

Adverse Effects of Poor Micronutrient Status During Childhood and Adolescence

Umesh Kapil, M.D., A Bhavna, M.Sc.

Despite India's substantial progress in human development since its independence in 1947, 5-7% of its children have vitamin A deficiency disorders in selected geographic areas, 53% have iron deficiency anemia, and 9% have goiter. Three micronutrients—vitamin A, iron, and iodine—are among the most important of all the nutrients needed by the body because they are vital for developing normal learning and cognitive functions, immunity, work capacity, and reproductive health. The body cannot synthesize them, so they must be made available through the diet. Deficiencies of these three micronutrients are known to have devastating effects on health.

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Introduction

Deficiencies of three micronutrients—vitamin A, iron, and iodine—are widespread in India. To call them micronutrients may be in conformity with the minute quantities needed by the human body, but it is certainly not consistent with the nature and extent of damage being caused by these deficiencies. Micronutrient deficiencies are a major impediment to the good health and nutrition status and development of a significant proportion of Indian children. This paper focuses on adverse effects of these three micronutrients that are responsible for significant mortality and morbidity, especially among women and children.

Vitamin A

Vitamin A is an essential nutrient needed in small amounts for growth and development, the normal functioning of the visual system, maintenance of epithelial cellular integrity, immune function, and reproduction. Vitamin A per se is obtained only from animal sources, while the carotenoid precursors are supplied in abun-

dance by dark green leafy vegetables, deep yellow and orange vegetables, and fruits with yellow or orange pulp. Being fat soluble, vitamin A is stored in the body when its intake exceeds physiologic needs. Nearly 90% of vitamin A stores are found in the liver. Depletion of these stores can occur when the dietary content of vitamin A is insufficient to replace the amounts used by the tissues or used during breastfeeding.¹ Although vitamin A deficiency (VAD) can occur in any age group, the most serious effects are seen in preschool children. Vitamin requirements are greatest at this age because of rapid growth, but dietary intake is precarious and illnesses such as diarrhea, acute respiratory infections (ARIs), and measles commonly deplete vitamin A stores. These conditions make children under the age of 5 most susceptible to the ravages of VAD.²

Magnitude of the Problem

Surveys carried out in different parts of the country during the early 1970s showed that 5-7% of all Indian children suffer from varying degrees of eye disorders associated with VAD.³ Although the prevalence rates were higher in school-aged children than in younger age groups, severe forms of the deficiency that result in blindness are confined to children under 3 years of age. Recent surveys conducted by the National Nutrition Monitoring Bureau (NNMB) in 10 Indian states showed a reduction in the prevalence of Bitot's spots from 2% in 1979 to about 0.7% in 1990.⁴ Although the national averages show a decline, there is a wide variation in the prevalence between the states and within the states. The prevalence rates of VAD among preschool children in different states are shown in Tables 1 and 2. A national blindness survey carried out by the Indian Council of Medical Research (ICMR) in 1974 showed that about 2% of total blindness in the country was due to VAD.⁵ The most recent survey of blindness, carried out under the auspices of the Indian government and WHO,⁶ showed that no more than 0.04% of all cases of blindness in the country could be attributed to vitamin A deficiency. Cases of functional blindness (visual acuity of the better eye 3/60; functional blindness being defined as visual acuity of the better eye being less than or equal

Dr. Kapil is with the Department of Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.

Table 1. Percent Prevalence of Bitot's Spots in Preschool Children

States	1975-1979 (n = 12775)	1988-1990 (n = 11535)
Andhra Pradesh	3.1	1.0
Gujarat	0.9	0.5
Karnataka	2.3	1.1
Kerala	0.1	0.5
Madhya Pradesh	0.4	NA
Maharashtra	0.4	0.3
Orissa	1.5	1.1
Tamil Nadu	2.9	0.6
Pooled data	1.8	0.7

Source: National Child Survival and Safe Motherhood Programme. Programme Interventions Child Survival. Maternal and Child Health Division, Ministry of Health and Family Welfare, Government of India, New Delhi, June 1994.

to 3/60) from all causes together accounted for 1.07% of the population (thus indicating that keratomalacia could have accounted for blindness in just .004% of the population). Even if we allow for the high mortality among victims of keratomalacia, these survey data would indicate that keratomalacia is currently an insignificant factor in the causation of blindness in India.

