Journal of Perinatology (2018) 38:233–239
https://doi.org/10.1038/s41372-017-0023-5

ARTICLE

Effect of maternal iron deficiency anemia on fetal neural development

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Received: 8 August 2017 / Revised: 3 November 2017 / Accepted: 20 November 2017 / Published online: 12 December 2017

Abstract

Objective: Perinatal iron deficiency may have deleterious consequences on fetal neural development. The present study was conducted to determine the effect of maternal iron deficiency anemia (IDA) on fetal hippocampal morphogenesis and production of brain-derived neurotrophic factor (BDNF).

Study design: Seventy term, singleton neonates born to mothers with IDA (hemoglobin <110g/L and serum ferritin <12 µg/L) formed the study group. Twenty gestational age-matched neonates born to healthy mothers without IDA (hemoglobin ≥110 g/L and serum ferritin >12 µg/L) served as controls. Maternal and fetal inflammatory conditions, infections and neonates with perinatal asphyxia were excluded. Cord blood BDNF concentrations were estimated by enzyme-linked immunosorbent assay. Volumetric analysis of hippocampus (right, left and combined, corrected for total intracranial volume) was done by cranial magnetic resonance imaging on days 3–5 of life.

Results: In the study group, 24 mothers had mild (hemoglobin 100.0–109.0 g/L), 24 had moderate (hemoglobin 70.0–99.0 g/L), and 22 had severe (hemoglobin <70.0 g/L) anemia. Both hippocampal volumes and serum BDNF concentrations of neonates born to iron-deficient mothers were significantly reduced compared to controls. A progressive decline in hippocampal volumes and BDNF concentrations was observed with increasing severity of maternal anemia. Pearson correlation showed significant correlations among maternal and cord blood hemoglobin, iron indices, hippocampal volumes and BDNF concentrations.

Conclusions: Maternal IDA adversely affects hippocampal morphogenesis and fetal production of BDNF. The degree of affection is proportional to the severity of maternal anemia.

Introduction

Anemia is the most common public health problem globally, affecting the lives of over two billion people [1]. As per recent estimates, 59% of children and 54% of pregnant women in India are anemic [2]. Approximately 50–60% of cases of anemia in pregnancy develop secondary to iron deficiency (ID) [3]. Perinatal ID may have deleterious effects on fetal neurodevelopment, leading to cognitive deficit, poor scholastic performance and behavioral abnormality, which can persist even after complete brain iron repletion [4–6]. ID induced experimentally in animal models at different stages of development showed behavioral, neuroanatomic, neurochemical, and neurophysiological consequences [6]. Alteration of brain structures, neurotransmitter synthesis, myelination, and energy metabolism conferred by ID during the period of rapid brain growth are thought to be the responsible factors for cerebral dysfunction [6, 7].

Within the developing brain, the hippocampus, a brain area important for learning, memory and cognition, appears particularly vulnerable to ID. Hippocampus-mediated recognition memory is found to be impaired in iron-deficient newborn infants [5]. Several studies have reported decreased hippocampal size in rodent models exposed to ID during the fetal and neonatal periods which failed to recover even after iron rehabilitation [8, 9]. Down-regulated expression of brain-derived neurotrophic factor (BDNF), critical for inducing and maintaining hippocampal differentiation and plasticity, is one of the most important factors responsible for this alteration [10].

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BDNF plays an important role in learning and memory [11, 12]. It regulates multiple aspects of hippocampal biochemistry, neural morphology, and electrophysiology [10, 13]. Attention deficit-hyperactivity disorder, autism spectrum disorder, and mental retardation in children are found to be associated with altered peripheral BDNF concentrations [14, 15].

There is paucity of literature regarding the effect of maternal iron deficiency anemia (IDA) on fetal hippocampal volume and serum BDNF concentrations. We hypothesized that maternal IDA may affect fetal hippocampal morphogenesis. In the present study hippocampal volumes and cord blood concentrations of BDNF of neonates delivered to iron-deficient mothers were compared with neonates delivered to mothers without IDA.

