

Disease Associations in Polymorphous Light Eruption

A Long-term Follow-up Study of 94 Patients

Taina Hasan, MD; Annamari Ranki, MD, PhD; Christer T. Jansen, MD, PhD; Jaakko Karvonen, MD, PhD

Objectives: To examine the long-term outcome of polymorphous light eruption (PLE) in a large patient population and to evaluate associated conditions, especially lupus erythematosus, during the course of the disease.

Design: A questionnaire-based follow-up study an average of 32 years after onset of PLE. The study was complemented by clinical examination of the patients with PLE similarly studied 16 years earlier or now reporting equal or worse PLE symptoms compared with the 1978-1979 follow-up or any symptoms suggesting an autoimmune disease.

Setting: A dermatologic clinic in a university hospital.

Patients: Ninety-four of the original cohort of 138 patients with PLE (87% of living patients) returned the questionnaire, and 46 (84%) of the 55 patients invited volunteered for clinical examination.

Intervention: None.

Main Outcome Measures: Clinical characteristics of

PLE and clinical and laboratory findings referring to associated diseases, especially lupus erythematosus.

Results: Twenty-three (24%; 95% confidence interval [CI], 16%-34%) of the 94 patients were cured, 48 (51%; 95% CI, 41%-62%) experienced milder symptoms, and 23 (24%; 95% CI, 16%-34%) experienced equal or worse symptoms than in the 1978-1979 follow-up. At least 1 autoimmune disease was diagnosed at some point in 14 patients (15%; 95% CI, 12%-29%) (in 13 [18%] of the female patients) and lupus erythematosus specifically in 2 (2%; 95% CI, 0%-7%) (in 2 [3%] of the female patients). The prevalence of a thyroid disease was 14% (13 patients) (95% CI, 8%-23%).

Conclusion: Polymorphous light eruption is a long-standing, slowly ameliorating disease with some tendency to development of autoimmune disease or thyroid disorder, especially in female patients, but the risk for lupus erythematosus is not increased.

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From the Departments of Dermatology, University of Tampere and Tampere University Hospital, Tampere (Dr Hasan), Helsinki University Central Hospital, Helsinki (Dr Ranki), Turku University Central Hospital, Turku (Dr Jansen), and University of Oulu, Oulu (Dr Karvonen), Finland.

POLYMORPHOUS light eruption (PLE) is the most common photodermatosis, affecting about 20% of the Scandinavian population.¹

Although the exact pathomechanism is unknown, a delayed hypersensitivity reaction to UV radiation induced by unknown neoantigen(s) remains the most popular hypothesis.² Lupus erythematosus (LE) presenting with photoaggravated skin lesions is the most important differential diagnosis of PLE, as similar clinical, histological, photobiological, and even serological findings can be observed in both disorders.³⁻⁹ Although, according to earlier follow-up studies, PLE seldom progresses into LE,^{3,10-12} LE has been reported in some patients with PLE^{7,9} after a few years of follow-up. It has been shown recently that every second patient with LE reports a history of PLE,¹³ which is more than twice the self-reported PLE prevalence among the Scandinavian population.¹ In most of these patients, PLE typi-

cally preceded LE symptoms, in some of them as long as 45 years before any manifestation of LE. Whereas our earlier follow-up evaluation¹² took place approximately 7 years after the original survey of 138 patients with PLE¹⁴ and an average of 16 years after the onset of PLE symptoms, we now performed a longer follow-up study of the same group 23 years after the original study and an average of 32 years after the first PLE symptoms. We focused on possible symptoms or signs referring to autoimmune diseases, especially LE. In addition, we recorded the outcome of sun sensitivity and other associated diseases in 94 of the original 138 patients.

