Effects of Early Iron Deficiency on Brain Development in Children and its Prevention and Treatment Progress

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Abstract: Iron deficiency is a very common nutritional deficiency that endangers children's health, with high morbidity among pregnant women and preschool children. Among all the outcomes caused by iron deficiency, the damage of early iron deficiency on brain development in children has received extensive attention. A large number of studies have shown that early iron deficiency affects the development of sensorimotor, cognitive behavior, language and social emotion by regulating the expression of genes and proteins, changing brain structure, neurotransmitter function and neurometabolism. At present, the mechanism of brain development damage caused by childhood iron deficiency is still unclear, and it is urgent to find effective intervention measures. This article overviews the effects of iron deficiency in early life on brain development, reiterates the importance of preventing iron deficiency in early life, and puts forward the prevention and treatment measures of iron deficiency, which provide scientific basis for the research on early iron deficiency and brain development.

1. Introduction

Iron deficiency (ID) means that an individual's serum ferritin (SF) is less than 15 μg/L[1]. ID can be divided into three stages: Iron depletion period that the decrease of serum ferritin is the main index; The iron deficiency stage of erythropoiesis that was characterized by elevated erythrocyte free protoporphyrin; A period of iron-deficiency anemia in which hemoglobin was decreased[2]. The most severe stage of iron deficiency is iron deficiency anemia. Iron deficiency is one of the three major micronutrient deficiency diseases identified by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). According to the WHO, it is estimated that iron deficiency anemia in women during pregnancy is 10%-20% in developed countries and 30%-60% in developing countries[3]. Early iron deficiency is defined as iron deficiency symptoms in the late fetal period up to the first 2 years of life, which seriously affects the development and function of the child's brain[4]. Studies have shown that iron is mainly stored in the substantia nigra, deep cerebellar nuclei, red nuclei, nucleus accumbens, and parts of the hippocampus of the brain, which are highly sensitive to ID[5]. Even after iron supplementation, children with brain damage caused by iron deficiency will have irreversible changes in the distribution of iron in the brain[6]. Therefore, it is of great significance to elucidate the mechanism of brain development injury caused by iron deficiency and to find the prevention and treatment measures for improving children's intelligence level.

2. The Primary Mechanism by which Early Iron Deficiency Affects Neurodevelopment in the Brain

2.1 Effect of Iron Deficiency on Brain Myelin Sheath

Myelination is a key dynamic process during brain development. The process of myelination plays an important role in cognitive development, in which iron is thought to be extremely significant[7]. The nerve myelin sheath is a membrane wrapped around the axon of the nerve, and its main components are lipids[8]. the segmental structure of myelin sheath can conduct nerve impulses by leaps and bounds, with the advantages of high-speed and accurate signal transmission[9]. The

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abnormal myelination process can slow down the conduction speed of nerve impulses, make the connection of neural networks have obstacles, and thus affect the development of cognitive behavior[10].

