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Early Life Nutrition Deprivation and Mental Functions

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Abstract

Babies born of rural undernourished mothers, showed inter and intra hemispheric asymmetry and abnormal paroxysmal discharges, suggesting dysmaturity of brain. The under nutrition, in early life showed impaired growth as well as the conceptual and sensory development. Primary school children (6-8 years) developed impaired intelligence particularly for performance tasks. The stunted wasted children showed persistence of 'Soft Neurological Signs' with EEG changes. Those with I.Q. >90 had learning disabilities. Nutrition supplement for 2 years, in 6-8-year rural children made partial improvement, only. These children in school age (adolescence) had : a) to mobilize muscle amino acids to maintain their body functions, b) persistence of soft neurological signs, c) deficit in higher mental abilities , d) prolonged reaction time and e) brain MRI showed that both the frontal lobes reduced in size with loss of asymmetry. Anemia affected placenta, fetus, and brain functions with irreversible changes in neurotransmitters.

Keywords: Under nutrition; Intrauterine; Childhood; Growth; Intelligence; Stunted-Wasted; MR spectroscopy; EEG; Soft neurological signs; Reaction time; Brain MRI; Anemia; Neurotransmitters

Introduction

For understanding the importance of nutrition in pregnancy, it is useful to note the experience, of world war II from Leningrad (USSR) famine period 16 months, suggesting that pre-pregnancy under nutrition when faced with acute malnutrition in pregnancy-results in fall of :birth weight by 530 gm; exposure in second trimester - 50% born with birth weight <2500 gm. In contrast, Dutch famine was imposed on a previously well-nourished mothers, it reduced birth weight by 327gm, and corresponding figure for those with weight <2500gm was 9%, only. The official daily food for the general adult population gradually decreased from 1800 calories in December 1943 to 1400 calories in October 1944 to below 1000 calories in the late November 1944. December 1944 to April 1945 was the peak of the famine during which the official daily ration fell abruptly to about 400-800 calories. Even though pregnant and lactating women had extra food during the famine, these extra supplies could no longer be provided at the height of the famine. What is unique about Dutch Famine is that it was imposed on a previously well-nourished population. These two historical examples illustrate the importance of pre-pregnancy nutrition and its impact on pregnancy outcome [1]. Optimal nutrition is necessary for brain growth during 20 weeks of intrauterine life to 20 months of age. The endemic under/malnutrition (intrauterine and in early childhood) affected physical growth and development, making these children unfit for precision work in later life. Studies conducted in the Department of Pediatrics, Institute Medical Sciences, Varanasi, India, showed gravity of maternal under nutrition and its effects on feto-placental axis [2-3]. Pregnancy in undernourished rural women was associated with high pregnancy wastage; poor weight gain; reduced birth weight which improved on nutrition supplementation. These undernourished mothers were spending considerable amount of energy in hard physical workload leading to reduced birth weight and length. The fetal weight gain in last weeks of pregnancy was as low as 15-53 g /

week, simulating situation of famine [4-7]. It seems Integrated Child Development Services, in INDIA (on pattern of WISC, USA), in last 4 decades have failed to address maternal and child malnutrition.

Materials and Methods

A prospective study was conducted in the rural settings of Varanasi in the eastern Uttar Pradesh, to study the effects of maternal nutrition on pregnancy outcome, and growth and development of their offspring's. Study evaluated the birth weight pattern in chronic as well as currently undernourished pregnant women. Anthropometry, hemoglobin, dietary intake, birth weight, fundal height, and abdominal girth data of 3700 eligible pregnant women at 16 ± 2, 28 ± 2 and 36 ± 2 weeks of gestation were recorded. Outcome measure was birth weight pattern of newborns.

Results

Out of 3700 births, 34.6% were of low birth weight and only 8.2% weighed more than 3000 g. Fundal height was <24.5 cm at 28 weeks of gestation (1368 women) and was associated with higher low-birth-weight deliveries. It did not increase during 35-39 weeks of gestation (was lower by 5 cm as compared to normal).With respect to the maternal weight gain, women in later pregnancy (during 35-43 weeks of gestation) showed weekly weight gain of 15-53 g. In contrast, healthy women gained 400 g/week in the second and third trimesters. Total weight gained during the entire period of pregnancy was about 6 kg, only, whereas ideally the gain should be between 13-15 kg [4].

The intrauterine growth retarded offspring of undernourished mothers showed hypotonia in 72% and hypo excitability in 56%. There was modification of responses in several reflexes e.g. limp posture, poor recoil of limbs, incomplete Moro's and crossed extensor responses. Their EEG had shortening of sleep cycle (REM and NERM), the reduction was marked for REM in babies weighing < 2000g. There was some inter and intra hemispheric asymmetry and abnormal paroxysmal discharges, suggesting dysmaturity of brain [8,9].

