ACRODERMATITIS ENTEROPATHICA SUCCESSFULLY TREATED WITH DIODOQUIN*

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In 1942 Danbolt and Closs (1) called attention to a group of cases in infants which are characterized by simultaneous occurrence of cutaneous and gastrointestinal disturbance, with periods of exacerbations and remissions, associated with alopecia of the scalp, eyebrows and eyelashes. The eruption consists of irregularly shaped fairly well defined vesiculo-pustulo-bullous plaques located in the region of the mucocutaneous orifices and on the peripheral areas of the extremities. The distal phalanges of the fingers and toes show severe paronychia and the nails are distorted. During the period of exacerbation the cutaneous lesions become acutely inflamed, the oral mucosa is covered with whitish spots and there is marked halitosis present. The children suffer from diarrhea and abdominal discomfort, associated with marked anorexia, listlessness and mental depression. Retarded body growth is another feature of the syndrome. As the authors assumed that the gastrointestinal disturbance is the primary factor and the cause of the eruption and the alopecia, they coined the name “acrodermatitis enteropathica.”

In 1953 Dillaha and collaborators (2) reviewed the literature, collected twenty cases which could fit into this group and added a case of their own. These cases have been reported under different diagnoses: Four, as epidermolysis bullosa; 2, moniliasis; 3, systemic thrush; six, “dermatitis in children”; 1, “unusual syndrome” and 4, “acrodermatitis enteropathica.” The onset of the condition varied from three weeks to one and one-half years of age.

In addition to these cases, we found in the literature three more cases which fit into this group. One case was presented by Finkelstein (3) and was thought to be related to epidermolysis bullosa. The other two cases are those reported by Romeo and Mattina (4) and by Ugland (5). In the latter case the clinical symptoms indicated fibrosis of the pancreas which was confirmed by autopsy.

In 3 cases monilia was found in the skin lesions and stools; in 1, in stools, the mouth and in some skin lesions; in 1, in the mouth and stools; in 3, no monilia was found, and in the others no examination for monilia was reported.

In 8 cases several siblings were affected. Consanguinity of the parents was reported in two of these cases, (4, 6), and in another case in which only one child was affected (5). Treatment in most cases was ineffective. In 2 cases conservative therapy and hospitalization led to recovery. In one case antisprue diet was of temporary benefit and in another thymol administration resulted in partial recovery. Cortisone was of temporary benefit in the case of Dillaha (2), and in the case of Ugland (5) it had a striking effect. However, in this latter case the child died 5 days after discontinuation of cortisone therapy, following an intratibial transfusion of blood. Death was probably due to fat embolism of the lung.

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The syndrome of acrodermatitis enteropathica is to be considered of serious nature as six of the children are known to have died, the oldest of which was 8 years of age.

Dillaha and collaborators were the first to report rapid curative effect from diodoquin (diodohydroxyquinoline). Not only did the eruption and gastrointestinal disturbance cease entirely, but the child grew a normal crop of hair. Four months after discontinuation of therapy the child was still well. Diodoquin contains 63.9 per cent of iodine and is being used in the treatment of intestinal amebiasis. It is only slightly absorbed from the gastrointestinal tract. The use of this drug in acrodermatitis enteropathica by those authors is due to the suggestion of Dr. Schlomovitz (7) who haphazardly had chosen diodoquin from several iodine compounds and had obtained a dramatic cure in a similar case of his own.

The purpose of writing this paper is to report a case of acrodermatitis enteropathica which is almost identical with that reported by Dillaha and collaborators and in whom diodoquin was also spectacularly successful, although in our case the drug had to be administered continuously in order to keep the patient well. Since Dillaha (8) has observed, in addition to his reported case, another one of acrodermatitis enteropathica which has similarly benefited by diodoquin, ours is thus the fourth case known to have responded rapidly to diodoquin. Because of the obscure features of this disease which require elucidation, the report of any additional case which is closely observed and carefully investigated should be recorded.

REPORT OF A CASE*

N. M., a boy aged 4, who was born in Italy and had resided for one month in the United States, was seen for the first time at the Skin and Cancer Unit, on June 5, 1953, with a generalized eruption and total alopecia of the scalp which had been present since early infancy, associated with gastrointestinal disturbance.

