Oedematous malnutrition

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Oedematous malnutrition, represented by its most severe form kwashiorkor, is rampant in many parts of the world and is associated with a high case fatality rate. Despite being first described more than a century ago, the pathogenesis of kwashiorkor is still not clear. The traditional thinking is that it results from a deficiency of dietary protein and is usually associated with an infection. This has now been challenged by the finding that there is no difference in diets of children developing marasmus or kwashiorkor. Nutritional oedema is associated with an increased secretion of anti-diuretic substance (probably anti-diuretic hormone) which prevents the normal excretory response to water administration. Experimental studies have shown that feeding low-protein, low-calorie diets results in delayed and incomplete response to a water load, and that the livers of the animals show a reduced capacity for inactivating anti-diuretic hormone. There is now evidence that links generation of free radicals and depletion of anti-oxidants with the development of oedema in kwashiorkor.

**Key words** Antidiuretic hormone - kwashiorkor - malnutrition - nutritional odema - oxidative changes

Kwashiorkor, the classical example of severe acute malnutrition, is characterised by the presence of oedema. In addition to oedema, the hallmarks of the condition include dermatosis, diarrhoea, and fatty liver. Typically there are skin lesions (pigmented or depigmented areas with or without ulceration), scanty lustreless hair, an enlarged fatty liver, loss of interest in the surroundings, and loss of appetite. Oedema may even progress to generalised swelling or anasarca. Fluid homeostasis in the body is altered resulting in excess accumulation of fluid in the extracellular space. Cicely Williams first introduced the name kwashiorkor in 1935, which in the Ga language of West Africa means “the disease of the deposed child”. This literally refers to the child who develops oedema after being weaned with starchy gruels following the birth of a sibling who is breastfed. Kwashiorkor, which occurs mostly in children 1-3 yr of age, results from a deficiency of dietary protein and is usually associated with an infection. However in India, Gopalan did not find any difference in diets of children developing marasmus or kwashiorkor. In response to infection, amino acids are used for the production of acute phase reactants at the expense of visceral protein synthesis. There is a decrease in blood albumin level, which is partly responsible for development of oedema. Beta-lipoprotein is not produced in adequate amounts, resulting in impaired transport of fat from the liver, accumulation of fat and an enlarged fatty liver.

There is no population-based data on prevalence of oedematous malnutrition. This is due to the fact that large-scale health and nutrition surveys do not make any attempts to detect oedema. Case fatality, however, is very high among children hospitalised with oedematous malnutrition. These observations
indicate the need for better information on the global, regional and national prevalence of kwashiorkor and other forms of oedematous malnutrition.

Mechanism of oedema

Oedema is facilitated by two biological processes; filtration is the movement of fluid out of the capillary and, reabsorption is the movement of fluid back into the distal end of the capillary and small venules. When capillary fluid filtration exceeds reabsorption, fluid accumulates within the interstitium over time if it were not for the lymphatic system that removes excess fluid from the interstitium and returns it back to the intravascular compartment. Circumstances, however, can arise where net capillary filtration exceeds the capacity of the lymphatics to carry away the fluid (i.e., net filtration > lymph flow). When this occurs, the interstitium will swell with fluid and become oedematous. Decreased plasma oncotic pressure, as occurs in hypoproteinaemia during malnutrition, precipitates oedema.

How does oedema occur in kwashiorkor?

The genesis of oedema of kwashiorkor is multifactorial, with electrolyte disturbance - potassium deficiency and sodium retention playing an important role. Nevertheless, the classical theory postulates that an inadequate intake of protein leads to a low plasma albumin concentration which in turn causes oedema. Association of protein for genesis of oedema was grounded further by indirect evidences gathered through some of the work of Gopalan and fellow Indian scientists, who found that diets based on protein were associated with satisfactory clinical and biochemical cure of kwashiorkor. However, this classical hypothesis has been challenged.

Golden et al. in a study examined the association between plasma albumin and nutritional oedema by observing the changes in albumin during loss of oedema in patients on a restricted diet. Since there was no difference in the concentration of plasma albumin before and after loss of oedema, the association is not causal. In another study, Golden demonstrated that loss of oedema from oedematous malnourished children was strongly associated with dietary energy intake but not with intake of protein. Gopalan et al., in a prospective study followed a group of Indian children on poor diet. Some children developed kwashiorkor and some marasmus, but there was no quantitative and qualitative difference between their diets. It was concluded that the difference lay in host’s response and that, kwashiorkor represented the theory of dysadaptation, i.e., adaptation failure, and good adaptation resulting in marasmus.

Anti-diuretic factor in the urine of children with nutritional oedema: Nutritional oedema is associated with an increased secretion of an anti-diuretic substance (probably anti-diuretic hormone) which prevents the normal excretory response to water administration. Gopalan and Venkatachalam in a study furnished indirect proof of the effect of posture on the urinary response to water load in normal subjects and in cases of nutritional oedema. The normal subjects were found to excrete over 100 per cent of ingested water within 4 h of ingestion in the recumbent posture, while in the erect posture they excreted only 80 per cent. In case of nutritional oedema, the urinary excretion was found to be much lower than in the normal subjects in both recumbent and erect postures. The effect of dietary protein deficiency on the hepatic inactivation of ADH in rats has also been investigated. It was found that the rats maintained on low-protein, low-calorie diets showed a delayed and incomplete response to a water load, and that the livers of these animals showed a reduced capacity for inactivating ADH (Gopalan & Srikantia, unpublished).

