



Early Life Malnutrition Diagnose, Physical Neurological and Cognitive Sequelae: Foods to Eradicate

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Abstract

Malnutrition in India has been rampant; in women and children this affects growth, development and skilled work. Diagnostic tools to assess degree of malnutrition, by using anthropometric indices developed on the nationwide data of affluent children < 5 yr and 5 to 18 yr. of age (physical growth & sexual development). In addition, methods, were developed on blood and saliva for rapid diagnosis. The fall in salivary ferritin was found sensitive as well as non-invasive in diagnosing early protein energy malnutrition (PEM). The fall of leucocyte F α N and increase of glutamic acid in erythrocytes were also sensitive tests in PEM. Studies were undertaken in rural areas to determine degree of malnutrition and the associated-physical, neurological and cognitive, lesions. To develop treatment for acute protein energy malnutrition, studies showed that fermented milk (with lactobacillus bulgaricus and streptococcus thermophiles) Dahi had immunonutrient properties. Thus, Dahi may replace the milk in WHO diet for treatment of malnutrition. Secondly, on feeding Berseem (Trifolium Alexandria) leaves with high protein and micronutrient to PEM II & III, also showed immunonutrient properties. Therefore, we recommend addition of Berseem leaves in commercial cereals and legumes to eradicate malnutrition.

Keywords: Malnutrition; Anthropometric indices; Leucocyte F α N; Erythrocyte glutamic acid; salivary ferritin; Physical; Neurologic and Cognitive sequelae; Milk; Fermented milk Dahi; Berseem leaves

Introduction

Identify and Grade the Degree of Malnutrition in Childhood

To identify and grade the degree of childhood malnutrition, anthropometric indices were developed, given the absence of nationwide growth data in India. Growth data from affluent Indian children were collected between 1989 and 1991, covering the period from birth to 5 years in seven states. The study included only full-term infants with a birth weight of ≥ 2500 g, and assessments were conducted at 3, 6, 9, and 12 months of age, with a minimum of three readings for each infant (cohort-I). In cohort-II, 1011 boys and 874 girls were followed from 12 months to 5 years, with a minimum of three measurements taken for each child every six months up to 72 months of age. Cross-sectional

multicentric data on physical growth and sexual development were collected from affluent Indian children aged 5-17.5 years in girls and 5-18 years in boys, representing 23 schools across 9 states with a total of 12,893 boys and 10,941 girls [1-4]. These data provided the basis for Indian national growth curves and criteria for categorizing children as normal healthy, stunted, wasted, and stunted-wasted. Recognizing that body stature changes take a long time to develop in malnutrition, efforts were made to explore biochemical tests on body fluids [5]. Biochemical tests revealed significant findings. For instance, blood leucocytes (with a lifespan of 13-20 days) showed decreased F α N in hypoproteinaemia [6]. Erythrocytes (with a lifespan of 100 days) exhibited a significant increase in glutamic acid [7]. Serum and salivary arginase activity, as well as levels of salivary protein and ferritin, decreased with the severity of protein-energy malnutrition (PEM). Salivary ferritin, in particular,

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demonstrated a significant fall even in PEM grade I, with a marked decrease in grade III compared to normal children. The innovative, non-invasive salivary ferritin assay proved sensitive in recognizing the severity and early stages of PEM, making it particularly relevant for practical use in rural areas [8]. Salivary iron was found to increase in cases of hypoproteinaemia and iron deficiency [9].

Maternal malnutrition on pregnancy outcome and growth in offspring

A prospective study conducted in K V block of rural Varanasi, India, focused on the effects of maternal nutrition on pregnancy outcomes and the growth and development of offspring. Among 3,700 eligible pregnant women examined at 16, 28, and 36 ± 2 weeks of gestation, 34.6% had a birth weight <2500 g (LBW), and only 8.2% had a birth weight >3000 g (10). Notably, fundal height (FH) was <24.5 cm at 28 weeks of gestation in 1,368 women, associated with higher LBW deliveries. These women exhibited no increase in FH during 35-39 weeks and gained weight at a rate of 15-53 g/week during 35-43 weeks of gestation, with a total pregnancy weight gain of only 6.0 kg. This was considerably below the recommended 13-15 kg for normal weight gain [10].