RESULTS

EVOLUTION OF PLE SYMPTOMS DURING LAST FOLLOW-UP

Of the 94 patients returning the questionnaire an average of 32 years (range, 23-68 years) after the onset of PLE symptoms, 23

PATIENTS AND METHODS

QUESTIONNAIRE SURVEY

Our patients were drawn from the original 138 consecutive patients with PLE volunteering for thorough investigation at the Department of Dermatology, University of Oulu, Oulu, Finland, from January 1, 1971, through December 31, 1973.¹⁴ The study was approved by the Ethical Committee of the hospital. As 24 men and 6 women of the cohort had died and the addresses of 7 women could not be traced, the questionnaire was sent to 25 men and 76 women in 1996. Ninety-four patients (68%; 87% of all living), including 23 men (92% of 25 men alive; mean age, 51 years; range, 31-72 years) and 71 women (93% of 76 women alive; mean age, 55 years; range, 26-90 years) returned the questionnaire, and 97% of the questions were answered. Eighty-eight percent of the patients lived between the latitudes of 63.0° and 67.0°.

The questionnaire included the following questions concerning clinical characteristics of PLE symptoms: (1) overall grade of PLE symptoms (worse, equal, less, or none) during the last 2 summers compared with those during the 1978-1979 follow-up¹²; (2) months during which sun-precipitated skin symptoms had begun and waned in 1994 and 1995; (3) length of threshold tolerance to summer noon-time sun exposure in 1994 and 1995 (<10 minutes, 15-30 minutes, 1-3 hours, or >3 hours); (4) latency from sun exposure to PLE symptoms in 1994 and 1995 (more or less than 12 hours); (5) existence of hardening phenomenon in 1994 and 1995 (no diminishing, some diminishing, or total disappearance of PLE symptoms by the end of the summer after repeated sun exposure); (6) appearance and distribution of PLE rash and possible differences in 1994 and 1995 vs the 1978-1979 follow-up; and (7) present PLE-affected skin area (face, breast, V area of the neck, back of the hands or forearms, or any sun-exposed skin area). Questions 2 to 5 and question 7 had been asked also during the 1971-1973 study¹⁴ and questions 1 to 3 and 6 and 7, during the 1978-1979 follow-up.¹² In case of equivocal answers, the patients were further interviewed by telephone.

Finally, to evaluate the overall health status of the patients, we inquired if they had ever suffered from other dermatoses, rheumatoid arthritis or other joint diseases, LE, thyroid diseases, or any other disease(s) diagnosed by a physician. In addition, the patients' medical records from the university hospital were thoroughly examined with the patients' consent.

CLINICAL, LABORATORY, AND PHOTOBIOLOGICAL INVESTIGATION

Of the 94 patients returning the questionnaire, 55 were invited to take part in a clinical examination. The main inclusion criteria was that they had been clinically examined in the 1978-1979 follow-up (n = 40). In addition, patients reporting worse or equal PLE symptoms compared with the

1978-1979 follow-up (n = 8) or any symptoms referring to an autoimmune disease (n = 7) were invited. After providing informed consent, 46 of the patients (12 men [mean age, 48 years; range, 31-66 years] and 34 women [mean age, 57 years; range, 28-80 years]) participated in this investigation, which was performed by 2 of us (T.H. and J.K.) in April or in November 1996. Two men and 7 women did not participate, mostly because of long travel distances. The overall grade of PLE symptoms was significantly worse in the patients clinically examined than in those not examined ($P = .008$), but there were no differences in age, sex, or duration of PLE symptoms between both patient groups.

During the visit, the clinical history and thorough dermatological status were recorded, with special reference to symptoms or signs of any autoimmune disease, especially LE. The data concerning associated diseases were checked, in a few cases also from medical records of other hospitals. The diagnoses of associated diseases were based on clinical history and laboratory and histopathologic findings. The laboratory tests included levels of antinuclear antibody (ANA ab), antibodies against native DNA, and extractable nuclear antigens; components of complement (C3 and C4); erythrocyte sedimentation rate (ESR); complete blood cell count; and levels of hemoglobin, serum creatinine, and urine albumin. Biopsy specimens from healthy upper arm skin were also obtained for demonstration of IgG, IgM, IgA, and C3 deposits using direct immunofluorescence microscopy. In case of LE-like skin lesions, a biopsy for routine histological and direct immunofluorescence evaluation was performed. The histological diagnosis of LE was based on generally accepted criteria,^{4,5} the main criteria being hydropic degeneration of the epidermal basal cells and perivascular and periappendageal lymphoid cell infiltrate.

