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Research Article

Chilblains Relapse During COVID-19 Waves in A Cohort of Children and Adolescents

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Abstract

Chilblains are a peculiar phenomenon described in children and adolescents during COVID-19 pandemic. Little is known about its recurrence and whether this condition may be prodromic to rheumatological disorders. We performed a follow-up study of 36 patients presenting chilblains during 2020-2021 at two Italian hospitals. We collected data regarding new episodes, signs-symptoms of systemic disease, treatment. We reached 27/36 patients who had been evaluated in 2020–2021 for chilblains. Seventeen patients (17/27) presented new chilblains' episodes during cold season. Most cases had a benign course with gradual resolution and no need for medications. None developed a systemic rheumatologic disorder. The recurrence of chilblains tended to be more common in patients with positive Interferon Signature at first evaluation. In our cohort, most subjects showed a relapse of the phenomenon when exposed to cold environmental temperatures in the following year. The mid-term outcome was benign, and no patients developed a definite rheumatological disorder.

Keywords: Chilblains; COVID-19; Interferon; Type I Interferon Signature; Hydroxychloroquine

Introduction

Chilblains, which are also called "perniosis," are a pleomorphic clinical condition whose cause is unknown. For some people, being outside in the cold can bring on the condition, even if they don't have any definite rheumatological conditions going on at the same time. Chilblains display a huge range of symptoms and signs, with erythematous or violaceous papular or nodular lesions on the hands and/or feet. Symptoms may last hours or days and, in some people, can relapse each cold season. Chilblains can be a sign of vascular inflammation accompanying several infectious and/or rheumatological conditions [1]. Aicardi-Goutières syndrome [2], a more uncommon condition where type I interferon (IFN)-driven inflammation is to blame, can occasionally be the cause of chilblains. However, in most cases, chilblains are an idiopathic complaint occurring in the absence of any definite systemic disorder. Viral infections have been proposed as triggers of such a phenomenon in predisposed individuals. The fact that the incidence of idiopathic chilblains increased significantly in teenagers and young adults following the first waves of the coronavirus disease-19 (COVID-19) pandemic may support the theory that a virus activating the immune system is the disease's cause [3-5]. The low positive rate of nasopharyngeal swabs and the absence of an anti-SARS-CoV-2 antibody response in many of these young patients may be due to a stronger type I IFN response with more efficient control of the viral burden before the adaptive response can raise [6-8]. Chilblain-like lesions (CLL) were found to have endothelial dysfunction in the blood during the COVID-19 pandemic. They also had type I IFN-driven inflammation and the histology of platelet microthrombi in the blood [9]. The recurrence of new episodes of chilblains with concurrent COVID-19 pandemic peaks [10,11] has further dismantled the dubious association with SARS-CoV-2. Additionally,

histopathological data from several case series evidenced local endothelial signs of viral infection [12-14].

Few studies have described chilblains and their recurrence in the pediatric population over the course of pandemic peaks. Furthermore, to our knowledge, it is not clear whether this cutaneous phenomenon may be a prodrome of systemic rheumatological conditions. Our study provides a 12-month follow-up of patients with chilblains during the first COVID-19 wave and focuses on long-term outcomes.

Materials & Methods

Study Design and Patients

We performed a follow-up study of 36 pediatric patients previously diagnosed with chilblains between May 2020 and May 2021 at the Pediatric Rheumatology services at the IRCCS Burlo Garofolo Hospital (Trieste, Italy) and at the Treviso Hospital (Treviso, Italy). The inclusion criteria were: age of onset before 18 years; anamnestic absence of the symptom before 2020; erythema pernio defined as presence of typical erythematous patches at the hands and/or feet, lasting weeks or months, with papules and/or ulcers. The exclusion criteria were: current or previous diagnosis of defined rheumatologic diseases, including Raynaud phenomenon; concomitant oncologic diseases.

We performed a telephonic survey in May 2022, evaluating whether chilblains had persisted or recurred. Moreover, we collected data regarding patients who had been reevaluated as outpatients because of recurring chilblains.

The study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Subjects or their parents/guardians were asked to sign a written informed consent to record their clinical and laboratory data, in anonymized form, on a structured database. The study was approved by the IRB of the IRCCS Burlo Garofolo with reference number RC24/17.

