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RESEARCH ARTICLE

EXERCISE IN AUTISM SPECTRUM DISORDERS: A PROMISING INTERVENTION

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ABSTRACT

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder, which is diagnosed by behavior in the absence of neuroimaging and reliable biomarkers. Sensorimotor impairment preceded the development of cognitive and adaptive deficits in autism. Multidisciplinary research demonstrate the malfunctions of the nervous systems in ASD and exercise can ameliorate ASD-like behaviors. In fact, motor behavior not only reflects and reveals the workings of the mind, but also reshapes its structure and function. In this article, we review evidence that a role for physical movement in the occurrence, development, early diagnosis and treatment of autism. Increasing evidence suggest that exercise is a promising intervention in pathophysiology and treatment for children with autism spectrum disorders. We highlight the importance of early exercise intervention because earlier intervention results in more successful outcomes.

KEYWORDS

neurodevelopmental disorder, physical activity, ASD, microglia

1. INTRODUCTION

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder, characterized by core features in impairments in social interaction, restricted narrowly interests and stereotyped behavior (Lai et al., 2014). As one subtype of pervasive developmental disorder, autistic is considered as very heterogeneous, ranging from very mild to severe. Although the etiology and pathogenesis of autism are not completely clear, gene mutations are commonly found in this disease, and the complex of its susceptibility loci retard the treatment (Glessner et al., 2009; Famitafreshi and Karimian, 2018). In addition to neurological abnormalities, ASD patients also immunologic disorders, gut microbiota dysbiosis (Yu and Zhao, 2021). Moreover, the majority of ASD individuals require lifelong support of some kind (Lord et al., 2018). Due to reliable biomarkers are not found, the diagnosis of autism must be based on behavior. Once diagnosed with autism, patients should receive personalized intervention and treatment as soon as possible, otherwise they will develop into permanent disorders, including intellectual disability and comorbid psychotic disorder, which worse their social skills, executive dys function, learning and linguistic abilities.

2. CLINICAL FEATURES

The latest statistics of Centers for Disease Control and Prevention (CDC) in 2021 showed that the incidence rate of ASD in the United States under the age of 8 increased from 1/149 in 2000 to 1/54 in 2016, and the male was 4.3 times that of women (Maenner et al., 2020.). The increasing prevalence may be due to changes in diagnostic criteria (especially the broader concept of ASD after the new concept was proposed in 2013) and people's continuous understanding of ASD symptoms (Famitafreshi and Karimian, 2018). This high incidence rate not only brings great pain to patients and families, but also causes heavy financial burden to the society.

At present, no reliable neuroimaging and biological markers are found to assist in the judgment of ASD yet, thus the clinical diagnosis of ASD mainly depends on behavioral and parental interview methods. The current behavioral diagnostic criteria includes social disorder, limited interests and repetitive behaviors according to Diagnostic and Statistical Manual of Mental Disorders, fifth edition [DSM-5]. However, this criteria cannot readily screen out ASD children aged within 1 years old because we cannot distinguish between the diagnostic symptoms of autism and developmental retardation (Shen and Piven, 2017). The symptoms of a more comprehensive diagnosis of autism seem to develop gradually between 12 and 24 months (Gammer et al., 2015). However, in the first year of life, the development of motor skills, language, eye contact and other aspects of autistic infants are indeed different from those of typical developing infants (Swanson et al., 2017; Chawarska et al., 2013; Gammer et al., 2015). These subtle differences can be detected by their parents. Therefore, if the parents doubt about their child, they should talk to the pediatrician and have their children screened for autism. The American Academy of Pediatrics recommends autism screening for the children aged 18 to 24 months. If the pediatrician believes that further screening is needed, the parent should refer the child to a specialized medical professional who can conduct a behavioral assessment of autism, such as a developmental pediatrician, child psychologist / psychiatrist or neurologist.

3. ABNORMAL DEVELOPMENT OF SENSORIMOTOR AND COGNITIVE

Skilled motor behavior is a sensorimotor behavior produced by the interaction between perception, cognition and action. This motor development process is driven not only by the growth and maturity of the neuromuscular system, but also by experience and interaction with the environment (Hallemans et al., 2020). Childhood is the key period of motor skill acquisition. The “mountain of motor development” theory points out that 1-7 years old and 7-12 years old are the important periods of typical development of sports and practical ability (JE and JS, 2002). The earlier children master basic motor skills during this period, it can bring positive significance to subsequent growth and life.

