

## A Case of Acrodermatitis Enteropathica

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### Abstract

Clinicians should be mindful of all paediatric skin diseases, which present in a similar manner during the first months of life. Acrodermatitis enteropathica (AE) is a rare, bullous disorder that has a significant impact on the child's quality of life and is fatal if untreated. AE is either a recessively inherited or a transiently acquired disorder. The hereditary form is caused by a genetic mutation in intestinal zinc absorption whereas the acquired form is caused by low nutritional intake or decreased peripheral release of zinc from the blood.

This case report describes AE which manifested in a similar way to other blistering skin disorders, but showed a dramatic clinical improvement to oral zinc therapy.

AE is characterised by a triad of periorificial and acral dermatitis, diarrhoea and alopecia. Both forms of AE affect males and females equally. The cutaneous lesions are annular, erythematous, scaly, crusted plaques, which are well demarcated. As the disease progresses these plaques become vesicobullous, pustular and erosive. The lesions are distributed symmetrically, around body openings such as the mouth anus, eyes and skin of the elbows, knees, hands and feet. The alopecia diffusely affects the eyelashes, eyebrows and scalp. As described in the case, secondary infection by candida albicans or staphylococcus aureus may complicate the disease.

Classically the disease presented after the child was making the transition from breast milk to solid foods. Breast milk has comparatively higher zinc content and absorbability compared to infant formulas, cow's milk or solid foods.

This case emphasises the need for an open mind when treating childhood skin disorders. Once bullous skin disorders are suspected the case should be referred promptly to a specialist. An early diagnosis and prompt treatment of AE reduces mortality and prevents the long-term consequences of zinc deficiency.

**Keywords:** Dermatitis; Paediatrics; Bulla; Alopecia; Genetics

### What's already known about this topic?

Acrodermatitis enteropathica (AE) is a rare but severe blistering skin disorder that presents in early life.

AE is either a recessively inherited or a transiently acquired disorder related to zinc absorption.

AE is characterised by a triad of periorificial and acral dermatitis, diarrhoea and alopecia.

### What does this study add?

Acrodermatitis enteropathica (AE) presents in a very similar manner to other paediatric skin diseases within the first months of life.

Clinicians should be conscious of other rarer causes of skin disease especially in newly born children.

Once bullous skin disorders are suspected, refer promptly to a specialist dermatologist or paediatrician.

An early diagnosis and prompt treatment of AE, reduces mortality and prevents the long-term consequences of zinc deficiency.

### Introduction

Clinicians should be mindful of paediatric skin diseases, which present in a similar manner within the first few weeks of life. Acrodermatitis enteropathica (AE) is a rare, bullous disorder that has a significant impact on the child's quality of life and is fatal if untreated. AE is either a recessively inherited or a transiently acquired disorder [6]. The hereditary form is caused by a genetic mutation in intestinal zinc absorption whereas the acquired form is caused by low nutritional intake or decreased peripheral release of zinc from the blood [1].

AE is characterised by a triad of periorificial and acral dermatitis, diarrhoea and alopecia [7]. Bullous cutaneous lesions, paronychia and failure to thrive can also be present [8]. Symptoms usually occur in bottle-fed infants within weeks after birth or breast-fed infants soon after weaning [9].

### Aim

This Case Report describes AE, which manifested in a similar way to other blistering skin disorders, but showed a dramatic clinical improvement to oral zinc therapy.

## Patient Information

A 15 month old female infant presented to her General practitioner (GP) with a progressive rash and golden yellow crusting around her face, groin and buttocks.

The child was conceived after *in-vitro* fertilisation and was born full-term, with a simple vaginal delivery. She was breast-fed, making the transition to solid food. She was up to date with her immunisations, not taking any medication and was achieving milestones appropriate for her age. There was no family history of skin disease.

A diagnosis of Impetigo was made and the child received antibiotic therapy for three weeks with no clinical improvement.

The child was subsequently admitted to hospital with tense, clear variable sized bulla and pustules with a well-demarcated, erythematous base, distributed around her mouth, perineum and the acral sites of

hands and feet (Figure 1). These lesions were distributed symmetrically, were not pruritic and had no other mucosal involvement. Her mother reported that the infant had been suffering from clumps of hair loss from the frontal areas of her scalp. The infant was not systemically unwell, without any diarrhoea or abdominal pain. She was treated for a further five days with intravenous antibiotics, before a dermatology review investigated other differential diagnoses.

## Diagnostic Assessment

Epidermolysis Bullosa is a group of rare, hereditary disorders characterised by epidermal blistering and erosions following minor trauma or abrasion. Epidermolysis bullosa and AE typically present shortly after birth. More severe forms of the disease can affect internal organs, leading to hair, mucosal, genitourinary and nutritional abnormalities similar to the case report [10].



