Socio-emotional and adaptive behaviour after severe anaemia in pre-schoolers at Lira Regional Referral Hospital, Uganda: a cross sectional study.

Andrew Sentoogo Ssemata (andrewssemata@yahoo.co.uk)
Makerere University College of Health Sciences
https://orcid.org/0000-0003-0060-0842

Robert O. Opoka
Makerere University College of Health Sciences

John M. Ssenkusu
Makerere University College of Health Sciences

Noeline Nakasujja
Makerere University College of Health Sciences

Chandy C. John
Indiana University

Paul Bangirana
Makerere University College of Health Sciences

Research article

Keywords: neurodevelopment, pre-school, children, severe anaemia, adaptive behaviour, socio-emotional, Uganda

DOI: https://doi.org/10.21203/rs.3.rs-36350/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background:** Severe anaemia is a global public health challenge commonly associated with morbidity and mortality among children <5 years of age in Sub-Saharan Africa. However, less is known about the behavioural performance of preschool children surviving severe anaemia in low resource settings. We investigated social-emotional and adaptive behaviour in preschool children diagnosed with severe anaemia in Northern Uganda.

**Methods:** We conducted a hospital based cross-sectional study among children 6 - 42 months who were treated for severe anaemia (n=171) at Lira Regional Referral Hospital, Uganda. Social emotional and adaptive behaviour were assessed 14 days post discharge using the Bayley Scales of Infant and Toddler Development, 3rd edition. Age-adjusted z-scores for each domain were calculated using scores from healthy community children (n=88) from the same environment for each age category. Multiple linear regression was used to compare z-scores in the social-emotional and adaptive-behaviour scales between the two groups after adjusting for weight-for-age z-score, social economic status, mother’s education, father's education and father's employment on all the scales.

**Results:** Compared with healthy community pre-schoolers, children with severe anaemia had poorer [adjusted mean scores (standard error)], social emotional [-0.29, (0.05) vs. 0.01, (0.08), P=0.002]; but not overall/ composite adaptive behaviour [-0.10, (0.05) vs. -0.01, (0.07), P=0.343]. Within the adaptive behaviour subscales, children with SA displayed significantly poorer scores on the community use [adjusted mean score (standard error)], [-0.63, (0.10) vs. -0.01, (0.13), P<0.001]; and leisure [-0.35, (0.07) vs. -0.02, (0.07), P=0.036] skills.

**Conclusion:** This study demonstrates that severe anaemia in the preschool period is associated with poor social-emotional scores in the short-term post clinical recovery in Northern Uganda. We recommend long-term follow-up to determine the course of these problems and appropriate interventions to reduce the behavioural burden among pre-schoolers surviving severe anaemia in Uganda.

**Background**

Severe anaemia (SA), is a common public health problem among children under 5 years of age in resource-constrained areas with the highest mean severity in all low and middle income regions (1). The prevalence of SA among African children is notably high with a burden close to 63% (2). In malaria endemic areas, severe anaemia is a prevalent complication of malaria among African children especially those below 5 years in endemic countries (3, 4).

Severe anaemia is associated with frequent infections, micronutrient deficiencies and inadequate feeding practices causing life-long health consequences including diffused cerebral hypoxia, tissue ischaemia, cognitive dysfunction, impaired cerebral vascular regulation, neurological injury and mortality (5–10). Evidence that the brain is vulnerable during acute and chronic anaemia is provided by human and animal studies where acute anaemia has been linked to cognitive dysfunction and evidence of cerebral cellular
hypoxia (11–13). Severe anaemia may lead to brain dysfunction and cerebral injury with the brain white matter identified as the predominant site of injury (13–15). Severe anaemia-induced injury may affect child growth and development including difficulties in learning complex task, short term memory deficits and decreased motor control (13, 15). The behavioural effects are of greatest concern because they can persist beyond treatment and resolution of anaemia (7, 16). They may affect the mental, physical and social growth and development in children affecting their academic and career prospects later in life (7, 9, 17).

