REVIEW

Iron deficiency and cognitive functions

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Abstract: Micronutrient deficiencies, especially those related to iodine and iron, are linked to different cognitive impairments, as well as to potential long-term behavioral changes. Among the cognitive impairments caused by iron deficiency, those referring to attention span, intelligence, and sensory perception functions are mainly cited, as well as those associated with emotions and behavior, often directly related to the presence of iron deficiency anemia. In addition, iron deficiency without anemia may cause cognitive disturbances. At present, the prevalence of iron deficiency and iron deficiency anemia is 2%–6% among European children. Given the importance of iron deficiency relative to proper cognitive development and the alterations that can persist through adulthood as a result of this deficiency, the objective of this study was to review the current state of knowledge about this health problem. The relevance of iron deficiency and iron deficiency anemia, the distinction between the cognitive consequences of iron deficiency and those affecting specifically cognitive development, and the debate about the utility of iron supplements are the most relevant and controversial topics. Despite there being methodological differences among studies, there is some evidence that iron supplementation improves cognitive functions. Nevertheless, this must be confirmed by means of adequate follow-up studies among different groups.

Keywords: iron deficiency, anemia, cognitive functions, supplementation

Introduction

The importance of iron in cognitive functions is highlighted in some early studies.[1,2] In those studies, some alterations with regard to psychomotor development and cognitive functions have been generally linked to the deficiencies of this mineral. Overall, micronutrient deficiencies are linked to different cognitive impairments, especially iodine and iron,[3–6] as well as to potential long-term behavioral changes.[6] Generally, a lack of iron in the neonatal period and early childhood is considered as a key to the development of disturbances in cognitive development.[7–9] At the same time, there is little consensus about the effectiveness of possible preventive programs.[10,11] Cognitive disturbances in general and visuomotor development have been related to iron deficiency (ID),[12,13] and more recently a possible link between dieting, ID, and the possible presentation of cognitive alterations has been studied.[14]

Experimental studies show that ID is capable of causing cognitive impairment in animals and humans,[15,16] with brain mitochondrial damage as a basis for these alterations.[17] Among the cognitive impairments caused by ID, those related to attention span, intelligence, and sensory perception functions are mainly cited, as well as those related to emotions and behavior. Generally, these impairments have been related to iron deficiency anemia (IDA). In addition, it must be noted that ID without anemia may cause cognitive disturbances.[11] With respect to ID and IDA, some concepts must be noted. Iron status is a continuum from IDA to ID without anemia to normal iron status with varying amounts of stored iron and finally to possible iron overload. ID is

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defined as a condition in which there are no mobilizable iron stores and in which signs of a compromised supply of iron to tissues, including the erythrocytes, are detected. When iron-deficient erythropoiesis occurs, hemoglobin concentrations are reduced to below optimal levels. The existence of anemia is considered when individual hemoglobin levels are below two standard deviations of the distribution mean for hemoglobin in an otherwise normal population of the same sex and age who are living at the same altitude.[18]

Twenty years ago, ID with anemia affected >45% of children aged <5 years in developing countries and >7% in developed countries.[5] Currently, it is estimated to affect 2%–6% of European children, with a significant reduction in prevalence. Enriched foods and the use of supplements have contributed to that reduction, among other factors.[19] Despite this improvement in the monitoring of ID, it seems that some health problems are associated with long-term deficits in cognitive and motor function and achievement gaps in education (small to gestational age infants, too short breastfeeding period, ID, severe and moderate protein energy malnutrition in early childhood, and intrauterine ID). In addition, behavioral differences have also been found in long-term follow-up studies of children who had protein energy malnutrition.[6]

In this field of study, the relevance of ID and IDA with respect to cognitive function is the main topic in the literature. The distinction between the cognitive consequences of ID and those affecting specifically cognitive development is another relevant point. The debate about the utility of iron supplements is also a topic that remains controversial.

Given the relevance of the problem of ID relative to proper cognitive development and the alterations that can persist through adulthood as a result of this deficiency, the objective of this study was to review the current state of knowledge about this health problem, trying to conclude with some practical conclusions.

Material and methods
Searching process
It was based on three relevant electronic databases (Medline, EMBASE, and Scopus), with a general strategy including terms related to "cognition" and "iron deficiency". The Medical Subjects Headings and the Boolean operators AND/OR were used for the searching process. The shared Mesh terms were: ((("Nutritional deficiencies"[Mesh]) OR ("Micronutrients"[Mesh]) OR ("Iron deficiency"[Mesh]) OR ("Iron deficiency anemia"[Mesh])) AND (("Attention deficit"[Mesh]) OR ("Intelligence"[Mesh]) OR ("Psychomotor

development"[Mesh]) OR ("Emotions"[Mesh]) OR ("Behavior"[Mesh]))).

