European Guidelines for Photodermatoses

2 Photoaggravated Disorders

Methodology

In the present guideline the strength of evidence for diagnostic and therapeutic recommendations is graded using the Methodology recommended by NICE and adopted by the BAD. Literature search was done using PubMed/MEDLINE and EMBASE, as far back as 1960. Studies that had no English abstract were excluded.. The overall assessment of each study is graded using a code '++', '+' or '–', based on the extent to which the potential biases have been minimized as in table 2. Studies with '–' will not be included in the guideline.

Methods adopted are NICE http://www.nice.org.uk/page.aspx?o=201982 and SIGN http://www.sign.ac.uk/methodology/index.html guideline websites. This takes into account recommendations from Harbour and Miller (2001) (Br Med J; 323:334-336). http://bmj.bmjjournals.com/cgi/reprint/323/7308/334?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=harbour&andorexactfulltext=and&searchid=1096544973383_6825&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=323&resourcetype=1

Conflict of interest

The authors state that they have no conflict of interest to declare.

Introduction

Many diseases occur independently to exposure to ultraviolet radiation (UVR). Many inflammatory diseases improve or clear following UVR exposure. This section will encompass diseases not

primarily caused by UVR, but usually or occasionally exacerbated by UVR. Aggravation or worsening of diseases by UVR may occur for a variety of different mechanisms. The disease may be an inflammatory disease and in some individuals UV exposure may just add to inflammation. The disease may be complicated by coincidence with a sun induced inflammatory disorder and appear to be aggravated by UV exposure. Given that polymorphic light eruption occurs in 14-20% of people in northern Europe, it is important to differentiate diseases occurring in their own right with an expected 14-20% of people having superimposed PLE. For the disease to be truly photo-aggravated it should show exacerbation with primary lesions of the disease itself. In this situation the disorder may actually be induced by UV exposure.

Diseases usually exacerbated by UVR

Lupus erythematosus & Sjogren's syndrome
Sinear Usher syndrome
Rosacea
Dermatomyositis
Darier's disease
Kindler-Weary syndrome

Diseases sometimes associated with photosensitivity

Psoriasis
Atopic eczema
Erythema multiforme
Seborrhoeic dermatitis
Immuno-bullous diseases
Mycosis fungoides
Smith-Lemli Opitz syndrome

Lupus Erythematosus

Subtypes of LE

Systemic lupus erythematosus SLE
Discoid lupus erythematosus DLE
Subacute cutaneous lupus SCLE

Rowell's syndrome
Lupus tumidus
Lupus profundus
Bullous LE
(Jessner's lymphocytic infiltrate, Reticular erythematous mucinosis)

The diagnosis of cutaneous LE rests on typical histological changes ranging from mild to severe. Classical features include liquefaction degeneration of dermo-epidermal junction basal keratinocytes, epidermal cytoid bodies and a lymphocytic dermal infiltrate hugging the dermal blood vessels and adnexal structures, with a lichenoid aspect adjacent to dermo-epidermal junction (DEJ) interface damage. Follicular plugging and basement membrane thickening are typical of DLE. Occasionally the epidermal component is not prominent and the most prominent features are dermal. In sub-acute LE dermal oedema is prominent the epidermal changes minimal and the diagnosis rests on mild vacuolar change with a dermal lymphocytic infiltrate as previously described, though subtle in mild lesions.
Lupus tumidus exhibits mucin deposition in addition to the above features, the epidermal changes may be minimal; the differential histologically rests between polymorphic light eruption (PLE) and Jessner's lymphocytic infiltrate but with mucin deposition and positive direct immuno-fluorescence (IMF) together with the distinctive clinical appearance, it is a clearly distinct entity. Table 1 outlines the diagnostic criteria which delineate PLE, Jessner's and the various forms of LE.

Evidence for photosensitivity in LE is strong (1) (Strength of evidence 2++). Detailed study of the relationship between ultraviolet radiation (UVR) and the clinical manifestations of patients with lupus erythematosus (LE) has been carried out. Cutaneous lesions are induced or exacerbated by exposure to UVR (2). Of patients with LE, 24-83% are reported to be photosensitive to UVR. LE tumidus appears to be the most photosensitive subtype of LE, followed by subacute cutaneous LE (SCLE). In general, the history of patients with LE correlates poorly with the presence or absence of photosensitivity, due to a delayed time interval between UV exposure and exacerbation of skin lesions. Phototesting using