Methods

This study was carried out in the Neonatal Intensive Care Unit (NICU), Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India after obtaining approval from the Institute Ethics Committee. A written informed consent in local language was taken from all parents before inclusion in the study.

Study population

Otherwise healthy, inborn, term (37–41 weeks), singleton neonates born to mothers with IDA (hemoglobin <110 g/L and serum ferritin <12 µg/L) formed the case group. Healthy, inborn, singleton, gestational age (GA) matched neonates born to healthy mothers without IDA (hemoglobin ≥110 g/L and serum ferritin >12 µg/L) served as controls. Mothers with chronic systemic diseases, infection/inflammatory states, antepartum hemorrhage, pregnancy induced hypertension, diabetes, chorioamnionitis, and congenital infections were excluded from the study. Neonates with perinatal asphyxia, neonatal sepsis, isoimmune hemolytic anemias, metabolic and thyroid disorders, and congenital malformations were excluded. To exclude perinatal infection/inflammation, serum C-reactive protein (CRP) was done in maternal and cord blood. Mothers and neonates with positive CRP (≥5 mg/L in maternal blood and 10 mg/L in cord blood) were excluded.

Severity of maternal anemia was graded as mild (hemoglobin 100.0–109.0 g/L), moderate (hemoglobin 70.0–99.0 g/L), and severe (hemoglobin <70.0 g/L) anemia according to WHO [16]. Anemia in newborns was defined as cord blood hemoglobin <130.0 g/L [17]. Low fetal iron stores was defined as cord blood ferritin levels <75 µg/L [18]. Ferritin <35 µg/L was defined as severe ID [5].

Clinical work-up

Maternal and neonatal details were recorded. Neonates were examined thoroughly after birth and anthropometric details were recorded. Maternal and cord blood samples were collected after delivery for hematological analysis and estimation of cord blood levels of BDNF. Cranial magnetic resonance imaging (MRI) of neonates was done between days 3 and 5 of life for volumetric analysis of hippocampus. Infants were observed for development of any complications during the hospital stay and managed as per our unit protocol. After discharge neonates were kept under follow-up in neonatal high-risk follow-up clinic.

Collection of samples and laboratory analysis

After complete delivery of the neonate, 5 mL of maternal venous blood was collected by aseptic venepuncture of a peripheral vein. Ten milliliters of free flowing cord blood was collected from the placental end of the umbilical cord without milking. Quantitative estimation of CBC was done by an auto analyzer (Coulter LH 750 Hematology Analyzer; Beckman Coulter, Inc., Brea, CA, USA). Serum iron, ferritin, total iron binding capacity and transferring saturation were measured by an auto analyzer (R_XSuzuka Clinical Chemistry Analyzer; Randox, Inc., Crumlin, UK). For the estimation of BDNF, serum was stored at −20°C till final analysis and was measured quantitatively by in vitro enzyme-linked immunosorbent assay using RayBio® Human BDNF ELISA kit (RayBiotech, Inc., Norcross, GA, USA) (Lot #: 0719160106).

MRI of brain

Cranial MRI of the neonates was done in the supine position using 1.5 Tesla MRI machine, Magnetom Avanto (Version BV-I7A) Siemens medical system (Erlangen, Germany). Infants were fed, swaddled, and oral dextrose/sucrose was used as a pacifier. Scan was done while sleeping to minimize motion artifacts. No sedation was administered. A bird cage type of quadrature head coil was used to acquire baseline scans parallel to the canthomeatal line. As part of the routine protocol, T1-weighted (W), T2W, fluid-attenuated inversion recovery and diffusion-weighted sequences in axial planes were performed after an initial three-plane localizer. An additional sagittal T2W image was also taken for angle correction in the volumetric scan of hippocampus. A 3D-T1W fast spoiled gradient scan was obtained in an oblique coronal plane. The angles were adjusted, so that the scans remained perpendicular to the gross *Z*-axes of the hippocampus bilaterally.

