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Research Advances on the Treatment of Myoclonus-Dystonia Syndrome

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Abstract

Myoclonus-Dystonia Syndrome is a movement disorder characterized by the association of myoclonus and dystonia as the sole or prominent symptoms. Non-motor features may include obsessive-compulsive disorder, depression, anxiety, personality disorders, alcohol abuse, and panic attacks. The pathogenesis of MDS is not very clear, and the current opinions are mainly focus on gene mutations. The diagnosis is mainly based on clinical features, and this disorder is confirmed by gene testing. Myoclonus-Dystonia Syndrome can't be cured, and the current therapy is mainly aimed to improve the symptoms, which includes medical and surgical treatment. All in all, MDS remains poorly responsive to medical treatment. Although the surgical treatment develops very quickly in recent years, due to the difficulty in predicting the range of operation and the large expense, surgical treatment is hard to be implemented in clinical practice widely. Currently, medical treatment is still the main method, and the surgery is considered when medication is ineffective.

Keywords Myoclonus-Dystonia Syndrome; Treatment; Medication; Surgery

Introduction

Myoclonus-Dystonia Syndrome (MDS) is a genetically heterogeneous movement disorder. Myoclonic jerks and dystonia are the main or the only symptoms. The core of MDS is inherited myclonus-dystonia, which is a rare inherited disease with autosomal-dominant inheritance. Inherited myclonus-dystonia is usually onset in childhood or adolescence, with myoclonus as the most predominant symptom. Non-motor features may include obsessive-compulsive disorder (OCD), depression, anxiety, personality disorders, panic attacks, and so on. The symptoms of MDS could be temporarily improved through alcohol ingestation [1-3]. The pathogenesis of MDS is not very clear currently. Zimprich reported MDS was induced by the mutation in the epsilon-sarcoglycan (SGCE) gene on chromosome 7q21. SGCE gene encodes transmembrane components of the dystrophin-glycoprotein complex, which links the cytoskeleton to the extracellular matrix [4]. However, MDS has obvious genetically heterogeneous. Mutations in the SGCE represent the major genetic cause, but other genes and loci are associated with the disease. Grimes and Han have described a large Canadian family with MDS, and localized a gene for this disorder to a 17-cm region on chromosome 18p11[5]. Some reports indicate that MDS is related with the mutation in the DRD2 (11q23) [6] DYT1 (9q34) [7]. In addition, in a proportion of patients no genetic mutation is found [8]. The diagnosis of MDS is based on clinical findings, family history, absence of other neurologic deficits, and normal neuroimaging studies [9], which could be confirmed by gene testing. The current therapy for MDS is mainly aimed to improve the symptoms, which includes medical and surgical treatment. Because inappropriate treatment may have a negative impact on motor development, participation, and emotional well-being of the patients, it is necessary to summarize the present treatment of this disorder to direct clinical management.

Benzodiazepines

Benzodiazepines could enhance the function of GABA-activated chloride channels. It acts on the alpha subunits of the channel complex, and promotes influx of Chloride ion and super-polarization of the cell membrane, which makes the muscle relax [10,11]. Although myospasm is not the indication of benzodiazepines, many reports describe they could reduce the frequency and degree of myospasm, so they are widely used to treat dystonia. In clinical, Clonazepam and Diazepam are widely utilized. The adverse reactions of benzodiazepines include dizzy, fatigue, Ataxia, Addiction, and so on. The white cell counts might decrease due to the large dose. Old people and persons with Renal insufficiency must be cautious for using benzodiazepines. Besides long-term use may induce tolerance, and the mechanism is probably benzodiazepines decrease γ-aminobutyric acid type A receptor (GABA(A)R) surface levels and the efficacy of synaptic inhibition [12]. Generally, the side effects of benzodiazepines are very mild and many patients can be well-tolerated, so it is widely used in clinical [13].

