Journal of Neonatal-Perinatal Medicine 12 (2019) 365–368
DOI:10.3233/NPM-190369
IOS Press

Editorial

Iron and zinc: Nutrients with potential for neurorestoration in premature infants with cerebral white matter injury

Joseph J. Volpe[a,b,*]
[a]*Department of Neurology, Harvard Medical School, Boston, MA, USA*
[b]*Department of Pediatric Newborn Medicine, Harvard Medical School, Boston, MA, USA*

Received 9 October 2019
Revised 16 October 2019
Accepted 16 October 2019

Keywords: Prematurity, white matter injury, zinc, iron

1. Introduction

Cerebral white matter injury (WMI) is the principal neuropathological lesion in premature brain [1, 2]. WMI is present in more than 50% of very preterm and extremely preterm infants, [3, 4] and the lesion and its morphological consequences underlie most of the subsequent neurological deficits observed [2]. The central cellular target of the WMI is the pre-oligodendrocyte (pre-OL), the precursor of the mature myelin-producing OLs, and injury to the pre-OL in the premature brain is followed by its dysmaturation and subsequently hypomyelination. The pre-OL injury leads to a variety of other dysmaturational events involving cerebral cortex, axons, and a variety of other neural structures, as discussed elsewhere [5]. Because the failure of maturation of this cell occurs over the ensuing *weeks and months*, the possibility of interventions in the premature period and in early infancy that prevent or correct this maturational failure, i.e., "neurorestorative" interventions, have become the focus of considerable research. Such interventions have included a variety related to nutritional factors, including quality and source of milk, components of milk, breastfeeding, but recent experimental and clinical studies have renewed focus on two metals, iron and zinc. These two so-called "transition" metals are the most abundant metals in human brain, and recent work indicates that they are critical for differentiation of pre-OLs to mature myelin-producing OLs. Their potential as neurorestorative interventions in WMI is the focus of this Commentary.

2. Pre-OL injury/dysmaturation

Pre-OLs, the principal cellular target in WMI of the premature infant [1, 2] are generated from OL progenitors and are the principal phase of the OL lineage during the premature period. Pre-OLs account for 90% of the lineage during the peak period of WMI in premature infants. Even at term, pre-OLs account

*Address for correspondence: Joseph J. Volpe, MD, Department of Pediatric Newborn Medicine Brigham and Women's Hospital, 221 Longwood Avenue, Room 343C, Boston, MA 02115, USA. Tel.: +1 617 525 4145; E-mail: Joseph.volpe@childrens.harvard.edu.

for 50% of the lineage in cerebral white matter, while approximately 50% of the lineage are the more differentiated "immature" OLs [6]. Mature, myelin-producing OLs do not develop in human cerebral white matter to an appreciable degree *until post-term*, i.e., in the weeks and months post-term. The pre-OL begins ensheathment of white matter axons at approximately 30 weeks' gestation [7]. This process is critical for axonal differentiation [2] and, as a consequence, axonal function. The latter is the critical driving force for cerebral cortical development (see later), which evolves rapidly as an activity-dependent process during the third trimester of gestation.

The pre-OL is a highly vulnerable cell, with particular susceptibility to such insults as hypoxia, ischemia, inflammation, which lead to death via excitotoxic and free radical mediated mechanisms in cerebral WMI [1]. Notably, however, in the premature infant with WMI, pre-OLs are *replenished* in the subacute period but *fail to differentiate* over the ensuing weeks/months to later phases of the OL lineage. Thus, as noted above, failure of pre-OL differentiation is the basis of the subsequent hypomyelination but, likely also, the neuronal-axonal dysmaturational disturbances that occur. Thus, factors that could enhance pre-OL differentiation and overcome the block in cerebral WMI would be of great restorative potential. As noted above, therein lies the focus on the two most abundant metals in human brain, iron and zinc, which now appear to be critical for pre-OL differentiation.

3. Iron and pre-OL maturation/myelination

Iron is the most abundant transition metal in brain, and the OL contains the highest concentrations of iron among brain cellular elements [8–10]. Experimental studies have shown that acquisition of iron by developing OLs is necessary for myelination and that perinatal iron deficiency results in impaired myelination [9, 11–14]. The particular importance of iron for OL development and myelination was illustrated by recent studies of a genetic model of mucolipidosis IV, a human disorder with impaired myelin development. The molecular deficit responsible for the disturbance was shown to involve a lysosomal ion channel necessary for iron uptake into developing OLs [15]. Iron is necessary for the function of numerous enzymes involved in OL differentiation and myelination [9].