Myelin in the central nervous system is formed by oligodendrocytes, which maintain the normal myelin structure by synthesizing a large number of myelin components such as lipids and proteins[10]. Therefore, oligodendrocytes have a relatively high metabolic rate and demand for energy[11]. The differentiation of neural stem cells into mature oligodendrocytes goes through several stages: neural stem cell, glia-restricted precusors, Oligodendrocyte type 2 astrocyte precursor cell, Oligodendrocyte progenitor cells and oligodendroglia cell[12]. Morath et al. found that iron deficiency can reduce the differentiation and proliferation rate of glial restricted progenitor cells (GRP cells) and oligodendrocyte progenitor cells (OPCs) in the central nervous system of iron-deficient fetal mice, which leads to the reduction of oligodendrocyte production, indirectly affecting myelination[13]. Iron deficiency affects oligodendrocyte energy metabolism and the synthesis of myelolipids[14]. Inadequate synthesis of any myelin component will affect the normal structure and function of myelin sheath. 70% of iron in the brain exists in oligodendrocytes[15]. As the cogroup of many active enzymes, iron is involved in important biochemical metabolic processes such as DNA synthesis, respiratory chain, neurotransmitter metabolism and lipid synthesis[16]. Many enzymes involved in energy metabolism require iron as a cofactor, such as cytochrome oxidase and reductase, succinate dehydrogenase, NADH dehydrogenase and glucose-6 phosphate cyclase[17]. In the rat model, de Deungria et al. treated the female rats with iron-deficient diet from the beginning of pregnancy to the 10th day after delivery, and then analyzed the brain iron content and the activity of cytochromecoxidase in young rats[18]. They found that iron deficiency not only significantly reduced the iron content in the brain of young mice, but also reduced the activity of cytochrome oxidase by about 42% compared with the control group, especially in the brain regions with cognitive and memory functions (such as hippocampus). Cytochrome oxidase is at the end of the respiratory chain and oxidative phosphorylation and plays a key role in ATP synthesis[19]. Thus, iron deficiency can affect oligodendrocytes in several ways, ultimately affecting myelination in the central nervous system.

In addition, iron deficiency affects the synthesis of myelolipids. It was found that maternal mice treated with iron deficient diet from pregnancy to lactation showed varying reductions in various lipid components of the brain myelin sheath, including a 30% decrease in cholesterol and a significant decrease in phospholipid and galactoside[20]. Due to the alteration of energy metabolism and enzyme activity caused by iron deficiency, saturated fatty acids in myelin were increased and unsaturated fatty acids were decreased, which could not be completely restored even after iron supplementation[21]. The effect of iron deficiency on myelolipids is due in part to changes in energy metabolism caused by iron deficiency, but also possibly through enzymatic changes. HMG CoA reductase is a rate-limiting enzyme for cholesterol synthesis, and Δ-6 and Δ-9 desaturases convert saturated fatty acids to unsaturated fatty acids[22]. Iron deficiency can affect the normal function of these enzymes. Moreover, ferrous iron may be one of the important factors of galactoside expression in oligodendrocyte differentiation[23].

In addition, iron deficiency affects the synthesis of myelin proteins. Myelin proteins account for about 30% of the total myelin weight, including protein lipoprotein (PLP), myelin basic protein (MBP), myelin associated glycoprotein (MAG), 2 '-3' cyclic nucleotide-3 '-phosphodiester enzyme (CNPase)[24-26]. Research showed that perinatal iron deficiency not only reduced the total myelin protein, but also significantly decreased the proportion of PLP and MBP. At present, the mechanism of how iron affects myelin protein synthesis is not clear, but Espinosa et al. found that the transcription of myelin basic protein (MBP) gene is directly affected by transferrin and iron, suggesting that iron can regulate protein expression and synthesis at the gene level[27]. Further, the ferritin and its receptors in the brain are also regulated by iron deficiency. Ferritin is an iron storage protein, which plays an important role in iron metabolism[28]. Oligodendrocytes are abundant in ferritin and its receptor. Ferritin contains two different subunits: the L and the H subunit, which polymerize in different proportions[29]. The L subunit is relevant to the formation of ferritin nuclei and protein

stability, whereas the H subunit facilitates ferritin to absorb iron and possesses an iron-oxidase activity, converting divalent iron to ferrivalent iron and transporting it from the cell membrane to the mitochondria[30]. Ferritin is associated with myelination, and its H subunit exerts anti-apoptotic effects, which is beneficial to cell survival[31]. Previous studies showed that iron deficiency decreased the iron by 20%-50%, and the ferritin and its receptor by 20%-25%[32].

