Review

Chilblains

Astrid Nyssen[1,2], Farida Benhadou[3], Marc Magnée[1], Josette André[4], Caroline Koopmansch[4], and Jean-Claude Wautrecht[2]

[1] Department of Cardiology, CHR Verviers East Belgium Verviers, Belgium
[2] Department of Vascular Diseases, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
[3] Department of Dermatology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
[4] Department of Dermatology and Dermatopathology, Hôpital Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium

Summary: Idiopathic chilblain is a relatively common yet poorly recognized acrosyndrome. This literature review aims to better understand and draw attention to this disorder. Chilblain is a localized inflammation of the skin that occurs on exposure to cold but non-freezing wet weather. It usually resolves spontaneously. The etiology is uncertain, but vasospasm seems to play a role in this abnormal reaction to cold. Diagnosis is most often based on clinical presentation, but a skin biopsy can be useful in dubious cases. In histology, dermal edema and an inflammatory infiltrate are usually present. A distribution of the infiltrate particularly around the eccrine gland is typical. Systemic symptoms and underlying autoimmune disease should be screened. Avoiding cold and keeping extremities warm is the first recommendation for management, as well as smoking cessation. Calcium channel blockers (in particular nifedipine) seems to be the treatment that has been most evaluated in chilblains. However, their effectiveness is not confirmed by all studies. Topical betamethasone is often used but its effect has not been confirmed by randomized clinical trials. Other treatments, such as pentoxifylline, hydrochloroquine and topical nitroglycerin have shown positive effects only in a reduced number of patients. Acupuncture seems to bring a benefit.

Keywords: Chilblain, pernio, acrosyndrom, microcirculation

Introduction

Chilblain, also called pernio, is a superficial and localized inflammatory skin disorder that results from a maladaptive vascular response to non-freezing cold [1]. *Chilblain* is derived from an Anglo-Saxon expression in which *chil-* means "cold" and *-blain* means "sore" or "blotch". *Pernio* is derived from the Latin word *perna*, meaning a "gammon of bacon". It has been described in the literature for over a century [2] but remains poorly understood. The objective of this work is to review the literature regarding the definition, epidemiology, physiopathology and treatment of pernio in order to improve its management in clinical practice. We will confine our study to idiopathic chilblains which should be distinguished from lupus pernio.

Definition and epidemiology

Idiopathic chilblains manifest as inflammatory cutaneous lesions in patients exposed to non-freezing wet weather during late winter or early spring when daily mean temperatures drop below the range of 12 °C to 15 °C [3]. Chilblain most commonly occurs on the toes, fingers, ears, and face [4]. Unusual localization can also occur like "equestrian-type chilblain" which appears on the hips due to prolonged cold exposure, provoked by tight-fitting jeans [5, 6]. Lesions typically present as a painful and pruritic erythrocyanotic discoloration and swelling, persisting for more than 24 hours (Figures 1–4). Sometimes blisters, erosions and ulcerations may be observed in severe cases [7]. They usually resolve spontaneously in one to three weeks [8] but sometimes it can take longer [7]. Patients may develop recurrences during subsequent winters or persistent disease [9]. Chilblain could be associated with another idiopathic acrosyndrome like acrocyanosis or Raynaud's phenomenon [10].

Women and young to middle-aged adults (especially before 40 years) are more often affected [4, 7]. Childhood pernio seems to be uncommon [11, 12] but is well described and probably under-diagnosed in this category of patients [13] (Figure 5). Low body mass index could also be a predisposing factor [3, 14]. A high prevalence of smoking is also described [7]. Risk factors are listed in Table I. Initially, chilblains were described in Western Europe, but many publications exist in other parts of the World. Characteristics seem to be similar in most regions of the World (Western Europe, North America, India, Turkey, Brazil, Iraq and Pakistan) [1, 7, 15–22].

A phenotypic familial aggregation in chronic chilblains with a relative risk of 3.6 has been reported [23].