**Figure 1:** Acrodermatitis Enteropathica on 15 month old female characterised by periorificial and acral dermatitis and alopecia. There are annular, well demarcated, erythematous, crusted plaques and vesicles distributed symmetrically around orifices and hands.

At fifteen months old, the child will be mobilising independently. If the child did indeed have epidermolysis bullosa, the blisters would be more profuse, distributed almost anywhere on the body and would have presented at a younger age. These blisters would not be intact, may worsen in warmer climates and would be more evident on exposed areas such as the feet, elbows, hands and knees. The blisters

would heal with thickening of the skin on soles and palms with no scarring evident. Conversely, delayed wound healing is inherent with AE. The severe fragility of the child's skin would raise suspicion of epidermolysis bullosa. Even though the blisters may be distributed bilaterally, they would have an asymmetrical shape compared to AE. This is because the environmental factor such as minor trauma to the

skin has a role to play in their appearance. The symmetrical, periorificial distribution of blistering described in the case suggests that AE is more likely (Figure 1).

Linear IgA Bullous Dermatitis is a rare autoimmune blistering disorder that presents with an abrupt onset of annular tense vesicles or bullae, with clear fluid, abundant on the extremities. The distribution of the disease is comparable to the case report. Linear IgA dermatosis has mucosal involvement, with blisters on the lips and mouth of the patient. The case does not describe any ocular involvement but both AE and IgA dermatosis can cause eye irritation, dryness, photophobia, and blurred vision.

Conversely, IgA dermatosis is associated with certain drug exposure, inflammatory bowel disease, and other autoimmune conditions unlike AE. AE is more likely to present in early age, whereas IgA bullous dermatitis although it can present at any age, becomes more common in the elderly.

Childhood Bullous Pemphigoid is rare, but presents with pruritic, inflammatory plaques followed by multiple, large, tense bulla. Unlike the case presentation, bullous pemphigoid typically involves the palms, soles of the feet and also the oral mucosa, which heal with minimal scarring. Although childhood pemphigoid primarily presents in infancy, older children can have bulla localised to the perineum. The onset of dermatitis, diarrhoea and alopecia after the transition to solid foods are the classic clues for AE, which would be absent in childhood bullous pemphigoid.

Malabsorption syndromes secondary to cystic fibrosis or intestinal disease may manifest in a comparable pattern to AE. Despite an adequate diet, key nutrients including zinc may not be absorbed because of colitis and persistent steatorrhea from cystic fibrosis [11]. This may result in a diverse range of systemic signs and symptoms. Malabsorption syndromes also become apparent in young children or during the transition to a solid diet. The diarrhoea could equally be attributed to cystic fibrosis or AE. Fortunately the recent expansion of newborn screening programs identifies cases of cystic fibrosis before the presentation of symptoms.

Nappy Contact Dermatitis is common and presents with an erythematous, pruritic rash sparing the child's skin folds. The disease is well demarcated and distributed in the anogenital region, which is described in a similar manner in the case report. Due to the breakdown in the skin's integrity, the disease can be coexistent with a variety of infectious or immunological factors such as psoriasis, fungus and atopy, complicating the presentation. Opportunistic impetigo infection results in irregular, golden blisters and pustules, which explains why these characteristics were present in the patient's original presentation. With both AE and Nappy dermatitis the child will be irritable. In contrast however the alopecia, blistering and systemic manifestations including photophobia, growth retardation are absent in nappy dermatitis, which are present in AE.

Biotin and multiple decarboxylase deficiencies similarly to AE, result in dermatitis and alopecia. However the presence of feeding difficulties and neurologic findings including hypotonia, impaired consciousness, seizures and ataxia may be more suggestive of a decarboxylase deficiency. There is no evidence of any neurological deficit in the case. Furthermore, the clinical presentation and age of onset of decarboxylase deficiencies are extremely variable whereas AE typically presents in paediatric population [12].

Essential fatty acid deficiencies in children may be due to diet, disease, or prematurity. Physical clues for fatty acid deficiencies include scaly dermatitis, alopecia, and thrombocytopenia. Fatty acid deficiencies also affect growth, and cognitive and visual function in infants. However the development of symmetrical bulla, optical or mucosal involvement will help distinguish cases of AE from fatty acid deficiencies.

### Investigations

After a multi-disciplinary team discussion of the case, cultures of the wounds were taken which showed mixed skin bacteria and isolated candida albicans. Skin biopsy at this stage was not deemed necessary. Her serum zinc level was tested and discovered to be  $<2.0 \mu\text{mol/L}$  ( $11.4 \mu\text{mol/L}$ - $24.8 \mu\text{mol/L}$ ). Subsequently a diagnosis of Acrodermatitis Enteropathica was made.