The adverse effects of iron deficiency on myelination are irreversible. Wang et al. reported through meta-analysis that there was no conclusive evidence that iron supplementation for 30 days could have a beneficial effect on psychomotor development in children with IDA[33], but Matiashvili et al. showed that the differences in psychomotor development would be reduced in children with timely and adequate treatment of iron deficiency anemia[34]. In addition, the infant with iron deficiency anemia after treated with iron can correct anaemia, at the age of four, but still can show the auditory brainstem response and visual evoked potentials were significantly prolong the incubation period of anomalies, clinically showed emotional indifference, irritability, inattention, decreased activity, impaired cognitive and learning ability, etc[35]. Research showed that pregnant women with iron deficiency anemia was found after full iron can correct anaemia, but their babies at 10 weeks showed low scores in the assessment of mental development scale, and at 9 months continues to show the development retardation, still can show the abnormalities in cognitive, emotional, social behavior, and motor tests at the age of 11-14[36]. All these suggest that iron deficiency has long-term effects on cognitive and behavioral development. Therefore, iron deficiency in pregnant women and infants should be detected and corrected in time, and early preventive intervention should be carried out. Given the important impact of iron deficiency in early life on children's psychomotor development, early screening and appropriate treatment are necessary, and future studies with large-scale randomized controlled trials with long-term follow-up are also needed.

2.2 The Effects of Iron Deficiency on the Hippocampus

The hippocampus is a key brain region for learning and memory in humans, which develops from the medial region of the telencephalon and is a crucial special structure in the brain[37]. The hippocampus is a part of the limbic system, which plays a significant role in information encoding, spatial navigation as well as short- and long-term memory[38]. Apart from many other important functions, the hippocampus is the center of rememory processing, especially the dorsal hippocampus, which includes a wide range of CA1 regions and plays an important role in the short-and long-term biochemical and structural changes involved in encoding declarative memory events in humans[39]. It was reported that pregnancy rats with ID reduced the expression of cytochrome C oxidase, a marker of neurometabolic activity, especially in the CA1 region at P10[40]. Serial neurometabolic evaluation of the hippocampus of ID offspring mice showed increased intracellular concentrations of phosphoinositol and phosphoylethanolamine during P7 to P28, suggesting disturbed neurotransmitter processing, possibly accompanied by inhibition of glutamyl release[41].

Iron deficiency affects neurometabolism in the hippocampus. The study of Kawano et al. showed that iron supplementation in mice with iron deficiency during pregnancy could reactivate the insulin-like growth factor system and promote hippocampal nerve formation and differentiation during the critical period of hippocampal development[42]. Tran et al. proposed that long-term iron deficiency in neonates would affect the activity of brain-derived neurotrophic factor (BDNF) in the hippocampus, which lead to the decreased expression of downstream target denes, transcriptional targets, and early growth effector genes 1 and 2 of BDNF[43]. BDNF is the cytological and molecular basis of short-term learning and memory impairment. Iron deficiency may cause short-term learning and memory impairment by reducing the content or activity of BDNF[44].

Further research on the effects of iron deficiency on the brain was initially hampered by the difficulty of assessing brain function in young infants until some studies about brain function that was assessed by using event-related potentials (ERPs). ERP is a form of neuroimaging that relies on noninvasive recording of the brain's electrical activity in response to stimuli[45]. Geng et al. found in a study that infants with normal iron status showed electrophysiological confirmation to recognize their mother's voice, but infants with ID did not[46]. In this study, they used EEG recordings of ERP

to infer auditory recognition memory. Late slow wave (LSW) quantification showed that fetal and neonatal iron deficiency had a negative effect on recognition memory. LSW is an ERP component that serves as a marker for novelty detection and memory update[47]. This is an important finding, showing the sensitivity of the developing hippocampus to iron deficiency in infants, which was first demonstrated in animal studies and then in human studies. Moreover, in animal models, developmental ID causes structural and functional abnormalities in the hippocampus, which are associated with dysregulation of genes involved in neurotransmission and synaptic plasticity[48]. Dysregulation of these genes may be the direct cause of lifelong defects after developmental ID. However, a direct functional link between iron and genetic disorders has not been elucidated. There is evidence that iron-dependent epigenetic modifications are mechanisms by which ID can alter gene expression throughout its life cycle. Jumonji and AT-rich interaction domain (JARID) proteins and eleven translocation (TET) proteins are two families of iron-dependent epigenetic modifiers that play a key role in hippocampal dysfunction by establishing appropriate gene regulation during critical periods in the brain[49]. Thus, JARIDs and TETs can promote iron-mediated epigenetic mechanisms by which early life ID directly leads to changes in the regulation of neurodevelopmental genes throughout the life cycle. Thus, JARIDs and TETs can promote iron-mediated epigenetic mechanisms by which early life ID directly leads to changes in the regulation of neurodevelopmental genes throughout the life cycle.

