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Pathophysiology of psoriasis: coping endotoxins with bile acid therapy

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Abstract

The authors have tested the hypothesis that the deficiency of bile acids and the consequent endotoxin translocation might play a role in the pathogenesis of psoriasis. Under normal conditions the bile acids act as detergents (physico-chemical defense) and can protect the body against enteric endotoxins by splitting them into nontoxic fragments and thus preventing the consequent release of cytokines [Persp. Biol. Med. 21 (1977) 70]. A total of 800 psoriasis patients participated in the study and 551 were treated with oral bile acid (dehydrocholic acid) supplementation for 1–8 weeks. The efficacy of the treatment was evaluated clinically and also by means of the Psoriasis Area Severity Index (PASI score). During this treatment, 434 patients (78.8%) became asymptomatic. Of 249 psoriatics receiving the conventional therapy, only 62 (24.9%) showed clinical recovery during the same period of time ($P < 0.05$). The curative effect of bile acid supplementation was more pronounced in the acute form of psoriasis (95.1% of the patients became asymptomatic). Two years later, 319 out of the 551 acute and chronic psoriasis patients treated with bile acid (57.9%) were asymptomatic, compared to only 15 out of the 249 patients (6.0%) receiving the conventional treatment ($P < 0.05$). At the end of the 2-year follow-up, only 10 out of 139 acute psoriasis patients (7.2%) receiving the conventional therapy and 147 out of 184 bile acid treated patients (79.9%) were asymptomatic ($P < 0.01$).

To conclude, the results obtained suggest that psoriasis can be treated with success by oral bile acid supplementation presumably affecting the microflora and endotoxins released and their uptake in the gut.

Keywords: Psoriasis; Bile acids; Endotoxin; Cytokines

1. Introduction

Psoriasis continues to be one of the commonest skin diseases [1]. Currently, the development of this disease entity is attributed primarily to polygenic inheritance [2] and numerous other factors such as metabolism [3–6], retrovirus [7–9] and various infections [10,11]. This is why diverse methods have been tried out in the therapy of this disease, with variable success [12,13]. Kemény and Dobozy [14] have called attention to the important role of cytokines in the pathogenesis of psoriasis. Namely, psoriasis is an inflammatory dermatopathy characterized by T-cell and endothelial cell activation, local vascular changes, neutrophil accumulation, and accelerated proliferation and abnormal differentiation of keratinocytes [2,15]. All these changes indicate the involvement of immunological processes and, primarily, cytokines [7,16–19]. Results of cyclosporin treatment also suggest that the immune system plays a role [13]. However, the studies performed so far have failed to identify the factor responsible for local cytokine release. Therefore, our earlier observation that the symptoms and changes seen in acute psoriasis (fever, leukocytosis, increase of capillary permeability, positive liver function tests, decrease of complement level, blood clotting disturbances, alterations of lipid metabolism including an elevation of VLDL, rise of lysosomal enzyme activities, etc.) resemble the changes occurring in experimental endotoxemia, seemed to be interesting. All these indicated that bacterial endotoxins might have a role in the pathogenesis of psoriasis. This hypothesis was supported by the detection of endotoxin in the blood of psoriatic patients by the so-called Limulus method [20]. As bacterial endotoxins are known to be one of the most

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important initiators of cytokine release, it seemed reasonable to suppose that toxins released from Gram-negative bacteria in the intestine may be involved in the pathogenesis of psoriasis, if they can enter the bloodstream. As, according to the current state of knowledge, cytokines are thought to have an important role in the pathophysiology of psoriasis, the possible involvement of bile deficiency in these events was suggested. Namely, in partial bile deficiency a varying amount of endotoxin enters the circulation and may induce cytokine release in the skin. The symptoms often seen in acute psoriasis patients (gastrointestinal and gallbladder complaints, etc.) suggest endotoxin translocation due to bile acid deficiency. The recently recognized consequent cytokine release may indeed be major factor in the pathophysiology of psoriasis. Thus, it seemed to be reasonable to suppose that by remedying the possible deficiency of bile acids an increased recovery rate from psoriasis could be achieved.