Behavioural outcomes after severe anaemia receive little or no attention in many public health spheres; despite causing so much disability partly due to the fact that emphasis is usually focussed on SA resolution and the reduction of risk factors of SA (3, 4, 18–22). Therefore, the effect of SA on a child's behavioural outcomes is unknown. A recent study among Ugandan children with severe malaria and community children showed that severe malarial anaemia (SMA) was associated with internalizing and externalizing behavioural problems in children < 5 years old at 12 and 24 months (23). In this study, a behavioural assessment was conducted for children who had severe malarial anaemia.

To address the gaps in knowledge regarding behavioural outcomes in children with SA, we conducted a prospective cross-sectional study using the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley–III) (24, 25) to characterize the effect of SA on socio-emotional and adaptive behaviour among Ugandan pre-schoolers in the immediate period post recovery. The preschool years have been reported as a time of great cognitive, psychological and behavioural growth and brain development involving dynamic and elaborative developmental changes (26). We hypothesized that children with SA would have poorer social emotional and adaptive behavioural scores compared to community children.

Methods

This was a cross-sectional study with a sample of 259 pre-schoolers (171 with severe anaemia and 88 community children) aged 6–42 months conducted between August 2016 and June 2017 at Lira Regional Referral Hospital (LRRH) in Northern Uganda. Participants with SA were in-patients of an implementation research study on management and outcomes of severe anaemia in Ugandan children where SA was defined as Haemoglobin (Hb) \( \leq \) 5 g/dL (20, 21). The healthy community children (CC) were siblings or neighbours of the enrolled children with SA who had been volunteered by the parents after invitation to participate in the study. They were examined at the time of enrolment to ensure that they did not have clinical pallor on clinical examination or a history of hospitalization for severe anaemia 6 months prior to enrolment.

Clinical And Demographic Assessment

Social economic status (SES) and demographic characteristics were obtained using a questionnaire of material possessions assessing housing quality, cooking resources, water accessibility and the presence of key amenities (radio, shoes for subject, mobile phone, poultry) in which lower SES scores have been
associated with worse cognitive functioning in healthy Ugandan paediatric population under 5 years of age (27). Nutritional status was obtained by comparing physical indicators (height and weight) with the US CDC published norms and standardized z-scores (Epi Info 6, CDC 2000 Growth reference, Centers for Disease Control and Prevention, Atlanta, GA), to calculate height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height z-scores (WHZ) (28). We followed internationally recognised cut-offs to consider children whose HAZ, WAZ, or WHZ fall more than two SDs below the international mean to be stunted, underweight or wasted, respectively (29).

**Behavioural Assessment**

Behavioural assessment was done using the Bayley III. It is one of the most commonly adapted comprehensive psychometric assessment tools used in research, in clinical practice, and to evaluate interventions as it assesses several developmental domains as a measure of early global development among very young children (24, 25, 30). The interviews with the caregivers were conducted in a quiet child-friendly room at the hospital. For uniformity and language concerns, trained assessors with Bachelor’s degrees in Psychology and fluent in Langi (a local dialect) administered the test to the child’s primary caregiver.

Assessments were conducted 14 days post discharge for the caregivers of the children with SA and at enrolment for the CCs or when appropriate for the caregiver to return to the hospital for assessment. We interviewed the primary caregiver of each child using the social–emotional and adaptive behaviour scales of the Bayley–III (24, 25). Majority of these were mothers, familiar with the child and could provide meaningful, accurate and complete response ratings of their child’s personal, adaptive and social skills necessary for daily living. The social-emotional scale assesses emotional and social development as well as sensory processing that influences a child’s emotional responses based on the Greenspan Social-Emotional Growth Chart (31). The scale provides a general indication of a child’s level of social-emotional development and presence or absence of sensory processing difficulties (32). The scale assesses the child’s functional, social and emotional milestones namely; self-regulation and interest in the world, relationship engagement, emotional engagement in an interactive and purposeful manner, communication with interactive emotional gestures, problem solving through interactive emotional gestures, communicating intentions and feelings using symbols and ideas, using symbols to express intentions, wishes or feelings more than basic needs, creating logical bridges between ideas and emotions (24, 31, 32).

