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A Review of MRI Studies in Children with Growth Hormone Deficiency

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Abstract

Growth hormone deficiency (GHD) refers to a partial or complete lack of growth hormone, with the characteristics of growth retardation, short stature, and growth hormone levels less than 10 ng/mL. Magnetic resonance imaging (MRI) is a non-invasive brain detection technology, and has been widely used in various neuropsychiatric diseases. This article reviews the research progress of MRI in patients with GHD from two aspects: structural MRI and functional MRI.

Keywords

Growth Hormone Deficiency; Magnetic Resonance Imaging; Structural MRI; Functional MRI.

1. Introduction

Short stature is a common developmental disorder in pediatrics [1]. Generally, the height is 2-3 standard deviations below the average of the reference population, and it is considered to be short stature [2]. Short stature can be caused by genetics, malnutrition, poor bone growth, or abnormal hormone production [3]. Depending on the etiology, short stature can be divided into normal growth variants and pathological short stature [4]. Among the types of pathological short stature, growth hormone deficiency (GHD) is the most common [5]. GHD usually refers to a complete or partial lack of growth hormone (GH) [6]. The stimulating GH testing is the first choice for the diagnosis of GHD [7]. Generally, after the stimulating GH testing, the peak GH in GHD patients is less than 10 ng/mL [8].

GH plays an important role in behavior, cognition, neurotransmission, and in the development and differentiation of the central nervous system [9, 10]. Studies have found that cognitive impairment in GHD patients is related to growth hormone deficiency [11, 12]. Cognitive and behavioral abnormalities are often associated with abnormal brain function and structure [13, 14]. MRI is an imaging technique widely used to investigate brain activity in various brain disorders [15-17]. In recent years, some studies have used MRI technology to explore the pathophysiological mechanisms of GHD. Therefore, this paper summarizes the application of MRI in GHD from structural MRI and functional MRI.

2. Clinical Characteristics of GHD

GH is secreted by the pituitary gland and acted on a variety of organs and tissues [18]. It plays a role in growth and development, metabolism and immune function [19]. GHD will cause short stature in children and GHD syndrome in adults [20]. Diagnosis of GHD requires that the results of two GH challenge experiments are abnormal [21, 22].

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Many studies found that GHD can impair cognitive function in patients[23, 24]. Webb et al. found that compared with idiopathic short stature, patients with GHD had lower scores on Intelligence Quotient, language comprehension, and motor assessments [25]. Social phobia, anxiety and depression have also been found in patients with GHD [26, 27]. Since GH is involved in the regulation of metabolism and cardiovascular function [28], metabolic disturbances and abnormalities of the cardiovascular system are common in GHD patients [29, 30]. Recently, Anisha et al. found that GHD patients were excessive sleepiness[31].

GH therapy has been used in GHD patients since 1958 [32]. However, due to the limited supply of human growth hormone (hGH), it is only used in patients with severe GHD [33]. With the discovery of recombinant hGH (rhGH), GH therapy can be used in other diseases caused by GHD [34]. Studies have showed that growth hormone replacement therapy can improve memory function in GHD patients [35, 36]. The rhGH treatment has positive effects on quality of life in adult GHD patients [37, 38]. Carotid artery intima-media thickness and lipids can be improved in GHD patients treated with rhGH [39]. GH replacement therapy needs to consider individual factors, and mild adverse reactions may occur in unsuitable individuals [40]. Nonetheless, GH replacement therapy has been shown to improve symptoms in GHD patients.

3. Application of MRI in GHD

3.1 Structural MRI

Structural MRI is a non-invasive technique for examining the anatomical structures of the brain, which is widely used to study brain morphology because of its high sensitivity and spatial resolution[41, 42].

Structural MRI has been commonly used in patients with GHD, especially pituitary MRI. Some studies demonstrated that MRI evaluation of pituitary shape and height is another tool for diagnosing GHD[43, 44]. For GHD patients, MRI scanning should be performed to determine the pituitary anatomical structure to help the diagnosis[45]. In addition, some studies suggested that the combination of pituitary MRI and hormone stimulation test is helpful to the etiological diagnosis of GHD[46, 47]. However, Schmitt et al. thought that the diagnostic value of brain MRI was not high for patients with growth hormone at 7.0 – 10 ng/mL, but it was necessary for patients with growth hormone below 3 ng/mL[48].

Structural changes in GHD patients include pituitary hypoplasia, absence or interruption of the pituitary stalk, and absence or ectopic posterior lobe[49]. Pampanini et al. found that 83.8% of GHD patients showed abnormalities on brain MRI, including 48.7% with isolated pituitary hypoplasia and 35.1% with complex defects[50]. Abnormal structures of sella and pituitary were also found in patients with isolated GHD[51-55]. However, these structural abnormalities are more likely to occur in patients with severe GHD[56-58]. For most GHD patients, the most common manifestation is hypopituitarism without neuroradiologic abnormality[59].

In addition to pituitary MRI, other studies found structural changes in other parts of the brain in GHD patients. Webb et al. found that the volume of right pallidus, right hippocampus, left thalamus and the splenium of the corpus callosum in isolated GHD patients was significantly smaller[25]. Furthermore, Zheng et al. found that the cerebral cortex and central sulcus of patients with isolated GHD had significant changes[60, 61].

Through these studies, we can find that structural MRI is widely used in the study of GHD patients. These studies showed that the pituitary structure of GHD patients was generally abnormal, and the more severe the GHD was, the more obvious the pituitary structure was abnormal. In addition, it can also be seen that GHD will affect the brain structure not only in the pituitary gland, but also in other brain regions.

