REVIEW ARTICLE IJD

Nutritional dermatoses in pediatric age group: an approach to clinical diagnosis

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Diet plays a critical role in the maintenance of various physiological functions in cutaneous structures. Inadequacy of a well-balanced diet gives rise to a constellation of skin manifestations, which are frequently mild and non-specific; hence, overlooked or misdiagnosed. However, it can lead to serious complications. This group of dermatoses affects both developing and developed countries. Children, in particular, are more prone due to increased demand for nutrients for growth and development, as well as negligence or inability to provide by the caretaker. The dermatologist might be the first physician to come across such patients since cutaneous features are more apparent. Hence, a strong clinical suspicion for multiple micro- or macro-nutrient deficiencies should be maintained since many conditions may have overlapping presentations such as xerosis, periorificial and intertriginous dermatitis, photo-distributed dermatitis, seborrheic dermatitis-like lesions, follicular hyperkeratosis, intracutaneous hemorrhages, impaired wound healing, pigmentary changes, and others including mucosal manifestations and hair and nail changes. This review article discussed an approach to nutritional dermatoses in the pediatric age group to aid in accurate diagnosis and timely treatment.

Keywords: nutrition, skin diseases, nutritional deficiencies, pediatric

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INTRODUCTION

Malnutrition is defined by WHO as "deficiencies, excess or imbalance in a person's intake of energy and/or nutrients" [1]. The major causes of deficiency in developing countries, such as India, include a lack of access to nutritious foods and a balanced diet, as well as poverty and poor intake. On the other hand, these disorders are common in developed countries, in which individuals follow restricted diets, and have anorexia, bulimia, malabsorption disorders, or other chronic diseases [2,3]. The pediatric age group is the most vulnerable to its effects due to a higher demand for micro- and macro-nutrients, and failure to meet this demand can result in altered immunity, long-term developmental delays, and increased mortality [1]. Cutaneous changes are among the most frequently encountered manifestations of these deficiencies, and they are generally neglected or misdiagnosed. This review focused on cutaneous manifestations of nutritional deficiencies in the pediatric age group.

General Features

Childhood is a crucial phase for proper growth and development. A lack of a balanced diet that

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includes adequate amounts of macronutrients as well as micronutrients might impede these milestones and lead to wasting, underweight, and stunting; all of which can have long-term detrimental consequences [4].

Table 1 enlists the various causes of nutritional deficiencies in the pediatric age group [2,3,5-12].

Failure to thrive and growth retardation is seen in protein-energy malnutrition, which includes

Table 1. Causes of nutritional deficiencies in pediatric age group [2,3,5-12]

Nutrient Deficiency	Cause
Protein-Energy Malnutrition	• Poverty, food shortage • Psychiatric or developmental disability • Chronic illness, post-gastrointestinal surgery
Essential Fatty Acid Deficiency	• Total parenteral nutrition without fat supplementation • Low-fat or restricted diets, anorexia nervosa • Prematurity • Fat malabsorption- Cystic fibrosis, biliary atresia, pancreatic insufficiency
Vitamin A Deficiency	• Vegetarian and low-fat diet • Eating disorders, autism • Chronic diarrhea, inflammatory bowel disease • Fat malabsorption- Pancreatic insufficiency, biliary disease, cystic fibrosis • Medications- Corticosteroids
Vitamin B1 (Thiamine) Deficiency	• Consumption of polished rice and cassava as a staple diet (low in thiamine) • High carbohydrate intake • Exclusively breastfed infants of thiamine-deficient mothers • Abnormal intestinal flora in SAM (Severe dermatitis, atopy, and metabolic syndrome) (reduced thiamine uptake) • Patients in intensive care or who are severely ill
Vitamin B2 (Riboflavin) Deficiency	• Low-dairy diets, vegetarians • Premature infants • Mothers with low vitamin B2 levels • Neonates on phototherapy for hyperbilirubinemia • Hypothyroidism • Medications- Long-term antibiotics, chlorpromazine
Vitamin B3 (Niacin) Deficiency	• Malabsorption- Colitis, ileitis, chronic diarrhea, gastrectomy, Crohn's disease • A staple diet containing maize and jowar • Medications- Isoniazid, pyrazinamide, 6-mercaptopurine, 5-fluorouracil, ethionamide, phenobarbital, azathioprine, chloramphenicol • Carcinoid syndrome • Hartnup disease
Vitamin B6 (Pyridoxine) Deficiency	• Renal insufficiency, cirrhosis • Medications- Isoniazid, penicillamine, hydralazine, antiepileptics
Vitamin B9 (Folic Acid) Deficiency	• Decreased intake, poor utilization • Concurrent vitamin B12 deficiency • Medications- Phenytoin, carbamazepine, some antibiotics (trimethoprim)
Vitamin B12 (Cyanocobalamin) Deficiency	• Mother with vitamin B12 deficiency • Malabsorption- Tropical sprue, enteritis, tuberculosis • Microbial competition- Intestinal bacterial overgrowth, infection with Diphyllobothrium latum • Pernicious anemia, gastrectomy, Crohn's disease
Vitamin C Deficiency	• Anorexia, food allergies • Neuropsychiatric, developmental disorders • Exclusive meat-based diets • Infants fed with evaporated or boiled milk- Barlow's disease • Second-hand smoke exposure • Antibiotic use • Viral infection, fever, stress • Patients on dialysis (vitamin C eliminated during the process)
Vitamin D Deficiency	• Exclusive breast-feeding • Reduced intake- Restricted diets, vegans, lactose intolerance • Reduced sun exposure • Obesity • Chronic renal and hepatic disease • Malabsorption- Crohn's disease, celiac disease, short bowel syndrome, cystic fibrosis • Medications- Anticonvulsants, rifampicin, corticosteroids, spironolactone, clotrimazole, nifedipine, cholestyramine

