

ERYTHROHEPATIC PROTOPORPHYRIA AND ITS TREATMENT WITH β -CAROTENE

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Abstract. Seven cases of manifest erythrohepatic protoporphyria (EPP) were treated with β -carotene. The patients were given 50-250 mg a day for 4-15.5 months (total dose 9-60 g). This treatment produced better clinical results than those obtained with previous methods tried. This impression was supported by phototests in 2 of the patients. The serum β -carotene was determined on different occasions during treatment. To some extent the therapeutic effect seemed to follow the serum β -carotene. Porphyrins in red blood cells, faeces and urine were also determined.

Erythrohepatic protoporphyria (EPP) is an inborn error of porphyrin metabolism, which is transmitted as a non-sex-linked Mendelian dominant (12). About 200 cases have been published since the first description of the condition as a distinct clinical entity in 1961 (17).

The photosensitivity, which is characteristic of these patients, generally appears within the first few years of life. Exposure to sunshine for about $1/2$ hour is, as a rule, sufficient to cause a sensation of burning of the exposed parts of the skin. This sensation, which is not infrequently painful, is often followed by erythema and oedema. Much less common are solar urticaria, purpura, vesicles and eczematoid changes. Crusts and scars are sometimes seen on the forehead and on the tip of the nose as well as on the earlobes.

The patient is predisposed to form gallstones, which contain much protoporphyrin (5, 12). Isolated cases of liver cirrhosis in patients with EPP have been described (3, 6). All of these patients have died from liver insufficiency. At autopsy the liver was found to contain large amounts of porphyrin. Owing to the involvement of the liver in this disease, Scholnick et al. thought that the previous name erythropoietic protoporphyria

was a misnomer and they suggested instead erythrohepatic protoporphyria (24). Hyaline material is deposited around vessels in the outer corium in those parts of the skin exposed to sunshine (21). Both histologically and histochemically the material closely resembles that found in lipoid proteinosis (28). There is no porphyrin fluorescence in the dermis or epidermis (23).

The protoporphyrin (PP) content of the erythrocytes, plasma and faeces is markedly increased. The urinary porphyrins are normal in amount. Haem synthesis is undisturbed; the patients are therefore not anaemic (22). The iron metabolism is normal (17, 22). The site of the inborn error of EPP is still unknown.

Sun-screening creams having little or no effect, treatment of the condition has been approached from other angles. After discouraging results with antihistaminics, antimalarials, vitamin E and adenylic acid, the report of the value of oral β -carotene by Mathews-Roth and co-workers (18) was welcomed with enthusiasm. As early as 1951 one case of solar urticaria had been successfully treated with carotene (15).

We thought it worthwhile to try this form of therapy on our EPP-material, part of which has been reported previously (13).

MATERIAL AND METHODS

Seven cases of manifest erythrohepatic protoporphyria were examined for the effect, if any, of treatment with β -carotene. Two of the patients were females (aged 18 and 27) and 5 were males (in the age range 9-56). Three (cases 3, 4 and 5) have been published previously (13). Only 2 (cases 1 and 2) were relatives. The patients were given a total dose of 9-60 g β -carotene by mouth in

Table I. Case reports

Case	Age	Sex	Age at onset years	Skin symptoms on sun-exposed areas (face, ears, hands)		Onset of symptoms after sun exposure (min)	Max. duration of symptoms (days)	Total dose of β -carotene (g)	Duration of treatment (months)
				Subjective	Objective				
1	56	♂	2	Burning Stiffness	Oedema. Until age 45, blisters, crusts on the nose, ears. Now scars	10-60	3	60	14.5
2	27	♀	2	Burning Stiffness	Slight oedema. As a child, crusts on the nose. Now scars	60-120	7	40	15.5
3	18	♀	4	Burning Pain	Oedema. As a child, crusts on the nose, hands. Now scars on the nose	5	4	45	13.5
4	37	♂	6	Burning	Erythema, oedema, petechiae	5	4	45	15.5
5	28	♂	3	Burning Pain	Erythema, oedema. As a child, crusts only once	30	3	20	8.5
6	23	♂	1	Burning	Erythema, oedema. As a child, crusts on the nose, now scars	30	4	20	7
7	8	♂	2	Itching	Erythema. Oedema of eye-lids and ears. As a baby, crusts on the nose, now scars	60-120	4	9	4

the form of 50 mg capsules. All the patients were residents of Malmö or its suburbs (latitude 56°).

