

Is High Dose Risperidone an Option for Treatment-Resistant Tourette Syndrome?

Tedaviye Dirençli Tourette Sendromunda Yüksek Doz Risperidon Bir Seçenek midir?

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ABSTRACT

Gilles de la Tourette syndrome (TS) is a chronic neuropsychiatric disorder that begins in childhood, in which multiple motor tics and one or more vocal tics are seen concomitantly. In this text, the treatment course of a severe TS case, with complete daily functioning loss, is described. Significant reductions in tics were observed with 8 mg/day risperidone treatment in this case who failed to respond to many neuroleptics. The Yale Global Tic Severity Scale (Y-GTSS) score, which was 85 before treatment, declined to 48. In our case, who used this dosing regimen for six months, the reduced tic status continued after the dose was switched to 6 mg/day, the reduction status was observed to go on after six months. No significant side effect was observed. This case was thought to be important in showing that high dose risperidone might be effective in treatment-resistant TS cases. (*Archives of Neuropsychiatry 2009; 46: 206-8*)

Key words: Tourette syndrome, risperidone, antipsychotics

ÖZET

Gilles de la Tourette sendromu (TS) çocukluk çağında başlayan, çoğul motor tik ve bir veya daha fazla ses tikinin eşlik ettiği kronik bir nöropsikiyatrik bozukluktur. Bu sunumda günlük fonksiyonlarını yapamayacak kadar ağır bir TS olgusunun tedavisi anlatılmaktadır. Birçok nöroleptik ile tedaviye cevap vermeyen olgumuzun tiklerinde, 8 mgr- gün risperidon tedavisi ile azalma görülmüştür. Tedaviden önce 85 olan Yale Genel Tik Ağırliğini Derecelendirme Ölçeği (YGTDD) skoru tedaviden sonra 48 olarak tespit edilmiştir. Olgumuz bu dozu altı ay boyunca kullanmış, doz 6 mgr-gün olarak azaltıldıktan altı ay sonra da tiklerdeki azalma devam etmiştir. Önemli bir yan etki ortaya çıkmamıştır. Bu olgu tedaviye dirençli TS olgularının tedavisinde yüksek doz risperidonun etkili olabileceğini düşündürmektedir. (*Nöropsikiyatri Arşivi 2009; 46: 206-8*)

Anahtar kelimeler: Tourette sendromu, risperidon, antipsikotikler

Introduction

Tourette Syndrome (TS) is a neuropsychiatric disorder starting at childhood, and is characterized with multiple motor tics and at least one or more vocal tic (1).

The first step in the treatment of TS is psychoeducation of the patient and the family (2,3).

Clinician must decide whether to use pharmacologic agents or not. Counseling and behavioral arrangements might be sufficient for the patients with moderate symptoms. Medication should only be considered when symptoms disrupt peer relationships and social interaction, and effect academic and occupational performance in a negative way (4,5).

Drugs such as haloperidole, pimozide, risperidone, sulpiride, clozapine, quetiapine and clonidine were shown to be effective in the treatment of this disorder (6-13).

The neurobiological mechanism of tics is not clearly known, but D2 receptor hypersensitivity is generally suggested. Dopamine antagonists are widely and effectively used for the treatment of tic disorders. Risperidone, a D2 and 5 HT2 receptor antagonist, has a high affinity to 5 HT2 receptors in low doses, but interaction with dopamine receptors occurs only at very high concentrations (14).

In the literature we could not find any description for treatment resistance in TS, however, no response to various high-dose antipsychotics suggests that this is a treatment-resistant case with TS.

Although we used several antipsychotics, the reported case had no improvement in his tic severity.

We report the treatment process of a case with TS, who had treatment failure after multiple neuroleptics, but responded successfully to 8 mg/day risperidone.

Case

MK, a 14-year-old male, referred to our clinic for his involuntary body movements and vocal tics. His motor tics (mouth movements, head banging, shoulder shaking, hand and leg swinging, stomach muscles stretching) started 3 years ago and his vocal tics one year later (winking, sniffing, copropraxy, coprolalia, echolalia, sudden bursting talks, coughing, snoring, whistling), affecting daily activities such as putting clothes on, eating and showering. His tics were severely continuous. His pediatric and neurological examination, routine laboratory blood tests, liver function tests, electroencephalogram (EEG), cranial magnetic resonance (MR) and sleep EEG findings were normal. He was diagnosed with TS according to DSM-IV-TR criteria (APA, 2000). He had comorbid major depressive disorder. The Yale Global Tic Severity Scale (Y-GTSS) was applied and he had a total of 25 on motor tics, 10 on vocal tics, 50 on general severity, and 85 as total (15). He was first started on haloperidol 1 mg/day, increased by 1 mg weekly up to 6 mg/day and due to lack of response it was increased by 2 mg weekly up to 15 mg/day for a period of one month. The medication was ceased as no response has been obtained. Risperidone was then started at 1 mg/day and the dose increased weekly by 1 mg up to 4 mg/day. It was stopped as no clinical improvement was observed and pimozide was started at 0.5 mg/day and increased by 0.5 mg every 3 days until a dose of 6 mg/day was reached. No reductions in symptoms severity led to cessation of pimozide treatment. Quetiapine was introduced at 25 mg/day, then dose increased by 25 mg every 3 days up to 200 mg/day, after which it was increased by 50 mg/day until 600 mg/day dose was achieved, but still no improvement was detected. After the cessation of quetiapine, amylsurpirid was started at 100 mg/day and titrated up to 800 mg/day, with no response at all. The patient has dropped school, stopped his treatment and started using alcohol and marijuana from time to time at which he reckoned that his tics were reduced for several hours and that he felt better.