Iron deficiency in human premature infants is a common phenomenon that is likely to be associated with impaired OL maturation and myelination. Although the data are not entirely consistent, most studies show impairments of motor, cognitive and behavioral development in iron-deficient infants [16–20]. Iron deficiency in the neonatal period is usually related to dietary deficiency, particularly in the context of breast-feeding and prematurity [13, 21, 22]. Indeed, as many as 10% of infants in the first two years of life in the United States and 15% of breast-fed Canadian infants exhibit iron deficiency. Because premature birth deprives the infant of the primary period of fetal iron deposition, i.e., the third trimester of gestation, the risks are still higher in such infants. Supportive of an effect on myelin development in iron-deficient infants is the finding on studies of auditory and visual evoked potentials of prolonged latencies, without impairment of amplitudes [23–26]. (The normal maturational decline in latencies relates to acquisition of myelin, whereas changes in amplitude relate more to neuronal development [27]). A recent study of delayed umbilical cord clamping (DCC) in full-term infants suggests a beneficial effect of iron on MRI-quantitated myelin at four months of age [28]. Thus, infants followed after DCC had 48% higher serum ferritin levels and myelin content at 4 months of age, when compared to infants who had immediate cord clamping. Moreover, because infants with higher iron stores at 4 months of age have been shown to persist with higher stores later, the findings suggest that the positive effect on myelination may persist [29]. More data are needed, but higher iron stores could represent an important neurorestorative goal in premature infants.

A particular need to assess deficient iron in developing human brain *in vivo* is apparent. Recent work suggests that newly developed MRI methods, capitalizing on the potent effects of iron on magnetic properties of brain, could satisfy that need [9]. It now appears feasible for such advanced MRI methods to detect infants with deficient brain iron and thus to target such infants for iron therapy. Since premature infants with WMI exhibit impaired OL maturation, treatment of such infants with iron according to the quantitative levels of iron present in their white matter would seem possible and, perhaps, optimal. Such treatment would probably best be commenced after the acute/subacute period when exposures to insults (e.g., ischemia, etc.), that could lead to free radical production have ceased. This caveat relates to the capacity of intracellular free iron to lead to production of superoxide anion [2]. As these advanced MRI methods evolve further, in the interim careful attention to iron homeostasis and supplemen-

tation as needed in premature infants (beyond the acute/subacute period) could have neurorestorative potential. This notion demands further research

4. Zinc and pre-OL maturation/myelination

Following iron, zinc is the second most abundant metal in the brain and is obtained exclusively through dietary intake [30]. Experimental studies have shown that zinc is critical for a variety of aspects of brain development, including OL development [31–35]. The effect is mediated particularly by an OL-specific zinc finger protein (Zfp 488) that functions as a transcriptional co-regulator important for OL differentiation [36]. The recent development of synthetic fluorescent sensors has identified the pre-OL as the key cell involved in the role of zinc in oligodendroglial differentiation. Thus, utilizing such a sensor, Bourassa et al., [37] have shown recently that zinc concentrations in *developing* OLs are relatively *high* during differentiation and decline after maturation is achieved. These findings suggest that the zinc content of pre-OLs is important for their differentiation. Notably, as with iron, altered zinc balance is involved in experimental models of ischemic and excitoxic death [38–40]. Thus, exogenous zinc should probably be considered after the acute/subacute period when ischemic insults are no longer prevalent.

The clinical relevance of this work on zinc and pre-OL differentiation remains to be clarified fully, but it is notable that preterm infants are vulnerable to zinc deficiency because of high zinc requirements, diminished zinc stores (most zinc stores are acquired in the last trimester of gestation), and suboptimal zinc absorption [41–43]. Moreover, zinc concentrations in human milk are highly variable, and current dietary guidelines for zinc intake for preterm infants are based on limited data [42, 44]. More data are needed in human preterm infants on OL maturation, myelination and neurological development, in relation to zinc status, and on ideal amounts of dietary zinc intake. Nevertheless, on balance, the data raise the real possibility that zinc intake (beyond the acute/subacute period) could have restorative potential for premature infants with WMI and its associated failure of pre-OL maturation. More data are clearly needed.

