Update Treatment of Tourette's syndrome

［Abstract］

Tourette is a chronic neuropsychiatric disorder affect children with normal learningjiving, social interaction. Treatment were divided into two categories,including drug treatment and non-drug treatment, and mainly drug treatment.This paper literature on treatment are reviewed.

Object: To study the way of the treatment of children with tourette syndrome.

Method: Collected 17 references in English byA retrospective in internet of reviewing the new treatment methods .

Results: Treatment were divided into two categories,including drug treatment and non-drug treatment, and mainly drug treatment.

Conclusion: The two categories of therapy has different curative effects and needs to be selected according to the actual clinica situation ofpatients **.**

［Key words］ Tourette syndrome; Child; Nervous ;treatment;

BACKGROUND :

Tourette syndrome, characterized by phonic and motor tics, is a neurodevelopmental disorder that significantly affects the quality of life of people with the condition. With over 1500 articles published in the last decade .,tourette syndrome (TS), also known as Tourette syndrome or "Tourette syndrome", is a syndrome characterized by multiple involuntary tic, speech or behavior disorders. The disease usually occurs at the age of 3-15 years, with more males than females, with a ratio of (3-4) : 1 Although some scholars have studied some risk factors as factors of Tourette's disease, the specific cause of Tourette's disease is unknown at present,but Role of histidine decarboxylase gene in the pathogenesis of Tourette syndrome. Histidine decarboxylase (HDC) mutation is a rare genetic cause with high penetrance in patients with TS. HDC-knockout (KO) mice have similar behavioral and neurochemical abnormalities as patients with TS.[1]

Tourette syndrome is a common neurodevelopmental disorder in children. About 90% of children are combined with neuropsychiatric disorders, the most common of which are OCD and ADHDO. Although the pathogenesis of TS is still unclear, the treatment of TS has become mature. Children with mild TS may only need psychological and behavioral intervention. A large number of studies support the application of habit reversal training as an alternative or auxiliary treatment for some children with TS. However, the vast majority of children still need medical treatment to relieve their tics and related behavior disorders. Classic TS treatment drugs include Tepilide, fluepislebore, pimozide, risperidone, clonidine, etc. Due to poor efficacy or serious adverse reactions, alipetic, atamoxetine, immune agents, etc., have been gradually tried, and significant efficacy has been achieved in some studies [18-20]. However, both old and new drugs inevitably have adverse reactions, which will inevitably affect the compliance of children and seriously affect the clinical efficacy. How to enhance the clinical efficacy while minimizing the serious adverse reactions of drugs is the focus of current research. Traditional Chinese medicine in the treatment of TS has the characteristics of overall regulation, safety and effectiveness, and recurrence rate, which cannot be ignored, but it is still in the preliminary exploration stage. At present, large-scale, multicenter,

randomized, double-blind and controlled studies should be conducted more widely to explore the rules of syndrome differentiation and treatment of TS, so as to provide a solid scientific basis for the treatment strategy of TS. Treatments are symptomatic, not curative; they consist of long-term treatment, to be taken regularly over periods of at least several months, often years; the goals set must be realistic, with a desired reduction in tics of 30–50% as a rule of thumb. Otherwise, self-medication and overmedication may be observed; nevertheless, especially in children and adolescents, a reduction or even interruption of treatment once a year, usually during summer vacation, may be considered in order to assess the basal state of the syndrome and subsequently decide.

