Acta Dermatovener (Stockholm) 54: 377–381, 1974

ZINC THERAPY IN ACRODERMATITIS ENTEROPATHICA

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Abstract. In an 18-year-old boy with acrodermatitis enteropathica treated with quinoline preparations since the age of 21 months, and who had suffered from hypertension, proteinuria, increased serum creatinine since the age of 17, and from incipient optic injury with imparied colour vision at the age of 18, chlorquinaldol was replaced by zinc sulphate given orally. This treatment resulted in complete healing of the skin, in abundant hair growth and the disappearance of gastrointestinal symptoms which was never achieved with the quinoline therapy. Colour vision and serum creatinine have returned to normal.

Acrodermatitis enteropathica (A.E.) is a serious illness which starts in early infancy after weaning. The pathogenesis of the disease is unknown. The onset is insidious. Gradually the condition becomes characteristic and is recognized primarily by changes in the skin and hair. As the name implies, there are also gastrointestinal symptoms, especially diarrhea. Skin lesions are acral, i.e. are localized on the hands and feet, as well as near the orifices, especially in the perioral and in the diaper regions. During inactive phases the skin in these areas is dry, erythematous, peeling, sometimes psoriasis-like, while during the active periods it is vesicopustular, red and erosive. Secondary infection from yeasts and bacteria is common. The hair grows poorly and total alopecia and loss of eyebrows are seen in untreated cases. Without treatment the disease is progressive. After the report by Schlomovitz in 1953 on the effect of quinoline preparations given orally to patients with A.E., the prognosis of the disease has improved (12). How quinolines accomplish their effect is unknown. Hansson has proposed that the effect of quinolines might be the result of competition between quinoline and a toxic tryptophan metabolite (9). Continual treatment with large doses of quinolines is required. A daily minimum dose for a teenager is likely to be between 2 000 and 3 000 mg chlorquinaldol (Sterosan®—Hässle-Ciba-Geigy, Mölndal, Sweden). However, a serious side effect of quinoline preparations, first described by Berggren & Hansson, is an optic atrophy (4). Regular ophthalmological controls of these patients are therefore required.

Recently we have had another A.E. patient with incipient optic injury probably caused by chlorquinaldol treatment. A replacement of the quinoline therapy by oral administration of zinc has produced a dramatic relief with healing of the A.E. and normalization of the colour vision. Excellent results with zinc therapy in several A.E. patients has been reported by Moynahan (11). A preliminary report is therefore presented in order to draw attention to zinc as a probably superior alternative treatment for this disease and which should be tried on other A.E. patients before side effects from the high doses of quinolines become evident. Furthermore, the treatment with zinc has induced complete healing in our patient which was not achieved with the quinoline treatment.

CASE HISTORY

The patient is an 18-year-old boy (born 1955) whose case history has previously been described by Thyresson (14) and by Hansson (9). The first symptoms of A.E. appeared at the age of 5 months, 1½ months after weaning, with "eczema" of the face. Later, similar changes occurred in the diaper region and on the hands and feet. At 8 months of age the skin in these areas was erythematous, vesicopustular and crusty. No definite diagnosis could be made. When the boy returned after one year, he had developed a typical picture of A.E., with widespread skin changes, almost total loss of hair, eyebrows and eye lashes. He also had periodic diarrhea. At the age of 21 months (1957) treatment was begun with 600 mg of 5-7-diiodo-8-OH-quinoline (Enterosept®—AB Ferrosan, Malmö, Sweden) with good results. Since the age of 7 years he has been prescribed 5-7-dichlor-8-OH-quinoline, i.e. chlorquinaldol (Sterosan®). The daily dose was between 800 and 1 200 mg chlorquinaldol, depending upong the condition of the skin. Even with this dosage the skin never healed completely and, since the age of 13,