2. Methods and patients

Psoriasis patients ($n = 800$, women $n = 258$, men $n = 542$, age range 6–80 years) participated in the study. They were clinically examined. They had no severe signs of illness except the skin problem and some distension, eructation, gallbladder-related pain or stool abnormalities. On the basis of their case histories, they reported hereditary factors in 38%, drug therapy in 12%, and different mild infections in 50% of the patients.

The intervention patients ($n = 551$, women $n = 191$ and men $n = 360$) received bile acid supplement (Suprachol® sugar-coated pills, G. Richter, Budapest, Hungary) 2–3 × 1 daily or dehydrocholic acid powder (acidum dehydrocholicum pulvis) 2–3 × 0.25 g daily (in wafer or capsule) 1–6 and 3–8 weeks in acute and chronic cases, respectively. The patients took the bile acid preparations with meals. These treatments caused neither gastric nor intestinal complaints and eliminated the symptoms listed above. Acute psoriasis patients did not receive external treatment. An ointment for washing (Ung. hydrophilicum nonionicum—FoNo) was given only to patients with a dry skin. In chronic cases, the usual external treatment with ointment was needed only 1 or 2 weeks after starting the bile acid therapy. The treatment results of this group were compared with those of 249 psoriatic patients (women $n = 67$, men $n = 182$) receiving only the conventional treatment according to the assumed eliciting factor.

Both groups of patients were advised to avoid hot spices (pepper, red pepper, horseradish, bay leaf, etc.), spirits, raw onion, garlic and carbonated soft drinks. They were also recommended to eat a diet high in vegetable fiber (vegetables, fruits, etc.). They continued their other therapies (suitable antibiotics and antihistamines).

The numerical evaluation of the results was based on the so-called Psoriasis Area Severity Index (PASI score) and the usual statistical calculations were made [21,22].

3. Results

The results have been summarized in Table 1. As shown, 434 out of the 551 patients treated with bile acid (78.8%) became symptomless. In further 117 cases (21.2%) an improvement was observed better in the PASI values. At the same time, only 62 out of the 249 patients given the conventional treatment (24.9%) became asymptomatic. The difference between the two groups was statistically significant ($P < 0.05$). Table 1 also indicates that in the acute cases the ratio of patients becoming asymptomatic was higher (95.1%) than in the chronic cases (70.6%).

Also at the end of a 2-year follow-up period, the ratio of asymptomatic patients was markedly higher among bile acid treated than among conventionally treated patients (Table 1). Two years absence of clinical symptoms was observed in 319 out of 551 patients in the bile acid treatment group. This means that 57.9% of the 551 patients receiving bile acid treatment were symptomless after 2 years (79.9%) in the acute and (46.9%) in the chronic cases. This was significantly higher ($P < 0.05$) than in the 249 patients receiving the conventional treatment where only 15 patients (6%) were symptomless. Only 10 out of 139 acute psoriasis patients (7.2%) receiving the conventional therapy and 147 out of 184 bile acid treated patients (79.9%) were asymptomatic ($P < 0.01$). No gender difference was observed in the efficacy of bile acid supplementation (Table 1).

4. Discussion

The high incidence of psoriasis makes the treatment of this disease an important public health issue. Any treatment modality appearing to be better than the previously used methods can rightfully command interest.

The treatment modality presented here represents one of the practical applications of the so-called physico-chemical defense based on the detergent effect of bile acids, a defense system of the organism recognized by one of the authors (Bertók, [24–30]). It has long been known that in the healthy organisms the endotoxin produced in the intestine is practically not absorbed. Even large doses of endotoxin administered orally for experimental purposes do not cause any pathological symptoms or changes [31]. Experimental endotoxin shock can only be induced by endotoxin administered by the parenteral route (intravenously or intraperitoneally). In natural disease, however, endotoxin gets from the intestine into the bloodstream. The exact mechanism responsible for this is not known. Later on it has been found out that bile acids present in the intestine and having detergent effect detoxify the endotoxins released from the Gram-negative bacteria [24,30,32,33]. In the absence of sufficient amounts of bile acids, endotoxins are translocated into the bloodstream and produce pathological conditions of varying severity depending on

