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Title: Chilblains during lockdown are associated with household exposure to SARS-CoV-2. A multicentre case-control study.

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Abstract

Objectives: During the COVID-19 pandemic, numerous cases of chilblains have been reported. However, in most cases, RT-PCR or serology did not confirm SARS-CoV-2 infection. Hypotheses have been raised about an interferon-mediated immunological response to SARS-CoV-2, leading to effective clearance of the SARS-CoV-2 without the involvement of humoral immunity. Our objective was to explore the association between chilblains and exposure to SARS-CoV-2.

Methods: In this multicentre case-control study, cases were the 102 individuals referred to 5 referral hospitals for chilblains occurring during the first lockdown (March to May 2020). Controls were recruited from healthy volunteers' files held by the same hospitals. All members of their households were included, resulting in 77 case households (262 individuals) and 74 control households (230 individuals). Household exposure to SARS-CoV-2 during the first lockdown was categorized as high, intermediate or low, using a pre-established algorithm based on individual data on symptoms, high-risk contacts, activities outside the home and RT-PCR testing. Participants were offered a SARS-CoV-2 serological test.

Results: After adjustment for age, the association between chilblains and viral exposure was estimated at OR=3.3, 95%CI (1.4-7.3) for an intermediate household exposure, and 6.9 (2.5-19.5) for a high household exposure to SARS-CoV-2. Out of 57 case households tested, 6 (11%) had positive serology for SARS-CoV-2, whereas all control households tested (n=50) were seronegative (p=0.03). The effect of potential misclassification on exposure has been assessed in a bias analysis.

Conclusions: This case-control study demonstrates the association between chilblains occurring during the lockdown and household exposure to SARS-CoV-2.

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Introduction

In the early months of the COVID-19 pandemic, the emergence of acral lesions, similar to classic chilblains, have been reported worldwide [1–9]. As an outbreak of chilblains is extremely unusual, especially during the spring season and in areas with a mild climate, they were rapidly attributed to COVID-19 under the term “COVID toes” [1,2,4,10]. However, the association between SARS-CoV-2 and chilblains could not be ascertained, due to negative tests for SARS-CoV-2 infection, whether direct (RT-PCR) or indirect (serology), in the large majority of patients with chilblains. Instead, non-viral hypotheses arose: lifestyle changes associated with community lockdown (changes in physical activity, unsuitable footwear, etc.) [3,9,11–15], or a surveillance bias during this anxiogenic pandemic [3].

Several hypotheses have been raised regarding an immunological rationale for SARS-CoV-2 as a trigger for chilblains. Some researchers have suggested that chilblains could result from a strong interferon response, as seen in genetic interferonopathies. The interferon response could lead to rapid clearance of SARS-CoV-2, without the involvement of humoral immunity, explaining the negative SARS-CoV-2 serology in most patients [8,16–18].

To address the controversy, we conducted a multicentre case-control study in Western France to estimate the association between chilblains occurring during the first lockdown (March 17, to May 11, 2020) and household exposure to SARS-CoV-2 within confined homes. We used an algorithm based on self-reported features related to SARS-CoV-2 exposure rather than serological tests, because the underlying pathophysiological hypothesis implies low sensibility of serology to document SARS-CoV-2 exposure.

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Methods

Overview of the study

This multicentre case-control study took place in Western France. Individuals who developed chilblains during lockdown and individuals who had been confined with them (case households) were questioned in June and July 2020 about their exposure to SARS-CoV-2 during the first lockdown (March 17 to May 11, 2020). For the control group, individuals from households where no one developed chilblains (control households) were questioned using the same questionnaire covering the same period. Household exposure to SARS-CoV-2, assessed by self-reported information on the questionnaire, was compared between case households and control households. All individuals from these households were offered a COVID-19 serological test.