Additional searching was carried out on references included in the papers, published reviews, and via hand searching. The literature search was mainly but not exclusively based on the last 15 years. Some former articles considered as pioneers and/ or especially relevant were also included.

Studies meeting the following criteria were included in the review: 1) studies focused on cognitive disturbances and ID and 2) controlled trials, randomized controlled trials, and comparative studies. The exclusion criteria were 1) case reports, 2) populations with nonspecific ID-related problems, 3) participants with special conditions/pathologies other than ID (eg, iodine deficiency), and 4) full text/abstract not available. Previous studies (reviews and meta-analysis) were considered as another source of articles, provided that they fitted the inclusion criteria. An analysis was carried out about references included in the papers as well as via hand searching.

The initial search yielded 269 references. References were included in an EndNote 9 library and screened on the basis of title and abstract. As a result, 26 duplicates were excluded. Thereafter, selected references were analyzed based on the full text. After applying the exclusion criteria, 89 studies were finally included.

Thematic analysis
To analyze the selected articles, a thematic analysis was used following the six-step framework of Braun and Clarke:[20] becoming familiar with the data, creating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report. Fragments of data that identify a significant feature of such data were acknowledged and grouped together into related themes.[20,21] As a result, the following main different topics were obtained: anemia vs ID, neurocognitive development and educational performance, and the controversy about treatment and supplementation.

Results
Anemia versus iron deficiency
In a study about the effects of children's IDA on executive functions at 10 years, it has been found that those who had anemia showed slower reaction times, less accuracy, and higher latency peak N2 and smaller amplitud of the P300 wave (which is related to working memory) in the electroencephalogram (EEG).[22,23]

Compared with a control group (non-IDA infants), IDA infants (aged 3–15 months) showed lower scores in cognition,

fine motor, and social/emotional areas. In addition, they had higher delta/theta and lower alpha power in EEG activity.[24] Children aged 8–10 years were studied in order to determine the cognitive effects of IDA by means of the EEG P300 wave and some psychometric tests.[25] As a result, P300 latency in the anemic girls was delayed as compared with the control group, but no statistically significant difference was observed for P300 latency and P300 amplitude between the control group and the anemic group. The psychometric test scores for intelligence quotient and transformed quotient were also better but not statistically significant in the control group of girls as compared with anemic girls. However, the hematocrit values showed a significant correlation, with the P300 wave latency showing that hematological status is associated with some effects on cognition. In a recent review, it was concluded that with respect to ID, of particular importance is the effect on the central nervous system, which leads to the defects in the cognition and learning processes in humans.[26]

A poorer object permanence and short-term memory encoding and/or retrieval have been shown in infants with IDA aged 9–12 months. These cognitive effects were attributable, in part, to IDA-related deficits in socioemotional function. Children with poor socioemotional performance seemed to be more vulnerable to the effects of IDA on cognitive function.[27]

If IDA occurs during the first 2 years of life, it is associated with poor psychomotor performance and changes in behavior, such as reduced levels of responsivity to persons and stimuli, irritability, and inhibition. Different studies demonstrate that effects observed during infancy persist in the long-term. It has been reported that formerly anemic preschool children are less active, more inhibited, and more timid than the corresponding controls.[28]

ID and IDA may have some prolonged effects on behavior and development.[29] In a review about the effects of ID in the first 2 years, it is concluded that the relationship between ID and IDA to cognitive and mental development in childhood is still unclear. Generally, follow-up studies have found poorer cognitive scores on measures of mental and cognitive functioning in the long run.[30]

Non-IDA predominantly due to anemia inflammation has been related to lower performance on tests of cognitive function, this likely being due to decreased delivery of iron to host tissues including the central nervous system.[31] In fact, cognitive achievement is strongly related to hemoglobin level (higher hemoglobin levels result in better central nervous system function) and could be expected in anemic patients.[32]

