TMJ
Original research

Published by OJS
dx.doi.org/10.4314/tmj.v29i1

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Iron deficiency and neurodevelopment among low birth weight infants: a cross-sectional study in a tertiary center in Tanzania

Albion Kasasa (Late) [1], Festus M. Kalokola[1], Karim P. Manji[1*]

[1] Department of Paediatrics and Child Health, Muhimbili University of Health and Allied Sciences.

***Corresponding author:**
Prof. Karim P. Manji
Muhimbili University of Health and Allied Sciences
P.O. Box 65001, Dar-es-Salaam,
Tanzania.
Email: kpmanji@gmail.com

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dx.doi.org/10.4314/tmj.v29i1

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ABSTRACT.

Background: iron deficiency anaemia is known to cause delayed neurodevelopment. Likewise infants born with low birth weight are also prone to neurodevelopment. The impact of both presence of iron deficiency and low birth weight is therefore expected to augment this delayed or impaired neurodevelopment. This relationship has not been elucidated in any appreciable level. We therefore considered studying iron deficiency among low birth weight infants and assessing their neurodevelopment. In children, however its impact is not clearly known among low birth weight infants.

Broad objective: To assess neurodevelopment of low birth weight infants and its relation to their iron status and nutritional status.

Methods: A cross-sectional study of 270 low birth weight infants was assessed during follow-up at neonatal clinic at Muhimbili National Hospital at 12 weeks postnatal. . They underwent the Bayley Mental Developmental Scoring Tests, serum ferritin and complete blood counts. The BMDS test raw scores were converted into percentiles. Cognitive, language and motor development scores were considered normal with score of ≥85 percentile of raw scores and poor with if the score was <85. Iron deficiency were considered if serum ferritin was <12µ/dl.

Results: The prevalence of poor scores were 90% in cognitive, 60% in language (60%) and 88% in motor development. The prevalence of iron deficiency was 34.1%. Among those not receiving iron supplementation, Poor cognitive and language scores were associated with iron deficiency, while motor scores were not. Wasting was associated with poor language score.

Conclusion. Low birth weight, iron deficient and wasted infants had significant poorer neurodevelopmental outcomes confirming that Iron deficient, low birth weight infants are more prone to poor neurodevelopmental outcomes. Recommendations; Early iron supplementation program should be adhered to and a close follow-up of these vulnerable children be done to ensure that their iron and hemoglobin levels are normal. Further large scale studies on the temporal relationship of iron and neurodevelopment are required.

Key Words: Iron deficiency, Low birth weight, neurodevelopment.

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Introduction.

Low birth weight (infant born with a weight of <2500 grams, and includes both preterm and intra-uterine growth restricted infants) are prone to have neurodevelopmental delays due to various intra-uterine and post-natal events which affect them , such as reduced cerebral blood flow , Intraventricular hemorrhage and hypoxia. Iron deficiency is recognized to cause delayed neurodevelopment, and among the common conditions associated with poor iron stores and iron deficiency are low birth weight infants due to poor intra-uterine accretion in the last trimester as well as poor availability of iron from the nutrients. Both Iron deficiency and Low birth weight are therefore recognized causes of impaired neurodevelopment. (1-8)

Iron deficiency is the most common single-nutrient deficiency disease in the world and may present with neuro-developmental abnormalities even before causing anemia. Iron deficiency has a spectrum and before even it reflects on the hemoglobin. (9-11)

In study done in Dar es salaam-Tanzania 1994, Iron deficiency was the most common cause of severe anemia in the first year of life and was prevalent in both severe anemic group as well as moderate or mild anemic infants. (12, 13).

The evidence of causal relationship of the poor neurodevelopment due to iron deficiency is mostly studied in the animal models. (14)

The incidence of low birth weight is 16 % in Tanzania, and these groups of infants are prone to iron deficiency. (1, 2) Therefore iron deficient low birth weight infants are expected to have a significant neurodevelopment impairment. This has not been elucidated in any appreciable level and therefore we considered assessing the presence of iron deficiency in low birth weight infants and perform neurodevelopment tests on these infants.

The main objective of this study was look for the influence of iron deficiency on the neurodevelopment of infants born with low birth weight and correlate with birth weight and gestational age , anemia, iron deficiency, anthropometry and maternal age .

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METHODOLOGY

Study design: This cross sectional study of 270 low birth weight (LBW) infants attending the neonatal follow-up clinics ate the Muhimbili National Hospital was carried out between August 2009-January 2010. The study population is infants who were admitted during neonatal period and are discharged home after a period of stabilization and established breast feeding. They are followed up at the neonatal unit regularly.