Antiepileptic drugs

Antiepileptic drugs (AEDs) could inhibit neuronal abnormal impulse conduction. Its mechanisms include the role of the voltage-dependent sodium channels, blocking sodium-dependent action potentials releasing fastly or acting onγ-aminobutyric acid (GABA) receptors, enhancing the inhibition of GABA receptor, limiting the frequency of action potentials [14-15], etc. It has been reported that electrophysiology suggested the myoclonus was of subcortical origin [16,17], and thus, AEDs can improve myoclonus of MDS. Commonly used in the treatment of MDS are valproic acid, topiramate, levetirazetam and so on. The adverse reactions include: specific adverse reactions (eg. valproic acid could cause acute liver failure, and topiramate could cause less sweat or no sweat in children), headache, drowsiness, behavior change, teratogenic effects and so on.

Anticholinergic Drugs

Anticholinergic Drugs can compete with acetylcholineacting on acetylcholine receptor, thereby antagonizing action of acetylcholine, so the muscle is relaxant. Such drugs have a role in both myoclonus and dystonia. It has been reported that a 19 year-old girl with a 14-year historyof MDS which was genetically diagnosed. After taking a small dose of trihexiphenidyl (2 mg tid), her myoclonus and dystonia were alleviated. She stopped taking the medication many times, which resulted in recurrence of the myoclonus and dystonia. When trihexiphenidyl was discontinued at 7 years after initiation of treatment, neither the myoclonus nor dystonia recurred [18]. Anticholinergic drugs include Artane, benztropine, etc. The side effects of these drugs are peripheral and central reversible, dose-dependent muscarine-like effects, such as dry mouth, blurred vision, drowsiness, memory loss, hallucinations, behavioral abnormalities. The adverse reactions may be avoided or limitedby starting with a small dose and gradually increasing the dose.

Levo-dopa

One of the possible mechanisms of MDS is TH gene mutation which causes tyrosine hydroxylase deficiency (THD).Tyrosinehydroxylase participates in the process of the L-tyrosine transformating into L-dopa in dopaminergic neurons, so the THD could cause the lack of levodopa in central nervous system [19]. Levodopa (L-dopa) replacement therapy is the first choice for the MDS patients with such mechanism. Maria Stamelou and Niccolo reported three MDS patients from a THD family showed good reactivity for levodopa, and found that early treatment with levodopa was crucial for the final motor outcome in THD [16]. However, we should pay attention to the other type of THD, which is early onset presenting as a more complex encephalopathy, perinatal abnormalities, diurnal fluctuations, autonomic function disorders, and less response to levodopa [16,20]. The adverse reactions include dyskinesias, switching phenomenon, gastrointestinal discomforts. Starting with very low doses of levodopa and associated with adequate amounts of carbidopa could minimize the adverse effects [21].

Botulinum toxin

Botulinum toxin is a neurotropic bacterial toxin produced by the Gram-positive anaerobic Clostridium botulinum. According to the toxicity and antigenicity, it could be divided into A, B, C1, C2, D, E, F, G types. Botulinum toxin can inhibit presynaptic release of acetylcholine, resulting in muscle relaxation, and eliminate or mitigate excessive muscle contraction [22]. Because neurons could reinnervate the muscles through giving birth to new connections, the efficacy of botulinum toxin just lasts for 3-5 months [23]. The main side effect of botulinum toxin is specificity systemic reaction, but generally it is very mild and transient. In addition, other adverse effects includepain on the injection site, swelling, numbness, ptosis, muscle weakness of distant parts and so on [22]. Botulinum toxin is a kind of variant protein with immunogenic. When botulinum toxin is injected into the person,the body may produce high levels of specific anti-toxin, so repeatedly injection might weaken the response. In principle, the injection interval of botulinum toxin should not be shorter than 3 months in order to avoid the failure of continued treatment.