Table 1
Bile acid supplementation in psoriatic patients on the basis of their improvement or becoming asymptomatic

Type of psoriasis	Number of cases PASI[a] (x)	Type of treatment	Duration of treatment (weeks)	Asymptomatic PASI (x)	Improved PASI (x)	Asymptomatic also after 2 years PASI (x)	Remark/significance
Acute (P. punctata, guttata, confluens, numularis)	139 (34 F + 105 M)[b] 14.2 ± 5[c]	Conventional[d]	1–6	40 (28.8%) (10 F + 30 M) 0	99 (71.2%) (24 F + 75 M) 2.1 ± 2.0	10 (7.2%) (3 F + 7 M) 0	$P < 0.01$
	184 (81 F + 103 M) 12.6 ± 5	Bile acid [e]	1–6	175 (95.1%) (76 F + 99 M) 0	9 (4.9%) (5 F + 4 M) 1.2 ± 1.0	147 (79.9%) (51 F + 96 M) 0	8 patients did not come back for check up
Chronic (P. anularis circinata, inveterata, verrucosa)	110 (33 F + 77 M) 23.7 ± 10	Conventional	3–8	22 (20%) (2 F + 20 M) 0	88 (80%) (31 F + 57 M) 12.3 ± 1.5	5 (4.6%) (1 F + 4 M) 0	P <0.05
	367 (110 F + 257 M) 25.6 ± 10	Bile acid	3–8	259 (70.6%) (84 F + 175 M) 0	108 (29.4%) (26 F + 82 M) 11.6 ± 1.2	172 (46.9%) (61 F + 111 M) 0	65 patients did not come back for check up
Acute + chronic together	249 (67 F + 182 M) 18.9 ± 7.5	Conventional	1–8	62 (24.9%) (12 F + 50 M) 0	187 (75.1%) (55 F + 132 M) 14.4 ± 2.1	15 (6.0%) (4 F + 11 M) 0	$P < 0.05$
Acute + chronic together	551 (191 F + 360 M) 19.1 ± 7.4	Bile acid	1–8	434 (78.8%) (160 F + 274 M) 0	117 (21.2%) (31 F + 86 M) 12.8 ± 1.1	319 (57.9%) (112 F + 207 M) 0	73 patients did not come back for check up

[a] PASI: Psoriasis Area and Severity Index (22) (PASI 0 = asymptomatic).
[b] F: females; M: males.
[c] Mean ± S.D.
[d] Conventional treatment according to the eliciting factor.
[e] Treatment with bile acid (Suprachol® or acidum dehydrocholicum).

their amount. Endotoxins are known to exert their adverse effects via mediator substances, of which cytokines are very important.

In our view, the success of this treatment method can be attributed to the fact that by remedying the temporary bile deficiency the absorption of endotoxins and thus the release of cytokines are prevented. Thus, the recognized effect played by cytokines in the pathogenesis of psoriasis underlines the indirect role of bacterial endotoxins. This effect, however, probably occurs only, if bile secretion or discharge is disturbed (cholecystokinin deficiency, disturbances of cholesterol metabolism and bile secretion). Therefore, the treatment of psoriasis with bile acids is actually the supplementation of a physiological substance rather than a medicinal therapy.

The actual results of the present study are even better than now reported, although it cannot be determined precisely, as many patients ($n = 73$) did not come back for check-up examination after they had gotten better. From incidental information received from such patients' relatives or acquaintances sent to us for treatment we learned that the patients themselves had now been symptom free.

In the presence of sluggish intestinal activity, the prolonged administration of bile acids may increase the incidence of malignant tumors in the large intestine [23]. However, this is unlikely to have relevance in the case of the treatment recommended here, as patients who became asymptomatic were treated only few weeks and they took the bile acid preparation later on only after rich (fatty) meals rather than on a continuous basis.

Our studies encourage studying further the pathophysiology of psoriasis and intestinal factors. Furthermore, in our view, effectiveness, safety, simplicity and low cost of the bile acid supplementation make this treatment modality suitable for a wider use in the therapy of psoriasis. Dehydrocholic acid is available in several countries and accepted for use.

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