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OPHTHALMOLOGICAL STUDY OF PATIENTS UNDERGOING LONG-TERM PUVA THERAPY

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Abstract. In the present study 46 patients with severe psoriasis maintained on long-term PUVA therapy have been followed up to 6½ years after the initiation of treatment. Repeated ophthalmological examinations were performed in order to detect any early sign of lens changes. No ocular side effects attributed to the photochemotherapy were revealed during this period. Continued use of appropriate eye shielding is recommended and also routines to remind patients to actually wear their protective glasses.

A combination of oral psoralen and UVA radiation (PUVA) is now widely used for treatment of psoriasis, vitiligo, mycosis fungoides and some other skin diseases.

The fear of possible eye damage has arisen from earlier animal experiments (3, 4, 5, 10, 18, 20). More recent studies indicate that 8-methoxypsoralen (8-MOP) can be found in the lens after intake. If the lens is not exposed to long UV-radiation (UVA) the substance diffuses out unchanged in about 12 hours. Exposure to such radiation, however, results in the production of photoaddition products with tryptophan and with lens proteins, which can lead to the permanent retention of the substance in the lens (13, 14). Whether these photoaddition products can contribute to the formation of lens opacities, cataract, is not known (12).

If adequate ocular shielding is prescribed for patients for 12 hours after oral psoralen administration and further UVA exposure thus avoided, the potential risks of lens damage are reduced—from a theoretical point of view (6, 7, 15, 22). However, this implies that the patients are likely to wear prescribed glasses.

One case report of cataract developing during PUVA treatment has been published, but the correlation with PUVA therapy seems very uncertain (19). Follow-up studies on psoralen-treated patients have not proved any significant ocular side effects (2, 8, 17).

We have now for several years followed a group of patients with severe psoriasis maintained on long-term PUVA therapy and performed repeated ophthalmological examinations in order to detect any early sign of lens changes. The majority of our patients have now been followed up to 5 or 6½ years after the initiation of photochemotherapy and the results are documented in the present study.

MATERIAL AND METHODS

Patients

46 patients were investigated, 23 males and 23 females. They all had a history of long-standing severe psoriasis. Clinical data such as mean age and duration of their disease prior to the therapy are given in Table 1. An earlier course of arsenic treatment had been given to 13 and earlier methotrexate therapy to 5 patients. Age distribution is outlined in Figs. 1 and 2.

PUVA therapy

PUVA treatment was started in 1974. An oral dose of approximately 0.6 mg/kg of 8-methoxypsoralen was given 2 hours before the UVA radiation. The initial UVA dose was about 1.5–2.5 $J \cdot cm^{-2}$ and was gradually increased by 0.25–1.0 $J \cdot cm^{-2}$ each time up to a maximum dose of 20 $J \cdot cm^{-2}$, but many patients required considerably less before healing was obtained. UVA irradiation was provided by light sources giving longwave ultraviolet radiation ranging from 320 to 380 nm, intensity maximum at 365 nm. Lamp intensities were regularly measured with a Hewlett-Packard radiant flux meter or with a PUVA meter (H. Waldmann Werk für Lichttechnik). The PUVA meter used has its greatest sensitivity in the UVA region, with a maximum around 365 nm.

Initially, treatment was given 3 to 4 times per week during the period 1974–77, but 2 to 3 times per week later on. After total clearing, maintenance therapy has been given once weekly for about 2 months afterwards for the majority of the patients. Because of the severity of their disease most patients have received repeated courses of

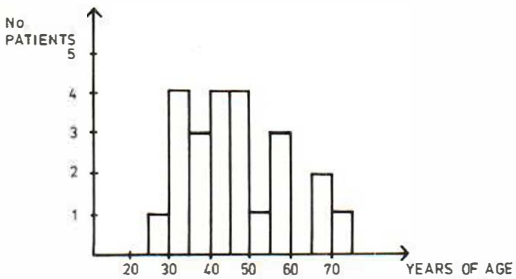

Fig. 1. Age distribution of PUVA-treated female patients ($n=23$).

