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Neuropathogenesis of tic disorders in children and adolescents

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Abstract. Tics disorder (TD) is a chronic neuropsychiatric disease typified by recurrent involuntary tics, speech, or behavioral abnormalities. Different populations are at risk of developing this disease, and it can pose serious physical harm. For example, TD can cause learning difficulties, make patients isolated, and have anti-social psychological and conduct disorders, which seriously affects their normal life. To this end, how to treat or prevent this disease is particularly important. Studying the pathogenesis of TD can be beneficial for developing more effective treatment methods. The study of the pathogenesis of TD is related to the onset and progression of the disease, and it can play a role in diagnosing and treating it. This research will discuss neurobiochemical factors, neuroimmune factors, and neuroanatomical factors, and summarizes the neural mechanism of TD. A thorough analysis of these mechanisms is beneficial for a better understanding of this disease, and it can provide effective strategies for prevention and intervention.

Keywords: Tics disorder, Mechanism, Treatment.

1. Introduction

Tics disorder (TD) is a long-term neuropsychiatric condition characterized by muscle movement tic or vocal twitch, which starts in children and adolescents. Depending on the age at which the condition first appears, how long it lasts, how it manifests clinically, and if vocal twitching is present, there are different types of this disease, such as provisional tic disorder (PTD). According to a meta-analysis, the prevalence of TD in children in China is 1.7% for PTD [1]. Moreover, about 50% of TD patients have at least one neuropsychiatric or behavioral disorder. Comorbidities such as obsessive-compulsive disorder (OCD), anxiety and depression seriously affect the social function of children, thus causing lifelong regrets for individuals and families. Various treatment methods have been developed and successfully used to treat TD.

Existing treatments include comprehensive behavioral intervention for tics and α-adrenergic agonist or antipsychotic drugs. In addition to commonly used medication, the treatment methods for TD also include psychological therapy and environmental therapy. Psychological therapy is the main means to prevent the recurrence of TD and reduce complications. Psychological transfer and cognitive-behavioral therapy are commonly used. Among them, cognitive-behavioral therapy is beneficial for treating obsessive-compulsive disorder associated with TD, and behavioral correction is beneficial for treating impulsivity and hyperactivity symptoms associated with TD. Environmental therapy, on the other hand, can be treated through environmental adjustments to gradually alleviate the tension and fatigue of TD caused by external stressors. Summarizing the research progress in recent years, the pathogenesis of

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children's tics disorder is mainly affected by neurological factors, genetic factors, pathological factors and other factors. However, there are still problems with unclear specific pathogenesis. Therefore, clarifying the pathogenesis is crucial to the development of more treatment methods.

This research will summarize the relevant studies on the neuropathogenesis of TD in children, and elaborates them from the three aspects of neurobiochemical factors, neuroimmune factors and neuroanatomical factors, aiming to contribute to the pathophysiological research, treatment and intervention of TD.