5. Conclusions

Recent advances in methodologies to study the status of iron and zinc have enabled insight into the critical roles these two most abundant metals play in developing brain. The data point to a critical role in pre-OL differentiation, impairment of which underlies the hypomyelination characteristic of premature infants with cerebral WMI. Premature infants have high requirements for these metals and have been deprived of the critical transplacental transfer in the third trimester. Careful attention to iron and zinc status in such infants and appropriate supplementation after the acute/subacute period could serve as important restorative interventions in infants with cerebral WMI.

References

[1] Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: Key cellular target in brain injury in the premature infant. Int J Devl Neurosci. 2011;29:423-40.

[2] Back SA, Volpe JJ. Encephalopathy of Prematurity: Pathophysiology. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. Chapter 15, 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 405-24.

[3] Neil JJ, Volpe JJ. Encephalopathy of prematurity: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, du Plessis AJ, Darras BT, Perlman J, Neil J, et al., editors. Volpe's Neurology of the Newborn. Chapter 16, 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 425-57.

[4] Pierson CR, Folkerth RD, Billards SS, Trachtenberg FL, Drinkwater ME, Volpe JJ, et al. Gray matter injury associated with periventricular leukomalacia in the premature infant. Acta Neuropathol. 2007;114:619-31.

[5] Volpe JJ. Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8:110-24.

[6] Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci. 2001;21:1302-12.

[7] Back SA, Luo NL, Borenstein NS, Volpe JJ, Kinney HC. Arrested oligodendrocyte lineage progression during human cerebral white matter development: Dissociation between the timing of progenitor differentiation and myelinogenesis. J Neuropathol Exp Neurol. 2002;61:197-211.

[8] Reinert A, Morawski M, Seeger J, Arendt T, Reinert T. Iron concentrations in neurons and glial cells with estimates on ferritin concentrations. BMC Neurosci. 2019;20:25.

[9] Moller HE, Bossoni L, Connor JR, Crichton RR, Does MD, Ward RJ, et al. Iron, myelin, and the brain: Neuroimaging meets neurobiology. Trends Neurosci. 2019;42:384-401.

[10] Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Oligodendrocytes and myelination: The role of iron. Glia. 2009;57:467-78.

[11] Rao R, Tkac I, Unger EL, Ennis K, Hurst A, Schallert T, et al. Iron supplementation dose for perinatal iron deficiency differentially alters the neurochemistry of the frontal cortex and hippocampus in adult rats. Pediatr Res. 2013;73:31-7.