For children, the development of motor behavior is very important for the development of cognitive, psychological and social communication ability,

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but largely ignored. In children diagnosed with autism, about 80 - 90% of autistic children show persistent defects in perceived movement (Kaur et al., 2018). Abnormal development of sensorimotor seems to be the first manifestation of autistic-like behaviour (Hilton et al., 2012). Motor symptoms are one of the earliest identifiable disorders found in infants and young children, who may further develop into autistic patients (Kaur et al., 2018). At 6 months, infants at high-risk (HR) for ASD showed lower gross exercise; By 12 months, they showed increased ASD - behavioral characteristics and decreased cognitive and adaptive functions (Estes et al., 2015). Also, more stereotyped motor mannerisms were found in HR-ASD group aged 12 months (Elison et al., 2014). These findings reveal early-onset motor dysfunction in infants with autism. Sensorimotor differences preceded the development of cognitive and adaptive deficits and behavioral characteristics in autism and atypical sensorimotor development in early life may have a role in the development of autism. Even in older autistic children, motor skills are severely impaired and are highly relevant to the severity of autism and IQ (Hilton et al., 2012). Thus, motion deficits is suggested to be a potential core symptom of ASD (Fournier et al., 2010).

4. Exercise Ameliorates ASD-Like Behaviors

One of the treatment options for autism is drug therapy, such as antipsychotics, antiseizure medications, and immunomodulator drugs (Famitafreshi and Karimian, 2018). It is worth noting that the pharmacology of ASD is currently limited to the treatment of co-occurring behavior or diagnosis, rather than ASD itself. Moreover, some adverse events were observed, accompanied by medication, including sedation and weight gain, increasing the risk of subsequent physical health problems (Lord et al., 2018). Physical exercise offers many health benefits to human beings, exemplified by reducing body fat, strengthening intestinal barrier, improvement of chronic diseases and cardiovascular diseases. Not only for physical health, In recent years, exercise has shown good rehabilitation benefits and safety effects in brain health and function, including the prevention and treatment of Alzheimer's disease, alleviating drug addiction, depression and ASD syndrome (Deslandes et al., 2009; Morais et al., 2018; Gujral et al., 2017; De la Rosa et al., 2020). Among them, autism is a developmental disorder that occurs in early childhood, but scientific evidence suggests that exercise may not just be healthy but may in fact be therapeutic.

In 1974, Best et al. first reported that physical exercise (swimming) show positive effects on stereotyped behavior of children with ASD (Best and Jones, 1974). Increasing scientific evidence show that exercise can improve autistic-like behaviors in children with ASD, including social-emotional functioning, stereotypic behaviours, attention and cognition. For example, Harbourne et al. evaluate the effect of a simple toddler play (START-Play) intervention on young children with neuromotor disorders (Harbourne et al., 2021). For infants with significant motor retardation, the positive effects of START-Play on cognition and fine motor were observed at 3 months, and fine motor and frequency results were observed at 12 months; For infants with mild motor delay, START-Play has a positive impact on receptive communication n (Harbourne et al., 2021).8-week yoga intervention can improve the gross movement of children with ASD aged 5-13, and reduce their imitation/practice errors (Kaur and Bhat, 2019). After 12 weeks of jogging intervention, 27 children aged 8-12 displayed significant improvement in emotional regulation and reduction in behavioral problems (Tse, 2020). Found in individuals with autism, antecedent physical exercise can not only reduce challenging behavior, but also increase learning behavior (Neely et al., 2015). Additionally, some systematic reviews and meta-analyses in the literature supported the idea that physical exercise has a positive impact on autism (Tan et al., 2016; Ferreira et al., 2019; Bremer et al., 2016). Motor impairment can lead to functional disorders in daily life, limit communication opportunities, and lead to loneliness, anxiety, emotion and other social problems. In children with ASD, motor skill development is found to be closely related to social communication and cognitive development. Motor development is embodied, embedded, enculturated, and enabling (Adolph and Hoch, 2019). New motion skills create new learning opportunities and can promote a series of development. Indeed, motor behavior not only reflects and reveals the workings of the mind, but also reshapes its structure and function.

