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

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3 **A multicentre case-control study.**

4

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28 **Abstract**

29

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

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

45 **Results:** After adjustment for age, the association between chilblains and viral exposure was
46 estimated at OR=3.3, 95%CI (1.4-7.3) for an intermediate household exposure, and 6.9 (2.5-
47 19.5) for a high household exposure to SARS-CoV-2. Out of 57 case households tested, 6
48 (11%) had positive serology for SARS-CoV-2, whereas all control households tested (n=50)
49 were seronegative ($p=0.03$). The effect of potential misclassification on exposure has been
50 assessed in a bias analysis.

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

Journal Pre-proof

53 Introduction

54 In the early months of the COVID-19 pandemic, the emergence of acral lesions, similar to
55 classic chilblains, have been reported worldwide [1–9]. As an outbreak of chilblains is
56 extremely unusual, especially during the spring season and in areas with a mild climate, they
57 were rapidly attributed to COVID-19 under the term “COVID toes” [1,2,4,10]. However, the
58 association between SARS-CoV-2 and chilblains could not be ascertained, due to negative
59 tests for SARS-CoV-2 infection, whether direct (RT-PCR) or indirect (serology), in the large
60 majority of patients with chilblains. Instead, non-viral hypotheses arose: lifestyle changes
61 associated with community lockdown (changes in physical activity, unsuitable footwear, etc.)
62 [3,9,11–15], or a surveillance bias during this anxiogenic pandemic [3].

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

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

74

75

76

77 **Methods**

78 *Overview of the study*

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

88

89 *Participants*

90 Individuals with suspicion of chilblains were referred by dermatologists and general
91 practitioners from Western France to the Dermatology departments of 5 referral hospitals
92 (Rennes, Brest, Nantes, Angers and Tours) covering 3 French regions (Bretagne, Pays de la
93 Loire and Centre Val de Loire). The diagnosis of chilblains was established by a dermatologist
94 in presence of localized erythema and swelling involving acral sites, persistent for more than
95 24 hours [19]. All individuals who had chilblains during the first COVID-19 wave in France
96 (March to May 2020) were eligible to participate as cases, whether or not they had had
97 similar lesions in the past. French referral hospitals hold healthy volunteers' files to recruit
98 individuals for clinical research. The abovementioned hospitals used these files to recruit the
99 controls, so that the individuals would have consulted in the same settings as the cases if

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

106

107 *Exposure to SARS-CoV-2*

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

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

128

129 *SARS-CoV-2 serological testing*

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

133

134 *Statistical analyses*

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

143

144

145 *Research Ethics*

146 The study was approved on June 25th 2020 by the Comité de Protection des Personnes Ile de
147 France III for the authorization to perform the serological tests (Ref. CNRIPH
148 20.06.17.34600), and by the CHU Rennes's Ethics Committee on June 24th for the
149 questionnaire (Ref 20.79).

150

151

152 **Results**153 *Participants*

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

162

163 *Characteristics of individuals with chilblains*

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

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

171

172 *Characteristics of households*

173 The composition of the households and the conditions of lockdown are described in Table 1.

174 Case and control households did not differ for their main characteristics, except that they
175 were not evenly distributed across the 3 regions (all in Western France).

176

177 *SARS-CoV-2 household exposure*

178 Across the case households, 23 (29.9%), 39 (50.6%) and 15 (19.5%) respectively were
179 classified as having high, intermediate and low level of household exposure to SARS-CoV-2.

180 Across the control households, 9 (12.2%), 33 (44.6%) and 32 (43.2%) respectively were
181 classified as having high, intermediate and low level of household exposure to SARS-CoV-2.

182 Symptoms (fever, asthenia, rhinitis, sore throat, cough, dyspnea), and a prolonged
183 unprotected contact with an individual diagnosed with COVID-19 were significantly more
184 often reported in case households than in control households (Table 2).

