

Research Progress on the Relationship between BDNF, the Polymorphisms of Its Gene, and Childhood Autism

Zhuo Liu¹, Min Guo^{2*}, Yunsuo Gao², Xiangling Jiang²

¹Hainan Medicine University, Haikou, China

²Psychological Research Center, Hainan General Hospital, Haikou, China

Email: *g2002m@163.com

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Abstract

Studies have shown that the expression level of the brain-derived neurotrophic factor (also known as BDNF) is of great significance on neuron activity, which has a close relationship with the improvement of the learning and memory ability; it has effect on the physical growth and development of an individual as well. On the other hand, childhood autism is a group of serious neurodevelopmental disorders. Some literature has pointed out that the BDNF plays a tremendously important role in the pathogenesis and the treatment of neuropsychiatric diseases. In recent years, many scholars at home and abroad have done a lot of research and found that there is a close relationship between BDNF and autism. This paper therefore will give an introduction on and an analysis of the relationship between BDNF, the polymorphisms of its gene, and childhood autism based on the previous domestic and overseas literature.

Keywords

BDNF, Autism, Gene Polymorphisms

1. Introduction

Autism was first described in 1943 by professor Kanner L from John Hopkins University [1]. It was only 4 cases of autism that were reported in the 1980s in China [2], and the autistic people were officially included in the category of mental disability gradually in China since 2006. The diagnostic criteria are merged into two dimensions, which are social and/or communication disorders, narrow interests and stereotypic behaviors. Combined with the autism, Asperger

syndrome, childhood disintegrative psychosis, and undifferentiated pervasive developmental disorder in the previous DSM-IV, they are collectively referred to as autism spectrum disorder (ASD).

2. Epidemiology and Influencing Factors of Autism

There is a significant difference in the prevalence of autism for the sex of the population, and its effect on men is significantly higher than that on women. Because fetal testosterone (an important sex steroid produced by men) has a wide impact on the autism-related phenotypic variations [3]. Autism could be usually diagnosed in early childhood, with a median prevalence of 0.62% [4]. According to the estimate of the burden of autism in Global Burden of Disease Study 2010 [5], there are approximately 52 million cases of autism spectrum disorders worldwide, with 58 per 100,000 people suffering from autism. In China, the total number of people with autism has exceeded 10 million, and the number of children with autism has reached more than 2 million, and it has sharply sped up more than 200,000 cases each year. The prevalence of autism is related to many factors, such as genetics, environment, biology, family education, etc. Some studies on recognized risk factors included familial clustering and comorbidity rates of identical twins and fraternal twins were suggested that the heritability of autism is as high or over 90% [6]. Some certain infections during pregnancy, such as rubella, and the various biochemical factors such as use alcohol, valproic acid or cocaine during pregnancy could be affected the incidence [7]. Existing autism treatment options include psychological education, nursing coordination, and improved cognitive behavioral therapies. As the treatment efficiency is not ideal, more and more researches have been focusing on finding new strategies for the treatment of autism.

3. The Introduction of BDNF and the Correlation with Autistic Children of Its Expression Level

Brain derived neurotrophic factor (BDNF) is a small molecule protein that plays a key role in the growth and guidance of axons and dendrites, the formation of synaptic connections and plasticity, moreover, it is involved in the survival and differentiation of dopaminergic neurons in the brain development, which is closely related to the improvement on learning and memory abilities of children [8] [9]. Studies have found that BDNF is widely found in the hippocampus, cortex and striatum of mammals. If its gene is damaged or missing, it will seriously affect the memory and spatial perception of animals [10] [11]. A high correlation between BDNF expression in the brain and BDNF levels in peripheral serum has been demonstrated in animal experiments [12] [13]. Studies were also shown the similar relationships in humans. The human BDNF gene located on the 11p13 chromosome is consisted of 11 exons [14]. The BDNF concentration of plasma in normal people increases in the first few years after birth, and decreases slightly when towards adult. However, the opposite status is shown in