Adaptive behaviour is a collection of skills (conceptual, social, and practical) for effective functioning that concern the way individuals meet their personal needs while meeting their demands in their environment (33, 34). The adaptive behaviour scale is derived from items for children 0–5 years of the Parent/Primary Caregiver Form of the Adaptive Behaviour Assessment Scale – Second Edition - ABAS-II (35). The scale assesses ten areas categorized in three broader domains: (1) conceptual (communication, functional academics, and self-direction); (2) social (social and leisure); and (3) practical (self-care, home
or school living, community use, health and safety) (33, 36). A summation of the ten sub-scales composite scores was obtained to generate an overall adaptive behaviour score also known as the General Adaptive Composite (GAC) score.

### Statistical Methods

Data were entered into Filemaker 11.0v3 (FileMaker Inc. US) database, and exported into IBM SPSS 23 for statistical analysis. For this study, raw scores for each scale were converted into an age and sex-specific standardized z-score, based on the scores of healthy community children (CC, n = 88). The z-scores were computed as (actual score – mean score for a child’s sex and age)/SD, where the mean score for a child’s sex and age and SD were computed by fitting a linear regression model to data for all CC children (37). Z-scores have a mean of 0 and SD 1 in the CC reference population. Multiple linear regression was used to compare z-scores on all the scales between the two groups after adjusting for weight-for-age z-score, social economic status, mother’s education, father’s education and father’s employment. We adjusted for multiple testing for the adaptive subscales using the Hommel’s procedure (38) and $p < 0.05$ was statistically significant.

### Ethics

Approvals for this study were obtained from Makerere University School of Medicine Research Ethics Committee (REC Ref: 2015-045), Uganda National Council for Science and Technology (Ref: HS 2017) and the Lira Regional Referral Hospital administration. Participation in the study was voluntary and the caregivers of the study participants who took part in the study provided written informed consent.

### Results

#### 1. Characterization of the study sample children

We interviewed caregivers of 259 children (171 with SA and 88 CCs) with overall mean age of 1.94 years (CCs, $M = 2.07$ years, $SD = 0.96$; SA, $M = 1.88$ years, $SD = 0.94$). The pre-schoolers in this study resided in the same geographical region and their characteristics are described in Table 1. Children with SA had lower social economic status, mother’s education, father’s education and father’s employment statuses than CC children.
Table 1  
Demographic characteristics of severe anaemia and control study children

| Characteristic                                      | Severe Anaemia (n = 171) | Community Children (n = 88) | P value |
|-----------------------------------------------------|--------------------------|-----------------------------|---------|
| Age in years, mean (SD)                             | 1.88 (0.94)              | 2.07 (0.96)                 | 0.129   |
| Female sex, n (%)                                   | 75 (43.9)                | 47 (53.4)                   | 0.145   |
| Nutritional status indicators #                     |                          |                             |         |
| Underweight (WAZ<-2 SD) n (%)                       | 10 (6.2)                 | 13 (14.9)                   | 0.023*  |
| Stunting (HAZ<-2 SD) n (%)                          | 15 (11.9)                | 10 (11.8)                   | 0.975   |
| Wasting (WHZ <-2 SD) n (%)                          | 11 (8.3)                 | 12 (14.0)                   | 0.284   |
| Social economic status wealth indices, n (%)        |                          |                             | 0.048*  |
| Poor                                                | 44 (25.7)                | 10 (11.4)                   |         |
| Second                                              | 30 (17.5)                | 21 (23.9)                   |         |
| Middle class                                        | 31 (18.1)                | 24 (27.3)                   |         |
| Fourth                                              | 36 (21.1)                | 20 (22.7)                   |         |
| Wealthy                                             | 30 (17.5)                | 13 (14.8)                   |         |
| Maternal education level, n (%)                     |                          |                             | 0.038*  |
| Primary or less                                     | 151 (88.3)               | 69 (78.4)                   |         |
| Secondary                                           | 15 (8.7)                 | 14 (16.0)                   |         |
| Tertiary                                            | 5 (3.0)                  | 5 (5.6)                     |         |
| Paternal education level, n (%)                     |                          |                             | 0.036*  |
| Primary or less                                     | 120 (70.2)               | 48 (54.5)                   |         |
| Secondary                                           | 26 (15.2)                | 14 (16)                     |         |

