COVID-19 SPECIAL FORUM

Immunological and virological profile of children with chilblain-like lesions and SARS-CoV-2

Dear Editor,

The link between SARS-CoV-2 and the reported cutaneous manifestations has not been established. We assessed a possible correlation between the paediatric dermatological manifestations and the biological investigations, using for the first time three different SARS-CoV-2 tests.

From April to June, 2020, minors presenting with skin manifestations and symptoms of COVID-19 themselves or any of first-degree relatives (i.e. fever, influenza-like, respiratory, Ear–Nose–Throat and/or digestive symptoms), were enrolled. Epidemiological and clinical information, description of households and biological results including three types of SARS-CoV-2 tests [nasal PCR (systemic symptoms within the past 48 h), serology (IgG, techniques: Abbott ARCHITECT) and interferon-γ(IFN-γ)-ELISPOT-assay] were collected. IFN-γ-ELISPOT-assay, an early (since day 5) qualitative and quantitative analysis, evaluates specific memory T cells by quantifying the IFN-γ production after a short-term stimulation with SARS-COV-2 peptide. At least one test among serology and IFN-γ-ELISPOT-assay was performed on patients with chilblains.

Thirty patients (20 boys, average = 9.5 years) representing 28 households were included. Thirty-seven symptomatic first-degree relatives were analysed. In 23/30 patients (77%) and 14/17 (82%) of chilblains patients, COVID-19 was suspected in at least one first-degree relative and confirmed in four including two with chilblains.

Chilblains were reported in 17 patients with a large spectrum of severity (Fig. 1). Lesions occurred before (n = 2, average: 19 days), simultaneously (n = 2, 20%) or after systemic manifestations (60%, average: 22 days). Spontaneous resolution was complete in an average of 27 days (10–50). Two patients relapsed in 15 and 45 days, respectively. Other cutaneous manifestations occurred before (20%, average: 18 days), during (30%) or after systemic manifestations (50%, average: 25 days). Two patients, including one child, presented with a linear

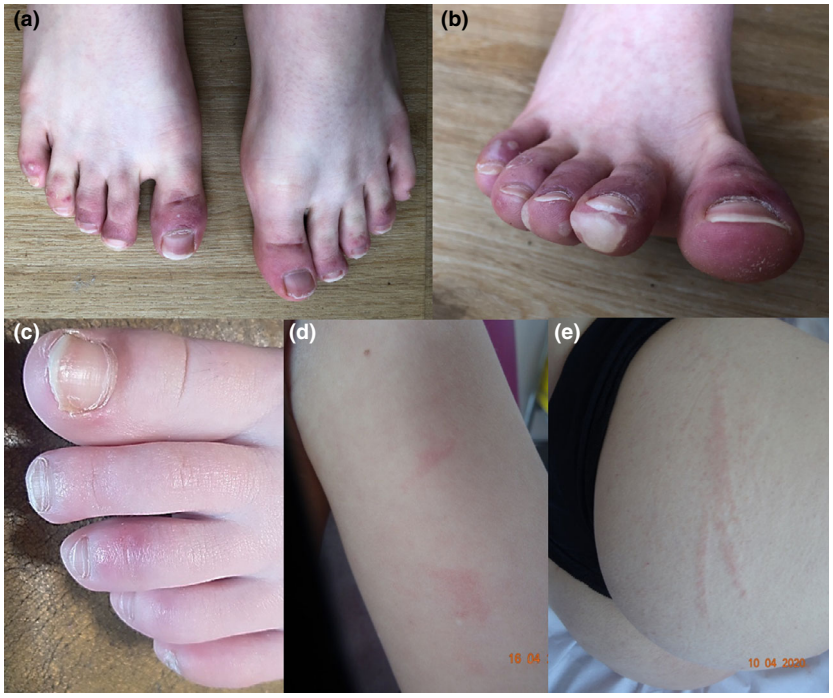

Figure 1 Clinical pictures of our paediatric series during the COVID-19 pandemic: chilblain-like lesions associated with livedo (a–c), spontaneous urticarial lesions with linear disposition (d, e).

