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Review Article

Beneficial effect of interventional exercise on autistic Fragile X syndrome

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Abstract. [Purpose] The purpose of the present review is to discuss recent published articles in the understanding of efficacy of interventional exercise on autistic Fragile X syndrome (FXS) with special emphasis on its significance in clinical application in patients. [Methods] This review article was identified scientifically and/or clinically relevant articles from PubMed that directly/indirectly met the inclusion criteria. [Results] Mutation of fragile X mental retardation 1 (*fmr1*) gene on the X chromosome is related with loss of fragile X mental retardation protein (FMRP) that affecting physiological and behavioral abnormalities. Autistic FXS individuals exhibit disturbed sleep and altered circadian behavior. Although the underlying molecular mechanisms are not been fully explored, interventional exercise in autistic FXS has been clinically used for the treatment of physiological and behavioral abnormalities as well as psychiatric disorder in autistic FXS. [Conclusion] This review describes beneficial efficacy of interventional exercise and its controversy in patients with autistic FXS. This review also provides interventional strategies for clinicians and scientists that the way of neurophysiological approaches according to the level of physical and behavioral abnormalities.

Key words: Therapeutic exercise, Autism spectrum disorder, Fragile X syndrome

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INTRODUCTION

Autism and autism spectrum disorder (ASD) are commonly used terms for a group of neurodevelopmental disorder that represents social deficits, communication difficulties, stereotyped or repetitive behaviors and cognitive delays[1, 2]. In general, the child with autism has not exhibited same symptom, but features very different type of autism characteristics. Since the child with autism does not appears same or a single symptom, newer term of ASD has been represented as a single diagnostic category of autism characteristic linking various conditions. It is known that ASD reveals substantial genetic variants, particularly fragile X syndrome (FXS), Rett syndrome, tuberous sclerosis complex and structural chromosomal variations confer a high risk for ASD[3]. FXS is the most frequent form of inherited intellectual mental retardation and commonly

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known as monogenic type of autism, which shows clinical behavioral features such as mental retardation, learning disorder, attention deficit disorder, hyperactivity disorder, anxiety and epilepsy[4–6]. Particularly, the individuals with FXS often exhibit characteristic of ASD or autistic behavior[7]. FXS is a genetic disorder that occurs by mutation of fragile X mental retardation 1 (*fmr1*) gene on the X chromosome. Mutation at this site is related with loss of fragile X mental retardation protein (FMRP) that affecting physical and behavioral abnormalities. The individuals with FXS also present with disturbed sleep and altered circadian behavior as well. In molecular studies, the absence of *fmr1* and *fmr2* gene induces the altered expression of clock gene related components and changes circadian rhythm. In addition, clinical studies reported that sleep and behavioral alteration of FXS would be associated with *fmr1* and *fmr2* gene.

THERAPEUTIC PHYSICAL EXERCISE IN PATIENTS WITH AUTISTIC FRAGILE X SYNDROME

As described above, ASD and FXS exhibit various clinical features including mental retardation and epileptic episodes[4, 6]. Recently, numerous studies have focused on understanding the pathophysiological mechanisms responsible for ASD and FXS, and on developing more effective therapeutic treatments.

Sairanen M et al.[8] reported that ASD is characterized by structural defects that include a reduction in forebrain volume and disruption of the neural network between the limbic system and other cerebral cortex regions. In addition, recent study demonstrated that ASD children presented an abnormal gait compared with that of age-matched controls, they showed a reduction in cadence, gait velocity, step length, and an increase in step width[9]. Interestingly, therapeutic physical exercise in patients with ASD increases hippocampal volume and promotes the robust growth of newly proliferated and/or differentiated cells by increasing brain-derived neurotrophic factor (BDNF) in the cerebral cortex[10]. Also, the *fmr1* gene was shown to play a critical role in the neural plasticity of dendritic spines in studies on neuropsychological function in ASD and FXS. Therefore, the absence of FMR1 results in dysmorphology and dendritic spine dysfunction[11, 12]. In addition, FMR1 knockout mice swim significantly slower than controls and take more time to arrive at the target platform in the Morris water maze[13]. Therapeutic physical exercise plays a critical role in neuronal cell survival in ASD patients, and forced aerobic exercise during light photoperiods promotes vascularization and neurogenesis[14–16]. Therapeutic physical exercise facilitates the production of neurotrophic factors, including nerve growth factor (NGF), fibroblast growth factor-2 (FGF-2) as well as BDNF, that improve neuropsychological function in infants with ASD[17, 18]. In a previous study using the valporic acid (400 mg/kg)-induced ASD animal model, the animals with intervention of physical exercise showed incremental improvement in spatial learning memory, decision making, and neurogenesis in the hippocampal region via stimulating the PI3 K/Akt/ERK signaling pathway[19]. Moreover, exercise that combines physical and mental activities has improved cognitive ability in individuals with ASD, and participation of people with ASD in these activities serves the additional purpose of decreasing stereotypes[20, 21]. Strikingly, a recent report suggested that a mind-body exercise program could positively affect neural functional connectivity and memory processing, and could therefore enhance memory function in individuals with ASD[22].

SUMMARY

In a study that examined the relationship between stress and exercise, one patient with autism showed abnormally high epinephrine, norepinephrine, and cortisol levels during maximal and submaximal treadmill exercise compared to resting levels. Even though therapeutic physical exercise is somehow stressful in patient, but the subjected patient was able to complete the entire protocol without experiencing any maladaptive behavior. Therefore, additional studies are needed to determine the beneficial effects of therapeutic physical exercise, and to provide the clinical application guideline of exercise for autistic FXS patients.

Conflict of interest

The authors declare that they have no conflicts of interest.

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