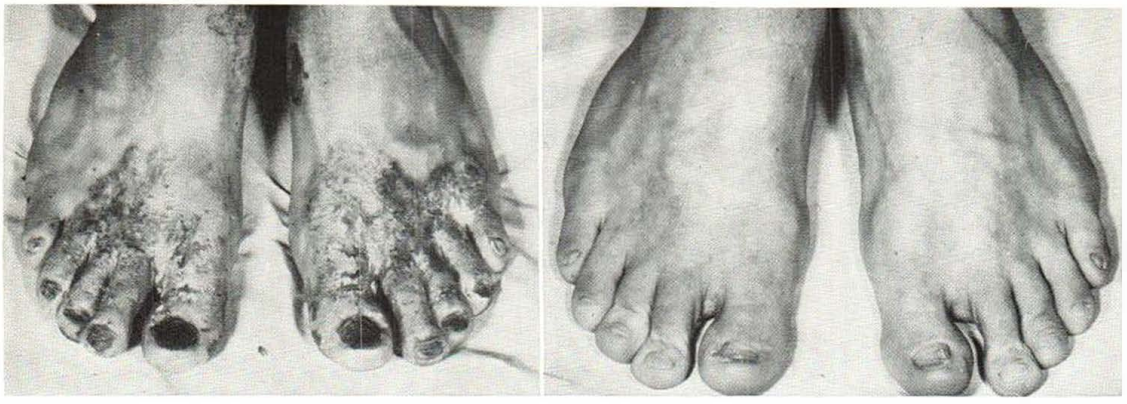

Fig. 1. Left: before start of zinc treatment; still on chlorquinaldol 1 200 mg daily. Right: after 4 months on zinc and decreasing doses of chlorquinaldol, and off this drug for 1 month.

his dermatitis became more active and a minimum dose of 1 800 mg/daily has been required in order to prevent the skin changes from becoming erosive. At 15 years of age there also developed a severe conglobate acne. In 1971 at 17 years of age, the patient was found to have developed hypertension with blood pressure 190/130, proteinuria, and a serum creatinine of about 1.5 mg%. After thorough examinations in the pediatric, medicine and geriatric clinics, the hypertension was interpreted as renal. A kidney biopsy showed nephrosclerotic changes. An abnormal plasma fatty acid spectrum was also present.

The hypertension has been satisfactorily corrected with propranolol. An attempt to radically reduce the dose of chlorquinaldol resulted in widespread erosive skin changes in the typical, predisposed areas. A full dose of chlorquinaldol was again prescribed in autumn of 1972. In order to obtain a satisfactory condition, a minimum of 2 400 mg/daily was now required. Despite the increased dose, the skin changes were periodically very active. There were also some complaints about a slightly impaired vision. An ophthalmological examination in May, 1973, revealed signs of impaired colour vision which was interpreted as a sign of incipient optic injury, possibly caused by chlorquinaldol. It was now considered necessary to reduce the dosage from 2 400 to 1 200 mg/daily. Within a week, the skin condition again deteriorated (Fig. 1). On this occasion the serum zinc value was 50 μg% (normal range 90–130 μg%). A low serum zinc value had also been observed some months previously.

The first attempts with alternative treatments had no effect. A diet deficient in tryptophan was tried but proved to be incompatible with a diet prescribed for lipid imbalance, as well as being without therapeutical value. Treatment with large doses of vitamin E—given on the basis of certain similarities between the acute phases of A.E. and epidermolysis bullosa—and with large oral doses of cromoglycate—given in view of its recently reported effect in milk-sensitive infants (6)—were also without results. A surprisingly good effect has been obtained, however, with zinc given orally in the form of zinc sulphate 0.2 g × 3 equal to zinc^{2+} 45 mg × 3 (Solvezinc®—AB Tika, Lund, Sweden). Within a week the patient began to notice an obvious improvement and, at a control 18 days after treatment was begun, the dermatitis was healed and only a slightly erythematous shade marked the places of earlier erosive changes. Three months after the start of treatment the appearance of the skin was completely normal (Fig. 1). Hair growth has also become normal and the patient now has thick, dark eyebrows, normal eyelashes (Figs. 2,3) and a thick head of hair is appearing. The hair which is now coming in is cendré and differs both in color and structure from the thin, silky, light and sparse hair that was always present earlier during quinoline therapy. Previously the limbs have always been hairless but during zinc treatment there has been a rich growth of hair, especially on the legs. The gastrointestinal problems have disappeared. Above all, the patient has a very positive feeling not only of being well for the first time in his life but also of being able to think, enjoy school, etc. The patient has now been off the quinoline preparation for 3 months. His serum creatinine has decreased from 1.3 to 0.9 mg% while undergoing the zinc therapy. His serum zinc levels are now normal. The effect on his lipid imbalance and kidney changes is not yet thoroughly analysed.

