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Effect of Iron-Deficiency on Cognitive Skills and Neuromaturation in Infancy and Childhood

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ABSTRACT

Background: Although, the literature is abundant on the adverse effects of micronutrient deficiencies on neurocognitive performance, iron deficiency is a major public health problem worldwide because it continues to be the single most common nutritional deficiency and the main cause of anaemia in infancy and childhood. Nutritional anemia occurs when body reserves for a specific nutrient are inadequate for the synthesis of hemoglobin. This deficiency is due to inadequate iron intake and poor bioavailability. According to the World Health Organization (WHO), more than 2 billion people in the world today are estimated to be deficient in iron deficiency. **Objectives:** Rates of the highest prevalences in the developing world were found among pregnant women with 56% of school children followed directly 53%. The distribution of iron in the brain is very heterogeneous, a characteristic of the species in which the concentrations were determined. The highest concentrations are localised in the nucleus accumbens, the substantia nigra (nigra), the nucleolus cerebellar deep red nucleus and some portions of the hippocampus. These distributions occur at an advanced age especially when all the neuro-developmental activity is performed. **Results:** Iron supplementation improves mental development scores of anemic children. These results are amplified by psychosocial stimulation at home or in specialized centers. In sectoriel studies that our team has made in the region of Kenitra with populations of school children, the results are unanimous on the correlation between martial status and school performance and/or overall intelligence score determined by Raven's Progressive Matrices when socioeconomic variables are controlled. **Conclusion:** A comprehensive study using evoked potentials is desirable to confirm the relationship between iron deficiency neuro-cognitive development.

Key words: Anemia, brain, iron deficiency, cognitive development

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INTRODUCTION

For primary school children, iron deficiency anaemia is a hemoglobin level of less than 11.5 g dL^{-1} and ferritin of less than 12 μg L^{-1}. Anaemia is further graded into mild (9.0-11.4 g dL^{-1}), moderate (6.0-8.9 g dL^{-1}) and severe (<6.0 g dL^{-1})[1].

Deficiency may be due to inadequate dietary intake of iron, low level of absorption because of small bowel pathology, increased physiological requirements during rapid growth in infancy and adolescence and chronic blood loss usually from the gastrointestinal or urinary tracts or because of menorrhagia in adolescent girls[2].

Iron-deficiency anaemia is a major nutritional problem throughout the world and leads to serious health problems, such as poor cognitive and motor development and behavioural problems, in children[3]. In a previous study in rural and urban Morocco, we observed a positive correlation between Serum Ferritin (SF) and hemoglobin (Hb) concentrations, suggesting that a significant proportion of anaemia cases might be related to iron deficiency[4].

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Globally, the estimates of iron deficiency are almost about 2 billion people according to the (WHO)[5]. In third world countries, the rate of the highest prevalences were found among pregnant women with 56% of school children followed directly 53%. However, in industrialized countries, pregnant women are affected by a rate of 18%, followed by 17% of preschool children[6].

Anemia: A comprehensive global estimate: In its latest report, the WHO estimated that anemia affects 1.62 billion people in the world which corresponds to 24.8% of the world population[7]. The preschool children and pregnant women were the most affected groups. The prevalence of anemia was 47.4% among preschool children and 41.8% in pregnant women. In non-pregnant women the prevalence of anemia was 30.2%. In addition to this, it has long been considered the most vulnerable bracket aged is between 6 months and 5 years. Certainly this child still suffers from anemia to high levels, particularly in Morocco with 31.6% (ACC/SCN)[8], however, Hall *et al.*[9,10] have demonstrated that even 90% of these children survive to their fifth birthday, their situation at school age remains worrying.

Iron on the nervous system: location and metabolism: The distribution of iron in the brain is very heterogeneous, a characteristic of the species in which the concentrations were determined[11]. The highest concentrations are in the nucleus accumbens, the substantia nigra (nigra), nucleolus cerebellar deep red nucleus and some portions of the hippocampus. These are close to the values in liver[12]. These distributions occur at an advanced age especially when all the neuro- developmental activity is performed. Iron is mainly contained in the enzymes, structural proteins and transport proteins as ferritin storage. It is located primarily in microglia and oligodendrocytes.