# The number of children assessed differed from the total number of children WAZ (n = 249); HAZ (n = 211); WHZ (n = 218)

* P value ≤ 0.05
| Characteristic                  | Severe Anaemia (n = 171) | Community Children (n = 88) | P value |
|--------------------------------|--------------------------|-----------------------------|---------|
| Tertiary                       | 25 (14.6)                | 26 (29.5)                   |         |
| Maternal employment n (%)      |                          |                             | 0.153   |
| Yes                            | 20 (11.7)                | 16 (18.2)                   |         |
| No                             | 151 (88.3)               | 72 (81.8)                   |         |
| Paternal employment n (%)      |                          |                             | 0.039*  |
| Yes                            | 74 (43.3)                | 50 (56.8)                   |         |
| No                             | 97 (56.7)                | 38 (43.2)                   |         |

*The number of children assessed differed from the total number of children WAZ (n = 249); HAZ (n = 211); WHZ (n = 218)

* P value ≤ 0.05

2. Behavioural Performance

Compared with healthy community pre-schoolers, children with SA displayed significantly poorer scores on the social emotional [adjusted mean score (SE)], [-0.29, (0.05) vs. 0.01, (0.08), P = 0.002] but not the composite adaptive behaviour [-0.10, (0.05) vs. -0.01, (0.07) P = 0.343] scales (Table 2). We also compared the SA group against the CCs group on the adaptive behaviour subscales. We found that children with SA displayed significantly poorer scores on the community use [adjusted mean score (standard error)], [-0.63, (0.10) vs. -0.01, (0.13), P < 0.001]; and leisure [-0.35, (0.07) vs. -0.02, (0.07), P = 0.036] skills subscales. Compared to the CC group, children with SA had lower scores on the communication, functional pre-academics, self-direction, home living and health and safety, self-care, social and motor scales but these were not statistically significant (Table 2).
### Table 2
Adjusted means for social-emotional and adaptive behavioural z-scores for children with severe anaemia and community control children

| Scales                      | Severe Anaemia n = 171 | Community Control n = 88 | Difference in means p-value |
|-----------------------------|------------------------|--------------------------|-----------------------------|
|                             | M, (SE)                | M (SE)                   |                             |
| Social emotional            | -0.29, (0.05)          | 0.01, (0.08)             | 0.002*                      |
| Overall Adaptive behaviour  | -0.10, (0.05)          | -0.01, (0.07)            | 0.343                       |
| Adaptive communication      | -0.11, (0.05)          | 0.00, (0.07)             | 0.776                       |
| Adaptive community use      | -0.63, (0.10)          | -0.01, (0.13)            | <0.001*                     |
| Adaptive pre-academics      | 0.06, (0.12)           | -0.02, (0.16)            | 0.976                       |
| Adaptive home living        | 0.26, (0.12)           | -0.03, (0.16)            | 0.656                       |
| Adaptive health and safety  | -0.11, (0.05)          | -0.01, (0.07)            | 0.931                       |
| Adaptive leisure            | -0.35, (0.07)          | -0.02, (0.09)            | 0.036*                      |
| Adaptive self-care          | -0.26, (0.06)          | -0.03, (0.09)            | 0.224                       |
| Adaptive self-direction     | 0.03, (0.08)           | -0.03, (0.11)            | 0.976                       |
| Adaptive social             | 0.25, (0.08)           | -0.04, (0.11)            | 0.273                       |
| Adaptive motor              | 0.00, (0.06)           | 0.00, (0.08)             | 0.976                       |

a - Children below one year are not assessed on these skill areas and the total number of children for these scales for each group were - Severe anaemia group n = 126; Control group n = 70

Associations with adaptive subscales have been adjusted for multiple testing using the Hommel's procedure (Hommel, 1988) and p < 0.05 is statistically significant.