The prevalence of chilblain is difficult to estimate due in particular to the diagnostic difficulties. In the Netherlands, the prevalence varies between 0.9 per 1,000 and 1.7 per 1,000 as reported by the Netherlands Institute for Health Services Research (NIVEL) [24]. The condition is more common among women than men, with respective prevalences of 0.9 to 2.1 per 1,000 vs 0.6 per 1,000.

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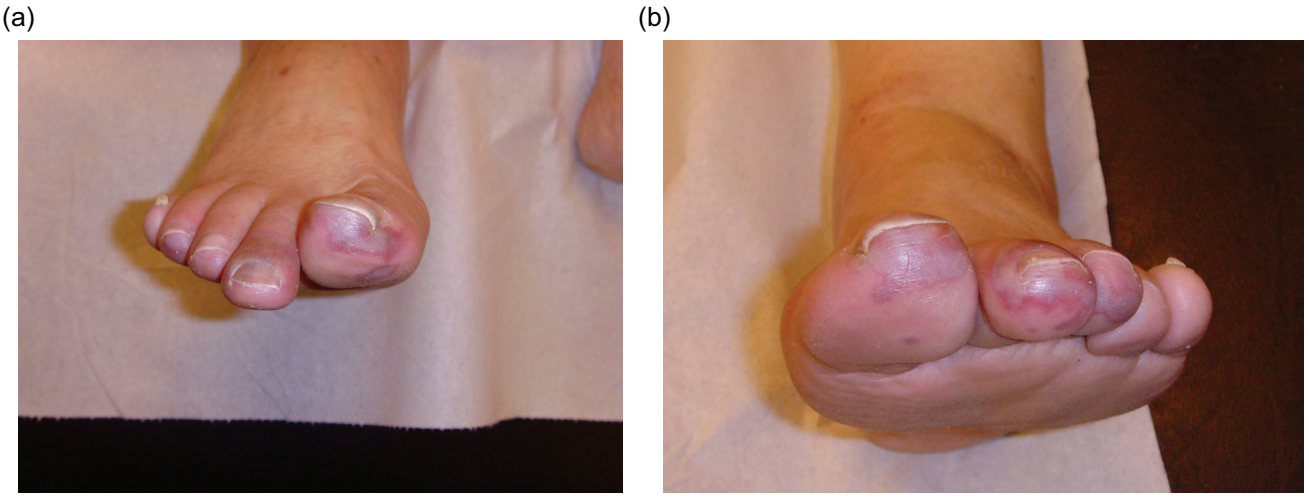

Figure 1. Typical chilblain: violaceous lesions of toes (a, b).

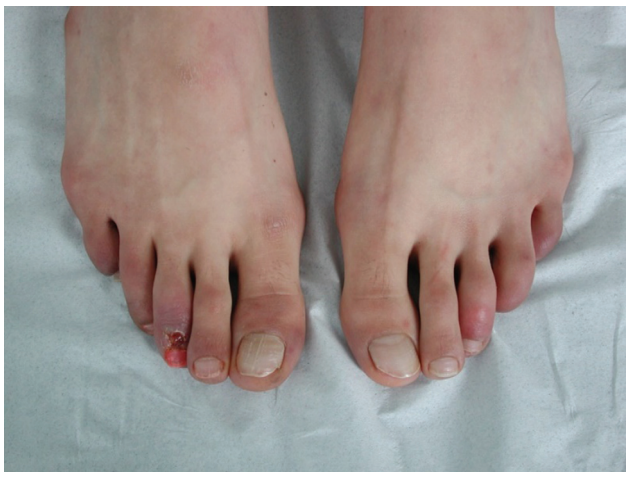

Figure 2. Chilblains: violaceous papule and ulceration of 3rd right toe.

The Mayo Clinic has proposed diagnostic criteria to help clinicians to diagnose and to provide expansive evaluation [4] of chilblain. A diagnosis of pernio requires the major criterion and at least one of three minor criteria (Table II). The Mayo Clinic team observes their occurrence between November and March, but it obviously depends on the latitude.