Table 1. Continued

Nutrient Deficiency	Cause
Vitamin E Deficiency	• Fat malabsorption- Pancreatic insufficiency, biliary disease • Second-hand smoke exposure
Vitamin K Deficiency	• Hemorrhagic disease of newborn (preterm infants more commonly affected) - Placenta does not transmit lipids and lipid-soluble vitamins, and the gut is initially sterile • Long-term antibiotic use • Fat malabsorption - Ileitis, tropical sprue, cystic • fibrosis, celiac disease, hepatobiliary diseases • Drugs- Warfarin, carbamazepine, phenytoin, barbiturates, cephalosporin, rifampicin, isoniazid
Biotin Deficiency	Inherited: • Neonatal or early onset- Holocarboxylase synthetase deficiency • Juvenile or late-onset- Biotinidase or sodium-dependent multivitamin transporter deficiency Acquired: • Low dietary intake, exclusive breast-feeding beyond 6 months • Total parenteral nutrition with inadequate supplementation • Drugs- Long-term antibiotics, anticonvulsants (carbamazepine, valproic acid, phenytoin) • Short-bowel syndrome • Excessive ingestion of raw egg whites (Contains avidin - glycoprotein which binds biotin)
Zinc Deficiency	Inherited: • Acrodermatitis enteropathica (autosomal recessive)- Mutation in SLC39A4 on chromosome 8q24.3 encoding ZIP4-transporter → Defective zinc absorption in the small intestine • Transient neonatal zinc deficiency (TNZD) (autosomal dominant)- Mutation in SLC30A2 encoding ZnT2 in mother → Decreased zinc secretion in breast milk → Deficiency in breastfed infants Acquired: • Inadequate intake- Vegetarian diet, anorexia nervosa • Preterm infants • Down syndrome, congenital thymus defects • Inflammatory bowel disease, chronic diarrhea, cystic fibrosis, copper or iron intake • Medication → Penicillamine, valproate • Increase elimination- Renal disease, diuretics, hemodialysis
Iron Deficiency	• Pre-term or low birth weight neonates • Decreased dietary iron intake and absorption • Menstruation • Active gastrointestinal bleeding, intestinal parasites (e.g., Ancylostoma duodenale)
Copper Deficiency	• Menkes kinky hair syndrome- X-linked recessive disorder of copper metabolism • Acquired causes (rare)- Infants with protein-energy malnutrition, strict cow's milk diet, gastrectomy, chronic zinc ingestion

marasmus and kwashiorkor, essential fatty acid deficiency, vitamin A, B1, and C deficiency, and certain micronutrient deficiencies such as zinc and copper [2,13].

Among the two entities comprising protein-energy malnutrition, patients with marasmus have a history of prolonged protein and calorie deficiency, while kwashiorkor is caused by periods of low protein in the diet and normal calorie intake. A child with marasmus appears emaciated, with loss of subcutaneous fat and a significant reduction in weight-for-height; weight is less than 60% of normal for that age. The child is usually alert, and may subsequently exhibit lethargy, hypothermia, and bradycardia. Children under the age of two are at higher risk [2,13]. Kwashiorkor, on the other hand, manifests with edema due to hypoalbuminemia, resulting in the appearance of "full faces". The "pot-belly" appearance is secondary to fatty infiltration of the liver. The subcutaneous fat is preserved, although muscle atrophy is evident. The body weight is generally more than 60% than what is normal for the age. Initially, the child is irritable, and as the condition progresses, they become lethargic. They also have anorexia, diarrhea, and can develop sepsis as a result of deficient immunoglobulin synthesis [2,3,5].

An irritable child can be seen in other nutrient deficiencies such as vitamin B1, B6, and zinc, whereas a lethargic child may have hypervitaminosis A, vitamin C, biotin, and copper deficiency [2,3].

Most nutritional dermatoses show no preference for age or sex. A major exception is iron deficiency, which is commonly seen in adolescent females during puberty due to menstruation [13]. Premature infants are

also susceptible to the development of nutritional deficiencies as they have fewer storages and higher demand. Many of these manifestations begin with weaning from breast milk and infant formulas, either due to a lack of adequate supplementation or diminished nutrient bioavailability or absorption [6,14]. In acrodermatitis enteropathica, the bioavailability of zinc in formula is lower than in breast milk. Therefore, manifestations of zinc deficiency develop a couple of weeks following weaning, or, in the case of formula-fed infants, symptoms develop within four to ten weeks of birth when the zinc reserves are exhausted [3]. Another entity associated with the development of zinc deficiency in breastfed infants is transient neonatal zinc deficiency, which occurs due to decreased zinc levels in breast milk secondary to reduced secretion. These infants improve once being weaned off breast milk [3,13]. In inherited biotin deficiency, holocarboxylase synthetase deficiency presents in the neonatal period, whereas biotinidase deficiency presents three months later [3,5].

Cutaneous manifestations

Skin reveals nutritional deficiencies in the form of a spectrum of manifestations, some of which may overlap.

Xerosis

Xerosis cutis (Figure 1), also known as dry skin, is defined as hydrolipid-deficient skin [15]. This is a common finding in children with protein-energy malnutrition and essential fatty acid deficiency. Other deficiencies associated with this feature include vitamin A deficiency and excess, vitamin D, vitamin B3, biotin, zinc, and iron deficiencies [5,13-15].

Marasmus presents with dry, thin, wrinkled skin [2,5,13,14]. The loss of subcutaneous fat in the buccal area results in a "wizened appearance", also known as "monkey facies" [5].

Shiny, varnished, fragile skin is seen in kwashiorkor. The skin is dry, with hyperpigmented, erythematous, or violaceous patches over intertriginous areas, along with fissures, and overpressure sites. Desquamation commences in perioral and edematous areas, and later forms erosions and patches of hypopigmentation. The term "enamel paint spots" refers to the well-defined, hyperpigmented, flat-topped plaques in traumatized areas such as elbows, knees, ankles, and intertriginous

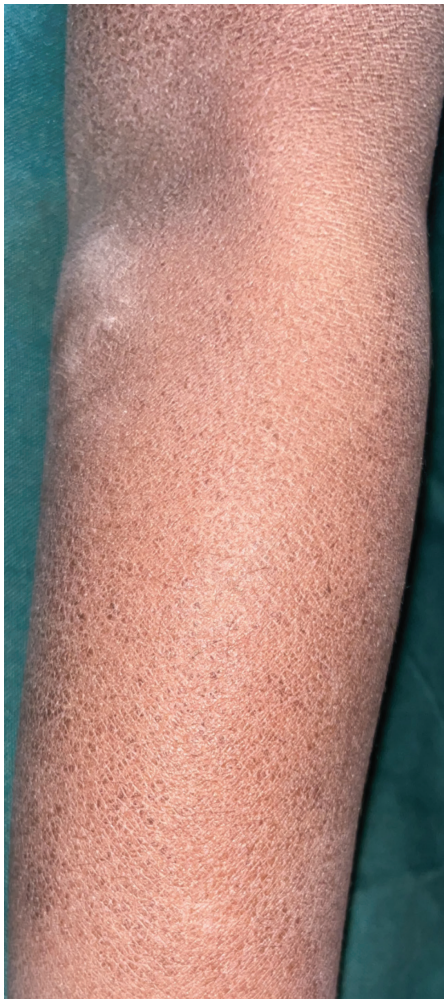

Figure 1. Diffuse xerosis over the upper extremity in a child with protein-energy malnutrition.

sites. These plaques have a polished surface and a waxy texture. Widespread desquamation is pathognomonic, sometimes characterized as "flaky paint" or "enamel paint", and can advance to erythroderma [3,5,13,14].

