Physiological Factors of Autism

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Abstract: Autism is a group of neurodevelopmental disorders caused by psychological and physiological factors. It mostly occurs in infants and young children, and the disease process is long, which has brought great material and spiritual pain to the patients themselves and their families. Studying the factors of autism is of great significance to develop treatment methods and alleviate the disease. This paper summarizes the physiological factors of autism by combing the literature on the causes of autism. The results show that heredity, heavy metals, maternal factors, nutrition, brain structure and function, intestinal microorganisms, and immune system are important factors for autism. Autism may be affected by a variety of factors. However, at present, the etiology of autism is not completely clear, and researchers need to further take interdisciplinary exploration and deepen existing research to further clarify the pathogenesis of autism.

1 INTRODUCTION

Autism, also known as autism disorder, is common in infants and young children. Its core symptoms are impaired social function, lack of verbal communication ability, and the emergence of repetitive and stereotyped behavior. Asperger syndrome, childhood disintegrated disorder, and other developmental disorders not otherwise specified (PDD-NOS) and autism or classic autism spectrum disorders are collectively referred to as autism spectrum disorder (ASD).

The incidence rate of autism has been rising since Kanner reported its autism in 1943. It has become a worldwide health issue. According to the statistics of the Centers for Disease Control and Prevention, the rate of autism spectrum disorder diagnosed before e the age of 8 in 2016 was 1 / 54, while the statistical data in 2014 was 1 / 59, and the prevalence increased by about 10%. By the middle of adulthood, the rate of autism increased to 1/45, and the incidence rate of the male was significantly higher than that of females, reaching 4:1. In China, there is no reliable national epidemiological survey report on autism, but according to the sampling survey of Hainan Province in 2017, the total prevalence of autism among children aged 0-6 years in Hainan Province is 0.62%, including 0.99% for men and 0.17% for women (Li 2018).

Because the etiology and pathogenesis of autism are not clear, there are some difficulties in prevention and treatment, and the treatment cost is relatively expensive, which leads to a lot of economic burden and emotional pain for autistic patients and their family members. At present, patients often use rehabilitation training combined with certain drugs for long-term treatment, and researchers have not reached an agreement on the treatment and pathogenesis of autism. This paper reviews the influencing factors (focusing mainly on the biological aspects) of autism found in recent years. Hopefully, it might provide some references and help for research on the pathogenesis and treatment of autism.

2 PHYSIOLOGICAL FACTORS OF AUTISM

2.1 Genetics

2.1.1 Family and Twin Studies

Researchers' research on family members of autistic patients found that the risk of autism in immediate

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relatives is affected by genetic factors. If one child in the family already has autism, the probability of having another child with autism can reach 5 ~ 6% (Duan 2015). Family members with autistic children often have affective disorders and more social skills or repetitive behavior abnormalities. Another study showed that the recurrence rate of autism spectrum disorders in the same family was 10 ~ 35%. At the same time, about 20 ~ 25% of the brothers and sisters of autistic families have language defects (Wu 2016). In the study of twins, one of the identical twins has autism, and the other has a probability of 60% ~ 90%, While only 5% of fraternal twins. This series of studies show that autism has obvious familial heredity.

2.1.2 Gene Variation Research

The research on genetic factors of autism mainly focuses on gene variation and chromosomes, including point mutation, copy number variations (CNVs), linkage region, and microRNAs. The pathogenic genes of some syndromic ASD patients have been identified. For example, Rett syndrome is caused by MeCP2 mutation. Neuroligin (NLGN3 and NLGN4) was the first mutant gene found in patients with non-syndromic ASD (Cao 2015). Copy number variations (CNVs) are a structural variation of genes, which refers to the loss or increase of genetic material due to deletion, insertion, or gene rearrangement, which affects gene expression. The results show that CNVs may have a certain impact on the specific components and severity of ASD (Huang 2018). Some studies believe that autism is more likely to be controlled by multiple genes.

