Progress in the treatment of Tourette syndrome

［Abstract］

Tourette Syndrome, a persistent neuropsychiatric condition predominantly encountered in childhood, significantly influences an individual's behavior, social engagement, and daily life activities. Current therapeutic strategies for managing Tourette Syndrome can broadly be classified into two primary categories: (1) pharmacological interventions, relying on medication, and (2) non-pharmacological approaches, which do not involve drug usage. This paper aims to delve into the existing literature on both these treatment modalities, with a primary emphasis on providing updated insights into pharmacological interventions.

Object: To investigate the methodology of treating children with Tourette Syndrome.

Method: Collected 19 English references through a retrospective review of new treatment methods on the internet.

Results: Treatments are divided into two categories: drug treatment and non-drug treatment, with drug treatment being the primary focus.

Conclusion: The two categories of therapy have different curative effects and must be chosen in accordance with the actual clinical situation of patients.

［Key words］ Tourettesyndrome; Child; Nervous ;treatment;

Introduction :

Tourette Syndrome, a disorder characterized by irresistible and uncontrollable spasms in speech and motor movements, significantly impairs the quality of life of individuals. Impressively, over 1,500 articles have been published in the past decade regarding this complex condition! Tourette Syndrome (TS), alternatively known as simply Tourette Syndrome, is a neurological disorder distinguished by the presence of multiple involuntary tics, as well as potential speech or behavioral disorders. It typically manifests within the age range of 3 to 15 years, affecting males more frequently than females at a ratio of approximately 3 to 4 to 1.Despite the efforts of researchers to identify potential risk factors and triggers for Tourette's disease, the precise cause remains elusive. However, there is growing interest in the role of the histidine decarboxylase (HDC) gene in the pathogenesis of TS. Mutations in the HDC gene represent a rare genetic anomaly that has been found to have a high penetrance in TS patients. Furthermore, HDC knockout (KO) mice have been observed to exhibit behavioral and neurochemical abnormalities that are similar to those seen in

TS patients. [1]

Developmental disorder, which affects roughly 92.5% of children in conjunction with neurological and psychiatric disorders, notably obsessive-compulsive disorder and ADHD, has garnered significant attention. Although the precise etiology of Tourette Syndrome (TS) remains elusive, its treatment modalities are well-established. Mild cases may necessitate solely psychological and behavioral interventions. Multiple studies have validated habit reversal training as a viable standalone or adjunctive therapeutic approach for select TS patients. However, the majority of children still rely on pharmacological management to control their tics and associated behavioral challenges. Commonly prescribed medications for TS encompass morphopeptides, sodium fluorophosphate, pimozide, risperidone, clonidine, among others. Despite their proven effectiveness, drugs such as Diazepam, Atamoxetine, and immunotherapy have undergone trials due to adverse reactions, with some studies yielding promising outcomes [18-20]. Nonetheless, all medications pose potential side effects, which can impact patient adherence and clinical outcomes.

The current research focus aims to augment clinical efficacy while mitigating drug-related adverse effects. Traditional Chinese medicine offers a holistic, safe, and effective approach to TS treatment, albeit in its nascent stage. Large-scale, multicenter, randomized, double-blind, controlled studies are imperative to elucidate TS syndrome differentiation and treatment principles, thereby furnishing a robust scientific basis for therapeutic strategies. Treatment is symptom-driven, necessitating long-term commitment, often spanning several months to years. Setting realistic goals, aiming for a 30-50% reduction in symptoms, is paramount. Vigilance against self-medication and overmedication, especially among children and adolescents, is crucial. An annual treatment evaluation, typically scheduled during summer holidays, facilitates an assessment of the syndrome's baseline status and informs future treatment decisions.

Treatment

1 PsychobehavioralTherapy

We delve into the latest evidence substantiating behavioral/psychosocial, pharmacological, and surgical interventions for patients suffering from seizures, and consolidate existing guidelines pertaining to treatment alternatives..

