prove to be false-positive cases based on a general practitioner's tentative diagnosis which was the case in a number of patients in the twin study.

Because as many as 88% of the self-reporting psoriatics told that they had been treated by a doctor, and 71% by a dermatologist, we believe that the prevalence rates presented, with the above-mentioned corrections, are valid. However, we are not able to estimate the number of false-negatives (i.e. psoriatics answering 'no' to the questions in the interview) but we believe this number to be negligible.

As is shown in Table I, no distinct increase appears in the prevalence of present *or* previous psoriasis eruptions during the examined decades which was to be expected for a disease like psoriasis that can manifest itself at any age. The lack of increase my be due to a large statistical uncertainty in calculating the prevalence rate in the older age groups due to the small number of interviewed persons. Theoretically, it may also be presumed that the lack of increase is due to the older age groups having had a lower risk of psoriasis than the younger persons, or that a higher mortality among the psoriatics had been present. However, the most probable cause is bias due to loss of memory among elderly persons concerning minor eruptions of psoriasis in their early years.

Based on corrected prevalence rates of 3.2% for men and 2.5% for women between 16 to 99 years of age, it is possible to estimate the number of psoriatics in the adult Danish population (7), as the total population has the same sex and age distribution as the random sample. Consequently, the number of adult psoriatics is estimated to be 62 000 men and 51 000 women, i.e. 113 000 psoriatics living in Denmark at present.

In the non-selected twin material published previously (1) it was attempted to graduate the severity of psoriasis into light recurring (LR), light constant (LC), moderate constant (MC), and severe constant (SC). In this twin material, with an as-yet unpublished extension, the grade of severity among genotypically different individuals is as follows: LR 22%, LC 41%, MC 30% and SC 7%. Provided that the distribution of severity is the same as found in the non-selected twin material it is estimated that in the Danish age group ranging from 15 to 90 years, 71 000 suffer from light psoriasis (LR+LC) and 42 000 from more severe psoriasis (MC+SC) of which the last-mentioned group is presumed to use the health authorities' remedial measures for longer periods.

ACKNOWLEDGEMENTS

Cand. real. Ørnulf Borgan is kindly thanked for helping with data analyses.

This study was supported financially by Essex Pharma A/S, Copenhagen.

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A Comparative Study of the Results of Phlebotomy Therapy and Low-dose Chloroquine Treatment in Porphyria Cutanea Tarda

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Received November 14, 1980

Abstract. Longer remissions after the phlebotomy therapy than after the low-dose chloroquine treatment were ascertained by means of the long-term follow-up of a large group of porphyria cutanea tarda patients. An attempt to prove the dependence of the length of laboratory and clinical remission on the values of initial porphyrinuria, on the degree of morphological liver changes, and on the total amount of blood withdrawn at phlebotomy was unsuccessful. On the contrary, a direct relationship was observed between the length of remission and the age of the subject on commencing treatment. At the same time, it was impossible to prove a causal relationship between the length

of remission and initial porphyrinuria, the degree of morphological liver changes, and the total dose of drug taken, in the group of patients on the low-dose chloroquine therapy.

Key words: Porphyria cutanea tarda; PCT; PCT therapy; Phlebotomy; Chloroquine

Most cases of porphyria cutanea tarda (PCT) recently have been treated either with repeated phlebotomy or with an application of low-dose chloroquine. Both phlebotomy and choroquine treatment have indeed certain limitations for use. One of them is the decision as to which therapy to use, which must be made in every individual case. Clinical and laboratory remission with normalization of porphyrinuria and healing of skin changes can be achieved as a result of both therapeutic methods over the course of several months.

Our objective in this work was to compare the result of both methods which we have been using since 1964 (phlebotomy) and since 1970 (chloroquine), evaluating the period of remission after termination of treatment. We also tried to ascertain the factors which could influence the differences in therapy results. In this connection we made an effort to compare these results with the age of the subjects in both investigated groups at the beginning of the treatment, with the degree of liver change, with initial excretion of urinary porphyrins, and finally with total amount of blood removed by phlebotomies or with total dose of chloroquine taken during the period of its administration.

MATERIAL AND METHODS

88 patients were studied—76 men aged between 29 and 78 (mean 59.5) years and 12 women aged 32 and 74 (mean 59.8) years. The diagnosis was established in all of them according to the presence of typical clinical changes with bullous photodermatosis and increased skin fragility on face and upper extremities. Urinary and faecal excretion of porphyrins and of their precursors, and liver function tests were examined in the laboratory, together with detailed hepatological examination including liver biopsy.