Cytogenetic studies have found that chromosome aneuploidy is associated with autism and is likely to be associated with language disorders. A study found that XYY individuals showed a significant impairment of language and social communication, and the incidence rate of ASD in aneuploidy males was higher than that in the general population (Lisa 2018).
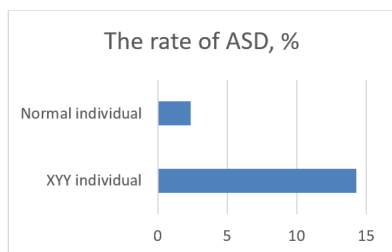

Figure 1: Comparison of the rate of ASD between XYY men and normal men (Joseph 2018).

After comparing the samples of nearly 4000 patients with "autism spectrum disorder" with the control group, researchers from Icahn School of medicine at Mount Sinai and other institutions in the United States found more than 100 genetic variants that increase the risk of autism. In addition, the researchers also focused on the genetic differences between autistic patients and their healthy siblings and speculated that the above genetic variation may be related to more than 20% of the incidence of autism (Deng 2016). Gene variation has a great impact on autism.

2.2 Heavy Metal

Although thiomersal has been shown not to increase the risk of autism in children, other heavy metals still have some effects on ASD. A controlled study of autistic children and normal children found that heavy metals were higher in the blood and urine of autistic children. Among them, the content of lead in the blood of children with autism is 41% higher than that of the normal group, the content of lead, thallium, tin, and other metals in urine are 74%, 77%, and 115% higher than that of the control group, and the content of calcium in the blood is 19% lower than that of the control group (Duan 2015). Another study found that children with high concentrations of hair lead and nail arsenic had a higher risk of autism than those with low concentrations; The risk of autism in children with higher concentrations of hair manganese and nail zinc is lower than that in children with low concentrations (Huang 2019). In addition, methylation of mercury can damage the nervous system and lead to brain atrophy (Duan 2015).

Table 1: Partial metal levels in autistic and control children (μg/g). (Huang 2019).

Hair		
	Case group	Control group
Lead (Pb)	1.60	0.80
Magnesium (Mg)	17.29	27.92
Manganese (Mn)	0.14	0.31
Zinc (Zn)	92.51	146.85
Calcium (Ca)	244.41	317.49
Nail		
Lead (Pb)	1.36	0.57
Zinc (Zn)	105.50	89.90
Arsenic (As)	0.17	0.13

2.3 Maternal Factors

2.3.1 Age of Parents

Research shows that the increase of parents' age will increase the risk of ASD in children, but the influence of mother's age is nonlinear, while the influence of

father's age is linear, and the influence of mother's age on ASD is greater than that of father's age (Selma 2014). Duan Yanrui et al. obtained the conclusion that the proportion of mothers with childbearing age greater than 35 in the autism group is higher than that in the normal group through the comparative study of children in the autism group and healthy group (Duan 2021). It can be seen that parents who are too old at childbirth increase the possibility of children suffering from ASD.

2.3.2 Influencing Factors during Pregnancy

The disorder of the intrauterine environment during pregnancy is a potential risk factor for autism. In the study of 190 autistic children in Tianjin, Chinese scholars found that smoking, chronic diseases unrelated to pregnancy, affective disorders, pregnancy complications, and edema are all risk factors for ASD (Cao 2015). Another study found that after injecting pregnant female mice with the human influenza virus, their offspring will have autism-like abnormal behaviors such as lack of inquiry behavior and communication behavior. Prenatal stress may have a similar effect on the human body (Duan 2015). In addition, Huang Danni found that prenatal depression in mothers increases the risk of autism in children. In terms of life behavior, the daily use of microwave ovens by mothers will increase the risk of autism in children (Huang 2019). Duan Yanrui et al. found that the proportion of mothers with depression during pregnancy in the autistic children group was higher than that in the normal group, which supported the above research conclusions (Duan 2021).
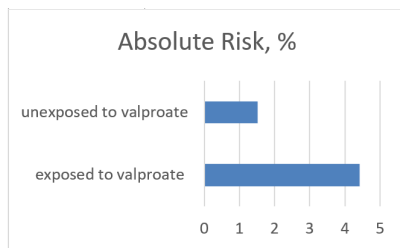

Figure 2: Association Between Any Maternal Use of Valproate During Pregnancy and Autism Spectrum Disorder (Christensen 2013).