The 2 patients suspected of having LE underwent a UV-A provocation test using a commercially available phototesting device (Sellas Sunlight device; Sellas Medizin Geräte GmbH, Gevelsberg, Germany; main emission spectrum, 340-400 nm) and a UV-B provocation test using commercially available light bulbs (TL 20W/12; Philips, Eindhoven, the Netherlands; main emission spectrum, 280-370 nm). The patients underwent irradiation using approximately 2 minimal erythema doses of UV-A and UV-B on 3 consecutive days on 2 separate intact skin areas, as described previously.¹⁵ A biopsy specimen was obtained from the UV-irradiated skin sites for routine histological investigation.

STATISTICAL METHODS

Fisher exact 2-sided test was used to test associations of clinical findings. Student *t* test and Mann-Whitney *U* test were used when parametric and nonparametric variables, respectively, were compared. Statistical analysis was performed using Statistica for Windows (version 5.1; StatSoft Inc, Tulsa, Okla). $P < .05$ was considered statistically significant. Confidence intervals (CIs) were determined using a commercially available software (Confidence Interval Analysis, version 1.0; British Medical Association, London, England).

patients (24%; 95% CI, 16%-34%) were considered cured, 48 patients (51%; 95% CI, 41%-62%) reported alleviation of symptoms, and the remaining 23 patients (24%; 95% CI, 16%-34%) had noticed equal or stronger symptoms than before (**Table 1**). The recovery from PLE did not depend on the original clinical subtype (**Table 2**), and the age of

71 patients with recovery or alleviation of PLE symptoms (mean age, 55 years) did not differ significantly from that of 23 patients with equal or stronger symptoms than before (mean age, 52 years; $P = .29$). Although not systematically asked, temporary symptom-free periods of 1 to 3 years were reported by 2 patients. The mean yearly dura-

Table 1. Evolution of PLE Symptoms During an Average Observation of 32 Years*

PLE Symptoms	Follow-up, No. (%) of Patients	
	1978-1979 vs 1971-1973† (n = 110)	1994-1995 vs 1978-1979† (n = 94)
Worse	5 (5)	5 (5)
No change	41 (37)	18 (19)
Less	52 (47)	48 (51)
No symptoms	12 (11)	23 (24)‡

*PLE indicates polymorphous light eruption.

†The PLE symptoms alleviated or disappeared significantly more often during the latter observation period ($P = .008$).

‡Fourteen patients were symptom free for more than 10 years; 4 patients, 5 to 10 years; and 2 patients, 2 years; the duration of the symptom-free period for the remaining 3 patients is not known.

Table 2. Association of PLE Subtype and Disease Outcome in 94 Patients Followed Up for an Average of 32 Years*

Original Subtype of PLE in 1971-1973	No. of Patients	
	With Active Disease in 1994-1995	Cured in 1994-1995
Vesicopapular†	26	9
Eczemalike PLE	4	1
Maculonodular	8	2
Prurigo-like PLE‡	19	6
Erythema solare perstans	2	2
Plaque	1	1
Erythema multiforme-like PLE	2	0
Hydroa vacciniforme-like PLE	2	0
Solar urticaria-like PLE	2	0
Juvenile spring eruption	0	1
Unclassified	5	1
Total	71	23

*PLE indicates polymorphous light eruption.