An overlap of both these conditions is known as marasmic kwashiorkor, presenting with growth retardation and edema as seen in marasmus and kwashiorkor, respectively, along with other features of both [13]. Figure 2A depicts flaky paint dermatitis in a child with marasmic kwashiorkor.

Essential fatty acid deficiency shows increased transepidermal water loss due to abnormal development of lamellar granules in the epidermis [5]. It is characterized by erythematous scaly plaques over the body and erosions over periorificial and intertriginous zones. The skin is thick and leathery. Flaking is generalized, initially manifesting over

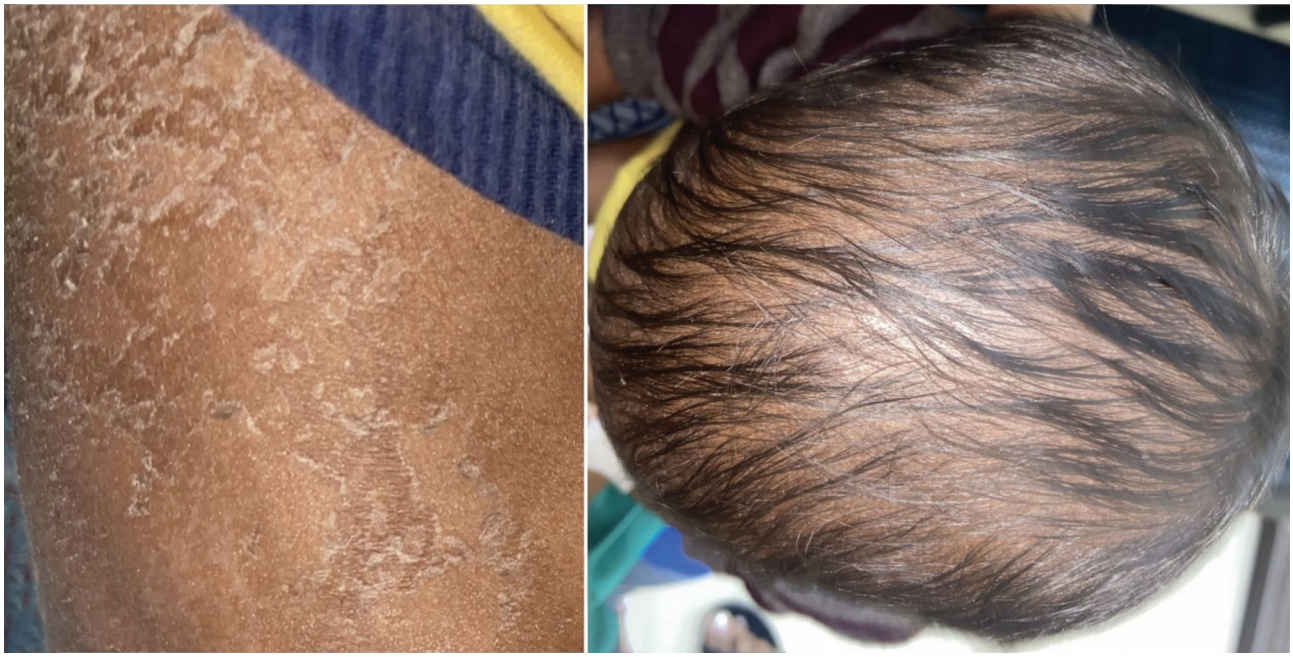

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Figure 2. A case of marasmic kwashiorkor with (A) flaky paint dermatitis over the trunk and (B) sparse, thin hair over the scalp.

the shins, and is released on rubbing resembling "snowflakes" over the sheets [2,3,5,14-16].

Periorificial and intertriginous dermatitis

The posterior distribution of lesions is a prominent feature of zinc and biotin deficiency. As discussed earlier, essential fatty acid deficiency also shows periorificial involvement [2,3,5,6,13,14].

Zinc deficiency could be inherited or acquired. Inherited zinc deficiency is an autosomal recessive disorder called acrodermatitis enteropathica (AE) [13,17]. It is caused by a mutation in zinc transporter protein zinc-ligand binding protein 4 (ZIP 4), leading to defective zinc absorption in the small intestine [17,18]. Transient neonatal zinc deficiency is an acquired form of zinc deficiency due to reduced secretion in breast milk as a result of an autosomal dominantly acquired mutation of a zinc transporter (ZnT2) in the mother [3,19]. The former presents in infants who are fed formula or were weaned off breast milk, whereas the latter presents in breast-fed infants and improves after weaning [3]. Zinc deficiency presents as a triad of periorificial and acral dermatitis, alopecia, and diarrhea, affecting only 20% of infants with AE [3,13,17]. Symmetrical, well-defined, erythematous, eczematous plaques progressing to vesicles, bullae, pustules, and erosions with peripheral crusting and scaling are seen predominantly around the oral cavity, anogenital area, acral areas, and scalp. Dermatitis of the perioral area causes sparing of the upper lip, in a "horseshoe-shaped" or "U-shaped" pattern. A psoriasis-like eruption may also be seen over acral areas (Figure 3) [3,13,14]. Altered cell-mediated immune response can lead to secondary infections with Gram-positive, rarely Gram-negative, bacteria, and Candida species, which may modify the skin lesions, leading to a delay in diagnosis [3,17,18].

Biotin deficiency can be inherited or acquired. Holocarboxylase synthetase deficiency presents in the neonatal period or, in rare cases, can be delayed until up to 15 months old. Cutaneous lesions are not very common and include a "fiery red", well-defined, seborrheic or crusted rash, initially over the scalp, eyebrows, and eyelashes, later involving perioral, perinasal, and intertriginous areas (Figure 4). Biotinidase deficiency manifests in infancy, after the age of 3 months. Skin manifestations resemble those of holocarboxylase synthetase deficiency, while some extracutaneous aspects differ. Immune dysregulation can commonly cause secondary infections with Candida, especially in skin folds [3,5,20].