This location is in function of developmental stage. Then the iron is transported into the cerebrospinal fluid by specific transferrin. In the elderly, a concentration of 15-25 mg L^{-1} was determined. These concentrations are 5-10 times lower than those in plasma. Reports 100: 1 have been reported for ferritin in elderly people suffering from overactive leg (Restless legs)[13].

The brain iron obtained through the transferrin receptor expressed in endothelial cells of the microvasculature. The transfer rate is increased when the individual reserves are low and vice versa. This process is highly selective and does not reflect the overall permeability of the nerve blood.

Recently two new carriers of iron have been identified: the «divalent metal transporter" (DMT1-iron/proton symporter that moves the iron acidified endosomes) and metal transporter protein 1 (MPT-1/ferroprotin/Ireg 1) export of iron[14].

Function of iron in the brain: Brain iron accumulates from birth to early adulthood, in addition to the stage of neurodevelopment, iron distribution in the brain's metabolic activity is some time a cause of degenerative diseases associated with aging.

The studies focused on the function of iron in the brain are very limited and are performed in animals or cell culture. Deductions from the data of Magnetic Resonance Imaging (MRI) in humans confirm that the relaxation time T2 weighted associated with the concentration of iron in brain regions[15].

Iron is necessary for myelination of the spinal cord and the grey matter. It is also a cofactor of the enzymes involved in the synthesis of neurotransmitters, such as tryptophan hydroxylase and tyrosine hydroxylase[16,17]. Cells containing more iron are oligodendrocytes in multiple species. These cells are responsible for the synthesis of fatty acids and cholesterol for myelin. Levels of monoamines are sensitive to changes in brain iron status, but these mechanisms are not yet clear[18].

Beard[19] has wishes in a review about the nerve function of iron by refined techniques of behavioral and cognitive measures will tell us more in the next five years on sensitive to iron deficiency periods in infant development.

Mechanisms conducting to cognitive delays are not all known, but it seems they might be connected with alterations in enzymes involved in the synthesis of neurotransmitters[20], decreased myelination[21] and changes in energy metabolism in the brain. They mainly affect neurotransmitters role as outlined in the review of Beard and Connor[19], the functioning of dopamine transporters, serotonin and noradrenaline[22]. The cortex, hippocampus, striatum and areas important for cognition, are more susceptible to iron deficiency than other areas of the brain[23].

Effect of iron deficiency and anemia on cognitive development: Iron deficiency among school children is more transitional than in young children, so they can easily respond to treatment. According to Sungthong[24], cognitive function (IQ: Intelligence Quotient test, language and math) is correlated with hemoglobin when ferritin is abnormal.

Using the Raven Progressive Matrices, electro-encephalogram and attentional span: in school children from 9 years on average, Bandhu *et al*.[25] reported that only the Raven score improved by the treatment. Rather it is the memory function and especially of figures associated with hemoglobin in Mexican children from 6-8 years, whereas, ferritin was negatively correlated with the revised codes WISC-RM (RM Version. Revised Mexican)[26], in the other hand, Bandhu *et al.*[25] reported that only the Raven score improved by the treatment. In another study, it's rather the memory function and especially of figures associated with hemoglobin among Mexican children from 6-8 years , whereas ferritin was negatively correlated with the dimensions of the test codes WISC-RM[25]. On school performance. Wang *et al*.[27] reported that anemia in post-adolescent is a determinant of dropout.

In their sides, Mukudi *et al*.[28] showed that the strongest predictor of academic performance is attendance. That is affected by malnutrition among girls with low socio-economic level. Neurological determinants of changes in cognitive performance are little explored. Nevertheless, some studies, including that of Otero *et al*.[29] found that in addition to impaired intellectual performance in school children aged between 6 and 12 years are iron deficient, their EEG shows slow activity (more energy Theta and Delta) suggesting a developmental delay or dysfunction of the central nervous system[29].