†Only 1 female patient met the criteria of benign summer light eruption.¹⁶

‡Although the original appearance was prurigo-like,¹⁷ most cases did not represent true actinic prurigo based on other clinical signs.

tion of symptoms in patients with active PLE was 5.5 months in the 1971-1973 study, 3.5 months at the 1978-1979 follow-up, and 5 months in 1994 and 1995. The short threshold tolerance to sun exposure (<30 minutes) and the short latency from sun exposure to skin symptoms (<12 hours) were as common, but the hardening phenomenon became significantly more frequent during follow-up (**Table 3**). At the previous 1978-1979 follow-up, an average of 16 years after the onset of PLE, 10 patients with active disease (12%) reported an extension of the PLE-affected skin area, compared with the 1971-1973 follow-up. In our study, an average of 32 years after the onset of the disease, the PLE rash had further extended in only 1 patient (1%). The face, chest, forearm, and back of the hand continued to be frequently affected, and in 40 patients with active symptoms (56%), all sun-exposed skin areas were sun-sensitive. Eighteen patients with persistent PLE symptoms (25%) now reported an alleviation of the PLE lesions.

The yearly duration of PLE symptoms was significantly shorter in women (median, 4 months) than in men (median, 6 months) ($P = .01$), and the latency from sun

Table 3. Patients With PLE Reporting Short TTS, Short Latency From Sun Exposure to PLE Symptoms, and Reduction of Symptoms Due to Repeated Sun Exposure*

Year of Observation (No. of Patients With Active Disease)	% of Patients		
	TTS <30 min	Latency <12 h	Hardening Phenomenon
1971-1973 (138)	60	81	51†
1978-1979 (98)	48
1994-1995 (71)	60	84	84†

*PLE indicates polymorphous light eruption; TTS, threshold tolerance to sun exposure; and ellipses, patients were not asked.

† $P < .001$.

exposure to PLE symptoms was short (<12 hours) significantly more often in women (46 women [90%]; 95% CI, 79%-97%) than in men (8 men [62%]; 95% CI, 32%-86%) ($P = .02$). The sex of the patient did not affect significantly any other clinical characteristics of PLE.

ASSOCIATED DISEASES IN PATIENTS WITH PLE

In 14 (15%) of the 94 patients with PLE (in 13 [18%] of the female patients), at least 1 disease of autoimmune origin was recorded (**Table 4**). In addition, 8 patients (8%) had hypothyroidism or nontoxic goiter, the exact cause of which could not be traced. Since nontoxic goiter is now considered an autoimmune disease,¹⁹ and since the most probable reason for hypothyroidism is an autoimmune process, as many as 22% (21 patients) of all the patients with PLE and 28% (20) of the female patients may have an associated autoimmune disorder. There were no statistically significant differences in the original clinical subtype of PLE or in the present clinical characteristics of PLE symptoms between patients with or without an autoimmune disease (P values ranged from .17-.99).

Lupus erythematosus developed in 2 female patients. In one of them, systemic LE (SLE) had been diagnosed according to criteria of the American Rheumatism Association²⁰ 10 years after the onset of PLE. The other patient presented with annular plaques and papules on her back, similar to subacute cutaneous LE (SCLE). In results of the photoprovocation test, an annulopapular SCLE-like lesion was induced with UV-A and a papular lesion with UV-B irradiation, both histologically compatible with LE. Based on these findings and on weakly positive ANA ab level (1:80), the diagnosis of SCLE was confirmed, although antibodies against extractable nuclear antigens were not found.²¹ A third female patient was suspected of having SLE, based on her skin symptoms (butterfly dermatitis, Raynaud phenomenon, and periungual edema and erythema). However, as her photoprovocation reactions did not refer to LE clinically or histologically, and in the absence of ANA abs or any other pathological findings, the criteria for a diagnosis of LE were not met. In 7 of 30 deceased patients with PLE, the cause of death could be traced from the medical records, and in each case it was unrelated to any autoimmune process.