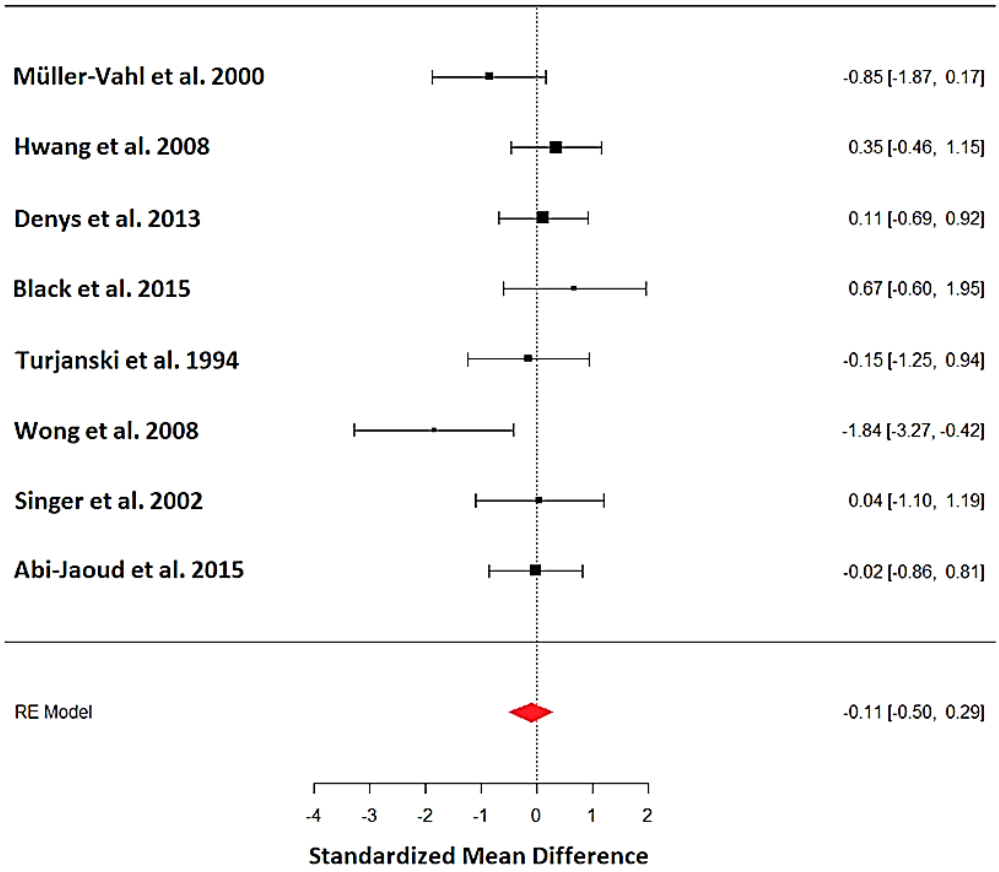

Figure 1. Forest plot for evaluating all $D_{2/3}$ studies in the striatum [2].

2. Neuropathogenesis of TD

The neuropathogenesis of TD has been analyzed. The pathogenesis of TD involves multiple links in the cortico-striatal-thalamo-cortical loop. The imbalance of dopamine (DA), norepinephrine (NE), serotonin (5-HT) and other central neurotransmitters in this pathway is an important neurobiological factor. Here, how these factors affect TD will be systematically discussed.

For DA, it is an important neurotransmitter and plays a long-term role in emotional regulation, motor ability and cognitive function. Central dopamine system disorder is one of the neurobiological factors in the onset of TD. There is a lot of evidence to prove that DA in patients with TS can be abnormal. For example, DA receptor antagonists are the most effective convulsive inhibitors. In addition, convulsions are classified as a habitual behavior disorder, and the increase of dopamine activity will accelerate the progress from goal-oriented to habitual behavior. Possible abnormalities in the DA system of TS patients include dopamine receptor hypersensitivity, pre-synaptic abnormalities, and excessive dominance of dopamine nerves [2]. To elucidate DA's function in TS, Hienert et al. conducted two meta-analyses of striatal DA receptors in adult patients and healthy control groups [2]. PET and SPECT were used to detect the subject's brain DA system and carry out meta-analysis of DAT in the striatum and its

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subregions, as well as in the cerebral hemisphere. The results show that because DAT is found in pre-synaptic dopamine neurons and regulates extracellular DA levels through dopamine reuptake in the synaptic space, an increase in DAT binding in TS patients can support both the pre-synaptic abnormality theory and the assumption of excessive dominance of DA energy nerves. In addition, as shown in Figure 1, the results of the low trend of $D_{2/3}$ receptor binding in TS patients are contrary to the hypothesis of DA receptor hypersensitivity, which may be due to reduced drug treatment or receptor availability. Summarizing the above studies, it can be concluded that understanding the pathophysiology of TS requires large-scale and systematic neuroimaging research on the control group, thus enabling the development of curative therapy.

For NE, it is a neurotransmitter with the ability to affect mood and attention. In the onset of TD, hyperfunction of the NE system also plays an important role. Studies have shown that clonidine therapy reduces the release of epinephrine by inhibiting the adrenaline system, thus controlling twitching. Also, aniline imidazoline can reduce central adrenaline and achieve the purpose of treating tics. When the twitching symptoms are aggravated by external pressure, the metabolite 3-methylamino-4-hydroxyphenylethylene glycol of NE in the patient's cerebrospinal fluid increased significantly. Zhu et al. measured the content of monoamine neurotransmitters in the blood of TS patients and found that the affected group's NE content was noticeably greater than that of the normal control group [3]. Their research findings suggest that high levels of catecholamines (mainly DA), increased serotonin conversion rate, and altered sodium potassium ATPase activity in children with Tourette's syndrome may be one of the pathogenic mechanisms of Tourette's syndrome. The above research has confirmed that the norepinephrine energy system contributes to the onset of TD. On the contrary, Wen et al. used the method of HPLC with electrochemical and ultraviolet detectors to determine that the MHPG in the cerebrospinal fluid (CSF) of TS patients, and the results show that there is no significant change compared with the control group [4]. In addition, Zhang et al. concluded through experiments that the increase in the central NE level of TS rats accompanied by a decrease in peripheral NE content [5]. In Tourette syndrome rats, there is a phenomenon of increased central NE levels and decreased peripheral NE content, and NE metabolism imbalance may be one of the pathogenesis of Tourette syndrome. Jing'an oral liquid may exert therapeutic effects by reducing central NE content, lowering NE hyperfunction, and regulating the sympathetic adrenal system to maintain dynamic balance between central and peripheral NE. The imbalance may be caused by the maladjustment of the sympathetic-adrenaline system. Through the above studies, it can be seen that in order to clarify the mechanism of NE's role in the onset of TD, conducting clinical trials with a large sample size is essential.

