What is the Optimal Method of Treating Autism?

Xueqi Zhu

Malvern College Qingdao, 77 Tieqishan Road, Chengyang District, Qingdao, Shandong, 266106, China
Corresponding Author: Xueqi Zhu, Email: 3041028551@qq.com

Abstract
In recent years, the global prevalence of autism has gradually increased, which seriously affects the mental and physical health of the children and brings a heavy burden on both families and society. Currently, specific therapeutic means are still lacking, and there is no case of complete cure. In this project, the effectiveness and limitation of different interventional therapies and medical treatments for autism are analysed and compared, showing that the intervention of intestinal microecology implements has quicker effects on autistic children, and acts as a more targeted treatment for different individuals. And it has a closer connection with different causes of autism and has a longer-time therapeutic effect. Therefore, it can be considered the most advanced and promising treatment for autism.

Keywords
Optimal method; Autism; Applied Behaviour Analysis; Intestinal Flora

Introduction

Autism spectrum disorders, ASD, also known as generalized developmental disorder or autism, are defined as a developmental disorder characterized by social interaction and communication disorders, a narrow range of interests, and repetitive stereotyped behaviours. They lack “Theory of Mind”，which means that they cannot understand other people’s emotions and goals.

For decades, a huge number of children have been suffering from autism and it brings harm and burden to their families and society. According to the "Blue Book" survey, one person in 52.4% of the families gave up their jobs to look after autistic children, and the mother accounted for 90.2%. This directly leads to a linear decline in the quality of life of autistic families. The disease itself is thought to have existed for a long time, but Leo Kanner, an American child psychiatrist, was initially reported to have come up with the name autism.

Autism can last for a lifetime and is difficult to be cured completely and the prevalence rate has increased year by year to a terrible number. A study done by the United States in 2016 showed that autism prevalence was 18.5 per 1,000 children aged 8 years, which means that 1 in 54 children have autism. And autism was 4 times as prevalent among boys as among girls. According to feedback from many parents with autism, in the rehabilitation classes and examinations of relevant institutions, it costs about ¥9,000 CNY to ¥15,000 CNY per month to treat children with

Citation:Xueqi Zhu. (2022) What is the Optimal Method of Treating Autism? The Journal of Young Researchers 4(12): e20220608

Received on May 13, 2022; Accepted on May 23, 2022; Published on June 08, 2022

autism, which is about ¥150,000 CNY a year. Autism has become an important disease that causes mental disability in children. With the increase in the incidence, it is and will continue to bring a huge social and economic burden to the family and society.

Many autism experts have developed a variety of treatments, including medical treatments (e.g., risperidone, aripiprazole, and citalopram) and psychological interventions (e.g., Applied Behavior Analysis, Treatment and Education of Autistic and Communication Handicapped Children and Developmental Individual differences Relationship). Intestinal flora treatment is also considered to be a promising treatment and it has shown results in experiments. It is currently the most promising treatment for autism.

At present, most studies on autism are analysed from the perspective of specific cases or experiments, and few of them are integrated to explore the effectiveness of these treatments. In this dissertation, I will introduce our the feasible treatment methods so far, like psychological intervention therapy, medical treatment, and intestinal flora treatment, and comprehensively analyse the pros and cons of the above treatments in order to find out the optimal method for the treatment of autism. I'm expecting to provide comprehensive and useful information for scientific researchers and medical workers and then contribute to the development of autism studies.

Literature Review

Autism is considered to be caused by both the environmental factors and the genetic factors. Environmental factors can be external factors that the mother receives during pregnancy or factors that the child receives during infancy. Genetic factors can be some specific genetic mutations that cause developmental problems. However, we have no way of knowing the specific causes of each child because the cause of autism are very complicated. At present, an effective treatment is also something we need to consider and study. These reasons have caused autism to become very difficult to cure, which affects the future of millions of children.

Etiology of Autism

Previous research has established that the cause of autism is complex as the cause of autism is the interaction between genetics and the external environment (Herbert, 2006). The controversy about the causes of autism has raged unbarred for over a century. So far, the exact etiology of autism has not been found.

Environmental Factors

Although genetic factors play a significant role in the pathogenesis of autism, it was pointed out in a 2015 meta-analysis report that autism caused by genes accounted for 64% ~ 91% of the total number of autistic patients. (Picerno, 2015) In addition, although the genes of identical twins are generally considered to be the same, studies have proved that the severity of autism symptoms is different between identical twins.(Hu, 2009) And there is even one with the disease and the other without (Macfabe, 2013), which indicates that environmental factors may play an essential role in autism. This shows that genetics cannot fully explain the etiology of autism.

The environmental factors can affect the development of language and cognitive ability of individuals by affecting their brains at different stages of development and then cause autism. It mainly includes pregnancy, diet, exposure to chemicals and intestinal flora, etc.

Influencing Factors During Pregnancy

Exposure to certain chemicals during pregnancy may cause harm to the fetus. Roberts et al. found that when the mother is pregnant for 1 to 8 weeks that is also an important period for the development of the embryonic central nervous system. Exposure to organochlorine pesticides increases the risk of autism in babies by 6.1 times (Roberts et al, 2007).