Table 1 Clinical and biological characteristics of the patients

	Total patients, *n* = 30 (%)	**Chilblain-like patients, *n* = 17 (%)**
Mean age (range), sex ratio F: H	9.5 years (1.8–17.3), 0.5	11.2 years (1.8–17.3), 0.4
Household contact with a case of COVID-19:		
- Probable cases	23 (77)	14 (82)
- Confirmed cases: PCR/serology/both	2 (7)/1 (3)/1 (3)	2 (12)/0/0
Households description:		
- Number of households	28	15
- Total of first-degree relatives	79	13
Past medical history of patients:		
- Raynaud phenomenon, photosensitivity	0	0
- Auto-immune disease	0	0
- Inflammatory bowel disease	1 (3)	0
- Asthma/atopic dermatitis	3 (10)/2 (7)	3 (19)/2 (12)
- Urticaria	1 (3)	1 (6)
- Obesity	0	0
Dermatological manifestations:		
- Chilblains: total/feet/hands/both	17 (57)/14 (47)/2 (7)/1(3)	17 (100)/14 (82)/2 (12)/1 (6)
- Eccrine hidradenitis	2 (7)	–
- Maculo-papular rash	8 (27)	–
- Urticaria	1 (3)	–
- Livedo	2 (7)	–
- Targetoid lesions	2 (7)	–
- Vascular/ecchymotic purpura	1 (3)/1 (3)	–
- Erythema nodosum	1 (3)	–
- Mucosal manifestations	0	–
Average time of cutaneous complete remission	22 days (1–50)	27 days (10–50)
Symptoms:		
- Mean pruritus scale from 1 to 10	7 (1–10), *n* = 11 (33)	6 (1–10), *n* = 6 (62)
- Mean VAS pain scale from 1 to 10	6 (2–10), *n* = 9 (27)	5 (3–8), *n* = 4 (50)
Systemic manifestations:	***n* = 20 (67)**	***n* = 10 (59)**
- Fever	10 (33)	3 (18)
- Influenza-like symptoms	13 (43)	7 (41)
- Respiratory symptoms	10 (33)	6 (35)
- ENT symptoms/anosmia	10 (33)/1 (3)	7 (41)/0
- Digestive symptoms	7 (23)	3 (18)
- Articular symptoms	1 (3)	0
Mean time lapse from systemic symptoms to lesions:	***n* = 20 (67)**	***n* = 10 (59)**
- Systemic manifestations before	25 days (3–77), *n* = 10 (50)	22 days (5–46), *n* = 6 (60)
- Cutaneous manifestations before	18 days (2–30), *n* = 4 (20)	19 days, *n* = 2 (20)
- Simultaneous manifestations	0 day, *n* = 6 (30)	0 day, *n* = 2 (20)
Laboratory tests:	***n* = 25 (80)**	***n* = 16 (94)**
- Anaemia (Hb < 11 g/dL)	1 (4)	0
- Hyperlymphocytosis (>5.2 G/L)	2 (8)	0
- Neutrophilic hyperleukocytosis (>8 G/L)	1 (4)	1 (6)
- Elevated liver enzymes (ALT, AST)	0	0
- Elevated creatinine	1 (4)	0
- Elevated CRP (>5 mg/L), mean (extremes)	3 (12), 14 (0–200)	1 (6), 5 (0–49)
- Low PT (<70%)	2 (8)	1 (6)
- Elevated aPTT (ratio >1.2)	6 (24)	3 (19)
- Elevated fibrinogène (>3.5 g/L) (*n* = 15)	0	0
- Elevated D-dimer level (>500 ng/mL) (*n* = 15)	1 (7)	0
- Positive antinuclear antibodies, mean title (extremes), specificity (*n* = 17)	14/17 (82), 264 (100–800), 0	11/14 (79), 263 (100–800), 0

Table 1 *Continued*

	Total patients, *n* = 30 (%)	Chilblain-like patients, *n* = 17 (%)
- APLA syndrome (β2GP1, cardiolipin, lupus anticoagulant) (*n* = 15)	1/15 (7)	1/12 (8)
- Positive C-ANCA, specificity (*n* = 17)	4/17 (23), 0	2/14 (14), 0
- Complement anomalies: C3, C4, CH50 (*n* = 9)	1 low CH50 at 66 (4)	1 low CH50 at 66 (7)
- Elevated cytokines serum concentrations:		
○ IL1 (>15 pg/mL), mean (range)	6/14 (43), 105 (17–280)	6/12 (50), 104 (7–280)
○ IL6 (>10 pg/mL), mean (range)	5/15 (33), 59 (10–127)	4/12 (33), 62 (10–127)
○ TNF-α (>20 pg/mL), mean (range)	7/15 (47), 33 (20–60)	7/12 (58), 31 (20–60)
○ Type 1 IFN (α) (>2 UI/mL), mean (range)	4/12 (33), 4 (2–6)	4/10 (40), 4 (2–6)
Tests of SARS-CoV-2:		
- PCR positive	0/8	0/3
- IgG positive (Abbott ARCHITECT)	1/26 (4)	1/16 (6)
- IFN-γ-ELISPOT-assay positive	0/11 (100)	0/10 (100)
Mean duration of follow-up	34 day (8–72)	42 day (11–72)

pattern of urticarial lesions, both also presented with chilblains (Fig. 1).