2.3 Effects of Iron Deficiency on Neurotransmitters

Iron deficiency affects neurotransmitters such as serotonin, norepinephrine and dopamine, which can lead to behavioral and developmental changes. Peirano et al. found that children with iron deficiency anemia had more rapid eye movement (REM) sleep in the first third of sleep and less in the last third of sleep compared with controls[50]. Thus, they concluded that iron deficiency anemia is associated with long-term changes in the timing of sleep patterns. Peirano et al. hypothesized that changes in the metabolism of neurotransmitters caused by iron deficiency would negatively affect sleep[50].

Iron has complex effects on dopaminergic function. As a cofactor of tyrosine hydroxylase, iron is indispensable for D2 receptor function [7]. Iron-deficiency anemia alters dopamine neurotransmission in specific areas of the brain, including those critical to sleep regulation[51]. Neuromodulation of the developing dopamine system plays a crucial role in sleep control, including regulating the quality, quantity, and timing of REM sleep[52].

It has been found that the most abundant iron in the brain is in the extracorporeal system[53]. Iron deficiency can reduce the metabolism of serotonin, catecholamine and acetylcholine, as well as the synthesis rate of dopamine[54]. Iron deficiency and the reduction of dopamine transfer interfere with the normal oxidative metabolism of the brain through the frontostriatal circuit and the pathway between the cortex, thus affecting the individual's cognitive functions such as attention, memory and understanding, then lead to inattention, loss of memory and decline in comprehension in children, which are likely to be irreversible and persist into adulthood[55]. Monoamine oxidase is one of many iron-dependent enzymes in the brain. It is an important enzyme to inactivate monoamine neurotransmitters[56]. Iron deficiency will reduce the activity of monoamine oxygenase in rat brain tissue and cause metabolic disorders of monoamine neurotransmitters such as 5-hydroxytryptamine, dopamine, norepinephrine and acetylcholine, leading to huge biochemical changes in brain tissue[57]. However, these neurotransmitters will also affect the changes of other neurotransmitters. FELT et al. found in their study on iron-deficient infants that the endocrine effect caused by iron deficiency, which increases dopamine and decreases prolactin, still plays a role 10 years later[58].

It has been shown that motor injury was observed in epileptic seizures after injection of ferricchloride into the left amygdala of normal rats, as well as apomorphine-induced stereotypic actions[59]. These behavioral changes are related to the changes of postsynaptic dopamine D2 receptors, which provide evidence for the contention that iron plays an important role in maintaining the proper functioning of the dopamine system. In vivo studies found that ventral midbrain iron concentration and dopamine D1 receptor density was highly correlated with exploratory and

repetitive behaviors, respectively; Anxiety-like behaviors are correlated with the density of dopamine transporters and dopamine D1 receptors in the frontal gray matter[60]. These results are consistent with the hypothesis that iron-dopamine chains are used to explain the behavioral disorders seen in children with iron deficiency.