Daily necessities containing triclosan also pose a risk of autism to the fetus. This is because triclosan has a negative impact on the retinoic acid signaling pathway in the nervous system after maternal contact with the fetus. Hormonal abnormalities of pregnant mothers are also one

of the causes of fetal autism. For instance, excessive androgen brought by mothers with polycystic ovary syndrome may increase the risk of fetal autism and correspondingly, excessive prenatal estrogen can also lead to autism (Dalman, Wildman, Arver, Lee, Magnusson & Gardner, 2016). Prenatal steroid hormone activity increases, which may affect gender differentiation, brain development, and function. In addition, hyperglycemia or anemia due to iron deficiency during pregnancy has a certain negative effect on the brain development of the fetus, and the risk of autism is also higher.

Data from several studies indicate that there is an obvious relationship between obesity during pregnancy and the prevalence of autism in the offspring. In 2011, Dodds et al. found that if the mother's weight before pregnancy exceeds 90 kg, it will increase the likelihood of children with autism (Dodds, Fell & Shea, 2011).

Diet

Autism has a close relationship with diets such as insufficient breastfeeding and unbalanced eating style whose influence on autism can also be realised through intestinal flora. Breast milk is an important source of beneficial organisms such as lactic acid bacteria and bifidobacteria for infants. Compared with babies who are breastfed for at least 6 months, babies who are breastfed for less than 2 months have a significantly higher risk of autism. In the intestines of infants fed with the milk powder, the numbers of bifidobacterium, Bacteroides, clostridium, and staphylococcus are close to each other, not showing the advantage of beneficial bacteria.

Exposure to Chemicals

More and more studies have shown that exposure to chemical substances in the environment is related to the onset of autism, such as heavy metals and pesticides (Kinney, Munir & Crowley, 2019).

The excretion of heavy metals in autistic children is significantly lower than that of normal children, excessive accumulation of heavy metals in the body may chelate with brain tissues and affect brain development. Studies have found that the level of the burden on the body of a child with autism is related to the severity of the disorder (Adams, Baral & Geis, 2009). However, few studies have investigated the etiological link between exposure to chemical substances in the environment and autism, which means further research is needed to confirm.

Intestinal Flora

The study found that the intestinal flora of patients with autism are unbalanced, and the composition and proportion of bacteria and fungi have changed. Compared with healthy people, the content of Clostridium in the intestines of patients with autism is significantly increased. The ratio of Firmicutes decreased, and the content of Lactobacillus and Desulfovibrio increased (Tomova, Husarova & Lakatosova, 2015). Among them, Clostridium is related to the production of neurotoxins. The released neurotoxins are transmitted to the Central Nervous System through the vagus nerve, inhibiting the release of neurotransmitters, thereby causing self behavioural manifestations related to autism (Finegold, Summanen & Downe, 2017).

Studies have revealed that in the intestines of patients with autism, the important bacterial genera that degrade and metabolize carbohydrates include Prevotella, Veronococcus, and Faecococcus (Kang, Park & Ilhan, 2013). These bacterial genera can regulate the integrity of mucosal and intestinal epithelial cells (Williams, Horning & Parekh, 2012). In 2017, Coretti et al. found that the intestinal flora of the autistic population is imbalanced, among which Sartreella, Bacteroides, and Paramimics Bacillus, Oscillatoria, and Dehalobacterium are gender-specific intestinal microbial communities and are associated with abnormal behaviours, increased intestinal permeability, and enteritis and it also causes some gut barrier defect which is also known as “leaky gut” (Coretti, Cristiano & Florio, 2017). Some neuroactive compounds that will affect brain functions can pass through the intestine and finally affect the brain. It will induce some abnormal behaviours.

Genetic Factors

Qiu said that the cause of autism is still mainly

genetic (Wang, 2017). After gene mutation, some proteins have changed in function, causing abnormality in the circuit function of brain nerves. Different neural circuits in the brain are responsible for different cognitive behaviors such as learning and memory, and abnormalities in neural circuits can lead to abnormal behaviors.

Neuroligin-3 Mutation

Recently, a research team led by Professor Peter Scheiffele of the Biological Center of the University of Basel in Switzerland discovered the connection between Neuroligin-3 and the oxytocin signaling pathway in a mouse model. It is worth noting that oxytocin is a hormone secreted by the neurohypophysis, which can regulate the social behaviour of mammals, especially social interaction. The researchers found that the Neuroligin-3 gene mutation disrupted the oxytocin signaling pathway in neurons in the reward system of the mouse brain, thereby reducing social interaction between the mice. Further research found that the loss of Neuroligin-3 affected the balance of protein synthesis in these dopaminergic neurons and affected the neuronal response to oxytocin (Peter, 2020). Because of this, the mutation of this gene is very likely to cause certain brain functions to be disordered.

SH3RF2 Single Copy Deletion

A mouse model with a single copy of SH3RF2 deleted has been made by Xu's lab to determine whether SH3RF2 is involved in brain development and whether SH3RF2 mutations can cause autism. (Xu, 2020) The team members found that SH3RF2 single-copy-deficient mice showed obvious, restricted, repetitive patterns of behaviours. There were obvious abnormalities in social interaction and communication, accompanied by common manifestations of autistic patients such as hyperactivity and seizures. For the first time, this study confirmed that SH3RF2 single copy deletion is a risk factor for autism and even a pathogenic gene.

Treatment of Autism

The existing studies have made a series of more reasonable explanations for the symptoms of different individuals, which have a positive effect on the treatment of autism. In many years of theoretical and practical research, researchers have proposed a variety of treatment methods for autism, among which various behavioral interventions are widely used.