Measures of outcome: These infants were subjected to a detailed Bayley Neurodevelopment test appropriate for their age, and the raw scores were then converted to percentiles. . They also had a blood test for iron levels and hemoglobin.

The sample size was calculated using the formula for cross-sectional study; with an assumption of expected proportion of premature infants with neurodevelopment difficulties of 51.45% (higher conservative rates). (15)

Inclusion criteria: LBW infants attending the Neonatal Follow-up clinic

No major or acute illness currently.

Exclusively breast feeding

Willing to participate in the study and obtain blood for CBC and iron studies.

Exclusion criteria: Not meeting above criteria, and those who had congenital malformations, Birth Asphyxia, Meningitis or convulsions during any time period from birth.

After consenting, a thorough clinical and standard WHO recommended anthropometry assessment was done. The interpretation of nutritional status was done by using the “Epi Nut” program on the “Epi Info” statistical package version 6.01.

Blood samples for Serum Ferritin and Complete blood count were drawn and tested at the Muhimbili National Hospital Central Pathology Laboratory by the Electro-chemi-luminescence Immunoassay on the Elycsys 2010 and Cobas Immunoassay analyzers. Iron deficiency anemia was defined as hemoglobin level of <11g/dl and low ferritin levels of ≤ 12ug/dl while only Iron deficiency was defined as serum ferritin levels of ≤12ug/dl. (15, 16)

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Bayley Scale of Infant Development version III (17) was used for the assessment of neurodevelopment that included Cognitive, Language and Motor components. This assessment was done by an experienced nurse who is trained in Bayley Scoring, and was supervised by competent BSID III expert.

Of the 270 children, 25 neurodevelopment scores were repeated separately by another assessor to allow for quality control of the tests. Interpretation of neurodevelopment status using raw scores were as follows; the percentile rank of ≥85 was considered as normal neurodevelopment status**,** the percentile rank of 70-84 was considered as impaired neurodevelopment status**,** the percentile rank of <70 was considered as significant impaired neurodevelopment status. Statistical Package for Social Scientists (SPSS) version 15 (Chicago, II) was used for data analysis. The association between neurodevelopment and iron status was assessed by Chi-square. Correlation between individual neurodevelopment components (cognitive, language, motor) were assessed by cross tabulation tables and Chi-square test. Multiple regression analysis model was performed to assess the relationships found between neurodevelopment and nutritional status, gestation age, current age, maternal age, iron status, birth weight and sex of infant. The associations were presented as odds ratio (OR) together with 95% confidence interval (CI). A p value of <0.05 was considered significant.

Ethical clearance:

Ethical clearance to conduct research was obtained from the Higher Degree Research and Publication Committee of the Muhimbili University of Health and Allied Sciences, Dar es salaam, Tanzania. (www.muhas.ac.tz). Permission to conduct the study in the clinics was obtained from MNH management.

Ethical consideration:

Written informed consent to participate in the study was obtained from parents/guardians prior to enrolment in the study. Parents were asked to return for results, these were provided and children were managed according to the management guidelines for infants with iron deficiency.

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RESULTS.

Of the 270 infants studied, 124 (45.9%) were male and 146 (54.1%) were female providing a male to female ratio of 0.8:1. Most of the children, 153/270 (56.5%) were in the age group of 1-4 months and the mean age was 4 months. Seventy four percent of infants studied had gestation age ≤34 weeks and 66.3% weighed between 1.5-2.5 kg. Most (65.2%) infants had moderate to severe wasting by weight for height Z-score. Majority of infants 169/270 (62.6%) were not on iron supplementation at the time of the study. (Table 1)

Table 1. Demographic basic characteristics of the study population

Variable		n	%
Sex	Male	124	45.9
	Female	146	54.1
Age (months)	1-4	153	56.7
	5-8	93	34.4
	9-12	24	8.9
Nutritional status *	Normal	94	34.8
	Moderate/severe wasting	176	65.2
Gestational age (weeks)**	28-30	79	29.3
	31-34	121	44.8
	**35-38	70	25.9
Birth weight (Kg)	0.8-1	15	5.6
	1.01-1.49	76	28.1
	1.5-2.50	179	66.3
Iron supplementation	Given	101	37.4
	Not given	169	62.6

* Weight for Height Z-score (WHZ) was calculated.
• Z - Between Mean & -1SD = Normal nutritional status
• Z - Between -1.0SD & -3SD = Moderate wasting
• Z - Below <-3.0SD = Severe wasting
** There were only 5 infants with gestational age 35 and 2 infants with 36 weeks, so they have been grouped together for analysis.