Treatment

1 Psychobehavioral Therapy

Tourette syndrome is a common neurodevelopmental disorder in children. About 90% of children are combined with neuropsychiatric disorders, the most common of which are OCD and ADHDO. Although the pathogenesis of TS is still unclear,Recent findings suggest that TS is likely due to a combination of several different genes and environmental factors[16]. the treatment of TS has become mature. Children with mild TS may only need psychological and behavioral intervention. A large number of studies support the application of habit reversal training as an alternative or auxiliary treatment for some children with TS. Their recognition is paramount for the introduction of efficient treatment strategies to promote healthy development and good quality of life[15].However, the vast majority of children still need medical treatment to relieve their tics and related behavior disorders. Classic TS treatment drugs include Tepilide, fluepislebore, pimozide, risperidone, clonidine, etc. Due to poor efficacy or serious adverse reactions, alipetic, atamoxetine, immune agents, etc., have been gradually tried, and significant efficacy has been achieved in some studies. However, both old and new drugs inevitably have adverse reactions, which will inevitably affect the compliance of children and seriously affect the clinical efficacy. How to enhance the clinical efficacy while minimizing the serious adverse reactions of drugs is the focus of current research. Traditional Chinese medicine in the treatment of TS has the characteristics of overall regulation, safety and effectiveness, and recurrence rate, which cannot be ignored, but it is still in the preliminary exploration stage. At present, large-scale, multicenter, randomized, double-blind and controlled studies should be conducted more widely to explore the rules of syndrome differentiation and treatment of TS, so as to provide a solid scientific basis for the treatment strategy of TS. Treatments are symptomatic, not curative; they consist of long-term treatment, to be taken regularly over periods of at least several months, often years; the goals set must be realistic, with a desired reduction in tics of 30–50% as a rule of thumb. Otherwise, self-medication and overmedication may be observed; nevertheless, especially in children and adolescents, a reduction or even interruption of treatment once a year, usually during summer vacation, may be considered in order to assess the basal state of the syndrome and subsequently decide.

We discuss the most recent evidence to support behavioural/psychosocial, pharmacological and surgical interventions in patients with tics and summarize existing recommendations about treatment selection.[14]

1.1 Habit Reversal Training

There is also habit reversal training. It is the most widely studied behavior therapy method at present. It mainly enhances children's self-awareness of tic attacks through a series of methods, such as description of tic response, detection response, early warning process and situational awareness training, and then learns to use certain competitive actions to interrupt or inhibit tic attacks. Habit reversal training may also include

relaxation training, mutation management, and general training. A large number of studies have shown that habit reversal training combined with or without drug therapy can effectively relieve the lobar onset of TS motor tics and vocal tics in adults or children [12]. However, the large-scale application of habit reversal training is limited due to the need to obtain the informed consent of the families of the affected children, the lack of professionally trained physiotherapists and adequate insurance coverage.

1.2 Biofeedback and transcranial magnetic stimulation

It is often used in the treatment of ADHD, anxiety disorders and Tourette's. Doctors placed multiple electrodes on the child's head to record the rhythm changes of the brain's bioelectricity. At the same time, specialized computer equipment converts information about changes in the rhythm of brain currents into cartoon animations that can be displayed on a fluorescent screen. When children's attention is focused, brain waves adjust to a better state, there will be a cartoon character shooting a successful animation. With this kind of reward method, can make the children intuitively feel their own brain current, experience and remember the "shot successful" when their state, so as to achieve the therapeutic effect.
transcranial magnetic stimulation (TMS) can be used to treat Tourette Syndrome (TS), little research exists to support this assertion. This meta-analysis examined the effcacy of TMS to reduce tic severity in Tourette Syndrome .
All studies included were required to be a randomized controlled trial, compare TMS toasham condition,and (3)haveall participantsmeetdiagnostic criteriafor apersistent tic disorder and/or TS. A random effects model meta-analysis examined the effcacy of using TMS to reduce tic severity and explored the effect of TMS to reduce premonitory urge severity. TMS did not signifcantly reduce tic severity but a moderate reduction in premonitory urge severity was found Trials with larger sample sizes and a preponderance of women were found to have greater therapeutic effects of TMS for tic severity. There is limited support for the use of TMS to reduce tic severity, though reductions in premonitory urge severity were observed. Major limitations of the existing literature are examined, with a call for research investigating newer TMS protocols and their use as a treatment augmentation strategy.

1.3 Dietary Adjustment

Strengthen nutrition, avoid the use of food additives, pigments, caffeine and other food, such as food can induce or aggravate twitch symptoms.

1.4 Other treatments

Acupuncture, immunotherapy, deep brain stimulation, transcranial magnetic stimulation and surgical treatment have been tried to treat the disease.

