IJBAF, June, 2020, 8(6): 292-301

ISSN: 2320 – 0774

International Journal of Biotechnology and Allied Fields (IJBAF)

www.ijbaf.com

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ACRODERMATITIS ENTEROPATHICA: A ZINC RELATED SKIN MANIFESTATION

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Received 9th June 2019; Revised 11th July 2019; Accepted 12th Aug. 2019; Available online 1st June 2020

ABSTRACT

Zinc is an important micro-nutrient for proper functioning, immunity, digestion and absorption of nutrients in body. Its necessity, and damage due to deficiency can be assessed by considering that it's a peculiar requirement for associated 300 body proteins named enzymes which cares body normality. Review is about zinc, it's over dose, toxicity, deficiency and associated manifestations, especially *Acrodermatitis Enteropathica*, covering etiology, signs and symptoms, histopathology, different diagnosis procedures, management and targeted nutrient treatment attributing to this skin ailment.

Keywords: Zinc, skin, plasma, *acrodermatitis enterpathica*, supplement

INTRODUCTION

ZINC

Zinc (Zn) is found in II-b group among 02 poisonous metals mercury and cadmium in the periodic table. Zinc (Zn) is regarded as safe for human beings **[1]**. There is no known role of mercury and cadmium in human body as compared to zinc (Zn) and it is recognized as an imperative and vital trace element for human beings as well as additional creatures. Zinc (Zn) plays a dynamic role in human wellbeing as it is a constituent of > 300 enzymes and of other proteins. Many important physiological functions like cell growth, cell division, optimum metabolism of protein and nucleic acid and proper cell functioning necessitates an adequate amount of zinc (Zn) **[2]**.

ACQUAINTANCE TO ZINC

Zinc (Zn) pass into the human body through 03 chief ways *i.e.*by ingestion, by inhalation and through skin **[3]**. Respective exposure type affects certain body parts and permits an altered quantity zinc (Zn) to be absorbed.

INGESTION

An oral administration of minute quantities of zinc is mandatory for the survival. For an adult male and female, the recommended dietary allowance (RDA) for zinc (Zn) is 11 mg/day. Infants require a minute amount *i.e.*02 – 03 mg/ day while in children the recommended zinc (Zn) intake is 05– 09 mg/day). Quantity of zinc (Zn) is minute just due to body weights that are subordinate average **[4]**. This is considerably lower than the lethal dose value (LD_{50}), which is estimated at 27 gm of zinc per day in humans as compared to similar studies in mice **[3]**. 225 – 400 mg of zinc (Zn) is unlikely to be absorbed as it disturbs physiological functions and induces vomiting **[5]**. A case of demise of a female by ingesting 28 g of zinc sulfate ($ZnSO_4$) was reported. Hyperglycemia and tachycardia were happened after an ingestion and at last renal failure and hemorrhagic pancreatitis were also happened. After the lapse of 05 day she died **[6]**. Vomiting, nausea and abdominal pain are the instantaneous symptoms after the consumption of lethal dose (LD) of zinc.Dizziness, anemia and lethargy are some other possessionsof excessive zinc (Zn) intake **[7]**.

INHALATION

Manufacture workers/ labors are much prone to inhalation of zinc (Zn) encompassing smoke which is originated from industrial progressions like galvanization. Furthermore, zinc chloride ($ZnCl_2$) and zinc oxide (ZnO) that are present in military smoke bombs adversely affects soldiers by instigatinginnumerable inhalation cases respiratory system. Adult respiratory distress syndrome (ARDS) was happened in 02 soldiers after an inhalation of smoke of a bomb containing zinc chloride ($ZnCl_2$) and death was occurred after 25 – 30 days **[8]**.On the other hand, a case of adult respiratory distress syndrome (ARDS) in a soldier was also reported after an exposure of concentrated zinc chloride ($ZnCl_2$) for sometime throughout a military working out. That case was recovered after some interventions *i. e.* mechanical ventilation and tracheal intubation for a lapse of 08 days **[9]**. Walther *et al*. and Gil *et al*. in 2008 also reported some incidents of smoke inhalation having comparable possessions upon respiratory tract **[10, 11]**.

Metal fume fever (MFF) is recognized as an utmost and extensive identified consequence of zinc (Zn) containing smoke inhalation. Zinc oxide

(ZnO) is chiefly responsible for causing Metal fume fever (MFF). Industrial conditions like zinc welding and smelting are also the main factors in causing metal fume fever (MFF). An inhalation of fumes of metal having a particle size of <1 μm can even cause this industrial syndrome **[12]**. Dyspnea, cough, chest pain, fatigue, nausea, muscle soreness and fever are some symptoms of metal fume fever (MFF) **[13]**. The number of leukocytes in bronchioles is intensified along with above mentioned symptoms **[14]**. After a proper management and treatment, metal fume fever (MFF) vanishes and it is also not a life-threatening respiratory illness **[9]**.