Applied Behaviour Analysis (ABA)

ABA is one of the most commonly used treatments for children with autism, which can help autistic children to learn social skills, language, and motor behaviours as well as reasoning skills to deal with more complex and challenging behaviours. This therapy is based on teaching children these basic skills through positive reinforcement and observation.

The key of this method is to decompose the tasks into a series of small or relatively independent steps according to a specific method and sequence and then use suitable positive reinforcement methods to determine and decompose the tasks, gradually train each small step until the child has mastered all the steps. Finally, they would be able to finish the tasks independently and use the knowledge and skills that they learned in other situations. Children with autism will be given one or more stimuli and they respond according to the stimuli. The therapist gives reinforcements for the correct response to encourage them and does not provide reinforcement for the inappropriate behaviours.

Treatment and Education of Autistic and Communication Handicapped Children (TEACCH)

TEACCH was created by Eric Schopler in 1970. It is a public health project of the University of North Carolina in the US, which is also known as systematic teaching. This is a community-based educational project which is aimed at enhancing mutual understanding, mutual exchange, and communication among autistic children and social disabilities, their relatives, families, and society.

A social communication disorder is the main symptom of children with autism. They do not understand normal social interactions, lack response to other people's emotions, cannot adjust their behaviors according to the social situations, appear uncomfortable in the group, and may even exhibit abnormal behaviours.

In addition to their language and social difficulties, they also have certain defects in physical coordination and motor ability compared with ordinary people. Reasonable exercise training (gross and fine exercise) can help them to be like ordinary people. TEACCH mainly pays attention to the following points: 1. In the training of gross exercises, attention should be paid to the intensity of exercise to ensure that while improving the children's exercise ability and balance ability, it will not cause too much burden on the patient's body. 2. In terms of fine motor training, while promoting the patient's perception ability, it is also necessary to pay attention to the interval between each exercise should not be too long (Guan, 2014).

The Intervention of Intestinal Microecology

A large proportion of patients with autism have gastrointestinal problems, including constipation, diarrhea, vomiting, abdominal pain, flatulence, and unusually foul-smelling stools. Patients with autism who have gastrointestinal symptoms are more likely to have problems such as irritability, anxiety, social withdrawal, etc. After the gastrointestinal symptoms are improved, the severity of autism patients has been reduced. Several studies have proposed that in patients with gastrointestinal dysfunction, the diversity, stability, and metabolic activity of the intestinal flora have changed (Collins, 2019).

Based on the theory of intestinal microbial imbalance, the most effective and direct method is to supplement probiotics to improve autistic behaviours. Probiotics regulate the balance of intestinal flora and are beneficial to the physical and mental health of the host. It is considered to be a safe and effective biological agent for the treatment of the microbial-intestinal-brain axis. Probiotics rebuild the balance of the flora, improve metabolism, reduce abnormal metabolites, and thereby improve autism. A study showed that after probiotics were given, the ratio of Bacteroides/ Firmicutes in children with autism increased, and the ratios of Desulfovibrio and Bifidobacterium bacteria were improved. At the same time, probiotics help the host fight infection. Supplementing probiotics can improve Candida and Clostridium infections in patients with autism. Lactic acid bacteria produce a large amount of short-chain fatty acid(SCFA), such as butyric acid can effectively prevent the transformation of Candida albicans hyphae, which is the first step for Candida albicans to transform from symbiotic bacteria into pathogenic bacteria, leading to mycelial invasion and systemic infection, thereby effectively improving autistic behaviours (Bohmig, Krieger & Saemann, 1997).

Probiotics can promote the nutrient absorption of the host, help the host metabolize drugs or heavy metals, and have a therapeutic effect on digestion and metabolism-related diseases (Collins & Bercik, 2009). In helping autistic patients to improve the problem of gluten and casein intolerance, microorganisms with strong proteolytic ability play an important role in this process. Lactobacillus helveticus can alleviate the allergic reaction of infants to milk and the hydrolysis of αS1- and β-casein by lactobacillus protease reduces the specific recognition of human immunoglobulin IgE and improves the protein metabolism of patients (Ahmadova, EI-Ghaish & Choiset, 2013).

Medical Treatment

At present, there is no specific medication for autism and current medication is mainly antipsychotic for anxiety, depression or obsessive-compulsive disorder, etc. They are used to change 5-Neurobiochemical systems such as HT and DA. Antipsychotics are only used for really challenging behaviours or aspects of autism that are not used routinely.

Risperidone is the only medication approved by the US Food and Drug Administration (FDA). Although it deals with self-injury, tantrums and aggression of people with autism, it does not target the main defects of autism, namely social interaction, communication, repetitive behaviours, etc. Furthermore, there is also a drug called melatonin which is used to help autistic children sleep better to help them with their autistic behaviours.

Other selective 5-HT reuptake inhibitors, citalopram, escitalopram, and fluoxetine can be

used to deal with serious behavioral issues such as self-injurious behaviours and repetitive behaviours (Posey, Erickson & Stigler, 2006). Treatment of epilepsy symptoms antispasmodic medication and medication for attention deficit disorder can effectively help autistic patients reduce impulsivity and hyperactivity, and the anti-allergic drug cyproheptadine also relieves the symptoms of autism (Akhondzadeh, Erfani & Mohammadi, 2004).

