Chapter 1
History of Acrodermatitis Enteropathica

Acrodermatitis Enteropathica (AE) is an inherited autosomal recessive disorder which often presents in newborn infants [1]. This medical condition occurs as a result of mutation of a zinc transporter that affects the uptake of zinc in the intestine causing a decrease in the level of this elemental mineral in the blood [2]. Prior to this knowledge, untreated AE was considered deleterious to the infant's health and sometimes even fatal [3, 4]. Today however, the treatment involves adding zinc supplements to the patient's diet which can easily improve the condition [1, 3].

Except for the characteristic dermatitis, the symptoms of this disorder vary with age of the patient. Severe uncontrollable diarrhea, mood changes, anorexia, and neurological disorders are frequently reported in infants. Growth retardation, alopecia, weight loss, and recurrent infections have also been reported in toddlers and young children; and spontaneous remission may happen in adolescence [3]. Moreover, there have also been reports of mild sporadic cases in which the patient suffered from ophthalmic, hepatic, and encephalic complications [5]. Interestingly, the signs and symptoms of acquired zinc deficiency include dermatitis on hands and feet, alopecia, diarrhea, and the appearance of inflammatory rashes on the skin of face, hands, feet, and genitals, all of which represent the signs of AE [3].

The disorder was first discovered in 1902 by Wende [5], and further analyzed in 1936 by Brandt [6]. In 1942, it was

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labelled as Acrodermatitis Enteropathica (AE) by Danbolt and Closs, who proposed a clinical definition for AE, based on a triad of pathognomonic symptoms composed by acral and periorifical dermatitis, alopecia, and diarrhea [7]. Subsequently, in 1953 Neldner et al. reported a successful treatment of AE by diiodohydroxyquin, which was consumed orally in order to slow the progress of the disease in children and to prevent fatality in different stages of the disorder [8]. In 1974, Moynahan concluded that AE appeared in patients who suffer from zinc deficiency and that it could be abolished by oral zinc supplementation [9]. Prior to this finding, antibiotic amphotericin B, which increases intestinal membrane permeability to divalent cations, was used to treat the symptoms of this disorder [10].

Moynahan suggested that the absence of an enzyme called oligopeptidase in the intestine was responsible for the decreased serum zinc levels observed in AE patients [9]. Oligopeptidase is secreted by enterocytes for the degradation of proteins and Moynahan proposed that its absence resulted in the accumulation of oligopeptides which then would chelate with zinc, reducing available zinc for absorption. During the 1980s, it was suggested that zinc was mainly absorbed in the duodenum by binding with a low molecular weight zinc-binding ligand, which is mainly secreted by the pancreas and also present in small amounts in breast milk because infants are not capable of ZBL production during early infancy [11, 12]. Recently, it was revealed that the zinc-binding ligand does in fact facilitate zinc absorption [12]; however its mechanism is unknown and its main role in zinc absorption still needs to be elucidated.

In 2002 two independent studies showed that AE was due to homozygous or compound heterozygous mutations of *SLC39A4*, a gene located on chromosomal region 8q24.3, which codes for the zinc-specific transporter ZIP4 (or hZIP4) [13, 14]. This transporter is found more especially in the distal duodenal and proximal jejunal parts of the small [13], where it enables the absorption of zinc from the intestinal lumen. Through its function and localization, ZIP4 plays a major role in human zinc homeostasis, which explains the broad clinical picture of acrodermatitis enteropathica.

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