Histopathology

Some authors have studied the histopathology of idiopathic perniosis [25–29]. A dermal edema is usually present with mixed immune infiltrate invading the papillary and/or reticular dermis (Figure 6). The inflammatory infiltrate is composed of mononuclear cells, mainly lymphocytes. The perieccrine distribution of the infiltrate is a hallmark. Spongiosis is often observed in the epidermis and may contain necrotic keratinocytes. Vascular microthrombi can be found in the dermis but are not specific.

The perieccrine tropism seems to be a specific characteristic of idiopathic chilblain and is not observed in lupus-chilblains [26]. The same applies for epidermal spongiosis. In lupus-pernio, immunopathology reveals skin deposits of immunoglobulins and complement [30]. Dermal interstitial fibrin exudate is more frequently found in chilblain lupus but can also be present in idiopathic pernio [31]. Abundant dermal mucin is suggestive of lupus pernio.

Immunohistochemistry shows that the infiltrate is composed mainly of CD3 + T cells associated with CD68 + macrophages and a few CD20 + B lymphocytes. The same pattern is observed in both chilblains and lupus erythematous [26, 27]. A recent study showed a similar percentage and distribution of CD123 + cells in idiopathic pernio and chilblain lupus [31].

The main histopathological pattern for Equestrian-Type Chilblain has also been specifically evaluated [6, 32]. A similar perivascular and periadnexal, superficial and deep lymphoid cell infiltrate was observed [6, 33]. A perieccrine and a perineural lymphoid cell infiltrate was described in $^{2}/_{6}$ cases. With the exception of one case, the epidermal involvement was minimal. Dermal interstitial mucin deposition was a feature of $^{5}/_{6}$ cases. Immunohistochemical analysis showed a predominance of CD3 + lymphocytes with a few CD20 + cells. In two cases, small clusters of CD123 + cells were detected.

Physiopathology

Chilblains are the result of an abnormal reaction to cold. The etiology is uncertain. Cold-induced vasodilatory reflex is a protective physiologic response that intermittently opens blood flow to allow reperfusion and prevent skin ischemia [3]. The hypothesis is that patients with chilblains have persistent or prolonged cold induced vasospasm leading to hypoxemia, with a subsequent secondary inflammatory response. A recent study suggests that vasospasm plays a role in the physiopathology of pernio [34]. A neurovascular instability with inappropriate neural responses to temperature has been suggested [35]. The occurrence of chilblain in situations such as anorexia or conditions causing weight loss such as bariatric surgery, suggests that

