

Review Article

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**Progress in diagnosis and treatment of
delayed movement disorder**Qiang Xiong^{1*}; Yingchan Wang²¹Shanghai Songjiang Mental Health Center, No. 209 Tahui Road, Songjiang District, Shanghai, 201617, China.²Shanghai Mental Health Center, 600 Wanping South Road, Xuhui District, Shanghai, China.***Corresponding Author: Qiang Xiong**Shanghai Songjiang Mental Health Center, No. 209
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Abstract

Delayed movement disorder is an involuntary movement syndrome after long-term use of antipsychotic drugs, and also a serious adverse drug reaction. The treatment of delayed movement disorder has been an important issue. How to carry out related prevention is directly related to the vital interests of patients. This article reviews the etiology, pathogenesis, clinical features, diagnosis and treatment of tardive dyskinesia.

Keywords: delayed movement disorder; diagnosis; treatment.**Introduction**

Tardive dyskinesia (TD) is a common abnormal involuntary movement disorder in psychiatric clinic, mainly manifested as various involuntary movements or dystonia in the face, limbs and body parts. According to a Meta-analysis by Correll et al., the incidence of TD taking classic antipsychotics was 7.7%, and the prevalence was 32.4%. The results of Fei et al. in China showed that the TD occurrence rate of patients within five years of hospitalization was 23.7%, that of patients within five to ten years of hospitalization was 37.4%, and that of patients over ten years of hospitalization was 46%, with severe symptoms. Therefore, it is of great significance to seek the pathogenesis and effective intervention methods of TD for alleviating the pain and economic burden of patients with mental disorders, improving the daily living function of patients and returning to society. This article reviews the clinical features, diagnosis and differential diagnosis, pathogenesis, risk factors and treatment progress of TD.

Clinical features

TD belongs to a special extrapyramidal adverse reaction, most of which are abnormal involuntary movement syndrome

after long-term use of antipsychotic drugs, and can also occur during drug reduction and withdrawal. Women are more than men in clinical practice. It is generally believed that the older the age, the higher the incidence. Elderly patients, physical diseases, brain damage and combined anticholinergic drugs are risk factors. The clinical features are mainly characterized by oral movement, which is manifested as involuntary movement of mouth, lip, tongue and face, such as sucking, extending tongue, turning tongue, chewing, licking tongue, pursing mouth, bulging cheek, and tongue extending out of mouth (fly-catcher tongue). Severe patients may have unclear articulation and dysphagia. Some patients may have limb involuntary swing, trunk or limbs dance or finger-like movements. Occasionally gastrointestinal type, manifested as long-term use of antipsychotic drugs in patients with sudden withdrawal of stomach discomfort, nausea and vomiting, emotional tension, increased symptoms when excited, sleep disappeared.

Diagnosis and differential diagnosis

In 1982 Schooler NR et al. put forward the diagnostic criteria for TD as follows :

1. There is a slow occurrence of abnormal involuntary

movement, at least one part of the body moderate and above or at least two parts of the body mild and above abnormal involuntary movement

2. At least three months of intermittent or uninterrupted medication history, or when the sedative is discontinued.
3. Exclude other possible pathogenic factors, duration of more than 3 months. At present, there is no unified diagnostic standard for TD in clinic. Generally, the diagnosis of TD is mainly based on the patient's history of using antipsychotic drugs, the presence of corresponding clinical manifestations, and the exclusion of other diseases with similar clinical manifestations.

TD should be differentiated from drug-induced Parkinson's syndrome, Huntington's disease (HD), small dance disease, Meige syndrome and other dystonia diseases.

1. Drug-induced Parkinson 's syndrome: Since dopamine receptor is occupied or blocked by antipsychotics, endogenous dopamine cannot bind to dopamine receptor, showing clinical features such as tremor, hypermyotonia, akinesia and oculomotor crisis, which can be distinguished from TD.
2. Dance disease (Huntington disease, HD): According to the three main characteristics of family genetic history, dance disease and dementia, it is not difficult to distinguish from TD. Patients with HD also often use antipsychotic drugs. If there is no sedentary or repeated rigid involuntary movement, it is suggested that TD is complicated.
3. Small dance disease: Small dance disease caused by rheumatic fever is more common in children, and can be accompanied by other manifestations of rheumatic fever such as arthritis and myocarditis; small dance diseases caused by cerebrovascular diseases often occur suddenly. Dance symptoms are often confined to one side, or accompanied by hemiplegia symptoms, which can be identified by head CT. The most important thing is that the disease has no history of taking antipsychotic drugs and can be distinguished from TD.
4. Meige syndrome: TD patients with tongue chewing syndrome as the main manifestation need to be differentiated from Meige syndrome. Meige syndrome is a common oral movement disorder, complete detoxification, mandibular muscle tension disorder, and eyelid spasm. Incomplete type only oral, tongue, pharynx and mandibular muscle tension disorder, or only primary eyelid spasm. The patient has no history of taking antipsychotics and can be distinguished from TD.
5. Others: If TD patients with dystonia as the main manifestation should be differentiated from torsional spasm and Wilson disease, TD patients with tic as the main manifestation should be differentiated from tic-tourette syndrome.

