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# HEREDITARY ZINC DEFICIENCY (ADEMA DISEASE) IN CATTLE, AN ANIMAL PARALLEL TO ACRODERMATITIS ENTEROPATHICA

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*Abstract.* Adema disease and acrodermatitis enteropathica, two parallel syndromes in calves of Friesian descent and in man, are described. Both are congenital zinc deficiency disorders with a lethal course if left untreated. Complete recovery follows oral zinc therapy. Symptoms and findings are set out in Table I. Diseased calves may serve as animal models for further studies on acrodermatitis enteropathica and the biological role of zinc.

*Key words:* Acrodermatitis enteropathica; Animal model; Autosomal recessive inheritance; Paneth cell; Thymic hypoplasia; Zinc deficiency

Acrodermatitis enteropathica (a.e.) is a hereditary zinc deficiency disorder in man, the etiology of which is unknown. The disease seems to be identical with a genetic disease in cattle of Friesian descent, the so-called Adema disease (10, 13).

In the following, a short comparative description of the two syndromes is given.

*Adema disease in cattle* (Lethal trait A 46, congenital thymus hypoplasia, congenital parakeratosis, hereditary zinc deficiency).

The Adema disease is a congenital disorder in Black Pied cattle of Friesian descent, affecting the general condition, the gastro-intestinal tract, and the skin and mucous membranes. The first description was published by McPherson in 1964 (16). In Denmark the syndrome was reported in 1970 by Grønborg-Pedersen (10) under the name of Adema disease after the carrier bull (Adema 21 van de Woudhoeve). Because of the similarity to experimental zinc deficiency in cattle (18, 19) the disease was considered to be a zinc deficiency disorder, and has been successfully treated with oral zinc since 1970. Genetic studies have shown that the disease is transmitted by autosomal recessive inheritance (1).

Affected calves are born normal, the symptoms appearing in their first or second month with general loss of health and development of a dry, scaly coat. This is followed by loss of hair in certain areas and the formation of hyperkeratotic crusts around the muzzle, ears, and eyes as well as on the legs (Fig. 1). Stomatitis and conjunctivitis is a constant finding and respiratory tract infections and diarrhoea are frequent. The weight of the calves remains constant or decreases, and they seem mentally disturbed. If left untreated the calves will die within 3–4 months after birth.

*Post-mortem* examination in lethal cases reveals a marked hypoplasia of thymus and parts of the lymphatic system (5). Immunological investigations have demonstrated absent or deficient cellular immune response against *M. tuberculosis* antigen and DNCB (dinitrochlorobenzene) (6). A subnormal serum zinc concentration is a consistent finding (13) and alkaline phosphatase levels in serum are depressed (24). Recent studies have shown a poor intestinal uptake of $^{65}Zn$ in diseased calves, while the elimination rate of zinc is normal (9). A daily oral supplement of zinc restores the general condition, the integrity of skin and bowel as well as the lymphatic system (5, 13, 24).

*Acrodermatitis enteropathica*

In 1936 Brandt (4) described a syndrome in children which was subsequently named acrodermatitis enteropathica (8). The disease is a rare autosomal recessive disorder characterized by symmetrical demarcated eczematous skin lesions, varying from bullae to verrucous plaques in the mucocutaneous areas, flexures, and on the distal parts of the extremities. Paronychia, total alopecia, stomatitis, conjunctivitis with photophobia, and mental disturbances are often present. Growth is impaired,

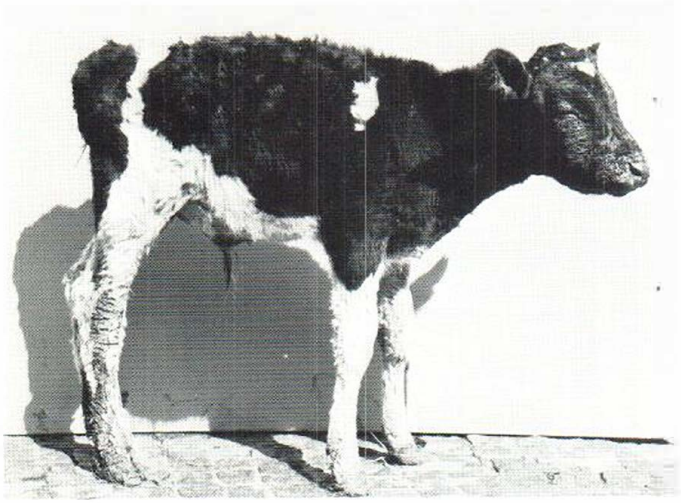

*Fig. 1.* Calf with Adema disease, approximately 3 months after birth. Note the hyperkeratosis around the muzzle and on the hind legs.

the health is poor with recurrent respiratory tract infections, purulent rhinitis and otitis, and local infections of skin lesions with *C. albicans* are common. Most patients suffer from intermittent diarrhoea with fatty, foamy motions. In some patients the bowel symptoms are transient.

