CASE REPORT

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Double-Edged Sword: A Case with Withdrawal-Emergent Dyskinesia

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SUMMARY

Tardive dyskinesia is defined as involuntary athetoid or choreiform movements that develop due to the use of neuroleptic drugs for at least a few months. Tongue, lower face, jaw, upper and lower extremities are the most affected parts of the body in tardive dyskinesia. Quality of life is negatively affected because of the low remission rates. Besides tardive dyskinesia, involuntary movements may appear after discontinuation, change or a reduction in the dose of antipsychotic medications, which is called withdrawal-emergent dyskinesia (WED). Unlike tardive dyskinesia, the involuntary movements involve mainly the neck, trunk, and limbs and regress in shorter period of time in WED. A consensus has not yet been reached for the treatment of WED. Restarting the previous antipsychotic agent with slow titration or switching to an atypical antipsychotic with low affinity for dopamine D2 receptors are among the primary options for treatment. As WED is one of the predictors of tardive dyskinesia development, early detection and treatment is believed to have positive effect on the quality of life. In this report, the case of a patient followed up for bipolar disorder type I (BD-I) and started on clozapine for WED after discontinuation of haloperidol on account of adverse effects is discussed. It is necessary for clinicians to consider these types of complications when discontinuing or changing treatment. Further research is needed in order to reach a common approach for the treatment of WED.

Keywords: Withdrawal-emergent dyskinesia, haloperidol, tardive dyskinesia, adverse effect

INTRODUCTION

Tardive (late) dyskinesia is defined in DSM-5 as involuntary athetoid or choreiform movements of the tongue, lower part of the face, chin, arms or legs, secondary to the use of a neuroleptic medication for at least a few months (American Psychiatric Association-APA- 2013). Despite being a likely side effect of all antipsychotic agents, the risk of tardive dyskinesia development is known to be higher with the first generation antipsychotic agents possessing D2 receptor blockade as compared to the atypic antipsychotic agents (Kim et al. 2014).

Tardive symptoms are believed to become evident typically after 1- 2 years of exposure to agents blocking D2 receptors, but not after their use for periods shorter than 3 months (Savitt and Jankovic 2018). Advanced age, female gender, diagnosis of bipolar disorder (BD), comorbid diabetes mellitus, a history of cervical trauma, alcohol or substance abuse and a history of adverse events with previous antipsychotic therapies are other factors that increase the risk of tardive dyskinesia (Kim et al. 2014). Remission after discontinuation of the agent causing tardive dyskinesia varies. Incidences below 25% are reported in most series (Vinuela and Kang 2014).

On the other hand, DSM-5 defines the dyskinesia presenting after changing, dose alteration or stopping neuroleptic agents, as the "withdrawal-emergent dyskinesia" (WED) (APA 2013). It is proposed that the WED usually subsides within 4 to 8 weeks, while a longer lasting dyskinesia might actually be tardive dyskinesia. WED differs from the typical tardive dyskinesia in the way it is localized in the neck, trunk and the extremities. There are studies reporting WED as a subtype of tardive dyskinesia, presenting as an early neurological sign predicting the development of tardive dyskinesia (Karaş et al. 2016, Shultz et al. 1995).

Despite the consideration of WED as a predictor of tardive dyskinesia, there are not adequate data in the literature on approaches for its diagnosis and treatment.This report

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discusses the diagnosis and treatment of WED that developed after terminating treatment of BD-I with a typical antipscyhotic that caused adverse side effects. Informed consent was obtained from the patient to use the personal data for scientific use.

CASE

The 58-year-old single lyceé graduate female patient consulted the emergency unit with complaints of slowed down walking over the previous month, feeling stiffness in the whole body, tremor in the hands, dull expression of the eyes and a 1-day history of vomiting.

Information acquired from the patient, her relations and the hospital records showed a 40-year history of BD-I diagnosis, hypomania epsiodes approximately every two years, irregularity of attending follow up controls except having taken regular treatment for 2 years after a manic episode 5 years earlier. Three months before consulting the emergency services, she had been hospitalised for 2 weeks with manic episode diagnosis and discharged eutyhmic after treatment with lithium carbonate (900 mg/day), quetiapine (100 mg/day), haloperidol (20mg/day) and biperiden (4mg/day); with readjustement of haloperidol (to 15mg/day) and biperiden (to 3 mg/day) by her phyhsician 10 days after her discharge. The patient could not attend follow up controls due to lumbar hernia surgery and continued with this treatment protocol. Her psychiatric examination showed proper self care, slowed down movements, prolongation of responses to questions, euthymic mood, restricted affect, normal judgement, without active psychotic symptoms, normal sleep hygiene and loss of appetite for the last 1 day. Neurological examination showed tremor in both hands, cogwheel rigidity bilaterally in the arms and legs, bradykinesia and loss of associative movements during walking.