Participants

Individuals with suspicion of chilblains were referred by dermatologists and general practitioners from Western France to the Dermatology departments of 5 referral hospitals (Rennes, Brest, Nantes, Angers and Tours) covering 3 French regions (Bretagne, Pays de la Loire and Centre Val de Loire). The diagnosis of chilblains was established by a dermatologist in presence of localized erythema and swelling involving acral sites, persistent for more than 24 hours [19]. All individuals who had chilblains during the first COVID-19 wave in France (March to May 2020) were eligible to participate as cases, whether or not they had had similar lesions in the past. French referral hospitals hold healthy volunteers' files to recruit individuals for clinical research. The abovementioned hospitals used these files to recruit the controls, so that the individuals would have consulted in the same settings as the cases if

they had had similar skin lesions. All controls were asked to check a series of images of chilblains, in order to exclude them if any reported they might have had such lesions during the lockdown. Each individual enrolled (whether case or control) was to get in touch with each person he/she was confined with to complete the questionnaire. Individuals confined together during the lockdown defined the households. Individuals living alone were included in a sensitivity analysis.

Exposure to SARS-CoV-2

Household exposure to SARS-CoV-2 was assessed by processing information from each household member, using an algorithm established before data acquisition by consensus between investigators (including dermatologists, a virologist (VT), an infectious disease specialist (PT), and an epidemiologist (EO)). As a first step, the algorithm determined the individual level of risk for each household member of promoting SARS-CoV-2 circulation at home. Individual risk was classified as high if the household member had RT-PCR-proven COVID-19, specific symptoms (i.e. anosmia or ageusia), or had had unprotected and prolonged contact with a person diagnosed with COVID-19. Individual risk was classified as intermediate in case of other symptoms (fever, asthenia, rhinitis, sore throat, cough, dyspnea), other types of contact (protected or short-lived) with a person diagnosed with COVID-19, or regular out-of-home activity during lockdown. Individual risk was classified as low otherwise (asymptomatic household member who had no contact with a COVID-19-infected individual and no regular out-of-home activity). As a second step, the algorithm classified household exposure to SARS-CoV-2 into 3 ordered categories, according to the individual risk obtained for each household member: a household with at least one high-risk

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household member was considered as having a high level of household exposure to SARS-CoV-2; a household composed exclusively of low-risk members was considered as having a low level of household exposure to SARS-CoV-2. Household exposure to SARS-CoV-2 was considered as intermediate otherwise (i.e., at least one intermediate-risk member, and no one at high risk). The algorithm is presented in Supplementary Table 1.

SARS-CoV-2 serological testing

A SARS-CoV-2 serological test was offered to all the members of each household, and performed between July 21, 2020 and October 19, 2020. Laboratory methods are detailed in the Supplementary Data 1.

Statistical analyses

The association between chilblains occurring during lockdown and household exposure to SARS-CoV-2 was based on odds-ratio and 95% confidence interval (OR, 95%CI) estimation. The analysis was first stratified on age, then adjusted for age. Age was divided into quartiles in the main analysis, and modeled using a spline function in a sensitivity analysis. The analysis was also stratified and adjusted for the number of individuals confined together. Two additional sensitivity analyses were conducted, one including single-individual households, the other excluding households with a past history of chilblains. The statistical methods are detailed in Supplementary Data 2.

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Research Ethics

The study was approved on June 25th 2020 by the Comité de Protection des Personnes Ile de France III for the authorization to perform the serological tests (Ref. CNRIPH 20.06.17.34600), and by the CHU Rennes's Ethics Committee on June 24th for the questionnaire (Ref 20.79).

Results

Participants

All individuals referred for chilblains answered the questionnaire. Out of 677 individuals included in the healthy volunteer files of the abovementioned hospitals, 109 (16.1%) answered the questionnaire. Three case and 4 control households were excluded because of incomplete questionnaires. Four additional control households were excluded because they reported having had lesions resembling chilblains during the lockdown. A total of 94 case households and 101 validated control households were thus included. Single-person households (17 cases and 27 controls) were excluded for the main analysis, leaving 77 case households (262 individuals) and 74 control households (230 individuals) (Figure 1).