The following history was obtained from the parents: Following an uneventful pregnancy of the mother, the boy was born at term and was delivered by a midwife. Two days after birth he developed convulsions which were considered to have been caused by an intrapartum cerebral hemorrhage. The convulsions never recurred. At the age of 3 months perianal and intergluteal erythema developed which lasted about three months and reappeared several months later. At the age of 1 year, following an attack of whooping cough and measles, the eruptions became exacerbated and extended, gradually involving other areas of the skin and the nails. The hair on the scalp was fuzzy since birth, except for a short period during the first year of age in which some longer hairs grew over the center and occipital area of the scalp.

Since the age of 6 months the child suffered from attacks of gastrointestinal disturbance consisting of abdominal discomfort and diarrhea with 4 to 5 daily bowel movements. These attacks recurred every few weeks and were associated with an eruption of white spots on the buccal mucosa, a thickly coated tongue and halitosis. The child became apathetic and refused to eat. These gastrointestinal attacks were associated with a simultaneous exacerbation of the cutaneous eruption. Although in the periods of remission the child improved considerably in regard to the gastrointestinal disturbance as well as the cutaneous and mucous membrane eruption, the illness never completely receded. The total alopecia of the scalp persisted without any change.

In the course of his sickness the boy was seen by several dermatologists in Italy. Some considered the alopecia independent of the skin and nail lesions and diagnosed the case as “epidermomycosis and onychomycosis.” Others made the diagnosis of “eczematoid dermatitis, epidermitis and aphthous stomatitis with perlèche.” At still another clinic a “rare type of

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Fig. 1. Exfoliation of vesiculo-bullous plaques

Fig. 2. Eruption in stage of exacerbation
cutaneous moniliasis was considered and on mycologic examination a fungus belonging to the genus Torulopsis was found. Treatment consisted of potassium iodide internally and antimycotic agents externally with only partial and temporary benefit.

The child was breast fed until the age of 15 months.

The family history revealed that the parents were first cousins. A younger sister was normal, and no other member of the family was affected.

On the first examination the boy appeared frail and underweight, unhappy and apathetic. He presented a generalized eruption which consisted of irregularly shaped, fairly well defined erythematous-vesiculo-pustular scaly plaques located on the Achilles tendons, ankles, dorsal and plantar surfaces of the feet, in the popliteal spaces, on the knees, in the inter-gluteal fold and adjacent parts of the buttocks, on the distal part of the penis, on the elbows, arms and forearms, and on the hands and fingers (Figs. 1 and 2). The periphery of some of the plaques consisted of vesicles and small bullae. In addition to the plaques there were present on the hands and feet satellite vesicles, bullae and pustules. The distal phalanges were erythematous, edematous and thickened. All the finger and toe nails were brownish discolored, distorted and associated with severe paronychia. There was perlèche and blepharitis present (Fig. 3). The buccal mucosa showed reddish and whitish spots and the tongue was coated with a white fur. The eyebrows were thin, particularly at the lateral aspect, and the entire scalp was covered with thin fuzzy hair.

Since the parents refused to permit hospitalization of the child, we had to observe and study the patient ambulatorily.

Although at first the eruption appeared as that of epidermolysis bullosa, further observation convinced us that we are dealing with the peculiar syndrome of acrodermatitis enteropathica.
In the course of our observation of the patient, we noted exacerbations and remissions of the eruption which ran parallel to the exacerbations and remissions of the gastrointestinal disturbance. During the period of exacerbation the eruption on the feet became so severe and painful that the child had great difficulty in walking. The sad appearance of the patient and his apathy during such attacks was impressive, and the change to cheerfulness during remissions was conspicuous. In the period of remission the vesiculo-bullous plaques became less inflamed and drier, and appeared hyperkeratotic, psoriasiform and exfoliating (Fig. 4). Frequently some of the plaques were still acutely inflamed while others were dry.

Laboratory studies consisted of examination of urine, blood counts, erythrocyte sedimentation rate and blood chemistry. The latter included examination for serum calcium, phosphorus, non-protein nitrogen, total protein, and also blood sugar and glucose tolerance tests. Of these the only abnormal finding was the increased sedimentation rate of 42 mm. (normal up to 10 mm.). The fasting blood sugar on one occasion was 30 mg. per cent, but on a second occasion it was 60 mg. per cent (normal, 60–100).