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Expression of poor cognitive, language and motor development is noted with increasing age (p=0.0001). While sex had no significant association with cognitive development, (p=0.213) it is significantly associated with language development (p=0.05) and motor development (p=0.006). Females expressed more poor language and motor development scores than males. The prevalence of poor cognitive, motor and language development were 90%, 88.2% and 59.2% respectively. (Table 2)

Table 2; Cognitive, language and motor development in relation to age and sex

Variable		Number of Babies with poor cognitive scores			Numbers of babies with poor language score		Number of babies with poor motor score	
		Total	N (%)	P-value	N (%)	P-value	N (%)	P-value
Sex	Male	124	110(87.7)		64(51.6)		106(85.5)	
	Female	146	133(98.9)	0.213	96(65.8)	0.05	132(90.4)	0.006
	Total	270	243(90)		160(59.3)		238(88.1)	
Age (months)	1-4	153	144(94.1)		76(48.7)		123(90.4)	
	5-8	93	75(80.6)	0.0001	66(71.0)	0.0001	92(98.9)	0.0001
	9-12	24	24(100)		18(75.0)		23(95.9)	

There were 87/92 (95%) infants with iron deficiency as depicted by low serum ferritin who had cognitive scores below 84 , while 155/178 with normal ferritin had cognitive scores below 84(OR 2.5, 95% CI: 1.14-1.7, p=0.007). Likewise 58/92 (63%) iron deficient infants had language score below 84 , compared to 101/178 (56%) with non iron deficient (OR 1.3, CI: 1.08-1.8, p=0.04) (Table 3).

Table 3: Association between infant's iron status and cognitive, language and motor percentile

Infant Iron status	Neurodevelopment percentile scores									Total
	Cognitive[a]			Language[b]			Motor[c]			
	<70	70-84	>84	<70	70-84	>84	<70	70-84	>84	
	Number of infants (%)									
ID	65(37)	22(34)	5(18)	35(35)	23(40)	34(31)	62(34)	19(35)	11(34.1)	92(34.1)
Non-ID	112(63)	43(66)	23(82)	66(67)	35(60)	77(67)	122(66)	36(65)	20(65)	178(65)

[a]p=0.007, OR: 2.58. CI: 1.14-.17 [b]p=0.04, OR : 1.3 CI:1.08-1.8 [c]p=0.94 , OR : 0.9,CI: 1.18-1.4.
ID = Iron Deficient

Iron deficiency anemia was defined as hemoglobin level of <12g/dl, low ferritin levels (≤ 50ug/dl for ≤3 months babies and ≤70ug/dl for infants>3 and<12 months of age) . Iron deficiency was defined as serum ferritin levels of ≤50ug/dl for ≤3 months infants and ≤70ug/dl for infants>3months and<12 months of age.

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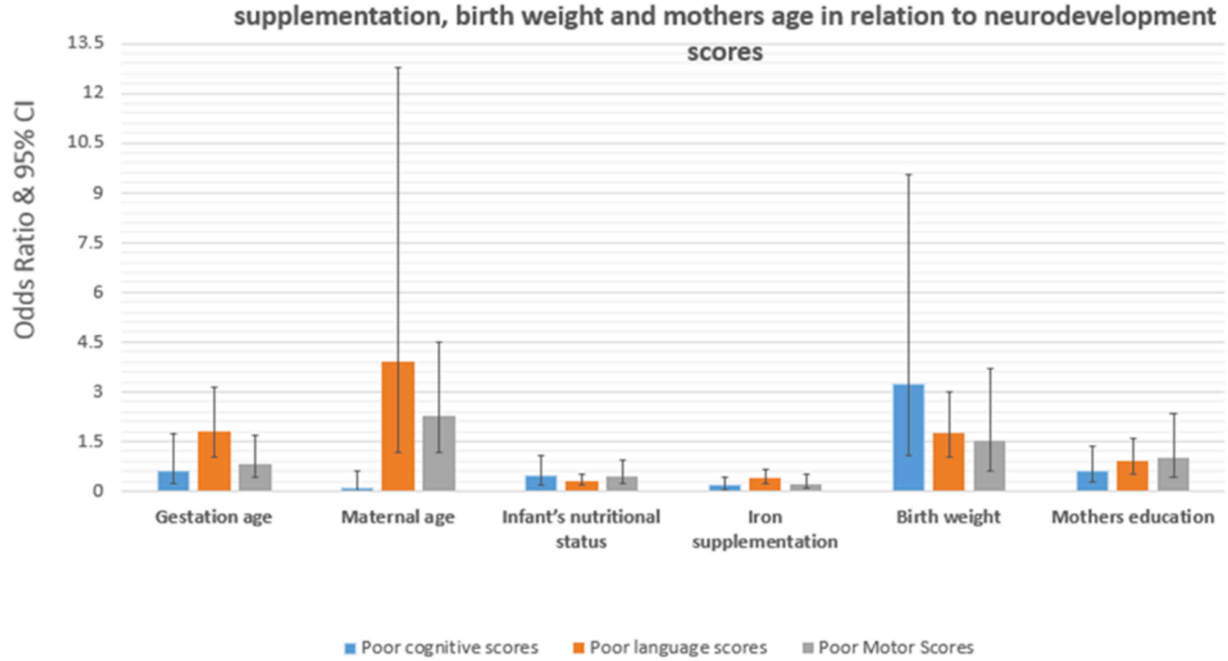
Infants with a history of not receiving iron supplementation had poor cognitive (OR 0.1795% CI =0.07-0.43),, language (OR 0.4, 95% CI = 0.24-0.67), and motor development (OR 0.23 , 95% CI 0.1- 0.5) (Figure 1). Maternal age, gestation age and maternal education were not significantly associated with poor neurodevelopment outcomes. Infants born with very low birth weight of 0.8-1.49kg were significantly associated with poor cognitive development. Wasting was a positive predictor of poor motor development and not predictive of cognitive and language development. (Figure 1)