Drugs also have an impact on the prevalence of ASD in children. Studies have shown that the use of acetaminophen by pregnant women is associated with ASD in boys, and also harms children's attention. The degree of correlation is related to the frequency of exposure (Huang 2018). Christensen, J. et al. analyzed the prenatal use of valproate by mothers of 5437 ASD children in Denmark from 1996 to 2006

and found that taking valproate significantly increased the risk of ASD in their offspring (Christensen 2013).

2.4 Nutrients

2.4.1 Glutenin and Casein

The study found that there were unresolved glutenin and casein in the urine of patients with autism spectrum disorders. This suggests that patients with ASD may have the disorder of decomposing glutenin and casein. The opioid excess theory holds that children's intake of glutenin and casein will have adverse effects on their behavior and development (Duan 2015).
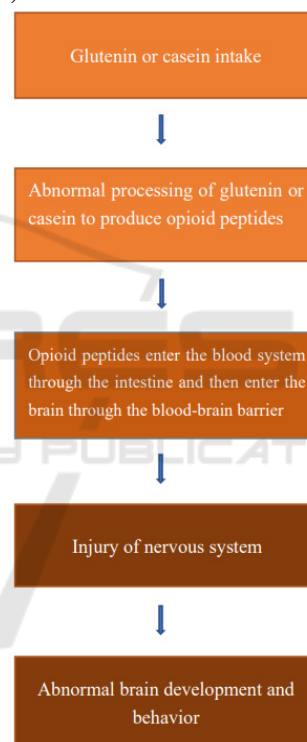

Figure 3: Schematic diagram of the opioid excess theory.

Knivsberg randomly divided 20 ASD children into experimental groups and control groups and gave them glutenin-free, casein-free diet (GFCFD), and ordinary diet respectively. After one year, the stereotyped behavior of children in the experimental group was reduced, and the nonverbal cognitive level and motor disorder were significantly improved (Knivsberg 2002). In addition, a study from Denmark investigated the impact of GFCFD on the social interaction of ASD children. The results showed that children given GFCFD for one year had significantly

lower scores on the Autism Diagnostic Observation Schedule (ADOS), the Gilliam Autism Rating Scale (GARS), and the Attention-Deficit Hyperactivity Disorder IV scale (ADHD-IV). This shows that the failure of normal decomposition of glutenin and casein is closely related to ASD.

2.4.2 Other Nutrients

The nutrients in food are very important to maintain the normal physical and mental health of the human body. Clinical studies have found that a lack of vitamins, minerals, and other nutrients will lead to psychological and behavioral changes. The occurrence of ASD may be caused by the abnormality of nutrients. For example, B vitamins and trace elements are very important for brain tissue health. After taking vitamin B6 and magnesium, ASD children's symptoms are improved, their alertness is improved, and their negative, self-mutilation and stereotyped behaviors are significantly reduced. Vitamin B12 injection can significantly improve the language ability, social communication behavior, and other problems of ASD patients (Duan 2015). Manohar's experiment shows that children with ASD have a lower level of breastfeeding than normal developing siblings, and exclusive breastfeeding can protect vulnerable children. Tseng Pt and others believe that breastfeeding can prevent ASD. Wang Yu's study found that infants who did not receive breastfeeding six months ago were risk factors for ASD in children (Huang 2018).

