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Chronic bullous dermatosis of childhood

by

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A study of 16 patients with chronic bullous dermatosis of childhood (CBDC) is reported. They were followed up for 0.5 to 4.5 years. Histological and immunofluorescent (IF) study of the skin and local provocation of skin lesions by Trafuril test were carried out in every case, intestinal biopsy in twelve cases. Four patients were found to have IgG, and three IgA, along the skin basement membrane. In nine patients, no immunoglobulins were detectable; these IF negative cases seemed to be pseudonegative. Repeated biopsy and immunoelectronmicroscopic study of the skin may be helpful. In the three patient groups classified on the basis of skin IF studies, there was no difference in the clinical and histological picture, in reaction to Trafuril test and in the result of treatment. The small intestinal mucosa was abnormal in three of twelve patients. A gluten-free diet introduced in two patients had no effect on the course of the disease. CBDC with negative or positive IF, juvenile pemphigoid and IgA linear dermatosis seem to be a common clinical entity, different in severity and with individual variations. The condition is not identical with dermatitis herpetiformis Duhring.

At the beginning of the century a strange bullous disease, different from Duhring disease or pemphigus, was observed in children. It was [16, 18] and sometimes still is [5] termed juvenile type dermatitis herpetiformis Duhring. On the basis of characteristic clinical and IF findings the name juvenile (bullous) pemphigoid has been introduced [26, 2, 14]. In 1970, JORDON et al. [24] termed a very similar condition CBDC and regarded it as an IF negative bullous disease. Recently, analogous cases have been described in which linear IgA was the predominant IF finding and the terminology was complemented by IgA linear dermatosis of childhood [7] and IgA bullous pemphigoid [40, 43].

The majority of cases was observed in toddlers or in children of late preschool age. The condition is characterized by tense blisters or bullous groups arising on a normal or erythematous basis, often around lesions in remission, circumorally or on the lower extremities, hips, inner thighs and around the genitals. Spells of periodic remission and exacerbation can be observed. Spontaneous recovery occurs in a few months or years, but at the latest by the time of adolescence. Till then the patient requires treatment with powerful agents like sulfapyridine, dapsone and/or steroids.

The frequency of CBDC appears to be increasing and not only because of the improved diagnostic methods.

TABLE I

IF		Patient	Sex	Age(ys) of Onset	Age(ys) of Duration	Course	IF	Treatment	Jejunal biopsy	Clinical features
Negative		S. M.	F	4	2	recovery 0.3 ys ago	di NEG idi	SP	1. PVA 2. NEG/after 1 year's GFD	mild
		S. Cs.	M	5	1	improving	di NEG idi	steroid + dapsone	NEG	severe
		S. E.	F	4.5	1.5	improving	di NEG idi	steroid + SP	NEG	severe
		S. A.	F	4.5	0.5	improving	di NEG idi	steroid + dapsone	ND	severe
		R. A.	M	2	3	recovery 0.5 ys ago	di NEG idi	steroid + dapsone	ND	severe
		B. M.	M	2	0.5	recovery 2.5 ys ago	di NEG idi	dapsone	NEG	mild
		C. K.	F	5	3	recovery 1.5 ys ago	di NEG idi	steroid + dapsone	NEG	very severe
		F. M.	M	1.5	1	recovery 1.5 ys ago	di NEG idi	steroid + dapsone	NEG	severe
		N. Z.	M	7	0.5	stationary	di NEG idi	SP	NEG	mild (localized)
DEPOSITION OF	IGG	S. A.	M	8.5	0.7	recovery 0.3 ys ago	di: IgG idi: IgG (1: 10)	SP	NEG	mild (localized)
		T. O.	F	4	4	stationary	di: NEG idi: IgG (1: 80)	SP (+ steroid sometimes)	ND	severe
		B. J.	M	1.5	0.5	stationary	di: IgG + compl. idi: NEG	steroid + SP	ND	very severe

BMZ LINEAR	IGG	T. L.	M	2.5	0.3	recovery 0.5 ys ago	di: IgG+ compl. idi: IgG(1: 10)	SP	NEG	mild
	IGA	F. V.	F	3	1	recovery 0.3 ys ago	di: IgA+ compl. idi: NEG	steroid+SP	SVA	severe
		H. Z.	F	6	3	stationary	di: IgA idi: NEG	dapsone	NEG	mild
		V. C.	M	1.7	0.3	stationary	di: IgA idi: NEG	steroid+SP	PVA	very severe

PVA = partial villous atrophy
SVA = subtotal villous atrophy
GFD = gluten free diet
ND = not done
SP = sulphapyridine
Compl. = complement

NEG = negative
IF = immunofluorescent findings
di = direct test
idi = indirect test

Clinical features = the most serious phase of the illness can be:
- mild = dapsone/SP suppresses the symptoms
- severe = steroid + dapsone/SP suppresses the symptoms
- very severe = steroid + dapsone/SP even in high doses fail to control the disease (doses are limited by their side-effects)

The increasing incidence and the diagnostic and therapeutic difficulties justify a detailed description of this often serious although not irreversible disease.

