Evolution of incidence of chilblain-like lesions in children during the first year of COVID-19 pandemic

Marta Bascuas-Arribas MD1 | David Andina-Martinez MD1 | Juan Añón-Hidalgo MD1 | Jose Antonio Alonso-Cadenas MD1 | Angela Hernandez-Martín MD2 | Nuria Lamagrande-Casanova MD1 | Lucero Noguero-Morel MD2 | Ana Mateos-Mayo MD2 | Isabel Colmenero-Blanco MD3 | Antonio Torrelo MD2

1Emergency Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain  
2Department of Dermatology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain  
3Department of Pathology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Correspondence  
David Andina-Martinez, Hospital Infantil Universitario Niño Jesús, Avenida Menéndez Pelayo, 65, 28009 Madrid, Spain.  
Email: david.andina@salud.madrid.org

Abstract

Background: The COVID-19 pandemic has brought innumerable reports of chilblains. The relation between pernio-like acral eruptions and COVID-19 has not been fully elucidated because most reported cases have occurred in patients with negative microbiological tests for SARS-CoV-2.

Methods: A retrospective study of 49 cases of chilblains seen during the first year of the pandemic in a children's hospital in Madrid, Spain. The incidence of these skin lesions was correlated with the number of COVID-19 admissions and environmental temperatures. Patients were separated into two groups depending on the day of onset (strict lockdown period vs. outside the lockdown period).

Results: Most chilblains cases presented during the first and third waves of the pandemic, paralleling the number of COVID-19 admissions. The first wave coincided with a strict lockdown, and the third wave coincided with the lowest ambient seasonal temperatures of the year. Systemic symptoms preceding chilblains were more frequent in the first wave (45.8% vs. 8.0%, \( p = .002 \)), as was the co-occurrence with erythema multiforme-like lesions (16.7% vs. 0%, \( p = .033 \)). Laboratory test and skin biopsies were performed more frequently in the first wave (75.0% vs. 12.0%, \( p < .001 \); and 25.0% vs. 0%, \( p = .007 \); respectively). Five patients developed recurrent cutaneous symptoms.

Conclusions: An increased incidence of chilblains coincided not only with the two major waves of the pandemic, but also with the strict lockdown period in the first wave and low seasonal temperatures during the third wave. Both increased sedentary behaviors and cold environmental temperatures may have played an additive role in the development of COVID-19-related chilblains.

Keywords
chilblain, COVID-19, pediatric dermatology, pernio, SARS-CoV-2
1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has brought many reports worldwide of pernio or chilblains, also called COVID toes, in children, adolescents, and young adults. Clinical and histopathological features have been extensively studied, and in most cases, the described findings are identical to primary chilblains triggered by cold exposure.

In spite of a strong epidemiologic link between COVID toes and SARS-CoV-2 COVID-19, the true relationship between pernio-like acral eruptions and COVID-19 has not been clearly determined, because most cases occurred in patients with negative SARS-CoV-2 polymerase chain reaction (PCR) and serology testing and conflicting results in the immunohistochemical and ultrastructural identification of SARS-CoV-2 in these skin lesions. Lifestyle changes associated with community containment and lockdown measures may have played a role in the pathogenesis of these lesions.

We previously reported a series of 22 pediatric patients with chilblain eruptions occurred in a very short period of time during the 6-week lockdown period imposed by the Spanish government in the first wave of the COVID-19 pandemic. Here, we present a series of 49 cases of chilblains in children and adolescents seen during the first year of the pandemic in the Emergency Department (ED) of a COVID-19 referral children’s hospital in Madrid, Spain, and correlate the incidence of these skin lesions with the number of admissions of COVID-19 and seasonal temperatures during this same period.

2 | MATERIAL AND METHODS

A retrospective study was conducted in children and adolescents (up to 18 years of age) presenting to the ED from March 1, 2020, to February 28, 2021, with skin manifestations of chilblains, in the form of erythematous to purpuric macules and violaceous swellings located on the toes, feet, fingers, and hands. We excluded patients with a clear antecedent history of intense cold exposure or presence of an illness predisposing to chilblains.

