

New Progress in Study of Tourette's Disease

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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 [1-2]. This paper reviews numerous domestic and foreign literature on the treatment of To urrette's syndrome, hoping to provide some insights and reference for the clinical treatment.

Keywords: Tourette syndrome, Children, Neuropsychiatric disorders, Clinical Treatment, Progress

Introduction

Tourette syndrome, characterized by phonic and motor tics, is a neurodevelopmental disorder that significantly affects the quality of life of people with the condition [1, 2]. 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]

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 [5, 6].

Genetics and Pathophysiology

Genetics

A significant locus on chromosome 5q15 was identified through genome-wide analysis. Further analysis involving expression quantitative trait locus, Hi-C data, and genome-wide association

study data pointed to the NR2F1 gene and related long noncoding RNAs within this locus. Heritability analysis showed enrichment in brain tissue histone marks, and polygenic risk scoring of brain volume data revealed associations with right and left thalamus volumes and right putamen volume [7].

A male patient with GTS and other anomalies was found to have a de novo duplication of the long arm of chromosome 7 (4-6), XY, dup (7) (q22.1-q31.1)], which was determined to be inverted. The distal chromosomal breakpoint was identified between the genetic markers D7S515 and D7S522, a region previously associated with GTS [8].

Yeast and bacterial artificial chromosome clones spanning the breakpoints were identified using FISH analysis. Further analysis revealed a 6.5-kb SacI junction fragment in the patient's genomic DNA, with two breaks in 7q31 within a 500 kb region. The IMMP2L gene, encoding the human homologue of the yeast mitochondrial inner membrane peptidase subunit 2, was disrupted by the breakpoint in the duplicated fragment and the insertion site in 7q31. The cDNA of the human IMMP2L gene was cloned, revealing a transcript with six exons spanning 860 kb. The potential role of IMMP2L and other candidate genes in the chromosomal rear-

rangement region, such as NRCAM, Leu-Rch Rep, and Reelin, is discussed. The 7q31 breakpoint interval has also been implicated in other neuropsychiatric disorders with clinical similarities to GTS, including autism and speech-language disorder [9].

The role of the histaminergic system (HS) in neuropsychiatric diseases is not well-documented, and few studies have reported patients with various neuropsychiatric conditions having disruptions in genes related to the HS. In humans, histamine is produced from histidine by the enzyme histidine decarboxylase encoded by the HDC gene (OMIM*142704), which is the only enzyme in our body capable of producing histamine from histidine. Histamine is also present in various foods. The HDC gene has previously been linked to Tourette Syndrome [10].

Individuals with Gilles de la Tourette syndrome (GTS) exhibit motor and vocal tics and often have comorbid conditions such as obsessive-compulsive disorder (OCD) and attention deficit-hyperactivity disorder (ADHD). The dopaminergic and serotonergic pathways are believed to play a role in the development of GTS. One recent study aimed to investigate the expression of the serotonin transporter (SERT) gene (SLC6A4) in GTS individuals compared to healthy controls and its association with genetic variants (including the 5-HTTLPR, rs25531, and rs25532 variants, and the Ile425Val variant) and promoter methylation of SLC6A4 [11].

The study found that SLC6A4 expression was increased in GTS individuals compared to controls. While no specific genotype, allele, or haplotype was more common in GTS individuals, the LAC/LAC genotype of the 5-HTTLPR/rs25531/rs25532 haplotype was associated with higher SLC6A4 mRNA expression levels in GTS individuals.

Preliminary neuroimaging studies suggest that during NREM sleep in TD, there is increased activity in the premotor cortex and decreased activity in the prefrontal cortex. The circadian rhythm of striatal dopamine is influenced by the suprachiasmatic nucleus through various molecular mechanisms. Dopamine receptors play a role in regulating circadian function and the expression of circadian genes in the striatum. The connection between TD and restless legs syndrome and periodic limb movements suggests a common underlying pathophysiology involving iron deficiency and variations in the BTDB9 gene. Mutations in the L-Histidine Decarboxylase gene in TD point to the potential involvement of the histaminergic system, which is known to play a role in arousal [12].

A further study aimed to investigate the molecular mechanisms underlying TS in a large group of pediatric patients. The analysis included array-CGH testing to identify copy number variations (CNVs) in the patients. The main objective was to characterize the neurobehavioral features of patients with or without pathogenic CNVs and compare these findings with those reported in the literature on neuropsychiatric disorders, including TS. This comprehensive approach helps in the clinical and molecular profiling of patients for better prognosis and management. The study found that rare deletions and duplications affecting genes involved in neurodevelopment were more common in children with tics and other conditions. Approximately 12% of the patients in the cohort had potentially causative CNVs, consistent with previous research. [13].