Material

In the past four years we have examined and treated 16 children suffering from CBDC. Histological and IF studies of the skin and local provocation of skin lesions by Trafuril were carried out in each case. Intestinal biopsy was performed in twelve patients.

Methods

Histology of skin. Excision from bullous area, haematoxylin-eosin staining, light microscopic study.

Immunofluorescent study. Intact skin specimens taken from the perilesional base of bullae were studied by direct, and sera of the patients by indirect IF method [4], using a HBO-200 mercury light source and $2 \times$G 12/3 mm primary and GG 9/1 mm + OG 1.15 mm secondary filters. Labelled goat antihuman sera (Hyland) were applied. The fluorescein/protein ratio was 8 μg/mg in cases of anti-IgG and anti-IgA conjugates and about 7.4 μg/mg in the case of anti-IgM. Specific concentrations of antibodies were approximately 90, 55 and 52 μg/ml in cases of anti-IgG, anti-IgA and anti-IgM, respectively.

Indirect tests were performed on rabbit oesophagus.

Intestinal biopsy was carried out under X-ray control with a Crosby capsule suitable for double biopsy. The findings were evaluated according to subjective criteria as follows. (i) intact villous structure; (ii) partial villous atrophy (PVA); and (iii) subtotal villous atrophy (SVA).

Trafuril test for local activation of skin lesions [33]. Trafuril or Bayolin ointment containing tetrahydrofurfuryl nicotinate and benzyl nicotinate, respectively, was placed under adhesive plaster on an intact area of the back for 24 hours. The reaction was read after 24, 48, 72 and 96 hours.

Results

Histology showed uniformly a subepidermal formation of blisters.

IF studies were negative in nine children. In seven cases linear deposits of immunoglobulins along the basement membrane were observed. In four cases IgG, in three IgA was detectable. Indirect positivity was observed only in cases of IgG positivity, in three out of four patients (Table I). In the beginning, the IgG-positive group was called juvenile pemphigoid [14, 22, 42, 46] and the IgA-positive one IgA linear dermatosis [7] reserving the term CBDC for the IF negative cases [3, 15, 24].

Clinical characteristics. In the three groups of patients classified on the basis of IF findings, we were unable to find differences in clinical picture (Figs 1—10, Table I). The cases were essentially uniform with individual variations within the groups or even in the case of repeated symptoms of the same patient. The three gravest patients whose symptoms could not be abolished in the most serious phase of the disease because of side effects of the drugs, belonged to three different groups. Two very similar cases, too, characterized by circumscribed lesions confined to the perigenital region, belonged to two different groups: S. A. had phimosis and the symptoms appeared after an

unsuccessful phimotomy, and then, after a successful operation (or eventually spontaneously) a remission was observed. N. Z. showed symptoms exclusively on the scrotum with simultaneous testicular retention although this could well be a mere coincidence.

Hardness of hearing of the perception type (grade 2) was observed in two cases (S. C., H. Z.), whereas spastic bronchitis was found in three patients (S. M., S. A., V. C.). Six out of 16 cases were treated only with sulfapyridine or dapsone independently of the IF finding. One very severe, three severe and four mild forms of the disease (Table I) recovered spontaneously, three other patients improved remarkably.

Jejunal biopsy was carried out in 12 of 16 children. Nine patients showed no disorder; SVA was observed in one case (F. V.) and PVA in two cases (S. M., V. C.). For F. V. and S. M. a gluten-free diet was prescribed but this did not affect their condition and both of them recovered in the course of gluten challenge (Table I). There were no clinical signs of malabsorption. In the case of S. M. a control intestinal biopsy performed after one year's gluten-free diet was negative but the existence of a genuine gluten sensitivity cannot be verified unless villous atrophy reappears on retro-induction of dietary gluten.

Administration of Trafuril resulted in a positive isomorphous reaction of blister formation, independently of the IF finding (Figs 11, 12).