There is a debate about the cause of the cognitive impairment with respect to the anemia/ID. Is the impairment a result of ID per se or a combination of ID and anemia? How do these conditions interact? It has been found that cognitive function increases with increased hemoglobin concentration in children with ID but does not change with hemoglobin concentration in children with normal serum ferritin level. It seems that children with IDA consistently have the poorest cognitive function. Children with nonanemic ID but with high hemoglobin levels have significantly high cognitive function. So a dose–response relationship between hemoglobin and cognitive function in children with ID has been found, whereas no similar evidence is found in iron-sufficient children.[33] Nevertheless, other authors support the idea that some cognitive symptoms get better with iron supplementation, this improvement being independent of the hemoglobin levels.[34] In fact, a significant inverse relationship has been found between body iron and central executive function (planning time) in nonanemic college women.[35]

In a study focused on the effect of ID on cognitive development among children, the authors concluded that the effect of short-term iron treatment in anemic children aged <2 years is controversial.[13] With respect to anemic children aged >2 years, it seems that iron treatment would be more effective. Finally, they stated that preventing IDA could produce benefits to development but that they would be small and transient.

Neurocognitive development and educational performance

A consequence of ID relies on alterations in cognition that occur among iron-deficient individuals during the early parts of their life cycle and perhaps at later times as well. While ID was presumed to cause most of its effects only if anemia was present, it is clear that many organs show morphologic, physiologic, and biochemical changes before there is any significant drop in hemoglobin concentration. ID is associated with alterations in many metabolic processes that may impact brain functioning (eg, mitochondria electron transport, neurotransmitter synthesis and degradation, protein synthesis, organogenesis). It is necessary to separate the developmental aspects of ID and neural functioning from the aspects of ID that could occur at any time in life.[36]

In a recent study,[37] a chronic ID group showed significantly lower scores on language, environmental sound perception, and motor measures when compared with infants with normal nutritional iron status at 6 months and 14–18 months. The conclusion was that the development of

language and motor skills and environmental sound perception appeared to be sensitive to the effects of chronic ID in infants. In fact, IDA produces alterations in cognitive processes related to visual attention and concept acquisition in children.[38] A lower school achievement and poorer fine-hand movements have been described in children.[39]

For some authors, iron status does not play a major role in educational performance and intelligence of school-going adolescents, stating that several factors (apart from ID) affect educational performance and intelligence.[40] Eden[41] highlights that children with ID and IDA, especially those in lower socioeconomic groups, are at high risk for neurodevelopmental impairment both from the ID itself as well as from central nervous system damage caused by the associated increased absorption of other metals like lead. With regards to the low socioeconomic groups, 26% of postinstitutionalized children have been shown to be iron deficient. ID is associated with neurobehavioral alterations months after postadoption, mediated by the effect on attention and activity levels (hyperactivity).[42]

Maternal genotypes at single nucleotide polymorphisms in the genes *HFE* (rs1799945) and (rs1800562), *TF* (rs3811647), and *TMPRSS6* (rs1800562) are related to iron, hemoglobin, or transferrin levels. In a study by Lewis et al[43] exploring the effect of prenatal iron levels on offspring cognition, the aforementioned mother's genotype loci were not associated with offspring intelligence quotient at age 8 years, so there is no evidence of an effect of exposure to low levels of iron (within the normal range) in pregnancy on offspring cognition at age 8 years. With respect to the genotypes, it has been shown that elevated iron levels may decrease cognitive speed in older individuals susceptible to cognitive impairment despite cognitive performance over 3 years not being associated with HFE C282Y genotype or iron parameters.[44]

There is evidence that, despite iron repletion, ID during the brain growth spurt alters metabolism and neurotransmission, myelination, and gene and protein profiles.[45] In humans, there is compelling evidence that 6- to 24-month-old infants with IDA are at risk for poorer cognitive, motor, socioemotional, and neurophysiologic development in short- and long-term outcomes. Alterations in the mesolimbic pathway, where dopamine plays a major role in behavioral activation and inhibition, positive affect, and inherent reward may help explain altered socioemotional behavior in iron-deficient infants.[46]

Different functions and several ages seem to cause controversy in this field of study. On the one hand, in animals,

deficits in motor activity are consistently associated with severe IDA, but adverse effects on performance in tests that target cognitive function have not been clearly shown. On the other hand, IDA resistant to iron administration (with the consequent failure of iron therapy) has been observed in most trials of children aged <2 years but not in older children. Similar observations have been made in rodents when IDA occurred before rather than after weaning. In children aged >2 years and in adolescents with IDA, evidence suggests cognitive or behavioral deficits.[47] In a recent review[48] it is stated that despite the clear elucidation of the neural mechanics of ID, there is not unequivocal support for a direct causal relationship between ID and abnormal development. Even accepting the evidence as being overwhelmingly in support of a direct causal link in experimental animals, we are far from being able to do so for humans, at least with any degree of specificity.