1.1 Habit Reversal Training

We also offer habit reversal training, which is currently a widely researched behavioral therapy approach. This methodology primarily focuses on enhancing children's self-awareness of tic attacks through discussions on strategies such as tic reactions, detection methods, warning signals, and situational awareness training. Subsequently, children are taught to employ specific competing behaviors to disrupt or halt tic attacks. Habit reversal training may also encompass relaxation techniques, mutation management,

and comprehensive training. Multiple studies have demonstrated that habit reversal training, whether administered in conjunction with or without pharmacological therapy, can effectively mitigate motor tics and lobar seizures in both adults and children [12]. Nevertheless, the widespread implementation of habit reversal training faces obstacles, including the need for informed consent from the families of affected children, the scarcity of professionally trained therapists, and adequate insurance coverage.

1.2 Biofeedback and transcranial magnetic stimulation

It is frequently employed in the treatment of ADHD, anxiety disorders, and Tourette's syndrome. Physicians strategically position numerous electrodes on the child's scalp to meticulously track alterations in the rhythm of brain bioelectricity. Simultaneously, advanced computer technology translates these intricate changes in brainwave patterns into engaging cartoon animations, which are vividly displayed on illuminated screens. As the child's attention sharpens and their brainwaves harmonize into a more favorable state, a cartoon character triumphantly executes a successful shot within the animation. This innovative reward system enables children to tangibly perceive their brainwave activity, fostering a profound sense of accomplishment and recall whenever they achieve this "shooting success," ultimately fostering therapeutic benefits.

Transcranial magnetic stimulation (TMS) can be used to treat Tourette's syndrome (TS), but few studies support this claim. This meta-analysis examined the effectiveness of TMS in reducing the severity of Tourette's syndrome tics.

The entirety of the encompassed research necessitates the conduct of randomized controlled trials to compare various TMS trial conditions. (3) It is stipulated that each participant fulfills the diagnostic prerequisites for persistent tic disorder and/or Tourette Syndrome (TS). A random-effects model meta-analysis has been undertaken to evaluate the efficacy of transcranial magnetic stimulation (TMS) in mitigating tic severity and its influence on reducing aura impulses. Despite TMS not significantly diminishing tic severity, trials with larger sample sizes have reported a more pronounced therapeutic effect. The existing evidence supporting the use of TMS for stimulation reduction is limited, albeit a decrease in the severity of aura impulses has been observed. The primary limitations inherent in the current literature underscore the need for exploring novel transcranial MS protocols and their potential as adjunctive treatment strategies.

1.3 Dietary Adjustment

Maintaining optimal nutrition while avoiding the inclusion of additives, artificial pigments, and caffeine, as these ingredients may potentially initiate or exacerbate convulsive episodes.

1.4 Other treatments

Acupuncture, immunotherapy, deep brain stimulation, transcranial

magnetic stimulation, and surgical interventions have all been attempted in the treatment of this disease.

2.Drug Therapy

2.1 Dopamine receptor blockers

Studies have uncovered a pivotal role of the frontal cortex-basal ganglia circuit, particularly the dopaminergic and 5-hydroxytryptamine systems, in the manifestation of Tourette Syndrome (TS) symptoms. Rigorous triple-blind, placebo-controlled studies have firmly established that conventional D2 dopamine antagonists, including fluperidone and pimozide, can effectively diminish the frequency of seizures in TS-affected children. Notably, a notable success rate of up to 80% has been observed with fluperidone administered at doses ranging from 1-20mg/day or pimozide at doses of 2-48mg/day [2]. Nevertheless, these medications may give rise to substantial side effects, such as extrapyramidal reactions, drowsiness, and cognitive decline, prompting some patients to discontinue their treatment regimens. Consequently, low-dose, long-term therapeutic approaches, such as fluperidone at 1-4mg/day and pimozide at 2-8mg/day, have become the norm in clinical practice.

Typilide, a benzoamide derivative, selectively inhibits dopamine receptors located within the basal ganglia. [3,13] A comprehensive 69-case study conducted by Zheng Yabing and colleagues uncovered that, in comparison to haloperidol, Typilide exhibits a reduced number of mild side effects, superior patient adherence, and equivalent efficacy in treating Tourette Syndrome (TS) among children aged 4-16. Nevertheless, Wu Beiyan and their team have thoughtfully pointed out that the efficacy of Typilide may not match the robustness of haloperidol, emphasizing the need for continued clinical observation to assess its performance.

