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## The consequences of COVID-19 pandemic on patients with monoclonal gammopathy–associated systemic capillary leak syndrome (Clarkson disease)

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### ► To cite this version:

Marc Pineton de Chambrun, Quentin Moyon, Stanislas Faguer, Geoffrey Urbanski, Alexis Mathian, et al.. The consequences of COVID-19 pandemic on patients with monoclonal gammopathy–associated systemic capillary leak syndrome (Clarkson disease). *Journal of Allergy and Clinical Immunology: In Practice*, 2022, 10 (2), pp.626-629. 10.1016/j.jaip.2021.11.023 . hal-04399103

**HAL Id: hal-04399103**

**<https://hal.science/hal-04399103v1>**

Submitted on 22 Jul 2024

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1 **TITLE:** The Consequences Of COVID-19 Pandemic On Patients With Monoclonal Gammopathy  
2 Associated Systemic Capillary-Leak Syndrome (Clarkson's disease)

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4 **RUNNING TITLE:** Consequences Of COVID-19 Pandemic In Clarkson's disease

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1 **Word count:** 979/1000

2 **Table count:** 2

3 **References:** 7

4

5 **Key words:** systemic capillary-leak syndrome; COVID-19; Clarkson’s disease; vaccination

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7 **Competing interest:** all authors certify they have no conflict of interest to disclose

8

9 **Funding:** none

10

11 **Acknowledgment:** none

12

13 **Patients and Public involvement in the research:** none

14

15 **Clinical Implications box:** SARS-CoV-2 infection and COVID-19 vaccination can trigger severe relapse  
16 of systemic capillary-leak syndrome (SCLS, Clarkson’s disease).

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1           The systemic capillary-leak syndrome (SCLS), also known as Clarkson’s disease, is a rare  
2 condition characterized by recurrent life-threatening episodes of capillary hyperpermeability in the  
3 presence of a monoclonal gammopathy. Viral infections, especially influenza virus, are known to  
4 reveal the disease and to elicit its recurrence<sup>1-3</sup>. Patients are asymptomatic between episodes.  
5 Monoclonal gammopathy of undetermined significance occurs in 3.2% of persons 50 years of age or  
6 older and in 5.3% of those 70 years of age or older<sup>4</sup>. However, the incidence and prevalence of  
7 Clarkson’s disease in this population is unknown, certainly very low<sup>1</sup>. The prevention of severe  
8 episodes rely on chronic perfusion of high-dose intravenous immunoglobulins (IVIg)<sup>5</sup>. Aside IVIg and a  
9 modest effect of terbutaline, no other treatment have shown to prevent recurrence. Moreover,  
10 despite some promising drugs, none have been proven effective in reducing capillary-leak during  
11 severe episodes. Several pathophysiological pathways, such as phosphodiesterase inhibition, are  
12 candidate for the treatment of severe episodes.

13           The coronavirus disease 2019 (COVID-19) and its preventive vaccines have been recently  
14 reported to trigger Clarkson’s disease first episodes and relapses<sup>6,7</sup>. We aimed to describe the  
15 outcome of European patients with Clarkson’s disease from the EurêClark Registry during the COVID-  
16 19 pandemic. All patients with a diagnosis of monoclonal gammopathy-associated SCLS included in  
17 the EurêClark Registry and alive at the start of COVID-19 pandemic (February 1<sup>st</sup> 2020), were included  
18 and evaluated until July 10<sup>th</sup> 2021 (**Table 1**). Thirty patients were included, with a female-to-male  
19 ratio 1.3 and a mean±SD age 58±14 years. Every patient had an IgG gammopathy with kappa (n=24)  
20 or lambda light chain (n=7). Most patients were under long-term treatment with intravenous  
21 immunoglobulins (n=27, 90%). Five patients (17%) experienced a relapse related to a proven (n=3) or  
22 highly probable (see Table 1 footnotes) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-  
23 2) infection, with a fatal outcome in 4 patients. None had evidence of COVID-19 pneumonia and all  
24 experienced typical flare of Clarkson’s disease with severe hypovolemic shock and refractory multiple  
25 organ failure. Twenty patients underwent COVID-19 vaccination with: BNT162b2 (Pfizer-BioNTech)  
26 n=17; Ad26.COV2.S (Janssen) n=1; and mRNA-1273 (Moderna) n=2. Vaccination was uneventful in 18

1 patients, including two not receiving IVIg. Two patients treated with IVIg had a relapse after a second  
2 dose mRNA vaccine, with favorable outcome in both cases. During the time of the study, 5 patients  
3 had a new diagnosis Clarkson's disease and were reported to the EurêClark Registry (**Table 2**). All  
4 required intensive care unit management, and one died during this opening episode. Four had their  
5 first flare triggered by a PCR-confirmed COVID-19 infection. The last patient, previously known to  
6 have a monoclonal gammopathy, had a typical opening flare of SCLS 3 days after the first injection of  
7 ChAdOx1 (AstraZeneca).

