

Case report of refractory tardive dystonia induced by olanzapine

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Summary: Tardive dystonia (TDt), a cluster of extrapyramidal symptoms that are caused by long-term use of antipsychotic medication, is characterized by difficulty in autonomic movements of skeletal (voluntary) muscles and consequent deformations of the body. TDt is rarely seen among patients taking olanzapine, but olanzapine was the precipitating antipsychotic medication in this 22-year old male patient with schizophrenia who developed lip puckering, persistent involuntary torticollis, muscular pain, axial dystonia and unstable gait after taking a standard dose of olanzapine regularly for about one year. His symptoms did not resolve after his olanzapine was stopped. Four months of treatment with clozapine combined with magnesium valproate, vitamin E, tiapride, and lorazepam did not lead to any improvement in the dystonia.

Key words: movement disorders/adverse effects, olanzapine, schizophrenia

1. Case history

A 22-year old male was admitted to our hospital in June 2013 with a 6-year history of paranoid beliefs and auditory hallucinations and a 2-year history of torticollis. Starting in 2007 the patient had trouble concentrating, developed odd behaviors and reported auditory hallucinations of others talking about him. He became paranoid and believed that people were talking behind his back. He was intensely nervous and frightened because he believed that someone was trying to frame him or kill him. The patient's family believed he was possessed, so they initially sought help from witch doctors and tried other folk remedies. But his condition continued to worsen and his social functioning became severely impaired.

He was first brought to the outpatient department of a local psychiatric hospital by family members in April 2010. At that time his physical exam was normal and he was conscious and fully orientated but he had disorganized speech and reported auditory hallucinations and persecutory and referential delusions. He was diagnosed with schizophrenia and treated with olanzapine 5 mg/d, which was increased to 10 mg/d one week later. His psychotic symptoms began to improve after two months of treatment. The dose of olanzapine was reduced to 5 mg/d in August 2010. He continued taking the olanzapine regularly (without any adjunctive medications), but in June 2011 he began to experience lip puckering, right-side torticollis, muscular pain, muscular spasms in the trunk and unstable gait. His family dismissed these symptoms as the result of intense physical labor so he continued to take olanzapine 5 mg/d regularly.

The physical impairment from the torticollis, spasms in the trunk muscles and gait instability continued to

increase so the family brought him back to the local psychiatric hospital in December 2012. At that time the olanzapine was discontinued and replaced with haloperidol (6 mg/d), trihexyphenidyl (4 mg/d), and sodium valproate (0.6 g/d). However, this change in medication did not resolve the dystonic symptoms so the patient was eventually brought to our hospital for assessment in June 2013.

On admission the patient had torticollis to the right side, axial dystonia and an abnormal gait, but was otherwise healthy with no history of severe physical diseases or allergies. His aunt had a history of mental illness, but there was no family history of tardive dystonia. Physical examination showed stable vital signs (body temperature: 37.5°C; pulse: 92/m; respiratory rate: 20/m; blood pressure: 110/70 mmHg), normal heart and lung functioning, soft abdomen, and palpable liver and spleen. Neurological examination showed no abnormal results in the cranial nerves, no muscle atrophy or weakness in the four limbs, and normal muscle tone and deep tendon reflexes. A MRI of the head revealed no abnormalities.

He was diagnosed with tardive dystonia and schizophrenia. He was treated with clozapine (starting at 12.5 mg/d and gradually increasing to 150 mg/d), magnesium valproate (sustained release tablets, 0.5 g bid), Vitamin E (1 g bid), tiapride (0.1 g bid), and lorazepam (1 mg tid). Despite taking this regimen regularly for one month as an inpatient and for a further three months as an outpatient, the TDt symptoms did not improve.

2. Discussion

Since the introduction of the first antipsychotics, there have been reports about persistent dystonia associated

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with their use. This antipsychotic-induced dystonia is considered a subtype of tardive dyskinesia. The concept of 'dystonia tarda' (subsequently called 'tardive dystonia' [TDt]) was proposed for the first time in 1973 when Keegan and Rajput reported a female patient who developed torticollis and scoliosis after taking antipsychotic medications.^[1] Currently, it is considered a condition with many clinical features that are different from tardive dyskinesia that is extremely difficult to cure. The occurrence of TDt is 2.7 to 5.3% among individuals taking antipsychotic medications.^[2] TDt can appear at any stage of treatment and any antipsychotic medication can cause TDt; the different frequency of reported TDt with different antipsychotics is probably due to the different rates of prescribing the various medications.^[2] The young male patient reported here developed lip puckering, persistent torticollis, pain, axial dystonia and unstable gait after one year of treatment with olanzapine. His symptoms, disease history, family history and physical examination were in line with the current diagnostic criteria of TDt.^[3]