Both of these micronutrient deficits must be differentiated since early treatment is imperative to prevent mortality. Children with zinc deficiency are

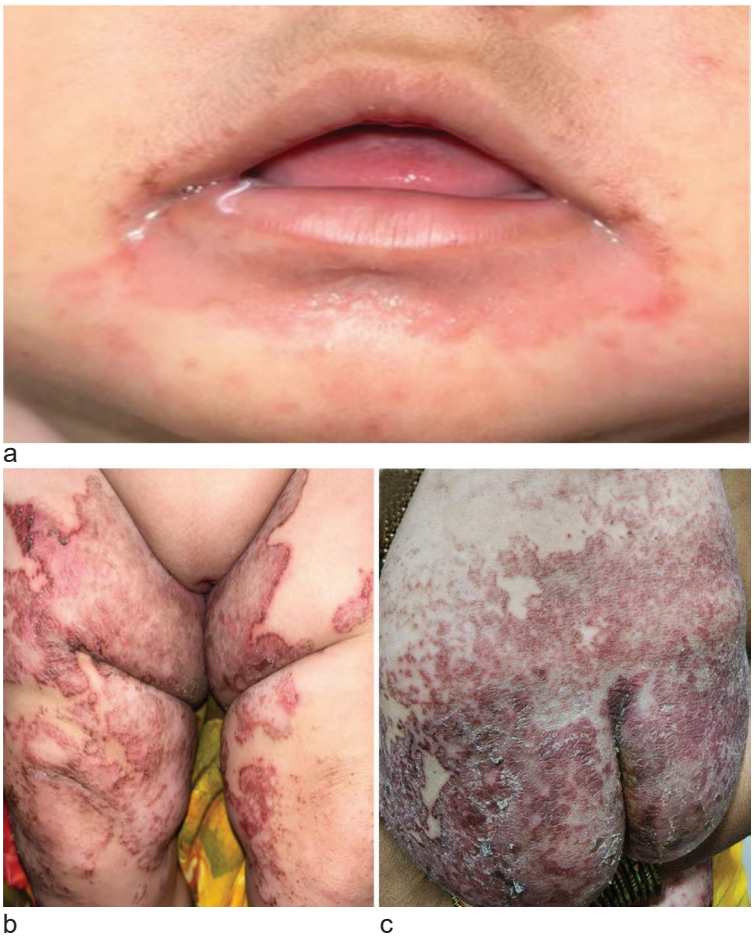

Figure 3. A case of acrodermatitis enteropathica with (A) perioral dermatitis sparing the upper lip, and (B, C) well-defined, erythematous, eczematous plaques with scaling, and crusting over the anogenital area, thighs, buttocks and back.

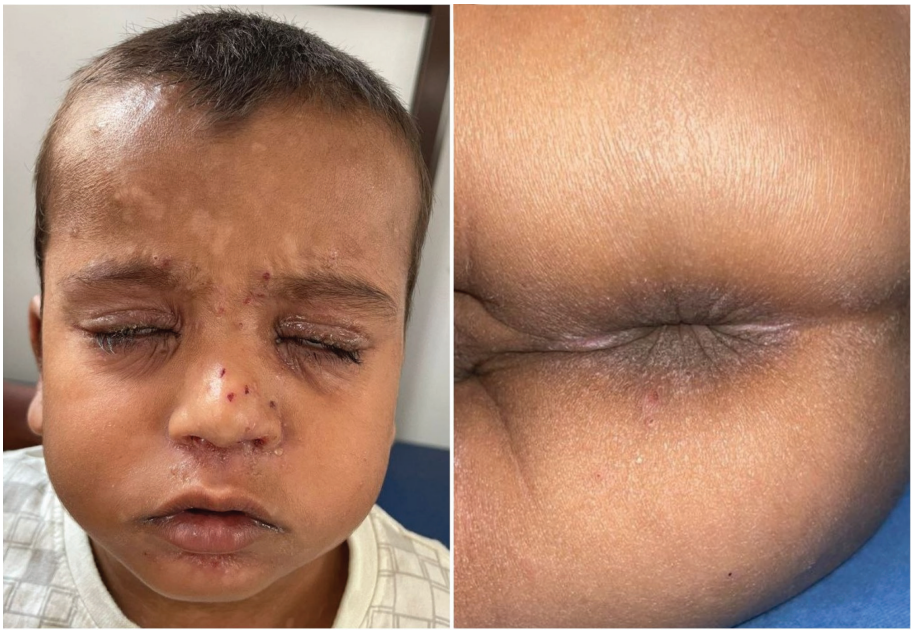

Figure 4. A case of biotin deficiency with (A) seborrheic rash over eyebrows, eyelashes, perioral and perinasal areas, and (B) rash over perianal area

usually irritable, and those with biotin deficiency are mostly lethargic. Myalgia and paresthesias are seen in those with biotin deficiency. Furthermore, neurological symptoms and seizures are common presenting features [5,6,20]. Diarrhea is a prominent feature of zinc deficiency, although it might be absent in certain cases [17,18]. Various laboratory investigations and clinical improvement with supplementation of the respective micronutrient would help confirm the diagnosis [3,5,6].

Photo-distributed dermatitis

Skin lesions at sun-exposed areas are evident in vitamin B3 (niacin) deficiency and, rarely, kwashiorkor, vitamin B2 (riboflavin), and B6 (pyridoxine) deficiency (known as "pellagra sine pellagra" –pellagra without pellagra) [5,8,13].

Chronic niacin deficiency leads to pellagra. The three dimensions that define this disease are dermatitis, diarrhea, and dementia. The fourth D is death, which occurs when the condition is not treated properly or at all [13,21]. Eruption involves the dorsum of hands, butterfly area of the face, neck, and upper chest, sparing eyelids, and auricles. Bony prominences show hyperpigmentation and hyperkeratosis. Perineal areas and scrotum are involved as well, with erythema and erosions. The rash is well-defined, limited to the margins of the clothes, and is similar to a sunburn. Lesions over the neck and upper chest are known as "Casal's collar/necklace", and if extending onto the sternum, are called "cravat sign". A rash over the dorsum of hands extending to forearms is known as a "gauntlet/glove sign", and those on the dorsum of feet up to the shins are known as "boot sign". Erythema and edema develop after sun exposure, along with burning, pain, and tenderness. Later, lesions become dry and darken to a "mahogany or cinnamon color" with exfoliation ("parchment-like/shellac-like/glassy appearance"). Long-standing lesions get lichenified with hyperkeratosis. Fissures associated with pain develop over hands and feet, known as "goose skin". In severe cases, vesiculobullous eruption, known as "wet pellagra", occurs. Defects in the healing of lesions lead to scar formation, as seen in the relapsing disease, known as "pemphigus pellagrous". Seborrhea spinulosa, prominent sebaceous glands, appear all over the face. The rough and powdery appearance of the nose is caused by dilated follicles projecting yellowish flakes [3,13,21,22].