5. Exercise and Malfunctions of the Nervous Systems in ASD

Abnormal changes in brain morphology, structure and function are closely related to the risk of ASD. The excessive growth of brain volume in autistic children during early development is accompanied by the expansion of cerebral cortex surface area rather than the increase of thickness (Hazlett et al., 2011), showing a different development trajectory from typically developing (TD) children. Children with autism have a short period of accelerated brain overgrowth at the age of 1-4, and then, from adolescence to late middle age, followed by an accelerated rate of decline in size and may even degenerate (Courchesne, 2002; Calhoun et al., 2011; Hazlett et al., 2017). Excessive brain growth is region specific, such as frontal and temporal lobes, which develop abnormally in children with autism (Carper and Courchesne, 2005). Moreover, high-level areas involving executive function, attention and motor coordination, such as the frontal lobe, mature later than other low-level functional areas. It can be seen that the maturation time and sequence of cerebral cortex in early brain development of autistic children are disordered (Gogtay et al., 2004). In addition, during the early development of autistic children, abnormal development of caudate nucleus, hippocampus, amygdala, basal ganglia and cerebellum are found (Ecker et al., 2015), which is related to the severity of repetitive stereotyped behavior. At the cellular level, the alterations in the composition of the neuronal cytoskeleton (Falougy et al., 2019), which may be the basis of abnormal brain structure in children with autism.

The brain functional connectivity of patients with autism is abnormal, and weaker interhemispheric brain network are found via brain imaging methods including MRI/fMRI/fNIRS (Sun et al., 2021). Local overconnectivity and long-range functional underconnectivity may be a feature of the ASD brain (Just et al., 2012; Hutsler and Casanova, 2016). For example, several findings have shown abnormal activation of superior temporal sulcus, prefrontal cortex (PFC) and subcortical areas such as basal ganglia, amygdala and cerebellum in patients with ASD (Wu et al., 2021; Clairmont et al., 2022). The overactivation of medial prefrontal cortex (mPFC) may be related to the generation of ASD social disorder (Rinaldi, 2008). The developmental changes of excitatory synapses are related to autism spectrum disorders. Dendritic spines play an important role in maintaining excitatory connections, but the shape, size and number of dendritic spines in patients with ASD have abnormal changes (Van and Hoogenraad, 2010). Studies have shown that ASD patients have the defect of insufficient pruning of synapses / dendritic spines, which leads to the increased synapses and dendritic spines density in adults (Tang et al., 2014), resulting in abnormal brain functional connection and imbalance of excitation / inhibition (E / I) in brain network, then resulting in ASD symptoms (Penzes et al., 2011). Microglia, as immune cells of the central nervous system, not only have immune monitoring function, but also play an important role in regulating synaptic / dendritic spine pruning (Paolicelli et al., 2011; Morgan et al., 2012). Specifically, deficits in synaptic pruning by microglia can lead to the increase of synaptic density and the pathogenesis of ASD, thus some of the symptoms reported in ASD may be improved through reorganizing neural circuits via microglia-dependent synaptic pruning (Suzuki et al., 2013; Andoh et al., 2019), in which microglia autophagy plays an important role in the regulation of the synapse and neurobehaviors (Kim et al., 2017).

Significant progress has been made in understanding the neurobiological mechanisms of how exercise protects and recovers the brain. Exercise may induce synaptic competition by promoting the release of neurotrophic factors and growth factors. Exercise induced increased expression of brain-derived neurotrophic factor (BDNF) (de Almeida et al., 2013) and insulin-like growth factor-1 (IGF-1) and improved the activity of hippocampal and PFC neurons (Voss et al., 2013). In addition, BDNF promotes synaptic maturation which depends on neuronal activity (Yoshii and Constantine-Paton, 2010), and IGF-1 can enhance synaptic stability by increasing the expression of synapsin I and PSD95 (Shcheglovitov et al., 2013). These findings suggest that exercise may promote the maturation and stability of some synapses by increasing the expression of BDNF and IGF-1 in hippocampus and PFC, so as to induce synaptic competition and improve synaptic pruning disorder. Additionally, animal and human studies have shown that hippocampal neurogenesis plays a key role in cognition and exercise is a potent inducer of hippocampal neurogenesis (Ryan and Nolan, 2016; Ma et al., 2017). It has previously been shown that a week of low-intensity or moderate intensity running can enhance neurogenesis in the dentate gyrus of hippocampus, resulting in a significant increase in hippocampal BDNF mRNA expression (Lou et al., 2008). Cheng et al. (2021) reported that 1-week running can restore the synaptic deficits induced by drug, improve in vivo spine formation, synaptic transmission, spontaneous activities of cortical pyramidal neurons, and motor - learning ability (Cheng et al., 2021). These findings confirm that the key mechanism of physical exercise to restore brain function is by promoting neurogenesis and synaptic function. Then, how does exercise modify synaptic connections which are fundamental structures for brain function? In 2019, Andoh et al. established a mouse model of ASD induced by maternal immune activation (MIA) and found that the phagocytosis of microglia in hippocampal CA3 of offspring mice decreased, resulting in the increase of synaptic density in adulthood and

the generation of ASD like behavior. After 30 days of voluntary running intervention, the synaptic density of offspring mice was normalized and ASD like behavior was improved. The synaptic surplus of MIA offspring is caused by the defect of synapse engulfment by microglia, which is normalized by motor through microglial activation. This evidence suggests that voluntary movement plays a role in regulating behavioral and synaptic abnormalities in neurodevelopmental disorders (Andoh et al., 2019).