185

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

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

192 The homogeneity of the effect of viral exposure across the 4 age subgroups was not rejected
193 (p -value for interaction, 0.54). The results of the stratified analysis on the 4 age subgroups
194 and the sensitivity analysis selecting the minimum age within households are presented on
195 the forest plot (Figure 2). When individuals living alone were included, the results were
196 similar, with an adjusted OR of 2.4 (1.2-4.6) for an intermediate level of exposure, and 5.8
197 (2.4-14.5) for a high level of exposure. When households with a past history of chilblains
198 were excluded, the adjusted OR was 3.4 (1.3-8.8) for an intermediate level of exposure, and
199 7.7 (2.3-25.7) for a high level of exposure.

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

202

203 *SARS-CoV-2 serological tests*

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

213

214

215 Discussion

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

220

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

227

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

236

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

240

241 The controls were unevenly recruited across Western France, but the area was overall
242 moderately affected by the COVID-19 pandemic, the highest incidence of COVID-19 in
243 France during spring 2020 being located in Ile-de-France (Paris area) and Grand-Est
244 (northeast of France) [21]. While we were initially concerned about a selection bias in the
245 inclusion of controls towards individuals who might have been more exposed and seeking a
246 confirmation of their infection by serological testing, our results rule out the possibility of an
247 overestimation of seropositivity among the controls, as none was positive. We used healthy
248 volunteers' files from the same referral hospitals where cases were recruited to limit
249 selection bias. Regarding a possible underestimation of the seropositivity rate, the
250 prevalence of SARS-CoV-2 infection in this area of France was estimated at 1.7% (weighting
251 the prevalence from the 3 regions of interest by the number of cases originating from these
252 regions) [21]. Among the 68 control households tested (including individuals living alone),
253 1.18 positive serology was expected, and a value of 1 was observed. Although seropositivity
254 was not the main outcome in this study, these findings suggest that we selected a fairly
255 unbiased control group.

256

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

261 exposure (Supplementary Table 1). In addition, protective measures during the lockdown
262 resulted in a low incidence of other respiratory viruses. Also, past exposures may be more
263 readily recalled by cases, possibly because of repeated questioning by physicians, leading to
264 a differential misclassification. However, the odds-ratio would remain significant, even with
265 a 20% misclassification rate. False positive and false negative rates among case households,
266 control households or both were simulated in the bias analysis in Supplementary Table 2
267 [22]. Furthermore, a significant association was also observed for objective criteria not
268 subject to misclassification, such as serology results. Second, asymptomatic cases make
269 analyses of intra-household transmission unreliable, and this is the reason why we
270 considered the household as a whole for the entire duration of the lockdown. Third, residual
271 confounding is possible. For example, urban and rural living area was not specified in the
272 questionnaire and could thus not be taken into account in the analysis. Last, seropositivity
273 could have been underestimated in our study, because serologies were performed 2 to 5
274 months after the study period, and anti-nucleoprotein antibodies may wane within months
275 [23]. However, antibody waning would have affected case and control households similarly,
276 which would have led to an underestimation of the association [24,25].

277

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

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

288

289

290 **Conclusion**

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

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306

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313 **Author contributions**

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

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

318 Substantial contribution to the statistical analysis or interpretation of data: FP, EO, SB, YLC,
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320 Drafting the manuscript: FP, AD.

321 Critical review of the manuscript for important intellectual content and final approval for
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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)	

429

430 **Table 2. Features used to define exposure to SARS-CoV-2 in cases and controls, at both**
 431 **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)	-

432 ^a features of at least one individual in the household

433 ^b among fever, asthenia, rhinitis, sore throat, cough, dyspnea

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

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

	Case households		Control households		<i>P</i> -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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439 **Figure Legends**

440

441 **Figure 1. Study flowchart**

442

443 **Figure 2. Forest plot of the analyses estimating the association between chilblains and**

444 **exposure to SARS-CoV-2 within households**

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