Figure 1: Odds ratio and 95% CI of maternal age,gestation age, nutritional status, iron supplementation, birth weight and mothers age in relation to neurodevelopment scores



Lack of iron supplementation was associated poor cognitive, language and motor neurodevelopment. In addition birth weight was associated with poor cognitive development and current nutritional status with poor language development. Low serum ferritin levels were associated with poor cognitive and language development scores among low birth weight infants and not associated with poor motor development. (Table 4)

Table 4: Multiple logistic regression analysis of cognitive, language and motor development in relation to the maternal age, gestational age, nutritional status, iron supplementation status, birth weight and ferritin levels

Variables	Neurodevelopmental scores of infants								
	Cognitive development			Language development			Motor development		
	S.E	β - coefficient	p-value	S.E	β - coefficient	p-value	S.E	β - coefficient	p-value
Maternal age	0.030	0.066	0.27	0.05	-0.025	0.663	0.03	0.109	0.062
Gestation age	0.025	0.083	0.19	0.04	-0.061	0.311	0.03	-0.094	0.129
Birth weight	0.032	-0.157	0.01	0.05	-0.055	0.369	0.04	-0.031	0.620
Iron sup status,	0.037	0.239	0.00	0.06	0.206	0.000	0.04	0.237	0.000
Nutritional status	0.028	0.063	0.29	0.04	0.249	0.000	0.03	0.105	0.078
Infants age	0.001	-0.067	0.31	0.02	-0.028	0.693	0.01	-1.39	0.166
Ferritin levels	0.890	0.274	0.00	0.11	0.16	0.023	0.08	-0.157	0.079

Sup: supplementation, β – coefficient = β – standardized regression coefficient and S.E = Standard Error.

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DISCUSSION

A high prevalence of poor cognitive, motor and language development was observed in the study population, which is probably a result of the predominance of premature babies (97.8%). Prematurity , Low Birth Weight and lack of early iron supplementation may all be contributing to high prevalence of poor neurodevelopment. Poor neurodevelopment outcome of preterm infants are due to immature organ systems and possible effects of neonatal and maternal obstetrics factors. Abbort et al in their study of Very Low Birth Weight (VLBW) and Extremely Low Birth Weight (ELBW) infants at age 18-22 months who had normal cranial ultrasound observed similar finding and attributed the outcome to prematurity, neonatal care and maternal social economic characteristics. (18). This poor neurodevelopment function continue, even during school age period.(19-22). Likewise low birth weight probably resulting from intrauterine growth retardation was also associated with high rate of poor neurodevelopment and maybe related to micronutrient deficiencies common in these infants.(20,23).. Iron deficiency is common in malnourished infants and this further aggravates the poor cognitive effects of malnutrition as indicated in various studies.(7,24-26) This study showed that the more the advanced age of the infant the poorer the cognitive, language and motor development; which was also related to their iron status. This implies that prolonged iron deficiency states may have a role to play in neurodevelopment.(27)

In our study population, iron deficiency was significantly related to birth weight as 80.5% of 0.8-1kg infants had iron deficiency compared with 42% of 1.5-2.5 kg infants. (P=0.019). O'Keeffe et al in Australia showed that the prevalence of iron deficiency in premature infants was 21% which is lower than the prevalence of 34.1% found in this study.(29)