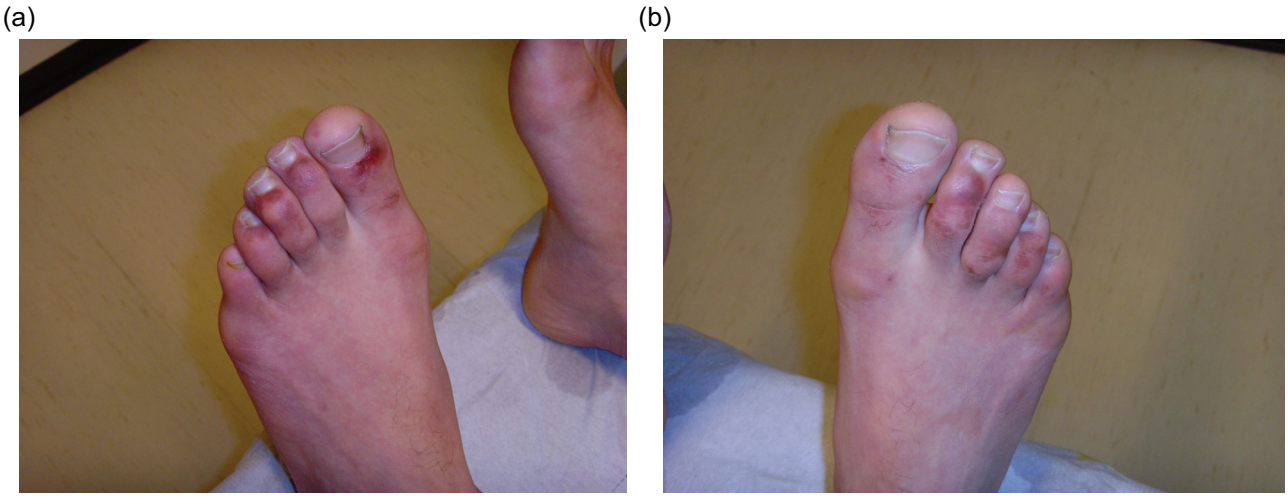

Figure 3. Chilblain: violaceous papules on the toes (a, b).

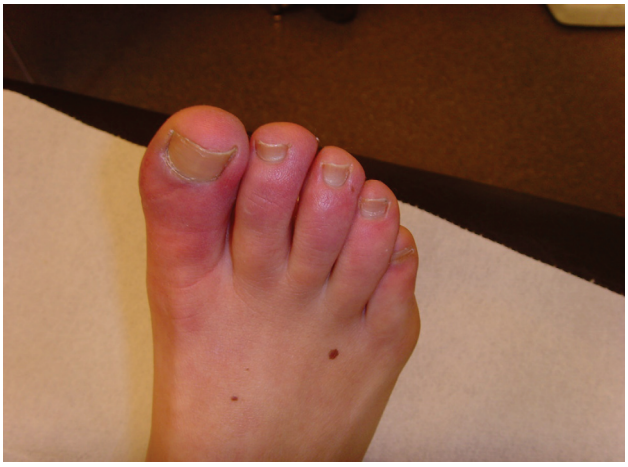

Figure 4. Typical chilblains: edematous and erythematous lesions on toes.

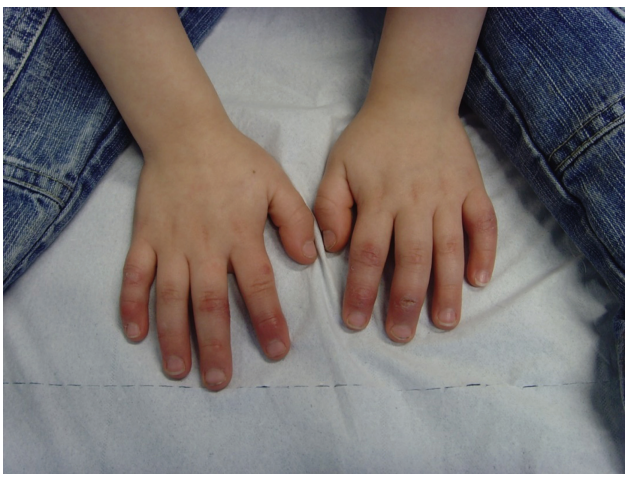

Figure 5. Childhood pernio: erythematous to violaceous edematous lesion on the fingers of a 8 years-old boy.

thermoregulation plays a central role in this disorder. A pathophysiological trial in such patients could provide useful information to understand pernio pathogenesis.

Table I. Risk factors for developing chilblains.

- Cold, non-freezing wet weather
- Female gender
- Young to middle-aged adults
- Low body mass index
- Smoking

Table II. Diagnostic criteria of pernio of Mayo Clinic [4].

Major criterion

- Localized erythema and swelling involving acral sites and persistent for > 24 h.

Minor criteria

- Onset and/or worsening in cooler months (between November and March).
- Histopathologic findings of skin biopsy consistent with pernio (e.g., dermal edema with superficial and deep perivascular lymphocytic infiltrate) and without findings of lupus erythematous.
- Response to conservative treatments (i.e., warming and drying of affected areas).

In myelomonocytic leukemia, malignant myocytic cells and hypergammaglobulinemia may interfere with vascular microcirculation, inducing hyperviscosity and vascular stasis and promoting chilblain onset [36].