Two patients (cases 4 and 6) were phototested with a Xenon arc lamp (Osram XBO, 150 W) equipped with an ordinary 3 mm window-glass filter and a 3 mm Schott filter BG 38 to eliminate short-wave radiation below 320 nm and the near infrared, respectively. Consequently the lamp gave full effect in the wavelength range around 400 nm, corresponding to Soret's maximum, light which is strongly absorbed by porphyrins. Radiation was given at a distance of 16 cm between the lamp and the outer side of the upper arm. The minimum time necessary to produce erythema at examination 24 hours after radiation was determined (minimal erythema dose = MED). Five persons not hypersensitive to sunshine served as controls. All of them were irradiated for 45 minutes.

The methods used for analysis of porphyrins in red blood cells, faeces and urine have been described earlier (10, 11, 12).

Determinations of β -carotene in plasma were made according to Fegeler & Quinkert (7).

CASE REPORTS

The case reports are given in Table I. Except for hypersensitivity to sunshine, the patients had always felt well.

Case 1. The patient, however, had since his youth almost had loose stools 2-4 times a day, especially after

certain sorts of food, such as meat, spiced sauces, apples, etc. Occasionally he had also had mild pain resembling that of cholelithiasis, but he had not been jaundiced. Cholecystography in May 1971 revealed a large gallstone. In the summer of 1970, during a period of fatigue, with a temperature of about 39°C and the passage of dark, loose stools, the patient was admitted to hospital. He then had a hypochromic anaemia with markedly decreased serum iron, but he responded promptly to iron therapy. Despite roentgen examination of the gastrointestinal canal the anaemia remained unexplained.

Case 3. The skin symptoms of this patient were occasionally accompanied by chills. EPP was diagnosed in 1963, when she was successfully treated with Triquin® (Winthrop Laboratories, New York, N.Y., U.S.A.). In 1964 another antimalarial was tried, namely Quinacrine® (May & Baker, Ltd., Dagenham, England), likewise with a good effect. This type of treatment was soon stopped, however, because of the risks of side-effects.

Case 4. After severe exposure to sunshine, the patient sometimes experienced an accentuated sensation of cold and heat in the skin: mild coldness produced an icy feeling; mild heat, a sensation of burning.

EPP was diagnosed in 1964 when a trial with Quinacrine® had no notable therapeutic effect.

When the patient himself noticed that he could tolerate sunshine better once he had been sunburnt, in 1971 he began of his own accord to drink carrot juice every day

to get an "artificial" pigmentation of the skin. He was at that time unaware of the American observation (18) that β -carotene may offer protection against the undesired effect of sunshine in EPP. After 3 weeks he was slightly yellow and found that he could tolerate the sunshine much better.

Case 5. This patient had also noticed an accentuated feeling of cold and warmth of the skin after exposure to sunshine.

RESULTS

During treatment with β -carotene the plasma β -carotene rose considerably (Figs. 1-5).

The PP/RBC tended to vary inversely with the plasma β -carotene, especially in cases 4, 5 and 6 (Figs. 4-5). Normal upper limit ($M+2$ S.D.) of PP/RBC is 25 $\mu\text{g}/100$ ml and of β -carotene/PL 140 $\mu\text{g}/100$ ml. The faecal PP was increased throughout treatment (normal upper limit: 40 $\mu\text{g}/\text{g}$ dry weight). No correlation was found between the faecal porphyrin and the PP-level in the red blood cells or the plasma β -carotene (Figs. 1-5).

The faecal coproporphyrin (CP) was largely normal in all the patients.

Urinary uroporphyrin (UP), CP, δ -amino-laevulinic acid (ALA) and porphobilinogen (PBG) were always found to be normal in cases 1-6. Case 7 was not studied in this respect.

In cases 2-6, the haemoglobin, red and white blood cells, the differential count of the white blood cells, platelets, E.S.R., serum iron, total

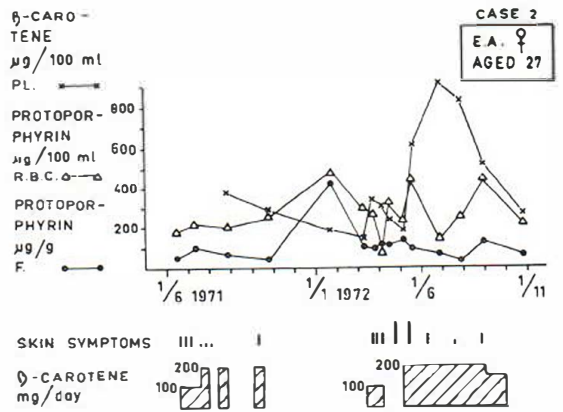


Fig. 2

iron-binding capacity and the haptoglobin were all normal both before and after treatment with β -carotene. In case 1, however, the haemoglobin was somewhat low (12.3 g/100 ml) during therapy. Before treatment it was 13.1 g/100 ml and after treatment 12.8 g/100 ml. On one occasion, also during treatment, that patient had leukopenia (3 300) and thrombocytopenia (84 000). Both counts were normal after treatment. The results of all the other tests in this patient were normal.