Grantham-McGregor and Ani[3] reviewed the literature on the relationship between iron deficiency anemia and cognitive development. On children over 2 years old, anemic often have cognitive levels and lower than those of non-anemic academic performance. However, they catch in cognition after diagnosis and treatment repeated but not school performance. According to the author, these findings are compelling and can be consolidated with one or two randomized controlled trials.

In 1993, Idjradinata and Pollitt published the results of a randomized double-blind trial in elderly Indonesian children 12-18 months[30]. Children were divided in three groups : children with iron deficiency anemia, children with non-iron-deficiency anemia and non anemic children.

In each of these groups, the children were randomized to receive a ferrous treatment or placebo for 4 months. Before receiving this treatment an assessment of mental and motor development, achieved by using the Bayley showed that children with iron deficiency anemia had a significantly lower score compared to the other two groups. After treatment, evaluation of mental and motor development showed an increase in scores in the group of children with iron deficiency anemia at the start[31].

In the other two groups (not deficient and not anemic) no change in scores was observed. This result confirms those of some studies have already shown the effect of iron deficiency anemia on child development[32,33]. In addition to this, it is interesting to note that a recent meta-analysis revealed that the increase in hemoglobin of 1 g dL^{-1} increase the IQ of 1.73[34]. However, regarding this point, as on many others, controversial results exist. In 1996, a similar study to the one of Idjradinata and Pollitt was conducted by Lozoff *et al*.[35] Costa Rica. In this study, where all children were 6 months of ferrous sulfate and no placebo was used, children with iron deficiency anemia at baseline had always score lower mental development. Tamura *et al*.[36] confirmed the association between iron status of the fetus and the low scores of cognitive development at age 5.

Iron deficiency, overload and brain function: A number of arguments advocates of early supplementation: the iron deficiency in animals at birth alter brain levels of transferrin, transferrin receptor and ferritin but these changes are quickly offset by a early supplementation suggesting a large brain capacity to regulate and use iron as needed. Meat consumption is positively correlated with psychomotor development 4-22 months[37]. The correlation between hemoglobin levels and academic performance is well established, especially among school-age children deficient iron[38,24]. The comparison between impaired children, anemic or non-anemic shows that cognitive scores are lowest in anemic children[39]. However, despite a large number of studies in children and newborns, the effects of iron supplementation on brain development remain disappointing[40,41]. In newborn small birth weight, the contributions of 13-20 mg day^{-1} showed no impact of this high dose of iron[42,43] but, on the other hand, benefits on mental and psychomotor development of the newborn supplementation with 7 mg day^{-1} of iron in the form of sulfate are observed in children 6 months breastfed by the same team[44].

CONCLUSION

This review of the literature shows that iron deficiency remains important to local and regional

worldwide. The relationship between iron deficiency cognitive performance exist but remain against paid. The biochemical and physiological mechanisms underlying often iron deficiency connecting a neuro-impaired cognitive function are not yet clear. Scientists rely on the use of new techniques and behavioral neurocognitive exploration (f MRI, EEG evoked potentials) to enlighten us benefits in the near future.

The consequences of anemia are extremely varied and include aspects as diverse as mortality, cognitive development or productivity. It is therefore, essential to be able to provide support and proper prevention.