Pathophysiology

Clinically, they are usually divided into three categories: motor twitch, vocal twitch and sensory twitch. Movement twitch finger face, neck and shoulders, trunk and limbs muscles involuntary, sudden, rapid contraction movement, manifested is blinking, frowning, mouth, nose, tongue, mouth, head shaking, nodding, neck stretching, shoulders shrugs, chest and other movements. Motor convulsions last for a certain period of time, usually within 2 years, and develop into vocal convulsions, most commonly in the throat, but also in the tongue muscles and nose. At the same time, patients will show abnormal mood changes and other manifestations, and have different degrees of decline in learning ability. In terms of treatment, classical drugs such as haloperidol, risperidone and thiapride are the main choices.

In addition, psychological and behavioral therapy, mental stimulation of the brain, traditional Chinese medicine acupuncture and moxibustion are also widely concerned. In this study, the progress in the treatment of Tourette's syndrome was described.

Biochemistry

This chapter comprehensively reviews the published record for neurosurgical, neurostimulatory, and neuroimaging evidence of the involvement of the cingulate gyrus in Gilles de la Tourette syndrome (TS). The most noteworthy evidence comes from neuroimaging. Neuroimaging findings were rarely exclusive to the cingulate cortex and tended to implicate multiple other cortices as well. Some results are reflective of obsessive-compulsive (OC) symptoms of TS. Copious findings, however, drawn from structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), resting-state functional magnetic resonance imaging (rsfMRI), task fMRI, and positron emission tomography (PET) implicate six of the eight cingulate subregions in TS [14].

Gauged by MRI, cortical thinning and/or below-normal volume are seen in subgenual anterior cingulate cortex (sACC), pregenual anterior cingulate cortex (pACC), anterior middle cingulate cortex (aMCC), and posterior middle cingulate cortex (pMCC), correlating with tic severity in sACC, pACC, and aMCC. Moreover, in pMCC, dorsal posterior cingulate cortex (dPCC), and ventral posterior cingulate cortex (vPCC), cortical thickness is a candidate biomarker shared across siblings with TS. Loss of cortex may reflect excitotoxicity secondary to insufficient local GABAergic inhibition, a notion supported by the few relevant MRS and PET studies conducted to date, recommending continued development of GABAergic and glutamatergic pharmacologic agents to treat TS. Measurements of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) obtained with DTI indicate that the white matter proximal to sACC, pACC, pMCC, and dPCC may also represent a seat of pathology in TS.

RsfMRI reveals abnormal functional connectivity of pACC and dPCC with the globus pallidus internus, a favored target of therapeutic deep brain stimulation (DBS) for TS. In whole-brain network (graph theory) analysis, dPCC functional connectivity is related to the severity and complexity of tics. In task fMRI, in contrast, the pMCC seems to play a preeminent role in premonitory urges and preparation for tics as well as normal urges to urinate, swallow, and yawn. Strong monkey PET and EEG evidence ties vocal tics to spike discharges, α -activity, and regional

blood flow in the pACC unleashed by failure of GABAergic inhibition in the ventral striatum.

Tic suppression in fMRI scans is associated with increased blood oxygenation level-dependent activity in sACC, pACC, and aMCC, but decreased activity in pMCC and dPCC. Activity in the former three subregions may represent volitional effort, physical discomfort, and emotional distress that accompanies mounting tic urges; pMCC and dPCC may be more instrumental in amplifying than suppressing urges. Needs for future neuroimaging work in TS include longitudinal studies—particularly those striving to predict which individual pediatric patients will continue to suffer from TS as adults and studies of treatment response—particularly of behavioral therapies, which are as efficacious as pharmacology [15].

Transcranial magnetic stimulation and related therapies such as cranial electrotherapy stimulation, which showed good efficacy in a recent trial, merit continued exploration. TS research using DTI, MRS, and PET will no doubt continue to benefit in coming years from technological advances such as ultrahigh-field scanners, multichannel head coils, and novel (including GABAergic and glutamatergic) ligands.

Functional Neuroimaging Studies

Functional neuroimaging studies show a disinhibition of the cortico-striatal-thalamo-cortical circuit, while structural imaging studies present conflicting results, with some indicating smaller volumes of the caudate nucleus (CN) in children with Gilles de la Tourette syndrome (TS) [17]. A recent interesting study aimed to investigate whether transcranial sonography (TCS) can detect alterations in the raphe nuclei, substantia nigra, lenticular nucleus (LN), or CN in children with Tic disorder or TS (TIC/TS) [17]. A recent study included 25 treatment-naïve children (average age: 12.2 ± 2.5 years) diagnosed with Tic disorder or TS based on DSM-V criteria (10 subjects), without any other psychiatric or neurological diagnoses, and 25 age- and sex-matched healthy controls (average age: 12.17 ± 2.57 years).

