

KORCZAK, Anna, WÓJCIK, Emilia, OLEK, Ewa, ŁOPACIŃSKA, Olga, STAŃCZYK, Katarzyna, KORN, Aleksandra, JEŃDRZEJCZYK, Justyna, SZEWCZYK, Oliwia, BURDA, Katarzyna and CZARNECKA, Karolina. The Long-term Effects of Iron Deficiency in Early Infancy on Neurodevelopment. Journal of Education, Health and Sport. 2024;70:51104. eISSN 2391-8306.

<https://dx.doi.org/10.12775/JEHS.2024.70.51104>

<https://apcz.umk.pl/JEHS/article/view/51104>

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przepisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2024; This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited. The authors declare that there is no conflict of interests regarding the publication of this paper. Received: 07.05.2024. Revised: 10.05.2024. Accepted: 14.05.2024. Published: 17.05.2024.

The Long-term Effects of Iron Deficiency in Early Infancy on Neurodevelopment

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Abstract:

Introduction and Purpose: Iron deficiency, alongside anaemia, is one of the most significant global health concern with potentially long-lasting implications on child development and health outcomes. The period of infancy represents a crucial phase of central nervous system maturation, rendering infants particularly susceptible to the adverse effects of iron deficiency. It is therefore crucial to pay close attention to this issue. The aim of this review is to elucidate the neurological implications of iron deficiency in infancy and emphasize the necessity of implementing preventive strategies to safeguard child development.

State of Knowledge: Iron deficiency in infancy can result in impairments of brain development. Extensive research highlights the influence of this micronutrient on various physiological processes, including the synthesis of neurotransmitters, neuronal metabolism, myelination, synaptogenesis and gene expression. Furthermore, iron deficiency during infancy is associated with adverse developmental outcomes, including cognitive, motor, and

socioemotional deficits. Long-term follow-up studies have elucidated the enduring neurological consequences of iron deficiency in infancy, with effects extending into childhood and beyond.

Summary: Given that the changes that occur during the infantile period are often irreversible and have long-lasting implications for future development, it is of the utmost importance to prioritize prevention strategies.

Key words: iron; deficiency; infantile; neurodevelopment

1. Introduction

Iron deficiency (ID), alongside anaemia, is one of the most significant global health concern. While both conditions frequently co-occur, it is crucial to distinguish between them. Anaemia is characterised by a decrease of two standard deviations in haemoglobin concentration below the mean for age 1 [1]. In contrast, ID occurs when physiological needs cannot be met due to depleted iron stores with the most commonly used biomarker for assessment being serum ferritin [2], [3]. According to the Global Burden of Disease Study 2021, the primary cause of anaemia years lived with disability worldwide was dietary ID. Needless to say, it remained the leading cause in all age groups, regardless of sex, both in 1990 as well as 2021 [4]. It has been estimated that globally 2 billion people are affected by ID. However, only 25% of those affected develop anaemia [5] as iron stores must decrease notably for a decline in haemoglobin concentration to occur [6].

Iron is considered a micronutrient, yet its role in the human body is invaluable. Not only does it make up haemoglobin, but also other proteins such as myoglobin, cytochromes and many more. Due to this fact, iron plays an essential role in immune regulation [7], growth processes and muscle metabolism [8]. Furthermore, it affects the endocrine system, particularly the thyroid function [8] as well as prolactin-influenced stress response [9]. However, the most crucial process iron impacts seems to be development of the central nervous system, including psychomotor and cognitive development [3], [10], [11].

When analysing the aetiology of ID, three main causes can be identified – excessive iron loss, inadequate iron supply and increased iron utilisation. It can be reasonably assumed that the greater the body's metabolic needs, the higher the iron demand, given that iron is an important factor in DNA synthesis and enzymatic activity [12] . Therefore, two main population groups that are at risk of developing ID are children under the age of 5 and women of reproductive age [13]. From a physiological point of view, infants gain the majority of their iron stores during the final trimester of pregnancy. In term neonates, these stores prove to be sufficient for the first 4 to 6 months of life. As this period concludes, infants simultaneously enter a phase of accelerated growth, leading to increased metabolic requirements and, therefore, heightened iron needs. This state continues until approximately 24 months of age [14]. Concurrently, the central nervous system develops significantly during this period. The aim of this review is to highlight the risks associated with ID in infants in regard to their neurological development.