### Discussion

This study set out to examine the effect of SA on social-emotional and adaptive behaviour using the Bayley III among Ugandan pre-schoolers aged 6–42 months in the immediate period post recovery in Lira district, Northern Uganda. The study findings showed that SA is associated with poor social-emotional behaviour among Ugandan preschool children. We found no significant differences between the two groups on overall adaptive behaviour.
These results reflect the potential effect of severe anaemia that greatly affects African preschool children in resource-limited setting (2). One possible explanation for these results is that the altered social-emotional behaviour may be accounted for by the alterations in the frontal-striatal circuits and the mesolimbic/ meso-cortical dopamine levels as observed among children with iron deficiency anaemia (39). Though not assessed in the present study, iron deficiency is estimated to be the commonest contributor to the aetiology of severe anaemia and these iron status changes affects certain brain regions (40). These alterations in social-emotional behaviour are associated with poor overall developmental outcomes (39) and may affect school performance, personal relationships and consequently adaptive behaviour that draws together a person's cognitive and personality characteristics (33, 41). Consequently, children with SA will be poor at negotiating complex social-emotional patterns and reaching functional emotional milestones that provide purpose to mental processes (24).

It is important to note that altered social-emotional behaviour as observed in the present study has been reported to affect how children react and experience their social and physical environment; thereby fuelling poor developmental outcomes that could significantly affect children's growth and development (42). Children's social-emotional development is reported to enhance children's adaptive behaviour, safety, home living, health, social relationships, self-awareness, emotional regulation, independence, academic outcomes and lifelong learning (43, 44). This may be a possible explanation for the significantly poor performance on community use and leisure skills among children with SA. These skills have been reported to hamper skills needed to function in the community for example adequately exploring the environment, home living (helping with chores), health and safety (following safety rules and avoiding physical danger), and self-care (eating, dressing, toileting, brushing teeth) among infants and pre-schoolers (41). This could indicate that children with SA may not achieve their potential across multiple adaptive behaviour skills particularly in the social (leisure) and practical (community use) domains; which are necessary for young children to become increasingly more independent. Deficits in these domains during the critical child development period, have the potential to affect the pre-schoolers' key functional developmental tasks (33, 45). As a result, children with SA may be unable to encounter daily needs and manage the natural and social demands of the environment critical to child survival.

Furthermore, adaptive behaviours are intricately connected to other developmental domains such as cognition, motor and language skills; and as children grow older and begin to exhibit more sophisticated behaviour (33–35, 46). Therefore, understanding the adaptive skills affected by SA in children may support the tailoring of interventions aimed at improving their functional outcomes. These interventions should focus on assessing and understanding the social emotional, sensory processing and adaptive skills present in early childhood (33). This is essential as these domains reflect the needs and feelings during the preschool years of life; critical to a child's future and survival (33, 35).

While research on neurodevelopmental impairment among pre-schoolers surviving SA in LMICs is limited, this study indicates that pre-schoolers with SA have poorer social-emotional behaviour compared to their healthy counterparts. Understanding the social, emotional and behavioural development of pre-schoolers after illness is important as it reflects the critical aspects of the child's well-being, awareness of risks to
brain function and the physiological adaptation to disease or environmental influences on brain development during formative early years (30). Therefore, additional research on the neurodevelopmental needs of pre-schoolers with SA and the integration of early childhood development services into paediatric SA treatment programmes in LMICs is recommended. Assessing adaptive behaviour and functional abilities focuses on an essential dimension of human function essential in the diagnosis of impairment and intellectual disability (34).

**Strength And Limitations**

Our study provides important and novel data on the effect of SA on the socio-emotional behaviour among Ugandan pre-schoolers in a resource-constrained setting. Realizing the level and risk of disruption of brain development during formative early years due to SA and identifying the neurodevelopmental concerns early in life may direct early intervention services aimed at averting the impairment trajectories and improve functionality. The study also highlights the need for early and appropriate interventions across all skill areas to avert socio-emotional and behavioural challenges these children may develop and reduce the burden of future developmental risk and dysfunction that may be associated with severe anaemia among pre-schoolers in Uganda and other resource-constrained countries in Sub-Saharan Africa that could further burden the health system.