ABSORPTION

The mechanism of dermal absorption of zinc (Zn) is not known clearly. According to Agren *et al*. it was stated that, the absorption of zinc (Zn) is influenced by multiple factors **[15]** like skin's pH, quantity of zinc (Zn) applied and the biochemical speciation **[16]**. A study was conducted in 2015 in which 2.9 mg/ cm^2 of zinc oxide patch was applied topically for 48 hours on human skin and it was noticed that, there was no dermal irritation **[17]**. On the other hand, zinc acetate caused moderate while zinc sulfate caused little irritations when it was applied topically on the skin of guinea pigs, rabbits and mice. In relation to the investigation by Agren *et al*. there was no irritant effect of zinc oxide on skin **[18]**. Zinc chloride is a caustic (as mentioned above) and this skin irritation not inevitably specify a noxious consequence of zinc (Zn). Zinc (Zn) is considered as a best supplement for the cure of wounds and multiple skin allergy conditions **[19, 20, 21 and 22]**. It has been shown and emphasized that, zinc (Zn) possesses no lethal hazard upon skin.

ACRODERMATITIS ENTEROPATHICA

Unembellished deficiency of zinc might either be acquired or inherited. Acrodermatitis enteropathica is an utmost inherited form of skin infection and it is aninfrequent autosomal recessive metabolic diseasethat caused by a mutation in Zip4 transporter in intestine **[23]**. The individuals with acrodermatitis enteropathica have an unadorned deficiency zinc (Zn) (MIM 201100) which happened due to an imperfect transport of zinc (Zn) in jejunum **[24]** and duodenum **[25]**.

Epidemiology

Acrodermatitis enteropathica is an inherited zinc (Zn) deficiency that happens globally. Its prevalence is very low even unnoticeable *i.e.* 01/ 500,000 children. There's an imperceptible preference for gender and race. Acrodermatitis enteropathica as a most critical and problematic situation happening in developing countries and ruled out that deficiency of zinc (Zn) is responsible for

causing this dermatological sickness. Children are much prone to this disease and it is estimated that, an insufficient intake of zinc (Zn) distresses a few inhabitants in sub Saharan Africa and Southeast Asia. Zinc (Zn) associated growth retardation distresses major proportion of preschoolers (40 %) and the supplementation of zinc (Zn) is revealed to expressively decrease communal diseases and deaths in infants in sub Saharan Africa and Southeast Asia **[26]**.

Etiology

A gene ***SLC39A4*** that is placed on 8q24.3 chromosome is responsible for the iron-regulated transporter-like protein or zinc (Zn)-ligand binding protein (ZIP4). Zinc (Zn)-ligand binding protein (ZIP4) is a histidine-rich membrane protein that acts as a zinc (Zn) absorption protein in order to transport zinc (Zn) ions from outside the cell or cavity to cytoplasm, where it is available for other proteins. Consequently, an autosomal recessive mutation in this particular gene leads to an absorption of defective zinc (Zn) so the signs and symptoms of zinc deficiency appears in an individual. An alternative case of mutation in ***SLC30A2*** gene on chromosome **1p36.11** was reported in lactating femalein which there was a reducedexcretion of zinc (Zn) in breast milk **[27, 28]**.

In many of the cellular processes and as an essential part of numerous transcription metalloenzymatic factors, zinc (Zn)possesses an imperative role. Moreover, zinc (Zn) is essential in free-radical scavenging, normal immune function, wound healing, protein and nucleic acid synthesis. Zinc (Zn) has no storage site in human body so the dietary/ supplementation of zinc (Zn) is really necessary for the normal functioning of human body. Zinc (Zn) is present in human breast milk and its quantity is maximum in first 02 months of lactation. In breast milk, a zinc-binding ligand is also present which intensify the bioavailability of zinc (Zn) in human breast milk. There's an absence of zinc (Zn) in animal milk. Small intestine (especially jejunum through transporting protein ZIP4) makes it possible to absorb zinc (Zn) enterally. Zinc (Zn) deficiency occurs when mutations happen in gene coding this protein that averta proper enteric absorption zinc (Zn) **[29]**.

Signs and symptoms

If there is a presence of low zinc (Zn) in breast milk then the infants might develop a skin inflammation resembling to acrodermatitis enteropathica **[30]**. Eczematous scaly and pinkish spots (that tend to become desquamative, pustular, bullous and vesicular) appears on the skin of people suffering from acrodermatitis enteropathica. Extremities, periorificial and anogenital areas are the specific sites where the lesions develop. In acrodermatitis

enteropathica, the common early manifestation is angular cheilitis that is followed meticulously by paronychia. If these manifestations are not treated then erosion of the skin happens and people develop diarrhea and generalized alopecia. The diagnosis of acrodermatitis enteropathica might be possible by some major signs and symptoms like diarrhea or any additional unclear gastrointestinal dysfunction, localized skin lesions around body orifices and extremities andtotal alopecia **[31]**. Hypogonadism in boys and men, delayed puberty, anorexia, hypogeusia, photophobia, anemia, poor wound healing, mental slowing and growth delay are other signs and symptoms of advanced state of acrodermatitis enteropathica. It has been reported that, hair shafts alternately show dark and bright bands in polarized light microscopy **[32]**. At last, the skin lesions are subordinately infested by *Candida albicans* and bacteria. Many times, the case of psoriasis and acrodermatitis enteropathica are thought to be confusing. E. g. the enduring lesions of acrodermatitis enteropathica might seem like the lesions of psoriasis along with dystrophy of nails. Fascinatingly, the 1st syndrome that was happened due to deficiency of zinc (Zn) was swine psoriasis (porcine parakeratosis) **[33]**.