Seborrheic dermatitis-like lesions

Such lesions are associated with deficiencies of vitamins B2 and B6 [14].

Lesions of vitamin B2 and B6 deficiencies have similar cutaneous presentations. The rash is found over nasolabial folds, ala nasi, forehead, cheeks, post-auricular area, and perineum (in infants) [13]. Genital involvement was reported with vitamin B2 deficiency. Patients with vitamin B6 deficiency might also affect the scalp, neck, shoulders, and buttocks [5,13].

Follicular hyperkeratosis

Follicular hyperkeratosis in the form of phrynoderma, also known as "toad skin", is associated with a deficiency in vitamins A, B-complex (commonly vitamins B2, B3, and B6), C, E, and essential fatty acids. It is common in the age group of 5-15 years [23,24]. It is characterized by symmetrical, discrete, brown to skin-colored, follicular, keratotic papules with central plug and broken hair, giving a "grater-like" sensation, present over extensor surfaces of elbows, knees, buttocks, and in case of generalized disease, over trunk and face (Figure 5) [3,5,23,24]. Available literature showed that phrynoderma was associated with deficiency of these nutrients occurring concurrently. Therefore, a better response was seen to supplement with a combination of these nutrients and a nutritious diet [23,25,26].

Petechiae, purpura and ecchymoses

These signs of intracutaneous hemorrhage are most commonly found in vitamin C and K deficiency, and rarely in marasmus and vitamin E deficiency [6,13,14].

Scurvy is caused by vitamin C deficiency. Four Hs that characterize this are hemorrhagic signs, hyperkeratosis of hair follicles, hypochondriasis, and haematologic abnormalities. There is the presence of perifollicular hemorrhage, predominant in dependant areas with increased hydrostatic pressure, such as legs and buttocks, which resembles cutaneous vasculitis [3,13].

Vitamin K is a lipid-soluble vitamin, which does not penetrate the placenta, causing hemorrhagic disease in newborns. Furthermore, the existence of sterile gut flora adds to the deficiency in neonates, as vitamin K is synthesized by the gut microbiome. It

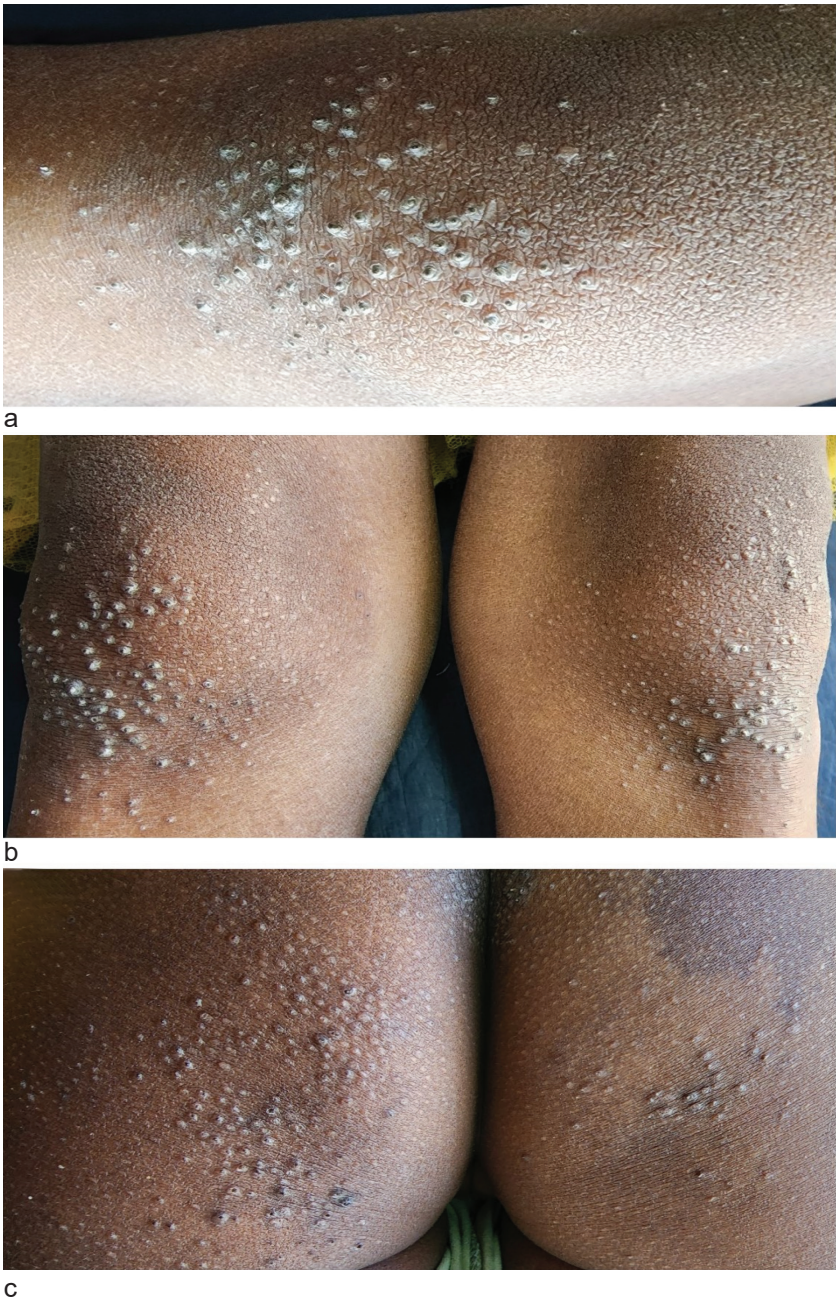

Figure 5. A case of phrynoderma with symmetrically distributed follicular keratotic papules with a central plug involving (A) elbows, (B) knees, and (C) buttocks.

is more prominent in premature than term newborns. Therefore, administration is required at birth to prevent serious complications such as intracranial hemorrhage [5,6].