Individual Differences

The individual differences are relatively large as symptoms of autism also tend to be diversified. Each child with autism exhibits different symptoms because they have different causes of the disease. Therefore, personalized treatment and training are needed for core symptoms, which also brings difficulties to curation. The existing studies have made a series of more reasonable explanations for the symptoms of different individuals, although they have a positive effect on the treatment of autism, which is not suitable for all patients. It is proved that a combination of treatments work (psychological and biological) work best together because the origins of autism and its symptoms are different for each individual. However, most of these methods lack strict control of clinical variables, and the long-term prognosis is not ideal.

Discussion

In recent years, researchers have discovered a more effective and promising treatment and they have found that there is a certain connection between intestinal flora and autism symptoms. Intestinal flora can affect autism through metabolites, immunity, neuroendocrine, and vagus nerves. Specific beneficial microbial strains mainly use the microbe-gut-brain axis to regulate the micro-ecological balance and fight infection, regulate host metabolism absorption, and intestines. Probiotics targeting the intestinal flora may be an effective auxiliary treatment for autism. Compared with other typical interventions and treatments, The reasons for this statement are as follows and the summary of this information is shown in Table 1.

Table 1. Treatments and therapies of autism spectrum disorder (ASD)

Type	Description	Advantages	Limitation
Applied Behavior Analysis(ABA)	Based on teaching children these basic skills like language and motor behaviours as well as reasoning skills through positive reinforcement and observation.	Can effectively change the behaviours of autistic patients.	This change is only temporary and cannot achieve long-term maintenance effects as it does not touch cognitive aspects of children with autism.
Treatment and Education of Autistic and Communication Handicapped Children (TEACCH)	A community-based educational project which is aimed at enhancing mutual understanding, mutual exchange and communication among autistic children and social disabilities, their families, and society.	Can take place in home and by the autistic children's parents.	It has not paid special attention to social and communication skills like other methods and its high level of structure may increase the stereotyped behaviour of children and weaken their social interest.
Medical treatment	No specific medication for autism and current medication are mainly antipsychotic for anxiety, depression or obsessive-compulsive disorder, etc. They are used to change 5-Neurobiochemical systems such as HT and DA.	Some medication can effectively help autistic patients reduce impulsivity and hyperactivity, and also relieves the symptoms of autism.	They have a range of serious side effects like rebound when it is stopped and easily lead to drug dependence, therefore pose a harmful impact on the health of children for a long time.
The intervention of intestinal microecology	To supplement probiotics to improve autistic behaviours. Probiotics rebuild the balance of the flora, improve metabolism, reduce abnormal metabolites, and thereby improve autism.	A safe and effective biological agent for the treatment of microbial-intestinal-brain axis diseases. And it has a more direct ,more targeted and longer effectiveness compare with other treatments.	It is necessary to identify bacteria strain rather than species when applied to improve disease states.Need further in-depth clinical safety research.

The Intervention of Intestinal Microecology Has Quick Effects

At present, for the treatment of autism, there are many interventional therapies like Applied Behaviour Analysis (ABA) and Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) which are widely used and there are also some medical treatments. However, the impact of these interventions on autism is not direct. It requires long-term treatment with a minimal improvement of autistic behaviours. It takes a long time to see a little effect and each of these therapies has some serious disadvantages. Normally, the symptoms will be improved after taking these therapies for years. It costs so much money and time that most families cannot bear that burden.

On the one hand, although ABA can effectively change the behaviours of autistic patients, data from several studies suggest that this change is only temporary and cannot achieve long-term maintenance effects as it does not touch the cognitive aspects of children with autism (White, Koenig & Scahill, 2015) (Kincade & McBird, 2010). In addition, some scholars believe that ABA is a treatment that deprives children of autism of their subjectivity and ignores the inner needs of children with autism, which is not conducive to the socialization of autistics and is more difficult for them to integrate into this society as well as being understood by others.

On the other hand, there are not enough research reports on the overall effect of the TEACCH model, which shows that its effectiveness has yet to be demonstrated. TEACCH has not paid special attention to social and communication skills like other methods. Finally, this method generally takes place in the structured classroom. What happens when children have to deal with situations outside the classrooms such as daily life? At the same time, its high level of structure may increase the stereotyped behaviour of autistic patients and weaken their social interests. In fact, the theory that supports this training mode itself has many contradictions and remains to be verified.

At the same time, most medications only inhibit or relieve some of the symptoms of autism and therefore cannot treat the core defects of autism which are social and communication disorders. At the same time, they all have some serious side effects, such as irritability, lethargy, involuntary hand waving, and loss of appetite. If the medication is used improperly, such as long-term and large-dose medication, it may also bring about some other side effects, such as a rebound when the medication is stopped, making the behavioural symptoms more intense.

As for the intervention of intestinal microecology, researchers have evaluated the clinical research effects of Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium longum on autism. Only after 3 months of supplementation with the above probiotics, has the total score of the autism treatment evaluation checklist (ATEC) for children with autism significantly reduced, indicating that the severity of autism symptoms is reduced. The expression, language communication skills, social skills, perception, cognitive skills, and healthy physiological behaviours of autistic children were improved. In addition, the six-item gastrointestinal severity index The (6-GSI) score was also significantly improved, and the symptoms of constipation, defecation, flatulence, and abdominal pain were significantly improved, while the symptoms of diarrhea, constipation, and stool smell were also significantly reduced. This indicates that probiotics may be used as a non-pharmacological and have quick effects for children with autism auxiliary treatment (Shaaban, Gendy & Mehanna, 2017).