Data from the School of Tropical Medicine in Calcutta, which was once the hotbed of keratomalacia, and from the Christian Medical College, Vellore, a leading center known for its studies on problems of vitamin A deficiency and undernutrition in children, are also suggestive of a sharp reduction in the incidence of keratomalacia (Table 3). In fact, a careful scrutiny of hospital data from Calcutta suggests that the decline in the incidence of keratomalacia had started even before the massive dose vitamin A prophylaxis program had been instituted.^{7,8}

There have been five major field studies on the effects of vitamin A administration on child mortality in Southeast Asian Region (SEAR) countries: (1) Sommer et al. in Indonesia,⁹ (2) Rahmathullah et al. in India,¹⁰ (3) Vijayaraghavan et al. in India,¹¹ (4) West et al. in Nepal,¹² and (5) Agarwal et al. in India.¹³ Two of these studies (by Vijayaraghavan et al.¹¹ at the National Institute of Nutrition and by Agarwal et al.)¹³ showed that there was no significant reduction in child mortality as a result of vitamin A administration. On the other hand, Sommer et al.⁹ and Rahmathullah et al.¹⁰ have claimed significant reduction in child mortality following administration of vitamin A, the former with massive doses at six-month intervals and the latter with smaller doses at weekly intervals. West et al.¹² found that vitamin A reduced the mortality risk from diarrheal diseases but increased the mortality risk from respiratory diseases, and that the overall effect was a significant reduction in

mortality. These studies, which were expensive exercises, generated controversy and confusion. The drawbacks of the studies that showed reductions in mortality, and the reasons the conclusions are untenable, have been discussed in several earlier publications.¹³⁻¹⁷

Health Consequences of Vitamin A Deficiency Disorders

Deficiency of vitamin A has long been known to be the most common preventable cause of blindness among children. But only recently has it become evident that vitamin A plays important roles in ensuring protection against infections and maintaining many normal body functions, especially body immunity.³ Mortality in childhood and infancy, as well as even intrauterine fetal loss, have been associated with vitamin A deficiency.

The integrity of epithelial barriers and the immune system are compromised before the visual system is impaired. This leads to increased severity of some infections and the risk of death, especially among children.¹⁸ When vitamin A depletion is sufficient to affect the visual system, night blindness, or the inability to see in dim light, occurs. On deterioration, this stage leads to xerophthalmia, which affects both conjunctiva and cornea. If unattended, corneal ulceration results and may lead to partial or total blindness (keratomalacia).¹⁹

In severe VAD, such as that resulting in keratomalacia, the mortality rate is as high as 60%. Lowered resistance to infections due to VAD has been observed in children even before eye symptoms appear. Vitamin A intervention in deficient children has been shown to restore cell-mediated immune response and enhance antibody response as well as macrophage functions, suggesting an immunopotential effect of vitamin A. Children with even mild VAD have a threefold higher risk of diarrhea, twofold higher risk of ARIs, and 6 to 9 times greater risk of death.¹⁹ In developing countries, diarrhea,

Table 2. Prevalence Rate of Vitamin A Deficiency in Children 0-6 Years of Age (National Survey 1986-1989)

Rate	State/Union Territories (Uts)
<1%	Kerala, Meghalaya, Sikkim Andhra Pradesh, Karnataka, Manipur, Orissa, Punjab, Chandigarh,
<1-3%	Lakshadweep, Mizoram Haryana, Himachal Pradesh, J&K, Maharashtra Mizoram, Nagaland, Tamil Nadu, Arunachal Pradesh Delhi, Goa,
3-6%	Pondicherry Assam, Bihar, Gujarat, Madhya Pradesh, Rajasthan, Tripura, Uttar Pradesh, West
>6%	Bengal, Andaman & Nicobar Islands

Table 3. Annual Incidence of Keratomalacia Cases in Leading Indian Hospitals (percentages in parentheses)

Hospital	Year	All Cases	Cases of Keratomalacia
Tropical Paediatrics Clinic	1964–1972 ⁷	1070	8.5 (average)
School of Tropical Medicine, Calcutta	1974–1985 ⁷	995	1.3 (average)
	1987 ⁸	1160	0
	1988 ⁸	1120	0
Christian Medical College, Vellore	1960 ⁸	13,641	5 (0.37)
	1970	21,844	6 (0.028)
	1981	28,931	5 (0.017)
	1984	31,137	3 (0.009)
	1987	35,377	0
	1989	37,219	3 (0.008)

ARI, and measles account for 58% of deaths among children under five years of age.

