

# Possible Case of Children Onset Systemic Lupus Erythematosus Triggered by Covid-19

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## Case Report

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# Abstract

This case report will present the case of an 11 years old child diagnosed with childhood-onset systemic lupus erythematosus (cSLE) during the coronavirus Covid-19 pandemic. Her initial symptoms were compatible with a Covid-19 infection but repeated PCR on naso-pharyngeal swabs were negative. Two serological assays were carried out but only one showed doubtful IgG results.

Considering that viral infection could be responsible for autoimmune disease outbreaks and with increasing evidences of SARS Cov 2 actions on human inflammatory and immune systems; we discuss here a potential cSLE diagnosis triggered by Covid-19 infection.

## Background

Childhood-onset systemic lupus erythematosus is a rare chronic auto immune disease characterised by a multisystemic involvement and various presentations. Treatment is usually initiated with corticotherapy and hydroxychloroquine for patients with mild symptoms whereas immunosuppressants and biologics medication are examined individually. [1]

The etiology of cSLE is not clearly defined in literature. It is known, however, that the main causes are a combination of genetics and environmental factors such as sun light exposure, medication or infection. [2] For instance, it has been described in literature that viral infections such as Epstein-Barr Virus (EBV) or cytomegalovirus (CMV) triggers autoimmune diseases.

Parvovirus B19 is also known to trigger inflammatory responses and could be responsible for an autoimmune reaction. [3]

More recently, SARS Covid-19 is being intensively studied to gain a better understanding of the physiopathology leading to the current pandemic. It has already been demonstrated that this coronavirus is responsible for a cytokine storm due to its fixation on ACE2 receptors and virus-linked pyroptosis. [4][5] Possible links were established between paediatric Covid-19 infections and a spike of autoimmune and autoinflammatory diseases such as Kawasaki or Kawasaki-like disease, macrophage activation syndrome and paediatric inflammatory multisystemic syndrome. Yet, the correlation between cSLE and Covid-19 has not yet been described. [6]

## Case Report

Our index patient is a 11 years old Black African female with a medical history of premature birth and minor alpha thalassemia. In May 2020, as the Covid-19 pandemic peaked in Europe and Northern America, she was firstly presented to her general practitioner for a left palpebral oedema, stiffness, myalgia, dysphagia and pyrexia that started on the 18th of May. Further symptoms included weakness, ageusia, anosmia, abdominal pain and cutaneous eruption. Initial examination showed a sensitive

abdomen mainly in epigastric and right hypochondria. The first Covid-19 screening with naso-pharyngeal polymerase chain reaction (PCR) was negative.

Complementary examinations revealed a facial butterfly cutaneous eruption, atypical papules on her arms and forearms, a pharyngitis and cervical adenopathy. Laboratory exams at the outset showed no inflammatory signs, neutropenia, elevated hepatic enzymes, positive anti-nuclear antibody and doubtful Covid-19 serology (negative IgM and IgG rate at 14 U/ml).

Based on her persistent fever and fatigue, she was sent to an emergency service for hospitalisation. Her admission results revealed a normal C reactive protein level but an elevated erythrocyte sedimentation rate at 63 mm/H, mild normocytic anaemia, persistent elevated hepatic enzymes, and hypergammaglobulinemia, positive anti-nuclear antibody (1/320 dilution) with anti-ds DNA antibody at 910.9 UI/ml and anti-nucleoprotein antibody (nRNP/Sm, Sm, SS-A60, Ro-52, AMA M2, SRP, Rib P protein, histone, nucleosome), positive ANCA (1/160 dilution) but negative anti MPO and PR3.

Viral serologies were negative for hepatitis B and C, HIV and toxoplasmosis. She was immunised against Herpes Zoster, parvovirus B19, EBV, CMV and measles. Urinary sediment was negative. Except for a thoraco-abdominal scan that showed axillar and cervical adenopathy and an ECG showing a first-degree atrioventricular block, every other exam appeared normal (cardiac and abdominal ultrasound, cerebral CT scan, renewed Covid-19 PCR). She was then transferred to the paediatric ward after five days as her general condition and biological exams worsened.