The first group of patients, 48 subjects (42 men and 6 women) was treated with repeated phlebotomies (6), while the subjects belonging to the second group (40 patients, 34 men and 6 women), were given chloroquine (Delagil®, G. Richter, Budapest) in low dosage according to previously published schemes (10, 14). Remission was usually achieved after on average 7 phlebotomies with 400–500 ml of blood removed at each session, or with the administration of 125 mg of chloroquine twice weekly for the period ranging from 4–11 months. All patients were subject to regular clinical and laboratory control examinations every third month after the cessation of therapy, which had been completed when the urinary porphyrin level fell below the value of 500 μg/day.

The degree of histopathological liver change was scored according to criteria described in detail elsewhere (1, 2, 11).

The results of therapy methods hitherto used were statistically evaluated using the Student's test and correlation tests.

RESULTS

Both therapeutic methods led to the laboratory and clinical remission of the disease in all patients studied. The maximum total amount of blood removed by phlebotomies, necessary for favourable therapeutic effect, was 5.8 litres (3.7±0.1 l); the longest period of chloroquine administration was 11 months (6.5±1.8 months). A certain precaution when using the chloroquine therapy was recommended in spite of the above-mentioned improvement for patients with active and/or advanced liver disease. An attempt to avoid the possible acute untoward reaction after the first dose of chloroquine by the use of phlebotomy at the beginning of antimalarial therapy was recently described (13).

Liver morphology did not change substantially when using either of the two methods (1, 2). As far as a change in this respect could be observed it could be taken rather as a result of the natural course of the disease. Comparing the initial liver histopathology with the result of the control examinations, a substantial loss of iron was observed in liver parenchyma.

A recurrence of the disease was later noted in some of the patients, after the remission with complete clinical and laboratory improvement had been achieved. Remission continues in the remaining subjects. The exacerbation appeared in 36 persons from the group on phlebotomy therapy and in 24 patients from those treated with chloroquine. The proportion of patients who relapsed and those proceeding further in remission cannot reveal any significant information because of the differing periods of follow-up in the two patient groups. Four patients (i.e. 8.3%) relapsed in the course of the first year, and 9 patients out of the remaining 44 (i.e. 20%) in the course of the second year, after the phlebotomy therapy was terminated (Fig. 1). Relapses were further observed in 15 out of 24 subjects, followed up for more than 3 years (on av-

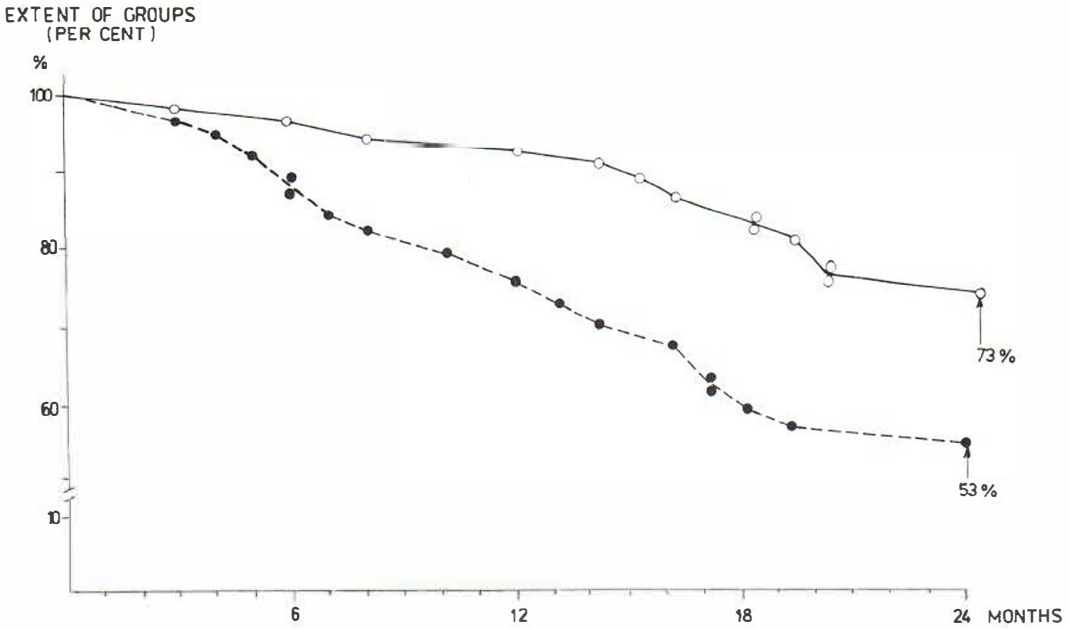

Fig. 1. The reduction of the extent of therapy groups (in per cent) in the dependence on the time elapsed after the termination of treatment (phlebotomies ○—○; chloroquine ●---●).