Iron

Iron deficiency anemia (IDA) is an important public health problem resulting in considerable morbidity and mortality in women and young children. Its impact on psychological and physical development, behavior, and work performance is phenomenal.²⁰ Iron deficiency anemia is defined as a condition in which the hemoglobin (Hb) concentration or hematocrit (Hct) of an individual is lower than the level considered normal for the person's age and sex group. The World Health Organization (WHO) has outlined criteria for the diagnosis of anemia (Table 4) for various age and sex groups. Anemia is considered to be mild when Hb concentrations are above 10 g/dL, but below the cut-off value; moderate when the concentration is between 7 and 10 g/dL; and severe when it is below 7 g/dL.²¹ Iron deficiency and its resultant anemia is currently the most widespread micronutrient deficiency in the world.

Magnitude of Iron Deficiency Anemia

Young children and pregnant women are the most affected, with an estimated global prevalence of 43% and 51%, respectively.²⁰ The condition is considerably more prevalent in the developing world (36%) than in the industrialized world (8%).²¹ Africa and South Asia have the highest overall regional prevalence rates. Except for adult males, the estimated prevalence of anemia in all groups is more than 40% in both regions and is as high as 65% in pregnant women in South Asia.²⁰ In India, IDA affects more than half the total population. Pregnant and lactating women and young children are affected most. In a study by the ICMR, about 53% of children were found to be suffering from anemia.²² Children under the age of three years had a higher prevalence compared with peers between the ages of three and five years (63% versus 44%).²³ Children between 1 and 6

years of age in major cities were found to have a high prevalence rate (64.8%) (Table 5).²⁴ There were no sex-related differences in prevalence in children 3 to 5 years of age. In children over the age of six, however, the prevalence rates were higher in girls compared with boys. With increasing age, the prevalence rate declines in males, while such a reduction does not occur in females.^{23,25} Estimates suggest that about 25–50% of girls become anemic by the time they reach menarche and both rural and urban girls are similarly affected.^{23,25,26} A collaborative study done in women in rural areas has shown the prevalence of anemia to range from 20.8% to 96.9%.²⁷

Health Consequences of IDA

Long before its cause was known, the pallor of anemia was associated with weakness and tiredness. It is now recognized that mild to moderate iron deficiency, even without anemia, has adverse functional consequences, although the effects are less obvious. It adversely affects the cognitive performance, behavior, and growth of infants, preschool, and school-aged children; the use of energy sources by muscle and thereby the physical capacity and work performance of adolescents and adults; and immune status and morbidity from infections in all age groups. Iron deficiency anemia also limits the maintenance of body temperature in individuals exposed to a cool environment. Iron-deficient animals and humans

Table 4. WHO Criteria for Diagnosis of Anemia

Age/Sex Group	Hb (g/dL)
Children 6 months–6 years	<11
Children 6–14 years	<12
Adult males	<13
Adult females (nonpregnant)	<12
Adult females (pregnant)	<11

Source: DeMayer EM, Dallman P, Gurney JM, et al. Preventing and controlling iron deficiency anemia through primary healthcare. WHO, Geneva, 1989.

Table 5. Percent Prevalence (%) of Anemia in India

Location	1-6 years		6-14 years		14-25 years	
	Boys	+ Girls	Boys	Girls	Boys	Girls
Hyderabad & Delhi (rural)		44.4	67.1	64.8	57.7	65.9
Calcutta (rural)		90.3	96.7	92.8	92.9	97.1
Madras (rural)		9.3	20.8	22.1	11.6	15.0

Source: Food and Nutrition Board Government of India, and UNICEF Regional Office for South East Asia. The use of common salt fortified with iron. A Report on Collaborative Study, 1981.

have altered hormonal production and metabolism, including changes in neurotransmitter and thyroidal hormones that are associated with neurologic, muscular, and temperature regulatory alterations.²⁸