Upon arrival, a thorough clinical exam in which multiple aphthous ulcers in the mouth, gingivitis and a loss of 5 kg since her initial medical visit were noticed. The laboratory exams showed an erythrocyte sedimentation rate of 35 mm/h, ferritin elevated at 830 µg/L, lowered complement C3 and C4 (0.21 and 0.03 g/L) and persistent elevated hepatic enzymes. Her immunophenotyping was normal for her age. A third Covid - 19 PCR on naso-pharyngeal swab was performed and remained negative.

Skin biopsies were collected; anatomopathology analysis concluded a connective tissue disease setting a differential diagnosis between acute erythematous lupus and dermatomyositis.

Based on her skin eruption, clinical appearance, biology and auto immune markers, a diagnosis of acute erythematous lupus was established.

Her treatment consisted of a bolus of solumedrol 125 mg intravenous injection on the second day of hospitalisation. Further treatment included oral corticotherapy (Medrol 16 mg per day) that started on day three, followed by hydroxychloroquine (200 mg per day) one week after the first injection. Shortly after the implementation of corticoids, her fever decreased, and finally stopped on the fourth day of hospitalisation.

During her hospitalisation, she remained free of nephrological, neurological and rheumatological impairments.

She was authorised to return home after her oral feeding and stamina improved, and when headaches and abdominal pain lowered.

Close follow-up in consultation indicated a discrete enhancement of biological exams and general condition. A control of Covid-19 serology came out negative for both IgG and IgM 16 days after the first control.

## Discussion

In this case, the diagnosis of cSLE was established based on clinical and immunological criteria as well as skin biopsy analysis. Relevant criteria are listed in the American College of Rheumatology (ACR) classification criteria of SLE; including 10 systemic or biological signs. [7] Other studies show a gain of sensitivity, even though with a loss of specificity, when using the Systemic Lupus International Collaborating Clinics (SLICC) for cSLE diagnosis. [8]

Her follow up will be based on frequent controls with her paediatrician to detect first signs of a possible complication such as lupus nephritis, gastrointestinal or neurological involvement or cardio-vascular manifestation.

As the main cause of cSLE remains uncertain, it is now admitted that a viral infection could be a trigger of the clinical manifestation. It is increasingly argued that herpesviruses like EBV or CMV are responsible for the development of autoimmune disorders. Studies show EBV and CMV DNA are found at high rates in blood samples of SLE patients. EBV serological analysis shows a higher rate of early antigen IgG and IgA in SLE patients compared to healthy EBV carriers. Cross reactions between anti EBV nuclear antigen 1 antibodies and lupus associated autoantigens were also highlighted as viral mediated autoimmunity. [9]

Parvovirus B19 is also known to trigger inflammatory responses with a cytokine production and high specific antibodies rate such as rheumatoid factor or antinuclear/ antiphospholipid antibodies in SLE patients. However, its role in lupus outbreak remains ambiguous. [3]

Similar inflammatory response and immune trigger could be expected from the recently discovered Covid-19 virus. As it became a global concern during the first half of year 2020, different studies were made on sera from patients with SARS CoV 2 infection to obtain a broader understanding of the inflammatory and immunopathogenesis of this virus.

Foremost, the fixation of coronavirus on ACE2 receptors causes the endocytosis of the virus, the downregulation of the ACE2 receptors and the rise of angiotensin II rate. As a result, an important cytokine and chemokine storm is released, especially IL 1  $\beta$ , IL-4, IL-6, IL-8, IL-10, IFN  $\gamma$ , TNF-  $\alpha$ , MCP1 and IP 10. [4] [10] Furthermore, a study from Zhou *et al* showed another side to the coronavirus-linked autoimmunity; they studied blood samples from twenty Covid-19 positive patients and discovered a rise in autoimmune antibody with a prevalence of anti-52 kDa SSA/Ro antibody, anti-60 kDa SSA/Ro antibody and antinuclear antibody of 20%, 25% and 50% respectively. Other antibodies were all negative