Characteristics of individuals with chilblains

Eighty-five individuals had chilblains, 8 case households including several affected individuals. Fifty-three (62.4%) were women, the median age was 24 (range, 12-70). Chilblains were located on the feet (75.3%), hands (11.8%) or both (12.9%). The median duration of lesions was 33 days (range, 4-143). Eighteen patients (21.2%) reported a past

history of chilblains, with less severe episodes in all these patients. Ten (11.8%) reported a previous Raynaud phenomenon. Only 3 patients reported exposure to cold before the occurrence of the lesions.

Characteristics of households

The composition of the households and the conditions of lockdown are described in Table 1. Case and control households did not differ for their main characteristics, except that they were not evenly distributed across the 3 regions (all in Western France).

SARS-CoV-2 household exposure

Across the case households, 23 (29.9%), 39 (50.6%) and 15 (19.5%) respectively were classified as having high, intermediate and low level of household exposure to SARS-CoV-2. Across the control households, 9 (12.2%), 33 (44.6%) and 32 (43.2%) respectively were classified as having high, intermediate and low level of household exposure to SARS-CoV-2. Symptoms (fever, asthenia, rhinitis, sore throat, cough, dyspnea), and a prolonged unprotected contact with an individual diagnosed with COVID-19 were significantly more often reported in case households than in control households (Table 2).

Association between chilblains and level of household exposure to SARS-CoV-2

The univariate analysis showed a significant association between chilblains and the level of household exposure to SARS-CoV-2, with a crude OR (95%CI) of 2.5 (1.2-5.4) for an intermediate level of exposure, and 5.5 (2.0-14.6) for a high level of exposure. After adjustment for age, the association was estimated at 3.3 (1.4-7.3) for an intermediate level of household exposure and 6.9 (2.5-19.5) for a high level of household exposure (Figure 2).

The homogeneity of the effect of viral exposure across the 4 age subgroups was not rejected (*p*-value for interaction, 0.54). The results of the stratified analysis on the 4 age subgroups and the sensitivity analysis selecting the minimum age within households are presented on the forest plot (Figure 2). When individuals living alone were included, the results were similar, with an adjusted OR of 2.4 (1.2-4.6) for an intermediate level of exposure, and 5.8 (2.4-14.5) for a high level of exposure. When households with a past history of chilblains were excluded, the adjusted OR was 3.4 (1.3-8.8) for an intermediate level of exposure, and 7.7 (2.3-25.7) for a high level of exposure.

The stratified, crude and adjusted analyses taking into account the number of individuals confined together did not show substantially different results (Supplementary Figure 1).

SARS-CoV-2 serological tests

Out of 57 tested case households, 6 (10.5%) had at least one SARS-CoV-2 seropositive household member, whereas out of 50 tested control households, none (0%) had a seropositive member (*p*=0.03) (Table 3). Among the 6 seropositive case households (17 seropositive individuals), 3 individuals with chilblains had SARS-CoV-2 antibodies, while in the other 3 households, all members were seropositive except the individual with chilblains. All seropositive households were categorized at a high level of exposure to SARS-CoV-2 following our algorithm. Among the individuals with serology but excluded because they were living alone (10 individuals with chilblains and 18 without), only one individual, without chilblains, was positive (Table 3).

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Discussion

In this case-control study comparing 77 case households to 74 control households, we observed a strong, significant, and proportional association between chilblains occurring during the lockdown and household exposure to SARS-CoV-2. This result is consistent with another case-control study based on serological tests [20].

The association between chilblains during the lockdown and exposure to SARS-CoV-2 within households is an important finding. While numerous reports of chilblains-like cases emerged throughout Europe and the United States during the first lockdown, the proportion of virologically confirmed SARS-CoV-2 infections was generally low, and discordant across studies [2–4,6–9], while the absence of a reference group without chilblains hampered the interpretation.

The main strength of our study is the comparison with a control group. Although we identified high exposure to SARS-CoV-2 in only 30% of the case households, the case-control design highlighted the fact that high exposure was about 7 times more frequent among case than among control households. In addition, the consistency of the results across age subgroups, with both statistical methods taking age into account, the evidence for a dose effect for chilblains according to the level of viral exposure, and the more frequent seropositivity among case households than control households (10.5 *vs* 0%) are additional arguments to support the validity and robustness of our results.