Milder degrees of anemia with iron and folate deficiency are associated with low birth weights and placental hypertrophy. Nearly half of low-birth-weight infants are born to anemic women. Anemia is believed to be the contributing factor in the increased incidence of genitourinary infections during pregnancy. Puerperal sepsis has been found to be three to four times higher in severe anemic women compared with those with milder degrees of anemia. Of 500,000 maternal deaths ascribed to childbirth and puerperium every year, essentially all of these occur in the less developed countries, in which anemia is the major contributor to 20-40% of such deaths.²⁹ It is also estimated that at childbirth, anemia may raise the risk of maternal death by 500% and infant death by 600%. Infants born to anemic mothers have less than half the iron reserves of those born to non-iron-deficient mothers. This disadvantage places the infant at serious risk of becoming anemic during early infancy and of suffering long-term consequences in health and development. There are many consequences of iron deficiency, and especially iron deficiency anemia, in infants and children, including impaired motor development and coordination, impaired language development and scholastic achievement, psychological and behavioral effects, and decreased physical activity.^{23,25,26,29} In adults of both sexes, iron deficiency anemia can result in decreased physical work and earning capacity and decreased resistance to fatigue.^{30,31} In pregnant women, iron deficiency anemia can lead to increased maternal morbidity and mortality, increased fetal morbidity and mortality, and increased risk of low-birth-weight babies.³²⁻³⁶

There is a growing body of evidence, based on animal studies, that iron deficiency adversely affects the immune system even before the level of frank anemia is reached. Defects in cell-mediated immunity and in ability to kill bacteria have been well demonstrated. Some of the important adverse effects are:

Physical work performance. Minimal work capacity, work output, and endurance are impaired in iron defi-

ciency. This is proportional to the severity of anemia and is corrected by iron therapy. Aerobic capacity in anemic children is reduced and anaerobic metabolism makes a greater contribution to the stress of exercise, resulting in early fatigue.

Mental and psychomotor functions. There are studies to suggest that children with anemia or even mild iron deficiency show poor attentiveness, memory, and academic performance in the areas of vocabulary, reading, and knowledge. Children with iron deficiency perform less well on standardized scholastic tests and have impaired motor development.

Growth retardation. Weights of children with iron deficiency anemia are below normal at the time of diagnosis. Rapid weight gain following iron therapy has been reported.³⁷

Immune response. Defects in the cell-mediated immunity and in bactericidal capabilities have been well documented. Morbidity from infectious diseases is increased in an iron-deficient population.³⁸

Temperature regulation. In both experimental animals and human subjects, those with iron deficiency anemia more readily become hypothermic and have depressed thyroid function.³⁹ This may explain some of the discomfort from cold felt by poorly nourished individuals at temperatures in which well-nourished persons are comfortable.

Iodine

Unlike nutrients such as iron, calcium, or the vitamins, iodine does not occur naturally in specific foods. Rather, it is present in the soil and is ingested through foods grown on that soil. Iodine deficiency results from inadequate content of iodine in the earth's crust. Soils in mountain ranges, such as the Himalayas, Alps, and Andes, and in areas with frequent flooding, are particularly likely to be iodine deficient.⁴⁰ The problem is aggravated by accelerated deforestation and soil erosion. This deficiency in the soil cannot be corrected and the food grown in iodine-deficient regions can never provide enough iodine to the population and livestock living there. Living on the seacoast does not guarantee iodine sufficiency, and significant pockets of iodine deficiency

Table 6. The Spectrum of Iodine Deficiency Disorders

Stage in Life	Health Effects
Fetus	Abortions Stillbirths Congenital anomalies Increased perinatal mortality Increased infant mortality Neurologic cretinism: mental deficiency deaf mutism dwarfism Myxedematous cretinism mental deficiency deaf mutism
Psychomotor Defects	
Neonate	Neonatal goiter Neonatal hypothyroidism
Child and Adolescent	Goiter Juvenile hypothyroidism Impaired mental function Retarded physical development
Adult	Goiter with complications Hypothyroidism Impaired mental function

Source: Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, 2001.

have been reported from the Azores, Bombay, Bangkok, and Manila. A recent WHO/UNICEF/ICCIDD report estimates that currently at least 1.5 billion people (or 29% of the world's population) live in areas of iodine deficiency and need some form of iodine supplementation. Most of these are in developing countries in Africa, Asia, and Latin America, but large parts of Europe are also vulnerable.⁴¹

Magnitude of Iodine Deficiency Disorders

Iodine deficiency disorders are known to be a significant public health problem in 118 countries. At least 1572 million people worldwide are estimated to be at risk of IDD because they live in areas where iodine deficiency is prevalent (total goiter rates above 5%), and at least 655 million of these are affected by goiter.^{42,43}