Apart from infants and children, women of reproductive age are specially affected by ID, and cognitive–behavioral consequences of that deficiency have been described in that population.[49] Not only has ID (eg, as a result of a low intake of foods rich in bioavailable iron) been related to cognitive impairments but a high consumption of foods rich in inhibitors of iron (such as phytate, certain dietary fibres, and calcium) has too.[16]

The controversy about treatment and supplementation

Several benefits of iron supplementation, independent of increasing hemoglobin, such as those on immune function, physical performance, thermoregulation, cognition, and restless leg syndrome, among others, have been described.[10] Considering the cognitive functions, the point is whether iron supplementation can improve them.[50]

With respect to the behavioral problems associated with ID, it seems that an early iron supplementation of marginally low birth weight infants does not affect cognitive functions at age 3.5 years but significantly reduces the prevalence of behavioral problems.[51] For other authors, iron seems to have a modest effect on linear growth in deficient populations.[52]

Considering a positive effect of iron, does it depend on the previous ID (without anemia) or is it necessary to suffer from IDA? In this regard, Bruner et al[53] reported the benefits of iron supplementation in an urban population of nonanemic iron-deficient adolescent girls. That supplementation improved verbal learning and memory. Another study showed that in healthy formerly iron-deficient anemic children the altered cognitive function might be prolonged despite the iron

treatment. The authors suggested that long-lasting changes in myelination and energy metabolism, perhaps especially in the hippocampus, might account for these long-term effects on an important aspect of human cognitive development.[54] Devaki et al[55] tested two groups of adolescents (nonanemic ID and iron-deficient anemic) after 8 months of iron supplementation. This supplementation resulted in significant improvements in cognitive function and school achievements. In a shorter follow-up study (6 months of iron supplementation), Ebenezer et al[56] did not find a significant impact on concentration levels and educational tests scores. Comparing iron-deficient anemic children with those who are iron replete, it seems that anemic children show faster motor development than the control children do.[57] Another study highlights that there seems to be a dose–response relationship between hemoglobin and cognitive function in children with ID, whereas no similar evidence has been found in iron-sufficient children.[58]

Another relevant point is the moment to introduce the iron supplementation. In a study by Christian et al[59] it was reported that fine motor functioning among offspring was positively associated with prenatal iron/folic acid supplementation in an area where ID was prevalent. In another study, Friel et al[60] gave an iron supplementation to term breastfed infants (aged 1–6 months). With respect to the development effects, that supplementation resulted in higher visual acuity and developmental indexes at age 13 months. After controlling for background factors, children who had severe, chronic ID in infancy showed poorer arithmetic achievement and written expression, motor functioning, and some specific cognitive processes (spatial memory, selective recall, and tachistoscopic threshold), and this occurred 10 years after treatment.[61] Sachdev et al[62] have also reported that iron supplementation improves mental development modestly. This effect is particularly apparent for intelligence tests on children aged >7 years and in initially anemic or iron-deficient anemic subjects. There are controversial results with respect to the effect of iron therapy in children. While Sachdev et al state that there is no convincing evidence that iron treatment has an effect on mental development in children aged <27 months or on motor development, and Yalcin et al[63] consider that short-term iron supplementation does not change developmental test scores despite the hematologic response in iron-sufficient healthy infants, others seem to report more positive results. Thus, Matiashvili et al[64] found that children aged between 16 months and 24 months improved their performance in neurodevelopmental measures when they had received iron in a timely manner.

In preschool children, some improvements in cognitive functions have been reported after iron supplementation: eg, in discrimination, specifically selective attention.[65] In a former study, it was reported that the administration of heme iron-fortified cookies might improve the intellectual performance of low-income preschool children.[66] In addition, Soewondo et al[38] and Idjradinata and Pollitt[67] have reported cognitive improvements after iron supplementation in children. With respect to the cognitive development, Thompson et al[68] state that iron supplementation produces a small improvement. It has been reported that iron treatment of young children with IDA has a positive short-term effect on psychomotor development or cognitive function, but the effect of longer-term treatment remains unclear.[69] Not only iron but also a mixture of iron and folic acid supplementation seems to produce beneficial effects on cognition in young adolescent girls.[70] On the contrary, Siegel et al[71] state that neither combined nor individual supplements improve the performance on tasks such as A-not-B or fixation duration in infants. Solon et al[72] reported similar results. These authors did not find any improvements in cognitive performance after supplementation with a multiple micronutrient-fortified drink. The effect of several drinks containing different micronutrients and sugar seems to be positive when those beverages are given alone. In other cases, the combination attenuates that positive effect on cognition.[73] Baumgartner et al[74] found that in children with poor iron and n-3 fatty acid status, iron supplementation improved verbal and nonverbal learning and memory, particularly in children with anemia. In contrast, docosahexaenoic acid/eicosapentaenoic acid supplementation had no benefits on cognition and impaired working memory in anemic children and long-term memory and retrieval in girls with ID.