Iron deficient infants had lowered cognitive and language scores than iron sufficient infants. Tamura et al also observed poor cognitive and language development among iron deficient children aged 5 years (30). Several studies cited earlier have shown that cognitive and language development is poorly developed among iron deficient infants. These studies are variable in the age and their cohorts, but have similar finding, (11,24,30-35). The level of hemoglobin in our study did not appear to influence cognitive, language and motor development. However levels of ferritin were significantly associated with cognitive and language scores. Animal models show that Iron is required for normal myelinogenesis (24-26) ˒ perinatal iron deficiency affects dendritic growth and structure, neural metabolic activity, and synaptogenesis (24,25,36,37). It may be hypothesized that these neural processes may also play an important role in determining the effect of low iron on poor neurodevelopment.

Absence of iron supplementation in infant in current study was a predictor of poor cognitive, language and motor development. This finding was observed in previous studies done in Bangladesh (8), Zanzibar(38) and Germany(30). The Costa Rica (4) study showed that there were no improvements in cognitive and motor scores in both iron deficient and normal iron status children after 3 months of iron supplementation. The difference in the effects of supplementation of iron to premature or low birth weight infants may be due to delay in starting supplementation because it has been shown (39) that the late enteral iron supplementation is associated with failure to correct the existing neuro-dysfunction. At birth in both rat and human , blood brain barrier is incomplete (40) and lacks the ability to regulate the transfer of material from the blood to the interstitial fluid of the brain. The blood-brain barrier matures within 7 to 10 days of birth in the rat and may take up to 6 months in the human (41). Thus the ability to regulate brain iron availability according to need may not be well developed in early life (42) and infant rats and humans may be susceptible to the effects of iron deficiency in early neonatal period. The premature infant with an incomplete blood-brain barrier when subjected to iron deficiency would be most vulnerable. Whether iron supplementation is able to correct neurodevelopmental effects of iron deficiency may depend upon the point at which iron supplementation occurs relative to the developmental stage of the brain region at the point of supplementation. Studies in rat pups born to iron-deficient dams showed that repletion of iron commencing at post-natal day 4(i.e. before the peak iron demand) was able to correct the effect of iron deficiency on both iron levels and monoamines function in various brain regions. Giving iron around postnatal day 21(i.e. beyond the peak in iron demand) was unable to completely correct for the deficits in monoamine function despite correcting iron levels(43). There are limited studies on human infants but for those few done have shown some beneficial effect on cognitive and motor development after initiating early iron supplementation at 6 weeks postnatal as compared with late enteral supplementation. Gestation age at birth and maternal age were not statistically significantly associated with cognitive, language and motor development of the infant. This observation is supported with studies in Italy(21) and USA(18) in which the cognitive, language and motor score was lower in preterm children as compared to full term children. In the other studies low maternal age and more advanced age have been associated with poor neurodevelopment for their

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infants.(20,23) The birth weight of the infant was found to be a negative predictor of poor cognitive development but not of language and motor development. These findings are consistent with previous studies where an increase in birth weight was related to better psychomotor development outcomes (31,37,44,45). In contrast, increased birth weight was not significantly related to overall motor impairment. These findings indicate that having a lower birth weight and a lower gestational age are related with poor motor outcomes in the first years of development but the biological basis is not clear. Nutritional status (wasting) was positive predictor of poor language development and was not significantly associated with the cognitive and motor development. Low body protein, fat and carbohydrates act as raw material and building block of the brain through metabolic processes (27). Although Hinz et al showed that the males are more prone to poor neurodevelopment as compared to females, this study did not show any significant difference. (28)

The limitations of this study include inability to establish a temporal relation of iron deficiency on poor neurodevelopment. The differentiation between LBW who were preterm and those who had intra-uterine growth retardation thus small for gestational age (SGA) or appropriate for gestational age (AGA) was not done. Also, the details of maternal demography including home environment, economic status and educational status were not studied.

Conclusion: Low birth weight , iron deficient and wasted infants had poor neurodevelopment and may need early intervention. Randomized clinical trials with more specific measures of neurodevelopment are needed to confirm the exact nature of the causal relations between low iron status and neurological impairments in premature infants

Acknowledgements. We would like to thank the staff of the Neonatal Unit of Muhimbili National Hospital for their assistance.

Conflict of Interests: None declared

Funding: The Muhimbili University of Health and Allied Sciences for Dissertation funding and Tanzania GID training grant ((NIH/ Fogarty GID grant number: 2 D43 TW007886-05) for funding the laboratory tests.

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dx.doi.org/10.4314/tmj.v29i1

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