Olanzapine is an atypical antipsychotic that binds to 5-tryptamine 2A receptors more than dopamine receptors and affects the mesolimbic dopamine pathway more than the nigrostriatal dopamine pathway.^[4] Reports of olanzapine-induced TDt are rare. Searches of the China Journal Full-text Database (CNKI) and the Wanfang Database using keywords 'olanzapine' and 'tardive dystonia' identified no report about tardive dystonia induced by olanzapine. A similar search of Pubmed only identified nine case reports of olanzapine-induced TDt: Aggarwal and colleagues^[4] report on a 17-year-old female with schizophrenia who developed symptoms of TDt after 15 months of treatment with olanzapine; Charfi and colleagues^[5] report on a 17-year-old female with schizophrenia who manifested TDt symptoms after nine months of treatment with olanzapine; Singh and colleagues^[6] reported on a case of TDt after using a single 10 mg dose of olanzapine; Aggarwal and colleagues^[7] report on a case of delayed Meige syndrome (a combination of blepharospasm and oromandibular dystonia) after long-term usage of olanzapine; and Praharaj and colleagues^[8] report on a young male patient who developed delayed oculogyric crisis following the use of olanzapine.

The pathological and physiological mechanism of olanzapine-induced TDt is not clear. Trugman and colleagues^[9] considered the sensitization of the D₁-mediated striatal output after repetitive stimulation of the D₁ receptor by endogenous dopamine the fundamental mechanism of TDt. According to this theory, olanzapine may cause TDt by persistent inhibition of dopamine neurotransmitters leading to overly sensitive postsynaptic dopamine receptors.^[10]

When treating patients with antipsychotic-induced TDt the first step is to change the current antipsychotic to another atypical antipsychotic. Clozapine should be tried first^[5]; quetiapine and aripiprazole can then be tried. If the dystonic symptoms are serious, high dose anticholinergic agents (such as trihexyphenidyl at doses of 20 mg/d or higher) should be considered^[11] (especially among young patients) because this would deplete the excess of presynaptic dopamine; but this approach should not be used if symptoms of tardive dyskinesia

are also present because anticholinergic agents can worsen these symptoms. There has been a report of TDt successfully treated by tetrabenazine.^[12] There are also reports about the effectiveness of benzodiazepines such as diazepam, clonazepam or lorazepam.^[13] Bhattacharjee and colleagues reported a case of olanzapine-induced TDt effectively treated by carbamazepine.^[14] For TDt with only localized or mild symptoms, botulinum toxin A can be considered. For severe refractory axial dystonia, continuous intrathecal baclofen injection is considered the treatment of last resort,^[16] but there is only limited evidence of the clinical effectiveness of this treatment. There have also been several case reports on using electroconvulsive therapy^[17] and transcranial magnetic stimulation^[18] to treat TDt; however, the evidence supporting these treatments is limited.

In the current case, the patient's family members failed to recognize the importance of the dystonia symptoms, so it took 18 months before his dystonic symptoms were first evaluated by a medical professional. The initial treatment for the dystonia (changing olanzapine to haloperidol) at the local hospital was probably not helpful (haloperidol can induce myotonic dystrophy syndrome^[19]). By the time the dystonia was seen at our hospital it had already persisted for two years. We treated the patient's refractory tardive dystonia with clozapine, magnesium valproate, vitamin E, tiapride, and lorazepam, but four months of treatment did not result in any improvement in the symptoms. The patient remains severely disabled by these symptoms so further more aggressive measures will need to be attempted, but the long-term prognosis for the patient remains guarded.

There is no guarantee that earlier recognition and treatment of the tardive dystonia in this patient or in other patients with antipsychotic-induced TDt would improve their eventual outcome. Most reports indicate that the TDt symptoms persist after patients stop taking antipsychotics.^[20] Further research is needed to identify effective treatments for TDt. Nevertheless, the severe disability associated with this uncommon side-effect makes it imperative that patients, their family members, and all clinicians who prescribe antipsychotic medications be well informed about this potential side effect and the need to urgently seek treatment when dystonic symptoms occur. Family education is particularly important in rural settings where the intervals between follow-up medical visits for medicated psychiatric patients can be several months. Clinicians who prescribe antipsychotic medication must carefully monitor extrapyramidal symptoms at every follow-up visit and keep up-to-date on the best methods for dealing with this severe adverse reaction.

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Conflict of interest

The authors report no conflict of interest related to this manuscript.

奥氮平所致难治性迟发性肌张力障碍 1 例

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摘要: 迟发性肌张力障碍是长期使用抗精神病药物所致的一系列锥体外系症状, 主要特征包括骨骼肌肉(随意肌)自主运动困难和随后的躯体变形。迟发性肌张力障碍在服用奥氮平患者中罕见, 但本文报道中奥氮平正是这名 22 岁男性精神分裂症患者的促发抗精神病药物, 他坚持服用标准剂量的奥氮平大约 1 年后出现撅嘴、持续不自主斜颈、肌肉疼痛、轴向肌张力障碍

和步态不稳的症状。停用奥氮平后, 他的症状没有缓解。奥氮平合并丙戊酸镁、维生素 E、硫必利和劳拉西泮治疗四个月也没有让肌张力障碍得到任何改善。

关键词: 运动障碍 / 不良反应, 奥氮平, 精神分裂症

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