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All individuals with chilblains had a diagnostic validation by a dermatologist. The multicentre recruitment ensured the diversity and representativeness of the cases. These cases were similar to those reported in several case series [2–9].

The controls were unevenly recruited across Western France, but the area was overall moderately affected by the COVID-19 pandemic, the highest incidence of COVID-19 in France during spring 2020 being located in Ile-de-France (Paris area) and Grand-Est (northeast of France) [21]. While we were initially concerned about a selection bias in the inclusion of controls towards individuals who might have been more exposed and seeking a confirmation of their infection by serological testing, our results rule out the possibility of an overestimation of seropositivity among the controls, as none was positive. We used healthy volunteers' files from the same referral hospitals where cases were recruited to limit selection bias. Regarding a possible underestimation of the seropositivity rate, the prevalence of SARS-CoV-2 infection in this area of France was estimated at 1.7% (weighting the prevalence from the 3 regions of interest by the number of cases originating from these regions) [21]. Among the 68 control households tested (including individuals living alone), 1.18 positive serology was expected, and a value of 1 was observed. Although seropositivity was not the main outcome in this study, these findings suggest that we selected a fairly unbiased control group.

Our study has limitations. First, our main outcome was based on self-reported items. Hence, exposure misclassification may have occurred. Non-differential misclassification, affecting both cases and controls, may have occurred for viral symptoms that are not specific to SARS-CoV-2. However, these were only used to determine the intermediate level of SARS-CoV-2

exposure (Supplementary Table 1). In addition, protective measures during the lockdown resulted in a low incidence of other respiratory viruses. Also, past exposures may be more readily recalled by cases, possibly because of repeated questioning by physicians, leading to a differential misclassification. However, the odds-ratio would remain significant, even with a 20% misclassification rate. False positive and false negative rates among case households, control households or both were simulated in the bias analysis in Supplementary Table 2 [22]. Furthermore, a significant association was also observed for objective criteria not subject to misclassification, such as serology results. Second, asymptomatic cases make analyses of intra-household transmission unreliable, and this is the reason why we considered the household as a whole for the entire duration of the lockdown. Third, residual confounding is possible. For example, urban and rural living area was not specified in the questionnaire and could thus not be taken into account in the analysis. Last, seropositivity could have been underestimated in our study, because serologies were performed 2 to 5 months after the study period, and anti-nucleoprotein antibodies may wane within months [23]. However, antibody waning would have affected case and control households similarly, which would have led to an underestimation of the association [24,25].

Several issues remain regarding the relationship between chilblains and SARS-CoV-2. Among them, one can wonder~~;~~ whether SARS-CoV-2 exposure acts as a stimulus for a flare (a first or a subsequent one) among subjects with an immuno-genetic background predisposing to chilblains, or whether SARS-CoV-2 is an independent cause of chilblains; whether any other clusters of chilblains have occurred following anti-SARS-CoV-2 vaccination, since 8 cases have been reported in a registry-based study [26]; and on practical grounds, what is the medium-to-long term evolution of patients with chilblains occurring during the first

lockdown, given that persistent symptoms following COVID-19 are increasingly being described [27–33]. Persistent systemic and acral manifestations among the individuals with chilblains included in this study have been described in another article [34].

Conclusion

This comparative multicentre case-control study demonstrates an association between chilblains during lockdown and exposure to SARS-CoV-2 within confined households.

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Author contributions

Substantial contribution to study concept and design: FP, EO, SB, YLC, MS, EB, CL, LMa, LMi, AD.

Substantial contribution to the acquisition of data: FP, SB, YLC, MS, EB, HA, VG, CH, AT, VT, AD.

Substantial contribution to the statistical analysis or interpretation of data: FP, EO, SB, YLC, MS, EB, EC, CD, CH, CL, PT, VT, AD

Drafting the manuscript: FP, AD.