Role of ferritin and aldosterone: Srikantia observed presence of ferritin in children with kwashiorkor. With a view to reveal the precise role of ferritin in the pathogenesis of nutritional oedema, Gopalan and Srikantia investigated the sequence of changes occurring in induced protein and calorie under-nutrition with focus on oedema formation in monkeys. On the basis of the findings, they suggested that calorie-protein undernutrition leads to structural and functional changes in the liver, further leading to defective inactivation of ADH. Active ferritin is released from damaged liver leading to increased secretion of ADH. The net result is water retention. Among other factors, aldosterone, the salt retaining hormone, which is known for influencing water metabolism by altering renal tubular reabsorption of sodium, is also known to be inactivated by the liver. Altered aldosterone metabolism has been reported in diseases of the liver. Associated hyperaldosteronism could account for the sodium retention. In oedematous children aldosterone secretion becomes higher during loss of oedema.

Oedema of kwashiorkor - environmental and metabolic factors: Environment, particularly diet,
certainly has an important role in the pathogenesis of kwashiorkor; the condition is not seen in children with an adequate nutritional intake. Intrinsic characteristics of the host may also be required for the development of kwashiorkor. It is possible that variant isozymes or variations in concentration of enzymes in the metabolic pathways lead to the development of kwashiorkor in children with poor diets. Differences in the pattern of amino acid concentrations between children with kwashiorkor and marasmus have been used in favour of this assumption20.

The serum amino-acidogram may show distinct differences in cases of marasmus and kwashiorkor. Very high levels of glutamate with low or undetectable levels of alanine are the hallmark of kwashiorkor21. One possible explanation for this can be the low level of transaminases in kwashiorkor. Low transaminase levels in the liver biopsy specimens in case of kwashiorkor have been reported earlier22. It has also been shown that they remain low even during recovery. It is possible that this deficiency is present right from birth and is genetically transmitted and is made clinically overt when the child is exposed to stress of dietary inadequacy and may be responsible for development of kwashiorkor. Those children who have normal transaminase function develop marasmus under the same dietary insult. In addition to dietary and nutritional investigations, genetic techniques including genome-wide association to delineate host factors may prove useful in unscrambling the enigma of kwashiorkor.

Evidence for free radicals/anti-oxidants

Golden and Ramdath23 proposed that kwashiorkor results from an imbalance between the production of free radicals and their safe disposal. This theory is supported by the observations in other studies where blood concentrations of vitamin E derivatives, glutathione, and red cell antioxidant enzymes are lower in children with kwashiorkor than in marasmic children24-26. The study of Sive et al27 shows that, ‘free’ circulating iron may contribute to oedema in kwashiorkor. Srikantia28, using a bioassay, had reported that children with kwashiorkor had high levels of circulating ferritin, which was further confirmed by a Jamaican study when immunoassays became available29. The study of Okunade et al30 shows that the extent of lipid peroxidation in the erythrocytes of kwashiorkor subjects was three times that found in erythrocytes of normal subjects. This finding was supported by another study which also demonstrated excessive lipid peroxidation in kwashiorkor30. In a clinical trial, the administration of N-acetylcysteine, a glutathione precursor, resulted in more rapid resolution of oedema in kwashiorkor31. These associations between oxidative stress and kwashiorkor indicate that antioxidant depletion may cause kwashiorkor which can therefore be prevented with antioxidant supplementation.

Challenge to the oxidative stress theory?

The study by Ciliberto et al32 examined the impact of an antioxidant cocktail containing riboflavin, vitamin E, selenium, and N-acetylcysteine in a dose three times that of required daily intakes, as a possible preventive treatment for kwashiorkor in children in a highly endemic area of Malawi but failed to find any protective effect. Although the result may be a deterrent to the antioxidant hypothesis, it would be premature to discard the theory altogether. The specific antioxidants used in the Ciliberto study are known to have a high relative antioxidant capacity, but the amounts taken by the children may have been insufficient to overcome high oxidative stress and prevent kwashiorkor. Since neither antioxidant capacity nor oxidative stress was measured, the adequacy of the antioxidant mix or the dose can be questioned. Moreover, the study did not assess the children’s HIV status, which may have contributed to or affected their responses to oxidative stress33.

Thus more than a century has elapsed but the theories on pathogenesis of kwashiorkor oedema continue to unfold. The age old classical theory of dietary protein inadequacy now continues to be challenged. The theory of dysadaptation explains a different perspective related to differential host response leading to different outcomes (kwashiorkor or marasmus) under nutritional stress, and underpins a wider perspective of metabolic and enzymatic variances leading to oedema formation. Hormonal factors (ADH) also demonstrate a plausible explanation of the pathology. Evidence for free radicals/anti-oxidants, which essentially propose an imbalance between free radicals and their disposal, is increasingly becoming strong. Evidence of oxidative changes in the cell membranes of the oedematous kwashiorkor subjects i.e., lipid peroxidation has been established by some studies. Indirect evidences of anti-oxidant therapy improving oedema further consolidate the free radical/anti-oxidant theory; yet this theory is not without question- the enigma of kwashiorkor oedema continues!
References


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