Discussion

CBDC was described as a distinct childhood syndrome with negative IF pattern [24, 3]. These earlier studies were, however, incomplete as the skin was not examined for IgA [30]. Later the same diagnosis was applied to cases with linear IgA positivity [7, 9, 11, 30] and to those of mixed type-linear IgA + IgG − positivity [6, 7, 12, 13, 39]. Today a number of authors separates juvenile pemphigoid with exclusive IgG positivity [22, 30], whereas according to others, linear IgA positivity, too, is indicative of pemphigoid [1, 10, 32, 43]. From the varieties and discrepancies of the clinical diagnosis and the IF findings, however, the image of an essentially common disease seems to emerge despite the differences in gravity and individual characteristics.

In order to explain the behaviour of IF findings, we may suggest that in the course or in some phase of the disease, antibodies are too specific to be detected by current methods. Repeated biopsies and immunoelectronmicroscopic studies may be helpful. In blistering diseases the specificity of antibodies may be reduced or modified, as indicated by the negative IF cases becoming positive [6] and also by the changes of the same patient's Ig type during the disease [21]. In conditions like CBDC, where recovery is typical, an immunological change is inevitable, due to normalization of the immunopathological events.

In patients with CBDC, any kind of prolonged local vasodilatation in the skin elicits a local activation of the immune process, either by a massive precipitation of circulating antibodies or by some other mechanism. In the given area, blisters arise in response to isomorphous stimuli. This is a common observation in children with CBDC; tight belts, scratches or even sudamina can act as provoking agents. Blister formation can be provoked artificially [10, 33], by the local application of nicotinic esthers such as the ointments Trafuril and Bayolin. As shown by the figures (Figs 11–12), blister formation, an isomorphous reaction indicative of the immunological basement membrane impairment, occurs even in cases where neither circulating antibodies nor antibodies bound to the basement membrane can be detected.

The uniform character of juvenile pemphigoid, IgA linear dermatosis and CBDC with negative IF is further supported by electron microscopic (EM) and EM-immunohistochemical studies furnishing evidence that antibodies are damaging the lamina lucida in all three groups [9, 10, 23, 37]. These data are not completely unequivocal [9]; it has to be taken into account that the fine localization of antibodies found in Duhring disease [19, 36, 49] has been a matter of debate among several authors [25, 27, 50, 51].

In our opinion, CBDC has sharply to be distinguished from dermatitis herpetiformis Duhring in children. The distinction can be done without difficulty if one considers the differences in clinical picture, the typically granular direct IgA positivity of the skin, the gluten sensitive intestinal villous atrophy and the favourable therapeutic effect of dapsone [25, 41]. In the rare cases of Duhring disease with linear IgA positivity, EM-immunochemistry can be used as an aid [35, 36, 37, 47].

In CBDC no intestinal symptoms can be found, microscopic lesions of the mucous membranes either do not occur [8, 29] or only sporadically [15, 31, 49], and they are not always characteristic [6, 7, 48]. We have performed intestinal biopsies for comparison with Duhring disease; out of 12 cases, we observed SVA in one and PVA in two patients without any clinical symptoms of malabsorption. Probably even these positive cases do not reflect a gluten enteropathy as they would in dermatitis herpetiformis, but something else, for example, a so-called dermatogenic enteropathy [28, 44] which disappears with the improvement of skin symptoms [45]. As intestinal symptoms are lacking and rapid spontaneous remissions can often be seen, the effect of a gluten-free diet on CBDC can only be judged by repeated studies of the intestinal mucous membrane; further, the lack of an effect of the gluten-free diet on skin symptoms may also be informative.

In treatment, several kinds of drug can be applied. In some cases sulphapyridine or dapsone is sufficient by itself (Table I) [13, 38, 39],