Differential diagnosis

Chilblains may be primary (idiopathic) or secondary to an underlying condition (connective tissue disease, cryoglobulinemia, monoclonal gammopathy, proliferative blood

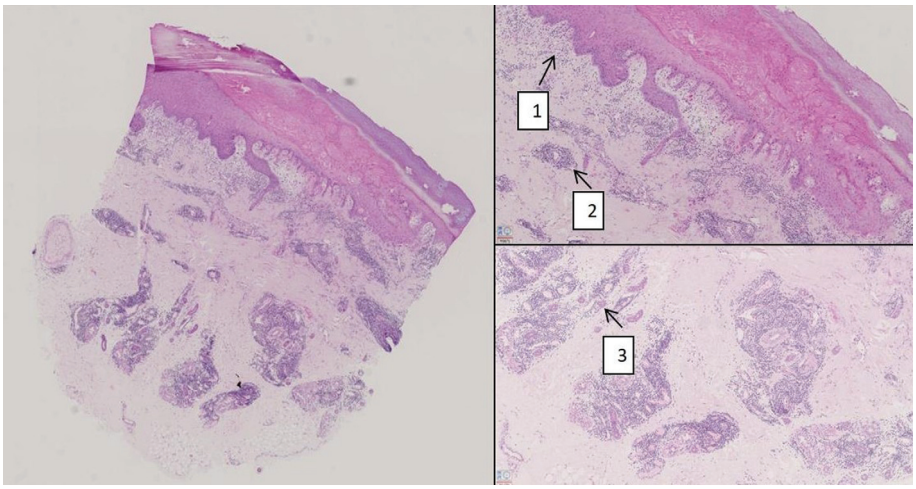

Figure 6. Histopathology of chilblain: edema of papillary dermis, superficial (1) and deep perivascular and perineural infiltrates (2), perieccrine reinforcement (3).

cell line disorders, anorexia and diseases causing weight reduction) [4, 37].

Patients with secondary perniosis are older than those with primary chilblain. There is no significant gender difference in secondary perniosis while primary perniosis is more frequent in women [38]. In chronic myelomonocytic leukemia, chilblain can precede a hematologic disorder by a few months.

Differential diagnoses are listed in Table III.

Differential diagnosis is usually made on history and clinical examination [10]. Frostbite and cold urticaria are not confined to the extremities and can be reproduced by the ice cube test. Acrocyanosis is permanent and painless. It presents with chronic coolness and violaceous discoloration of extremities [39]. Erythromelalgia evolves in paroxystic crisis and is characterized by the triad of burning pain, recurrent redness and warmth of the extremities [40, 41]. These symptoms occur during exposure to heat, during exercise and in response to gravity and can be relieved by cooling and elevation. A classical triphasic colour change is usually seen in Raynaud phenomenon: initial blanching of the skin resulting from vasospasm, usually followed by cyanosis due to deoxygenation of the static venous blood and lastly, by rubor as a consequence of reactive hyperaemia after return of flow. But this classical triphasic colour change is not always present [42]. Gangrene, by definition, is the occurrence of necrotic tissue. Vasculitis is more purpuric and more necrotic and is often associated with systemic symptoms but is easily confused with chilblain. Cold panniculitis is a form of lobular panniculitis that results from direct cold exposure. Erythematous, indurated plaques develop at the sites of cold exposure and resolve within a few weeks. In this condition, biopsy show lobular panniculitis and a superficial and deep perivascular lymphohistiocytic infiltrate [43]. Blue toe syndrome, due to distal embolism, is caused by ischemia of the toe. In cryofibrinogenemia, the skin lesions are different from those of pernio with purpura or skin necrosis in acral areas [44]. The clinical presentation of Cold Agglutinin Disease is variable and nonspecific. A large proportion of patients have cold-induced circulatory symptoms, which can range from slight acrocyanosis to disabling Raynaud phenomena [45]. Cutaneous sarcoidosis can present various types of lesions such as erythema nodosum [46]. The face is the main location. The best way to make the diagnosis is by skin biopsy, which shows the presence of sarcoidal granuloma. Lupus pernio may also be present in cutaneous sarcoidosis, most often localized in middle-face.