After the symmetrical positioning of the head on axial and sagittal images, contiguous 1-mm-thick sections were

obtained using three-dimensional magnetization prepared rapid gradient-echo (3D-MPRAGE) imaging. Hippocampal volumes were measured from the oblique coronal MR images perpendicular to the long axis of hippocampus and were manually delineated on successive coronal slices using a protocol based on previously published methods [19, 20]. The left and right parts of hippocampal volumes were obtained using manual tracing.

To adjust for the variation in the head circumference of the study neonates, hippocampal volume was corrected for the total intracranial volume according to the techniques described previously [20, 21]. All MRI images were interpreted by a single qualified radiologist to avoid any inter-observer variation. The radiologist was blinded to the infant's clinical details. MRI was done without any economic burden to the parents.

Sample size calculation

The prevalence of IDA in pregnant mothers attending our hospital was calculated to be 65% in last 1 year. Expecting the same prevalence, with the level of confidence of 95% and precision of 10%, the minimum total sample size was calculated to be 88 (http://sampsize.sourceforge.net/iface/). We planned to divide the total sample size in four groups with similar number of mothers with varied severity of anemia and controls.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for data entry and analysis. Independent samples *T*-test, Mann Whitney *U*-test and chi square test were used to compare parametric and non-parametric continuous and categorical variables between groups. Parametric one-way analysis of variance test with post hoc Tukey test and non-parametric Kruskal Wallis with rank sum test was used to find out the significant difference among multiple groups. Pearson correlation was calculated to identify correlation between different variables. *P*-value <0.05 was considered as statistically significant.

Results

Hematological profile of the study groups

The final study group comprised of 90 neonates; 24 born to iron-deficient mothers with mild anemia, 24 born to mothers with moderate anemia, 22 born to mothers with severe anemia, and 20 neonates as controls born to non-anemic, non-iron-deficient healthy mothers. Neonates requiring delivery room resuscitation were excluded from the study. Median (inter-quartile range) of 1 and 5 min Apgar scores were 8 (7–9) and 9 (8–10) in both the groups (p-value >0.05). Hematological profile of mothers and their newborns are summarized in Table 1. A significant decline in hemoglobin and iron indices with increasing severity of maternal anemia was seen both in maternal and cord blood.

Measurement of hippocampal volumes

Neonates born to iron-deficient mothers had significantly reduced right, left, and combined (right + left) hippocampal volume compared to controls (0.89 ± 0.09 vs. 1.14 ± 0.03 cm^3 for right, 0.86 ± 0.09 vs. 1.11 ± 0.06 cm^3 for left, and 1.74 ± 0.18 vs. 2.24 ± 0.09 cm^3 for combined hippocampal volumes; $p < 0.001$ for all parameters) (Table 2). Paired samples *T*-test, done for comparison of the symmetry, showed significantly larger right-sided hippocampus than the left in both IDA and control groups ($p < 0.001$). A progressive reduction in hippocampal volume was observed among anemia subgroups ($p < 0.001$) (Table 3). Male neonates in both the groups had larger hippocampal volume than female neonates, though the differences were not statistically significant (data not shown). All measured hippocampal volumes were corrected for total intracranial volume.

Cord blood BDNF concentrations

Mean cord blood BDNF concentration of neonates born to mother with IDA was significantly lower compared to neonates born to mothers without anemia (7402.2 ± 4129.2 vs. $15{,}299.3 \pm 1190$ pg/mL; $p < 0.001$) (Table 4). A significant decline with the severity of anemia was documented on subgroup analysis ($p < 0.001$).

Pearson correlation

In Pearson correlation test, significant linear correlations were observed among maternal and cord blood iron indices, neonatal hippocampal volumes, and cord blood BDNF concentrations (Table 5).

Discussion

The present study demonstrated a progressive decline in both neonatal hippocampal volumes and cord blood BDNF concentrations with increasing severity of maternal anemia. A linear correlation among maternal and cord blood iron indices, hippocampal volumes, and BDNF concentrations might be suggestive of an important and decisive role of maternal iron nutriture with hippocampal morphogenesis and fetal production of BDNF.