artificial UVR and visible light is a reliable way of diagnosing photosensitivity. Investigation of the photoreactivity of patients with various subtypes of LE has been carried out using an individualized phototest protocol (1). The results of phototests were correlated with the history of photosensitivity, the subtype of LE, the presence of autoantibodies and the use of anti-inflammatory medication by these patients.
Phototesting with UVA, UVB and visible light was performed in 100 patients with LE. The diagnosis of LE was established both on clinical examination and skin histology. Serological studies were also performed in all patients. The phototests were performed on large skin areas of the forearm or trunk; the first dose was twice the minimal erythema dose and the dosage was increased according to the individual reactions of the patients at the test sites. Follow-up of skin reactions at the test sites was performed for up to 2 months. Histological examination of the photoprovoked skin lesions was carried out in 57 patients. Of 100 patients included (81 women and 19 men; mean age 41 years, range 17-79), 46 had chronic discoid LE, 30 SCLE and 24 systemic LE. An abnormal reaction to UVR and visible light was found in 93% of patients with LE. There was no correlation between photosensitivity and LE subtype, presence of autoantibodies or medical history. Concomitant use of anti-inflammatory medication seemed to exert only minimal influence on the results of phototesting: When using an extended phototesting protocol, almost all patients with LE in this study showed clinical and histological evidence of aberrant photosensitivity. One may conclude from this and other studies demonstrating photosensitivity in Lupus no matter which type that patients with LE should receive thorough advice and instruction on photoprotective measures, regardless of their history, LE subtype or presence of autoantibodies. The photosensitivity is almost always to UVB but may extend into the UVA range. Photosensitising drugs such as nonsteroidal anti-inflammatory agents are likely to induce UVA photosensitivity in some patients in addition but this is a modest effect.

Management of Lupus depends on the clinical symptoms but should include a broad spectrum High SPF sunscreen such as those currently designated SPF 50+ (Strength of evidence 4). Those patients completely avoiding UV should take vitamin D3 supplements to prevent vitamin deficiency and where relevant calcium supplementation may be relevant. (3) (strength of evidence 2+)

Photosensitivity in Jessners lymphocytic infiltrate has been described but the differentiation of Jessner's and DLE may at times

be difficult (4) (Strength of evidence 3) Treatments such as thalidomide may work for both in intractable cases (5)

Sjogren's syndrome

Most patients with Sjogrens syndrome deny photosensitivity. Photosensitivity in Sjogrems's syndrome has been little studied but it is known to occur, possibly related to cytotoxic Ro antibodies and externalisation of Ro antigen to the cell surface induced by exposure to UV (6) A Japanese study indicates further disease mechanisms (7). Annular erythema (AE) in Sjogren's syndrome (SS) may develop on areas of sun-exposed skin and is exacerbated during summer. Phototesting with UVA and UVB was performed on 14 SS patients, including 10 with primary SS. Clinical and histological features as well as expression of inducible nitric oxide synthase (iNOS) in the evoked skin lesions were compared with those of lupus erythematosus (LE). Eleven SS patients had a history of photosensitive AE (n = 4), papules (n = 3) or other types (n = 4) of lesions on their sun-exposed skin that were induced or aggravated by sunlight exposure. Phototesting induced a prolonged erythematous response (n = 8), infiltrated erythema (IE) (n= 4) and/or papules (n = 3) in 11 of 14 SS patients, including one with primary SS without a history of photosensitivity. Histologically, the induced IE and papules showed coat-sleeve-like or sparse perivascular infiltration of lymphocytes similar to that in primary skin lesions of AE in SS. No epidermal changes characteristic for LE were found except for partial and mild liquefaction degeneration in three cases. In contrast, two cases wereindistinguishable from the papular type of polymorphic light eruption in several aspects, including their primary skin lesions and early response to a photoprovocation test. Immunohistochemistry revealed diffuse expression of iNOS throughout the epidermis, which is characteristic for LE, in the three SS patients with minimal liquefaction degeneration, while the remaining seven SS patients examined exhibited no iNOS staining or a normal expression pattern. These results indicate that photosensitivity exists in certain primary SS patients, and that UV is critical to the development of AE in SS, probably through a pathological mechanism distinct from that in LE (Strength of evidence 2++). Some patients developed PLE-like lesions. A careful history of photosensitivity should be taken, those with skin lesions appearing in exposed sites should have phototesting carried out and photoprotection as for LE should be advocated where relevant.