Table III. Differential diagnoses of chilblain.

- Frostbite
- Lupus
- Cold urticaria
- Acrocyanosis
- Erythromelalgia
- Raynaud phenomenon
- Gangrene
- Vasculitis
- Cellulitis
- Cold panniculitis
- Cryofibrinogenemia
- Cold agglutinin disease
- Sarcoidosis
- Blue toe syndrome
- Aicardi-Goutières syndrome
- Antiphospholipid syndrome

The distinction from lupus pernio is sometimes difficult (Figure 7). Lupus chilblain is a form of chronic cutaneous lupus erythematosus already described in 1888 by Hutchinson [47]. In lupus chilblain, symptoms are present regardless of seasonal temperature changes, are predominant in women and immunologic disorders are generally present. Most cases are sporadic but familial forms can occur [48]. Viguier et al. demonstrated that patients with atypical chilblains can develop lupus erythematous some months later [30]. This highlights the need for a long-term follow-up of patients affected with severe chilblains, especially those showing laboratory evidence of immunologic

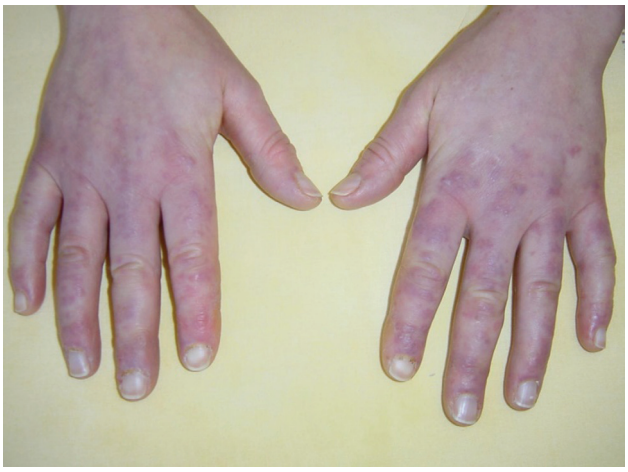

Figure 7. Lupus chilblain: erythrocyanotic inflammatory lesions of fingers.

dysfunction. Indeed, patients may develop clinical manifestation of lupus erythematous after the onset of chilblain lesions. The discovery of antinuclear antibodies in idiopathic pernio and the histopathological features of connective tissue disease suggest that idiopathic chilblain may be a form of connective disease that follows a limited, indolent course [28].

A form of familial lupus chilblains exists and is associated with a TREX1 gene mutation, mostly in the Asian population. Mutation in TREX1 is also found in Aicardi-Goutières syndrome, a rare neurogenetic disorder. This syndrome must be included in the differential diagnosis of a child presenting with neurological symptoms and chilblains [49].

Evaluation

All patients with pernio require thorough history and clinical examination and a review of systemic symptoms to exclude a differential diagnosis. Once the diagnosis of chilblain is made, screening for an underlying autoimmune disease should be performed (complete blood count, antinuclear antibodies, complement levels, cold agglutinin, antiphospholipid antibodies). Especially in elderly people, perniosis is unusual and may be an indication of another systemic disorder [50].

Cryoglobulin levels are not clinically relevant [51]. Yang et al performed a retrospective study and a review of the literature to search for an association between adult perniosis and cryoglobulinemia. They found none of the 14 patients tested had cryoglobulinemia. In their literature review, they found 65 cases of chilblain for which cryoglobulins levels had been tested. Of these, only two were found to have cryoglobulinemia. Furthermore, Cohen et al performed a retrospective study of 72 cases of cryoglobulinemia and none were suffering from perniosis [52]. The association of adult perniosis and cryoglobulinemia therefore, lacks evidence-based data.

Childhood pernio may be associated with cryoproteins [12]. An American study that studied eight children with pernio showed cryoglobulins or cold agglutinins in four children.