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3.2 Functional MRI

Functional MRI (fMRI) is a non-invasive technique to measure the hemodynamic changes after enhanced neural activity[62]. The change of local hemodynamics is due to the change of neuronal activity[63]. In many instances, fMRI signals reflect underlying neural activity[64]. The fMRI has been widely used in various neuropsychiatric diseases[65, 66]. The following will introduce the application of fMRI in GHD through task-based fMRI and resting-state fMRI.

3.2.1 Task-based fMRI

Task-based fMRI requires patients to complete corresponding tasks to explore the brain regions related to this task. Arwert et al. required GHD patients to perform memory tasks, and found that there was no difference in the performance quality of GHD patients and the control group in working memory tasks, but the memory speed was lower than the normal level [67]. In addition, they also found that growth hormone treatment improved the long-term memory and working memory of GHD patients through the same method[68]. Through test-fMRI related to memory tasks, we can find some abnormalities in the memory of GHD patients, and improve it after treatment with growth hormone.

3.2.2 Resting-state fMRI

The resting-state fMRI (rs-fMRI) refers to the magnetic resonance scanning conducted by the subject without any task and any intentional thinking. Compared with task-based fMRI, rs-fMRI has some advantages in clinical environment. For example, data acquisition is simple, and can be carried out in individuals who cannot cooperate with the particular task[69]. At present, many researchers have proposed a variety of methods to analyze fMRI data. The following will introduce the application of several fMRI analysis methods in GHD.

In the resting-state brain, Biswal et al. observed that low-frequency fluctuations are highly correlated across different brain regions [70]. Zang et al. proposed a method to calculate the amplitude of low-frequency fluctuation (ALFF) and used it to explore spontaneous neural activity [71]. Using ALFF analysis, Zhang et al. [5] found that GHD children had significantly increased ALFF in the right lingual gyrus and angular gyrus, while significantly decreased ALFF in the right dorsolateral superior frontal gyrus, left postcentral gyrus, superior parietal gyrus, and middle temporal gyrus compared with HCs, which may explain aggression, somatic complaints, attention deficit, and language withdrawal in children with GHD. Their study found the changes of ALFF in patients with GHD, and proved that GHD can affect the spontaneous neural activity of patients.

Regional homogeneity (ReHo) is a measure of the synchrony of a given voxel with the time series of surrounding voxels using the Kendall Coefficient of Consistency (KCC) [72]. A larger KCC value for a given voxel shows higher regional coherence within a cluster consisting of the voxel and its neighbors [73]. Zhang et al. [74] applied the ReHo analysis to children with GHD for the first time and found that the ReHo of the left putamen in children with GHD was significantly increased, while the ReHo of the right precentral gyrus, the orbital part of the bilateral superior frontal gyrus and the medial part of the left superior frontal gyrus were significantly decreased. They suggested that abnormalities of ReHo in these regions may reflect dysfunction of inhibitory control in children with GHD and may be associated with anxiety and depression in children with GHD. Abnormal ReHo in children with GHD indicated that GHD affects the neural activity of local brain regions of patients.

Functional connectivity (FC) refers to the temporal correlation of neuronal activation patterns in different brain regions [75]. Biswal et al. were the first to use correlation coefficients of time series of BOLD-fMRI signals in different brain regions to measure functional connectivity of different brain regions [70]. Functional connectivity density (FCD) is the use of resting-state FC datasets to analyze correlations in the temporal dimension on local functional connectivity clusters [76]. FCD overcomes the limitation of seed-based methods, it doesn’t require a priori hypotheses about the location of seed points [77]. The larger FCD value of a voxel indicates a greater role for this voxel in the brain's information processing [78]. A study by Hu et al. [79] found that FC and FCD in children with GHD had significant changes compared with idiopathic short stature (ISS). They believed that GHD would affect patients' somatosensory, somatomotor and cerebellar networks, and might help to understand

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the behavioral problems of children with GHD. The abnormality of FC and FCD in children with GHD illustrates the effects of GHD on different brain regions.

Some studies have found that FC between and within brain networks will change over time [80, 81]. Dynamic functional connectivity (dFC) analysis reveals common state patterns of the brain and transitions between states [82]. Tang et al. [83] investigated dynamic changes of FC in GHD patients using dFC analysis. Their results showed that compared with ISS, children with GHD exhibited significant dynamic abnormalities in the intra-networks of the central executive network and the cerebellar network, and in the inter-networks of the central executive network to the attentional, sensorimotor and visual networks. Abnormality of dFC in children with GHD provides new evidence for the change of brain function caused by GHD.

From the above fMRI studies, both task-based fMRI and resting-state fMRI can be used to explore the impact of GHD on the brain function of patients. At the same time, these studies have reported the relationship between cognitive and behavioral abnormalities and changes in brain function in GHD patients. These findings can provide imaging support for the study of cognitive and behavioral abnormalities in GHD patients.

4. Conclusion

In conclusion, this review provides a brief review of recent MRI studies in children with GHD. The current results indicate that the brain structure and function of GHD patients have significant changes. These changes have a certain relationship with the abnormal cognition and function of GHD patients. It also shows that MRI can be used to detect abnormal brain function and structure in GHD patients, which can contribute to our understanding of the pathophysiological basis in GHD.

The current research on MRI in patients with GHD has some limitations, such as a small number of samples and a single experimental method. Therefore, future research can be carried out from the following aspects: first, increasing the number of samples, a larger sample size can reduce the influence of individuals on the results; second, combining MRI technology with other imaging techniques to comprehensively understand the mechanism of GHD.

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