Table 1 Hemoglobin and iron indices in maternal and cord blood (mean ± SD)

Parameter	Mothers with IDA ($n = 70$)	Mothers with IDA categorized as per the severity of anemia			Controls ($n = 20$)	ANOVA (F-value)[a]
		Mild anemia ($n = 24$)	Moderate anemia ($n = 24$)	Severe anemia ($n = 22$)		
Maternal blood						
Hemoglobin (g/L)	80.6 ± 23.0	103.6 ± 2.2	85.5 ± 8.3	50.2 ± 8.0	128.8 ± 6.6	517.738 ($p < 0.001$)
Serum iron (μmol/L)	7.82 ± 2.14	9.71 ± 1.26	7.90 ± 1.70	5.68 ± 1.17	24.62 ± 2.56	511.995 ($p < 0.001$)
Serum ferritin (μg/L)	7.06 ± 2.86	9.68 ± 1.21	7.88 ± 1.02	3.33 ± 1.01	21.13 ± 3.63	310.122($p < 0.001$)
TIBC (μmol/L)	71.87 ± 22.72	51.25 ± 11.29	69.40 ± 11.64	97.08 ± 15.82	40.75 ± 10.82	83.435 ($p < 0.001$)
Transferrin saturation (%)	12.83 ± 7.01	20.02 ± 5.87	11.77 ± 3.40	6.15 ± 2.08	63.32 ± 13.86	250.120 ($p < 0.001$)
Cord blood						
Hemoglobin (g/L)	142.1 ± 18.4	161.4 ± 12.8	139.9 ± 5.5	123.4 ± 10.4	166.6 ± 11.6	80.125 ($p < 0.001$)
Serum iron (μmol/L)	14.54 ± 3.62	17.52 ± 2.40	14.30 ± 2.34	11.55 ± 3.34	21.79 ± 3.38	49.608 ($p < 0.001$)
Serum ferritin (μg/L)	68.51 ± 31.12	104.04 ± 9.95	67.08 ± 11.20	31.32 ± 6.42	161.9 ± 30.0	243.488 ($p < 0.001$)
TIBC (μmol/L)	67.14 ± 12.60	60.43 ± 7.92	64.33 ± 10.89	77.53 ± 12.25	51.83 ± 5.41	26.524 ($p < 0.001$)
Transferrin saturation (%)	22.81 ± 8.25	29.76 ± 7.0	22.68 ± 4.62	15.37 ± 5.79	42.32 ± 7.10	72.515 ($p < 0.001$)

IDA iron deficiency anemia, *SD* standard deviation, *TIBC* total serum iron binding capacity

[a]One-way analysis of variance (ANOVA) was used to compare hemoglobin and iron indices among anemia subgroups and non-anemic controls

Post hoc Tukey test showed significant decline in hemoglobin and iron indices with increasing severity of maternal anemia both in maternal and cord blood

Table 2 Hippocampal volumes in study population

Hippocampal volume (cm^3)	Mean ± SD		Mean difference (cm^3)	95% CI	P-value
	Neonates born to mothers with IDA ($n = 66$)	Neonates born to mothers without anemia ($n = 20$)			
Right	0.89 ± 0.09	1.14 ± 0.03	−0.25	−0.30, −0.21	<0.001
Left	0.86 ± 0.09	1.11 ± 0.06	−0.25	−0.29, −0.20	<0.001
Combined	1.74 ± 0.18	2.24 ± 0.09	−0.50	−0.58, −0.42	<0.001
Paired right–left hippocampal volume differences					
	Mean	SD	95% CI	P-value	
Neonates born to mothers with IDA ($n = 66$)	0.03	0.01	0.02, 0.03	<0.001	
Neonates born to mothers without anemia ($n = 20$)	0.03	0.02	0.02, 0.05	<0.001	

SD standard deviation, *CI* confidence interval, *IDA* iron deficiency anemia

Table 3 Hippocampal volumes in relation to maternal hemoglobin (mean ± SD)