The Intervention of Intestinal Microecology Is a More Targeted Treatment

As I mentioned in the previous section, there are a variety of causes of autism, which also lead to different symptoms in different autistic individuals. For instance, some autistic children have repetitive movements, some have poor athletic ability, and some lack the ability to communicate with others. If the intervention therapy is used, it is difficult for us to determine the cause of this child's disease, and can only be treated by improving the symptoms of autism displayed, but this therapy does not treat autism from the root cause.

Luckily, if we treat autism by improving intestinal flora, there will be no such problems. Since 2007, countries have successively launched national microbiome projects, all of which is to understand the gut microbiome of healthy individuals through large-scale sequencing, and using this as a reference to study the changes in the gut microbiome under disease conditions. Compared with Applied Behaviour Analysis (ABA) and Treatment and Education of Autistic and Communication Handicapped Children (TEACCH), this therapy reduces the difficulty of autism treatment. By testing the genome, proteome, and metabolome of the intestinal flora of each child, different individual treatments are used for different results and supplemented with the corresponding probiotics. This treatment can treat autism from the root cause and is more targeted, and at the same time more effective.

Some experiments have proven that it is feasible to improve autistic behaviour by supplementing probiotics. Parracho et al. found that 17 children with autism were treated with Lactobacillus Plantarum WCFS1 (dose: 4.5×1010 CFU, 1 time/d, for 3 weeks). Compared with placebo, fluorescence in situ hybridization showed intestinal lactic acid. The number of bacillus and enterococcus increased, the clostridia were significantly reduced, and the behavioural

symptoms and cognitive abilities of the children were also improved to a certain extent (Parracho, Bingham & Gibson, 2005).

In fact, probiotic intervention does not directly affect the brain and behaviour, but is directed at the intestine. As Figure 1 shows (Li, Han, Dy & Hagerman, 2017), metabolites produced by certain microbial groups can pass through the gut barrier defect, which is also known as "leaky gut" and affect brain function. Some neuroactive compounds can directly affect the HPA axis and then the brain. If we correct the imbalance of intestinal microbes, reconstructing or restoring the normal information exchange between the intestine-brain and the brain, thereby improving the function of the microbe-gut-brain axis is more likely It is the best choice for autism treatment presently.

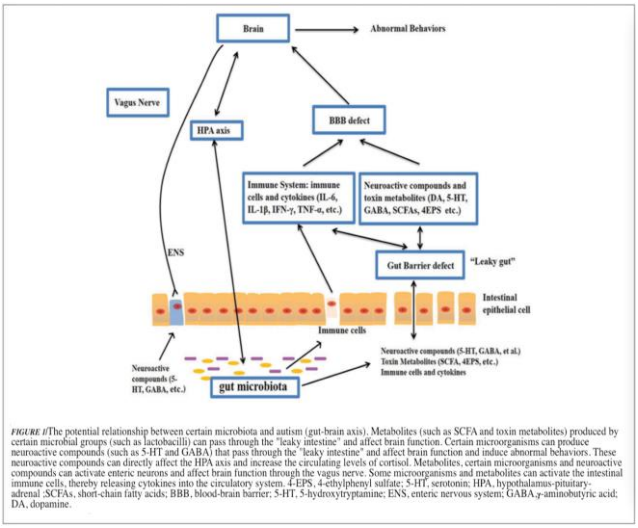

*FIGURE 1*The potential relationship between certain microbiota and autism (gut-brain axis). Metabolites (such as SCFA and toxin metabolites) produced by certain microbial groups (such as lactobacilli) can pass through the "leaky intestine" and affect brain function. Certain microorganisms can produce neuroactive compounds (such as 5-HT and GABA) that pass through the "leaky intestine" and affect brain function and induce abnormal behaviors. These neuroactive compounds can directly affect the HPA axis and increase the circulating levels of cortisol. Metabolites, certain microorganisms and neuroactive compounds can activate enteric neurons and affect brain function through the vagus nerve. Some microorganisms and metabolites can activate the intestinal immune cells, thereby releasing cytokines into the circulatory system. 4-EPS, 4-ethylphenyl sulfate; 5-HT, serotonin; HPA, hypothalamus-pituitary-adrenal ;SCFAs, short-chain fatty acids; BBB, blood-brain barrier; 5-HT, 5-hydroxytryptamine; ENS, enteric nervous system; GABA,γ-aminobutyric acid; DA, dopamine.

Figure1. The potential relationship between certain microbiota and autism

Probiotics can significantly reduce abnormal fungi in patients with autism and significantly improve autism-like behaviours. D-arabitol is used as a diagnostic indicator of fungal infection to detect fungal conditions in the body. The content of D-arabitol in the urine of patients with autism is higher than that of normal people. Researchers found that after taking Lactobacillus acidophilus to 22 autistic children, the amount of D-arabinitol (D-DA), a marker of fungal infection in the urine, and D-arabinose were significantly reduced. The ratio of alcohol to L-arabinitol (DA/LA) is also significantly reduced. At the same time, autistic behaviours such as gaze avoidance, social interaction, and feedback behaviours have also been significantly improved (Blaszczyk, 2012). Probiotics can promote the balance of intestinal flora, inhibit the growth of harmful bacteria, especially the growth of Clostridium difficile, reduces the toxic substances produced by harmful bacteria and it has been used in the clinical treatment of Clostridium difficile infection (Kaur, Kuhad & Garg, 2012). At the same time, it also suggests that probiotics can be used to treat autistic patients with Clostridium difficile infection.