ASD patients. Due to their low expression in the early stages of development, ASD patients have a group of neurodevelopmental disorders [15]. Some scholars also believed that BDNF may interfere with the 5-hydroxytryptamine nervous system through its neurotrophic effect, affect the cerebral cortex and cortex-thalamus of autistic patients, and cause their dysontogenesis, which may cause the onset of autism [16]. While studied the correlation between BDNF and oxidative stress in patients with autism, some scholars have found that the levels of oxygen free radicals in patients with autism are significantly higher than those in normal people. Therefore, it is speculated that BDNF may be related to oxidative stress in ASD [17], which were also elaborated by researches of Zhang *et al.* [18]. It is confirmed a new direction for the pathological study of patients with autism and also suggested patients with autism have neurodevelopmental abnormalities in the structure and function of the brain, which is a kind of neurodevelopmental disorders. More than 70% of autistic patients have other comorbidities of different types and degrees in their lifetime. When autistic patients have intellectual disability, their serum levels of BDNF will also change [19] [20]. Therefore, the level of BDNF in brain tissue can be reflected by detecting the serum BDNF concentration level. Wang Min *et al.* [21] had studied 150 children (including 75 children each with autism and 75 healthy children), it was shown that the serum levels of BDNF in children with ASD was increased significantly. Compared with healthy children, the difference was statistically significant. In one-way logistic regression analysis, the higher levels of BDNF can be identified as an independent risk factor for the diagnosis of ASD, so we can guess that high levels of BDNF is a pathological compensatory mechanism of self in autism patients [22]. It also provides an important breakthrough point for clinical treatment of autism. Bryn *et al.* [23] had found that serum levels of BDNF in children with autism were moderately elevated, and there were significant differences compared with children in the normal control group. However, Halepoto *et al.* [24] had showed that the BDNF of serum in patients with severe autism was not significantly different from that of normal people, and only the BDNF of serum in patients with mild autism was higher than that of the normal group, which was indicated that expression level of BDNF in serum may be up-regulated after the patients with autism suffered the functional damage brain. When it was up-regulated to a certain level, it would inhibit the expression of BDNF. Therefore, it is necessary to study the correlation between ASD and peripheral blood BDNF levels in the control group by a systematic review and meta-analysis method to explain the differences between the studies. A search was conducted in the PubMed, Embase, and Cochrane Library databases for the studies published before February 2016, which was included 14 studies involving 2,707 participants and 1,131 incidents. This meta-analysis was shown that [25] peripheral blood BDNF levels were higher than the control group, with the statistically significant difference. Therefore, peripheral blood BDNF level was the potential biomarkers of ASD [23] [25] [26].

4. BDNF Levels and Gene Polymorphisms Affect the Incidence of Various Diseases

BDNF levels in human are associated with a variety of neuropsychiatric diseases [27]. Although the latest research has different opinions, Balietti [28] found in a study with the health experimental controls, the level of BDNF in the blood of patients with Alzheimer's disease may be higher, lower or unchanged. However, Bhattarai Prabesh believes that BDNF can enhance the neural stem cells plasticity and the glial cells regeneration capacity by stimulating nerve growth factor receptors [29], and reduce the process of synaptic decline. Therefore, BDNF can be used as a solution for the treatment of gray matter degeneration of Alzheimer's disease, which needs further investigation. Depression due to long-term psychosocial pressure, its effect on the expression level of BDNF has been gradually confirmed. More research especially in severe depression, but the role of its translation mechanism in depression still unknown [30]. A test of patients with anorexia nervosa found that the decrease in serum BDNF levels of patients was positively correlated with the severity of malnutrition. After the improvement of malnutrition, its factor levels gradually recovered, and BDNF levels may also affect the patients with abnormal eating behaviors [31]. BDNF is a factor known to regulate the adaptive behavior of humans. Huntington's disease (HD) is a defective disease in social cognitive processes. The importance of its factors has aroused research interest among experts. L Betti [32] showed that the longer the disease was found in patients with BDNF in platelets, the higher the level. For patients in a mildly ill state, the initial BDNF may increase slightly due to the compensation mechanism. Of course, brain-derived neurotrophic factors, as important signaling pathways in the body, are not limited to neuropsychiatric diseases. In a comparison of women's dysmenorrhea with serum BDNF levels, it was found that BDNF levels were significantly lower in patients without dysmenorrhea and patients with mild dysmenorrhea than in patients with moderate or severe dysmenorrhea [33]. This also provides us with a method of treating dysmenorrhea, which can reduce the degree of dysmenorrhea by regulating the level of brain-derived neurotrophic factors in the body. Because BDNF has antioxidative and apoptotic capabilities. An experiment showed that by using BDNF to treatment of human spermatozoon. The sperm count and vitality of the experimental group increased significantly, and the percentage of death decreased significantly [34]. This technique improves sperm quality and also helps men to reduce the probability of infertility. In addition, the elevated levels of BDNF were observed in patients with allergic diseases such as asthma, urticaria or atopic dermatitis [35]. At the same time, there have been many studies on the association between BDNF gene polymorphisms, central nervous system diseases and mental disorders. For example, Meng *et al.* [36] believed that the formation of internalized neurological disorder is related to the BDNF gene rs10835210. Yang *et al.* [37] had found that the increased risk of schizophrenia is related to the BDNF gene rs2030324. The polymorphism of BDNF gene

Val66Met (rs6265) is a functional single nucleotide polymorphism documented in the literature. The single nucleotide polymorphism is associated with personality characteristics associated with anxiety and diseases pathogenesis associated with anxiety and depression, such as attention deficit hyperactivity disorder, which is considered a phenotypic variation of autism spectrum disorder. Studies were also shown that an increased risk of Alzheimer disease is positively correlated with rs6265, especially among the white race and female patients with delayed Alzheimer disease [38]. Val66Met polymorphism is one of the many polymorphic locus studied in many genes of BDNF, and it is found that patients with the allele have less frontal cortex tissue, thus, it is difficult for patients to concentrate on learning and memory, and their work efficiency is decline significantly [39]. The study was found that children in the west region of China had higher AA and GA genes frequency of the Val66Met polymorphism. In contrast, Chen Jiehong *et al.* [40] had found that GA was slightly lower in healthy people in Taiwan, China, but it was higher GA among children with autism of Han nationality in southern China. Compared with the French population, three of the five alleles of the BDNF gene dinucleotide repeat polymorphism in the patients from southern China are similar, only the A1 (174 bp) allele was more frequent, while A3 (170 bp) was lower frequent. Therefore, there were some differences in the distribution of alleles and gene frequencies on BDNF gene polymorphisms among populations in different countries and regions.