Histopathology

Histology rests on the duration of lesion and it is much typical. In early lesions, there is a reduction in granular layer along with confluent parakeratosis. There is also a presence of an infiltrate of slight spongiosis and polymorphonuclear leukocytes (PMNs). A noteworthy reticular degeneration and ballooning along with keratinocytes necrosis develop with increasing age. Psoriasiform hyperplasia of epidermis might be resulted in the end stage of acrodermatitis enteropathica.

Diagnosis

Diagnosis of acrodermatitis enteropathica is confirmed by the measurement of plasma zinc (Zn) levels. Disease is considered when the level of serum zinc (Zn) is < 65 µg/ dL in non-fasting while < 70 µg/L in fasting conditions. In order to get accurate results, a satisfactory care should be employed throughout the testing of zinc (Zn) levels. Level of zinc (Zn) is maybe augmented by the utilization of contaminated rubber stoppers, needles, catheters and tubes. Inflammation, stress and the time of day may cause a variation in levels of zinc (Zn). Acid-washed tubes or glass bulbs are used to collect the sample and collection time must be morning. Serum albumin should also be measured while measuring of zinc (Zn) levels because low level of albumin might cause low level of zinc (Zn). In few cases, measurement of a zinc-dependent

enzyme (alkaline phosphatase) might also be valuable. When the diagnosis is unsure, affected skin is evaluated for histopathological examination that may be obliging but it is not a confined diagnostic tool. The distinguishing fluctuations comprises a hyperplasia psoriasiform with necrolysis that is a terminology utilized for unfolding focal dyskeratosis, spongiosis, confluent parakeratosis and cytoplasmic pallor **[34]**.

Differential diagnosis

Acrodermatitis enteropathica is sometime confused with seborrheic dermatitis, mucosal candidiasis, malabsorption syndromes, leucinosis, aciduria type 1, glutaric, human immunodeficiency virus, essential fatty acid deficiencies, epidermolysis bullosa, cutaneous candidiasis, dietary iatrogenic deficiency of branched-chain amino acids, atopic dermatitis, acquired zinc deficiency, nonketotic hyperglycinemia, kwashiorkor, biotin and multiple decarboxylase deficiencies **[28]**.

Management

Zinc (Zn) replacement is mandatory to treat hereditary acrodermatitis enteropathica.03 mg/ kg/ day of elemental zinc (Zn) should be given (there is 50/ 220 mg of mg of elemental zinc in $ZnSO_4$). Plasma and serum levels of zinc (Zn) must bescrutinizedafter03– 06 months, altering the dosage of zinc (Zn), consequently. Clinical improvement is usually seen within days to weeks, even before serum zinc levels normalize. Whereas oral zinc supplementation seems counterintuitive in the absence of a zinc transporter, high-dose supplementation causes increased paracellular zinc absorption. In patients with acquired or dietary zinc deficiency, oral supplementation should begin at 0.5–1 mg/kg/day of elemental zinc, and the underlying cause of malnutrition should also be addressed. A significant side effect of zinc supplementation is gastrointestinal upset in the form of nausea, vomiting, or gastric hemorrhage. In our experience, the zinc gluconate formulation carries less risk of gastrointestinal upset. Furthermore, zinc has been shown to decrease copper absorption in patients with Wilson's disease, so serum copper levels should be followed during zinc supplementation **[35]**. Zinc deficiency may coexist with other vitamin, mineral, or amino acid deficiencies, so a thorough work-up should be performed **[36]**.

Targeted nutrient treatment

From 35 – 100 mg/ day, the factor is usually enough in divided doses. Sodium sulphate heptahydrate (50 mg on the prime element in 220 pieces) is commonly used, but aspartate, oxide and gluconate salts are also available. Individual needs for zinc vary, but in anabolic reactions after treatment, it is relatively higher in

childhood and before puberty. Clinical experience shows that zinc requirements decrease after puberty. However, they still managed 200 and 300 mg of zinc sulfate/ day for managing their young wife during pregnancy. The metallic taste of zinc solution can make them indescribable. In addition, large doses may cause nausea. Fortunately, there are forms enclosed in salt. Consumption of zinc salt with food may enhance its flavor, but zinc intake may decrease **[37]**.

CONCLUSION

The manifestations upon skin might cause supplier to diagnose nutritional deficiencies. In a child with peripheral or acral dermatitis, a deficiency of zinc, biotin, protein or EFA deficiency should be diagnosed, especially if it is accompanied by systemic symptoms of failure. Clinical history and complete work should be done because there may be more than one nutritional deficiency at a time. Nutrient deficiencies are easily treated with supplements, leading to rapid clinical improvement. Finally, nutritional deficiencies are a problem not only in developing or poor countries, but also in developed countries, as well as due to inherited or acquired diseases.

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