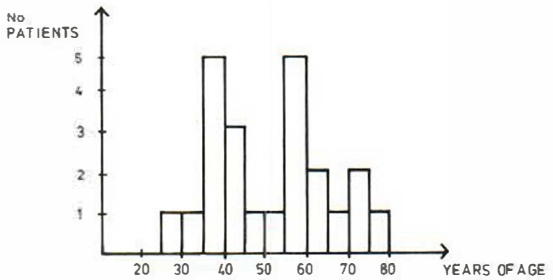

Fig. 2. Age distribution of PUVA-treated male patients ($n=23$).

PUVA treatment for several months, 2 to 4 times annually, or continuous regular treatment once or twice weekly. During therapeutic irradiation, eye protection was provided by small black non-transparent spectacles. The patients were furthermore instructed to wear Polaroid® sunglasses and avoid sun exposure on the day of medication.

Patients included in this study have been undergoing extensive prolonged PUVA therapy for 4.3±1.4 years, on average (cf. Fig. 3). Therapeutic data are given in Tables II and III.

Eye examinations

The patients were examined within a year after initiation of PUVA therapy and thereafter once every 12–24 months. The examinations comprised determination of visual acuity and refraction, after which the pupils were dilated to 7–8 mm. The anterior segment of the eye was examined with a Haag-Streit 900 slit lamp with special attention to the lens. This examination was carried out by two ophthalmologists (E. L. and P. J.) who examined all the subjects independently on each occasion. The intraocular pressure was measured in persons over 40 years of age and the central fundus inspected ophthalmoscopically. 23 different parameters were examined and graded, 14 of which concerned the lens. The parameters examined in the lens are listed in Table IV.

RESULTS

A reduction of visual acuity over the 5 years of follow-up occurred in 3 patients, aged 52, 68 and 78 years. This reduction was in all 3 cases explained by senile macular changes. One of these patients, a 68-year-old woman, also had initially slight cortical lens opacities that increased somewhat.

In one patient, a 35-year-old woman with a myopia of 10 dioptres, an additional 0.5 dioptre of myopia developed during the follow-up period. The other patients showed no signs of increasing myopia.

Except for the changes mentioned above, no alteration in any registered parameter occurred in any of the patients. The results of the fourteen examined lens parameters are presented in Table IV.

DISCUSSION

Cataract is common in ageing people and it occurs most often without any known cause. There are however some factors that are known to contribute to the development of lens opacities. Toxic agents, such as steroid therapy, ionizing radiation and trauma are the most well known, but non-ionizing radiation may also induce cataract—such as glass blowers cataract from infrared radiation.

Ultraviolet radiation in the spectral region 300–400 nm is to a large extent transmitted by the cornea and absorbed in the lens (1). There is considerable

Table I. *Clinical data of PUVA-treated patients completing ocular examinations*

	Males	Females
No. patients ($n=46$)	23	23
Mean age (years)	51.9±13.7	46.4±12.9
Mean duration of psoriasis before therapy (years)	23.5±14.8	18.9±12.0
Earlier arsenic therapy	6 (26%)	7 (30%)
Earlier methotrexate therapy	4 (17%)	1 (4%)

Table II. *Therapeutic data of PUVA-treated patients ($n=46$)*

	Males	Females
Mean numbers of treatments	210±103	208±93
Total UVA dose $J \cdot cm^{-2}$ accumulated (mean)	1 311±816	1 244±875
Total 8-MOP dose, mg accumulated (mean)	10 788±6 426	8 895±3 539

Table III. *Data of PUVA treatment: number of treatments and total UVA dose given*

No. of treatments accumulated	No. of pats.	Total UVA dose accumulated, $J \cdot cm^{-2}$	No. of pats.
<100	7	<500	10
101–200	17	501–1 000	13
201–300	17	1 001–1 500	4
301–400	3	1 501–2 000	6
401–500	2	2 001–2 500	8
		2 501–3 000	5

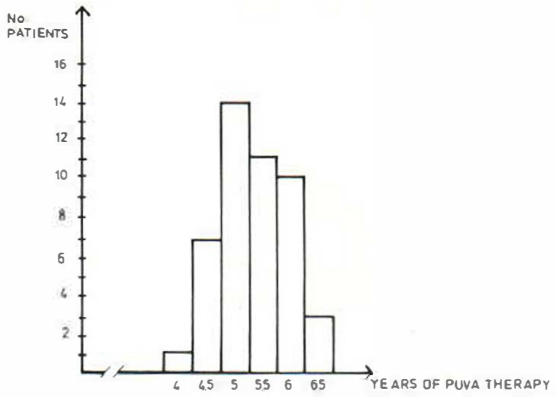

Fig. 3. Follow-up period for PUVA-treated patients ($n = 46$).