The diagnosis of pernio was made by an ED physician; furthermore, all cases were documented photographically and shown to a consultant dermatologist who confirmed the diagnosis. After referral to the Dermatology Department, all cases were followed up either by onsite visit or by phone call.

We recorded age, sex, personal history of previous diseases, contacts with potentially infected cases, skin symptoms, type and location of lesions, systemic symptoms, and outcomes. Laboratory analyses performed were also recorded, as well microbiologic tests (SARS-CoV-2 PCR from oropharyngeal and nasopharyngeal swabs or rapid antigen test [RAT] from nasopharyngeal swabs).

Patients were sorted into two groups depending on the day of onset of the skin symptoms: children under strict lockdown measures in the Madrid region (March 14 2020 to April 30, 2020) and children who developed chilblains outside the lockdown period (May 1, 2020, to February 28, 2021).

3 | RESULTS

Fifty-three patients were seen in the ED with acrally located erythematous lesions consistent with chilblains. Two patients were excluded due to intense cold exposure at home without a proper heating system. Two other patients were excluded due to systemic illnesses that could be linked with chilblains: one patient with systemic lupus erythematosus and one patient with bone marrow transplant for Fanconi anemia. Finally, 49 patients (30 males and 19 females) with a median age of 13 years (range 6–17 years; interquartile range 11–14 years) were included.

Epidemiologic, clinical, and analytical characteristics of patients included are summarized in Table 1. Twenty-four patients presented during the strict lockdown period. The remaining 25 patients were seen after the first wave of the pandemic. No differences were found between groups regarding age and sex. In the first wave, 5 patients (20.8%, 5/24) had a diagnosis of attention deficit hyperactivity disorder (ADHD) and were on pharmacological treatment with no change in dosage within the previous 6 months, while in the second period, 2 patients (8.0%, 2/25) reported a previous history of Raynaud’s phenomenon. In the first period, caregivers sought care in the ED earlier in the course of the illness compared with the second period (54.2%, 13/24 seek for attention in the first week of symptoms vs. 12.0%, 3/25).
| Characteristics | All cases (n = 49) | Strict lockdown YES (n = 24) | Strict lockdown NO (n = 25) | p value |
|-----------------|-------------------|----------------------------|-----------------------------|---------|
| Age median (interquartile range) | 13 (11–14) | 13 (11–15) | 13 (11–14) | .473 |
| Age group, n (%) | | | | |
| 6–9 years | 3 (6.1) | 1 (4.2) | 2 (8.0) | .697 |
| 10–13 years | 25 (51.0) | 13 (54.2) | 12 (48.0) | |
| 14–17 years | 21 (42.9) | 10 (41.6) | 11 (44.0) | |
| Sex, n (%) | | | | |
| Male | 30 (61.2) | 15 (62.5) | 15 (60.0) | .857 |
| Female | 19 (38.8) | 9 (37.5) | 10 (40.0) | |
| Underlying medical condition, n (%) | 5 (10.2) | 5 (20.8) | 0 | .016 |
| History of Raynaud phenomenon, n (%) | 2 (4.1) | 0 | 2 (8.0) | .157 |
| Duration of cutaneous symptoms before coming to the emergency department, n (%) | | | | |
| 1–7 days | 16 (32.7) | 13 (54.2) | 3 (12.0) | <.001 |
| 8–14 days | 10 (20.4) | 6 (25.0) | 4 (16.0) | |
| >14 days | 23 (46.9) | 5 (20.8) | 18 (72.0) | |
| Site of involvement, n (%) | | | | |
| Feet | 47 (95.9) | 24 (100) | 23 (92.0) | .157 |
| Hands | 13 (26.5) | 3 (12.5) | 10 (40.0) | .029 |
| Concomitant erythema multiforme, n (%) | 4 (8.2) | 4 (16.7) | 0 | .033 |
| Symptoms, n (%) | | | | |
| Cutaneous symptoms n (%) | 32 (65.3) | 15 (62.5) | 17 (68.0) | .686 |
| Local pruritus | 21 (42.9) | 11 (45.8) | 10 (40.0) | .861 |
| Local pain or tenderness | 18 (36.7) | 7 (29.2) | 11 (44.0) | .281 |
| Systemic symptoms, n (%) | 13 (26.5) | 11 (45.8) | 2 (8.0) | .002 |
| Respiratory symptoms (cough or rhinorrhea) | 10 (20.4) | 9 (37.5) | 1 (4.0) | .003 |
| GI symptoms (abdominal pain or diarrhea) | 4 (8.2) | 3 (12.5) | 1 (4.0) | .277 |
| Fever | 1 (2.0) | 0 | 1 (4.0) | .322 |
| Epidemiologic background, n (%) | | | | |
| Close contact with a probable case of COVID-19 | 16 (32.7) | 14 (58.3) | 2 (8.0) | .002 |
| Close contact with a confirmed case of COVID-19 | 5 (10.2) | 1 (4.2) | 4 (16.0) | .171 |
| Diagnostic test done, n (%) | | | | |
| Laboratory test | 21 (42.9) | 18 (75.0) | 3 (12.0) | <.001 |
| SARS-CoV-2 microbiological test | 34 (69.4) | 20 (83.3) | 14 (56.0) | .038 |
| Follow up, n (%) | | | | |
| Phone call | 49 (100) | 24 (100) | 25 (100) | - |
| Office visit | 42 (85.7) | 22 (91.7) | 20 (80.0) | .243 |
| Skin biopsy obtained | 6 (12.2) | 6 (25.0) | 0 | .007 |
| Outcome, n (%) | | | | |
| Improvement or healing | 49 (100) | 24 (100) | 25 (100) | - |
| Worsening | 0 | 0 | 0 | - |
| Relapse | 5 (10.2) | 3 (12.5) | 2 (8.0) | .602 |
| Duration of chilblains | | | | |
| 1–2 weeks | 0 | 0 | 0 | .243 |
| 3–4 weeks | 7 (14.3) | 2 (8.3) | 5 (20.0) | |
| >4 weeks | 42 (85.7) | 22 (91.7) | 20 (80.0) | |