REFERENCES

1. WHO., 2000. Global burden of disease 2000: Iron deficiency anaemia. World Health Organization, Geneva.
2. WHO/UNICEF., 2001. Iron deficiency anaemia, assessment, prevention and control: A guide for programme managers. World Health Organisation (WHO), United Nations Children's Fund (UNICEF), Geneva, Switzerland.
3. Grantham-McGregor, S. and C. Ani, 2001. A review of studies on the effect of iron deficiency on cognitive development in children. J. Nutr., 131: 649S-668S.
4. El-Hioui, M., A.O. Ahami, Y. Aboussaleh, S. Rusinek and K. Dik *et al*., 2008. Risk factors of anaemia among rural school children in kenitra, morocco. East Afr. J. Public Health, 5: 62-66.
5. Allen, L.H., J.L. Rosado, J.E. Casterline, P. Lopez, E. Munoz, O.P. Garcia and H. Martinez, 2000. Lack of hemoglobin response to iron supplementation in anemic Mexican preschoolers with multiple micronutrient deficiencies. Am. J. Clin. Nutr., 71: 1485-1494.
6. Lindsay, A. and S. Gillepsie, 2001. What works? A review of the efficacy and effectivness of nutrition interventions. ACC/SCN Nutrition Policy Paper No 19 and ADB Series No 5, Manilla, Phillipine, pp: 43-54.
7. WHO., 2008. Worldwide Prevalence of Anaemia 1993-2005: WHO Global Database on Anaemia. World Health Organization, Rome, Italy, ISBN-13: 9789241596657, Pages: 48.
8. ACC/SCN., 2000. The Fourth Report on the World Nutrition Situation: Nutrition Throughout the Lifecycle. ACC/SCN, Geneva, Pages: 121.
9. Hall, A., E. Bobrow, S. Brooker, M. Jukes and K. Nokes *et al*., 2001. Anaemia in schoolchildren in eight countries in Africa and Asia. Public Health Nutr., 4: 749-756.
10. Hall, A., N. Roschnik, F. Ouattara, I. Toure and F. Maiga *et al*., 2002. A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren. Public Health Nutr., 5: 413-418.
11. Aoki, S., Y. Okada, K. Nishimura, A.J. Barkovich, B.O. Kjos, R.C. Brasch and D. Norman, 1989. Normal deposition of brain iron in childhood and adolescence: MR imaging at 1.5 T. Radiology, 172: 381-385.
12. Hill, J.M., 1988. The Vdistribution of Iron in the Brain. In: Brain Iron: Neurochemistry and Behaviuoral Aspects, Youdhim, M.B.H. (Ed.). Taylor and Francis, London, UK., pp:1-12.
13. Earley, C.J., J.R. Connor, J.L. Beard, E.A. Malecki, D.K. Epstein and R.P. Allen, 2000. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology, 54: 1698-1700.
14. Cornford, E.M., L.D. Braun and W.H. Oldendorf, 1982. Developmental modulations of blood-brain barrier permeability as an indicator of changing nutritional requirements in the brain. Pediatric Res., 16: 324-328.
15. Abboud, S. and D.J. Haile, 2000. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. J. Biol. Chem., 275: 19906-19912.
16. Burdo, J.R., J. Martin, S.L. Menzies, K.G. Dolan and M.A. Romano *et al*., 1999. Cellular distribution of iron in the brain of the Belgrade rat. Neuroscience, 93: 1189-1196.
17. Walker, S.P., T.D. Wachs, J.M. Gardner, B. Lozoff and G.A. Wasserman *et al*., 2007. Child development: Risk factors for adverse outcomes in developing countries. Lancet, 369: 145-157.
18. Algarin, C., C.A. Nelson, P. Peirano, A. Westerlund, S. Reyes and B. Lozoff, 2013. Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years. Dev. Med. Child Neurol., 55: 453-458.
19. Beard, J.L. and J.R. Connor, 2003. Iron status and neural functioning. Annu. Rev. Nutr., 23: 41-58.
20. Erikson, K.M., B.C. Jones, E.J. Hess, Q. Zhang and J.L. Beard, 2001. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. Pharmacol. Biochem. Behav., 69: 409-418.