2.5 Brain Structure and Function

2.5.1 MRI Study

People with autism have the problem of early brain development abnormalities. Liu Yang extracted the brain sMRI data of 59 ASD children aged 2-4 years and compared them with 50 normal children. The results showed that there were significant differences between the ASD group and the normal control group in 66 of 150 cerebral cortex and volume indexes. The cortical thickness of the parietal lobe, occipital lobe, frontal lobe, temporal lobe, precuneus, brainstem, and amygdala was significantly higher than that of normal children, and there was overdevelopment of brain structure (Liu 2020). At the same time, the excessive development of the frontal lobes and temporal lobes of the brain is mainly concentrated in cortical white matter and limbic structures. These regions play an important role in social communication and sports. The study also found that ASD patients have

problems with cerebellar hemisphere overdevelopment and corpus callosum volume atrophy (Wu 2016). In addition, fMRI study found that there was extensive blood supply deficiency in the early brain of ASD patients, resulting in delayed or abnormal brain development (Deng 2016).

2.5.2 EEG Study

Using electroencephalography (EEG), researchers found that ASD patients had extensive functional integration disorders, mainly manifested in the asynchronous activation of signals (Wu 2016). Duan Keyi found that the brain network topology of ASD patients is different from that of normal people. This difference makes the performance of autistic people in cognitive behaviors such as visual-spatial attention, environmental perception, and language expression lower than that of normal people (Duan 2019).
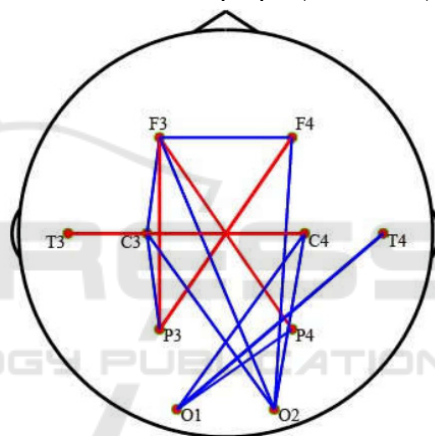

Figure 4: Topological differences of brain networks between autistic children and normal children in resting state. The red and blue solid lines represent respectively the weak and strong coupling relationship between autistic children and normal children. (Duan 2019).

2.5.3 Broken Mirror Theory

The broken mirror theory originated in the early 1990s. Researchers found some neurons in rhesus monkeys. When the monkeys themselves made action or observed the researchers doing the same action, these neurons showed a similar activation response. Therefore, these neurons were named mirror neurons. Later, a similar nervous system was found in the human brain, which is mainly composed of the inferior parietal lobe, inferior frontal gyrus, and superior temporal sulcus, called the mirror neuron system, MNS. According to the broken mirror theory, the abnormal function of MNS leads to the social cognitive defects of autistic patients. Individuals have

inconsistent social cognitive functions, such as empathy, imitation, and movement understanding, which leads to the diversity of symptoms among autism patients.

Oberman used EEG research results to show that normal subjects showed significant μ -wave suppression when observing and performing actions, whereas autistic subjects had μ -wave suppression when performing actions, but not when observing actions (Oberman 2005). This indicates that the sensorimotor cortex of autistic patients performing movements is normal, but MNS involving movement imitation is abnormal. In addition, many studies by dapretto et al. have found abnormal MNS function in patients with autism (Meng 2017). However, many scholars have questioned the theory. For example, Hamilton analyzed 25 research reports on MNS function and found that there was no conclusive evidence for the statement of abnormal MNS in patients with autism; Raymaekers, Dinstein, fan, et al. also concluded that MNS function in patients with autism is normal (Pan 2016). Therefore, the broken mirror theory is still controversial in academic circles, and its correctness needs to be further verified.

2.6 Intestinal Microorganisms

Intestinal microorganisms can help the human body digest and absorb nutrients. By secreting various enzymes, they synthesize some vitamins and bioactive substances, affect human metabolism, control body weight, shape the human immune system and help resist the invasion of pathogenic microorganisms. About 70% of the substances in the blood come from the intestine. The balance of intestinal microorganisms is very important to human health. Once this balance is broken, it may lead to a variety of diseases.