2. State of Knowledge

2.1. The Pathophysiologic Role of Iron in Central Nervous System

Based on animal models several theories have been proposed regarding the mechanism by which ID affects neural function. Iron plays a crucial role in the synthesis of monoamines (dopamine, noradrenaline, adrenaline, and serotonin) and the metabolism of neurotransmitters, both of which are sensitive to its deficiency[15]. The disruption of these processes, caused by ID, can have an impact on socio-emotional development. Observed dopamine-related rat behaviours, such as hesitancy to new experiences during decreased levels of brain iron were persistent and were not completely normalized despite iron replenishment [16]. Hyperactivity in relation to the new experiences was the effect of the damage to the dopaminergic pathways. Moreover, the altered striatal dopamine system affects the development of the basal ganglia system, which is crucial for movement functions cognition, and memory function[17]. As a component of cytochrome oxidase, iron disturbance impacts energy production and utilisation, thus diminishing the metabolic activity of brain neurons responsible for memory processes[18, 19] . Further animal studies indicate that ID can result in delayed myelination and even hypomyelination of neurons by oligodendrocytes. This is the effect of ID impacting other enzymes besides those mentioned earlier, affecting DNA synthesis, neurotransmitter metabolism, or lipid synthesis [20] . Perinatal ID significantly altered the neurochemical

profile of the developing hippocampus and striatum [21], [22] and also changes in the expression of genes [18] or specific growth factors[23]. The explanation of long-term effects on Central Nervous System (CNS) might be caused by the critical timing and the epigenetic modification of the chromatin mechanism [24].

IDA might also affect CNS by decreased oxygen supply and decreased energy metabolism causing lowered oxygen levels disturbing the brain development. Furthermore, a few studies have indicated that infants living at altitude are at high risk for neurodevelopmental problems [25]. One potential explanation for this phenomenon may be the lower oxygen concentration, which could lead to hypoxia.

2.2. The Impact of Iron Deficiency on Cognitive Functions in Infants

Numerous observational studies have linked ID with impaired cognitive function in infants. Children diagnosed with IDA at 6 months of age showed prolongation of central conduction time (CCT), which is an exponent of CNS development. This effect persisted even longer despite effective supplement therapy at 12, 18 months of age, at 4 [26], and also at 10 years of age [27]. Furthermore, long-term deficits in executive function and recognition memory were observed in young adults who had suffered from chronic, severe ID in early life [28]. These studies confirm that a deficiency at a critical time for brain development causes long-term consequences in myelination and anergy metabolism despite iron supplementation. Subsequent studies have indicated that IDA is associated with an increased likelihood of mild to moderate mental retardation [29] and a negative impact on association of neurobehavioral development [20]. A study by Navarro et al. [30] demonstrated that chronic ID in children was associated with significantly lower scores on language, perception of environmental sounds, and motor measurements, compared to infants with normal iron status whereas it reported no difference in cognitive performance between IDA, ID and iron sufficient (IS) groups. Nevertheless, the effectiveness of iron supplementation in children remains inconclusive. A number of reviews with meta-analysis have demonstrated that iron supplementation has no effect on cognitive function among infants who are IS [31], [32] or with IDA [32].

2.3. The Impact of Iron Deficiency on Motor Functions

During ID, dopaminergic transmission is altered in the developing brain, as previously described. The changes that occur in the basal ganglia, in addition to the impaired myelination of the motor cortex and associated areas, can result in overall motor delay [32]. Several observational studies have shown poorer motor function in both ID and IDA infants [30], [33]. These findings are consistent with those of the Densie study, which additionally demonstrated a correlation between the severity of ID and poorer gross motor development [34]. According to McCann et al., iron supplementation during the early infant period (0 to 6 months) has been shown to promote motor development. However, the beneficial effects of this intervention diminish with age [32]. In the systematic review conducted by Wang B. et al., it was concluded that there is no evidence of the effect of iron treatment on psychomotor function after 30 days from the initiation of treatment on infants with ID or IDA. The authors suggested that neurodevelopmental changes induced by deficiency may be irreversible in children under three years of age, or that the period of supplementation may have been insufficient [35].

2.4. The Impact of Iron Deficiency on Neuropsychiatric Disorders

Given the established roles of ID in different areas of the brain, numerous studies have been conducted to investigate the potential link between this deficiency and specific neuropsychiatric disease entities.

One of the well-known pathophysiological mechanisms of Attention Deficit Hyperactivity Disorder (ADHD) is the disturbance of dopaminergic neurotransmitters [36]. As previously demonstrated, ID also affects these neurotransmitters. A systematic review assessing iron concentration in the brain found that children with ADHD had statistically lower thalamic concentrations compared to a healthy control group [26]. Similarly, several studies have demonstrated a correlation between low blood ferritin levels and the occurrence or severity of ADHD symptoms [37], [38]. Moreover, research has indicated that ID in infancy can have long-lasting consequences on ADHD symptoms. Postnatal ID has been linked to an increased frequency of sluggish cognitive tempo and ADHD symptoms [39].

A greater proportion of parents and teachers of children who had suffered from chronic severe ID in infancy reported behavioural problems that persisted consistently throughout adolescence, despite iron treatment. The findings indicated that these individuals exhibited a higher incidence of internalising problems, such as anxiety or depression, externalising problems, social problems and delinquent behaviours during adolescence [40],[41]. Subsequently, 25 years of adolescence also demonstrated poorer emotional health and a greater prevalence of negative emotions and feelings of dissociation/detachment [42]. A less effective emotional regulation during childhood, resulting from ID in the developing brain, was associated with a higher occurrence of rule-breaking behaviour, excessive and problematic alcohol consumption, as well as risky sexual behaviour during adolescence [43]. A study conducted by P. East et al. also found a higher occurrence of rule-breaking behaviour, excessive and problematic alcohol consumption, as well as risky sexual behaviour during adolescence [43]. However, the results of studies attempting to explain these correlations remain inconclusive. These include, among others, changes in the developing brain and particularly in neurotransmitters, less effective regulation of emotions, and the influence of the parent-child relationship. The latter factor was assessed in a study where externalising behaviour in 5-year-old children (with ID in infancy) was associated with a more negative maternal response [44].