Examination of the feces for lipid partition gave normal findings. Pathogenic bacteria and monilia albicans were not found. However, cysts of giardia lamblia were seen. Mycologic examination by smear and culture from the pericoccal lesions, the nails and from a large pustule on one foot revealed candida albicans. From this pustule there were also cultured many colonies of staphylococcus aureus coagulase positive and non-hemolytic streptococci. The other skin lesions and those of the tongue, however, did not grow any monilia. Intradermal test to stock oidiomycin in 1 to 1,000 dilution gave a mild erythematous reaction, while a 1 to 30 dilution produced an indurated erythematous papule. A complement fixation test with an extract of candida albicans, done by Dr. Charles Rein, gave

![Fig. 4. Eruption in remission](image)
a strongly positive reaction, in contrast to the serum of control patients which did not give any reaction.

Because of reports of intestinal organic damage being associated with giardiasis (10) a roentgenogram of the gastrointestinal tract was done, but no abnormality was noted. A roentgenogram of the chest also gave normal findings.

A biopsy specimen from an erythematous-bullous lesion of the hand, examined by Dr. Charles Miller, showed an acanthotic epidermis with large intraepidermal vesicles filled with serum containing a few cellular elements, most of which were leukocytes. In the upper and middle cutis there were dilated blood vessels with a mild perivascular inflammatory reaction of round and connective tissue cells in the middle cutis and a marked diffuse infiltration in the papillary bodies and upper cutis (Fig. 5). A biopsy from an erythematous scaly plaque on the leg showed acanthosis of the epidermis with an increased granular layer and slight hyperkeratosis. In the upper and middle cutis the blood vessels were dilated, some of which were filled with erythrocytes. In the upper cutis and in the papillary layer there was a diffuse cellular infiltration consisting of round cells and wandering connective tissue cells (Fig. 6).

Treatment which consisted of application of antibiotic and tioform ointments, gentian violet solution and potassium permanganate baths was of some benefit. But marked improvement was noted only following administration of diodoquin. This drug was given first on July 13th, in the dosage of 210 mg. twice a day, and increased to three times a day on July 29th. On September 9th, the dosage was increased to four times a day, and, soon after, the eruption began to disappear, leaving after several weeks no trace of the eruption. The gastrointestinal attacks ceased. The hair on the scalp, which had consisted of mild lanugo hair, became thicker. Although the administration of diodoquin was discontinued on November 9, 1953, the child was still well when seen three months later. He had developed a normal appetite and had gained in weight. The scalp showed normal hair growth.

However, soon after, the child again complained of mild abdominal discomfort associated with two loose stools a day. This was followed by a mild eruption which consisted of

![Fig. 5. Erythematous-bullous lesion: Large intradermal vesicles with marked inflammatory reaction of papillary layer.](image-url)
ACRODERMATITIS ENTEROPATICA AND DIODOQUIN

elongated erythematous pustular lesions on each popliteal space, a scaly plaque on the right temple and blepharitis. The tongue and buccal mucosa were covered with white lentil-sized spots. This exacerbation was rapidly suppressed by administration of diodoquin, but recurrence of mild or moderately severe symptoms of gastrointestinal disturbance and cutaneous changes took place each time the drug was discontinued.

During these attacks examination of the feces was done on several occasions and revealed on one occasion a moderate number of monilia organisms and a few cysts of giardia lamblia. On another occasion no cysts or ova of giardia were found, no pathogens, but numerous yeast-like organisms which were identified as candida albicans. Scrapings of a scaly lesion of a toe of one foot and from smears of the tongue and buccal mucosa showed on cultural examination a few colonies of monilia albicans, but no monilia were grown from the lesions on the skin. An intradermal injection of a suspension of the patient's own organisms of monilia albicans in saline gave no reaction.

No by-effects from diodoquin were noted. However, the parents observed that the child developed on several occasions following ingestion of diodoquin a stuttering speech which became worse when the dosage was increased and ceased when diodoquin was discontinued. We were not convinced that this speech difficulty was due to the effect of diodoquin.