Alipid dopamine system stabilizer is an exciting new atypical antipsychotic drug, highly binding to dopamine D2, D3, 5-HT1A, and 5-HT2A receptors, making it particularly beneficial in treating TS. A prospective multicenter controlled study involving 195 Chinese TS children aged 5-17 years revealed that after 12 weeks of Alipiperol treatment (5-25 mg/d), the YGTSS score significantly improved, with comparable clinical efficacy and adverse reaction rates to Tipilide (100-500 mg/d). [4] L Murphy et al. retrospectively analyzed 6 TS patients aged 8-19 years with obsessive-compulsive disorder, finding that after 12 weeks of treatment with 5-20 mg/d, the YGTSS score and C-YBOCS score decreased by 56%25 and 71%25, respectively. Meanwhile, Winter et al. reported a female TS patient with obsessive-compulsive disorder who experienced significant relief from convulsions and obsessive-compulsive symptoms after taking aripebi (5-7.5 mg/d) orally for just 2 weeks. In a study of 7 patients with refractory TS (resistant to other antipsychotics or unable to tolerate adverse reactions), Frolich et al. found that aripebi 5-30 mg/d, given over 8 weeks, notably alleviated motor and vocal convulsions in children, but did not noticeably affect obsessive-compulsive disorder and ADHD. The common side effects of Aripebi include drowsiness, weight gain, restlessness, headache, and vomiting. Approximately 20.7%25 to 25.0%25 of patients

discontinue treatment due to drug intolerance. The clinical efficacy and drug tolerance of Aripebi in TS with obsessive-compulsive disorder, particularly refractory TS, warrant further discussion. In a randomized, double-blind, placebo-controlled study, Jankovic et al. found that Topivate was effective in treating moderate to severe Tourette's syndrome, although the mechanism of action remains unclear..

2.2 Monoaminergic Antagonists

Specialized single-action antidepressants, including risperidone, clozapine, olanzapine, and zirapitone, show potential in managing Tourette Syndrome (TS). At present, risperidone, despite being thoroughly researched, effectively antagonizes both serotonin 5-HT2 and dopamine D2 receptors. Numerous trials highlight its significant ability to diminish seizures in TS patients across various age groups, frequently surpassing fluoxetine. It is particularly advantageous in treating TS in children and adolescents experiencing anxiety, depression, and obsessive-compulsive disorder [5-6], as evidenced by its success in randomized, double-blind, placebo-controlled trials and open-label studies. Notably, zirapitone seems to manage TS in pediatric and adolescent patients without inducing weight gain concerns. Nevertheless, following Scahill et al.'s report of a sudden death associated with zilapidone during a clinical trial, caution is advised. Further research into its safety and tolerability is necessary before widespread adoption.

2.3 Levetiracetam

Levetiracetam, an intriguing pyrrolidine derivative, possesses an unparalleled chemical structure, distinct from conventional anti-epileptic drugs. Recent research has yielded exceptional findings: it proficiently inhibits hippocampal epileptic discharges while maintaining normal neuronal function unscathed. This distinctive attribute prompts speculation that levetiracetam precisely zeroes in on the supersynchronous activity of epileptic discharges, thereby stemming the progression of epilepsy. An intriguing, ongoing open-ended study has revealed astonishing results: a remarkable 72.25% of children suffering from Tourette's syndrome experienced significant improvement after 12 weeks of levetiracetam treatment! However, it's crucial to underscore that levetiracetam does not directly stimulate GABA neurotransmission; instead, it seems to disrupt the inhibitory regulation of GABA and glycine-gated current activity in cultured nerve cells.