Hippocampal volume (cm^3)	Mild anemia ($n = 20$)	Moderate anemia ($n = 24$)	Severe anemia ($n = 22$)	Controls ($n = 20$)	ANOVA (F-value)[a]
Right	0.99 ± 0.04	0.87 ± 0.02	0.78 ± 0.02	1.14 ± 0.04	440.973 ($p < 0.001$)
Left	0.96 ± 0.04	0.85 ± 0.03	0.76 ± 0.02	1.11 ± 0.05	301.262 ($p < 0.001$)
Combined (right and left)	1.95 ± 0.05	1.72 ± 0.05	1.54 ± 0.04	2.24 ± 0.09	381.569 ($p < 0.001$)

SD standard deviation

[a]One way analysis of variance (ANOVA) was used to compare hippocampal volumes among anemia subgroups and non-anemic controls

Table 4 Brain-derived neurotropic factor (BDNF) concentrations in study population

Serum BDNF (pg/mL)	Neonates born to mothers with IDA ($n = 70$)	IDA categorized as per the severity of anemia			Controls ($n = 20$)	Kruskal Wallis H test[a] P-value
		Mild anemia ($n = 24$)	Moderate anemia ($n = 24$)	Severe anemia ($n = 22$)		
Mean ± SD	7402.2 ± 4129.2	11,865.3 ± 1443.7	7621.3 ± 1357.2	2294.0 ± 1253.7	15,299.3 ± 1190	<0.001

IDA iron deficiency anemia, *SD* standard deviation

[a]Kruskal Wallis H test was used to compare cord blood BDNF levels among anemia subgroups and non-anemic controls

Different developing processes of the fetal brain such as myelination, dendritogenesis, synaptogenesis, and neurotransmission are highly dependent on iron-containing enzymes and hemoproteins [22]. These processes are disrupted by ID in a regionally specific manner, depending on the rapidly developing brain areas at the time of the deficiency [23]. Fetal serum ferritin concentration <35 µg/L at birth suggests >70% decrease in liver storage with a likelihood of brain ID [5]. Hippocampal development is least regulated genetically and is dependent on environmental influences such as hypoxia, stress hormones, undernutrition, and alteration of micronutrient supply [24]. In our study even mild maternal anemia with reasonably maintained fetal iron store was found to affect fetal hippocampal development. Consistently larger volume of the right-side hippocampus found in the present study confirms the previous finding that hippocampus is an asymmetrical structure [25]. Traditionally, the left hippocampus is associated with verbal memory, and right hippocampus is associated with visual memory [26]. Gender-wise difference in hippocampal volumes was not significant in any group.

In animal models, Rao et al. [9] demonstrated a 12% decrease in hippocampal cross-sectional area in iron-deficient rats [9], whereas Ranade et al. [8] demonstrated an approximately 17% decrease in hippocampal volume following gestational and lactational ID in mice. Alteration in hippocampal size is expected to have functional consequences in human infants also, though very few studies have dealt with hippocampal morphogenesis in iron-deficient human infants. Reduced hippocampal size in preterm infants has been related to impaired cognition and memory [27, 28].

BDNF is an important regulator for learning and memory and plays a crucial role in pre- and post-natal brain development [29]. It reduces apoptosis and promotes axon growth, increases survival, and maintains specific neuronal populations [30]. BDNF is also important for developmental maturity of the cortex and synaptic plasticity, leading to refinement of connections [31], morphologic differentiation, and neurotransmitter expression [32].

The highest levels of central nervous system (CNS) BDNF are found in the hippocampus, frontal cortex, and amygdale [33]. Both endogenous BDNF and intra-hippocampal BDNF infusion may induce hippocampal long-term potentiation, critical for long-term memory formation [34]. Animal experiments showed that though the physiological amount of BDNF is helpful in learning and memory, an increased or decreased level of BDNF induces inhibitory and excitatory neurotransmission in the brain, causing loss of synaptic refinement and impairment of learning and memory [12].

