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Research progress of the relationship between abnormal vestibular reflexes and adolescent idiopathic scoliosis

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ABSTRACT

Adolescent idiopathic scoliosis (AIS) is an agnogenic structural scoliosis occurring in adolescence, and the main diagnostic criteria is coronal Cobb angle >10° in total spine X-ray. Studies have shown that AIS may be associated with abnormal postural reflexes, vestibular system is an important component of postural reflexes and its mechanism in the occurrence and development of scoliosis has received wide attention in recent years. In the study, the research progress on the role of abnormal vestibular reflexes in the pathogenesis of AIS was mainly introduced to help the clinicians better understand the pathogenesis of AIS and provide new ideas for AIS study.

1. Introduction

Adolescent idiopathic scoliosis (AIS) is an agnogenic 3D spinal deformity occurring after 10 years old. Weistein *et al* have reported that AIS patients account for 80% of scoliosis population, 1%–3% of teenagers have different degrees of scoliosis, and women 10–16 years old, in particular, are susceptible[1]. AIS is a recognized multifactorial pathogenic disease that involves the abnormality of genetics, tissues, hormones, biomechanics, nerve reflex and so on[2–5]. The research on the abnormality of vestibular reflexes in nerve reflexes for scoliosis has begun to receive wide attention[6–9]. Vestibular system includes the peripheral vestibular organ, vestibular centre and motion output system, and the main function is regulating paravertebral muscle contraction to adjust the relative position between the head and torso and maintain the body balance[10,11]. Study shows that abnormal vestibular reflexes will lead to asymmetric paravertebral muscle contraction, which causes the spine cartilage and bone structure dysplasia and eventually leads to scoliosis[12–16]. At present, the vestibular system research about scoliosis mainly focuses on the vestibular organs and vestibular centre at all levels, the effect of abnormal vestibular system on scoliosis was mainly elaborated from the semicircular canal system, otolith system and vestibular reflex center in the study, and the latest research progress was reviewed.

2. Semicircular canal system and scoliosis

There are three mutually perpendicular semicircular canals in the human body, the adequate stimulus they perceive is rotational acceleration, and the nystagmus can be measured to detect the semicircular canal function of AIS patients and normal subjects[17]. Studies of Jensen's team[18], Sahlstrand's team[19] and Herman's team[20] show that compared with the normal subjects, AIS patients are all with abnormal semicircular canal function. However, Sahlstrend *et al* have used the electronystagmography to compare the vestibular function between 40 patients with AIS and 29 healthy subjects, and found that there is no significant difference in nystagmus in supine and upright pressure tests between experimental group and control group[21].

The development of iconography has provided a new research method for studying the effect of abnormal semicircular canal on scoliosis. Rousie *et al* have used CT and MRI to examine the labyrinth bone tube and lymphatic morphology in 445 patients with

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vestibular lesions, and found that 95 (55%) patients with abnormal bone tube and lymphatic morphology are with scoliosis[22]. The study has reported for the first time that the incidence of abnormal connection between the lymphatic lateral and posterior canal (LPCC) in patients with AIS is higher than that in normal subjects, and the abnormal nystagmus reflex may be associated with it, resulting in spinal deformity. Hitier *et al* have detected by MRI that the left semicircular canal direction is more vertical and deviated from the midline in AIS patients, and the abnormal vestibular system morphology occurs before birth[23]. Given its impact on vestibular spinal cord, hypothalamus and cerebellum, it is further speculated that the asymmetric semicircular canal may cause the secondary abnormality of body morphology, hormone levels and nervous system excitability in patients with AIS. The assumption needs further study, and once confirmed, using MRI to screen the semicircular canal morphology can early detect the high-risk groups of AIS and conduct preventive intervention. In another study, Shi *et al* have used computer-assisted technology to measure the geometric shape and relative position parameters of vestibular organs (semicircular canal, alveus communis and saccule) segment by segment, and the results show that in patients with AIS, the centre distance and the Angle between the lateral semicircular canal and the superior semicircular canal of the left labyrinth are significantly smaller than those of control group obviously[24]. Xin *et al*, meanwhile, have propose a MRI image matching method to measure the vestibular organ morphology, and the study has found that the semicircular canal morphology is statistically different between AIS patients with right thoracic curve and control group[25]. Study of Zeng *et al* also shows the significant differences in the semicircular canal system morphology between AIS patients and normal subjects[26]. Recently, Wen *et al* also puts forward a set of new algorithm to realize the precise matching of vestibular organ surface mark points, further finds the differences in semicircular canal morphology between patients with scoliosis and normal subjects by geometry morphology, and has achieved good results[27]. At present, the morphological analysis of the semicircular canal benefits from the improved accuracy of CT and MRI, but there is no recognized and widely accepted image detection method. Therefore, a set of standard imaging algorithm for vestibular organs is urgently needed to obtain more accurate and comparable test results.