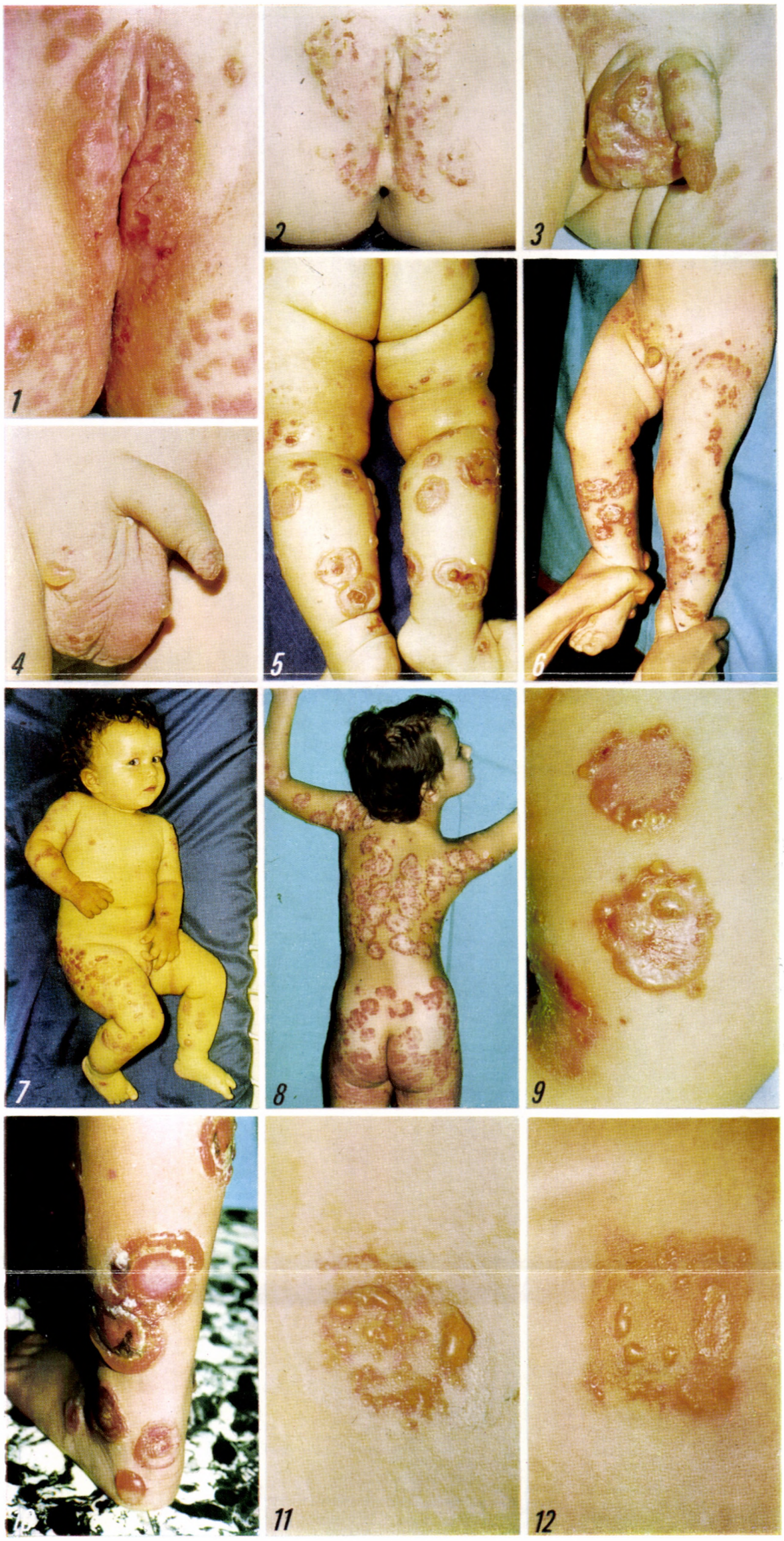

Fig. 1. H. Z. IgA positivity. IgA linear dermatosis?
Fig. 2. T. O. IgG positivity. Juvenile pemphigoid?
Fig. 3. V. Z. IgA positivity. IgA linear dermatosis?
Fig. 4. T. L. IgG positivity. Juvenile pemphigoid?
Fig. 5. F. M. IF negative CBDC?
Fig. 6. B. J. IgG positivity. Juvenile pemphigoid?
Fig. 7. F. M. IF negative case. Spontaneous recovery after 1 year
Fig. 8. S. E. IF negative, improving case
Fig. 9. V. Cs. Annular lesions in IgA linear dermatosis
Fig. 10. S. E. Annular lesions in IF negative case
Fig. 11. S. E. Isomorphous lesions induced by Trafuril. IF negative case
Fig. 12. B. J. Isomorphous lesions induced by Trafuril. IgG positive case

whereas in other cases, even its combination with steroids in high doses fails to suppress the symptoms in the most serious phase of the illness (C. K., B. J., V. C.).

On the basis of our clinical experience and the cases reported in the literature, we regard this disease with its characteristic clinical pattern, the subepidermal formation of blisters and a benign prognosis, as a distinct nosological entity including IgA linear dermatosis of childhood and juvenile pemphigoid.

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