Dermatomyositis is frequently photoaggravated (8) (Strength of evidence 3) , The mechanism of this may relate to its similarity to Lupus and lichen planus histologically. The incidence and nature of

cutaneous photosensitivity were studied in 10 patients suffering from dermatomyositis. Five reported an abnormality, which consisted of photoaggravation of preexisting cutaneous lesions in three, and abnormal transient erythemal responses in two. Monochromatic irradiation testing of all 10 patients demonstrated reduced minimal erythemal doses in two, at 307.5nm, and at 340 and 360 nm, respectively; only the latter individual had clinical light sensitivity. Exposure to low-dose, solar-simulated radiation of the unaffected skin of the former patient, and five others who agreed to the procedure, three of whom complained of light sensitivity, induced a lesion with the clinical and immunofluorescence characteristics of dermatomyositis in only the first one. Four other patients replied to a mailed questionnaire, and three of these reported aggravation of their rash and provocation of new lesions by sunlight. Photosensitivity may thus be an important cutaneous feature of dermatomyositis. Treatment of the underlying disease together with Photoprotection seems appropriate (Strength of evidence 4)

Lichen planus may be caused by sun exposure and often presents with pigmented lesions on the face. It is seen in the tropics and especially on pigmented skin It should be distinguished from other causes of lichenoid eruptions such as drug-induced Lichen planus and allergic contact dermatitis which may also be lichenoid. Thus patch testing as well as light testing may be relevant (9). Photosensitive lichen planus has been described associated with AIDS (10) (Strength of evidence 3). Lichenoid photodistributed eruptions in HIV disease are also described. One patient with lichen nitidus the rest probably drug induced (10,11). (Strength of evidence 3). The prevalence of photosensitivity in HIV infection has been found to be 5.4 % of patirents, with a prevalence of 7.2 in African-americans. Two distinct subtypes of photosensitivity were found, lichenoid and eczematous (12).
The eczematous pattern is now well recognised as (Strength of evidence 2+) chronic actinic dermatitis which occurs in the context of AIDS and may be the presenting feature, also it is reversed by HAART treatment (13) (Strength of evidence 3). Determination of whether an eruption is drug-induced or due to chronic actinic dermatitis is helped by the pattern of wavelength abnormality found on monochromator testing. The action spectrum for CAD is similar to that of the erythema action spectrum whereas drug-induced disease has UVA photosensitivity dissociated from UVB reactions. (14) (Strength of evidence 2+)

Granuloma annulare in a photodistributed pattern is also described in HIV infection (15) (Strength of evidence 3)

Sinear Usher Syndrome is where pemphigus foliaceus is accompanied by a positive antinuclear factor occurring on the face and exacerbated by exposure to ultraviolet radiation. This is a relatively rare type of pemphigus and may represent coincidence of both Pemphigus and lupus possibly as a consequence of epitope spread. There are several reports of photoaggravation of pemphigus foliaceous by ultraviolet radiation (16-17). Pemphigus vulgaris has also been shown to be photoaggravated with UVR enhancing antibody homing to the epidermis (18). Patients should therefore be protected from UVR to prevent disease exacerbation by UVR (Strength of evidence 2++).

Lichen planus pemphigoides may be the same, one or other disorder leading to disruption of the basement membrane such that basement membrane antigens become exposed and generate an immune response. Ultraviolet exacerbation may occur.

Darier's disease (DD) is an autosomal dominant skin disorder characterized by abnormal keratinization and acantholysis. Deleterious mutations in the gene ATP2A2 which encodes SERCA2, a calcium pump of the sarco/endoplasmic reticulum underlie the disease (Strength of evidence 1++). Darier.s disease is well known to be photoaggravated (19) (Strength of evidence 2++). Complete lesions of Darier's disease arose with repeated exposure of ultraviolet B (2,600 mJ/cm2 for 10 days), and sunscreen and topical ascorbic acid protected against its appearance. UVA failed to produce the lesions of Darier's disease (20) The mechanism is not clear but may relate to UV-induced inflammation affecting skin which is easily damaged because of the faulty cell connections. Hailey Hailey disease, genetically distinct but mechanistically related is also photoaggravated in some patients (20). Photoprotection is therefore a logical part of the management strategy for both disorders.

Kindler Weary syndrome is a consequence of a defect in the actin cytoskeleton. Clinically keratoderma occurs which is complicated by photosensitivity and on testing patients reduced responses to erythema may be found in the UVB and UVA range.(Strength of evidence 3) (21)

Smith Lemli Opitz syndrome is better understood. It is a disorder of cholesterol metabolism and is a consequence of 7-dehydrocholesterol reductase. Abnormal amounts of metabolites lead to mental retardation. UVA photosensitivity occurs in about 2/3 of patients (22). (Strength of evidence 2++) A detailed UK study revealed the following: All known cases of SLO in the U.K. were reviewed and clinical details of photosensitivity were recorded in

detail. The action spectrum of the photosensitive eruption was defined by monochromator light testing. Thirteen of the 23 subjects (57%) had severe photosensitivity, and in 10 there was no photosensitivity. No correlation was identified between levels of 7-dehydrocholesterol and severity of photosensitivity, suggesting that the photosensitivity in SLO is not caused by a direct phototoxic effect mediated by 7-dehydrocholesterol. A novel pattern of photosensitivity was observed, with onset of a sunburn-like erythema on sun-exposed skin within minutes of sun exposure, which persisted in most cases for up to 24-48 h before fading. Monochromator light testing in three subjects showed an ultraviolet (UV) A-mediated photosensitivity eruption with greatest photosensitivity at 350 nm. Photosensitivity is a common and prominent feature of SLO and appears to be UVA-mediated (22).