DISCUSSION

The basic biochemical defects involved in A.E. are unknown. As the disease does not appear until after weaning, it has been logical to suspect some form of food intolerance, primarily for cow's milk. The symptoms, especially those of retarded growth and development, also could represent a deficiency syndrome. Since gastrointestinal disturbances with diarrhea often occur, it seems probable that there is some form of intestinal dysfunction which might be of essential pathogenetic importance. Hansson has suggested as imbalance of the tryptophan metabolism, possibly secondary to an enzyme defect (9). A period with a tryptophan-deficient diet was tried by our patient but gave no positive results. Defective metabolism of unsaturated fatty acids and

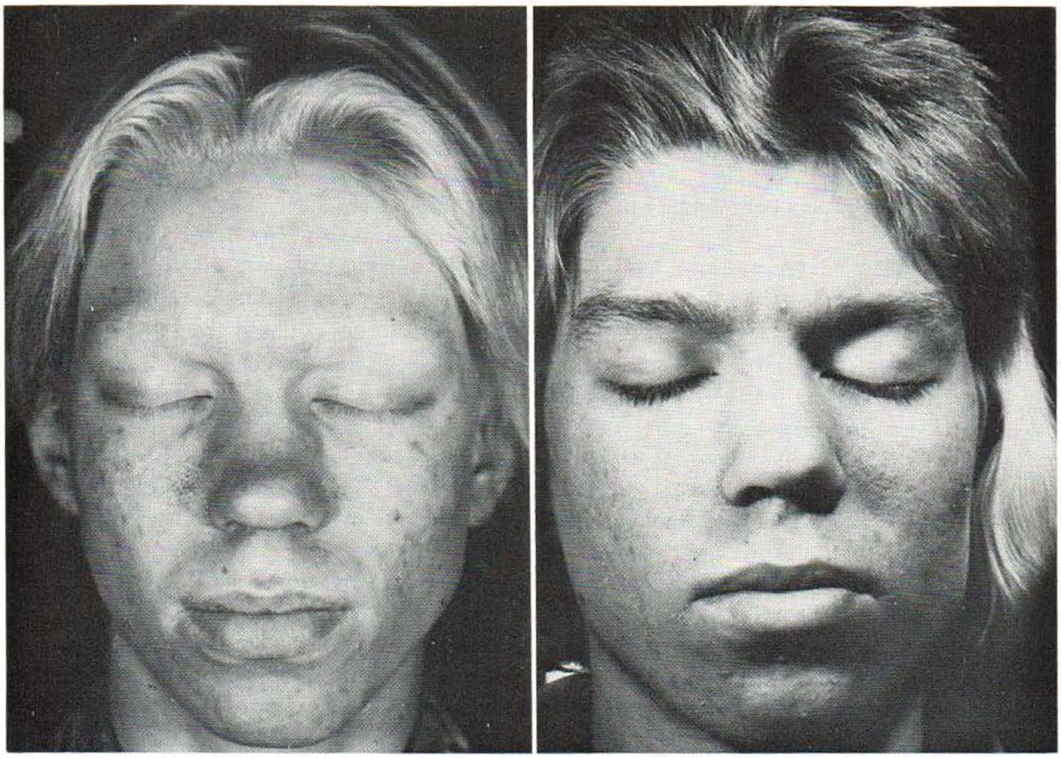

Fig. 2. Left: optimal condition obtained by chlorquinaldol. Hair light, sparse, silky, no eyebrows; eyelashes light and sparse. Right: after 5 months on zinc—hair, eyebrows, eyelashes growing.