After 2 years of drug-free period, the patient reapplied to our clinic showing increase in the count of motor and vocal tics, in the frequency and severity to a degree to hinder own daily activities (he could not button up his clothes, tie his belt or even drink water). His drug misuse (marijuana) was still continuing as once per week. Due to his tics, he expressed having difficulties to leave the house, eat, drink or put clothes on without having assistance from others. At 19 years of age, ziprasidone was started at 20 mg/day and increased by 20 mg every 5 days up to 120 mg/day for 2 weeks, but it also had no beneficial effect and was stopped. Clozapine was then started at 12.5 mg/day and titrated up to 150 mg/day, then stopped due to sedation and no efficacy on symptom severity. He was then started on haloperidol at 2.5 mg/day, which was increased up to 20 mg/day for a period of 3 weeks. The medication was ceased due to lack of response. Risperidone was then started at 1 mg/day and the dose was increased up to 4 mg/day and after 1 week it was more increased up to 6 mg/day. One week after risperidone treatment at 6 mg/day, the patient stated a subjective improvement in his symptoms, which was supported objectively

by a decrease in Y-GTSS score down to 68. Risperidone was then increased up to 8 mg/day and 1st week, 2nd week, 4th week and 8th week evaluation with Y-GTSS revealed a score of 15 on motor tics, 3 on vocal tics, 30 on general severity, and 48 as total. He could not show himself in public before, but now he stated that he could go out with his friends, eat and drink, and put clothes on. At 8 mg/day, he reported mild side effects including increased sleep time, fatigue, difficulty in concentration, restlessness, polyuria, polydipsia and total weight increase of 10 kg in 3 months. Then we decided to lower the risperidone dose to 6 mg/day and we did not observe any increase in his tic symptom severity. But these side effects were not at a level to necessitate cessation of the treatment. Besides, electrocardiogram (EKG), blood pressure, pulse, routine laboratory test, prolactin and thyroid stimulant hormone (TSH) levels were within normal limits. Six months after continuous drug use, the patient was still showing decrease in tic symptoms.

As no increase in tic scores was observed in the assessment with Y-GTSS after six months, risperidone dose was continued as 6 mg/day. EKG, blood pressure, heart rate and routine biochemistry were assessed to be normal after 6 months and after 1 year, and no side effect was described, except fatigue. A total of 15 kgs of weight gain after 6 months, and no weight gain after 1 year was noted. Our case is still stable with 6 mg/day risperidone.

Discussion

The maximum risperidone dose for TS is reported to be 6-8 mg/day, however, in clinical practice risperidone is generally used in lower doses (0.5-3 mg/day) (16). This case suggests that, in TS, higher doses may be effective and be an alternative option for non-responders to low dose risperidone.

The neurobiology of TS is still unknown. It has been suggested that TS is associated with a pathophysiological involvement of five distinct parallel frontal subcortical circuits (17). Furthermore, it has been suggested that abnormal function of basal ganglia circuits with abnormal excessive activity of multiple discrete sets of striatal neurons can produce tics (18).

Most neurotransmitters involved in frontal-subcortical circuits have been suggested to play a role in the pathobiology of TS, including the dopaminergic, gamma-amino butyric acid (GABA)-ergic, glutamatergic, cholinergic, serotonergic, noradrenergic, opioid, second messenger and cannabinoid receptor systems. Central cannabinoid CB1 receptors have been found to be located at high concentrations in the output nuclei of the basal ganglia and it has been suggested that cannabinoids regulate motor activity in the basal ganglia (19).

Dopamine-blocking drugs (neuroleptics) are considered to be the most effective agent in the treatment of tics.

In the literature, the maximum dose of risperidone in the treatment of TS was reported to be up to 6-8 mg/day (16). Our case was a patient with severe Gilles de la Tourette syndrome. Pharmacotherapy was indicated because the number of tics, their severity and frequency were hindering his daily life activities. Although high doses of multiple neuroleptics were administered, no improvement in tics number, frequency and severity was achieved.

The described case did not respond to high doses of multiple antipsychotic drugs and no improvement in tic number, frequency and severity was achieved. Additionally, he had no response to risperidone at 4 mg/day, but had improvement at higher doses of risperidone.

No increase in the number, severity and the frequency of tics, and no important side effect, except weight gain, was seen in the assessment after one year. This case demonstrates that TS cases that are non-respondent to other neuroleptics might respond to high doses of risperidone. Therefore, high dose risperidone might be administered to severe TS cases which are non-respondent to other neuroleptics.

Some studies also showed that nicotine and marijuana, when taken alone or with neuroleptics, could be efficient in TS treatment (20-22).

As risperidone dose titrated up to 8 mg/day and his tic severity improved, the patient ceased cannabis misuse. Cannabinoid receptors are found with a high density in TS-related brain regions. A possible explanation for the cannabis misuse seems to be due to this relationship.

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