The results of the hemogram and the biochemical investigations were within normal limits and the blood lithium was 0.57 mmol/L. Symptomatic Parkinsonian effect of the typcial antipsychotic used was suspected and 5 mg biperiden was administered in the emergency room. Haloperidol dose was tapered for 3 days and discontinued while biperiden dose was increased to 4 mg/day, but it was discontinued in 2 weeks with the subsidence of the symptoms of parkinsonism. Five days after haloperidol therapy was stopped, her physician observed rhythmic and stereotypical involuntary movements to emerge in both legs, not causing significant discomfort and temporarily suppressed by the patient. The amplitude of the dyskinetic movements increased in the following days and the orobuccolingual region became involved. The Abnormal Involuntary Movement Scale (AIMS) examination score of the patient was 16 (lips and perioral movements: 3 points, lower extremity movements: 4 points, the severity of abnormal movements: 4 points, incapacitation due to abnormal movements: 2 points, awareness of abnormal movements: 3 points). Neurological consultation with EEG evaluation did not reveal any pathologies. Dyskinesia presenting shortly after terminating antipsychotic medication was preliminarily attributed to WED and clonazepam (1 mg/day) treatment was started . A week of regular clonazepam regimen did not improve the patient's symptoms. The patient was euthymic and clozapine (12.5 mg/day) was started with gradual titration to 175 mg/day. In approximately 2 months almost all dyskinetic movements subsided when the AIMS score was 3 (lips and perioral movements: 1 points, lower extremity movements: 1 points, the severity of abnormal movements: 1 points).

DISCUSSION

WED was first described in 1973 after observing development of choreiform movements resembling Sydenham's chorea after sudden termination of antipsychotic treatment in children on chronic use of these agents (Polizos et al. 1973). Although the pathophysiology of WED is yet unclear, the hyperdopaminergic processes in basal ganglia secondary to the termination of the medications blocking dopaminergic receptors are believed to underlie the phenomenon (Lo and Peng 2017). Another possible cause is the development of D2 receptor hypersensitivity on the nigrostriatal dopaminergic pathway similarly to that in tardive dyskinesia. The indirect reversal of the inhibition on the globus pallidus internus and subthalamic nucleus by the D2 receptor hypersensitivity is believed to result in a hyperkinetic movement disorder (Teo et al. 2012). This is attributed to the GABAergic hypofunction as well as the increase in dopamine D3 receptors (Kumar et al. 2018).

Laboratory tests and the EEG evaluation did not implicate any possible metabolic factor or epileptic activity, that may have caused dyskinesia. WED was considered since the dyskinetic movements initially involving the upper extremities emerged shortly after haloperidol treatment was terminated and were suppressed almost completely by 2 months of therapy. Despite some rare cases with tardive dyskinesia secondary to short-term antipsychotic therapy, most of which were observed in elderly patients(APA 2013), recent studies reported that the tardive syndromes negligibly emerge before 3 months (Waln and Jankovic 2013, Savitt and Jankovic 2018).

Previous reports have proposed a predictive significance of WED in tardive dyskinesia development (Kane et al. 1988, Perényi et al. 1985, Schultz et al. 1995). Therefore, timely diagnosis and proper management of WED is of utmost importance to prevent potential tardive dyskinesia following a future exposure to an antipsychotic agent. It is reported that the controlled tapering of dopamine receptor blockers reduce the risk of WED.

Despite the lack of consensus on the management of WED, resarting treatment with the slow titration of the discontinued agent or the initiation of atypical antipsychotic therapy, particularly with clozapine or quetiapine, which have a lower affinity for D2 receptors, are two commonly preferred strategies (Savitt and Jankovic 2018). A re-emerged tardive dyskinesia with re-administration of risperidone after it was stopped was previously reported and the symptoms of this case regressed once clozapine therapy was initiated with dose escalation to 250 mg/day (Mendhekar and Inamdar 2010). In the case discussed here, clozapine therapy was preferred since parkinsonism was evident following haloperidol therapy and the symptoms were suggestive of possible development of tardive dyskinesia with future antipsychotic therapies and also since the symptoms did not improve with quetiapine. With almost complete symptom subsidence after clozapine dose was titrated on a weekly basis to 175 mg/day, the therapy was maintained on this dose. Although the management of WED is currently debatable, maintenance with the initiated antipsychotic for one to three months is recommended (Chouinard and Chouinard 2008). Diagnosis of BD-I, symptoms of parkinsonism secondary to haloperidol and the presence of WED are risk factors for tardive dyskinesia in the discussed case. Within the scope of previous knowledge, it can be said that the typical antipsychotics should be avoided as much as possible in the future because of the increased risk of tardive dyskinesia. It has also been reported in the literature that glutamate receptor blockers, benzodiazepines or vitamin E can be used in tardive dyskinesia (Angus et al. 1997, Soares and McGrath 2000, Thaker et al. 1990). Some studies have concluded that WED regresses over time and does not require any specific management (Chouinard and Chouinard 2008).

It is important for clinicians to keep WED in mind while terminating antipsychotic therapies. The paucity of data on WED in the existing literature has prevented a consensus on its pathophysiological features and management. In order to arrive at definitive judgements for prevention of tardive dyskinesia development there is need for further high quality research.

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