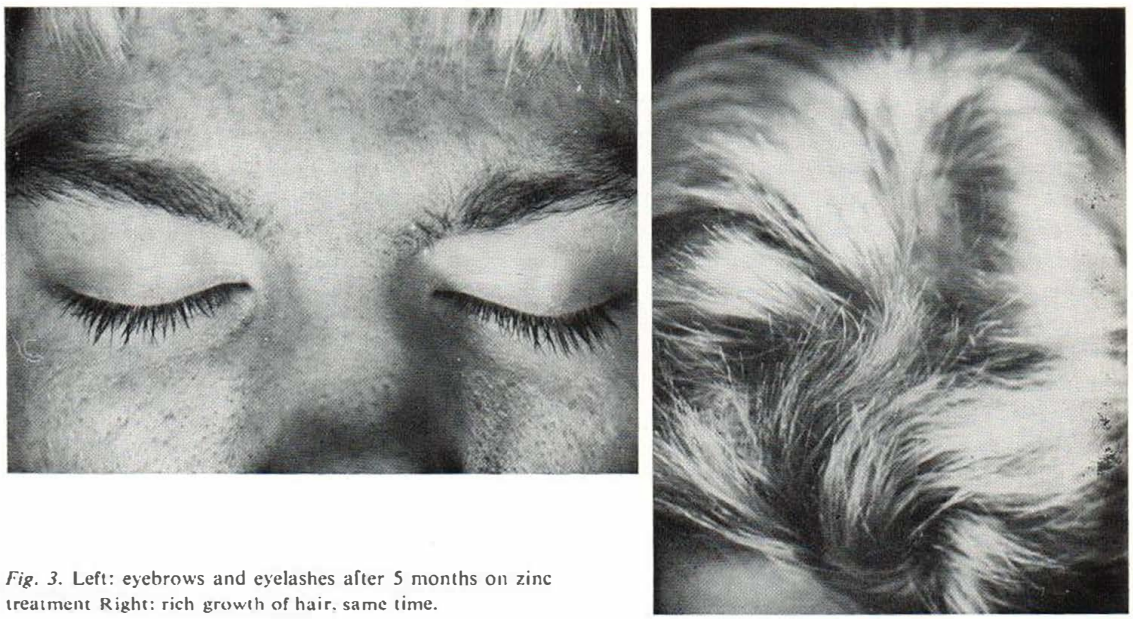

Fig. 3. Left: eyebrows and eyelashes after 5 months on zinc treatment Right: rich growth of hair, same time.

especially an impaired synthesis of arachidonic acid has been described by Cash & Berger in this disease (5). They also observed improvement after intravenous lipid infusions. As lipid changes have been reported in zinc-deficient animals, it might, however, be speculated that the changes in the lipid metabolism present in A.E. may be secondary to the zinc deficiency (10).