21. Rao, R. and M.K. Georgieff, 2001. Neonatal iron nutrition. Semin. Neonatol., 6: 425-435.
22. Burhans, M.S., C. Dailey, Z. Beard, J. Wiesinger, L. Murray-Kolb, B.C. Jones and J.L. Beard, 2005. Iron deficiency: Differential effects on monoamine transporters. Nutr. Neurosci., 8: 31-38.
23. Lozoff, B. and M.K. Georgieff, 2006. Iron deficiency and brain development. Semin. Pediatr. Neurol., 13: 158-165.
24. Sungthong, R., L. Mo-Suwan and V. Chongsuvivatwong, 2002. Effects of haemoglobin and serum ferritin on cognitive function in school children. Asia. Pac. J. Clin. Nutr., 11: 117-122.
25. Bandhu, R., N. Shankar, O.P. Tandon and N. Madan, 2003. Effects of iron therapy on cognition in anaemic school going boys. Indian J. Physiol. Pharmacol., 47: 301-310.
26. Kordas, K., P. Lopez, J.L. Rosado, G.G. Vargas and J.A. Rico *et al*., 2004. Blood lead, anemia and short stature are independently associated with cognitive performance in mexican school children. J. Nutr., 134: 363-371.
27. Wang, Z., A. Ma, D. Xu and J. Zou, 2003. [Comparison of hemoglobin level and anemia prevalence between female and male post-adolescent high school graduates]. Wei Sheng Yan Jiu, 32: 144-146.
28. Mukudi, E., 2003. Nutrition status, education participation and school achievement among Kenyan middle-school children. Nutrition, 19: 612-616.
29. Otero, G.A., D.M. Aguirre, R. Porcayo and T. Fernandez, 1999. Psychological and electroencephalographic study in school children with iron deficiency. Int. J. Neurosci., 99: 113-121.
30. Idjradinata, P. and E. Pollitt, 1993. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. Lancet, 341: 1-4.
31. Beltran-Navarro, B., E. Matute, E. Vasquez-Garibay and D. Zarabozo, 2012. Effect of chronic iron deficiency on neuropsychological domains in infants. J. Child. Neurol., 27: 297-303.
32. Lozoff, B., 1989. Methodologic issues in studying behavioral effects of infant iron-deficiency anemia. Am. J. Clin. Nutr., 50: 641-654.
33. Walter, T., J. Kovalskys and A. Stekel, 1983. Effect of mild iron deficiency on infant mentaldevelopment scores. J. Pediatr., 102: 519-522.
34. Ezzate, M., A.D. Lopez, A. Rodgers and C.J. Murray, 2004. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. World Health Organization, Geneva.
35. Lozoff, B., A.W. Wolf and E. Jimenez, 1996. Iron-deficiency anemia and infant development: Effects of extended oral iron therapy. J. Pediatr., 129: 382-389.
36. Tamura, T., R.L. Goldenberg, J. Hou, K.E. Johnston, S.P. Cliver, S.L. Ramey and K.G. Nelson, 2002. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. J. Pediatr., 140: 165-170.
37. Morgan, J., A. Taylor and M. Fewtrell, 2004. Meat consumption is positively associated with psychomotor outcome in children up to 24 months of age. J. Pediatr. Gastroenterol. Nutr., 39: 493-498.
38. El Hioui, M., F.Z. Azzaoui, A.O.T. Ahami, S. Rusinek and Y. Aboussaleh, 2012. Iron deficiency and cognitive function among Moroccan school children. Nutr. Therapy Metab., 30: 84-89.
39. Halterman, J.S., J.M. Kaczorowski, C.A. Aligne, P. Auinger and P.G. Szilagyi, 2001. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics, 107: 1381-1386.
40. Grantham-McGregor, S., 2001. Cognition and nutrition: Evidence for a vulnerable period. Ann. Nutr. Metab., Vol. 45(Suppl.1).
41. Lozoff, B., M. Castillo, K.M. Clark and J.B. Smith, 2012. Iron-fortified vs low-iron infant formula: Developmental outcome at 10 years. Arch. Pediatr. Adolesc. Med., 166: 208-215.
42. Sachdev, H., T. Gera and P. Nestel, 2005. Effect of iron supplementation on mental and motor development in children: Systematic review of randomised controlled trials. Public Health Nutr., 8: 117-132.
43. Friel, J.K., W.L. Andrews, K. Aziz, P.G. Kwa, G. Lepage and M.R. L'Abbe, 2001. A randomized trial of two levels of iron supplementation and developmental outcome in low birth weight infants. J. Pediatr., 139: 254-260.
44. Friel, J.K., K. Aziz, W.L. Andrews, S.V. Harding, M.L. Courage and R.J. Adams, 2003. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. J. Pediatr., 143: 582-586.