Compared with other neuropsychiatric diseases, there are few studies on BDNF gene polymorphisms in children with autism. When studied the average serum levels of BDNF in children with ASD, Meng *et al.* [41] had found that they were significantly higher than healthy children, and the children with ASD were positively correlated with the CARS score, while the BDNF genotyping results were shown no significant difference between the ASD group and the control group. Analysis on polymorphism locus of BDNF gene and children with autism from the papers published by other Chinese scholars such as Zhou Jiaxiu on domestic core journals was suggested that “The repeat polymorphisms of BDNF gene dinucleotide are associated to the children with severe autism or linkage disequilibrium.” They think it suggests that the children with mild to moderate autism may have different genetic pathogenesis compared with children with severe autism, which may be caused by the fact that the candidate genes in children with severe autism are located near by the dinucleotide repeat polymorphisms locus of BDNF gene. The patients with different genotypes of BDNF were divided into groups according to the Childhood Autism Rating Scale (CARS), and it was found that the scores of the GA group and the GG group were significantly different by performing an analysis of variance. The score of GA group was lower than the GG group, which may indicate that after G mutated as A, it can inhibit the symptoms of autism. At the same time, they also had performed analysis of variance on the dinucleotide repeat polymorphism locus of BDNF gene based on CARS and found that the interaction factor score

of A1A3 group was significantly lower than that of A3A3 group. The interaction factor was related to A3 (170 bp). There was a negative correlation with the A1 and A3A3 genotypes, which means that the A1 allele can suppress the symptoms of autism, and the A3 allele can trigger the symptoms of autism. A recent study on the risk of autism in northern Iran populations [42] was shown that the G allele of its MTR A2756G gene polymorphism (rs1805087) was associated with an increased risk of autism. The domestic scholars such as Li Jiaxin *et al.* had found that compared with healthy infants, there were no statistically significant difference on the GG, AA, and AG gene frequencies and the A and G allele frequencies of autistic children receiving rehabilitation training; while on the allele and genotype distribution, children with severe autism receiving rehabilitation training were shown the statistically differences with and mild-to-moderate autistic children, which suggests that the early pathological process of autism may be related to expression levels and protein levels of BDNF gene. Further researches had found that serum BDNF levels in autistic children receiving rehabilitation training were higher than those in healthy children. Among the autistic children who received rehabilitation training, compared with AG and GG, patients with AA genotype had the lowest BDNF concentration in serum, which indicated that AA genotype can reduce the expression level of BDNF.

However, Lu *et al.* [43] believed that compared with the normal population, patients with autism were shown no difference on the allele and gene frequency of Val66Met, which is different to the association study of BDNF polymorphism in patients with autism by Raznahan, Gadow, and KD [44] [45]. Studies in South Korea have shown that the polymorphisms of BDNF gene may affect the pathogenesis of ASD, which plays a key role in the differentiation of normal neuronal cells during the development of embryos and postnatal neurons through its neurotrophic effects [46]. In a survey of autism patients in China [47], some researchers had selected the MECP2 genes which were previously thought to be mainly associated with Rett syndrome, and confirming that mutations in this gene may also cause autism spectrum disorders. However, other scholars had failed to determine the association between autism and rs6265 polymorphism in the study about polymorphism of BDNF gene. Therefore, we need a larger sample size and further expand the locus to study the BDNF gene polymorphism in order to conduct further learning.

5. Conclusions and Suggestions

Autism is one of the hot topics in the current research on neuropsychiatric diseases. Although hundreds of susceptible genes have been detected, all the genetic mutations found can only explain about one-third of patients. Taking the role of brain-derived neurotrophic factors in synaptic plasticity and synaptic growth as discussed above as an example, it can only explain some of the symptoms of children with autism and/or as a direction to provide treatment for neurodegenerative diseases. Looking at all the current surveys of autistic children at home

and abroad, most of them are dominated by genetic studies, but the author thinks that parents are a safe haven and a comfort zone for children, and they are the closest people to children, the strongest spiritual and emotional pillars. If one party cannot bear the pressure of the spirit and economy, they will be neglecting and tired of coping with the child. This will surely plunge the child into psychological confusion and psychological contradiction, thus worsening the evolution of the severity of the child with autism the day after tomorrow. Therefore, we should pay more attention to the demographic characteristics, geographic environment, family education, and parental education of autistic patients for a long time and large samples. This may explain the remaining symptoms of children with autism. I am more convinced that over time, we will know more about the symptoms of childhood autism, and more patients will benefit from it.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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