erage for 6±1.2 years) after termination of the treatment. The longest remission observed continues for the time being for 11.5 years.

As for the situation in the group on chloroquine treatment, laboratory and clinical relapse was noted in 9 patients (i.e. 22.5%) in the course of the first year, and in 8 out of 28 followed up for at least 2 years (28.5%) during the second year (Fig. 1). From 19 patients, followed up for more than 2 years, 7 relapsed after an average of 3.75±1.4 years. The longest remission in this group continues meanwhile for 7.25 years.

When evaluating the difference in the length of remissions in both therapy groups, using abovementioned statistical methods, we found that the average remission was significantly longer in the phlebotomy group ($t=3.128>_{t0.05}=2.044$) than in the group treated with chloroquine. Correlating the results of phlebotomy therapy, i.e. the length of remissions, with initial values of porphyrinuria in the phlebotomy group, no significant dependence between them can be proved. Just the same can be said about the total amount of blood withdrawn and the degree of morphological liver change. However, a significant relationship was found between the duration of remission and the age of the patients ($r=0.3469>r_{0.05}=0.3295$).

Somewhat different results were obtained in the group on chloroquine treatment, revealing not only an independence of the length of remission from initial porphyrinuria, total dose of the drug taken, and the degree of morphological liver change, but even from the age of the patients.

DISCUSSION

Our studies proved a significantly longer therapeutical effect of serial phlebotomies, as compared with the effect of low-dose chloroquine therapy. The difference is probably not related to the depletion of porphyrian liver stores, which can be obtained by both the methods. According to the original hypothesis the draining of protoporphyrin together with hemoglobin, removed by phlebotomy, leads to the regulation of newly synthesized porphyrin intermediates (i.e. uro- and coproporphyrinogens) towards the production of haem, instead of thir useless accumulation in the liver parenchyma and excretion in large quantities in the urine. This fact was considered more important than the depletion of liver iron stores, which has been assumed to be a main therapeutic mechanism of phlebotomy by later authors (4, 7, 9). Supporters of the theory of the prime importance of iron-stores depletion suggested

it especially on the basis of experiments with the replenishment of iron stores in those PCT patients, where the remission had already been achieved. In those cases the replenishment led altogether to the biochemical exacerbation of the disease (4, 9).

The question raised here is definitely not solved yet. The depletion of iron is presumably not the only factor responsible for the favourable result of serial phlebotomies. Liver siderosis and hypersideraemia are present in only a part of PCT patients. The experiments with chelating agents introduced the same uncertainty into this problem. Recent etiological theories suppose, however, that the role of iron ions constitutes one of the most important factors in the origin and development of the disease. PCT has recently been considered to be an enzymic disturbance with decreased activity of uroporphyrinogen-decarboxylase (URODecarb), which catalyses the synthesis of lower-carboxylic porphyrinogens from 8-COOH uroporphyrinogen (8). The reduction in liver-iron content achieved with phlebotomies does not directly influence the activity of the enzyme in erythrocytes of PCT patients (5). This fact does not contradict, however, the findings of authors (3) who assume the participation of iron ions in the etiopathology of the disease. Iron can be involved in the mechanism of URODecarb inhibition in at least two ways. Divalent iron is toxic for enzymes and is probably responsible for oxidation processes damaging the cell membranes of hepatocytes and also probably of certain SH-dependent enzymes, participating in porphyrin synthesis. There are certain conditions, for example the addition of excess iron, where the activity of the electron transport system in microsomes, utilizing NADP-cytochrome-*c* reductase, is considerably stimulated and thus uncoupled from the oxidation of substrates of the cytochrome P-450 system. The activated oxygen, which may be toxic, is produced in excess in this way. Conditions for mobilization of active ferrous ion and for increased oxidative processes may ensue in the liver of genetically predisposed persons, also in porphyria patients with depressed URODecarb activity. Nor can the fact that iron may increase the rate of porphyrin accumulation in liver by direct stimulation of 5-aminolaevulinate-synthetase, a rate-limiting enzyme of porphyrin biosynthesis, be omitted. Every process leading to a marked decrease in disposable iron in liver tissue, i.e. also the phlebotomy, may be generally held as a principle, acting towards the metabolic relief, and thus for the therapeutically useful method.