Note: Data show numbers seen from transect lines at all observable distances, i.e., not limited to 100 m.
Regarding epidemiologic data, a household contact with a probable case of COVID was more frequent in the first period (58.3%, 14/24 vs. 8.0%, 2/25). A household contact with a confirmed case was documented in 4 cases in the second period (16.0%, 4/25) but only in 1 case in the first period (4.2%, 1/24). The presence of cutaneous symptoms associated with chilblains was similar in both periods (62.5%, 15/24 vs. 68.0%, 17/25), while the presence of systemic symptoms preceding chilblains was more frequent in the first wave (45.8%, 11/24 vs. 8.0%, 2/25). Hands were more frequently involved in cases occurring during the second period (12.5%, 3/24 vs. 40.0%, 10/25).

Laboratory tests were performed more frequently in the first period (75.0%, 18/24 vs. 12.0%, 3/25). Apart from two patients (4.1%, 2/49), all of them showed normal results. D-dimer levels were elevated in one case (900 ng/ml; normal <500 ng/ml), but this abnormal result was believed to have no clinical significance. An abnormal complete blood count in the other patient consisted of mild neutropenia (1390 cells/mm³), again without clinical significance. Microbiological tests for SARS-CoV-2 were performed in more patients in the first period (83.3%, 20/24 vs. 56.0%, 14/25). PCR or RAT were performed in a total of 34 cases (69.4%, 34/49), with 1 positive case (2.9%, 1/34). After diagnosis of pernio was made by an ED physician and confirmed by a consultant dermatologist, follow-up was done onsite at the Dermatology Department for 42 cases (85.7%, 42/49) and by phone calls for 7 cases (14.3%, 7/49). Skin biopsies were obtained only during the first wave of the pandemic in 6 patients.