3. Neurological Diseases Caused by Early Iron Deficiency

3.1 Iron Deficiency Causes Sensorineural Deafness

The changes in axon diameter and neuromodulation of auditory nerve, prolonged latency of brainstem auditory evoked potentials, and changes in latency and amplitude of visual evoked potentials can be observed in iron-deficient non-anemic mice, which are difficult to be corrected by traditional treatment. The abnormalities of brainstem auditory evoked potentials and visual evoked potentials reflect the damage of the central sensory conduction pathways of hearing and vision. Lou et al. [12] found that the auditory brainstem response (ABR) long waves iii-v in iron-deficient infants were delayed in the first 10 months of life compared with the normal population. It is suggested that the impaired auditory pathway may be related to the myelination of the central nervous system affected by iron deficiency. Yu Fei et al. observed the effects of ron deficiency on hearing of 9 days old Guinea pigs by using distortion product otoacoustic emission (DPOAE) detection and deoxyriboxylate terminal transferase mediated dUTP notch end labeling. Results showed that the amplitude of DPOAE decreased, indicating the hearing impairment of Guinea pigs. Additionally, moderate iron deficiency anemia during pregnancy and lactation can trigger a cascade effect involving Caspase-3 or 9, resulting in cochlear hair cell apoptosis and hearing impairment in neonatal guinea pigs.

3.2 Iron Deficiency Causes Behavioral and Cognitive Impairment

Iron deficiency is implicated in emotion, attention, motor and other signaling pathways by affecting the synthesis and metabolism of neurotransmitters. There is strong evidence that iron deficiency not only causes developmental delay, but also increases feelings of fear, anxiety and depression, which is closely related to abnormal monoamine metabolism and abnormal neural signaling caused by iron deficiency. Some researchers studied anxiety-related behaviors by light (dark) box test in iron-deficient rats, and found that iron-deficient rats entered the dark compartment more quickly, but the time taken to enter the light compartment was not different from that of control rats; While iron-deficient rats took less time to enter the open-field center, indicating increased fear and anxiety. The study also showed that iron levels in the ventral midbrain and prefrontal cortex are pivotal for anxiety-related behaviors. The cognitive impairment caused by iron deficiency cannot be attributed to the action of a single neurotransmitter, but is achieved by changing the interaction of neurotransmitters in multiple systems in different brain regions. Studies in animal models of iron deficiency suggested that the interaction between the opioid system and cholinergic transports of polypamine in these animals may be defective.

3.3 Iron Deficiency Causes Hyperactivity

ADHD (attention deficit hyperactivity disorder), characterized by inattention, hyperactivity, and impulsivity, is a disorder caused by highly heritable and associated genetic abnormalities involved in the neurotransmission of dopamine. Because iron interacts with multiple steps in dopamine neurotransmission, iron deficiency is strongly associated with ADHD. Cortese et al. found in the MRI measurement results of 36 ADHD patients that iron content in the thalamus of such patients decreased significantly. The serum ferritin level of ADHD patients is obviously lower than the normal level, and the symptoms of ADHD can be improved by iron supplementation. This finding provides new ideas for clinical treatment of ADHD.