Type I Interferon Signature

The IFN Signature (IS) assessment was performed by analyzing the expression of 6 IFN Stimulated Genes *(IFI27, IFI44L, IFIT1, ISG15, RSAD2* and *SIGLEC1*) by qPCR with the CFX Opus 96 instrument (BioRad), TaqMan Gene Expression Master Mix (Applied Biosystems) and TaqMan probes (Applied Biosystems). Using Maestro software (BioRad), the quantities of target genes were normalized with the expression level of two housekeeping genes, *HPRT1* and *G6PD*. Relative analysis of gene expression was conducted using the $2^{-\Delta\Delta Ct}$ method compared with the control group. The IFN score, corresponding to the median of the relative quantifications of the 6 genes, was calculated for each subject. The IS was considered positive when higher than a cut-off determined by measuring the mean value + 2 SD of healthy controls (positive IS when IFN score >2.2).

Statistical analysis

Descriptive analysis provided a summary of the enrolling children's data. Continuous variables were described using means and standard deviation, or medians and range. Categorical variables were described using frequencies (%). Data were entered into a Microsoft Excel spreadsheet, and statistical analyses were performed using R software (version 4.0.3, 2020).

Results

Study participants

Twenty-seven families of children and adolescents previously evaluated between May 2020 and May 2021 were reached by telephonic survey, and gave information on follow up (27/36, 75%). The study flowchart is shown in Figure 1.

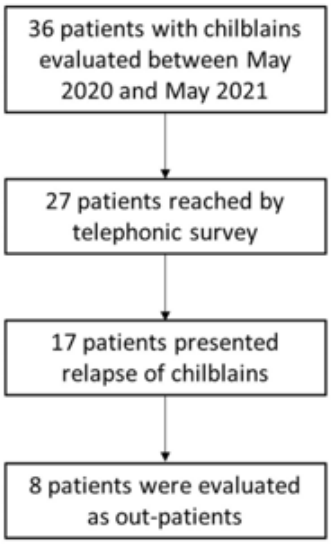

Figure 1: Study flow chart.

Seventeen patients (17/27, 63%), mostly girls (15/17, 88%), reported resolution of chilblains during the summer with subsequent relapse between November 2021 and March 2022. The median age was 13.9 years (±2.6). All the patients complained of chilblain recurrence at the same site as the previous episode.

Clinical and demographic characteristics of the 36 patients who reported chilblains during the first period (March 2020–May 2021) are shown in Table 1.

Table 1: Demographic and clinical characteristics at baseline of patients during the first episodes between May 2020 and May 2021.

	Total (N = 36)
Demography	
Age (median, IQR)	13.1 (3.5 – 17.2)
Female (n, %)	29 (80%)
Signs and symptoms (n, %)	
Feet chilblains	10 (27.8%)
Hands chilblains	18 (50%)
Hands and feet chilblains	8 (22.2%)
Other symptoms	
Headache	2 (5.5%)
Asthenia	1 (2.7%)
Tenosynovitis	1 (2.7%)
abdominalgia	1 (2.7%)
Ankle synovitis	1 (2.7%)
Duration (weeks) (median, IQR)	11.9 (1 – 47.7)
SARS-CoV2 documentation (n, %)	
General symptoms	0 (0%)
Contact with COVID-positive patients	5 (14%)
Positive COVID-nasal swab	3 (8%)
Laboratory (n, %)	
Lab test performed	26 (72%)
Positive ANA test	4 (15%)
ANA range values	1:80 - 1:320
Positive IS	9/22 (43%)
IS range values	2.4 – 32.4
Treatment (n, %)	
Systemic steroids	17 (42%)
Nifedipine	4 (11%)
NSAIDs	4 (11%)
HCQ	3 (8%)

IQR: Interquartile Range; ANA: Antinuclear Antibodies; IS: Interferon Signature; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; HCQ: Hydroxychloroquine.