Offspring's of intrauterine growth-retarded mothers showed hypertonia in 72% and hypo excitability in 56%. Various reflexes, such as limp posture, poor recoil of limbs, incomplete Moro's, and crossed extensor responses, demonstrated modifications [11]. EEG results indicated a shortening of sleep cycles, with marked reduction in REM sleep for babies weighing <2000 g. Inter and intra-hemispheric asymmetry and abnormal paroxysmal discharges suggested brain dysmaturity [12]. Subsequent follow-up studies in the same rural area, where 13% of children experienced severe malnutrition and 50% had moderate to mild malnutrition, revealed impaired growth and development. Gessell's developmental schedule assessments from 4 to 52 weeks of age demonstrated poor development in motor, adaptive, language, and personal-social areas for children with grades II and III malnutrition [13]. Children followed from birth to preschool years (13% severe and 50% moderate to mild malnutrition) showed that under nutrition resulted in impaired growth and development. Those with grades II and III malnutrition showed poor development in all areas of behaviour i.e., motor, adaptive, language and personal social [14].

Effect of malnutrition on social maturity and intelligence

Rural children aged 6-8 years, assessed for social maturity (Vineland Social Maturity Scale), visuomotor coordination (Bender Gestalt Test), and memory (free recall of words, pictures, and objects), displayed deficits associated with malnutrition.

These deficits were observed in social competence, visuomotor coordination, and memory, with a more pronounced impact on immediate memory. Intelligence assessments using the Wechsler Intelligence Scale for Children (WISC) showed decreasing IQ scores with the severity of malnutrition. Performance IQ and specific subtests, such as information and digit span among verbal subtests, exhibited significant decreases. The study indicated that, despite a decrease in full-scale IQ, different neuropsychological functions were affected to varying degrees. Stunting was associated with delayed development of cognitive functions and permanent cognitive impairments, with minimal improvement with age. Attention, executive functions, working memory, and visuospatial functions were more severely affected by childhood protein-energy malnutrition [15]. Even among undernourished children with an IQ >90 , perceptual maturity and conceptual grasp were impaired, suggesting learning disabilities [16]. Higher mental abilities related to personal and current information, orientation, mental control, logical memory, attention span, visual reproductive and associative learning were also affected. There was impairment in overall memory function, including set formation and conditional learning [17]. Reaction time studies demonstrated effects on perceptual abilities, information processing, and analytical capabilities. Importantly, even undernourished children who had achieved normal nutrition in later years continued to exhibit prolonged reaction times [18]. Soft neurological signs observed in preschool years, which typically disappear or reduce in school years and adolescence, persisted in early life undernourished (stunted) children. These signs included impaired repetitive speed movements with a higher degree of overflow and dysrhythmia [19]. Stunted-wasted children demonstrated soft neurological signs along with EEG changes, characterized by slow and sharp waves, particularly in the frontal lobe but also in the parietal and temporal lobes. Motor deficits were more pronounced on the contralateral side of EEG changes. Brain MRI revealed structural changes in both frontal lobes, including a reduction in size anteriorly and posteriorly, as well as a loss of asymmetry, supporting the EEG abnormalities observed in the frontal lobes [20-21]. A study on mental functions in 388 rural anemic primary school children (6-8 years of age) investigated the impact of nutrition on intelligence, attention, and concentration. Intelligence, as assessed by WISC and arithmetic tests, was not significantly affected by anemia, except for the digit span subtest. However, attention and concentration in arithmetic tests were found to be poor in anemic children [22]. Follow-up studies on rural adolescent children revealed that, although their height gain was similar to affluent Indian children, the deficit in early life height was not corrected during the adolescent growth spurt. No specific age period could be identified for peak height velocity. Weight gain was only 38% compared to affluent Indian children. In terms of sexual development, boys exhibited delayed

maturation of genitals by 1.54 years, pubic hair by 0.82 years, and auxiliary hair by 0.65 years, while testicular volume remained comparable. Rural girls experienced delayed breast development and menarche by 2.19 years and 0.82 years, respectively, compared to affluent Indian girls [4-23]. Throughout school age until 17.5 years, follow-up studies on these early-life undernourished children demonstrated that they maintained their vital functions by mobilizing amino acids from body muscles, as evidenced by increased serum enzyme activities such as LDH, ALP, AST, ALT, CK, CK-MB, and CK-mm. Phosphorus magnetic resonance spectroscopy revealed increased β -ATP and Pi in muscles at the expense of Pcr (Phosphocreatinine). These changes simulated a myopathic status [24].