(i.e. anti-Scl-70, AntiJo-1 antibody, anticentromere B antibody, anti-SmD1 antibody, antiSSB antibody, anti-double-stranded DNA antibody, Anti-Streptolysin O antibody, the rheumatoid factor, Anti-Neutrophil Cytoplasmic Antibodies (ANCA) ), except for the anticyclic peptide containing citrulline antibodies (anti-CCP antibody) which was positive for only two patients. [10]

While those studies show biological evidences of inflammatory and immunity reaction triggered by SARS Cov-2 infection, other observations reported a rise in autoimmune disease in children, some of them overlapping a coronavirus infection. [5]

Considering all this information, the idea of a possible cSLE triggered by a Covid-19 infection is plausible but, to our knowledge, has not yet been described.

For this case's patient, initial symptoms were consistent for a coronavirus infection.

Even though ageusia and anosmia are not commonly found in Covid-19 positive children; chemosensory disfunction is estimated to be present in up to 19.4% in adults. [11] [12] In addition, a recent paper reports anosmia and ageusia as solely symptoms in 3 Covid-19 positive children. [13] Due to its tropism for the gastrointestinal tract and intense viral replication in the small and large intestines, SARS Cov 2 also causes digestive symptoms. A recent cohort study on children in Europe demonstrated that gastrointestinal manifestation is present in 22% of positive children. The two main symptoms were pyrexia and upper respiratory tract infection, found in 65% and 54% of patients, although 16% of positive children were asymptomatic. A great majority (87%) never needed respiratory support and, in 5% of cases, a co-infection with another virus was found. However, this European study considered patients eligible if SARS Cov 2 was detected in an RT-PCR from any clinical sample; serological testing was not taken into consideration. [14]

For the index patient, we faced an ambiguous situation where clinical symptoms were suspicious of a Covid-19 infection, but repeated RT-PCR were negative and serological assay was only once doubtful. Other symptoms were typical of cSLE and disappeared with adequate treatment, thus leading to the assumption that her Covid-19 presentation was probably paucisymptomatic.

As initial treatment, the patient received hydroxychloroquine (HCQ) in addition to corticoids for cSLE. As this molecule inhibits type 1 interferon, it has also been studied during the Covid-19 pandemic. Indeed, by blocking this immune response path, HCQ helps decrease viral replication and moderate the cytokine storm responsible for complicating Covid-19 clinical damages. A study by Gautret *et al* also reported a significant reduction of the viral carriage with HCQ in 20 patients. However, another study on 30 patients showed no superiority between HCQ versus placebo in viral clearance nor in the progression of radiological pneumonia. [15] With this knowledge, it is conceivable to say that treatment with HCQ for cSLE in a possible Covid-19 positive patient will, at worst have no action on Covid-19 symptoms or, at best avoid autoimmune dysregulation.

## Conclusion

While an increasing number of studies incriminate viral infection for autoimmune disease, the main cause for cSLE remains unknown. In this case, the diagnosis of cSLE in a child during the SARS Cov 2 pandemic was discussed. As the PCR testing or serological assay still needs to be improved for diagnosis, it is now common knowledge that this virus has pro inflammatory actions causing autoimmune dysregulation. Further studies will be needed to assess the role of this coronavirus as an autoimmune disease trigger.

## **Abbreviations**

ACE2: Angiotensin-Converting Enzyme 2

ACR: American College of Rheumatology

ANCA: Anti Neutrophil Cytoplasmic Antibody

CMV: Cytomegalovirus

(c)SLE: (children) onset Systemic Lupus Erythematosus

DNA: Deoxyribonucleic Acid

EBV: Epstein-Barr Virus

ECG: Electrocardiogram

HCQ: Hydroxychloroquine

HIV: Human Immunodeficiency Virus

IFN: Interferon

Ig: Immunoglobulin

IL: Interleukin

IP10: Inducible Protein 10

MCP1 : Monocyte Chemoattractant protein-1

PCR: Polymerase Chain Reaction

RT-PCR: Reverse-Transcription Polymerase Chain Reaction

SARS Cov 2: Severe Acute Respiratory Syndrome Coronavirus 2

SLICC: Systemic Lupus International Collaborating Clinics

TNF: Tumor Necrosis Factor

## Declarations

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval has been obtained from the medical ethics committee of CHU UCL Namur.