2.Drug Therapy

2.1 Dopamine receptor blockers

Neuroanatomical and neuroimaging studies suggest that frontal cortical-basal ganglia circuit disorders, especially dopaminergic neurotransmitter system and serotonin system dysfunction, play an important role in the pathogenesis of TS. Long-term randomized, double-blind, placebo-matched studies have confirmed that classical dopamine (D2) blockers fluopectlebore and pimozide can significantly reduce the frequency of convulsions in children with TS. The effective rate of treatment with fluopectlebore 2-20 mg/d or pimozide 2-48 mg/d can be up to 80% [2], but the adverse

reactions are large. For example, extrapyramidal reactions, lethargy, and cognitive bluntness, many patients stop taking the drug during the course of treatment. Currently, low-dose long-term therapy is generally used in clinical practice, such as fluopectlebore 1-4 mg/d and pimozide 2-8 mg/d.

Typilide is a benzamide derivative that selectively blocks basal ganglia dopamine receptors [3,13]. In a prospective study of 69 children with TS aged 4-16 years, Zheng Yabing et al., showed that compared with haloperidol, the adverse reactions of TS in the treatment of children with TS were fewer and less severe, and the patients' compliance was better, and there was no significant difference in the efficacy. However, Beiyan Wu et al. reported that the efficacy of Tiride was not as good as haloperidol, and its clinical efficacy still needed further observation.

Aripetic dopamine system stabilizers are novel atypical antipsychotics with high affinity to dopamine D2, D3, 5-HT1A, and 5-HT2A receptors, so they play a particularly important role in the treatment of TS. A prospective multicentered controlled study of 195 children with TS aged 5-17 years in China showed that the YGTSS (yale global tic severity scale) score of TS children was significantly improved after 12 weeks of aripiperol treatment (5-25 mg/d). The clinical efficacy and incidence of adverse reactions were similar to those of Tipilide (100-500 mg/d) [4]. LMurphy et al. Retrospective analysis of 6 patients aged 8-19 years with TS complicated with OCD showed that aripiperol was treated with 5-20 mg/d After 12 weeks, the YGTSS score and C-YBOCS score decreased by 56% and 71%, respectively. Meanwhile, Winter et al. reported that a female patient with TS and OCD was treated with oral aripebi (5-7.5 mg/d) for only 2 weeks, and her tic and OCD symptoms were significantly relieved. In the study of 7 patients with refractory TS (refractory to other antipsychotics or unable to tolerate severe adverse drug reactions), Frolich et al. found that aripebi 5-30 mg/d for 8 weeks could significantly alleviate motor and vocal tic seizures in children, but had no significant effect on OCD and ADHD. It has been reported that the common side effects of Aripebi are drowsiness, weight gain, inability to sit still, headache and vomiting. About 20.7% to 25.0% of patients discontinue treatment because they cannot tolerate the medication. The clinical efficacy and drug tolerance of Aripebi in TS with OCD and especially refractory TS need to be further discussed. In a randomized, double-blind, placebo-controlled study, Jankovic et al. found that Topivate was effective in the treatment of moderate to severe Tourette's disease, but the principle of Topivate in the treatment of Tourette's disease is not very clear.

2.2 Monoaminergic Antagonists

Selective monoaminergic antagonists such as risperidone, clozapine, olanzapine, and zilapidone are also effective in treating TS. Currently the most widely research of risperidone, it can simultaneously antagonism serotonin 5 - HT2 receptors and dopamine D2 receptors, a large number of studies have shown It can significantly reduce TS patients with different age twitch, curative effect is similar or even better than fluorine sent several alcohols, horse mo qi, especially for TS with anxiety, depression, OCD [5-6] heart 1. Randomized, double-blind, placebo-controlled studies and open experimental studies have shown that chilapidone can effectively treat TS in children and adolescents without adverse effects of weight gain. However, it is worth noting that Scahill et al. reported that a patient with TS died suddenly during clinical trial treatment with zirapperidone, and its safety and tolerability need to be investigated with a large sample. Clinical application of this drug should be cautious, close observation and monitoring of patients with discomfort.

