

Pandemic chilblains: are they SARS-CoV-2 related or not?

Axel De Greef¹, Pierre G. Coulie², Marie Baeck¹

axel.degreeef@saintluc.uclouvain.be

¹Division of Dermatology, Cliniques universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Avenue Hippocrate 10, 1200, Brussels, Belgium

²Department of Immunology, de Duve Institute, UCLouvain, Avenue Hippocrate 74, UCL 7459, 1200, Brussels, Belgium



Chilblains observed when and where COVID-19 cases are more frequent?

- Temporal correlation between chilblains and peaks of COVID-19
- Chilblains observed when and where lockdowns were imposed¹⁻⁶
- Pandemic chilblains observed during first and second waves only
- In Nordic countries, no strict lockdown was imposed, and no chilblain outbreaks occurred⁷

Association between SARS-CoV-2 and chilblains at the individual level?

- Patients with pandemic chilblains had no or mild symptoms compatible with SARS-CoV-2 infection
- RT-qPCR on swabs and anti-SARS-CoV-2 antibodies were negative in most patient series⁸
- RT-PCR or RNA in situ hybridization on pandemic chilblain lesions did not detect SARS-CoV-2^{1,5,9-11}

Role of interferon pathway?¹²

The hypothesis is that some individuals display an unusually strong type I interferon (IFN-I) response that (i) eliminates the virus before the appearance of symptoms and of detectable antibody responses and (ii) causes chilblains, like those observed in patients with interferonopathies. However:

- No evidence for higher levels of IFN-I in the blood of patients with pandemic chilblains than in blood of those with seasonal chilblains
- No higher levels of the IFN-I-induced genes *MX1* and *IRF7* in skin biopsies of pandemic chilblains than in those of pre-pandemic chilblains¹⁰
- Similar transcriptomic signatures, including IFN-I target genes in both pandemic and seasonal chilblains¹³
- If a strong IFN-I response at the very onset of the infection quickly eliminates the virus, we would not expect to still detect viral proteins weeks later. It follows that if SARS-CoV-2 virions or proteins were confirmed in pandemic chilblain sections¹⁴, it would not fit with this current IFN-I hypothesis
- No systemic symptoms as described in interferonopathies^{15,16}

Pandemic Chilblains: a stimulating puzzle!



Impossible to exclude SARS-CoV-2 as the triggering agent

Environmental factors insufficiently considered i.e. cold exposure and unprecedented containment measures

Spatial transcriptomics or proteomics may confirm hypotheses or open new mechanistic fields.

Same triggering factor(s) as for classic cold-related chilblains

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RT-(q)PCR: reverse transcription-(quantitative) polymerase chain reaction. MX1: Myxovirus Resistance Protein 1. IRF7: Interferon Regulatory Factor 7