The symptoms may start after the child has been weaned or shortly after birth if not breast-fed. Without treatment, the disease is progressive and has a fatal outcome in early childhood as a result of septicaemia or bronchopneumonia. Mother's milk was the only known therapy until the early 1950s, when treatment with halogenated hydroxyquinolines was introduced. This treatment was life-saving but not curative of all symptoms. Furthermore, there were potential side effects, especially damage of the visual function (3).

In 1973 Barnes & Moynahan (2) reported a low serum zinc value in a patient with a.e. and dramatic improvement following oral zinc therapy. Later reports have confirmed this and established the fact that a.e. is an inherited zinc deficiency disorder (17, 21, 25, 26). Lombeck et al. (15) found a decreased intestinal uptake of $^{65}Zn$ and normal elimination rates of zinc. Histological examination of biopsies from the intestine has revealed abnormal inclusions in Paneth cells—both before and after hydroxyquinoline therapy (14). Autopsy findings in a.e. have shown a marked hypoplasia of the thymus (12) and other lymphatic tissues (22). In untreated a.e. there seems to be a defective conversion of linoleic acid to arachidonic acid, resulting in low serum levels of arachidonic acid (7, 20); the catabolism of tryptophan seems to be disturbed (11, 23). Alkaline phosphatases in serum are abnormally low, especially the bone fraction, but rise promptly during zinc therapy (21, 26), reflecting the activation of growth.

In Table I the major symptoms and findings in Adema disease and a.e. have been listed for comparison.

## DISCUSSION

As seen from Table I, Adema disease and a.e. seem to be identical disorders with identical symptoms which can all be attributed to zinc deficiency.

The mechanism of the reduced intestinal zinc absorption in both diseases is unknown, but might be connected with an abnormal Paneth-cell function interfering with the transport of heavy metal ions, especially zinc and calcium. How hydroxyquinoline acts in a.e. is still not understood, but administration of the drug is associated with a modest increase in serum zinc concentration (21). To solve these problems, animal models might be useful.

In a.e. the reported abnormal metabolism of unsaturated fatty acids, which are precursors of prostaglandins, may explain the eczematous skin changes and the bowel symptoms.

Analyses of the prostaglandins in the affected organs before and after zinc therapy would be of great interest and can be made on diseased calves. Such studies are being pursued in our departments.

The immunological findings and the hypoplastic lymphatic organs as well as the reduced resistance

Table 1. *Major findings in Adema disease and acrodermatitis enteropathica*

For explanation and references, see text, n.s.=not studied

| | Adema disease | Acrodermatitis enteropathica |
|---|---|---|
| Autosomal recessive inheritance | + | + |
| Onset of symptoms a few weeks after birth | + | + |
| Loss of hair, skin lesions in mucocutaneous areas, in flexures and distally on extremities | + | + |
| Retarded growth | + | + |
| Diarrhoea | + | + |
| Decreased resistance to local and general infections | + | + |
| Mental disturbances | + | + |
| Hypoplasia of thymus and lymphatic tissues in lethal cases | + | + |
| Lethal course if untreated | + | + |
| Halogenated hydroxyquinolines improve the condition | + | + |
| Reduced intestinal uptake of zinc. Low serum zinc. Zinc therapy effective | + | + |
| Reduced concentration of alkaline phosphatases in serum | + | + |
| Abnormal Paneth cells | n.s. | + |
| Abnormal metabolism of unsaturated fatty acids and of tryptophan | n.s. | + |

to bacterial infections in both diseases indicate that zinc plays an important role in the development and function of the immunological system. This finding merits further investigations.

The attitude to genetic diseases in cattle is one of trying to eradicate the disorder rather than allowing affected calves to reach sexual maturity. Therefore, treatment experiments and metabolic studies on Adema disease have been of limited interest. By this report we hope to stimulate interest in carrying out such studies in order to gain more information about a.e. and the biology of zinc.

Zinc was used as therapy for diseased calves for more than three years before it was introduced in the treatment of a.e. No one had thought that the two diseases might be identical until both were classified as zinc deficiency disorders.

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