When seen on June 9, 1954, one week after having received 975 mg. of diodoquin daily for one week, the child was well, except for some thickened skin in the area of previous

Fig. 6. Histopathology of erythematous scaly plaque
bullous lesions on the dorsum of the right foot and in the popliteal spaces. The speech of the child was normal. Diodoquin was then reduced to 650 mg. a day. * 

COMMENT

This peculiar syndrome of acrodermatitis enteropathica requires elucidation. In the differential diagnosis and in consideration of the possible etiologic factors moniliasis, sprue, giardiasis and epidermolysis bullosa have to be discussed.

We agree with Dillaha and others that monilia infection in this syndrome is a secondary phenomenon. The interrupted progressive disease process, the total alopecia not preceded or accompanied by dermatitis of the scalp, the familial occurrence and, last but not least, our inability to find monilia on each occasion in the feces and in the lesions of the mouth and skin speak against moniliasis as a primary factor. Also the failure to produce cutaneous lesions by inoculating the patient with a culture of his own organisms of candida albicans favors this conception. The strongly positive complement fixation test in our case does not contradict this opinion. According to MacKenna (11) serologic and cutaneous sensitivity tests cannot be relied upon in the diagnosis of moniliasis. For positive results can be obtained also in healthy persons who harbor the fungus in the alimentary canal or elsewhere. Epstein (12) states that the “immunity reaction in moniliasis while of biological interest is not of practical importance.” The frequent occurrence of oral monilial infection in infants is explained by Berg (13) as due to the fact that “every depression of vital energy favors development of thrush in infants.” According to Holt and McIntosh (14) thrush is common in young infants and in all protracted exhausting diseases of early life.

Another diagnosis can be eliminated in our case, namely, that of sprue. For the absence of steatorrhea, the normal roentgenogram of the gastrointestinal tract and the normal glucose tolerance test speak against it. In the case of Danbolt and Closs no benefit was obtained from antispue diet.

The presence of giardia lamblia in the feces of our patient forces us to consider the question of giardiasis being a factor in the causation of the syndrome of acrodermatitis enteropathica. It is true that the majority of authors consider giardia lamblia as a saprophytic protozoan of the intestinal tract. It is also true that no case in a child is on record with conclusive autopsy findings to prove that the parasite is responsible for pathologic lesions. Nevertheless, Véghelyi (15), McGrath, O’Farrell and Boland (16), Ormiston, Taylor and Wilson (17), O’Donovan, McGrath and Boland (10), Dunn (18) and Daecke (19) report cases which suggest that the giardia parasite may be pathogenic. Although only one other case of acrodermatitis enteropathica is known to us in which giardia lamblia was found in the feces (4), it does not prove that this parasite was not present in the gastrointestinal tract. Only duodenal intubation can exclude giardiasis with certainty. Although there is no case of giardiasis reported as such in the literature in which the syndrome of acrodermatitis enteropathica was associated, nevertheless, this parasite must be kept in mind as a possible etiologic agent.

* Further observation of the patient after presentation of this paper at the New York State Medical Society permitted us to add some of these data.
The familial incidence in 8 cases of acrodermatitis enteropathica in the literature suggests a hereditary factor. The presence of consanguinity in the parents of our patient may be of significance. For it is the fourth reported case of consanguinity and, from a genetic point of view, an addition to the eight familial cases of this syndrome. It strengthens the concept that we are dealing with a congenital hereditary abnormality of a recessive mode of transmission.

Thus the question of the possible relation of acrodermatitis enteropathica to hereditary epidermolysis bullosa seems of interest and importance. It appears to us that it is possibly no coincidence that several cases like those of Wende (6) and Guy (20) were reported under the title of epidermolysis bullosa, that the case presented by Finkelstein (3) was thought to be related to epidermolysis bullosa and that the case of Dillaha (21) was presented first as dystrophic epidermolysis bullosa. There are, of course, several points which would make one hesitate to consider any relation of the disease to epidermolysis bullosa: 1) The association with alopecia of the scalp, which is usual in acrodermatitis enteropathica, is not commonly known in epidermolysis bullosa. 2) Mechanical trauma does not seem to play the role in acrodermatitis enteropathica as it does in epidermolysis bullosa. 3) The gastrointestinal dysfunction which is common in the syndrome of acrodermatitis enteropathica is unknown in epidermolysis bullosa. 4) The dramatic response of diodoquin observed in 4 cases of acrodermatitis enteropathica would seem strange if it occurred in hereditary epidermolysis bullosa.