Hypergammaglobulinaemia and rheumatoid factor are significantly higher in patients with secondary perniosis [38]. A few cases of chilblains with antiphospholipid antibodies have been published so testing for these antibodies could be relevant [53] since the prevalence of the antiphospholipid syndrome in patients with chilblain is unknown.

The usefulness of a cutaneous biopsy is controversial. The authors from the Mayo clinic study [4] suggest considering skin biopsy for patients who don't meet criteria of pernio to search other causes of acral erythema and swelling. According to them, skin biopsy and/or laboratory testing are not necessary if diagnostic criteria of pernio are filled and there are no other symptoms or signs normally associated with other systemic conditions.

Capillaroscopy may be normal or can show nonspecific abnormalities as in acrocyanosis [10, 54] so this diagnostic technique is not very informative. However, this technique may be useful for excluding another condition such as connective tissue disease.

Management

The treatment of chilblains remains unsatisfactory. The first priority in management is avoiding cold and keeping extremities warm and dry. Simple measures such as using heaters can help. Smoking cessation is also encouraged.

The different treatments evaluated in chilblains are summarized in Table IV.

Calcium channel blockers are reported to be effective causing peripheral vasodilatation. Nifedipine (20–60 mg given three times daily) seems to give the best results [55, 56] and is more effective than diltiazem. Nifedipine reduces healing time of the lesions (mean of 8 days in nifedipine group against 24 in placebo group) and the duration of pain [57]. In this early pilot randomized trial (10 patients), 20 mg of nifedipine retard was given three times daily over 6 weeks. This drug reduces relapses and is usually well tolerated. However, the efficacy of nifedipine is not confirmed by all studies and remains controversial [24]. Indeed, Souwer et al have recently performed a randomized controlled trial in 32 patients with chilblains. In the placebo-first arm, patients received no medication for 1 week, followed by use of placebo once a day for 2 weeks, followed by use of placebo twice a day for 4 weeks, followed by nifedipine 30 mg controlled release once a day for 2 weeks, followed by nifedipine 30 mg twice a day for 4 weeks. In the nifedipine-first arm, patients received no medication for 1 week, followed by nifedipine 30 mg once a day for 2 weeks, followed by nifedipine 30 mg twice a day for 4 weeks, followed by use of placebo once a day for 2 weeks, followed by use of placebo twice a day for 4 weeks. They didn't find any clinically or statistically significant

Table IV. Main studies concerning treatment of chilblains.

Treatment	Trial	Year	Patients	Method
Nifedipine	Dowd et al. [56] Randomized placebo-controlled double-blind	1986	10	Nifedipine Retard 20 mg 3×/day versus placebo.
Nifedipine	Rustin et al. [57] Open study	1989	34	Nifedipine retard 20 mg/day 3 days then 20 mg 2×/day for 3 days and then 40 + 20 mg/day for 2 months
Nifedipine	Patra et al. [55] Randomized	2003	36	Group A: diltiazem 60 mg 3×/day Group B: Nifedipine 10 mg 3×/day until complete relief and then 20 mg 2×/day
Nifedipine	Souwer et al. [24] Randomized placebo-controlled double-blind cross-over	2016	32	Nifedipine retard 30 mg 1×/day for 2 weeks, 30 mg 2×/day for 4 weeks
Pentoxifylline	Noaimi et al. [58] Randomized	2008	40	Group A: Oral prednisolone (0.5 mg/Kg) in 2 doses and topical clobetasol ointment for 2 weeks Group B: pentoxifylline (1200 mg/day) in 3 doses for 2 weeks
Pentoxifylline	Al-Sudany [19] Randomized placebo-controlled double-blind	2008	110	Pentoxifylline (400 mg 3×/day) versus Placebo
Hydroxychloroquine	Yang et al. [59] Retrospective	2010	5	Hydroxychloroquine 200–400 mg/day
Topical betamethasone	Souwer et al. [60] Randomized	2017	34	Betamethasone valerate 0.1 % 2×/day for 6 weeks versus placebo
Topical nitroglycerine	Verma [61] Prospective	2015	22	Topical nitroglycerine 0.2 %
Vitamin D3	Souwer et al. [62] Self-controlled	2009	33	2000 IU vitamin D3 per day versus placebo
Acupuncture	Xiang et al. [63] Randomized	2005	264	Acupuncture group (136): acupuncture at 9 acupoints such as Yamen (GV 15), Laogong (PC 8), Sanyinjiao (SP 6), etc. plus massage, Medicine group (128): dong chuang Plaster.