The serum electrophoretic pattern, the result of the bromsulphthalein test and the transaminase and alkaline phosphatase levels were normal, as were the serum sodium, potassium, urea and creatinine. Case 7 was not studied in these respects.

None of the patients had albuminuria or glycosuria before, during or after treatment with β -carotene.

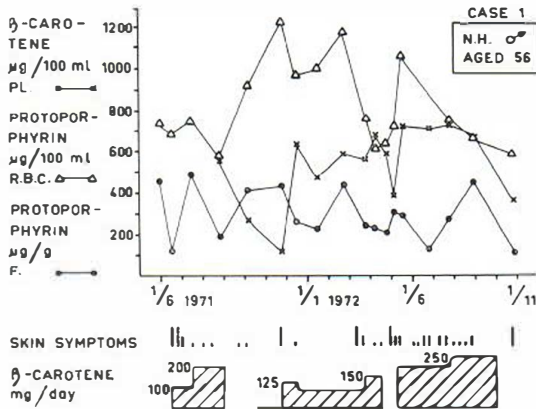


Fig. 1

Figs. 1-5. Protoporphyrin in red blood cells and faeces as well as skin symptoms relative to dose of β -carotene and its concentration in the plasma in 7 cases of EPP. In cases 4 and 5 the minimal erythema dose (MED) was recorded.

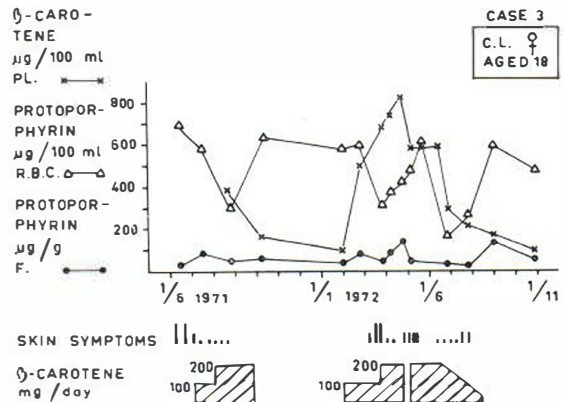


Fig. 3

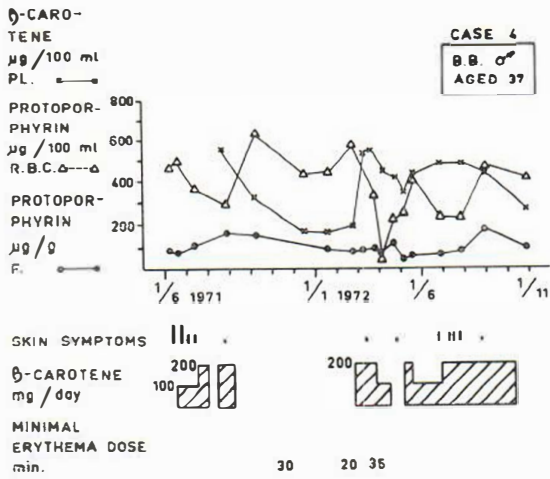


Fig. 4

Cholecystography revealed a gallstone only in case 1. Case 7 was not studied in this respect.

As for the clinical effect (Figs. 1-5), all 7 patients said they were satisfied. The patients in cases 2 and 7, however, reported that the symptoms varied widely and that sometimes they had been able to tolerate sunshine fairly well even before treatment. Apart from yellow discoloration of the skin, especially of the palms of the hands and the face, the treatment produced no side-effects. Two patients (cases 1 and 4) reported that they felt especially fit during treatment.

Case 1. This patient reported regression of the symptoms even after he had received β-carotene in a dose of 100 mg/day. After the dose had been increased to 200 mg a day he could be out in the sunshine for several hours without any consequent symptoms. But the symptoms returned as soon as he stopped taking β-carotene.

