (Wise & Rapoport, 1990).

**Comorbidity**

In contrast to a lifetime prevalence for OCD in the general population of 2%, it is reported that 15–18% of patients with severe tics also suffer from OCD (Karno et al., 1988). Indeed as many as 20–25% of children with OCD are reported to suffer from tics (Swedo et al., 1989; Riddle et al., 1990a; Rapoport, 1991), though OCD symptoms usually become manifest some years after the tics (Cohen, 1991). This was broadly the case with patient P who showed tics at the age of 5 years and OCD at 8 years. ICD-10 prohibits a separate coding for OCD symptoms in the context of TS as they are considered part of TS psychopathology (see F 42; see also above).

Phobias are often present in OCD (e.g., in up to 50% of Knöllker’s young patients (1987)), and have been reported by Comings (1987) to be present in TS patients three times more often than in the general population.

Impaired speech fluency or stuttering is a frequent accessory symptom in tic disorders and TS (Shapiro et al., 1978). Indeed impaired fluency was a feature of all 27 children with tic disorder in the study of Eggers (1982) and in 32% of Comings’ patients (1987). Yet in this sense ICD-10 omits any separate coding of this symptom. Impaired fluency, as with other neurological soft signs, is in ICD-10 seen as an expression of cerebral dysfunction, that may occur with varying degrees of severity in tic disorders and is perhaps more often seen associated with ADHD.

**Provocation of Tics by Sulpiride and Imipramine**

While the danger of provocation or exacerbation of tics in ADHD patients treated with psycho-stimulants is well-known (Golden, 1977, 1988; Lowe et al., 1982; Eggers et al., 1988; Sverd et al., 1989; Gadow & Sverd, 1990), being particularly a problem where 50–60% of tic patients aged 6–16
years also suffer from ADHD (Matthews, 1988; Cohen & Leckman, 1989), we are unaware of reports that sulpiride can provoke tics. On the contrary positive effects of sulpiride on tic symptoms in children have been reported (Le Heuzey & Dugas, 1985).

Sulpiride and tiapride are both benzamide derivatives and specific dopamine-D2 receptor blockers. In contrast to sulpiride, tiapride has no antipsychotic effects. They show little or no propensity for evoking extrapyramidal side effects. Tiapride has proved effective in the treatment of childhood tic symptoms showing no dyskinetic side effects (Eggers, 1982, 1984b; 1985; Eggers et al., 1983, 1988; Rothenberger, 1991) and is now considered to be the first choice of treatment for tic disorder, though, according to Food and Drug Administration (FDA) limits, experience does not exist in the United States (Shapiro et al., 1989). The need to discontinue medication owing to neuroleptic side effects in child TS cases was formerly reported to be 33% (Singer et al., 1986). At a low dose of 7 mg/kg (3 × 75 mg) we had expected sulpiride to have a positive effect on tic symptoms, obsessions and anxiety. In fact at the initial dose (3 × 25 mg/d) we observed a reduction of stuttering and tic frequency. But after 10 days when target maintenance levels were reached motor and vocal tics emerged accompanied by moderately severe autoaggression. Discontinuation of medication resulted in an improvement.

Correlates of neural activity with tic symptoms usually involve the dopaminergic system and implicate, in particular, an increased sensitivity of dopamine receptors according to some hypotheses (Cohen et al., 1978; Eggers et al., 1988). These changes affect interactions of dopamine with cholinergic and serotonergic systems, which may in turn affect serotonergic-noradrenergic interactions (Eggers, 1982). Via multiple feedback mechanisms these monoamine systems exert mutual control over each other; changes may occur at different points of this control system in individual tic patients. In turn these changes will have separate consequences which give rise to the variety seen in the clinical picture with which these patients may present (Eggers, 1984a).

Should an increase in the number of D2-receptors be the case, as has been reported from animals chronically treated with sulpiride (Memo et al., 1981), this would be seen clinically as tardive dyskinesia and might be expected only if subjects were treated for a long period with a relatively high dose. Yet in this context it is of interest to note that a subtype of dyskinesia, “tardive TS”, has been reported following neuroleptic medication in children (Singer, 1981). Further Weiden and Bruun (1987) reported that raising the neuroleptic dose early can cause an increase in the severity of tics and a deterioration of TS in both children and adults suffering from TS and chronic motor tics. Coincident with the deterioration they found that the patients showed much akathisia-like restlessness.

Recent neuropharmacological reports suggest that sulpiride could exert an indirect dopamine agonist effect by inhibition of the serotonergic system (Morgenstern et al., 1988; Drescher et al., 1990), and there is some evidence for the possible mediation of this effect by dopaminergic autoreceptor blockade by sulpiride. One must assume that such a presynaptically based effect would only follow treatment with low doses of sulpiride (7 mg/kg in patient P). Of course small doses of neuroleptics may block dopamine autoreceptors in ascending dopamine projections, thus increasing the levels of dopamine in the synapse, and thereby directly provoke tic behaviour (Gualtieri & Hicks, 1985). Indeed tics were reported from 2 children, both aged 9 years, who had been treated with low doses of haloperidol and thioridazine (Gualtieri & Patterson, 1986).