Photoaggravation of Rosacea occurs in 60% of cases. Forty percent are improved by sun exposure. Most patients with rosacea are fair skinned, with skin type 1-3. Misclassification in the past has lead to confusion with facial telangiectasis due to chronic UV-exposure, but papulopustular rosacea may be exacerbated by UV without a clear mechanism other than speculation that failure to downgrade immune responsiveness after sunexposure could lead to increased inflammation. Adequate treatment of the disease such that the skin is clear prevents photoaggravation of the disease. Formal phototesting does not reveal evidence of photosensitivity either on the skin of the back or the face unless patients are taking photosensitising drugs such as doxycycline (23) (Strength of evidence 3)

Atopic dermatitis

Russell et al (24) described seven young patients with atopic dermatitis (AD) who presented with a marked photoexposed site dermatitis. The results of phototesting, patch testing and other investigations were compatible with the diagnosis of chronic actinic dermatitis. It is known that AD patients may have photoaggravation of their dermatitis or exacerbation secondary to a photodermatosis, such as polymorphic light eruption, actinic prurigo or drug-induced phototoxicity. The patients described, however, appear to be an uncommon AD subgroup affected by CAD (Strength of evidence 2+). All AD patients who have a history of sunlight-induced exacerbation or marked intolerance of PUVA or ultraviolet B phototherapy should have phototesting and patch testing conducted.

Seborrhoeic dermatitis occurs as a consequence of overgrowth of pityosporum yeasts on the skin. It occurs in Atopics, it occurs in the

immunosuppressed (drug-induced, HIV) and those who are severely stressed. It often occurs together with rosacea, and may represent a consequence of failure to adequately police epidermal flora due to an abnormal stratum corneum (in Atopy) or impaired immune responsiveness in the immunosuppressed. In an increasing proportion of individuals it is now recognised to flare with sun exposure, failing to clear up as is the norm. Light testing these individuals shows some with normal responses as in rosacea, but a proportion with abnormal responses. Treatment of the basic disorder eradicates the UV-induced flare (25) (Strength of evidence 2+) as in the case of rosacea. Photosensitive seborrhoeic dermatitis may occur in patients taking immunosuppressive medication and with HIV disease: abnormal phototest responses were found in one patient with monochromator test results showing UVB and UVA photosensitivity. Topical treatment with antifungal agents and topical steroids and topical tacrolimus prevents the photoaggravation.

Psoriasis

Photosensitive psoriasis is rare. The prevalence among psoriasis patients was estimated to be 5.5% (26). (Strength of evidence 3) (Strength of evidence 3) Photosensitive psoriatics have a statistically significant higher frequency of skin type I, a family history of photosensitivity, advanced age, and psoriasis affecting hands compared with nonphotosensitive psoriatics. Half of the patients with photosensitive psoriasis have polymorphous light eruption (PLE), with psoriasis appearing as a secondary phenomenon in the PLE lesions. The other half slowly develop psoriasis after sun exposure but without preceding PLE. These reaction patterns may be confirmed with phototesting. Photochemotherapy is effective treatment for photosensitive psoriasis (Strength of evidence 2+).

Coincidence of psoriasis and chronic actinic dermatitis is described: a patient whose clinical and histopathologic findings were originally interpreted as representative of actinic reticuloid but who later developed psoriasis with pustules The authors propose that the original photosensitive eruption could have represented an unusual presentation of photosensitive psoriasis, although koebnerization of psoriasis into areas of photosensitivity remains a definite possibility.(27) (Strength of evidence 3)

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Table 1

Disorder	DEJ	Dermal lymphocytic infiltrate	mucin	IMF DEJ	Lupus serology
PLE	normal	Perivascular (PV)	negative	negative	negative
Jessner's	normal	PV	negative	negative	negative
REM	normal	PV	positive	negative	negative
Lupus tumidus	Normal	PV Periadnexal (PAD)	Positive	negative	negative
SCLE	normal	PV PAD	negative	Usually –ve	Ro+
Discoid lupus	Vacuolar degeneration thickening	PV PAD	+/-	20% positive	20% ana/Ro positive
Lupus profundus	normal	PV PAD panniculitis	negative	Positive or negative	Positive or negative
Rowell's	Vacuolar change-necrosis of epidermis	PV	negative	May be +	Ro & ANA may be positive
SLE	variable	Variable	variable	positive	positive

Table 2

Level of evidence	**Type of evidence**
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding bias or chance and a high probability that the relationship is causal

2^+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence '–' should not be used as a basis for making a recommendation (see section 7.4)	