The current study has limitations worth noting. The aetiology and diagnosis the SA was largely symptomatic. We were not able to collect any further clinical data like malaria diagnosis. However, it is worth noting that anaemia among children in LMICs is a result of micronutrient deficiencies, acute and chronic inflammation, malnutrition and frequent infections (10) that may also affect socio-emotional behaviour. This study did not assess post transfusion Hb or if SA had cleared prior to assessment as both anaemia and transfusion are independently associated with organ injury and increased morbidity (5). Future research should assess post-discharge Hb prior to assessment. Socio-emotional and adaptive behaviour were assessed by caregiver reports of aspects of their child’s development basing on their perceptions of their children and may be over- or under-represented. Parental reporting may be less valid in settings where the background level of awareness about early child development is low guided by cultural values and norms with a bias to portray their child in a positive light (43).

This was a cross-sectional study assessing the socio-emotional and adaptive behaviours skills performance in a resource-constrained setting at a single time point therefore causality could not be established and findings may not be representative of the entire population. However we used healthy community children as a comparator group for normal test results in this age group in this area.

**Conclusion**

The investigations of this study demonstrate severe anaemia is associated with poorer social-emotional behaviour among pre-schoolers aged 6 to 42 months in Uganda. Deficits reported in these areas could become significant risk factors for the later development of social and academic difficulties. The
evaluation of socio-emotional and adaptive behaviour among pre-schoolers surviving SA may have important diagnostic, clinical, and therapeutic implications more so as these assessments are not part of standard of care in many LMICs. Future research is needed to evaluate the long-term course of these behavioural problems, their risk factors and to develop targeted interventions.

List Of Abbreviations

Bayley-III: Bayley Scales of infant and toddler development, 3rd edition; CC: community children; GAC: general adaptive composite; HAZ: height-for-age z-score; Hb: Haemoglobin; LRRH: Lira regional referral hospital; SA: severe anaemia; SES: social economic status; SMA: severe malarial anaemia; WAZ: weight-for-age z-score; WHZ: weight-for-height z-score.

Declarations

Ethics approval and consent to participate

Approvals for this study were obtained from Makerere University School of Medicine Research Ethics Committee (REC Ref: 2015-045), Uganda National Council for Science and Technology (Ref: HS 2017) and the Lira Regional Referral Hospital administration. Participation in the study was voluntary and the caregivers of the study participants who took part in the study provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study supporting the conclusions of this article are included in this manuscript text [and its tables].

Competing interests

The authors have declared that no competing interests exist.

Funding

This work was supported by funding from grant number D43TW010132 from National Institutes of Health and a Fogarty International Centre grant number D43 NS078280, awarded to CCJ. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the funders.

Authors' contributions
ASS, ROO, PB, and NN designed the research (project conception, development of overall research plan, and study oversight). ASS and ROO conducted research (conduct of the assessments and data collection); AS and JMS cleaned the data and performed statistical analysis. NN, CCJ and PB gave oversight to study conduct, ASS drafted the paper, and had primary responsibility for final content. All authors contributed significantly to the intellectual design, provided critical revisions to the manuscript and approved the final version.

Author details

1Department of Psychiatry, Makerere University, College of Health Sciences; Kampala, Uganda.
2Department of Paediatrics and Child Health, Makerere University, College of Health Sciences; Kampala, Uganda. 3Department of Epidemiology and Biostatistics, Makerere University, College of Health Sciences; Kampala, Uganda. 4Ryan White Center for Pediatric Infectious Disease & Global Health, School of Medicine, Indiana University, Indianapolis, Indiana, United States of America.

Acknowledgements

We thank the children and caregivers who participated in the study; the research team (Isaac Oruru, Joan Apili, and Norine Apio) who supported data collection and the Lira Regional Referral Hospital administration for permission to conduct the study.