Critical review of the manuscript for important intellectual content and final approval for publication: all authors

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428 **Table 1. Characteristics of case and control households**

	Case households N = 77	**Control households N = 74**	***P*-value**
Age of the youngest individual in the household in years, median (range)	17 (1-69)	25 (2-72)	0.10
Age of the oldest individual in the household in years, median (range)	49 (23-70)	47 (25-94)	0.33
Proportion of men, median (range)	50 (0-100)	50 (0-100)	0.38
Geographical area			$<10^{-5}$
Bretagne	50 (64.9)	18 (24.3)	
Centre Val de Loire	7 (9.1)	26 (35.1)	
Pays de la Loire	18 (23.4)	23 (31.1)	
Not specified	2 (2.6)	7 (9.5)	
House (vs apartment), n (%)	57 (74.0)	47 (63.5)	0.16
Home surface area in m^2, n (%)			0.21
< 50	5 (6.5)	7 (9.5)	
50-100	26 (33.8)	30 (40.5)	
100-150	26 (33.8)	22 (29.7)	
> 150	20 (26.0)	15 (20.3)	
Number of individuals confined, n (%)			0.16
2	25 (32.5)	34 (45.9)	
3-4	41 (53.2)	30 (40.5)	
> 4	11 (14.3)	10 (13.5)	

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Table 2. Features used to define exposure to SARS-CoV-2 in cases and controls, at both household and individual levels

	Cases		Controls		Comparison of households *P*-value
	Households[a] N = 77	**Individuals N=262**	**Households[a] N = 74**	**Individuals N=230**	
Symptoms					
Anosmia, ageusia	10 (13.0)	16 (6.1)	4 (5.4)	4 (1.7)	0.16
Other symptoms [b]	41 (53.2)	59 (22.5)	15 (20.3)	22 (9.6)	$<10^{-3}$
Contact with a person diagnosed with COVID-19					
Any contact	30 (39.0)	40 (15.3)	22 (29.7)	29 (12.6)	0.30
Prolonged contact without protection	18 (23.4)	21 (8.0)	8 (10.8)	13 (5.7)	0.05
Activities outside the home					
Health care workers	19 (24.7)	25 (9.5)	12 (16.2)	14 (6.1)	0.23
Other regular activities outside the home	31 (40.3)	43 (16.4)	25 (33.8)	36 (15.7)	0.50
RT-PCR test [c]					
Positive	2 (2.6)	2 (0.8)	0	0	-
Tested	6 (7.8)	6 (2.3)	2 (2.7)	2 (0.9)	-

[a] features of at least one individual in the household

[b] among fever, asthenia, rhinitis, sore throat, cough, dyspnea

[c] period when RT-PCR testing was restricted to hospitalized patients or health care workers.

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435 **Table 3. Anti-SARS-CoV-2 serology in case and control households**

	Case households		**Control households**		***P*-value [a]**
	N=57	N=67 [b]	N=50	N=68 [b]	
Positive serology	6 (10.5%)	6 (9.0%)	0 (0%)	1 (1.5%)	0.03

436 [a] Comparison of households included in the main analysis and who were tested for serology (57 case
437 and 50 control households), using Fisher's exact test
438 [b] Including individuals living alone