Intestinal Flora Has a Closer Relationship with the Causes of Autism

As we discussed in the literature review part (2.1), autism is not caused by a single factor but is affected by both genetics and the environment. Environmental pollution, biological heterologous substances, maternal health during pregnancy, intestinal health status, diet and nutrition, and other factors may cause autism. These causes eventually affect the intestinal flora and cause the onset of autism. Children with autism often have gastrointestinal problems related to the severity of autism and abnormal intestinal microbiota has been proven to be one of the causes of symptoms of autism. Therefore, intestinal flora may be the key factor for autism. Disorders of the intestinal flora and their lack of function in regulating metabolites (corticosterone, indole pyruvate, and 4-ethyl phenyl sulfate), will affect neurobiological conditions and gastrointestinal function, leading to symptoms of autism. At the same time, the virus may also affect the symptoms of autism through the abundance of the intestinal flora, evolutionary trajectory, and metabolic output. It has been found that the overall bacterial diversity and abundance of Prevotella, Desulfovibrio, and Bifidobacterium increase after the treatment of microbial flora transfer increased. These changes can last at least 8 weeks after the treatment is stopped. Gastrointestinal symptoms have been reduced by about 80% and the behavioural symptoms of autism have also been significantly improved continuously (Kang, Adams, Gregory & Borody

et al, 2019).

Clinical studies have shown that the development of intestinal flora may begin in the fetal period, and the flora can be transferred in the uterus and affected by maternal factors during pregnancy (Tapiainen, Paalanne & Tejesvi, 2018). Factors affecting the fetus may increase the risk of fetal autism by affecting the intestinal microbes of the fetus. In the modified high-fat diet (MHFD) model of pregnant rats, a high-fat diet induces obesity in pregnant rats, and their offspring have changed intestinal flora and have abnormal brain development, showing social deficits. Further research found that the significantly reduced Lactobacillus reuteri (a decrease of more than 90%) in the intestinal flora is the key to causing social deficits in mice (Buffington, Prisco & Auchtung, 2016).

Wrong eating styles and unsafe products can cause intestinal flora disorder and cause autism-like behaviours. Autism children generally have serious eating problems, which are mainly manifested by a narrow range of food choices and a preference for high-fat, high carbohydrate diet, and processed foods whereas they reject fruits, vegetables, eggs, and protein foods. Additives in modern processed food threaten children's intestinal health. Emulsifiers such as polysorbate 80 and carboxymethyl cellulose can cause changes in the intestinal flora of wild-type mice, low-grade inflammation, and obesity/metabolic syndrome. Therefore, wrong eating styles lead to a serious imbalance of intestinal flora in patients with autism, which may increase the host's diet problems and form a vicious circle.

At the same time, with the development of industry, the discharge of some heavy metal pollutants will also affect children. Among them, some waste sewage or waste gas discharge pollutes the environment, causing the pollution to penetrate into our lives. The water we use or the air we breathe is polluted to a certain degree. Living in such an environment, the intestinal flora is likely to be changed, leading to intestinal disorders, which means the incidence of autism has increased significantly.

A considerable amount of research proved that leaky gut syndrome can be regarded as one of the important mechanisms of autism. It refers to the dysfunction or damage of the intestinal barrier and its characteristics are the ectopic entry of substances, bacteria, or their metabolites into the lamina propria which is the cause of many diseases (Maes, Kubera & Leunis, 2012). Compared with normal control children, they have increased intestinal permeability, even their parents have an expressively higher rate of abnormal intestinal permeability as well.

There are many factors that cause intestinal leakage, intestinal flora, and their metabolites play a central role. Studies have shown that before and after birth, intestinal flora determines the correct development of the blood-brain barrier and intestinal barrier in mice, the construction of intestinal barrier function is completely controlled by intestinal flora (Braniste, AI-Asmakh & Kowal, 2014). The change in intestinal flora composition may lead to an increase in intestinal permeability and the impairment of intestinal barrier function. The imbalance of the ratio of pro-inflammatory and anti-inflammatory bacteria in the intestine of patients with autism also leads to a leaky gut syndrome, resulting in toxic metabolites of intestinal flora entering the blood circulation.

In summary, these various causes are inseparable from intestinal flora, which precisely illustrates the importance and influence of intestinal flora treatment.

The Intervention of Intestinal Microecology Has a Longer-term Effect

In recent studies, intestinal microbial therapy has also been proven to have long-term effects on patients with autism. Medical treatments, have a range of serious side effects and easily lead to drug dependence, therefore posing a harmful impact on the health of children for a long time. In contrast to the treatment of intestinal flora, the children with autism symptoms have steadily improved after two years of treatment (Wook, James & Coleman et al, 2019).

Experiments have shown that two years after treatment, most participants reported

gastrointestinal symptoms remaining improved. The families generally reported that autism-related symptoms had slowly, steadily improved. At the beginning of the trial, 83% of participants rated severe autism on Childhood Autism Rating Scale (CARS). At the two-year follow-up, only 17% were rated as severe, 39% were in the mild to moderate range, and 44% of participants were below the autism diagnostic cut-off scores. There were significant improvements both in gastrointestinal and behaviour symptoms as compared with baseline measurements collected at the beginning of the trial.

Gastrointestinal benefits were mostly maintained from the end of treatment, and autism symptoms were reported to have improved significantly since the end of treatment. And also, changes in gut microbiota persisted for two years, including in overall community diversity and relative abundances of Bifidobacteria and Prevotella. This proves that the treatment of intestinal flora has a certain long-term nature and can be considered the best treatment at present method.