References

1. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615-24.
2. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. The Lancet Global Health. 2013;1(1):e16-e25.
3. Biemba G, Dolmans D, Thuma PE, Weiss G, Gordeuk VR. Severe anaemia in Zambian children with Plasmodium falciparum malaria. Tropical Medicine & International Health. 2000;5(1):9-16.
4. Crawley J. Reducing the burden of anemia in infants and young children in malaria-endemic countries of Africa: from evidence to action. The American journal of tropical medicine and hygiene. 2004;71(2_suppl):25-34.
5. Shander A, Javidroozi M, Ozawa S, Hare G. What is really dangerous: anaemia or transfusion? British journal of anaesthesia. 2011;107(suppl_1):i41-i59.
6. Casals-Pascual C, Idro R, Gicheru N, Gwer S, Kitsao B, Gitau E, et al. High levels of erythropoietin are associated with protection against neurological sequelae in African children with cerebral malaria. Proceedings of the National Academy of Sciences. 2008;105(7):2634-9.
7. Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian S. Anaemia in low-income and middle-income countries. The Lancet. 2012;378(9809):2123-35.

8. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function—. The American journal of clinical nutrition. 2007;85(4):931-45.

9. World Health Organization. The global prevalence of anaemia in 2011. Geneva, Switzerland: World Health Organization, 2015.

10. Perkins DJ, Were T, Davenport GC, Kempaiah P, Hittner JB, Ong’echa JM. Severe malarial anemia: innate immunity and pathogenesis. International journal of biological sciences. 2011;7(9):1427.

11. Li M, Bertout JA, Ratcliffe SJ, Eckenhoff MF, Simon MC, Floyd TF. Acute anemia elicits cognitive dysfunction and evidence of cerebral cellular hypoxia in older rats with systemic hypertension. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2010;113(4):845-58.

12. El Hasnaoui-Saadani R, Pichon A, Marchant D, Olivier P, Launay T, Quidu P, et al. Cerebral adaptations to chronic anemia in a model of erythropoietin-deficient mice exposed to hypoxia. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2009;296(3):R801-R11.

13. Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2000;92(6):1646-52.

14. Loureiro B, Martinez-Biarge M, Foti F, Papadaki M, Cowan FM, Wusthoff CJ. MRI Patterns of brain injury and neurodevelopmental outcomes in neonates with severe anaemia at birth. Early human development. 2017;105:17-22.

15. Hare GM, Tsui AK, McLaren AT, Ragoonanan TE, Yu J, Mazer CD. Anemia and cerebral outcomes: many questions, fewer answers. Anesthesia & Analgesia. 2008;107(4):1356-70.

16. World Health Organization. The global prevalence of anaemia in 2011. 2015.

17. Clarke SE, Jukes MC, Njagi JK, Khasakhala L, Cundill B, Otido J, et al. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. The Lancet. 2008;372(9633):127-38.

18. Kiguli S, Maitland K, George EC, Olupot-Olupot P, Opoka RO, Engoru C, et al. Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness. BMC medicine. 2015;13(1):21.

19. Milman N. Anemia—Still a major health problem in many parts of the world! Annals of hematology. 2011;90(4):369-77.

20. Opoka OR, Ssemata SA, Oyang W, Nambuya H, John CC, Tumwine KJ, et al. The management of severe anaemia in children admitted to Ugandan hospitals: high rate of unnecessary blood transfusions due to inadequate utilisation of laboratory services. 2018.

21. Opoka RO, Ssemata AS, Oyang W, Nambuya H, John CC, Karamagi C, et al. Adherence to clinical guidelines is associated with reduced inpatient mortality among children with severe anaemia in Ugandan hospitals. PloS one. 2019;14(1):e0210982.
22. VanBuskirk KM, Ofosu A, Kennedy A, Denno DM. Pediatric anemia in rural Ghana: a cross-sectional study of prevalence and risk factors. Journal of tropical pediatrics. 2014;60(4):308-17.

23. Ssenkusu JM, Hodges JS, Opoka RO, Idro R, Shapiro E, John CC, et al. Long-term behavioral problems in children with severe malaria. Pediatrics. 2016;138(5):e20161965.

24. Bayley N. Bayley scales of infant and toddler development: Technical manual San Antonio, TX: Pearson PsychCorp; 2006.

25. Bayley N. Bayley scales of infant and toddler development. Third Edition. 3rd ed. San Antonio, TX: Harcourt Assessment, Inc.; 2006.