The original hypothesis on the mechanism of chloroquine action in the PCT resulted from the observed ability of this substance to form hydrosoluble complexes with accumulated liver porphyrins, thus mobilized and excreted in the urine (12). In spite of more recent observations suggesting a presumably direct effect of the drug on the synthesis of porphyrian intermediates by influencing the enzyme activities or inducing activity of iron ions (14), the above-mentioned explanation seems for the time being to be the most valid. It has been proved, anyway, that the application of chloroquine leads to the depletion of porphyrin liver content and thus to the remission of the disease. The varying length of remission after the effect of investigated therapy methods was achieved, provides evidence against the identity of their mechanism. An important role may have the extent of inhibition of already defective URODecarb, which may be directly or indirectly affected by chloroquine.

Neither initial porphyrinuria and the degree of liver damage, nor the total dose of the drug taken and/or quantity of blood withdrawn by phlebotomies, can play any significant role regarding their effect on the duration of remission. Surprisingly, increasing age is favourable for the prospect of a beneficial therapy result in PCT patients treated with phlebotomy. The dependence of the degree of liver changes on the age of the patients (11) seems to be interesting from this point of view.

It could well be that the reduction in enzymic activity occurs in accordance with the burning-out of active porphyrogenic centres in the liver of elderly patients.

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The Effects of Photochemotherapy on Endocrine Secretion in Patients with Psoriasis

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Received December 8, 1980

Abstract. Blood and urine hormone levels were measured in four patients with psoriasis up to 24 hours after their first PUVA treatment. The changes were minimal and unlikely to explain the feeling of well-being experienced after PUVA therapy.

Key words: Photochemotherapy; Endocrine secretion in Psoriasis

The feeling of well-being many people experience after sunbathing or exposure to ultraviolet (UV) radiation from an artificial source precedes the appearance of tanning. Likewise, patients with psoriasis treated with PUVA (8-methoxy-psoralen (8-MOP) and long-wave UV (UVA)) have reported similar feelings even before their skin has started to pigment or their rash to clear. This mood change might be a direct psychological effect or might be secondary to a UV-provoked action such as a change in endocrine function. We therefore measured the concentration of various hormones in blood and urine before and after PUVA given therapeutically to 4 patients with psoriasis.

PATIENTS AND METHODS

Four female patients aged 19, 21, 33, and 72 years, admitted to hospital for treatment of chronic plaque psoriasis, were studied. The 72-year-old patient also had psoriatic arthritis for which she took prednisone 5 mg a day; none of the others was receiving systemic medication or had used topical corticosteroids during the previous month.

PUVA treatment

Each patient received 0.6 mg/kg of 8-MOP by mouth and 2 hours later the whole body was exposed to a high intensity source of UVA (PUVA 4000 Sylvania Lifeline F.R. 90 T12/PUVA/HO fluorescent tubes emitping up to 12 mw/cm^2 of UV radiation at 320–400 nm). The duration of exposure in individual patients depended upon their response to natural sunlight and is described elsewhere (3).

Blood hormones

Blood was taken from an indwelling venous catheter before treatment at 09.00 h, and 1 hour, 5 hours and 24 hours after treatment. Immunoreactive MSH-like peptides were measured as β-lipotropic hormone (β-LPH) (2), and thyroid-stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicular-stimulating hormone (FSH), prolactin, adrenocorticotrophic hormone (ACTH), cortisol, oestradiol, testosterone, triiodothyronine (T3), thyroxine (T4) were measured by standard methods. Additional samples were taken at midnight for ACTH and cortisol estimations.

TRH response

Twenty-four hours after PUVA treatment, blood was taken for basal TSH levels and then synthetic TRH 0.2 mg in 2 ml solution was administered intravenously, further blood samples being taken for TSH estimations at 20 and 60 min.

Urine hormones

17-oxosteroids (17 OS), 11-hydroxycorticosteroids (11 OHCS) and 4-hydroxy-3-methoxy-mandelate (HMMA)