In India, iodine deficiency disorders are present throughout the country. Of 275 districts surveyed by government of India institutions, Indian Council of Medical Research, and Central Goiter Survey Teams in different states and union territories, 235 have been found to be endemic for iodine deficiency disorders.^{42,43}

Consequences of Iodine Deficiency Disorders

Healthy humans require iodine, and it is an essential component of the thyroid hormones thyroxine and triiodothyronine. Inadequate iodine leads to insufficient pro-

duction of these hormones, which affect many different parts of the body, particularly muscle, heart, liver, kidney, and the developing brain. Inadequate hormone production adversely affects these tissues, resulting in the disease states collectively known as the iodine deficiency disorders, or IDD (Table 6). These consequences include: (1) mental retardation, (2) other defects in development of the nervous system, (3) goiter, (4) physical sluggishness, (5) growth retardation, (6) reproductive failure, (7) increased childhood mortality, and (8) economic stagnation. The most devastating of these consequences affect the developing human brain.⁴⁴

Mental retardation. Iodine deficiency has been called the world's major cause of preventable mental retardation. Its severity can vary from mild intellectual blunting to frank cretinism, a condition that includes gross mental retardation, deaf mutism, short stature, and various other abnormalities. In areas of severe iodine deficiency, the majority of individuals risk some degree of mental impairment. The damage to the developing brain results in individuals poorly equipped to learn, work effectively, fight disease, or reproduce satisfactorily.

Goiter. Goiter is another important consequence of iodine deficiency. In this instance, thyroid enlargement can be viewed as an attempt to compensate for inadequate hormone production by the thyroid, which, in turn, is a consequence of insufficient iodine for hormone synthesis. The pituitary gland at the base of the brain secretes its own hormone, thyroid-stimulating hormone (TSH), in response to the levels of thyroid hormone circulating in the blood. When thyroid hormone production is low, the pituitary secretes more TSH. This increased stimulation causes thyroid enlargement.⁴⁵

Cretinism. Severe iodine deficiency in pregnant mothers leads to poor development in the brains of newborns. These children are called cretins. There are two types of cretins, neurological cretins and myxoedematous cretins. Typically, neurologic cretins are extremely mentally retarded and most are reduced to a vegetative existence. Most are deaf mute and many have impaired voluntary motor activity, usually involving paresis or paralysis of pyramidal origin, chiefly in the lower limbs, with hypertonia, clonus, and plantar coetaneous reflexes in extension, and occasionally extra pyramidal signs; spastic or ataxic gait (in severe cases, walking or even standing is impossible); and strabismus (squint). In milder cases, individuals have varying degrees of impaired motor coordination, such as the inability to play games, and they are clinically euthyroid. There is less mental retardation among typical myxoedematous cretins and they may be capable of performing simple manual tasks.^{44,45}

Neonatal Hypothyroidism. Signs of long-standing

Table 7. Incidence of Neonatal Hypothyroidism in Three Endemic Goiter Districts of Uttar Pradesh State, India, Before and After Successful Salt Iodization¹

District	Incidence per 1000 births
	Preiodation
Deoria	133
16	
Gonda	75
9	
Gorakhpur	85
17	

¹ Data on the basis of 5500 newborns in the three districts screened so far (studies are continuing). Source: Kochupillai N. Neonatal hypothyroidism in India.⁴⁷

hypothyroidism include dwarfism, myxoedema, dry skin, sparse hair, retarded sexual development, and retarded maturation of body proportions and naso-orbital configuration. The clinical picture is confirmed by extremely low levels of serum T4 and T3, low thyroidal uptake of radioiodine, and very high levels of serum TSH. Lesser degrees of hypothyroidism have fewer clinical signs and biochemical abnormalities.^{44,45} Using radioimmunoassay techniques, Kochupillai⁴⁶ in India showed that the incidence of neonatal hypothyroidism in endemic goiter regions is more than a 100-fold higher than in nonendemic regions. This finding has given much needed momentum to the goiter prophylaxis program by revealing a dimension of the problem hitherto not well appreciated. In highly endemic areas of the country, with the introduction of the salt iodation program, the incidence of neonatal hypothyroidism was found to have declined impressively (Table 7).

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