2.3 Levetiracetam

Levetiracetam is a pirolidine derivative whose chemical structure has no correlation with existing antiepileptic drugs. In vitro and in vivo tests showed that levetiracetam inhibited epileptiform burst discharges in hippocampus, but had no effect on the excitability of normal neurons, suggesting that levetiracetam may selectively inhibit the

hypersynchrone of epileptiform burst discharges and the propagation of seizures. A prospective open study showed that 72% of children with Tourette's disease responded to treatment after 12 weeks of levetiracetam. However, levetiracetam does not directly facilitate GABAergic neurotransmission, but has been shown to have adverse effects on GABA and glycine-gated current negative regulator activity in cultured neurons.

2.4 Norepinephrine

In addition to dopamine and serotonin neurotransmitter systems, other neurotransmitter systems such as cholinergic, noradrenergic, glutamatergic, aminobutyric acid neurotransmitter system imbalance may also be involved in the pathogenesis of TS. Some scholars believe that decreased dopamine and increased norepinephrine in the central nervous system may be associated with ADHD-related pores in TS patients [7], which provides a theoretical basis for the treatment of TS patients with ADHD. Clonidine is a mesoaxis a2 adrenergic blocker, available in oral tablets and percutaneous patches, which reduces norepinephrine activity in the central nervous system. Clonidine has been used in the treatment of TS since 1980, but its clinical efficacy is still controversial. Attomoxetine, a selective norepinephrine reuptake inhibitor, has been shown to be effective in children and adolescents with ADHD in multiple randomized, double-blind, placebo-controlled studies. Spencer TJ [8]and others lost in a prospective study on 117 children aged 7-17 years with TS complicated with ADHD showed that atomoxetine can significantly improve the symptoms of ADHD in children and reduce their tic attacks. During the treatment, adverse reactions such as rapid pulse, nausea, anorexia and weight loss were observed. Moreover, some studies have reported that some children with TS suffer from exacerbation of tics and disease recurrence after treatment with atoroxetine. At the same time, the authors should also be aware of the limitations of the efficacy studies of atoroxetine. Children with severe TS (severe tic or ADHD) may not be included in double-blind, placebo-controlled trials because of the high rate of drug withdrawal [9]. Patients with TS and ADHD who are well controlled with other medications may participate in such studies only if they cannot tolerate current treatment. As a clinical drug for the treatment of children with TS complicated with ADHD, the general safety and efficacy of atoroxetine in the population still need to be explored by large sample control.

3. Anti-inflammatory and immunoregulatory therapy

The pathogenesis of TS is still unclear. Studies have shown that immune dysfunction or inflammatory response may be involved in the pathogenesis of TS. Some studies have reported that celecoxib, a COX-2 inhibitor, combined with antibiotics can significantly improve tic seizures and behavior disorders in TS patients [10]. Zykov et al. treated 7 children with TS who had failed to respond to long-term antipsychotics. After immunomodulatory therapy (intravenous propyl globulin), the symptoms of motor twitch, vocal twitch and behavior disorder were significantly improved, and the remission was maintained for more than 6 months. These meaningful but very preliminary results need further controlled studies.

4. Magnesium sulfate and vitamin B6

Approved by the Council of the Government of Andalusia, Spain, Spanish pediatricians and medical experts conducted a randomized, double-blind placebo study of magnesium sulfate 0.5 mg/ (kg • d) and vitamin B62mg/ (kg-d) (nK) in children aged 7-14 years with tic according to DSM-IV criteria (307.23) and clinical data and YGTSS (Yale Scale) The efficacy and safety of magnesium sulfate and vitamin b6 were investigated, and the results suggested that the new treatment could improve and control seizures and help reduce side effects.

5 Remote therapy

Kareem Khan et al. digital therapy is implemented as a widely accessible first-line treatment using a purely online or therapist supported approach.

Digital technology evolves at a rapid pace meaning that as technology changes and interfaces

are updated it cannot be certain that a program that was efficacious five or ten years ago would be equally efficacious today. Although RCTs are still the gold standard for which to assess the efficacy of DHIs.

It could provide immediate access to these treatments for those who otherwise would not have access due to long waiting lists or their geographical location, which could also potentially free up existing resources and services for those requiring more complex treatment and assessment. Thus,cutting costs and waiting times would be a two-fold benefit for healthcare services and patients alike. There is a need to conduct more robust research in this domain but also an urgency to implement a digital intervention for children with tic disorders in real-world settings [11].

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