differences in favor of nifedipine over placebo for the treatment of chronic chilblains.

Recently, two studies conducted in Iraq, showed efficacy for pentoxifylline in the treatment of primary perniosis [19, 58]. The first, conducted in 2008, evaluated the use of pentoxifylline in comparison with oral prednisolone plus topical clobetasol [58]. Patients in Group A received oral prednisolone 0.5 mg/kg divided into two doses and topical clobetasol ointment for 2 weeks. Patients in Group B received pentoxifylline tablets 1200 mg/day divided into three doses for two weeks. In group A, only $^{3}/_{11}$ patients (27.2 %) showed improvement compared to $^{5}/_{9}$ patients in group B (55.5 %). In the second trial (2016) [19], 110 patients were randomly divided into two groups: Group A received pentoxifylline 400 mg thrice daily, orally for 3 weeks whereas group B received placebo thrice daily for 3 weeks. The therapeutic response was significantly better in group A compared with group B. Development of new lesions was noticed in five patients in group B whereas no new lesions were detected in group A. The authors suggest that the beneficial effect of pentoxifylline was due to its vasodilatator effect and its potential immunologic and anti-inflammatory effects.

Hydroxychloroquine has also demonstrated some positive results, but studies were retrospective and performed only on 5 patients [59]. Improvement of symptoms was obtained in four patients.

Although often used, the effect of topical betamethasone remains controversial. In a randomized trial of 34 patients (betamethasone valerate 0.1 % twice daily) for six weeks compared with placebo, there was no significant difference in symptoms between the two groups [60]. In their literature review, the Mayo Clinic shows a benefit of topical corticosteroid in 6 out of 8 patients [4]. Topical nitroglycerine 0.2 % has shown promising results in a small trial (22 patients) [61]. Vitamin D3 (oral administration of 2000 IU vitamin D3 per day) is not effective for the treatment of chronic chilblains [62]. In China, acupuncture combined with massage was found to be effective to treat chilblain [63]. Some case reports mention the interest of laser for treatment of lupus pernio [64, 65]. A very old Italian article reports a positive effect of the use of the combination of ionizing radiation and ultrasound in the treatment of frostbite [66].

In our practice, we and others observed a positive effect with Neocutigenol® (ointment combining chlorhexidine diacetate and retinol palmitate) but this topical treatment has never undergone clinical trial for efficacy in the treatment of chilblain.

Chilblains resolve most of the time spontaneously. Considering the important spontaneaous healing rates, it is even difficult to distinguish placebo effect from the natural course of disease. It is therefore difficult to evaluate treatments in randomized studies for this condition.

In practice, cold protection is the first step to recommend. Smoke cessation should also be recommended. If these conservative measures are not enough, treatment with calcium channel blocker (nifedipine) may be prescribed in the absence of contraindications (such as hypotension). Topical corticosteroids are sometimes helpful, but their effects remain uncertain. In some cases, pentoxifylline and/or topical nitroglycerin may be tested.

Conclusions

Our literature review reevaluates the chilblain, which remains a frequent acrosyndrome still poorly recognized by clinicians. Many questions remain unresolved. Further studies are needed to better understand the pathophysiology and improve the management of this disorder.

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Correspondence address
Dr. Astrid Nyssen
CHR Verviers East Belgium
Cardiology
Rue du Parc 29
4800 Verviers
Belgium
astrid.nyssen@chrverviers.be