### CONSENT FOR PUBLICATION

Not applicable.

### AVAILABILITY FOR DATA AND MATERIALS

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

### COMPETING INTERESTS

The authors declare that they have no competing interests.

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### AUTHORS' CONTRIBUTION

CB and JN participated in data collection and in literature review. CB wrote the article. DT carried out the rheumatological consultation and follow up, and reviewed articles on the subject. All authors read and approved the final manuscript

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### AUTHORS' INFORMATION

Not applicable

## References

- [1] Thong B, Olsen NJ. Systemic lupus erythematosus diagnosis and management. *Rheumatology* (Oxford). 2017;56 (suppl\_1):i3-i13. <https://doi.org/10.1093/rheumatology/kew401>
- [2] Mayo Clinic. [Internet] Rochester (USA): 2017. Lupus, symptoms and causes [Updated 2017 Oct 25; cited 202 June 28]; [about 8 screens]. Available from :

<https://www.mayoclinic.org/diseases-conditions/lupus/symptoms-causes/syc-20365789>

[3] Illescas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, Ruiz C, Costela-Ruiz VJ. Infectious processes and systemic lupus erythematosus. *Immunology*. 2019;158(3):153-160.

<https://doi.org/10.1111/imm.13103>

[4] Birra D, Benucci M, Landolfi L, et al. COVID 19: a clue from innate immunity [published online ahead of print, 2020 Jun 10]. *Immunol Res*. 2020;1-8. <https://doi.org/10.1007/s12026-020-09137-5>

[5] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20(6):363-374. <https://doi.org/10.1038/s41577-020-0311-8>

[6] Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19 [published online ahead of print, 2020 Jun 4]. *Nat Rev Rheumatol*. 2020;1-2. <https://doi.org/10.1038/s41584-020-0448-7>

[7] Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am*. 2012;59(2):345-364. <https://doi.org/10.1016/j.pcl.2012.03.007>

[8] Groot N, de Graeff N, Avcin T, et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. *Ann Rheum Dis*. 2017;76(11):1788-1796. <https://doi.org/10.1136/annrheumdis-2016-210960>

[9] Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses*. 2019;11(8):762. Published 2019 Aug 19. <https://doi.org/10.3390/v11080762>

[10] Gao ZW, Wang X, Lin F, Dong K. The correlation between SARS-CoV-2 infection and rheumatic disease. *Autoimmun Rev*. 2020;19(7):102557. <https://doi.org/10.1016/j.autrev.2020.102557>

[11] Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. *J Clin Virol*. 2020;128:104395.

<https://doi.org/10.1016/j.jcv.2020.104395>

[12] Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope*. 2020;130(7):1787. <https://doi.org/10.1002/lary.28692>

[13] Mak PQ, Chung KS, Wong JS, Shek CC, Kwan MY. Anosmia and Ageusia: Not an Uncommon Presentation of COVID-19 Infection in Children and Adolescents. *Pediatr Infect Dis J*. 2020;39(8):e199-e200. <https://doi.org/10.1097/INF.0000000000002718>

[14] Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study [published online ahead of print, 2020 Jun 25]. *Lancet Child Adolesc Health*. 2020;S2352-4642(20)30177-2. doi:10.1016/S2352-4642(20)30177-2

[15] Askanase AD, Khalili L, Buyon JP. Thoughts on COVID-19 and autoimmune diseases. *Lupus Sci Med.* 2020;7(1):e000396. Published 2020 Apr 3. <https://doi.org/10.1136/lupus-2020-000396>