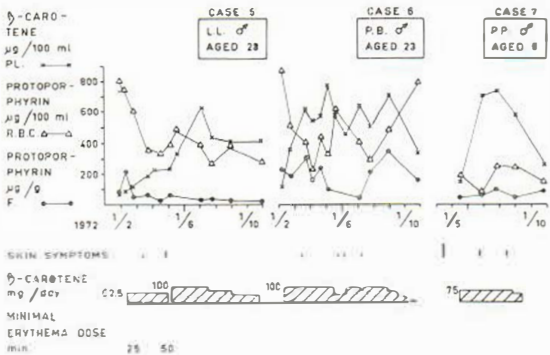


Fig. 5

In the summer of 1972 the carotene dose had to be increased further to 250 mg a day to keep the symptoms down to an acceptable level on exposure to sunshine.

The patient in case 2 was able to spend 2 weeks at the Mediterranean in 1971 and enjoyed the sunshine without any notable symptoms. After withdrawal of carotene for 3 weeks in April 1972 she again had severe skin symptoms with a sensation of burning and swelling of the face. One week after resumption of β-carotene in a dose of 200 mg a day the symptoms abated and she could again expose herself to sunshine without complications.

Despite treatment with β-carotene in a dose of 100 mg a day the patient in case 3 developed severe skin symptoms in March 1972 after exposure to sunshine when the ground was covered with snow and on one occasion she also had attacks of shivering and exudation with crusts and scaling around the mouth and nose. After the dose of carotene had been doubled the symptoms quickly abated. With this dose the patient could be out in sunny weather in summer with only moderate symptoms. Sometimes she could even spend a whole day in the sunshine in her bathing costume without any subsequent symptoms.

Since the beginning of treatment with carotene the patients in cases 4 and 6 have been able to spend whole days in strong sunshine with but negligible symptoms. They had never before been out so much in summer without symptoms, as in 1972.

While receiving carotene the patient in case 5 had transient pricking of the face after 2 hours' exposure to sunshine and snow in the middle of March 1972. Later that spring, however, he could spend several hours in the sunshine without subsequent symptoms and for the first time in his life he was able to work in the open air. In the middle of the summer of 1972 the carotene dose was reduced without recurrence of the symptoms of hypersensitivity to sunshine.

In case 7 the patient had only negligible symptoms during the summer despite severe symptoms in the spring of that year. Treatment with carotene was started in mid-May 1972.

Phototests

Case 4. In the middle of November 1971, 2 months after the end of treatment with β-carotene

tene, the MED was 30 minutes. After a further 3 months it was only 20 minutes, suggesting a reduced tolerance to the radiation compared with that at the first examination. After he had been treated for 1 month in February–March in 1972, the MED had increased to 35 minutes, which may be regarded as a sign of increased tolerance of the radiation.

Case 5. Before the beginning of treatment with β -carotene in January 1972 the MED was 25 minutes, while even after 6 weeks of treatment it was as long as 50 minutes. The patient was thus then much less sensitive to the radiation than before treatment.

None of the 5 controls developed erythema.

COMMENTS

Though the results of treatment are difficult to judge in such a widely varying clinical picture as that of EPP, it appears that β -carotene therapy is the most effective method of those hitherto tried (4, 18). Phototests lend support to this conclusion. The effect generally begins 2–4 weeks after the beginning of therapy. β -carotene does not appear to produce side-effects (2, 29).

The effect of treatment seems to vary to some extent with the plasma concentration of β -carotene but levels $>500 \mu\text{g}/100 \text{ ml}$ did not always give complete freedom from symptoms (cases 1, 2, 3, 6, 7). Yet levels about $200 \mu\text{g}/100 \text{ ml}$ offered protection in spring in case 5.

The mode of action of β -carotene in EPP is not known. It is possible that the yellow colour, which acts like an accessory pigment, absorbs the light (16). The deposition of melanin in the skin after exposure to sunshine has a known protective effect (20). EPP has been described in only two negroes (1).

The phototoxic reaction in patients with EPP, in which the PP of the skin is activated by light with a wavelength of about 400 nm, is accompanied by the formation of free radicals of peroxide type with consequent injury to the cell membranes (25). The reaction requires the presence of free, molecular oxygen. β -carotene may have a quenching effect in this process (8, 9, 27).

β -carotene has no therapeutic effect on photosensitivity of normal persons on exposure to solar radiation (290–320 nm) or of patients with porphyria cutanea tarda (14, 19). Polymorphous light

eruptions have been treated successfully with β -carotene (26).

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