6. The Microbiota-Gut-Brain Axis in ASD and Exercise

In addition to the core symptoms, ASD patients also show gastrointestinal disorders which is closely related to the severity of autism (Chaidez et al., 2014; Adams et al., 2011). Intestinal microflora imbalance has been found in ASD patients, and probiotic therapy may reshape gut microbiota and improve the symptoms of autism (Shaaban et al., 2018; Adams et al., 2011), suggesting that imbalanced gut microbiota may play an important role in the pathogenesis of autism. It is considered that the interplay between brain function and the microbiota is within the context of the microbiota-gut-brain axis (Cryan et al., 2020; Yu and Zhao, 2021). For example, demonstrated for the first time that microbiota is essential for the programming and presentation of normal social behavior in germ-free mice (Desbonnet et al., 2014). Treatment with human symbiotic Bacteroides fragilis can alter microbial composition, and ameliorates ASD-like behaviors (Hsiao et al., 2013). Similar effects have been found in the management of ASD-related social dysfunction with Lactobacillus reuteri (Sgritta et al., 2019).

In ASD, specific pathways that mediate the crosstalk between intestinal microbiota and brain include neuronal, and immune, chemical signaling (Yu and Zhao, 2021). Within the neural pathways, the vagus nerve and the enteric nervous system are the direct pathways connecting the intestine and the brain. Lactobacillus rhamnosus reduces stress-induced corticosterone and anxiety- and depression-related behavior, but these effects are not observed in vagotomized mice (Bravo et al., 2011). In additon, L. reuteri are reported to rescue the synaptic plasticity induced by social interaction in the ventral tegmental area of ASD mice in a vagus nerve dependent manner (Sgritta et al., 2019). Moreover, vagus nerve stimulation has been proved to be a potential strategy for the treatment of ASD (Wang et al., 2021), which provides more evidence for this pathway. Within the immune pathways, gut microbiota regulates neural activities by regulating the functions of intestinal mucosal immune system, peripheral immune system and immune cells of central nervous system (Yu and Zhao, 2021). For example, microglia dysfunction is described in several neurological diseases, and gut microbiota can affect microglia homeostasis through short-chain fatty acids (SCFAs) signal transduction (Zheng et al., 2020; Erny et al., 2015). In the chemical pathway, metabolites produced by gut microbiota, including short chain fatty acids, serotonin, and gamma-aminobutyric acid, can be used as a chemical signal to regulate the homeostasis of the central nervous system (Dalile et al., 2019; Mazzoli and Pessione, 2016).

Exercise is a stronger regulator of gut intestinal homeostasis, which can diversify intestinal microorganisms and rebuild the balance between the richness of beneficial and harmful microorganisms (Campbell and Wisniewski, 2017). Furthermore, exercise increases fecal concentrations of SCFAs (Allen et al., 2018), modulates the multiple systems related to neuroinflammation and glial activation (Mee-Inta et al., 2019). At present, there is no direct evidence that exercise can improve ASD symptoms by rebuilding unbalanced intestinal flora. However, given that diet can improve ASD by improving intestinal flora, we proposed that the modification of the gut microbiota driven by exercise may be also one of the signal pathways for exercise to improve ASD.

7. Conclusion

Mounting evidence supports the importance of physical movement in the occurrence, development, early diagnosis and treatment of autism. An important and often under-recognised feature of ASD is the motor development ability of children with ASD. Compared with TD children of the same age, autistic children tend to show more movement development obstacles, which will reduce the opportunities of physical activity or movement, and will have a negative impact on the cognition, social ability and language development of autistic children. Moreover, limited physical activity increase the incidence rate of related diseases of sedentary behavior. In view of the complex heterogeneity of ASD etiology and symptoms, the biological mechanism of exercise improving autism symptoms still needs to be explored. Increasing data from multidisciplinary research collectively support the effectiveness and comprehensiveness of exercise in the treatment of autism. Childhood is an important and sensitive period for cognitive development. We highlight the importance of early exercise intervention, because earlier intervention results in more successful outcomes.

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