2.4 Norepinephrine

Alongside the continuously fascinating dopamine and serotonin neurotransmitter networks, there are other neurotransmitter marvels like the cholinergic, noradrenergic, glutamatergic, and GABA (γ-aminobutyric acid) neurotransmitter systems, whose disorders may contribute significantly to the intricate pathogenesis of Tourette Syndrome (TS)! Some researchers posit that a diminished dopamine level and a heightened noradrenaline content in the central nervous system may be associated with ADHD-related symptoms observed in TS patients [7], offering an intriguing theoretical foundation for the treatment of TS patients with ADHD. Clonidine, an oral tablet and transdermal

patch-administered central α 2 adrenergic receptor antagonist, efficiently dampens the activity of noradrenaline in the central nervous system. Since its introduction in 1980, Clonidine has been employed in the management of TS, though its clinical effectiveness continues to be a subject of intense debate.

Atomoxetine, a selective norepinephrine reuptake inhibitor, has consistently demonstrated efficacy in treating ADHD in children and adolescents, as evidenced by numerous randomized, double-blind, placebo-controlled studies. Spencer TJ [8] and his team uncovered in a prospective study involving 117 TS children aged 7-17 with ADHD, that atomoxetine significantly alleviates ADHD symptoms and mitigates seizures in these individuals. While treatment with atomoxetine may elicit adverse reactions such as elevated heart rate, nausea, anorexia, and weight loss, there have been reports of exacerbated seizures and disease recurrence in some TS children post-treatment.

It is crucial for researchers to acknowledge the limitations surrounding the efficacy of atomoxetine, particularly in cases where severely affected TS patients (with intense seizures or ADHD) may be excluded from double-blind, placebo-controlled trials due to high dropout rates [9]. Furthermore, TS and ADHD patients who are adequately managed with alternative medications may only participate in such studies if they are unable to tolerate their current therapeutic regimen.

As a clinical intervention for children with TS comorbid with ADHD, the overall safety and effectiveness of atomoxetine in this population necessitates further investigation through large-scale, controlled studies.

3. Anti-inflammatory and immunoregulatory therapy

TS's pathobiology remains a mystery. Investigations suggest an interplay between immune dysfunction or inflammation in its development. Certain studies indicate that the combination of COX-2 inhibitor celecoxib and antibiotics can notably enhance tics and behavioral disorders in TS patients [10]. Zykov et al. treated seven TS children unresponsive to long-term antipsychotic drugs. Following immunomodulatory therapy (intravenous injection of propyl globulin), the symptoms of motor convulsions, voice convulsions, and behavioral disorders noticeably improved, with relief lasting over 6 months. These promising yet preliminary findings necessitate further controlled studies.

4. Magnesium sulfate and vitamin B6

Upon receiving the approval from the Andalusian Government Council, Spanish pediatricians conducted a randomized, double-blind, placebo-controlled study on the administration of magnesium sulfate at a dosage of 0.5 mg/(kg • d) and vitamin B6 at 2mg/(kg-d) (nK) in children aged 7 to 14 years old who suffered from seizures, adhering to the diagnostic criteria outlined in DSM-IV (307.23), alongside clinical data and the Yale Global Tic Severity Scale (YGTSS). The results demonstrated that this innovative treatment strategy had the potential to improve seizure management and alleviate associated adverse effects.

5. Remote therapy

Kareem Khan et al. have implemented digital therapy as a widely accessible first-line treatment, utilizing either a purely online approach or one supported by therapists. As digital technology progresses rapidly, the efficacy of programs that were once effective five or ten years ago remains uncertain due to interface updates and technological advancements. Nonetheless, Randomized Controlled Trials (RCTs) continue to serve as the gold standard for evaluating the effectiveness of Digital Health Interventions (DHIs).

DHIs have the potential to provide immediate access to treatments for individuals who might otherwise encounter lengthy waiting times or geographical obstacles, potentially freeing up existing resources and services for those requiring more intricate treatment and assessment. This could lead to a dual advantage of reduced costs and waiting times for both healthcare services and patients. While there is a pressing need for more rigorous research in this field, there is also an urgency to implement digital interventions for children with tic disorders in real-world settings [11].

Conclusion

In summary, significant progress has been made in the treatment research of Tourette's syndrome, but continuous exploration and innovation are still needed to seek more effective and safe treatment methods.

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