Elevated CRP [average 14 mg/L (0–200)] and/or increased inflammatory cytokines were noted in 11 children (37%) including 8/17 with chilblains (47%). Cytokine levels were increased in 58%, 50%, 40% and 33% of chilblains patients tested for: TNF-α (range 20–60 pg/mL), IL-1 (range 7–280 pg/mL), type 1 IFN (range 2–6 UI/mL) and IL-6 (range 10–127 pg/mL), respectively (Table 1). In chilblains, tests were performed in an average of 18 days (5–98) and 21 days (6–51) after skin lesions and systemic manifestations onset respectively.

The 3/3 nasal PCR were negative. Serology was positive in only 1/16 chilblains patient among the 26 patients tested. IFN-γ-ELISPOT-assay was negative in all the 10 chilblains patients tested. In children with chilblains, these tests were performed in an average of 45 days from lesions onset (5–82) and 56 days from systemic manifestations (35–89).

High levels of cytokines, mostly TNF-α, IL-1, type 1 IFN and IL-6 were noted in 47% of chilblains patients. Biological inflammation was not correlated with: (i) time lapses from cutaneous or systemic symptoms to the blood test, (ii) severity of chilblains. A cytokine storm was described in adults with COVID-19[1] and in the paediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 infection (PIMS-TS): elevated CRP and IL-6 levels.[2]

The peak of incidence of COVID-19 and the reported chilblains occurred simultaneously.[3–9] In 28/68 reported patients presenting chilblains,[7,9,10] serology was negative. Only 1/16 chilblains children serology was positive. Sensitivity of our technique varies from 100 to 85% in severe or mild symptomatic patients respectively. Moreover, it is known to be positive after 19 and 30 days of evolution in 85% and 94% of the patients, respectively. In all our patients, the COVID-19 was confirmed only once, using three different methods. Our result might reflect the estimated prevalence of seropositivity for SARS-CoV-2 in the general French population.

While epidemiological data, clinical manifestations and elevated cytokines level suggest an association with SARS-CoV-2, no evident link could have been made.

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Conflicts of interest

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Diagnosis of hair disorders during the COVID-19 pandemic: an introduction to teletrichoscopy

To the Editor

The COVID-19 pandemic has limited dermatologic care with >50% decrease in the number of patients seen and biopsies completed.[1] Even after this pandemic has passed, social distancing may limit the number of patients seen in-person and telemedicine will likely play a larger permanent role.

Teletrichology describes the use of telecommunication platforms to interact with hair disorder patients remotely and to select patients who need in-person consultation for diagnostic or therapeutical procedures. Teletrichology is excellent for both initial and follow-up examinations of patients with different types of hair loss including telogen effluvium, androgenetic alopecia, alopecia areata and scarring alopecia. With teletrichology, dermatologist can effectively evaluate patients by instructing them to perform the pull/tug tests, measure thickness of the ponytail, measure distance from the hairline to the glabella and show daily/shampoo hair shedding. Since April 2020, one of the authors has visited 235 patients using teletrichology and teletrichoscopy.

Trichoscopy is a valuable diagnostic tool to differentiate inflammatory, infectious, scarring and non-scarring conditions.[2] However, some concerns regarding the use of trichoscopy during the COVID-19 pandemic have recently been raised due to the possible risk of viral contamination of hair. Although, currently,

Table 1 Summary of appropriate teletrichology clinical evaluations that can be completed during hair disorder consult

Hair condition	Teletrichology visit evaluations	Instrument	Instrument findings
Telogen effluvium†	Pull test Hair shedding Ponytail measure	Macro-imaging app/handheld microscope	Lack of hair shaft variability
Alopecia areata†	Pull test SALT PGA	Macro-imaging app	Yellow dots Broken hairs Exclamation mark hairs
Androgenic alopecia†	Pull test Hair shedding Ponytail measure	Macro-imaging app/handheld microscope	Hair shaft variability
FFA§	Measure hairline distance from glabella	Macro-imaging app/handheld microscope	Absence of vellus hair
CCCA¶	Clinical pattern suggests diagnosis	Macro-imaging app/handheld microscope	Hair shaft variability
Other scarring alopecias†	Patchy alopecia	Macro-imaging app/handheld microscope	Absence of follicular openings and peripilar casts

Type of instrument patient can use remotely and findings that can be seen in each disorder. Additionally, recommendations on telemedicine or in-person follow-up and treatment have been provided.
CCCA, central centrifugal cicatricial alopecia; FFA, frontal fibrosing alopecia; PGA, Physician Global Assessment score; SALT, severity of alopecia score. †Treat and follow up with telemedicine. ‡Treat and follow up with telemedicine except for patients requiring intralesional corticosteroid treatment. §You can diagnose and follow up with telemedicine, in-person visit only required to confirm diagnosis with biopsy at first visit. ¶Need to see in person for biopsy and procedures.