No differences in duration of chilblains lesions between both groups were found. Up to 86% of patients (42/49) reported cutaneous symptoms lasted more than 4 weeks. The incidence of chilblains through the pandemic related to the incidence of weekly COVID admissions and median temperature in the Madrid region is reflected in Figure 1. From March 2017 to February 2020, no documented patient with chilblains or pernio had presented to the ED of our institution.

We identified three cases of recurrent cutaneous symptoms after being completely asymptomatic for more than 1 month in the first wave and two additional cases during the second period. They occurred in three different contexts: (1) two cases (an 11-year-old girl in the first wave and a 14-year-old girl in the second period) showed recurrence of chilblains coinciding with close contact with a confirmed case of COVID-19; they both showed the same lesions in the same locations as during their first presentation, and both again had negative PCR/RAT tests for SARS-CoV-2; (2) an 11-year-old boy had a relapse of chilblains coinciding with a confirmed infection of SARS-CoV-2 with a positive RAT (Figure 2); and (3) two 16-year-old boys had a recurrence of chilblains with no documented contact with a positive case, and they were again both negative on routine microbiologic tests (Figure 3).

### DISCUSSION

As reflected in Figure 1, three major waves of new COVID admissions in the Madrid region during the first year of the COVID-19 pandemic

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**FIGURE 1** Correlation of pediatric chilblains with weekly COVID-19 admissions and mean temperatures in Madrid region during the first year of the pandemic
have been found: the first and most severe occurred during March and April 2020; the second, less severe, from August to October 2020; and the third, with intermediate severity, from December 2020 to February 2021. The incidence of chilblains clearly paralleled the number of COVID-19 admissions and most chilblains cases presented during the first and third waves. The first wave coincided with strict lockdown, and the third wave coincided with the lowest temperatures of the year, reaching 0°C for several days.

The second outbreak of chilblain-like lesions coinciding with the second wave of new cases of COVID-19 has already been described in other countries, such as Italy. A retrospective cohort study in California from January 1, 2016, to December 31, 2020, found that the incidence of chilblains increased during the pandemic. Nevertheless, this study found a weak temporal correlation of COVID-19 cases with chilblains cases, concluding that the increase in the incidence may have resulted from behavioral changes. In our institution, we have found a dramatic increase in the incidence of pediatric chilblains during the COVID-19 pandemic with no cases diagnosed in the ED during the previous 3 years. Chilblain cases did not parallel the number of COVID-19 admissions only during the less severe second wave when lockdown measures and cold temperatures were absent.

We compared the features exhibited by patients with chilblains in both main periods (first wave vs. rest of the year). Regarding epidemiologic background, more patients during the first wave had a close contact with a suspected case, but in the second period, more patients had a close contact with a confirmed case. This observation may be explained by the fact that in the first period, PCR tests were restricted to severe cases, making it impossible to confirm milder ones. Later on, when PCR tests became widely available, cases were classified as confirmed COVID or not and were no longer classified as suspected. Systemic symptoms preceding chilblains, either respiratory or gastrointestinal, were more frequent in the first wave as was the co-occurrence of erythema multiforme-like lesions. On the contrary, chilblains during the second period coincided with lower seasonal temperatures and more frequently involved the hands. It has been stated that COVID-19 chilblains affect the feet mainly, with other sites of involvement more frequent in idiopathic cases.

Microbiological tests to confirm active SARS-CoV-2 infection showed similar findings as other series. Only 1 out of 34 patients had a positive PCR, and another one had a positive RAT for SARS-CoV-2 coinciding with a relapse of chilblains. Although our institutional guidelines recommend continuing testing of all patients with new-onset chilblains, nearly half of the patients in the second period were not tested, either because of physician’s refusal due to the frequently known negative results of the test or because in this period most of the patients sought attention later in the disease course, when PCR and RAT are less sensitive.