Iron supplementation has been studied in adults with IDA by means of the Mini Mental State Examination, Wechsler Memory Scale – Revised, Wechsler Adult Intelligence Scale – Revised, event-related potentials, and EEG. As a result, authors concluded that IDA is a key in cognitive performance in adults, which can be partially reversed by treatment.[75] In young women, Murray-Kolb and Beard[76] have found that an improvement in serum ferritin after iron supplementation correlated to better cognitive performance, whereas a significant improvement in hemoglobin correlated to improved speed in completing the cognitive tasks. Recently, Leonard et al[77] have analyzed some differences between iron-deficient and iron-sufficient young women with respect to their cognitive function after receiving placebo versus iron supplement. As a result, they have found out that

change scores for impulsivity and attention were significantly greater in plasma ferritin improvers than in nonimprovers.

Discussion

Previous reviews on this field of study concluded that ID has a negative impact on cognition, behavior, and motor skills that can have long-term implications.[13] Many studies highlight that the relationship between ID and cognitive consequences could be confounded by external factors such as low socioeconomic background. Apart from socio-economic factors, ID seems to impact on areas such as the hippocampus,[61] and the cognitive dysfunction might be due to mitochondrial damage.[78] In addition, changes in brain dopamine metabolism are presumed to occur,[1,2] as well as altered serotonergic neurotransmission[5] and alterations in the dopamine receptors.[79] In fact, brain ID and/or IDA result in major changes in dopamine levels in brain crucial areas.[80] These changes related to central (brain) ID might cause different effects than those caused by IDA. More recently, Lozoff[46] has reported that alterations in the mesolimbic pathway, positive affect, and inherent reward might give support to explain the altered socioemotional behavior that has been described in children with ID. This author states that poorer motor sequencing and bimanual coordination and lower spontaneous eye blink rate in children with IDA are consistent with impaired function in the nigrostriatal pathway. Generally, nutrition has been shown to affect the brain's macrostructure (eg, development of brain areas such as the hippocampus), microstructure (eg, myelination of neurons), and level and operation of neurotransmitters (eg, dopamine levels or receptor numbers), all of which can have an impact on cognitive development.[81] Specifically, nutrients such as iron and omega-3 – polyunsaturated fatty acids, in particular – might have specific effects on frontal lobe functioning.[9]

There are works in which it is possible to obtain a clear idea about the effects of ID and IDA on behavior and development.[29] Generally, in non-IDA, there seems to be lower performance in cognitive functions,[31] so a question arises as to whether ID, IDA, and anemia (other than IDA) may cause the same cognitive deficits. This question has an unclear response to date. Some studies correlate hemoglobin levels to cognitive function,[33] while others report an improvement in cognitive functions after iron supplementation, which seems not to be correlated to those levels.[34] Despite the specific effect of hemoglobin levels or iron status not being clear, IDA has proved to cause different cognitive alterations in all stages of life. A relevant effect of ID is caused during brain growth, as stated by Lozoff et al.[45] For others, the effect of ID is not unequivocal considering a possible direct causal relationship between ID and abnormal development.[48] Along with the work of Lozoff et al others seem to point out that there are critical periods in which ID might have long-term effects on cognition and behavior (eg, premature babies, infants aged <1 year, and preschool children).[82–84] Apart from those critical periods, it seems that there are not any substantial different effects of ID or IDA on cognitive functions depending on the age reported clearly in the literature. With regards to the sex, it seems that there are no differences between boys and girls with ID in cognitive test performance.[74]

With more or fewer consequences and major or minor effects depending on age and sex, for example, there is a common practice that consists of supplementing with iron in case of ID and/or IDA. Here another debate arises. Is it useful?