Associated diseases other than those of autoimmune origin are listed in Table 4. The prevalences of the most frequently associated diseases, atopic eczema and

Table 4. Associated Diseases in Patients With PLE During the Course of the Disease*

Disease	No. (%) of Patients			95% Confidence Interval
	Men (n = 23)	Women (n = 71)	Total (N = 94)	
Autoimmune origin				
Thyroid disease (probably of autoimmune origin)†	0	8 (11)	8 (9)	4-16
Autoimmune thyroid disease‡	0	4 (6)	4 (4)	1-11
Rheumatoid arthritis	0	3 (4)	3 (3)	1-9
Vitiligo	1 (4)	2 (3)	3 (3)	1-9
Lupus erythematosus	0	2 (3)	2 (2)	0-7
Celiac disease	0	2 (3)	2 (2)	0-7
Alopecia areata	0	1 (1)	1 (1)	0-6
Patients with at least 1 disease of autoimmune origin	1 (4)	13 (18)	14 (15)	8-24
Patients with at least 1 disease admittedly or probably of autoimmune origin§	1 (4)	20 (28)	21 (22)	14-32
Other				
Eczema	7 (30)	26 (37)	33 (35)	26-46
Actinic reticuloid¶	1 (4)	1 (1)	2 (2)	0-7
Actinic keratosis	0	2 (3)	2 (2)	0-7
Malignancy + neoplasm of skin#	0	2 (3)	2 (2)	0-7
Other skin diseases**	3 (13)	5 (7)	8 (9)	4-16
Type 2 diabetes mellitus	0	6 (8)	6 (6)	2-13
Other than malignant neoplasms of skin††	1 (4)	2 (3)	3 (3)	0-9

*PLE indicates polymorphous light eruption.

†Includes 5 patients with hypothyroidism and 3 with nontoxic goiter.

‡Includes 3 patients with hypothyroidism caused by verified autoimmune thyroiditis and 1 patient with Graves disease.

§Diagnosed after the onset of PLE except for 1 patient with vitiligo, which began simultaneously with PLE, and 1 patient with nontoxic goiter, which began before PLE. In 18 patients, PLE was still active during the present follow-up; in 1 patient with vitiligo and in 2 patients with thyroiditis, PLE was cured.

||Includes 15 patients with atopic; 13, toxic or allergic; 3, seborrheic; and 2, nummular eczemas.

¶An extreme form of chronic actinic dermatitis.¹⁸

#Includes 1 patient with basal cell carcinoma and 1 with mycosis fungoides.

**Includes 2 patients with lichen planus; 2, lichen amyloidosis; 1, psoriasis; 1, prurigo nodularis; 1, urticaria chronica; and 1, urticaria pigmentosa.

††Includes 1 patient each with a malignant neoplasm in the kidney, breast, and thyroid gland.

type 2 diabetes mellitus, do not differ from those estimated for the normal Finnish population.^{22,23}

Ninety-four percent of the data on associated diseases (74 diagnoses) were obtained from hospital medical records or through thorough patient interview, and in these cases, the diagnosis had been made by a specialized physician according to generally accepted criteria. Only 5 diagnoses (6%) were based solely on the questionnaire. In only few clinically examined cases, medical records of other hospitals were also available and, thus, more data of general health status were received compared with those merely answering the questionnaire.

LABORATORY TESTS

In 8 (17%; 95% CI, 8%-31%) of 46 patients clinically examined, findings were positive for ANA abs with a low (1:40 or 1:80) titer, always with a homogeneous staining pattern. These values were not different from those recorded during the 1978-1979 follow-up. The presence of slightly elevated ANA ab levels was not associated with the grade of overall PLE symptoms or with the diseases of autoimmune origin. In 24 skin biopsy specimens, results of direct immunofluorescence showed only slight unspecific IgM and/or C3 deposits at the dermoepidermal junction, whereas the remaining 22 biopsy specimens were negative for IgM and C3. Erythrocyte sedimentation rates were elevated in 9 patients (20-70 mm/h). There were no significant abnormalities in the remaining laboratory test results, including antibodies against native DNA and extractable nuclear antigens.