Data from the literature also suggest that ID may be a factor associated with breath-holding spells (BHS). It is one of the most common non-epileptic paroxysmal disorders in childhood. According to a review conducted by Zehetner AA. et al. iron supplementation reduced the frequency and severity of BHS [45]. These effects have been observed in both anaemic and non-anaemic children. A further prospective study is consistent with these findings and additionally demonstrates similar responses to iron supplementation between IDA and ID groups [46].

A meta-analysis of 20 case-control studies demonstrated that there is an association between ID and an increased risk of febrile seizures in children [47]. Additionally, another study revealed that mean ferritin levels were lower in children with a first episode of febrile seizures than in the febrile control group [48]. However, contrary to these findings, Kobrinsky et al. demonstrated that ID increases the seizure threshold [49]. Similarly, a protective effect of ID has been identified in several additional studies [50], [51].

3. Discussion

It is indisputable that ID and IDA represent significant public health issues. However, the majority of research tends to focus purely on the risks associated with anaemia, resulting in a lack of data on the burden implied by ID in isolation. Anaemia is considered an end-stage of ID, yet during the period in which anaemia develops, infants are already exposed to concerning health implications, some of which can prove to be irreversible. In infancy, the period of heightened iron requirements coincides with the intensive development of the central nervous system. Needless to say, the consequences of depleted iron stores on the developing infant nervous system may extend well into adulthood. It remains crucial to prevent this negative impact.

The data currently available regarding iron supplementation in the state of its deficiency is either inconclusive or demonstrates a minimal or absent effect of said supplementation. The medical community should therefore prioritize identifying whether an infant presents risk factors for ID. These children require the greatest attention to prevent depletion in their iron stores since supplementation later on may not prove to be as effective.

Due to the fact that infants derive the majority of their iron stores in the final trimester of pregnancy, it is understandable that any disturbance at this stage may increase the risk of ID. Neonates born prematurely, with a low birth weight or from anaemic mothers may fail to create appropriate levels of iron [52]. Once the child reaches the age of 4 to 6 months, their prenatal iron stores are gradually depleting and the diet becomes the most crucial factor in maintaining sufficiency. Exclusive breastfeeding beyond the age of 6 months is considered a risk factor for ID as breastmilk is unable to meet the infant's nutritional requirements at this age. However, the early introduction of cow's milk, before the age of one, may disrupt the process of iron absorption as well as cause blood loss due to microhaemorrhages within the infant's digestive tract [53]. Therefore, the medical community ought to focus on comprehensive nutritional education of the parents with the aim of minimising the long-term adverse effects of ID.

Iron absorption can be negatively influenced by additional factors, such as chronic inflammation or recurrent infections. Although rare in high-income countries, children in low- and middle-income countries are more prone to parasitic infestations including hookworm and

schistosomiasis. These are not only responsible for chronic inflammation, but also blood loss – both of which are risk factors for ID. Malaria, HIV and tuberculosis can lead to ID in the same manner, that is by inducing inflammation in the body. Infants are more susceptible to developing the conditions mentioned above due to the immaturity of their immune system. In the regions where malaria prevalence is high, only up to approximately 30% of anaemia tends to respond to iron supplementation [5]. It seems reasonable to conclude that in low- and middle-income countries the battle against ID and its negative impact should be aimed at improving sanitary conditions as well as prevention and treatment of infections [4], [8], [54].

4. Conclusions

While the global community has become increasingly aware of the consequences of IDA, ID in isolation remains largely under-recognised. Infants are particularly susceptible to ID not only due to their physiology but also as a result of various external factors. Insufficient iron stores in infancy have been linked to cause potentially irreversible impairment of the development of the nervous system. By prioritizing research and intervention efforts focused on early identification, prevention, and treatment of ID, we can effectively mitigate its adverse effects and promote optimal neurological health and development in infants.

Author's Contribution: Conceptualization: AMK, EW; methodology: KC; software: AK; check: OŁ, KS, JJ, OS; formal analysis: EO, KB; investigation: EO, KB; resources, JJ, KC, EW; data curation: EW; writing – rough preparation: AMK, EW, OŁ, KS, KC, AK, JJ, OS, EO, KB; writing – review and editing: EW, AMK, JJ, OS, EO, KB, OŁ, KS, KC, AK; visualization: OS, EO; supervision: EW, AMK; project administration: OŁ, KS, AK, KC; **All authors have read and agreed with the published version of the manuscript.**

Disclosures

Funding:

This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest Statement:

The authors declare no conflict of interest.

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