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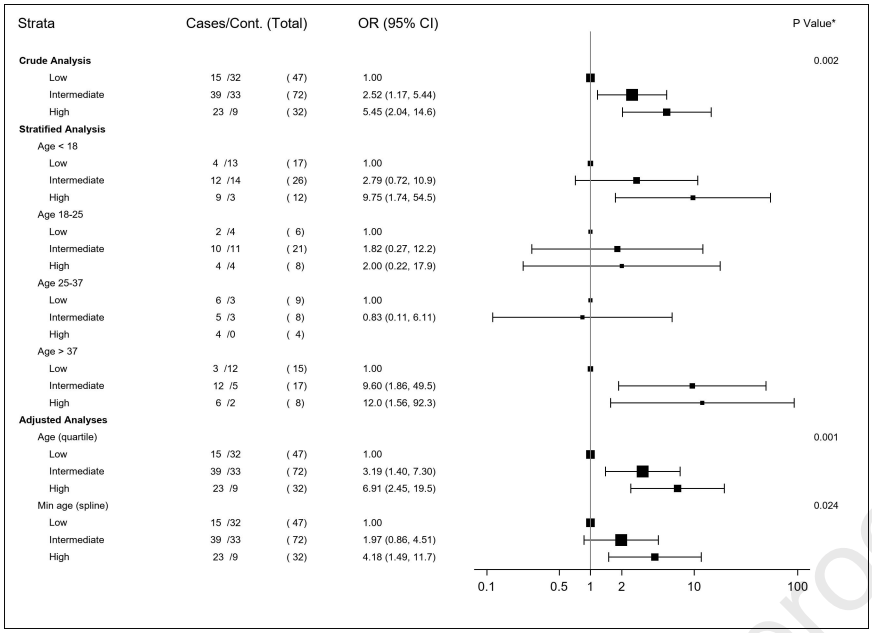
Figure Legends

Figure 1. Study flowchart

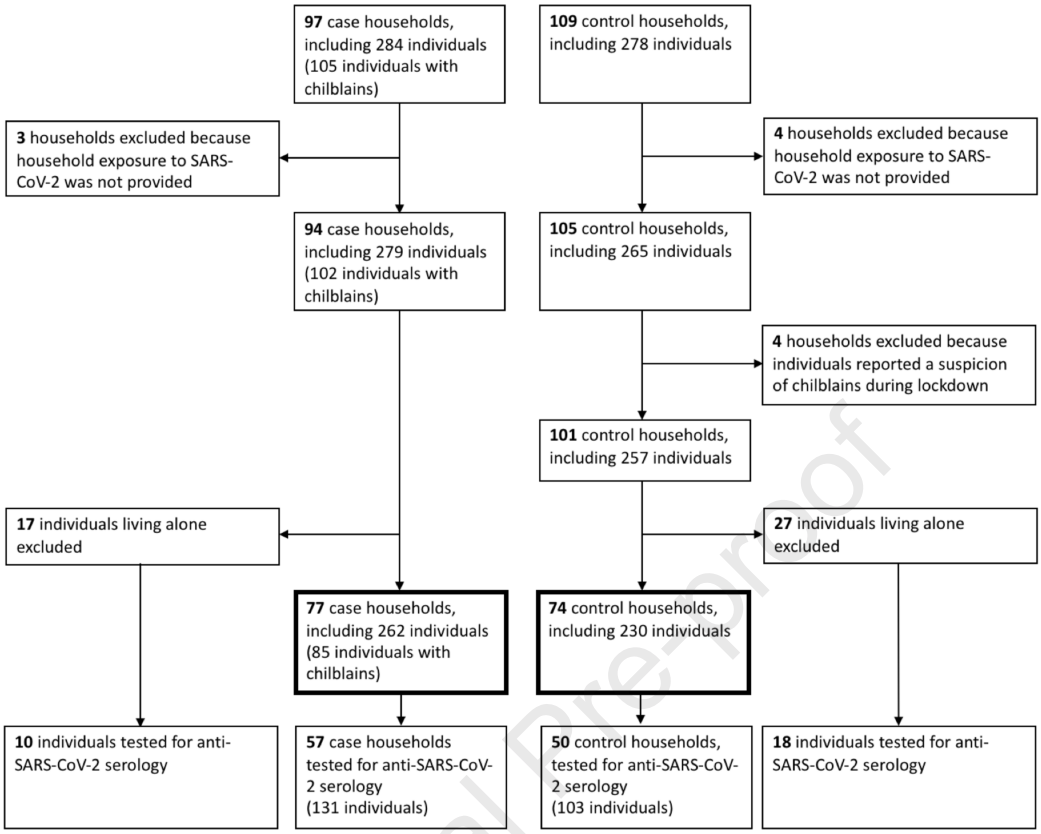
Figure 2. Forest plot of the analyses estimating the association between chilblains and exposure to SARS-CoV-2 within households

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