evidence that this radiation causes photochemical changes in lens proteins, with formation of the fluorescent compounds that are responsible for the yellow-brown discoloration of the ageing lens and even more in senile nuclear cataract (21). The UV radiation from the sun is suspected to contribute to the development of senile cataract. A correlation between the prevalence of cataract and the number of sunny hours per year has been shown in an epidemiologic study by Hiller et al. (11). There are, however, no reports on increased occurrence of cataract in patients with psoriasis who are exposed to massive doses of sunlight for many years.

The 8-methoxypsoralen itself seems to be non-toxic to the lens, but on exposure to ultraviolet radiation photoaddition products are formed which are retained in the lens (14, 15).

The dose of UV radiation received by the lenses of patients while they are under the influence of 8-MOP is difficult to estimate. The dose given in the actual PUVA treatment is known exactly, but the eye protection during the treatment precludes ex-

Table IV. *Results of lens examination*

For each parameter the patient is classified according to the most affected eye

Object of examination	Evaluation	Findings[a] (number of patients, $n = 46$)
Lens capsule		
Pigmentary deposits	Presence noted	11
Pseudo-exfoliation	Presence noted	0
Subcapsular area		
Anterior vacuoles	Presence noted	5
Anterior opacities	Presence noted	2
Posterior vacuoles	Presence noted	15
Posterior opacities	Presence noted	1
Lens cortex		
Punctate opacities	Counted[b]	7 (10 opacities or more)
Larger opacities	Presence noted[c]	14
Zones of discontinuity–zones with a slightly increased light scattering	Counted	25 (1 zone) 19 (2 zones) 2 (3 zones)
Light scattering in the deep anterior cortex–the supranuclear zone	Graded from 1 to 5	16 (grade 3 or more)
Nucleus		
Transparency	Graded from 1 to 5	2 (grade 3 or more)
Colour	Graded from 1 to 5	6 (grade 3 or more)
Punctate opacities	Presence noted	30
Larger opacities	Presence noted[c]	2

[a] The findings observed remained unchanged during the observation period
[b] In a 0.2 mm wide slit beam.
[c] Marked in a schematic drawing of the lens.

posure of the lens. During the rest of the day that the 8-MOP is taken, the patients are instructed to wear protective polaroid sun glasses (22)—but do they acutally wear the prescribed glasses? In a recent thorough inquiry in another 46 patients during PUVA therapy it was found that 92% had bought the recommended protective glasses but only 72% used them regularly and others only in sunny weather. As many as 15% did not use any glasses at all and the main reason was mere thoughtlessness. Economic and cosmetic reasons or inadequate information were not important factors (23).

One problem in evaluating some of the lens findings is the lack of an objective method for registration. The degree of transparency of the nucleus and the deep cortex and the colour of the nucleus are graded without an objective reference system. The present examination form was used previously by one of the investigators (E. L.) in two epidemiological studies and we consider this subjective grading gives a reasonable accuracy (9, 16).

Furthermore, nuclear cataract is very often associated with myopia and none has developed in these patients, except in a woman with a pre-existing high degree of myopia. The other 11 parameters can be recorded more exactly.

Retinal changes should theoretically not occur, as the radiation in the spectral region of interest does not reach the retina (1). The macular changes we have seen in 3 of our patients can therefore be considered as senile macular degeneration.

In conclusion, no ocular side effects attributed to photochemotherapy with 8-methoxypsoralen and UVA irradiation was found in patients on long-term PUVA therapy when followed up for 5 to 6 years after the initiation of treatment. However, it is unadvisable to interpret these data as evidence that no risk can occur with further continuous therapy later on. We recommend further use of occlusive, ultraviolet-opaque spectacles during treatment and appropriate protective glasses for up to 12 hours after 8-MOP has been ingested. Furthermore, routines should be arranged to remind patients of the importance of actually wearing the prescribed ocular shielding.

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