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Conflict of interest

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Solar urticaria

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Summary

Solar urticaria is a rare IgE-mediated and chromophore-dependent photodermatosis. In some cases, these chromophores, designated as “serum factor”, may be detected in serum or plasma. To date, the exact pathogenesis of solar urticaria has, however, not been elucidated. Typical clinical features include the onset of urticarial lesions within a few minutes after light exposure, which already raises diagnostic suspicion. The most common triggers are UVA and visible light. Determination of the action spectrum as well as the minimal urticarial dose (MDU) is diagnostically crucial. Other photodermatoses such as polymorphic light eruption or porphyrias (especially erythropoietic protoporphyria) have to be ruled out. Apart from sunlight avoidance, which is always required, further therapeutic options used include nonsedating antihistamines as well as light hardening. Newer treatment modalities such as plasmapheresis or the anti-IgE antibody omalizumab are reserved for severe, recalcitrant forms of solar urticaria.

Introduction

A photodermatosis as it is triggered by light [1, 2], solar urticaria is also considered a form of physical urticaria as it presents with wheals following light exposure [3]. By definition, it is a “rare urticarial reaction triggered by electromagnetic radiation of the optical radiation spectrum, which usually occurs a few minutes after the start of sun exposure or irradiation with artificial light” (Hölzle) [2]. The first description in 1904 is attributed to Merklen [3], though other authors credit it to Borsch in 1719 and Veiel in 1887 [4]. Duke coined the term *solar urticaria* in 1923; he was also the first to use repeated sun exposure for prophylaxis [3]. In 1928, Wucherpfennig performed the first light tests aimed at triggering an urticarial reaction [4]. Other experimental studies were conducted in the 1950s and 1960s, and led to the classification of solar urticaria into six types by Harber et al. in 1963 [3]; following a review of the entire literature by Leenutaphong et al. in 1989, the disorder was eventually classified into two types [5].

Epidemiology

Occurring in all ethnic groups and skin types worldwide, solar urticaria appears to more commonly affect women [1–4, 6]. Given its rarity, there are no precise figures regarding its incidence and prevalence. Among patients clinically presenting with a photodermatosis, figures ranging from 2.3 % to 17.8 % have been reported in the literature [3, 6]. While most cases first present between the ages of 20 and 40, initial manifestations have also been described shortly after birth, in early childhood as well as in the elderly [1, 2, 4].

Pathogenesis

The pathogenesis (Figure 1) remains largely hypothetical. It is based on the results of in vitro activation as well as on passive and reverse passive transfer tests, which led to the classification into type 1 and type 2 according to Leenutaphong et al. [1, 5]. This hypothesis rests on the assumption of a precursor substance in the skin that acts as a chromophore

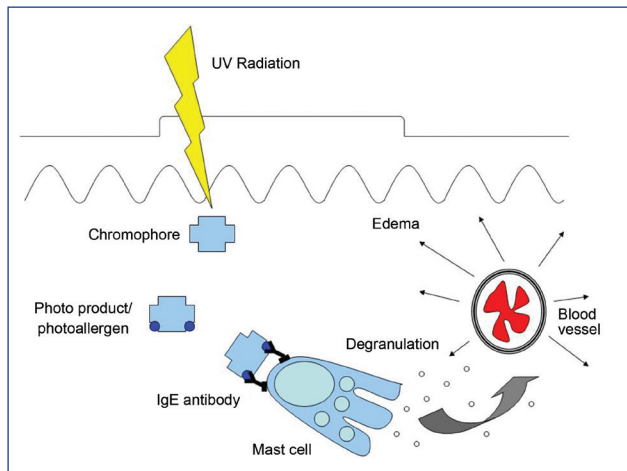


Figure 1 Pathogenesis of solar urticaria [modified from Hölzle E. 2003 [2]].

and absorbs light of a wavelength corresponding to the triggering action spectrum (AS). The resultant photoproduct acts as photoallergen, against which specific IgE antibodies are produced, which – in analogy to type I allergy – binds to mast cells. Formation of the photoallergen after renewed AS exposure leads to mast cell degranulation and histamine-mediated wheals with erythema and pruritus [1, 2, 4]. Apart from the skin, the chromophore has also been found in some patients' serum or plasma, and has thus been designated as "serum factor" [2, 7].

Besides the AS, the inhibition spectrum (inhibition of wheal formation by primarily longer-wavelength rays, especially visible light) and the augmentation spectrum (augmentation by wavelengths outside the AS) have also been described in some patients. However, the AS is the most important with respect to the further course of action [2, 4, 6].