Parental assessments of behavioral, emotional abnormalities, somatic complaints, and social competencies were conducted using the Child Behavior Check List (CBCL/4-18R). TCS of deep brain structures was performed through the preauricular acoustic bone windows using a 2.5-MHz phased-array ultrasound system. Fisher's exact test and Mann-Whitney-U test were used for comparisons between TIC/TS patients and healthy controls. The TIC/TS group showed a higher prevalence of hyperechogenic area in the left CN compared to the control group [16].

TIC/TS patients with hyperechogenic CN exhibited more thought- and obsessive-compulsive problems. The study identified pathological structural changes in the CN, a higher prevalence in TIC/TS patients compared to healthy controls, and its association with comorbid thought problems. Future research should investigate the underlying molecular mechanisms, potentially related to disrupted iron metabolism [17].

Treatment

Drug Therapy

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 flupenthixol and pimozide can significantly reduce the frequency of convulsions in children with TS. The effective rate of treatment with flupenthixol 2-20 mg/d or pimozide 2-48 mg/d can be up to 80% [4], 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 flupenthixol 1-4 mg/d and pimozide 2-8 mg/d [18].

Typilide is a benzamide derivative that selectively blocks basal ganglia dopamine receptors. 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) [19].

L Murphy 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 aripibi (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 aripibi 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 Aripibi 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 Aripibi 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 [20].

Monoaminergic Antagonists

Selective monoaminergic antagonists such as risperidone, clozapine, olanzapine, and zipilapone 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 heart [21].

Randomized, double-blind, placebo-controlled studies and open experimental studies have shown that chilapridone can effectively treat TS in children and adolescents without adverse effects of weight gain. However, it is worth noting that Scabill 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.

Levetiracetam

Levetiracetam is a pyrrolidine 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 hypersynchronous 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.

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 [9], which provides a theoretical basis for the treatment of TS patients with ADHD. Clonidine is a mesoaxis α_2 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 [22].

Atomoxetine, 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 [10] 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 atomoxetine. At the same time, the authors should also be aware of the limitations of the efficacy studies of atomox-

etine. 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 [11]. 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 atomoxetine in the population still need to be explored by large sample control [23].

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. 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.

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 B₆ 2mg/(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.

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 [24].

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.

Psychobehavioral Therapy

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 [22].

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 [14]. 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.

Biofeedback

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 [22].

Dietary Adjustment

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

Other Treatments

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

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 ADHD. 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, fluprisole, pimozide, risperidone, clonidine, etc. Due to poor efficacy or serious adverse reactions, alipetic, amoxetone, 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, multi-center, 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 [23].

Discussion

Hyperextension whole bone method is a traditional Chinese medicine treatment of spinal fractures, yuan dynasty Wei Lin also in the specialized to affect the "ankles suspension method" is introduced, the method of "door drag climbing stretching method" in Ming dynasty "the party phuket, broken doors," qing "YiZong Jin Jian • bone setting loading message" and the "climbing rope stacked bricks method" reset method. In recent years, many domestic scholars have combined hyperextension osteoplasty with PVP in the treatment of OVCF, which has achieved good short-term analgesic effect. However, it often fails to achieve comparable effects with PKP in the recovery of the height of the affected vertebra and correction of kyphosis, and the bone cement leakage rate is still high, and there is a lack of mid-and long-term clinical observation.

Bai B et al. found that restoring vertebral height can reduce vertebral kyphosis after fracture and has the potential benefit of reducing malform-related sequelae. In this study, the surgeon followed the principle of anti-trauma mechanism in preoperative manipulative reduction, and used progressive pad elevation restoration method to fix the fracture and exercise the lumbar and back muscles. This can not only restore the height of the vertebral body, correct the deformity, and the occurrence of late chronic low back pain will be greatly reduced back.

It is generally believed that PVP in the treatment of OVCF single vertebral bone cement perfusion volume is less than PKP, in this study, the PVP group and PKP group single vertebral bone cement perfusion volume has no significant difference ($P > 0.05$), and the incidence of bone cement leakage is lower than that reported in the literature, the reasons are investigated. Comprehensive closed reduction can reduce or return to normal bone density in the compression area of the injured vertebra, and even form local cavities, which greatly increases the volume of the vertebral body and can accommodate more bone cement [24].

Bone cement can at low pressure and high viscous state of dispersion in the vertebral body, seeping into the vertebral body bone trabecular bone cement is increased and the contact area of the vertebral body, effectively reduce hair born of leakage of bone cement and bone trabecular micro fracture risk again because of bone cement has overcome between the vertebral can-

cellous bone and elastic modulus decrease due to the differences and thus reduce the adjacent vertebral body fracture again hair [24].

In the current economic conditions in our country, postures, manual reduction of OVCF patients treated + PVP is relatively safe, simple operation, less X-ray exposure time, patients with vertebral height restoration and protrusion deformity correction effect after apparent, analgesic effect is good, durable, less cost, and low incidence of diseases, treatment can achieve the maximum price down, It's a good treatment.

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