Pathogenesis and risk factors

At present, the etiology and pathogenesis of TD have not been clarified. The dopamine receptor hypersensitivity hypothesis, which is dominant in the etiology of TD, believes that TD is mainly related to the compensatory increase of DA

sensitivity caused by the long-term continuous blockage of DA receptors in the postsynaptic membrane by antipsychotic drugs. Due to the striatal dopaminergic neurotransmission function, the inhibition of cholinergic nervous system is enhanced, resulting in the relative balance between the two is broken, and a series of involuntary movements characterized by excessive exercise appear. But the hypothesis remains limited. Not only antipsychotics, but all drugs that may block the DA receptor may induce TD, especially non-psychotics, such as metoclopramide (metoclopramide). The situation of TD induction is often ignored in clinical practice, and the occurrence rate of TD induced by this drug is currently estimated to be between <1% and 30%. However, the original symptoms of patients with TD did not worsen when DA agonists were applied, and neurobiochemical studies did not find a clear correlation between the excessive DA receptor activity after striatum synapse and the long-term persistence of TD, which made the hypothesis questioned. In addition, there are also theoretical hypotheses in TD etiology, such as D1D2 receptor imbalance hypothesis, choline deficiency hypothesis, GABA depletion hypothesis, neurotoxicity damage, synaptic plasticity change, and neuropeptide change. However, no satisfactory explanation has been made for the pathogenesis of TD, and no direct evidence supporting the hypothesis has been obtained. The corresponding clinical research results also have contradictions.

The risk factors for TD, it is generally believed that the older the higher the incidence of TD, women than men, especially postmenopausal women. Other risk factors include race, diabetes and other physical diseases as well as brain damage, alcohol and drug abuse, previous movement disorders, early onset of acute extrapyramidal reactions or drug-induced Parkinson 's disease may increase the risk of TD [9-13]. The risk factors associated with treatment include long-term exposure, unreasonable high-dose medication and combination of lithium or anticholinergic drugs [14,15].

Treatment

Drug therapy

In the 1990s and the beginning of the 21st century, the second-generation antipsychotics (SGA) were widely used in clinical practice, and largely replaced the first generation of drugs. At the same time, they were also widely used in adjuvant treatment of refractory depression, Alzheimer's disease and other diseases. Existing clinical data show that the risk of extrapyramidal side effects (including TD) is relatively small compared to the first generation of drugs, so the application of SGA was once considered promising for eventual elimination of TD. However, a recent control study showed that the prevalence of TD in SGA was 13%, which was significantly lower than 32% of the first generation of drugs, but this result showed that TD would still be a problem [2]. However, another study of long-term hospitalized patients between 2003 and 2007 found that the incidence of TD in SGA was 28 %, similar to the first generation of drugs [16]. Among the 12 papers published recently, the annual incidence rates of SGA and FGA are 3.9 % and 5.5%, respectively [2] and other studies have not found significant differences in the incidence rates between them [16-19].

Due to the unclear pathological mechanism of TD, there is no specific drug treatment for TD, and the key is prevention. Benzodiazepines such as diazepam and clonazepam can enhance GABA function. Antioxidants such as vitamin E are considered to inhibit free radical production. In addition, a variety of exploratory treatments for TD, including resveratrol, botulinum toxin, ginkgo biloba, butylphthalide, melatonin, unsaturated fatty acids (Omega-3), zonisamide, levetiracetam, branched-chain amino acids, drug combinations, etc., have not been approved by the US Food and Drug Administration for the treatment of TD. Soares et al. found that bromocriptine, clonidine, estrogen, γ -linolenic acid, hydergine, licithin, lithium, progabide and selegiline were not superior to the control group in the treatment of TD. However, L-dopa, Tapride, Oxypertine, VitE, reserpine and insulin were slightly better than those in the control group. There is evidence that anticholinergic drugs can improve extrapyramidal reactions, such as acute dystonia, akathisia. Some studies have shown that [24-26] anticholinergic drugs may lead to delayed exercise.