The neurobiochemical mechanism of TD may also be related to serotonin. 5-HT is an inhibitory neurotransmitter that can regulate neural activity and immune function. Clinical and pharmacological studies have shown that 5-HT reuptake inhibitors are effective in 40% of TS patients [6], and risperidone, which has a high affinity for 5-HT receptors, also has a good therapeutic effect on TD patients. The pathogenesis of OCD is related to the low function of the 5-HT energy system, and TD is often comorbid with OCD, so it is speculated that the pathogenesis of TD and OCD is similar. It has been reported that 5-hydroxytryptamine, a metabolite of 5-HT, is considerably reduced in TS patients' CSF, and the concentration of another metabolite, 5-hydroxyindoleacetic acid, affects the extent of the tic involved site [4]. Gao et al. found that the contents of 5-HT in brainstem and plasma of TS rats were increased and tended to be normal after treatment with Changpu yujin decoction [7]. Therefore, it was confirmed that the disorder of 5-HT may be related to the incidence of TS. ELISA and RT-PCR technology can be used to detect that the striatal 5-HT and 5-HIAA content of TD rats was substantially lower than that of the control group, while the Qiangzhi prescription could relieve the symptoms of TD by enhancing the activity of the 5-HT energy system and improving its functional deficiencies. However, some studies have shown that 5-HT is not directly involved in the central nervous effect in peripheral blood, so it is not directly related to TD onset. Thus, the exact relationship between 5-HT and TD still needs to be further explored.

For neuroimmune factors, the immune-effector cells in the central nervous system are called microglial cells. The basal ganglion transcriptomes in the caudal nucleus and basal ganglia of 9 TS

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sufferers and their control groups through RNA sequencing can be obtained. It was found that the expression of transcription factors in microglial cells in the striatum of patients was up-regulated, proving that microglia were involved in the pathogenesis of TD. Chen et al. found that the immune function of TD children's cells was shown to be weaker than that of the healthy control group. And after interferon treatment, the activity of T lymphocytes and natural killer cells in the patients' peripheral blood increased, so it was confirmed that the cellular immune function disorder of TD children [8]. Qiao et al. used the case-controlled method to check the blood antinuclear antibodies and T lymphocyte subgroups of children with TD and their control groups, and found a decrease in the ratio of CD3/CD4 and CD4/CD8 in the case group, which supported the above study [9]. Liu et al. showed that aripiprazole can regulate immune function while improving TD symptoms, explaining the important role of neuroimmunity in the onset of TD [10]. Children with TD exhibit cellular immune dysfunction, characterized by decreased cellular immune function and the production of autoantibodies (anti-nuclear antibodies) after viral or bacterial infections. Cold and other factors before onset may be risk factors for children to develop tic disorders. In addition, it has been documented that lgG and lgM in children with TD are lower than normal, while lgA is higher than healthy controls [11]. There is still debate about the specific neuroimmune mechanism of TD, which needs further in-depth exploration.

For neuroanatomical factors, the study of Plessen et al. showed that the volume of the caudate body of children with TS decreases, the sensorimotor cortex becomes thinner, and there are structural abnormalities in the limbic cortex, prefrontal cortex and corpus callosum [12]. In addition, Peterson et al. found that the caudate nucleus volume in TS patients became significantly smaller, and the volume of the lenticular nucleus of TS adults and children with OCD was also smaller, suggesting that the decrease in the volume of the caudatum may be a sign of abnormal basal ganglion structure of TS patients [13]. Since the existing research conclusions are relatively consistent, the interconnection between TD and neuroanatomy can be preliminarily determined.

3. Conclusion

This research discusses the neuropathogenesis of TD, including neurobiochemical factors, neuroimmune factors and neuroanatomical factors. This research also explains how each pathogenesis of TD arises. Among them, neurobiochemical factors can be analyzed from the aspects of DA, NE and serotonin. The preliminary conclusion is that monoamine neurotransmitter abnormalities are the main neurobiochemical mechanism; immune cells and some antibodies play a role in the neuroimmune mechanism; and neuroanatomical factors are related to brain structural abnormalities. The analysis of the pathogenesis of TD can help develop new methods for treating TD and can also be used to develop new preventive measures for TD.

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