Impaired wound healing

This feature is seen in protein-energy malnutrition, essential fatty acid shortages, vitamins A, C, B, zinc, and other micronutrient deficiencies.

Proteins are imperative for cell activity, collagen synthesis, and an adequate immune response [27,28]. Deficiency, therefore, disrupts inflammatory response in wounds and impairs the progression of wound healing to the proliferative phase. In the later stages, the fibroblast activity is reduced, angiogenesis is delayed, and production of collagen decreases [27].

Essential fatty acids affect the integrity of the lipid bilayer of the cell membranes by increasing lipoprotein

unsaturation. They ultimately form prostaglandins, which influence inflammation and cell metabolism and are involved in various signaling pathways [5,27].

Vitamin A deficiency impairs inflammatory response, reduces epithelialization, and decreases collagen and granulation tissue formation.

Vitamin C promotes collagen synthesis, fibroblast recruitment, angiogenesis, neutrophil migration, and function, and has antioxidant properties. Deficiency impairs this function and affects wound healing.

Certain vitamins in the B group (B1, B2, B6, B12, and folic acid) also participate in the process of wound healing by influencing leukocyte and collagen synthesis and immune function.

Zinc regulates immune response, DNA, protein, and collagen synthesis, as well as cell recruitment. Magnesium, iron, and copper all contribute to the process of wound healing [27,28].

Pigmentary changes

Hyperpigmentation is seen in vitamin B12, folic acid, and vitamin B3 deficiencies. Copper and essential fatty acid deficiencies result in hypopigmentation. Both hyperpigmentation and hypopigmentation can be seen in kwashiorkor [3,13].

Vitamin B12 and folic acid deficiencies cause global hyperpigmentation, which is most prominent over the face, palms creases, flexures, and knuckles. Multiple pigmented macules might be noticed on the palms and soles. Pigmentation of nails and mucosal surfaces is present as well [5,13].

Hypopigmentation is seen in copper deficiency due to altered melanin synthesis, as tyrosinase is copper-dependent.

Patients with carotenoderma secrete carotenes from their sebaceous and eccrine glands, which are then deposited in the stratum corneum, giving the skin a yellow-orange hue. This is more evident in areas with higher concentrations of sebaceous glands (nasolabial folds, forehead) and sites with a thicker stratum corneum (palms, soles) [13].

Other skin manifestations

An early sign of vitamin C deficiency is atrophy of the dermis. There is a loss of elastic resistance to external pressure, which is more noticeable over the dorsum of hands, forearms, and temple. If the condition is severe, the epidermis becomes transparent, making the underlying extensor tendons and venous plexus (known as "plastic wrap") more visible [16]. These patients may also have "woody edema" of the legs. This feature, coupled with limited motion (due to pseudoparalysis), petechiae, ecchymoses, and pain, can resemble cellulitis [8,13].

Impaired copper absorption causes a condition known as Menkes disease or kinky hair disease. Infants with this condition have hypopigmentation, cherubic face, pudgy cheeks, Cupid's bow upper lip, doughy skin, and pallor [5,13].

Pruritus and pallor can be seen in individuals with iron deficiency [13].

Although cutaneous manifestations of vitamin B1 deficiency (beriberi) are infrequent and not the primary symptoms, wet beriberi is characterized by pale, edematous, and waxy skin [2].

MUCOSAL MANIFESTATIONS

Angular cheilitis, stomatitis, cheilosis and glossitis

B-group vitamins (vitamins B2, B3, B6, B12, and folic acid), vitamin E, and other minerals, such as zinc and iron, are frequently associated with angular cheilitis, stomatitis, cheilosis, and glossitis (Figure 6) [2,3,5,6,13,14,16,29].

Inflammation involving the vermilion commissures and adjacent buccal mucosa with redness, maceration, erosions, fissures, and crust formation is known as angular cheilitis [5,30]. Stomatitis, also known as oral

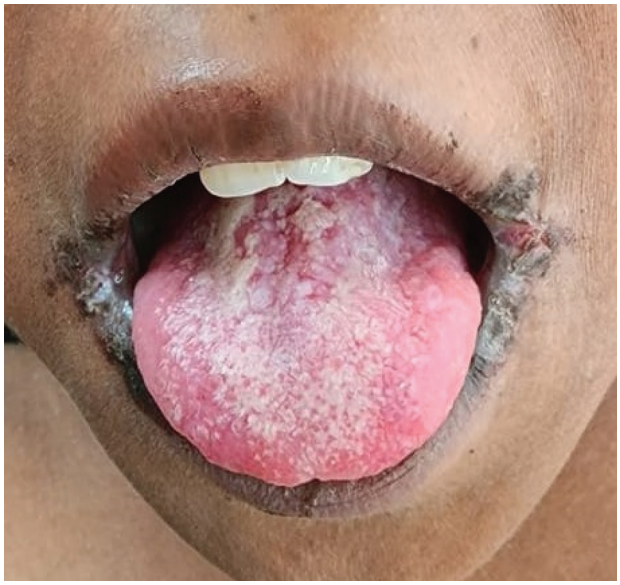

Figure 6. Angular cheilitis

Table 2. Changes in hair and nail in nutritional deficiencies in pediatric age group [3,5,6,13,17,34]

Hair changes	Deficiencies
Fine, sparse, brittle hair	Protein-energy malnutrition, vitamin A, zinc deficiency
Diffuse alopecia	Essential fatty acid, biotin (acquired > hereditary deficiency), zinc deficiency, hypervitaminosis A
Lightening of color	Protein-energy malnutrition, essential fatty acid, vitamin B12, biotin, zinc, copper deficiency
Excess lanugo hair	Marasmus
Dry, lustreless hair, reddish tinge, "flag sign"	Kwashiorkor
Pili torti, steel wool hair, horizontal eyebrows, trichorrhexis nodosa, monilethrix	Menkes disease (at 2-3 months of age)
Corkscrew hair, swan-neck hair	Vitamin C deficiency
Telogen effluvium	Iron, and zinc deficiency
Nail changes	**Deficiencies**
Thin, fissured, slow growing	Protein-energy malnutrition
Pigmented longitudinal lines	Vitamin B12 deficiency
Brittle nails	Biotin deficiency
Splinter hemorrhages	Vitamin C deficiency
Paronychia, onycholysis, onychodystrophy	Zinc deficiency
Koilonychia	Iron deficiency
Half-and-half nails	Vitamin B3 deficiency

mucositis, is an inflammation and ulceration of the oral cavity [31]. Cheilosis is defined as xerosis, erythema, and vertical fissures over the lips [5]. Glossitis is a sign of vitamin B deficiency, where the tongue is red and smooth due to villous atrophy [16].