Stereotactic thalamotomy and pallidotomy

The mechanism of Stereotactic thalamotomy and pallidotomy has not yet been explained very well. It has been reported that dopamine deficiency causes disinhibition and overactivity of the sub-thalamic nucleus (STN). Output neurons from the STN are excitatory and use glutamate as a neurotransmitter. They project to the external and internal segments of the globus pallidum (GPe and GPi), and the pedunculopontine nucleus (PPN). The former leads to polycythemia movement, and the later causes Akinesia [24], so this surgery mainly relieved patients' myoclonic symptom. Adam and Marek reported30 patients with primary dystonia were implemented the stereotactic thalamotomy and pallidotomyon CT and MRI-guided,and the postoperative results showed dyskinesia symptoms of the patients were significantly improved and complications (such as dysarthria, hemiplegia, etc)were rare, so they Proposed this surgical treatment was an effective and safe method for primary dystonia [25]. Because the surgery requires high-level skill, and it is very difficult to predict the range of operation, it is hard to be widely carried out in clinical practice [26].

Deep brain stimulation

Deep brain stimulation (DBS) is often called "brain pacemaker", and we can stimulate the specific parts of brain through implanting electrodes. DBS is an effective method to treat refractory movement disorders, and the mechanism is probably inhibiting neuronal pathological disorders and motivating high-frequency output instead of other network excitatory effect of the basal ganglia and thalamus [27]. Kuncel and Turner reported that the myoclonus and tremor symptoms of a 74 year-old woman with MDS were not significantly improved after using valproate, clonazepam, diazepam, gabapentin, levetiracetam, levodopa, botulinum toxin and other drugs, but after she underwent bilateral ventral intermediate nucleus DBS treatment, her symptoms were moderately improved [28]. Beukers and Contarino recruited 5 patients with MDS into two groups. Three of them as an experimental group received the DBS of globuspallidus medial nucleus, and the other two did not undergo surgery as a control group. 2 years after surgery, movement disorder symptoms of theexperimentalgroupwere significantlyimproved,and (123-I)-IBZM-SPECT Scan examination showed their dopamine D2 receptorswere notsignificantlychangedcomparedwith pre-surgery.While the level of dopamine D2 receptors of the control group significantly decreased. The result suggested that DBS of the pallidum has beneficial effects on motor symptoms in MDS and the procedure might stabilize dopamine D2 receptor binding.However, the number of patients is too small and a much larger sample size is needed to warrant firmer conclusions [29]. Rughani and Lozano recently reported a study which aimed to appraise the value of these two DBS targets (medial nucleus of the globuspallidus and ventral intermediate nucleus).They presented medial nucleus of the globuspallidus may be a better target.Although both targets achieve similar improvements in myoclonus, medial nucleus of the globuspallidus stimulation may achieve greater improvements in dystonia, compared to ventral intermediate nucleus stimulation [30].

Frucht and Bordelon reported that the movement disorders of the MDS patients could be significantly improved after using the sodium oxybate, and the adverse reactions can be tolerated well [31]. Scheidtmann described a MDS patient with panic attacks took nefazodone (a kind of 5 hydroxytryptophan reuptake inhibitors), whose panic attack and myoclonus were relieved [32]. Park reported

that zolpidem was effective for MDS patients [33]. Of note, a lack of vitamin E may also cause myoclonus and dystonia, which must beconsidered,because vitamin E supplementation could markedly improve both symptoms [34].

Conclusions and future directions

Overall, MDS remains poorly responsive to pharmacological treatment, so novel, effective and safe drugs are needed. In recent years, with the surgical treatment carried out, the symptoms of many MDS patients have been improved to a certain extent. But due to the difficulty in predicting the range of operation and the large expense, surgical treatment is hard to be widely implemented in clinical practice. Currently, medical treatment is still the main method,and the surgery is considered when medication is ineffective. In the future, more efforts are needed to make to enhance the skill and reduce the cost of surgical treatment.

Search strategy and selection criteria

We searched PubMed, EBSCO, and Cochrane Library. We also searched reference lists of retrieved articles. Search terms included “myoclonus-dystonia syndrome”, “myoclonus-dystonia”, “myoclonic dystonia”, “myoclonus”, “dystonia”, “inherited myoclonus-dystonia syndrome”, “inherited myoclonus-dystonia”, “primary dystonia”, “treatment”, “management”. Papers published from 1980 to 2014 with no language restriction were reviewed. Articles were selected on the basis of relevance to the topics covered in the Review.

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