3. Otolith system and scoliosis

Otolith system includes alveus communis and saccule, and they mainly perceive horizontal and vertical motor stimulation. De Waele *et al* have found that for guinea pigs with unilateral otolith system damaged, their thoracic vertebra rotates to the offside, the head deflects to the same side and the paravertebral muscle contraction is asymmetric, resulting in scoliosis[28]. But the deformity is only temporary, which may be associated with the compensatory function of anti-gravity muscle proprioceptors. Wiener-Vache *et al* were the first to adopt off-vertical axis rotation (OVAR) to determine the otolith system function of patients with scoliosis and normal subjects[29]. Results show that 67% of children with scoliosis have OVAR directional preponderance, which is irrelevant with the direction of scoliosis. But the OVAR results of 3 patients with congenital scoliosis are not significantly abnormal, so the aquired otolith system exception might be the cause of the scoliosis. At present, subjective visual vertical (SVV) and electrophysiology are mainly used to detect otolith function. Krode *et al* first reported the differences in otolith system function measured by SVV between AIS patients and normal subjects, and finally confirmed that the SVV was not significantly different between AIS patients and normal subjects[30]. The study of Cakrt *et al* that applies SVV to evaluate the differences in the vertical direction and gravity spatial awareness between AIS patients and normal subjects gets the opposite results[31]. The study has used the Angle between natural plumb line and the central body axis to measure the differences in SVV, and the results show that the angular deviation (1.50+/-0.94 degrees) of AIS group is significantly greater than the angular deviation (0.04+/-0.64 degrees) of control group, and comparison between AIS group (2.46+/-0.82 degrees) and control group (1.50+/-0.94 degrees), the vertical direction and gravity spatial awareness is with obvious uncertainty. In addition, Pollak *et al* have used vestibular evoked myogenic potentials (VEMP) to test otolith system function, and the study finds that there is no statistical difference in the latency of the first forward wave P13 between scoliosis group and control group, but the latency of the first negative wave N23 of scoliosis group is significantly longer than that of control group; N23 latency of scoliosis group is correlated with age, but it is not detected that VEMP latency is associated with Cobb Angle[32]. There is not much research about the relationship between otolith system exception and scoliosis, the SVV results of different studies are different, and electrophysiological studies indicate that there is otolith system exception in patients with scoliosis. Therefore, more high-quality studies are needed to provide more specific evidence.

4. Vestibular reflex centre exception and scoliosis

Vestibular reflex center mainly includes the brain stem, cerebellum and cerebral cortex. The vestibular reflex center in the brainstem is mainly composed of vestibular nucleus complex, it receives afferent nerve from the vestibular organs, and vestibular oculomotor reflexes can be used to measure its function[33]. Study has shown that only 11 out of 44 rats with unilateral vestibular nuclei damaged have different degrees of scoliosis[34]. But in the study, the unilateral vestibular nerve, superior colliculus and other nuclei are also damaged, so there is no clear relationship between the vestibular brainstem nuclei and scoliosis, and it only shows that abnormal nerve reflex may cause asymmetric paravertebral muscle contraction

and then cause scoliosis. Lion *et al* have used vestibular oculomotor reflexes to study the relationship between AIS and vestibular centre exception, the included AIS patients are divided into two groups: the Cobb Angle of the first group was 5–15 degrees and the Cobb Angle of the second group was 15–25 degrees[35]. Research results show that the second group has shown longer latency and the uncertainty of instantaneous eye movement direction, and the eye movement velocity of the second group is generally slower than that of the first group, but there is no visible difference in metabolic levels between the two groups. The study indicates that the vestibular dysfunction of cerebellum and brainstem level may be associated with the level of AIS development. By specific MRI cerebellum partition technology, Shi *et al* have reported for the first time that the right VIIIa, right VIIIb, left X and right X cerebellum capacity of AIS patients are 7.43%–8.25% higher than those of normal subjects, the symmetry of left and right cerebellum hemispheres of AIS patients are different between AIS patients and the control group, but there is no obvious difference in total cerebellum volume[36]. Further research has also found that the four cerebellar areas with differences are closely related to the vestibular function. In another study, Wang *et al* have included 50 AIS patients with right thoracic scoliosis and 40 normal subjects in the study, and the high effective area measurement method was used to measure the ectocinerea thickness of two groups[37]. Study shows that the ectocinerea thickness of normal group is negatively correlated with age (r<-0.4, P<0.05) the ectocinerea thickness of AIS group is not obviously correlated with age; the thickness of focal cerebral cortex that controls vestibular reflexes of both groups are obviously different. The study indicates that in the development of cerebral cortex, the advanced center of vestibular reflexes of AIS patients may be different from that of normal subjects.

In addition, the gravity factors are closely related to the onset of AIS. Lambert *et al* have found through the peripheral vestibular system of Africa toads with different development stages damaged that only the Africa toads with the incompletely developed anti-gravity muscle proprioceptors can develop permanent scoliosis[38]. But considering that its species are far from human beings, Lambert *et al* cannot guarantee that there is no damage to other neural structures in the experiments, repeated experiments are short, so it can't be analogized to human beings[39]. Damaging mammalian vestibular reflex arc and establishing vestibular reflex rat models with gene knockout can better provide the relevant evidence.

To sum up, the current research on scoliosis and vestibular reflex exception mainly focus on the overall test, mostly focus on the measurement of semicircular canal and otolith system function in patients with AIS and uses affecting examination method to intuitively describe the geometrical morphology of vestibular organs and vestibular centre, and the validation of the relationship between function-related tests and the development of scoliosis is short. Although many scholars believe that the vestibular system exception is involved in the process of scoliosis[40–44], in the systematic evaluation of Catanzariti[45], the correlation between unilateral destroyed vestibular system and the occurrence as well as development of scoliosis is not concluded, and no exact mechanisms associated with it is established in a large number of clinical studies[32–44]. Patten and Moldovan[46] and Cody *et al*[47] propose the assumption that inner ear system-related gene exception may be correlated with scoliosis, but the vestibular system-related molecular biology and genetic levels have not been reported yet, and further studies are needed to verify. In addition, vestibular postural reflex system has the general network integration features of nerve reflex system, the bias from nervous compensation should be eliminated in the study on scoliosis, this has undoubtedly increased the difficulty of the design and implementation of the test, and larger sample-size tests and more efficient schemes need to be designed in the future to get more robust evidence.

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