Treatment with quinoline preparations has improved the prognosis of the disease, but serious side effects of quinoline preparations such as optic atrophy in several patients has darkened the picture, especially as no other therapy has been available. Our first alternative treatment attempts were without results. Barnes & Moynahan in a report in 1973 with the title "Zinc Deficiency in Acrodermatitis Enteropathica: Multiple Dietary Intolerance Treated with Synthetic Diet" described a 2-year-old child with A.E. who was given a synthetic diet including vitamin and mineral complement in which, at first, the quinoline dose could be reduced without worsening the condition (2). Later, however, higher doses of quinolines were required but even so they were not effective. It was found that the synthetic diet contained too low an amount of zinc. After being given extra zinc, the child improved and gradually could tolerate normal baby food. That a zinc deficiency could have been of direct pathogenetic importance for A.E. was not obvious at that time, but with this finding, attention was directed to zinc as an important substance in this disease. Moynahan has since found low zinc levels in several A.E. patients (11). Our patient has previously always had an ordinary diet, with the exception of the attempt to maintain a low fat intake. A deficient supply of zinc has probably not existed. Treatment with zinc sulphate was tried when other therapy attempts had failed. The effect of zinc has been dramatic, with extraordinarily good results on the skin condition, the hair and nail changes, and on the gastrointestinal symptoms, as well as on subtle psychological symptoms. The patient is now completely without symptoms—a situation which never occurred during the quinoline treatment. His ophthalmologic condition has been normal for several months. His spontaneous comment that, "I feel like a new person and it is also much easier to think" is noteworthy.

The function of zinc in man, as well as the symptoms associated with a zinc deficiency, are still incompletely known (for reviews, see 1,7). Zinc occurs in large amounts in the testes, kidneys, liver, pancreas, thyroid gland, and also in the skin, hair and nails. For many plants and animals, zinc is of essential importance for normal growth. In pigs a zinc deficiency syndrome has been described by several authors and especially by Tucker & Salmon (15). The syndrome is called "Parakeratosis or Zinc Deficiency Disease in the Pig" which consists of dermatitis, anorexia, vomiting, diarrhea, poor growth and, in extreme cases, death. A detailed description of pig dermatitis has not been given by these authors but, judging by the photographs, it is especially prevalent around the snout, buttocks, and on the extremities, i.e. the localization of the affected areas is comparable to that in A.E. After zinc supplement, the pigs quickly improved and obvious changes in the skin were noted even after only one week. The time course for healing is the same as with our patient. Tucker & Salmon have also shown that development of dermatitis is influenced not only by zinc deficiency but is also dependent on the amount of calcium supplied. The frequency of dermatitis with a concurrent low zinc supply increased in those pigs which received a larger calcium ration, compared with those on a low-calcium diet. The occurrence of such a zinc–calcium antagonism in man could not be verified by Spencer et al. (13). However, their study included only 5 middle-aged patients, 2 of whom had osteoporosis and one, chronic dermatitis.

It now seems quite clear that zinc and zinc deficiency occupies a key position in A.E. Moynahan now has 10 A.E. patients who are all treated with zinc and all of them are responding very well (11). The mechanism behind the zinc deficiency in these patients cannot yet be explained. A purely exogenous zinc deficiency appears to be less probable than a defective absorption of zinc, since the level of zinc in cow's milk does not differ greatly from that in breast milk (8). Information concerning the zinc content of milk varies, however, and apparently there are large variations in the zinc levels in both human and cow's milk (3). The difference, between the calcium content of cow's milk and human milk is considerable (125 resp. 33 mg%). In healthy infants the change at weaning in the dietary zinc–calcium ratio does not seem to result in lowered plasma zinc levels during the period between 4 and 11 months, compared with the levels in the period between 2 and 12 weeks (3). One possible explanation for the fact that the disease appears parallel

with the change from breast milk to cow's milk in the diet might be the result of a difference between A.E. patients and healthy infants with regard to a calcium–zinc antagonism. There are, however, many other differences between human and cow's milk which might be of importance in this disease. It is not yet known if there is an isolated defect in zinc absorption or if the absorption defect is secondary to other factors such as to food intolerance or to enzymatic errors or to changes in the intestinal mucosa which might lead to a disturbance of the transportation of zinc.

It has been very instructive to observe, as through a magnifying glass, the dramatic effects of zinc in our zinc-deficient patient on his skin, hair, and general condition. Zinc is without doubt worth further attention.

ACKNOWLEDGEMENT

I wish to thank Dr E. J. Moynahan, Guy's Hospital, London, for his kind and stimulating information concerning acrodermatitis enteropathica and zinc.

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Received December 19, 1973

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