4. Progress in the Prevention and Treatment of Iron Deficiency

4.1 Prevention of Iron Deficiency

There are many measures to prevent iron deficiency, namely dietary improvement through education, medicinal iron supplementation, iron fortification in milk and food, and the screening for anemia or iron deficiency[61-63]. (1) Diet education. Clear to prevent iron deficiency of nutrition information, such as promote breastfeeding during the first 6 months of life and avoid milk during the first year of life; provide iron-fortified formulations and an iron-rich diet (e.g., meat, fish, breakfast cereals, legumes and vegetables), provide vitamin C to increase iron absorption, and avoid tea and high-fiber foods to inhibit its absorption. (2) Supplemental administration of iron. International organizations recommend oral iron supplementation for people at high risk of iron deficiency. It is the policy of the Israeli Ministry of Health to supplement all infants with iron syrup in order to overcome a high incidence of iron deficiency anaemia (30-60%) caused by short-term breastfeeding and early consumption of milk. However, adherence to oral iron was low (only 26% continued iron supplementation until 9 months of age), so high morbidity persisted. If bottled iron were available in every home, there would also be a potentially fatal risk of accidental iron poisoning. Medicinal iron is known to taste bad, may cause gastrointestinal discomfort, and can interfere with the absorption of other essential nutrients, especially zinc. In addition, studies have shown an increased risk of Escherichia coli sepsis in neonates treated with intravenous iron, and concerns about the safety of iron supplementation were increased[64]. However, a recent systematic review of randomized clinical trials confirmed that oral iron supplementation had no detrimental effect on other infections in children, except for a slight increase in the risk of diarrhea[65]. (3) iron fortified food. The incorporation of absorbable iron into food may be the most cost-effective primary prevention of iron deficiency, but it must depend on the availability of suitable milk in the population or consumption of adequate amounts of staple food. Studies have suggested that by using the micronutrient and making it into a fine powder spray that is added directly to food, children who have this fine powder added to their cereal show a definite reduction in the incidence of iron deficiency anaemia[66]. (4) Anemia screening. Blood tests offer the possibility of secondary prevention of iron deficiency anaemia by identifying anemic individuals and then providing treatment along with dietary recommendations. The American Academy of Pediatrics recommends that Hb or haematocrit be measured routinely between 9 and 12 months of age, and again after 6 months in communities with a high incidence of iron deficiency anemia, and selective screening of children at risk for iron deficiency in low-incidence communities, which will help reinforce the importance of dietary messages that clinicians communicate to parents[67]. The most promising measure to prevent iron deficiency in children at the population level would be to supplement the basic diet with iron supplements.

4.2 Treatment of Iron Deficiency

The goal of treatment for iron deficiency is to replenish iron reserves or, in the case of anemia, to normalize hemoglobin. For children with ID and IDA, food therapy alone is not advisable. According to the "Recommendations for the Prevention and Treatment of Iron Deficiency and Iron Deficiency Anemia in Children", iron drugs can be used for the prevention and treatment of ID and IDA, with relatively loose indications. Therefore, children with ID should also be treated with iron. However, during acute infection and recovery, iron supplementation should be deferred. Usually, ferrous iron preparations containing divalent iron are more conducive to gastrointestinal absorption, such as ferrous fumarate and ferrous succinate[68]. Organic iron usually has a better absorption rate than inorganic iron, but do not be too obsessed with organic iron. It has been found that long-term supplementation of polysaccharide iron complex has a lower effect on increasing hemoglobin than ferrous sulfate[69]. In addition, ferrous sulfate is a kind of widely used iron agent, with a long application time, which can be chosen for people who have good taste and gastrointestinal tolerance to iron[70]. At the beginning of oral iron treatment, digestive tract discomfort and other irritation may occur temporarily. However, starting from a low dose, continued treatment can be spontaneous remission. During the oral administration of iron, intake of vitamin C - rich beverages will contribute

to iron absorption. All kinds of dairy products should not be taken at the same time with iron, so as not to affect the absorption of iron. In addition, after effective iron supplementation treatment, hemoglobin can rise faster and the phenomenon of small cell low pigment index can be corrected. However, after the indicators return to normal, it is necessary to continue taking iron for two to three months to replenish the iron stores in the body. After iron treatment, Hb begins to rise after 2 weeks of treatment and increase by 20 g/L after 4 weeks of treatment compared with the original level, which is judged as effective. If iron treatment is ineffective, diagnostic review and differential diagnosis should be performed. If the diagnosis is correct, the possible causes such as improper drug selection, insufficient dose, and improper medication method should be analyzed and properly solved.

5. Conclusion

Although the prevention and control of child iron deficiency has been carried out for decades, the incidence of iron deficiency in children is still at a high level. The effects of iron deficiency on the brain are multifaceted and the specific pathogenesis has not been elucidated yet, but a large number of studies indicate that: Iron deficiency can affect brain function, especially in infants and toddlers, which is irreversible. Early prevention, detection and treatment of iron deficiency are of great significance to improve the quality of individual, especially children.

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