Clinical variants, disease course, associated disorders

Clinically, solar urticaria is similar to any other form of urticaria. Within 5–10 minutes after exposure to the corresponding AS (especially electromagnetic waves between 280–500 nm; UVA and the visible light spectrum have been described most commonly), typical wheals – marked by erythema and pruritus – appear. The reaction depends on exposure duration, intensity of the sun's rays, type of clothing (densely woven, dark fabrics offer more protection), as well as the location and extent of the exposed skin [1, 2, 4, 6]. Due to habituation, chronically light-exposed skin (especially the face and dorsum of the hands) is usually relatively resistant to



Figure 2 Fixed solar urticaria (isolated occurrence at the same site even after repeated irradiation) below the right shoulder blade, following UVA-1 irradiation of the entire integument at a dose of 10 J/cm².

the development of solar urticaria. However, there have also been reports of delayed reactions after more than an hour following exposure and delayed resolution after more than 24 hours, as well as angioedema with involvement of the oral mucosa and even anaphylaxis [1, 3, 4].

A special form of the disease, fixed solar urticaria is characterized by its repeated recurrence in only certain areas of the skin (Figure 2). Given the condition's localized extent and lack of systemic reactions, patients are usually not particularly troubled by symptoms [1, 2, 8, 9].

Marked by a spontaneous onset and recurrence, solar urticaria may also spontaneously subside after months or years. Because of its rarity and only small cohort sizes, large datasets are lacking. However, studies in up to 87 patients have shown complete resolution in approximately 25 % of cases within the first ten years [1, 6, 10].

Associated disorders include polymorphic light eruption (described in up to 23 %), atopic disorders, various forms of urticaria (heat, pressure, cold), cystic fibrosis, Churg-Strauss syndrome, and hypereosinophilic syndromes; the occurrence after Stevens-Johnson syndrome has recently been reported [1, 2, 4, 6, 10–12].

Diagnosis

If solar urticaria is suspected, the diagnostic workup starts with a detailed history. It is imperative that the initial differentiation from other diagnoses (for example, polymorphic light eruption, erythropoietic protoporphyria, urticarial vasculitis, drug-induced urticarial phototoxic reaction, heat urticaria) include questions regarding the use of medication,

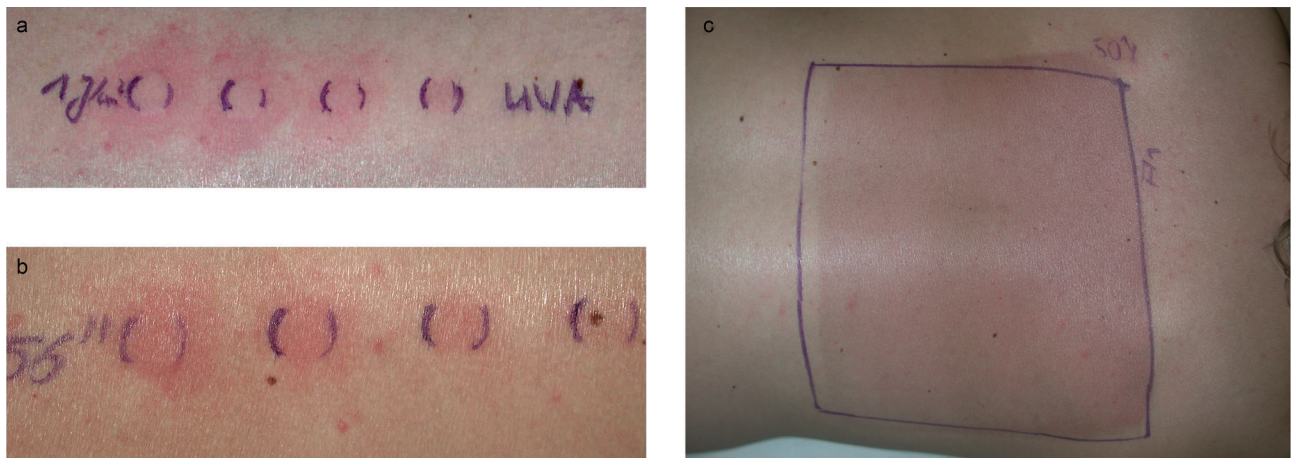


Figure 3 Positive diagnostic UVA light testing (a). Positive diagnostic UVB light testing (b). Provocation test using 50 J/cm² UVA-1 showing no wheals after 20 minutes, following successful induction of UVA/UVA-1 ultra rush hardening (previous MUD for UVA-1: 1.25 J/cm²). The (immediate) UVA erythema is also clearly visible (c).

time of onset, duration of lesions, subjective cutaneous sensations (pruritus, burning, stinging), skin changes once the wheals have subsided, as well as the site of manifestation and, possibly, any spread to non-light-exposed skin. In addition, targeted questioning may shed some light on the triggering action spectrum potentially involved. For example, in case of wheals triggered behind a windowpane, UVA or visible light may be considered responsible, as UVB light is filtered out by the glass, leaving – depending on the quality of the glass – only up to 35 % (of the initial dose). A special kind of glass, laminated safety glass in automobile windshields only allows UVA-1 and visible light to pass through [1, 2, 13].