### Therapeutic Intervention

After administration of zinc sulphate 1 mg/kg/day orally for one week, the cutaneous lesions showed improvement and her serum zinc level increased to  $9.4 \mu\text{mol/L}$ . Subsequently oral zinc sulphate 2.5 mg/kg/day, mometasone ointment and mupirocin 2% ointment were prescribed. All lesions have since disappeared and are now under observation (Figure 2). Genetic testing revealed that the child's parents were not carriers of AE.



**Figure 2:** Acrodermatitis Enteropathica clinical resolution after oral zinc therapy.



## Discussion

Both forms of AE affect males and females equally. AE is characterised by a triad of periorificial and acral dermatitis, diarrhoea and alopecia.

The cutaneous lesions are distributed symmetrically, around body orifices such as the mouth, anus and eyes or extremities such as the elbows, knees, hands and feet [13].

On closer inspection these lesions appear as annular, erythematous, scaly, crusted plaques, which are well demarcated. The plaques can become vesicobullous, pustular and erosive in advanced disease [14]. Secondary infection by candida albicans or staphylococcus aureus may complicate the presentation, as illustrated by the case.

The patient's nails can be affected with paronychia and ridging. The alopecia diffusely affects the eyelashes, eyebrows and scalp.

Clinicians should be observant of the mucosal findings associated with acrodermatitis enteropathica. Examination of the mouth may reveal angular cheilitis and glossitis. The presence of conjunctivitis, blepharitis and punctate keratopathy affecting the eyes will provide further clinical evidence for the disease.

Systemic manifestations include photophobia, irritability, growth retardation and delayed wound healing. Males can have delayed puberty and hypogonadism in the long term. The histopathology of acrodermatitis enteropathica is non-specific and thus not required to diagnose this condition.

Zinc is an essential element of our diet. It is a constituent of the enzymes carbonic anhydrase, alkaline phosphatase, dehydrogenase, and carboxypeptidase. These assist with brain function, cytokine and antioxidant production and carbohydrate metabolism. Therefore zinc depletion can account for the patient's, impaired taste, impaired immunity, growth retardation and hypogonadism encountered in clinical practice [3].

Crucially the disease presented after the child was making the transition from breast milk to solid foods. This is typical given the comparatively high zinc content and absorbability of breast milk compared to infant formulas, cow's milk or solid foods. Zinc is found in meat, shellfish, spinach, nuts and wheat germ. Phytates present in cereals and soy, and high levels of calcium in the diet, can reduce the absorption of zinc. The transient form of acquired zinc deficiencies can occur in premature infants secondary to their greater physiological demand for zinc combined with their lower body stores.

AE is either a recessively inherited or a transiently acquired disorder [15]. The hereditary form is caused by a genetic mutation in intestinal zinc absorption. The acquired form of the disease is due to low nutritional intake or decreased peripheral release of zinc from the blood [1].

The variant of AE associated with decreased peripheral release of zinc from the blood is often characterised by normal serum zinc levels. In such cases, it is important to measure zinc-dependent enzymes levels, especially alkaline phosphatase. Clinicians should be wary that alkaline phosphatase levels could be normal in the early phases of the disease.

Hereditary AE is caused by recessive mutations in the SLC39A4 gene on chromosome 8q24.3, which codes for the zinc transporter protein ZIP4 [3]. As a result a faulty copy of ZIP4 is created, leading to intestinal zinc malabsorption. Zinc absorption can be as low as 2%-3%,

compared to 27%-65% in unaffected adults [3]. In this case the clinicians performed a parental genetic analysis in order to highlight mutations in the SLC39A4 gene. Both parents were not carriers of the disease; therefore clinicians assumed that the child had a 'de novo' mutation.

A zinc replacement dose of 3 mg/kg/day is recommended as early as possible and can be given during pregnancy [4]. Zinc levels are measured every three to six months, adjusting the dose as required. Although zinc is usually non-toxic, high doses for a long period can result in gastrointestinal symptoms, dizziness, copper deficiency, and anaemia. Secondary bacterial and/or fungal infection of lesions requires appropriate antibiotic therapy.

## Conclusion

This case emphasises the need for an open mind when treating childhood skin disorders. Clinicians should be mindful of other rarer causes of skin disease especially in newly born children. Once bullous skin disorders are suspected, refer promptly to a specialist dermatologist or paediatrician. A review from a dietician is very beneficial in ensuring patients have adequate zinc consumption. The early diagnosis and prompt treatment of AE, reduces mortality, prevents discomfort, stress and the long-term consequences of zinc deficiency.

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