It is found that the development of intestinal microorganisms is synchronized with the development of children's brains, and the occurrence time of ASD is similar to the development node of intestinal microorganisms. The intestinal microbiota of ASD patients was unbalanced, and the composition and proportion of bacteria and fungi changed. This change can affect ASD through metabolites, immunity, neuroendocrine, and vagus nerve. For example, most ASD patients suffer from gastrointestinal diseases, and the symptoms of gastrointestinal diseases are positively correlated with the severity of ASD. ASD patients with gastrointestinal diseases may also have abnormal behaviors such as anxiety, self-mutilation, and attacking others. Functional constipation is associated

with stereotyped obsessive-compulsive behavior in ASD children (Wu 2018). Gastrointestinal symptoms and behavioral abnormalities are affected by intestinal microorganisms, suggesting that ASD is related to the changes of intestinal microorganisms.

2.7 Immune System

Autism is closely related to the immune system. Studies have found that autoimmune diseases are related to autism. The percentage of autistic family members with autoimmune diseases is significantly higher than that of normal families. About 46% of the families of children with autism have more than two members who have suffered from autoimmune diseases, and the more patients, the greater the risk of children suffering from autism (Duan 2015).

Autism may also be related to immune factors. Some studies have found that the contents of some immune factors such as tumor necrosis factor (TNF), interferon, and interleukin (IL) in the blood of ASD patients increased. Pro-inflammatory cytokines in the cerebral spinal fluid (CSF) also increased (Wu 2016). Autism is often accompanied by an excessive inflammatory response of the nervous system. In the central nervous system of autistic patients, the inflammatory response can activate microglia. Some researchers believe that microglia may be the intermediate hub between immune response and ASD. Microglia are phagocytes that settle in brain tissue. Under inflammatory stimulation, antigenicity is enhanced, and nerve cells are killed. The excessive inflammatory reaction leads to abnormal activity of microglia, and a large number of normal brain cells are attacked and phagocytized, thus affecting individual neural activities (Jin 2018).

In addition, using the method of identifying genes that promote the generation of autism, other researchers have found evidence that several pathways associated with the immune system are disturbed to promote the generation of autism spectrum disorders (Anonymous 2013), which strongly shows that immune function plays a role in autism.

3 CONCLUSION

With the development of science and technology, people's understanding of autism has also stepped onto a new level. Autism is not caused by a single factor, but by a variety of factors. Biological factors are very important. Genetics, heavy metal intake, maternal health during pregnancy, nutrients, brain

function and structure, intestinal health, and immune system may cause autism. The exploration of etiology has also made continuous progress in treatment methods. Microbial intervention therapy, food therapy, and other methods have also entered the vision of doctors. These emerging therapies have made some achievements in combination with the original methods of behavioral intervention, special education, drugs, psychotherapy, and so on.

However, due to the complex etiology of autism, we can not fully understand its pathogenesis. For example, heredity can only explain 10% - 30% of the causes of autism, and many autistic patients do not show any genetic signs; The intestinal microbial population is also affected by individual living habits, diet, drug use, and other factors, so it is difficult to determine the specific intestinal microbial map of patients with autism. When the researchers reported that these abnormalities were related to autism, they simply explained a statistical connection, and could not explain the causality and the underlying physiological principles. At the same time, due to the limitations of sample size or research methods, the scientificity of emerging hypotheses such as broken mirror theory has not been unanimously recognized by scholars. Therefore, these conjectures need more and more convincing research to support.

In the future, we need to carry out cross-exploration of different disciplines. The causes of autism span a wide range, and the differences in theories and methods of different disciplines will help us better eliminate irrelevant variables and improve the credibility of the research. At the same time, it is necessary to continue to deepen the research on the conclusions already obtained, dig out the complex causal relationship, clarify the pathogenesis behind it, and improve the cognitive level. Moreover, it is important to design and conduct more convincing studies to verify the emerging hypotheses and reference the research methods of other types of mental disorders to provide new ideas for autism research.

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