Imipramine treatment was initiated because of the positive indication in childhood depression and hyperactivity. Results with TS patients have proved contradictory: symptoms have been reported to improve (Messiha & Knopp, 1976; Yaryura-Tobias & Neziroglou, 1977; Dillon et al., 1985; Hoge & Biederman, 1986; Sandik & Bannford, 1988), show no change (Shapiro et al., 1978; Caine et al., 1979) or to deteriorate (Fras & Karlavage, 1977).

Imipramine inhibits the reuptake of the monoamines noradrenaline, serotonin and, what is less widely appreciated, at moderate concentrations also dopamine, particularly in the limbic system (De Montis et al., 1990). Further, chronic treatment of rats with imipramine results in a down-regulation of dopamine D1- but not D2-receptors. This is accompanied by a corresponding increase in the sensitivity of adenylate cyclase to stimulation. Both effects are more marked in limbic than in striatal projection areas of the dopamine system (De Montis et al., 1990). In addition, it would seem that a given level of dopamine neurotransmission (in terms of synthesis and release) is nec-
assy for the effect to become apparent. Thus paradoxically it is feasible that imipramine treatment can facilitate dopaminergic transmission, a feature that would not help to ameliorate tic symptoms.

Imipramine, as a serotonin uptake blocker (facilitating serotonergic transmission), could exert two separate, opposing effects on the dopamine system. Increases of serotonin may exert an inhibitory effect presynaptically at terminals in the dopamine system. This may account for the exacerbation of neuroleptic-induced catalepsy by serotonin-uptake blockers (Carter & Pycock, 1977). However the nuclei of origin of ascending dopamine pathways contain high concentrations of imipramine binding sites (Langer et al., 1981). Here increases of serotonin-mediated inhibition could disinhibit ascending dopamine activity (see discussion in Korsgaard et al., 1985; Castrogiovanni et al., 1989).

Yet, fluoxetine, a selective serotonin uptake inhibitor, was not effective in reducing the severity of tic symptoms in 6 TS children and adolescents with comorbid OCD, but three of these patients had improved OCD symptomatology (Riddle et al., 1990 b).

Conclusions

It remains difficult to assess the efficacy of tricyclic antidepressants or atypical neuroleptics in the treatment of tic disorders with or without other comorbid syndromes (e.g. ADHD, OCD, phobias). Usually pharmacotherapy is initiated with the administration of dopamine receptor-blockers (e.g. tiapride, pimozide, haloperidol). Where the effect is unsatisfactory other agents (e.g. clonidine) may be co-administered and the dose skillfully tuned to the clinical symptoms. However in the absence of an unequivocal neurochemical impairment specific to the tic disorders, the possibility of an exacerbation of symptoms must always be taken into account.

In assessing the potential effects of pharmacotherapy on behaviour one should not neglect individual, personality-related and family-dynamic components that interact and make up the condition of the patient being treated. Thus in patient P we showed there was a dynamic interaction between compulsions, phobias, stuttering and tics which correlated with his intra- and inter-personal psychological conflicts. These conflicts arose from the (in)ability to exert control, to deal with drives and to strive for a balance between dominating and being dominated.

From a psychodynamic point of view, if tics are considered as a "preverbal mode of expression" (Abraham, 1921), they could be seen as a form of expression of hostile impulses that is a more effective way of making the patient feel subjectively better than the use of compulsions or phobias as a form of defense against such impulses. Nonetheless even reports of successful psychoanalytic courses of treatment with severe cases of tic-disorder (e.g. Urban, 1985) do not compromise a more holistic view of TS as a psycho-somatic disorder with strongly individually determined somatic components. Thus, when a course of therapy is under consideration, reciprocal and constructive interactions between potential forms of psychotherapy and physiological requirements are desirable.

Résumé

Cet article traite du problème des effets cliniques d’interférences des agents neurotropes dans le traitement des enfants avec une cormorbidity complexe. Un garçon de 8 ans souffrant de symptômes complexes tels que des tics moteurs chroniques, de compulsions, de phobies, d’incapacités anxieuses et de dégagement, présentait la totalité du syndrome de Gilles de la Tourette tout en prenant de l’imipramine. Le Sulpiride renforçait aussi les tics moteurs et vocaux. Dans la discussion, une revue des mécanismes neuro-métaboliques de la maladie des tics, actuellement connus est faite ainsi que des médicaments pouvant favoriser les tics ce qui est le cas pour un bon nombre d’agents neurotropes. Les données psycho-dynamiques et liées à la dynamique familiale sont une autre question qui doit être envisagée indépendamment.

Zusammenfassung

Gegenstand der Arbeit sind die sich übergreifenden bzw. gegenseitig antagonistizierenden klinisch-pharmakologischen Effekte neurotroper Substanzen bei der Behandlung von Kindern mit Tics, die eine Komorbidität mit anderen Symptomen wie Zwänge, Phobien oder ADHD aufweisen. Ein 8-jähriger Patient, der unter chronisch motorischen Tics, Zwangshänenomenen, Phobien, ängstlicher

References


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