In vitamin B2 deficiency, the lingual papillae are prominent with a "pebbly appearance" at first and later cause a magenta-colored, smooth, flank steak-like tongue [5,13,16].

Vitamin B6 deficiency is characterized by burning and erythema of the tongue and oral mucosa. The tongue might be swollen with flattened filiform papillae. Small ulcers might appear in the oral cavity [5].

In vitamin B3 deficiency, the tongue develops hypertrophic papillae, pseudomembranous furrows, and hyperpigmentation, also known as "black tongue", which eventually leads to atrophy [3].

Glossitis might be the presenting sign in patients with vitamin B12 deficiency before signs of anemia set in [6]. Hunter glossitis, also known as Moeller-Hunter glossitis, presents in two stages. Initially, the tongue is inflamed, with bright red plaques ("beefy red" tongue), and hypertrophic papillae, followed by papillar atrophy affecting more than 50% of the tongue's surface [5,16,32].

Angular cheilitis manifests early in case of zinc deficiency [3]. Individuals with iron deficiency might experience atrophic glossitis and a burning sensation on their tongue, which might be presented even before anemia has been diagnosed [29]. Cheilitis is sometimes a feature of hypervitaminosis A [13].

Ocular manifestations

Vitamin A deficiency is the leading cause of preventable blindness [13]. It is characterized by a series of changes occurring in the cornea and conjunctiva [33]. Initially, the patient complained of hemeralopia (inability to see bright light), diminished dark adaptation, and nyctalopia (night blindness).

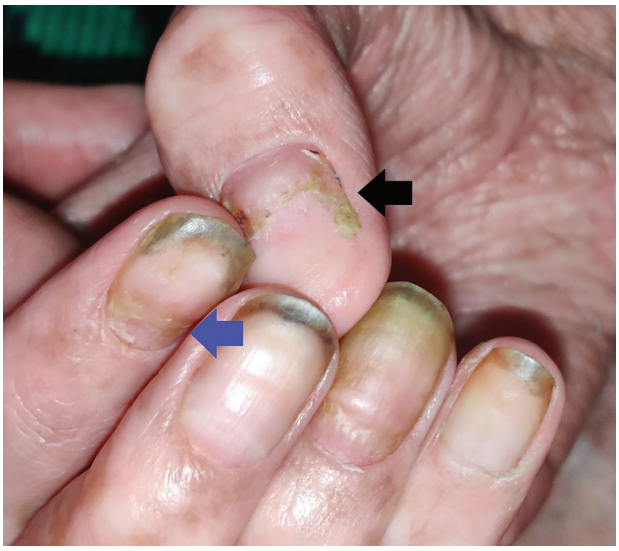

Figure 7. Nail changes in acrodermatitis enteropathica. Black arrow points to onychodystrophy and blue arrow to onychomadesis

This later progressed to xerophthalmia, Bitot's spots (discrete, foamy, white-grey plaques of keratinizing metaplasia over the conjunctiva), corneal ulceration, keratomalacia, and retinopathy [3,5,13,33]. Despite being mild stages of ocular disease, Bitot's spots and night blindness both signify moderate to severe systemic vitamin A deficiency [3,33].

The oculo-orogenital syndrome is a cluster of various manifestations associated with vitamin B2 deficiency. Conjunctivitis and photophobia are two examples of eye involvement [13]. Lesions over the scrotum are pruritic, erythematous, lichenified, and crusted, with the involvement of inner thighs and perianal regions, sparing the medial commissure. There may be fissures and swelling. Balanitis and phimosis could also be present. Involvement of the vulva is rarely seen [5,13]. Oral manifestations were discussed previously.

Ocular manifestations of zinc deficiency include blepharitis, conjunctivitis, and photophobia [3,5,13].

Table 3. Extracutaneous manifestations of nutritional deficiencies in pediatric age group [2,3,5,8,13,14,17,18,20-22,35,36]

Extracutaneous manifestations	Deficiencies
Gastrointestinal tract manifestations	
Diarrhea, villous atrophy	Pellagra, zinc deficiency, protein-energy malnutrition, infantile beriberi
Anorexia	Pellagra, zinc deficiency, protein-energy malnutrition, hypervitaminosis A
Nausea, vomiting, pain abdomen	Pellagra, beriberi, hypervitaminosis A
Hypogeusia, steatorrhea	Zinc deficiency
Hepatic manifestations	
Hepatomegaly, fatty liver, transaminitis	Kwashiorkor, essential fatty acid deficiency
Neurological manifestations	
Headache, poor attention, disturbed sleep → Dementia	Pellagra
Neuropsychiatric	Vitamin B12 deficiency
Seizures	Holocarboxylase synthetase deficiency, biotinides deficiency, copper deficiency
Hypotonia	Holocarboxylase synthetase deficiency, biotinides deficiency, vitamin D deficiency
Irreversible sensory neural hearing loss, ataxia	Biotinides deficiency
Ataxia	Biotinides deficiency, zinc deficiency
Neuritis	Pellagra, beriberi, vitamin B6 deficiency
Optic neuritis	Pellagra, biotinides deficiency
Wernicke encephalopathy	Beriberi
Tremors	Zinc deficiency
Delayed intellectual development, EEG changes	Vitamin B2 deficiency
Regression of motor milestones	Vitamin D deficiency
Hematologic manifestaions	
Megaloblastic anemia	Vitamin B12, folic acid deficiency
Microcytic anemia	Iron deficiency
Normocytic normochromic anemia	Vitamin C, B2, B6 deficiency
Hemorrhage (eg, intracranial)	Vitamin C, and K deficiency
Musculoskeletal manifestations	
Scurvy - Pseudoparalysis, scorbutic rosary, bowing of long bones, radiographic changes	Vitamin C deficiency
Ossification of sutures, metaphyseal widening, lateral spur, subperiosteal new bone formation, osteoporosis (later)	Menkes disease
Skeletal hyperostosis, myalgia, arthralgia	Vitamin A excess
Rickets, muscle weakness	Vitamin D deficiency
Metabolic abnormalities	
Metabolic acidosis → Ketoacidosis coma	Holocarboxylase synthetase deficiency
Other systemic manifestations	
Hyperventilation, stridor, apnea	Biotinides deficiency
Delayed puberty, hypogonadism, retarded growth	Zinc deficiency
Renal involvement	Copper deficiency
Aphonia, heart involvement	Infantile beriberi

Night blindness can also be seen due to diminished release of vitamin A from the liver [3].