[12] Connor JR, Benkovic SA. Iron regulation in the brain: Histochemical, biochemical, and molecular considerations. Ann Neurol. 1992;32(Suppl):S51-61.
[13] Georgieff MK, Innis SM. Controversial nutrients that potentially affect preterm neurodevelopment: Essential fatty acids and iron. Pediatr Res. 2005;57:99R-103R.
[14] de Vellis J, Carpenter E. Development. In: Siegel GJ, Albers RW, Brady ST, Price DL, editors. Basic Neurochemistry, Molecular, Cellular, and Medical Aspects. 7 ed. London: Elsevier; 2006. pp. 437-58.
[15] Grishchuk Y, Pena KA, Coblentz J, King VE, Humphrey DM, Wang SL, et al. Impaired myelination and reduced brain ferric iron in the mouse model of mucolipidosis IV. Dis Model Mech. 2015;8:1591-601.
[16] Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ. A double-masked randomized control trial of iron supplementation in early infancy in healthy term breastfed inifants. J Pediatr. 2003;143:582-6.
[17] Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in health full-term infants. Pediarics. 2003;112:846-54.
[18] Kon N, Tanaka K, Sekigawa M, Negishi Y, Yoshikawa N, Hisata K, et al. Association between iron status and neurodevelopmental outcomes among VLBW infants. Brain Dev. 2010;32:849-54.
[19] Berglund SK, Westrup B, Hagglof B, Hernell O, Domellof M. Effects of iron supplementation of LBW infants on cognition and behavior at 3 years. Pediatrics. 2013;131:47-55.
[20] Berglund SK, Chmielewska A, Starnberg J, Westrup B, Hagglof B, Norman M, et al. Effects of iron supplementation of low-birth-weight infants on cognition and behavior at 7 years: A randomized controlled trial. Pediatr Res. 2018;83:111-8.
[21] Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol. 2002;27:85-92.
[22] Gordon N. Iron deficiency and the intellect. Brain & Development. 2003;25:3-8.
[23] Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: Delayed maturation of auditory brainstem responses. Am J Clin Nutr. 1998;68:683-90.
[24] Sarici SU, Serdar MA, Dundaroz MR, Unay B, Akin R, Deda G, et al. Brainstem auditory-evoked potentials in iron-deficiency anemia. Pediatr Neurol. 2001;24:205-8.
[25] Algarin C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: Long-lasting effects on auditory andvisual system functioning. Pediatr Res. 2003; 53:217-23.
[26] Amin SB, Orlando M, Wang H. Latent iron deficiency in utero is associated with abnormal auditory neural myelination in>/=35 weeks gestational age infants. J Pediatr. 2013;163:1267-71.
[27] Neil JJ, Volpe JJ. Specialized neurological studies. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, Du Plessis A, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. Chapter 10, 6th ed. Philadelphia, PA: Elsevier; 2018. pp. 222-54.
[28] Mercer JS, Erickson-Owens DA, Deoni SCL, Dean DC, 3rd, Collins J, Parker AB, et al. Effects of delayed cord clamping on 4-month ferritin levels, brain myelin content, and neurodevelopment: A randomized controlled trial. J Pediatr. 2018;203:266-72.
[29] Rao R, Bora R. Timing of umbilical cord clamping and infant brain development. J Pediatr. 2018;203:8-10.
[30] Elitt CM, Fahrni CJ, Rosenberg PA. Zinc homeostasis and zinc signaling in white matter development and injury. Neurosci Lett. 2019;707:134247.
[31] Frederickson CJ, Koh JY, Bush AI. The neurobiology of zinc in health and disease. Nat Rev Neurosci. 2005;6:449-62.
[32] Li Y, Maret W. Transient fluctuations of intracellular zinc ions in cell proliferation. Exp Cell Res. 2009;315:2463-70.
[33] Fukada T, Yamasaki S, Nishida K, Murakami M, Hirano T. Zinc homeostasis and signaling in health and diseases: Zinc signaling. J Biol Inorg Chem. 2011;16:1123-34.
[34] Maret W. Zinc in cellular regulation: The nature and significance of "zinc signals". Int J Mol Sci. 2017;18.
[35] Kuspert M, Wegner M. SomethiNG 2 talk about-Transcriptional regulation in embryonic and adult oligodendrocyte precursors. Brain Res. 2016;1638:167-82.
[36] Wang SZ, Dulin J, Wu H, Hurlock E, Lee SE, Jansson K, et al. An oligodendrocyte-specific zinc-finger transcription regulator cooperates with Olig2 to promote oligodendrocyte differentiation. Development. 2006;133:3389-98.
[37] Bourassa D, Elitt CM, McCallum AM, Sumalekshmy S, McRae RL, Morgan MT, et al. Chromis-1, a ratiometric fluorescent probe optimized for two-photon microscopy reveals dynamic changes in labile Zn(II) in differentiating oligodendrocytes. ACS Sens. 2018;3:458-67.
[38] Zhang Y, Aizenman E, DeFranco DB, Rosenberg PA. Intracellular zinc release, 12-lipoxygenase activation and MAPK dependent neuronal and oligodendroglial death. Mol Med. 2007;13:350-5.
[39] Domercq M, Mato S, Soria FN, Sanchez-gomez MV, Alberdi E, Matute C. Zn2+-induced ERK activation mediates PARP-1-dependent ischemic-reoxygenation damage to oligodendrocytes. Glia. 2013;61:383-93.
[40] Mato S, Sanchez-Gomez MV, Bernal-Chico A, Matute C. Cytosolic zinc accumulation contributes to excitotoxic oligodendroglial death. Glia. 2013;61:750-64.
[41] Krebs NF, Miller LV, Hambidge KM. Zinc deficiency in infants and children: A review of its complex and synergistic interactions. Paediatr Int Child Health. 2014;34:279-88.
[42] Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, et al. Zinc in early life: A key element in the fetus and preterm neonate. Nutrients. 2015;7:10427-46.
[43] Ackland ML, Michalczyk AA. Zinc and infant nutrition. Arch Biochem Biophys. 2016;611:51-7.
[44] Griffin IJ, Domellof M, Bhatia J, Anderson DM, Kler N. Zinc and copper requirements in preterm infants: An examination of the current literature. Early Hum Dev. 2013;(Suppl 2):S29-34.