Relatively little research has been done to estimate neonatal serum BDNF concentrations. It is assumed that circulating BDNF could reflect the degree of neuronal maturity in neonates [29], since, at this age, due to the immature blood–brain barrier, serum BDNF concentration may represent its CNS concentration [35]. Karege et al. [36] have found that circulating BDNF concentrations correlate with cortical BDNF concentrations in newborn rats [36]. Malamitsi-Puchner et al. [37] have found significantly

Table 5 Pearson correlation matrix for iron indices, BDNF, and hippocampal volumes

Correlations								
		BDNF	CHV	MHb	MI	MF	CHb	CI	CF
BDNF	Pearson correlation	1	0.921**	0.935**	0.772**	0.821**	0.806**	0.765**	0.903**
	Sig. (2-tailed)	–	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CHV	Pearson correlation	–	1	0.923**	0.863**	0.907**	0.800**	0.765**	0.915**
	Sig. (2-tailed)	–	–	0.000	0.000	0.000	0.000	0.000	0.000
MHb	Pearson correlation	–	–	1	0.814**	0.872**	0.854**	0.759**	0.899**
	Sig. (2-tailed)	–	–	–	0.000	0.000	0.000	0.000	0.000
MI	Pearson correlation	–	–	–	1	0.928**	0.647**	0.723**	0.849**
	Sig. (2-tailed)	–	–	–	–	0.000	0.000	0.000	0.000
MF	Pearson correlation	–	–	–	–	1	0.705**	0.716**	0.867**
	Sig. (2-tailed)	–	–	–	–	–	0.000	0.000	0.000
CHb	Pearson correlation	–	–	–	–	–	1	0.682**	0.812**
	Sig. (2-tailed)	–	–	–	–	–	–	0.000	0.000
CI	Pearson correlation	–	–	–	–	–	–	1	0.774**
	Sig. (2-tailed)	–	–	–	–	–	–	–	0.000

BDNF brain-derived neurotropic factor, *CTV* combined hippocampal volume, *MHb* maternal hemoglobin, *MI* maternal blood iron, *MF* maternal serum ferritin, *CHb* cord blood hemoglobin, *CI* cord blood iron, *CF* cord blood ferritin, *N* number

**Correlation is significant at the 0.01 level (two tailed)

higher serum BDNF concentrations in 30 healthy, full-term neonates compared to healthy preterm neonates. Differential degree of peripheral and CNS maturity was probably responsible for this difference. BDNF has also been shown to be a protective agent against hypoxic–ischemic damage to the brain [38]. Cord blood BDNF concentration was increased in newborns with perinatal asphyxia [39]. Lower cord blood BDNF concentrations of neonates born to mother with IDA found in this study could be a reflection of inadequate production of BDNF in CNS which had led to impaired hippocampal morphogenesis.

We have assessed hippocampal volume using volumetric MRI, which is a non-invasive, less painful and easily reproducible method of measuring hippocampus [40]. We have excluded preterm neonates and those with perinatal asphyxia or infection/inflammatory conditions as these may alter hippocampal size [27] and BDNF concentrations [39]. We have corrected measured hippocampal volume with respect to total intracranial volume to eliminate the effect of difference in head circumference.

The major limitation of this study is that we did not perform any neurodevelopmental assessment to know the clinical implication of reduced hippocampal volume and lower BDNF concentration, though the infants are under our follow-up and we plan to do neurodevelopmental assessment at a later age. Secondly, we did not look for the expression of BDNF in hippocampus and only speculated that cord blood BDNF concentration was reflective of its cerebral concentration.

To conclude, maternal IDA was found to affect fetal neurodevelopment as indicated by smaller hippocampal volumes and lower cord blood BDNF concentrations. The degree of affection was proportional to the severity of maternal anemia. Though there is paucity of literature in this area, the enduring and deleterious nature of the reduction in neonatal hippocampal volume and cord blood BDNF concentrations highlights the importance of preventing IDA in vulnerable maternal populations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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