Outpatients

Eight patients out of the 17 who participated in the survey (47%) were also re-evaluated as outpatients at the rheumatology services of the two centers; their median age was 14 years (± 3), and there was only one male. No patient displayed a positive nasal swab for SARS-CoV-2. No patient presented other signs or symptoms of systemic disease. Specifically, no patient reported recurrent episodes of fever, cutaneous rash, abdominal pain, joint swelling, or weight loss. The physical examination of the eight patients was normal, with the exception of erythematous lesions of the toes (3/8, 37%), fingers (3/8, 37%), or both (2/8, 25%). Two girls presented with complex regional pain syndrome (CRPS) in the foot with significant allodynia and functional limitation, as they both needed crunches to walk. One patient was treated with a course of bisphosphonates and physical therapy and quickly regained the ability to walk. She presented with a mild form of chilblains during the second winter. The second patient presented with CRPS during the second episode of chilblains. She was started

on hydroxychloroquine combined with physical therapy and automassage, which was beneficial. Two other patients were started on hydroxychloroquine due to severe functional impairment and elevated IS, but this therapy was not beneficial for the one with the highest increase in IS values in our cohort (8.9 > 44). Clinical and demographic characteristics of the 8 patients with relapsed chilblains during spring 2022 are shown in Table 2.

Table 2: Demographic and clinical characteristics of patients with CLL relapse evaluated as outpatients.

	Relapsed patients evaluated as out-patients (N=8)
Demography	
Age (median, IQR)	14 (7.5-17)
Female (n, %)	7 (87%)
Signs and symptoms (n, %)	
Feet chilblains	3 (37%)
Hands chilblains	3 (37%)
Hands and feet chilblains	2 (25%)
Other signs	0 (0%)
Laboratory (n, %)	
Lab test performed	5 (62%)
Positive IS	4 (80%)
Positive IS during 2021	4 (50%)
Treatment (n, %)	
HCQ	3 (37%)
Systemic steroids	0 (0%)
Nifedipine	2 (25%)

ANA: Antinuclear Antibodies; IQR: Interquartile Range; IS: Interferon Signature; HCQ: Hydroxychloroquine.

Risk factors for chilblain recurrences. Even if differences were not significant, we observed a trend toward a higher risk of relapse in females or subjects with elevated IS (Table 3).

Table 3: Type I IFN Signature and Relapsed Patients.

	IS +	**IS -**
Relapsed	8	7
Not relapsed	1	5

Note: IS: Interferon Signature.

One patient presented an increased IS between the first screening test during spring 2021 and the second testing (from 1.6 to 6.5, normal values < 2.6). Another patient showed a four-fold increase in IS (8.9 > 44) and was started on hydroxychloroquine, but relapsed a few months later, so therapy was suspended. Only one patient with a positive IS (10.3) did not report a recurrence or develop other signs or symptoms during the follow-up.

Discussion

Our data aligned with other case series, where almost two-thirds of patients reported recurrence of chilblains with a clear temporal relationship with the highest peaks of the SARS-CoV-2 pandemic, especially during the winter months [10]. As in other reports [15], female patients showed a significantly higher incidence of chilblain recurrences. Even if no patient had a past history of chilblains or other rheumatological disorders, most of those who presented chilblains during the COVID-19 pandemic also presented relapses in the following two years. Whether this was associated with subsequent challenges with SARS-CoV-2 or just a seasonal cold cannot be told. Even though there isn't strong biological evidence of SARS-CoV-2 reinfection, one theory is that chilblains come back because of both the SARS-CoV-2 infection and the cold weather, since cold weather alone doesn't always seem to be enough to cause a recurrence. Of note, symptoms tended to display similar or reduced severity during relapses, usually occurring in the same areas as at the onset of the problem. The fact

that relapse mostly happens in the same places that were studied at the start of the disease is interesting because it could mean that longlasting changes in the blood vessels happened after the first waves of the pandemic, providing anatomical and pathological reasons for recurrence. Even though the pathogenesis of COVID-19 related chilblains remains largely unknown, several studies have evidenced the presence of vascular changes. Several studies have linked CLL to changes in the blood vessels, including spongiosis changes, edema, red cell extravasation, fibrin deposition, micro-thrombi, purpura, vascular ectasia, and dilated blood vessels [12 -14]. Other studies showed swollen endothelial cells or inclusions within the endothelial cells [16]. In some cases, lymphocytic vasculitis was seen, which involved both T and B cells and the deposition of immunoglobulins and complement [17-19]. Only a few studies detected SARS-CoV-2 components in the vascular lesion [18], supporting the hypothesis of a post-viral pathogenesis.