26. Brown TT, Jernigan TL. Brain development during the preschool years. Neuropsychology review. 2012;22(4):313-33.

27. Bangirana P, John CC, Idro R, Opoka RO, Byarugaba J, Jurek AM, et al. Socioeconomic predictors of cognition in Ugandan children: implications for community interventions. PLoS One. 2009;4(11):e7898.

28. World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Methods and development WHO (nonserial publication) Geneva: WHO. 2006;2007.

29. De Onis M, Blössner M. The World Health Organization global database on child growth and malnutrition: methodology and applications. International journal of epidemiology. 2003;32(4):518-26.

30. Kammerer B, Isquith PK, Lundy S. Approaches to assessment of very young children in Africa in the context of HIV. In: Boivin MJ, Bruno G, editors. Neuropsychology of children in Africa. New York: Springer; 2013. p. 17-36.

31. Greenspan SI. Greenspan social-emotional growth chart: A screening questionnaire for infants and young children. San Antonio, TX: Harcourt Assessment; 2004.

32. Breinbauer C, Mancil LT, Greenspan SI. The Bayley-III Social-Emotional Scale. In: Weiss LG, Oakland T, Aylward GP, editors. Bayley-III clinical use and interpretation. London: Academic Press, Elsevier Inc.; 2010. p. 147-74.

33. Harman LJ, Smith-Bonahue MT. The Bayley-III Adaptive Behavior Scale. In: Weiss GL, Oakland T, Aylward G, editors. Bayley-III Clinical use and interpretation. London: Academic Press, Elsevier Inc.; 2010. p. 177-99.

34. Tassé MJ, Schalock RL, Balboni G, Bersani Jr H, Borthwick-Duffy SA, Spreat S, et al. The construct of adaptive behavior: Its conceptualization, measurement, and use in the field of intellectual disability. American journal on intellectual and developmental disabilities. 2012;117(4):291-303.

35. Harrison PL, Oakland T. Adaptive behavior assessment system- Second Edition (ABAS-II). 2nd ed. San Antonio, TX: Harcourt Assessment; 2003.

36. Albers CA, Grieve AJ. Review of Bayley Scales of Infant and Toddler Development. Journal of Psychoeducational assessment. 2007;25(2):180-90.
37. Bangirana P, Opoka RO, Boivin MJ, Idro R, Hodges JS, Romero RA, et al. Severe malarial anemia is associated with long-term neurocognitive impairment. Clinical Infectious Diseases. 2014;59(3):336-44.

38. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika. 1988;75(2):383-6.

39. Lozoff B, Clark KM, Jing Y, Armony-Sivan R, Angelilli ML, Jacobson SW. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. The Journal of Pediatrics. 2008;152(5):696-702. e3.

40. Boele van Hensbroek M, Calis JC, Phiri KS, Vet R, Munthali F, Kraaijenhagen R, et al. Pathophysiological mechanisms of severe anaemia in Malawian children. PloS one. 2010;5(9):e12589.

41. Kirchner RM, Martens MA, Andridge RR. Adaptive behavior and development of infants and toddlers with Williams syndrome. Frontiers in psychology. 2016;7(1):598.

42. Lozoff B, Castillo M, Clark KM, Smith JB, Sturza J. Iron supplementation in infancy contributes to more adaptive behavior at 10 years of age. The Journal of nutrition. 2014;144(6):838-45.

43. Ren L, Garcia AS, Esteraich JM, Encinger A, Raikes HH, Acar IH. Parent–Child Relationships and Preschoolers’ Social-Emotional Functioning Among Low-Income Families: The Moderating Role of Parental Nativity. Infants & Young Children. 2019;32(2):123-38.

44. Trawick-Smith J. Early childhood development: A multicultural perspective. 6th ed. Upper Saddle River, NJ: Pearson Education Inc.; 2013.

45. Schalock RL, Borthwick-Duffy SA, Bradley VJ, Buntinx WH, Coulter DL, Craig EM, et al. Intellectual disability: Definition, classification, and systems of supports: ERIC; 2010.

46. Albers CA, Grieve AJ. Test review: Bayley, N.(2006). Bayley scales of infant and toddler development—third edition. San Antonio, TX: Harcourt assessment. Journal of Psychoeducational Assessment. 2007;25(2):180-90.