Future Prospect

Although the current treatment and intervention for autism is only limited to the relief of symptoms, its related research has put forward a constructive plan for the improvement and prevention of this disease. For example, keeping pregnant women's blood sugar normal may reduce the risk of autism in the fetus; avoiding exposure to chemicals such as triclosan can also reduce the possibility of autism in the fetus (Yuan, Gao & Shen et al, 2020). These years, researchers have done a series of scientific research on better and more effective treatments for autism, such as intestinal flora and which is in the bud.

Due to the wide variety of probiotics and different fungi with different functions, it is necessary to identify bacteria strains rather than species when applied to improve disease states. A large number of animal studies and clinical studies have revealed the role and good prospects of probiotics in the treatment of autism. Moreover, since each individual has different genetic background, flora composition, and living environment, the optimal treatment in the future, therefore, is to take individualized treatment and intervention measures according to different individuals. Although in-depth clinical safety research is necessary and the application of probiotics to improve and treat autism also requires further research and standardization, microbial intervention treatment of autism has begun to show its promise (Wu, Liang & Wang et al, 2018).

Conclusion

So far, there hasn't been a complete recovery of autism all over the world. Autism is caused by both genetics and environment, where gene mutations or abnormalities influenced by pregnancy, diet, intestinal flora, chemical exposure, and other factors can cause the onset of autism. Since the physiological mechanism of the cause of autism has not been fully explained, there is no specific medication for autism. With a range of side effects and efficacy limitations of psychiatric drugs, they are not currently recommended in autism treatment.

In addition, the individual differences of each child are also great and the symptoms shown are different. Currently, all interventional therapies like Applied Behavior Analysis (ABA) and Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) are not targeted at the treatment of autism, and their effect of it is not significant. But in recent years, a few constructive treatments for autistics have appeared. The latest and most promising treatment concept is the treatment of intestinal flora by improving the intestinal flora status in patients to improve autistic behaviors and already have certain effects. Compared with other therapies, it has quicker effects and is more targeted towards different individuals by suppling each autistic child with corresponding probiotics. Due to many causes having a certain relationship with the intestinal flora, treatment through this aspect is also considered feasible. The most inspiring thing is that the treatment of intestinal flora has a long-term impact. Unlike drug treatment and psychological intervention, which are dependent

and temporal, the intestinal flora will be improved for a long time over after treatment. Nevertheless, further research with improved standardization is still needed to enhance the wide acceptance of intestinal flora treatment.

Conflict of Interests: the author has claimed that no conflict of interests exists.

References

1. Adams, J.B., Baral, M., Geis, E. et al. The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels. *J Toxicol*, 2009, 2009: 532640 Assessed 17 Aug.
2. Ahmadova, A., El-Ghaish S., Choiset Y., et al. Modification of IgE binding to beta- and alpha(s1)-caseins by proteolytic activity of lactobacillus helveticus A75. *J Food Biochem*, 2013, 37: 491–500 Assessed 12 Nov.
3. Akhondzadeh,S., Erfani,S., Mohammadi, M.R. et al. Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial. *J Clin Pharm Ther*, 2004, 29: 145–150 Assessed 22 Aug.
4. Bohmigm G. A., Krieger P. M., Saemann,, M. D., et al. N-butyrate downregulates the stimulatory function of peripheral blood-derived antigen-presenting cells: A potential mechanism for modulating T-cell responses by short-chain fatty acids. *Immunology*, 1997, 92: 234–243 Assessed 11 Nov.
5. Braniste,V., Al-Asmakh,M., Kowal,C. et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*, 2014, 6: 263ra158 Assessed 26 Aug.
6. Buffington, S. A., Di Prisco G. V., Auchtung, T. A., et al. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell*, 2016, Assessed 12 Nov.
7. Collins, S. M., Bercik, P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. *Gastroenterology*, 2009, 136: 2003–2014 Assessed 11 Nov.
8. Collins, S.M.A. role for the gut microbiota in IBS. *Nat Rev Gastroenterol Hepatol,* 2014,11:497-505 Assessed 26 Aug.
9. Coretti, L., Cristiano C., Florio E., et al. Sex-related alterations of gut microbiota composition in the btbr mouse model of autism spectrum disorder. *Sci Rep*, 2017, 7: 45356 Assessed 11 Nov.
10. Dae-Wook K., James B. Adams, Devon M. Coleman, Elena L. Pollard, Juan Maldonado, Sharon McDonough-Means, J. Gregory Caporaso, Rosa Krajmalnik-Brown. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. *Scientific Report* 2019,9:5821 Assessed 13 Nov.
11. Dodds, L., Fell, D.B., Shea, S. et al. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord*, 2011, 41: 891–902 Assessed 14 Aug.
12. Finegold, S. M., Summanen P. H., Downes J., et al. Detection of clostridium perfringens toxin genes in the gut microbiota of autistic children. *Anaerobe*, 2017, 45:133–137 Assessed 10 Nov.
13. Guan, H. Research on Application of Structured Education (TEACCH) in Rehabilitation Training for Children with Autism,[A], *Journal of Educational Institute of Jilin Province*, No.02, 2014, VoL30, 1671-1580 (2014) 02-0073-02 Assessed 20 Aug.
14. Herbert, M.R. , Russo, J.P. , Yang,S. et al. Autism and environmental genomics. *Neurotoxicology*, 2006, 27: 671–684 Assessed 14 Aug.
15. Hu, V.W., Nguyen, A., Kim, K. S. et al. Gene expression profiling of lymphoblasts from autistic and nonaffected sib pairs: Altered pathways in neuronal development and steroid biosynthesis. *PLoS One*, 2009, 4: e5775 Assessed 14 Aug.
16. Kaluzna-Czaplinska J. Blaszczyk S. The level of arabinitol in autistic children afterprobiotic therapy. *Nutrition*, 2012, 28: 124–126 Assessed 12 Nov.
17. Kang, D. W., Adams, J. B., Gregory, A. C., Borody, T., Chittick, L., Fasano, A., Khoruts, A., Geis, E., Maldonado, J., McDonough, M. S., Pollard, E. L., Roux, S., Sadowsky, M. J., Lipson, K. S., Sullivan, M. B., Caporaso, J. G., & Krajmal- nik, B. R. Microbiota