Laboratory investigations are usually negative, apart from the detection of a positive IS in some studies [9], like in our experience. In one way, type I IFN inflammation may play a big part in how chilblains get worse, similar to what is believed to happen in "familial chilblain lupus," which is a single-gene interferonopathy caused by a dominant mutation in *TREX1* [20]. On the other hand, these patients may have a lower rate of positive anti-SARS-CoV-2 serology if their type I IFN pathway is activated strongly. This may explain the initial disagreement about whether or not there was a direct link between SARS-CoV-2 infection and chilblains. If type I IFN levels rise quickly, viruses may be cleared faster and the body may not be able to make enough antiviral antibodies [21,22]. The higher risk of COVID-19 related chilblains in adolescents and young adults may in part be explained by a higher capacity to produce interferons in this age group [9].

In our study, subjects with increased IS at the first episode also tended to have a higher risk of relapsing. Based on these findings, we chose to treat adolescents with severe symptoms and high IS with hydroxychloroquine, similarly to what is often proposed for subjects with type I IFN-mediated undifferentiated connective tissue diseases. Two out of three patients who started on hydroxychloroquine showed clinical benefit over the following weeks, while the one with higher IS values achieved no response. Thus, we cannot make any hypothesis on the possible effectiveness of such treatment in COVID-19 related chilblains. To the best of our knowledge, no treatment was found effective in curing the phenomenon. Several treatments, such as warming the limbs, systemic calcium channel blockers like nifedipine or diltiazem [23,24], and topical vasodilating drugs based on nitroglycerin [25], can help ease the symptoms. Hydroxychloroquine and oral prednisone have been used with questionable success [26,27].

The mid-term outcome of chilblains in our cohort was benign, and no patient developed further signs or symptoms of a rheumatological condition during follow up. As a matter of fact, we did not find signs or symptoms of systemic rheumatic diseases, with the partial exception of two similar cases of CRPS [28]. The first patient, a 16-year-old, developed CRPS after the first episode of CLL during spring 2021, with prompt benefit after a program of self-administered massages, an early mobilization program, and a complete course of bisphosphonate [29]. Magnetic Resonance Imaging of the foot showed diffuse soft tissue oedema and bone marrow oedema of the toes, suggestive of endothelial and microvascular damage. The second patient was a 15-year-old girl who presented with CRPS of the foot during the second episode of chilblains, between February and March 2022. Based on the previous experience, she started the same physical therapy. We did not find other cases of CRPS induced by chilblains in the literature, although it is highly likely that some patients with painful chilblain lesions may have fulfilled CRPS criteria. Other adult studies reported persistent and isolated acrocyanosis also during summer seasons, joining the "long COVID" spectrum, a still-debated entity in the pediatric setting [15].

Our report has some limitations. Firstly, we did not perform standardized teleconsultation, and we retrospectively collected data on patients who required a new clinical evaluation. Accordingly, our data may be fragmentary. Secondly, follow-up duration was limited, preventing definitive conclusions about long-term outcomes. Still, we showed one of the largest series of recurrences of chilblains in children caused by SARS-CoV-2, and we suggested IS as a useful laboratory marker that could be used to help treat these patients.

Conclusions

COVID-19 related chilblains, also described as "COVID toes" or erythema pernio, have been a common finding in adolescents during the first waves of the COVID-19 pandemic. We found that almost two-thirds of patients reported recurrence of chilblains in the follow up, particularly during the winter months. Female patients showed a significantly higher incidence of chilblain recurrences. It is not clear whether new challenges with SARS-CoV-2 are needed or not to trigger relapses of perniosis during the cold season. Even though lab tests usually come back negative, a strong type I IFN pathway activation in these patients may be linked to a higher risk of recurrence. However, it is not known if anti-IFN medication could help these patients. The relatively good prognosis that has emerged so far in follow up studies does not pose a clear indication for the development of clinical trials with systemic medication. Thus, our care is based only on symptomatic treatment already used to treat common chilblains. In our series, as in the literature, complex regional pain disorder can be a possible complication in subjects with COVID-19. Further follow-up will address the evolution of this problem over a longer observation period.

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Conflict of Interest

No conflict of interest.

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