It is particularly important to rule out porphyria, especially erythropoietic protoporphyria (EPP) or porphyria cutanea tarda. Instead of pruritus, however, the former in particular may be associated with a burning sensation and pain [2].

There are no specific laboratory tests [2]. In order to rule out the aforementioned differential diagnoses, tests should include a CBC with differential, clinical chemistry, antinuclear antibodies, and porphyrins (in blood, urine, and feces) [4]. Detection of the photoallergen (serum factor) may be attempted by means of in vitro activation of serum and plasma by the AS followed by prick and intracutaneous testing using the patient's serum (0.1 ml of irradiated serum; control: normal saline and nonirradiated patient serum) [1, 2, 8].

Phototesting is necessary to determine the action spectrum and the minimal urticarial dose (MUD), both also important with respect to potential further phototherapy of solar urticaria (Figure 3a, b). Different wavelengths should be tested, with UVB, UVA, visible light, and infrared rays being of particular importance (UVC radiation normally

does not reach the earth's surface). Given that visible light is a frequent trigger, PDT light sources with blue, green, or red light as well as slide projectors (with GG 420, GG 475, OL530 and OG 570 edge filters) may also be used [14]. If the clinical suspicion cannot be confirmed by these tests, exposure to natural sunlight is recommended [15]. Erythema and wheals usually occur within the first five minutes and, in our experience with light testing, usually require an individually adjusted procedure. Further readings should be done at 5-minute and then 15-minute intervals; late readings after 24 and 48 hours are recommended to exclude phototoxic and photoallergic reactions caused by systemic photosensitizers [1].

Prophylaxis and treatment

Once the action spectrum has been established, avoidance of the triggering spectrum – particularly in the visible range – poses great problems for many patients, resulting in considerable mental stress and even suicide [1]. Besides sunscreens, which are partially effective in case of a narrow action spectrum (UVA, UVB), textile light protection in the form of adequate clothing (densely woven, dark fabrics) is essential [1, 2].

While second-generation H1 antihistamines are recommended as first-line symptomatic therapy, most patients affected by solar urticaria require higher than standard doses [3, 16]. Combined therapy with up to three antihistamines and montelukast has also been described [17].

To date, the mechanisms involved in the development of tolerance, which are utilized in phototherapy (light hardening) of solar urticaria, are not yet fully understood. The hypothesis of tachyphylaxis or complete mast cell degranulation

does not appear to be accurate, as wheals or reflex erythema may be triggered in tolerant, treated skin after injection of histamine or a histamine-releasing substance (codeine, substance 48/80). The most likely mechanism seems to involve the blockade of mast cell-bound IgE by the photoallergen, thus preventing further degranulation [2]. Therapeutic use of repeated UV irradiation has been known for some time, and includes UVA, UVA/UVB, UVB 311 nm, and PUVA [1, 2]. First described by Beissert and Schwarz in 2000, UVA rush hardening is the most promising method. Even at low MUD levels, it allows for a maintenance dose of 10 J/cm² UVA to be reached within three days [18, 19]. We have modified this method to UVA/UVA1 rush hardening (reduction of the exposure time above a dose of 5 J/cm², thus saving time in the escalation phase), and have used it successfully since then (Figure 3c). The combination of light hardening and antihistamines has also been shown to have long-lasting therapeutic effects [2].

In severe forms and in the presence of a serum factor, plasmapheresis, cyclosporine A, and intravenous immunoglobulins may be attempted [2]. However, using a single-dose regimen, the latter did not yield convincing results in a multicenter phase II study (only 9 patients) [20]. Inconsistent results have also been reported for the monoclonal IgE antibody omalizumab. While one patient treated by Müller et al. at a dose of 150 mg every four weeks even experienced a deterioration of symptoms [21], a Spanish work group successfully used omalizumab at a monthly dose of 300–450 mg in three patients [22]. Ultimately, only randomized clinical studies can provide conclusive information on the efficacy of modern therapies. This, however, is rendered difficult by the small number of patients with solar urticaria.

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