There seem to be two tendencies considering the supplementation – on the one hand, the use of multimicronutrient supplements and, on the other hand, the use of specific micronutrients such as iron in this field of study. In addition, not always clear is the distinction between supplementation and fortification in the studies based on this topic. Nevertheless, this debate seems to be a perceptive problem. If both fortification and supplementation similarly involve the addition of micronutrients (vitamins or minerals) to the diet, why is there such a disparity in the perceptions of each? The fact is that while food fortification has been viewed by some as a nutritional triumph, individual supplementation with vitamins or minerals has, at best, been deemed unnecessary without underlying deficiency, and at worst been called potentially hazardous. So what are the differences between supplementation and fortification that make one more acceptable than the other?[85] So supplementation, fortification, or treatment should be considered without distinction in order to explore the cognitive improvements in case of ID and IDA.

Some authors report a behavioral improvement but not better results on cognitive function after iron supplementation,[52] while others highlight an improvement in verbal learning/memory in ID (nonanemic) individuals.[53] Despite years of treatment, there seem to be some cognitive alterations that persist.[54] The controversial results focus not only on the long-term follow-up studies but on short-term ones too. For example, some authors state that an iron supplementation over a period of 8 months or 30 days is effective, while others point out that the supplementation during 6 months is not effective.[55,56,69]

Another relevant point highlights the moment to introduce the iron supplementation. When should it be introduced? There are a lot of studies indicating the success of an early iron supplementation: prenatal,[59] age 1–6 months,[60] age <27 months,[62] age 16–24 months,[64] and preschool,[65,66] among others.

Finally, there are controversial results with respect to the "mixtures" used as supplements. Thus, a beneficial effect of iron and folic acid supplementation has been reported.[70] On the contrary, Siegel et al[71] and Solon et al[72] do not find positive results with combined supplements. For others, the combination of supplements might attenuate some positive effects.[73] With respect to the specific action of polyunsaturated fatty acids, Baumgartner et al[74] found that docosahexaenoic acid/eicosapentaenoic acid supplementation had no benefits on cognition and impaired working memory in anemic children and long-term memory and retrieval in girls with ID.

Despite iron excess cannot be excreted by the human body (in contrast with other nutrients), iron supplementation is often recommended, that supplementation not always being necessary. Iron supplements seem to be beneficial in iron-deficient children, but there is a risk of adverse effects in those who are iron replete. It has been suggested that excessive iron supplementation of infants may have adverse effects on growth, risk of infections, and even on cognitive development. In addition, excessive iron intake can have negative effects on brain development.[86] So in populations with a low prevalence of ID, general supplementation should be avoided. The same applies to iron-fortified foods. In this regard, more studies are needed to better determine the risks and benefits of iron supplementation and iron-fortified foods given to iron-deficient and iron-sufficient children.[86]

Despite there being methodological differences among studies, there is some evidence that iron supplementation may improve some functions, such as attention, concentration, and intelligence. Nevertheless, these results require confirmation with well-powered, blinded, independently funded, randomized controlled trials of at least 1 year's duration in different age groups including children, adolescents, adults, and older people and across all levels of baseline iron status.[87,88] Many studies differ in the characteristics of the study population, definition of exposure, type of treatment, and confounders, so it is difficult to assess a causal relationship between ID and IDA and cognitive and mental development in childhood,[30] and the same applies to the use of supplements.

Maybe, an early-introduced correct (adequate) diet is better than the use of supplements. Thus, some studies suggest that increased meat intake by breastfed infants aged >6 months would adequately support iron requirements.[89]

Conclusion

There is a consensus on the fact that ID has a negative impact on cognition, behavior, and motor skills. With respect to this negative impact, its causal link with ID might be confounded by external variables such as socioeconomic status.

ID, IDA, and non-ID anemia may cause some cognitive deficits, but it remains unclear if those deficits are the same. These cognitive deficits may appear at any age. Levels of hemoglobin seem to correlate to cognitive performance, but iron supplementation improves cognitive functions regardless of the hemoglobin levels.

Despite the possible action of confounders, ID is clearly related to alterations in areas such as the hippocampus, mitochondrial damage, brain dopamine metabolism, and myelination.

The use of supplements (fortification, treatment) must be based on well-established indications, avoiding their use as a routine. The use of multisupplements does not seem to add a plus with respect to the use of specific supplements. The success of the supplementation might be based on an early prescription after having diagnosed an iron deficiency. It remains controversial whether that supplementation is successful or not, depending on the timing of the therapy (eg, critical periods).

More studies of an appropriate duration in different age groups (children, adolescents, adults, and older people) and across all levels of baseline iron status are required.

Disclosure

The author reports no conflicts of interest in this work.

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