COMMENT

Polymorphous light eruption is considered to be a persistent disease,^{3,12} although the exact long-term prognosis is unknown. We found that 71 (76%) of the patients still suffered from PLE after some 30 years, but in most, the symptoms alleviated as the years went by. Since most symptom-free patients had been in remission for more than 10 years, we consider these individuals truly cured. The amelioration or total disappearance of the PLE rash was significantly more frequent in the present than in the previous (1978-1979) follow-up, which emphasizes the slow alleviation. In some individuals, the tendency to improve may be due to a deliberate or unintentional avoidance of sun exposure in the course of time. However, we do not regard this as the major reason for the alleviation of symptoms, since the recovery or alleviation of symptoms did not depend on the age of the patients, and since the patients were thoroughly informed of the risks of UV exposure from early on, and, therefore, probably would have learned to protect themselves from sun exposure during the first 16 years of the disease. The changes in the yearly duration of PLE symptoms, ie, a reduction during the shorter follow-up and an increase thereafter, may be due to the recovery of the patients with milder cases and the persistence in patients with difficult cases during the last follow-up. Sex did not affect the overall prognosis of PLE. However, women reported shorter yearly duration of PLE rash and noticed PLE lesions more quickly than men.

In our cohort of 94 patients (71 female patients), LE developed in 2 female patients following onset of PLE. This

observation is concurrent with the earlier finding of LE developing in 2% to 4% of patients with PLE.^{3,9} The prevalence of SLE in Finland is 28 per 100 000 inhabitants, and about 80% of these are female.²⁴ The corresponding figures for discoid LE and SCLE are not known. As discoid LE has been reported to be less frequent than SLE²⁵ and SCLE to account for about 10% of all LE cases,²¹ the total prevalence of all LE subsets in Finland obviously does not exceed 100 per 100 000 inhabitants, ie, 2 per 2000 inhabitants equal to 2 per 1000 female inhabitants. Although LE seemingly developed more often in the patients with PLE in our study than among the healthy Finnish population, the development of 2 single cases of LE may have happened by chance. Thus, LE among patients with PLE was not as frequent as could have been expected based on the observation that about half of patients with LE have experienced PLE symptoms, most of them before LE.¹³

On the other hand, the prevalence of any autoimmune disease in our 94 patients with PLE was as high as 15%, and even higher (22%) if hypothyroidism and nontoxic goiter were considered as autoimmune processes. This is more than the estimated 5% to 7% prevalence of autoimmune diseases in the population²⁶ and indicates that patients with PLE have an increased risk for contracting an immunological disorder, although cases of LE did not outnumber those of any other autoimmune disease. In general, autoimmune diseases are more common in women than in men, the actual prevalence ranging from 2 to 10 women for each man.²⁷ Thus, approximately 4% to 11% of women suffer from some autoimmune disease. In our patient population, only 1 man (4%) but 13 women (18%) had an autoimmune disease, and 7 other women (10%) had a thyroid disease, probably of autoimmune origin. Thus, especially female patients with PLE were prone to autoimmune diseases. However, the original PLE subtype or clinical characteristics of the disease did not have an impact on the development of an autoimmune disease.

The prevalence of hyperthyroidism or hypothyroidism, observed in 9 female patients (in 10% of all the patients and in 13% of the female patients), is also higher than the reported 3% (5% in the female population) prevalence in the normal population in Great Britain.²⁸ The exact prevalence of thyroid diseases in Finland is not known, but the estimated prevalence of hyperthyroidism or hypothyroidism, subclinical cases included, does not exceed 5%.¹⁹ To confirm our results of increased risk for autoimmune and thyroid diseases in patients with PLE, a larger and prospective study with age- and sex-matched controls would be needed.

Actinic reticuloid, an extremely photosensitive disorder regarded as part of the disease spectrum including chronic actinic dermatitis,¹⁸ developed in 2 patients. The overlapping of PLE and chronic actinic dermatitis, even with possible progression from PLE to chronic actinic dermatitis, has been discussed previously,²⁹ and our follow-up results further imply a possible relationship between both photosensitivity disorders.

We have found that PLE is a persistent disease that tends to ameliorate slowly. Although PLE could not be shown to be a risk factor for LE, female patients with PLE had a tendency toward development of diseases of autoimmune origin and thyroid dysfunctions.

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Reprints: Taina Hasan, MD, Department of Dermatology, Tampere University Hospital, PO Box 2000, FIN-33521 Tampere, Finland (e-mail: thasan@tays.fi).

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