However, some of these objections can be met with the following answers: First, hypotrichosis or total alopecia, although little known in typical epidermolysis bullosa, has been, nevertheless, observed by Mendes da Costa and van der Valk (22), by Linser (23) and by Sakaguchi (24).

Secondly, mechanical trauma does not always play such an important part in epidermolysis bullosa. For close observation of cases of epidermolysis bullosa, particularly of the dystrophic type, often reveals appearance of crops of bullae, preceded by and associated with malaise, independent of any apparent mechanical trauma. These cases can best be explained, in our opinion, by an underlying inherited metabolic disturbance of an obscure nature, which is also the opinion of Colombini (25) and Polland (26) who consider epidermolysis bullosa as caused by products of faulty metabolism.

A similar obscure metabolic disturbance may be assumed to be connected with the gastrointestinal dysfunction in acrodermatitis enteropathica. The possible nature of this dysfunction, which has been discussed at great length by Danbolt and Closs, lacks, so far, a satisfactory explanation.

We are now confronted with the question, how can the beneficial effect of diodoquin be explained, and can it be reconciled with the above theories in regard to the possible etiology of acrodermatitis enteropathica?

Considering the fact that diodoquin is only slightly absorbed from the gastrointestinal tract, one must assume that its effect is due to the action on the gastrointestinal tract itself by its antibacterial or antiparasitic effect, which prevents formation of toxic products and their absorption from the intestines.
How can the curative effect of diodoquin be reconciled with the concept of acrodermatitis enteropathica being a hereditary congenital condition, whether related to epidermolysis bullosa or not? In answer we may state that we are also met with a similar baffling problem in epidermolysis bullosa itself. For marked improvement or spontaneous cure may occur even in this definitely hereditary disease (Bamber (27); Cockaynie (28)). Although this occurrence cannot be explained satisfactorily, as long as there is no clear understanding of the underlying pathogenic mechanism of epidermolysis bullosa, we have to accept it as a fact. Similarly we have to consider it as a fact that diodoquin has a dramatic curative effect in acrodermatitis enteropathica, although we may be dealing with a hereditary congenital condition.

The idea of a possible relation of acrodermatitis enteropathica to epidermolysis bullosa made us try the use of diodoquin in the treatment of a severe case of dystrophic epidermolysis bullosa. To our surprise the severity of the eruption in this patient has decreased considerably following administration of the drug during several weeks. However, further observation of this and another patient made us doubt whether diodoquin has any value in epidermolysis bullosa.

The problem of the etiology of acrodermatitis enteropathica will be solved by further thorough study of future cases of this syndrome. Special attention will have to be given to the hereditary aspect, investigation of possible giardiasis by means of examination of the feces during an exacerbation and by duodenal intubation, and particularly to the study of the nature of the gastrointestinal dysfunction and the possible metabolic disturbance underlying it or associated with it. An example of a thorough gastrointestinal investigation to be pursued in future cases of acrodermatitis enteropathica is that performed by Romeo and Mattina (4).

SUMMARY AND CONCLUSIONS

1. A second case of acrodermatitis enteropathica is reported in which diodoquin was of great benefit. Two other such cases are known to have responded similarly to the drug.

2. Differential diagnosis and possible etiologic factors are discussed. Giardiasis and possible relation to epidermolysis bullosa are considered. The occurrence of the syndrome in siblings in 8 cases and consanguinity of the parents in 4 cases indicates strongly that acrodermatitis enteropathica is a hereditary condition of a metabolic and gastrointestinal disturbance leading to the syndrome.

3. So far, the nature of the gastrointestinal dysfunction in acrodermatitis enteropathica and the mechanism of the curative effect of diodoquin are not understood.

4. In future cases attention has to be given to possible giardiasis, fibrosis of the pancreas, the hereditary aspect, and search for the exact nature of the gastrointestinal dysfunction and possible metabolic disturbance associated with it.

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