Nutrition and/or iron-folate supplementation during pregnancy and childhood-one study involved 146 children receiving 450-500 calories with 10-12 gm protein in rural primary schools for 172 days (Mid-day meal) over two years. While height gain did not differ significantly, weight marginally improved. More supplemented children remained in grade I malnutrition, in contrast to the control group, which shifted to grade II malnutrition after two years. Supplemented children showed a marginal improvement in full-scale, verbal, and performance IQ (WISC), with significant improvements in all subtests except for comprehension and maze tests. Unstructured Piagetian development task, conservation of liquid also improved. The score of arithmetic achievement tests improved by 12-14 points in the supplemented group [25]. Another study involved a total of 916 pregnant women receiving nutritional supplementation in the national Integrated Child Development Programme (ICDS), which provided 600 calories with 18-20 gm protein. A control group of 1,453 pregnant women received healthcare and nutrition education, and 1,748 pregnancies from non-ICDS villages received simple healthcare. The ICDS-supplemented mothers gained 100g more in pregnancy, with birth weight increasing by 58g. The incidence of preterm and low birth weight decreased by 12.9% and 29.4%, respectively, compared to unsupplemented mothers (ICDS). Multiple regression analysis revealed that increased weight gain in pregnancy, length of gestation, caloric intake, and term haemoglobin were significantly associated with birth weight [26]. In another study, 418 pregnant women at 16-24 weeks of gestation were selected from six sub-centers of a rural block in Varanasi district. Pregnant women from three sub-centers received supplementation of 60 mg elemental iron as ferrous sulfate combined with 500 micrograms folic acid daily for 100 days (study group). A control group comprised pregnant women from the other three subcenters without supplementation. Haemoglobin and serum ferritin levels increased significantly in the study group. Mean birth weight in the study group was 2.88 +/- 0.41 kg with a low-birth-weight incidence of 20.4%, compared to control figures of 2.59 +/- 0.34 kg and 37.9%,

respectively [27]. Another study involving 40 pregnant women receiving daily and 40 receiving weekly oral therapy (335 mg of ferrous sulfate and 500 g folic acid) for 14 weeks found that weekly and daily iron supplementation were equally effective in treating anemia among pregnant women [28].

Mechanistic Studies in Animal Models

We investigated the impact of staple diets on neurological development in animal models. Rat mothers receiving wheat or lentil diets showed a dissociation of brain growth, affecting both brain and body growth equally. Fetal and weanling rat neurotransmitters were altered, only partially reversing on rehabilitation [29-30]. In a latent iron deficiency rat model, dietary iron depletion in pregnant rats reduced fetal hepatic iron and selectively reduced brain iron content in various regions. Fetal latent iron deficiency led to irreversible reductions in neurotransmitters related to glutamate metabolism, TCA-cycle enzymes, catecholamine metabolism, and serotonin metabolism. These changes were specific to iron deficiency and were not reversed with rehabilitation [31-35]. Observations from animal studies suggested that neurological and cognitive changes could be attributed to alterations in neurotransmitters. To address malnutrition, studies were conducted with Actimel (Danone) and Dahi (fermented milk), demonstrating their effectiveness in controlling diarrhea in hospitals and communities (36). Severe protein-energy malnutrition (PEM) in children was treated according to the WHO protocol (milk diet) and compared against fermented milk Dahi with *Lactobacillus bulgaricus* and *Streptococcus thermophilus* in the WHO regime to develop a better alternative to milk. Dahi, with immunonutrient properties, was found to be effective in treating and eradicating malnutrition. Berseem leaves (*Trifolium Alexandria*) with a protein content of 18-23% were also identified as a potential source of nutrition. Leaf protein concentrate (LPC) from Berseem leaves contained 20% protein and demonstrated immuno-modulating properties to control malnutrition in developing countries. These studies suggested that the WHO diet should consider incorporating fermented milk/Dahi instead of milk, and Berseem leaves (LPC) could be mixed with cereals/lentils to increase protein and micronutrient content [37-40].

Conclusion

In conclusion, this comprehensive study contributed significantly to the field of childhood and adolescent nutrition. It resulted in the development of national growth curves, a rapid and non-invasive test for malnutrition using salivary ferritin, the identification of sequelae associated with early-life malnutrition, and the exploration of potential preventative measures. The study



underscored the importance of addressing malnutrition through interventions such as fermented milk and Berseem leaves.

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