Transfer Therapy Alters Gut Ecosystem and Improves Gastrointestinal and Autism Symp- toms: An Open-Label Study. *Microbiome*, *5*, 10. Assessed 26 Aug.
18. Kang, D. W., Park J. G., Ilhan Z. E., et al. Reduced incidence of prevotella and other fermenters in intestinal microflora of autistic children. *PLoS One*, 2013, 8: e68322 Assessed 10 Nov.
19. Kaur I. P., Kuhad A., Garg A., et al. Probiotics: Delineation of prophylactic and therapeutic benefits. *J Med Food*, 2009, 12: 219–235 Assessed 11 Nov.
20. Kinney, D.K., Munir, K.M., Crowley, D.J. et al.Prenatal stress and risk for autism.*Neurosci Biobehav Rev*, 2008, 32:1519-1532 Assessed 17 Aug.
21. Kosidou, K., Dalman, C., Widman, L., Arver, S., Lee, B. K., Magnusson, C., & Gardner, R. M.. Maternal Polycystic Ovary Syndrome and the Risk of Autism Spectrum Disorders in the Offspring: A Population-Based Nationwide Study in Sweden. *Molecular Psychiatry*, *2016*, *21*, 1441-1448. https://doi.org/10.1038/mp.2015.183 Assessed 14 Aug.
22. Li Q., Han Y., Dy A. B. C. and Hagerman R. J. The Gut Microbiota and Autism Spectrum Disorders. *Front. Cell. Neurosci*. 11:120. Assessed 12 Nov.
23. Macfabe, D. Autism: Metabolism, mitochondria, and the microbiome. *Glob Adv Health Med*, 2013, 2: 52–66 Assessed 14 Aug.
24. Maes, M., Kubera,M., Leunis,J.C. et al. Increased iga and igm responses against gut commensals in chronic depression: Further evidence for increased bacterial translocation or leaky gut. *Journal of Autism and Developmental Disorders*, 2012, 141: 55–62 Assessed 26 Aug.
25. Parracho H. M.,Bingham M. O.,Gibson G. R.,et al.Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children[J]. *Journal of Medical Microbiology*, 2005, 54(10): 987-991. Assessed 12 Nov.
26. Picerno, J. The Heritability of Cognitive Ability across the Lifespan: A Meta-Analysis of Twins Studies. Rochester, NY: *Social Science Electronic Publishing 2015*. Assessed 14 Aug.
27. Posey, D.J., Erickson,C.A., Stigler,K.A. et al. The use of selective serotonin reuptake inhibitors in autism and related disorders. *J Child Adolesc Psychopharmaco*l, 2006, 16: 181–186 Assessed 22 Aug.
28. Roberts, E.M.,English P.B., Grether, J.K. et al. Maternal residence near agruculture pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ Health Perspect*, 2007,115:1482-1489. Assessed 14 Aug.
29. Shaaban S. Y., El Gendy Y. G., Mehanna N. S., et al. The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. *Nutr Neurosci*, 2017.
30. Tapiainen, T., Paalanne, N., Tejesvi, M. V., et al. Maternal influence on the fetal microbiome in a population-based study of the first-pass meconium. *Pediatr Res*, 2018, Assessed 12 Nov.
31. Tomova, A., Husarova V., Lakatosova S., et al. Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav*, 2015, 138: 179–187 Assessed 10 Nov.
32. Wang, W. The first large-scale Chinese population autism gene sequencing results released, *Science and Technology Review*, 2017, 35(3) Assessed 17 Aug.
33. White, S., Koenig, K., & Scahill, L. Social skills development in children with autism spectrum disorders: A review of the intervention research. *Journal of Autism and Developmental Disorders*, *37*, 1858–1868. Assessed 24 Aug.
34. Williams, B. L., Hornig M., Parekh T., et al. Application of novel pcr-based methods for detection, quantitation, and phylogenetic characterization of sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *MBio*, 2012, 3: pii: e00261-11 Assessed 10 Nov.
35. Wu, X. L., Liang, S., Wang, T. et al. Gut microbiota and autism (in Chinese). *Chin Sci Bull*, 2018, 63: 1803–1821, Assessed 26 Aug.

36. Yuan, R., Gao,Y., Shen, Y., Du Y., Li, X., Zhou, K. New Progress in the Etiology and Treatment of Autism,*Advances in Psychology*,2020, 10(5), 580-588 Assessed 26 Aug.