In the same rural study area (IMR 133/1000 and 26% low birth weight); children followed from birth to preschool years (13% severe and 50% moderate to mild malnutrition) showed that intrauterine and early life under nutrition resulted in impaired growth and development: intelligence, behavioral, conceptual and sensory motor development in preschool years of life. Children were assessed on the Gesell's developmental schedule from 4 to 52 weeks of age. Children with grades II and III malnutrition had poor development in all areas of behavior i.e., motor, adaptive, language and personal social [10,11].

Rural children studying in primary school between the ages of 6-8 years were assessed on measures of social maturity (Vineland social maturity scale), visuo-motor coordination (Bender Gestalt test), and memory (free recall of words, pictures and objects). Malnutrition was associated with deficits of social competence, visuo-motor coordination, and memory. Malnourished boys had greater impairment of immediate memory for words, pictures, and objects, while malnourished girls had impairment of immediate memory for only pictures. Delayed recall of words and pictures of malnourished boys was impaired. Malnourished girls had an impairment of delayed recall of words, only. The same team measured the intelligence of these malnourished children using WISC (Malin's Indian adaptation of the Wechsler's intelligence scale for children). IQ scores decreased with the severity of malnutrition. Significant decreases were observed in performance IQ, as well as on the subtests of information and digit span among the verbal subtests. Study has shown that though there is decrease in full scale IQ, yet performance on all the subtests was not affected. This suggests that malnutrition may affect different neuropsychological functions to varying degrees [12].

Stunting was associated with delay in development of cognitive functions as well as in permanent cognitive impairments. Rate of development of attention, executive functions like cognitive flexibility, working memory, visuospatial functions like visual construction is more severely affected by malnutrition in childhood, a period that is marked by rapid ongoing development of cognitive functions [13].

Nutrition Supplementation-146 children received 450-500 calories with 10-12 gm protein in rural primary school for 172 days in a year for 2 years. Height gain did not differ, weight marginally improved. More supplemented children remained in grade I, in contrast to the control that shifted in grade II malnutrition after 2 years. Supplemented children showed marginal improvement in full scale, verbal, and performance I Q (WISC). Improvement was significant in all subtests except for comprehension and Maze tests. The observations on unstructured Piagetian development task conservation of liquid also improved. The scores of arithmetic achievement test improved by12-14 points in the supplemented group [14,15].

The stunted-wasted children demonstrated presence of soft neurological signs and EEG changes, in form of slow and sharp waves, particularly in the frontal lobe, but also in parietal and temporal lobes. The motor deficit was more marked on the contra lateral side of the EEG changes [16]. Among these undernourished children even those with I Q > 90 showed impaired perceptual maturity and conceptual grasp, suggesting learning disability [17].

These undernourished rural children of age 10–12 years demonstrated the following, when compared to normal nourished children: (i) a relative deficit of memory quotients assessed by the Wechsler memory scale; (ii) lower scores for abilities related to personal and current information, orientation, mental control,

logical memory, digit span, visual reproduction and associative learning; (iii) impaired set formation and flexibility in attention as assessed by the card sorting test; and (iv) impairment in conditional learning on maze and conditional associative learning tests. The performance on the finger dexterity test for fine motor coordination was not affected in undernourished children [18].

The follow up studies on these early life undernourished school children until 17.5 years of age showed that they maintained their vital functions by mobilizing amino acids from body muscles as demonstrated biochemically by increased serum enzyme activities i.e. LDH, ALP, AST, ALT, CK, CK-MB and CK-mm. 31-phosphorus magnetic resonance spectroscopy showed that β -ATP and Pi in muscles was significantly increased at the cost of Pcr (Phosphocreatinine). These changes simulate myopathic status [19]. The Brain MRI and cognitive evoked potential studies- Frontal lobes- size was reduced and asymmetry of anterior as well as posterior lobes was less pronounced. P3 latency was normal, but the P2 and P3 amplitudes were higher suggesting neuronal compensation [20].

Soft neurological signs observed in preschool years, normally disappear, or reduce in school years / adolescence. However, early life undernourished (stunted) children, showed

persistence of impaired repetitive speed movements with higher degree of overflow and dysrhythmia. There was deficit in higher mental abilities- related to personal and current information, orientation, mental control, logical memory, attention span, visual reproductive and associative learning: impairment in overall memory function in set formation and conditional learning [21].

Reaction time studies showed effects on perceptual abilities, information processing and analytical capabilities. It is important to note that early life undernourished children continued to have prolonged reaction time, even if they had attained normal nutritional status in later years [22].

The fetal brains of rat mothers fed wheat or Bengal gram diets showed: i) dissociation of brain growth (brain and body growth equally affected) and ii) fetal and weanling rat neurotransmitters were altered, however, were reversible to some extent on rehabilitation [23,24].