Biopsies in selected patients were only performed in the first period. Histologic examination was not performed in the second period because it was deemed that no clinical benefit was expected from a biopsy. Also, laboratory investigations were progressively abandoned since all patients tested earlier in the pandemic had not shown any relevant abnormality. Coinciding with the largest registry of pediatric COVID patients published to date by Castello-Socio et al, children with acral pernio-like changes in our series were healthy and all recovered with no short-term sequelae.

Relapsing of chilblains in otherwise previously healthy children has already been documented. Recalcati et al. described relapsing chilblains in seven young patients with lack of any evidence of SARS-CoV-2 infection but emphasized that most of these patients were children of health workers. Hubiche et al. observed a relatively high frequency of relapses in their chilblain-like cohort; one-third of the patients who had relapses were exposed to possible or proved cases of COVID-19 within the household, suggesting that re-exposure to SARS-CoV-2 infection might trigger a relapse in chilblain-like lesions. In our series, we have documented 5 cases of recurrences in three different scenarios: close contact with confirmed cases and negative test (2 cases), no close contact with confirmed cases and negative test (2 cases), and one case with no documented contact with cases of COVID-19 who tested positive for SARS-CoV-2 on a RAT which indicated an active SARS-CoV-2 infection.
While investigations to understand the pathophysiology of pandemic-associated pernio continue, evidence has shown that SARS-CoV-2 spike protein and robust IFN-1 response are seen in the skin of patients with chilblains, suggesting an excessive innate immune skin response to SARS-CoV-2. These findings suggest IFN-1 signaling may affect host outcomes to COVID-19. Several limitations of this study were found. This is a single-institution review; however, our center is located in one of the regions of Europe most impacted during the pandemic and we think the population is representative and offers a large cohort of pediatric patients with pernio. Secondly, although the study project started early in the course of the pandemic in Spain, most of the data were retrieved retrospectively. Thirdly, increased care-seeking following "COVID toes" awareness in April 2020 and closure of other clinics during the pandemic wave peaks might have played a role in the increase in cases of chilblains seen in our institution’s ED. Fourth, home temperatures may be more relevant to chilblains than outdoor environmental temperatures during lockdown conditions. Although we cannot provide accurate data regarding home temperatures, all caregivers of included patients reported having a proper heating system at home. Finally, the Madrid region has a continental climate with moderately cold winters; furthermore, the temperatures during the third wave were 1–1.5°C lower than mean temperatures from the three previous years.

In conclusion, an unexpected increased incidence of pediatric cases of chilblains coincided not only with the two major waves of the pandemic, but also with the strict lockdown period in the first wave and extremely low seasonal temperatures during the third wave. Both increased sedentary behaviors and cold environmental temperatures may have played an additive role in the development of COVID-19-related chilblains. While investigations continue, ruling out an active SARS-CoV-2 infection by PCR or RAT seems to be a wise approach in chilblains cases during COVID-19 waves. A full laboratory evaluation and skin biopsy seem to be excessive in the absence of any alarming signs, due to the excellent outcome for these patients.

ACKNOWLEDGEMENTS
None declared.

CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
Data available on request from the authors.

ORCID
David Andina-Martinez https://orcid.org/0000-0002-3082-8832
Jose Antonio Alonso-Cadenas https://orcid.org/0000-0002-7648-1336
Lucero Noguero-Morel https://orcid.org/0000-0001-5694-8536
Ana Mateos-Mayo https://orcid.org/0000-0001-9507-005X
Antonio Torrelo https://orcid.org/0000-0002-5940-6916

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How to cite this article: Bascuas-Arribas M, Andina-Martinez D, Añon-Hidalgo J, et al. Evolution of incidence of chilblain-like lesions in children during the first year of COVID-19 pandemic. *Pediatr Dermatol*. 2022;39:243-249. doi:10.1111/pde.14948