Physical therapy

Deep brain stimulation (DBS)

DBS is an effective treatment for refractory dyskinesia and has been approved by the US Food and Drug Administration for the treatment of dystonia. It is also reported to be effective for patients with TD [27,28]. There are many reports that DBS in the medial pallidus is effective in the treatment of TD, and a few believe that thalamus and thalamus bottom stimulation are effective. Michaplan Sobstyl et al. reported that 59 patients with TD were treated with DBS in 19 articles, of which 55 cases acted on the pallidus and 4 cases acted on the hypothalamus. The literature analysis showed that the score of most patients with dystonia rating scale (BFMDRS) was increased by more than 80%. The literature believed that DBS acting on bilateral pallidus was an effective treatment for TD, with rapid effect, and it could be effective in a few days/week. The curative effect was equivalent to that of primary dystonia. Cloud LJ et al. believe DBS treatment for TD can last months or years. In a systematic review of 88 reports and 17 studies involving 50 patients with DBS in the treatment of dystonia, the average improvement rate of patients reached 77.5%. The study suggests that DBS is a relatively safe and effective treatment for refractory dystonia.

Transcranial magnetic stimulation (TMS)

It was initiated by Barker in 1985 as a noninvasive, safe, non-invasive and simple physical therapy. Repeated transcranial magnetic stimulation (rTMS) is a commonly used TMS treatment method. According to the stimulation frequency rTMS, it can be divided into high-frequency stimulation (≥ 3 -5 Hz) and low-frequency stimulation (≤ 1 Hz). The former is considered to be able to facilitate local neuronal activity and improve the excitability of stimulating brain area. The latter is considered to inhibit local neuronal activity and reduce the excitability of stimulating brain area. Current studies have shown that rTMS also affects the function of various neurotransmitters such as dopamine (DA), 5-hydroxytryptamine (5-HT), glutamate, NMDA and their receptors in the brain. Keck observed the physiological changes after TMS stimulation in the prefrontal cortex of rats, and speculated that stimulation changed the neural connection between the prefrontal cortex and the substantia nigra and the ventral tegmental side, increased the activity of axon terminals of hippocampal DA neurons and increased the release of

hippocampal DA. Strafella [34,35] found through PET that high-frequency rTMS stimulation could induce the release of DA in ipsilateral caudate nucleus and anterior cingulate gyrus (ACC). These effects all showed that rTMS might regulate the dopamine function of the midbrain marginal system through the cortical striatum pathway, thus playing a therapeutic role in TD. In recent years, rTMS has shown potential benefits in the treatment of motor disorders. Existing small sample clinical studies at home and abroad show that rTMS may have a therapeutic effect on TD [36,37]. However, these studies generally have some shortcomings, such as small sample size, no control group, short observation time, and no in-depth discussion on the related mechanism of TMS in the diagnosis and treatment of TD.

Electroconvulsive therapy (ECT)

Very few studies have reported that ECT is effective in the treatment of TD [38,39]. Yasui-Furukori et al. used ECT to treat 18 patients with TD, 3 times a week for the first 5 weeks and 2 times a week for the 6th to 15th weeks. The abnormal involuntary movement scale (AIMS) was used to assess the efficacy, and a 50% reduction was set as effective. After treatment, the average target score of 18 patients decreased from (19.1 ± 4.7) to (9.6 ± 4.2) , and seven patients responded, with the response rate of 39%. This study suggests that ECT has a mild and obvious effect on late-onset dystonia and dyskinesia.

Conclusion

Delayed motor disorder has seriously affected the quality of life of patients and has become an important obstacle for patients with chronic mental disorder to return to society. As a common adverse drug reaction of antipsychotics, the pathogenesis of TD is still unclear. Although effective methods have been sought for the treatment of TD at home and abroad, the existing drugs have not shown obvious curative effect on TD. Some literature proposed the treatment strategy of TD: firstly, the currently used antipsychotics were reduced or discontinued (or replaced with a new generation of antipsychotics). If the efficacy was not good, antioxidants and other drugs could be selected, and then physical therapy or neurosurgical intervention should be considered. However, due to the lack of strong evidence to support the effectiveness of these treatments for TD, the importance of prevention for TD treatment is still emphasized: the key is to limit the prescription dose of antipsychotic drugs, regularly assess the side effects and inform patients and their families of the risks of TD.

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