These studies raised question about Effects of maternal anemia (iron deficiency) on feto placental axis

The prevalence of anemia in the states of Assam, Himachal Pradesh, Madhya Pradesh, Orissa, Kerala, and Tamil Nadu, during 2002-2003. The study observed that 86.1% of pregnant women had anemia, with 9.5% of women having Hb< 7.0 g/dl and 81.7% of women lactating up to 3 months had anemia, with 7.3% having Hb<7.0 g/dl [25]. Even the results from 1st phase of the National Family Health Survey (NFHS-4), 2015-2016, which evaluated maternal and child health and nutrition in 13 states (viz., Andhra Pradesh, Madhya Pradesh, Goa, Bihar, Haryana, Karnataka, Meghalaya, Tamil Nadu, Sikkim, Telangana, Tripura, Uttarakhand, and West Bengal) and two union territories (viz. Puducherry and Andaman and Nicobar Islands)reflected that more than 50% of children in 10 of the 15 states/union territories and greater than 50% of women in 11 states/union territories are anemic [26].

The process of iron transport is purely a placental function over which mother and fetus has no control, as placenta continues to trap iron even when fetus is removed in animals. In maternal hypoferremia it was observed that a) transport of iron from mother to fetus through placenta remains at a gradient, but proportionate to the degree of maternal hypoferriemia; b) iron content in placenta reduced, and showed qualitative decrease in villous surface area, volume of villi and length of blood vessel, while surface area and volume of intervillous space was increased. These placental changes in anemia did not normalize on rehabilitation- suggesting “Maturational arrest”; c) the Fetal Liver - iron stores were reduced significantly in maternal hypoferremia [27-29] and d) Breast milk -physiological trapping- iron content is increased in hypoferriemia mothers [30].

Anemia in Children

Mental functions in 388 rural anemic primary school children (nutrition controlled) 6-8 yr of age, matched for social and educational status were studied by WISC and arithmetic test to assess “Intelligence, Attention and Concentration”. Anemia did not affect intelligence, except subtest-digit span. In Arithmetic test Attention and Concentration was poor in anemic children [31].

Studies in children 8-12 years of age having anemia (nutritional, serum ferritin <20ng) vs (thalassemia, serum ferritin >1000ng), on brain MRI spectroscopy showed similar iron content in globus pallidus, caudate and dentate nucleus in both the conditions. There was an increase in creatinine and aspartate and reduction in choline concentration. Such changes are also observed in Huntington’s chorea and Alzheimer’s disease. Reduction of choline, in iron deficiency is a significant effect. Choline is synthesized in the brain in very small amounts; its uptake is Na+ dependent, which requires oxygen [32].

Latent Iron deficiency in rat model

Dietary iron depletion in pregnant rats- reduced fetal hepatic iron and selectively brain iron content [33]

- Cerebral cortex 17%, Cerebellum 18%, Hypothalamus 19%, Mid brain 21%, and Corpus striatum 32%, but no change in – medulla oblongata and pons.
- Fetal brain iron content did not change after maternal “Fe” supplementation.

- Low brain "Fe" content was associated with significant alteration in brain Cu, Zn, Ca, Mn, Pb and Cd levels.

Fetal Latent Iron Deficiency- brain neurotransmitters showed-irreversible reduction. Glutamate metabolism- GAD, GDH, GABA-T and their receptors-binding, showed irreversible deficit in both excitatory and inhibitory pathways of the CNS, TCA-cycle enzymes-mitochondrial NAD+ linked dehydrogenase, Catecholamine metabolism- Whole brain-dopamine, nor epinephrine, tyrosine and TAT. Corpus striatum – same as in whole brain, except TAT increased. 5-HT metabolism-Tryptophan, 5-HT, 5-HIAA. The irreversible neurotransmitter changes were specific to "Fe" deficiency as in under nutrition, get corrected partially or completely on rehabilitation.

Today

For a country that the FAO describes as "the world's largest producer of milk and pulses" and "the second largest producer of rice, wheat, sugarcane, groundnut, vegetables and fruits", it's a tragic irony to highlight, that not only does India lose close to a million children under the age of 5 years to malnutrition (primarily) but also ranks among the lowest on the Global Hunger Index in South Asia (Times Of India, 16th Oct 2019-World Food Day).

India accounts for the second highest death rate of children under 5 years due to environmental risks - mainly pollution and poor sanitation - in the WHO south east Asia region which includes Bangladesh, Indonesia, and Bhutan. In fact, India fares far worse than China and is among the top 35 countries in the world with highest death rate among under-5 year's children, attributable to unhealthy environment. The health burden of poor water quality is enormous. It is estimated that around 37.7 million Indians are affected by waterborne diseases annually; 1.5 million children are estimated to die of diarrhea, alone.

Recently, India has distributed free food to over 6o% population (800 million), tried to provide water and practice hand washing, sanitizer use in Covid-19 year. Let us see how much improvement is achieved in nutritional status and reduction in mortalities (maternal, neonatal and children under 5 yr.).

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