Keratoconjunctivitis might be a feature of biotin deficiency in infants [5].

Other mucosal manifestations

Vitamin A deficiency is characterized by a sensation of mouth dryness, known as xerostomia. This is caused by squamous keratinizing metaplasia of the salivary glands [3].

Vitamin C deficiency could lead to hemorrhagic gingivitis. It is seen in cases of poor oral hygiene or pre-existing gingivitis, characterized by painful, erythematous, swollen, friable, shiny gingiva progressing to bleeding, necrosis, black discoloration, and bluish-red masses in the interdental papillae. There is soft, loose, poorly formed dentition which is prone to infections [5,8,13,14]. Infantile scurvy, also known as Barlow's disease, is caused by the consumption of heat-treated milk and manifests as gingivitis at the site of tooth eruption [14]. Rarely, a Sjogren-like syndrome is seen with xerostomia, keratoconjunctivitis sicca, and swollen salivary glands [5].

Pellagra can cause vaginitis, which is characterized by painful fissures, erosions, and vaginal mucosa atrophy [13,22].

Hair and nail changes

Hair and nail changes in nutritional dermatoses are listed in Table 2 [3,5,6,13,17,34]. Figure 2B shows sparse, thin hair in a child with marasmic kwashiorkor. Figure 7 depicts nail changes seen in acrodermatitis enteropathica.

Extracutaneous manifestations

Table 3 summarizes the systemic manifestations of nutritional deficiencies [2,3,5,8,13,14,17,18,20-22,35,36].

Figure 8 outlines cutaneous presentations in nutritional disorders and their approach to diagnosis.

CONCLUSION

Although the prevalence of nutritional deficiencies has decreased due to the advent of fortified foods and the spread of awareness regarding a proper nutritious diet, it remains still a problem in developed countries such as India, especially in areas with

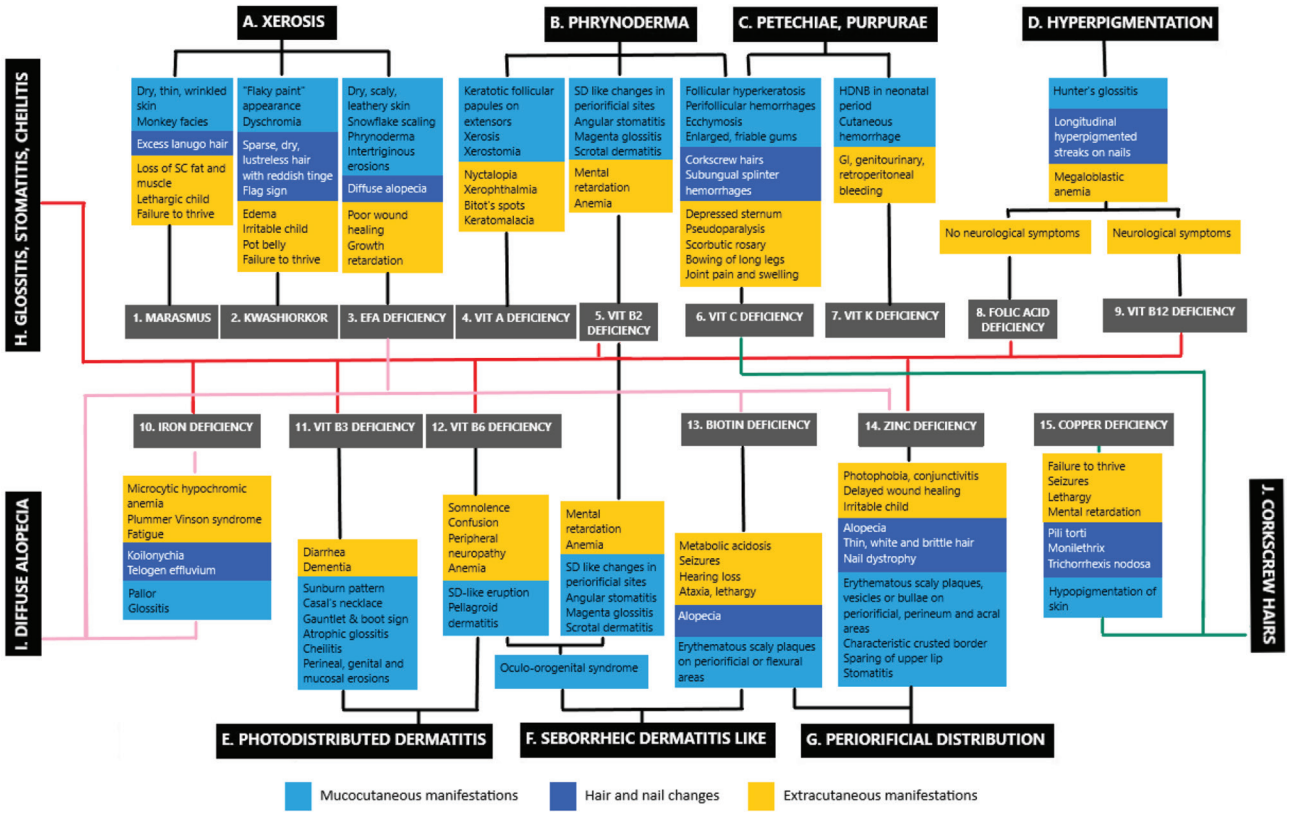

Figure 8. Various cutaneous manifestations of nutritional deficiencies in pediatric age group and its approach. Some of these features (e.g., hyperpigmentation) can have etiologies other than nutritional deficiencies and those should also be ruled out.

restricted access to proper and hygienic food supplies. Cutaneous manifestations are usually the first to be noticed. To improve the quality of life and minimize morbidity and mortality, swift and appropriate treatment administration necessitates a thorough understanding of the varied presentations and the ability to distinguish deficiencies from those that appear similar.

Authors Contribution

All authors contributed in the conception of the work, collection of data, drafting and revising the draft and approval of the final version of the manuscript.

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