8           Our results highlight the burden of COVID-19 pandemic for patients with Clarkson's disease.  
9 They face the threat of both the infection and its preventive vaccine. Moreover, IVIg seems to  
10 protect them imperfectly against these foes. Several lessons can be drawn from our results jointly  
11 with previous reports. First, COVID-19 infection seems to induce very frequently a relapse of  
12 Clarkson's. Every patient from our cohort with a proven or suspected SARS-CoV-2 infection had a  
13 severe flare, fatal in 80% of cases. To the best of our knowledge and in the published literature, there  
14 are no report of uneventful SARS-CoV-2 infection in these patients. As previously reported, viral  
15 infection frequently elicit relapse in Clarkson's disease patients. However, vascular leakage seems to  
16 play a major role in COVID-19 pathophysiology and may explain the high relapse risk during SARS-  
17 CoV-2 infection. While IVIg have been shown to prevent severe episodes<sup>8</sup> and to improve survival<sup>5</sup>,  
18 they failed to prevent the COVID-19-related relapses in 4 of our patients, including one treated at full  
19 dose (2g/kg/4 weeks). The tapered dose in the 3 others might have lowered their preventive effect.  
20 The lack of SARS-CoV-2 specific immunoglobulins in available preparations of IVIg could explain this  
21 lower efficacy<sup>6</sup>. A recent study revealed the apparition of anti-SARS-CoV-2 NP and S-RBD antibodies  
22 in IVIg preparation containing plasma collected in Italy after March 2020<sup>9</sup>. Yet, it cannot be denied  
23 that some patients from our cohort might have had asymptomatic COVID-19 during the time of the  
24 study. Second, while the incidence of Clarkson's disease is unknown, being probably very low, this  
25 pandemic has been associated with an elevated number of new diagnosis in a short period of time.  
26 This findings highlights the critical role of viral triggers in the onset of SCLS. Third, while we usually

1 recommended vaccination in our patients (especially against influenzae virus), COVID-19 vaccines  
2 have been shown to trigger Clarkson's disease episodes. All four vaccines authorised by the European  
3 Medicines Agency (EMA, BNT162b2, Ad26.COVS.2.S, mRNA-1273 and ChAdOx1) have be incriminated  
4 and not solely the ChAdOx1 (AstraZeneca) for which this adverse effect was recently pointed out by  
5 the EMA's safety committee. Conversely with cases reported by Kirk M. Druey's team<sup>7</sup>, our 2 patients  
6 relapsing after vaccination were given IVIg regularly. Furthermore, 18 patients, including 2 not  
7 receiving IVIg had no adverse event after COVID-19 vaccination.

8           This study has several strength and limitations. First, the small sample size of this series  
9 should be put in perspective with the rarity of the disease. Second, while the retrospective nature of  
10 this work is inevitably associated with selection bias, most informations originate from prospectively  
11 collected data. Third, only symptomatic episodes after vaccination were monitored but not any other  
12 vaccine adverse reactions. Last, we did not evaluate the anti-spike antibody response to confirm that  
13 vaccination participates in Clarkson's disease relapse prevention. In conclusion, COVID-19 pandemic  
14 has serious consequences in SCLS patients. SARS-CoV-2 infection is associated with a high risk of  
15 relapse and all COVID-19 vaccines can trigger episodes. High-dose IVIg remains the only effective  
16 preventive treatment and should not be stopped during the pandemic. In our opinion, the  
17 benefit/risk ratio favors COVID-19 vaccination in our patients under IVIg, but further data is needed  
18 to determine its safest modalities.

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**Table 1. Consequences and outcome of patients with known Clarkson's disease during the COVID-19 pandemic (2020-2021)**

| Patients | Sex | Age | Diagnosis | Monoclonal<br>Gammopathy | IVIg | Date | Dose        | Covid-19              | Covid-19<br>vaccine | Flare | Interval <sup>1</sup> | ICU <sup>2</sup> | Outcome |
|----------|-----|-----|-----------|--------------------------|------|------|-------------|-----------------------|---------------------|-------|-----------------------|------------------|---------|
| 1        | F   | 45  | 2013      | IgG K                    | 1    | 2013 | 0.5g/kg/4w  | PCR +                 | -                   | Yes   | Concomitant           | Yes              | Dead    |
| 2        | M   | 62  | 2015      | IgG K                    | 1    | 2015 | 2g/kg/4w    | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 3        | M   | 53  | 2010      | IgG K                    | 1    | 2011 | 0.5g/kg/4w  | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 4        | F   | 81  | 2012      | IgG K & L                | 1    | 2012 | 0.5g/kg/12w | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 5        | M   | 76  | 2004      | IgG K                    | 1    | 2021 | 1g/kg/4w    | -                     | -                   | No    | -                     | -                | Alive   |
| 6        | M   | 75  | 2007      | IgG L                    | 1    | 2009 | 0.5g/kg/16w | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 7        | M   | 56  | 2010      | IgG K                    | 1    | 2010 | 1g/kg/4w    | PCR +                 | -                   | Yes   | Concomitant           | Yes              | Alive   |
| 8        | F   | 54  | 2008      | IgG L                    | 1    | 2008 | 0.5g/kg/6w  | Probable <sup>3</sup> | -                   | Yes   | Concomitant           | Yes              | Dead    |
| 9        | M   | 61  | 2011      | IgG K                    | 1    | 2012 | 0.7g/kg/6w  | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 10       | M   | 67  | 2003      | IgG K                    | 1    | 2005 | 2g/kg/4w    | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 11       | F   | 81  | 2013      | IgG K                    | 1    | 2014 | 0.5g/kg/6w  | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 12       | F   | 80  | 2013      | IgG K                    | 1    | 2014 | 1g/kg/4w    | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 13       | F   | 59  | 2009      | IgG K                    | 0    | -    | -           | -                     | BNT162b2            | No    | -                     | -                | Alive   |
| 14       | F   | 62  | 2002      | IgG K                    | 1    | 2007 | 1g/kg/8w    | -                     | mRNA-1273           | No    | -                     | -                | Alive   |
| 15       | F   | 73  | 2011      | IgG L                    | 1    | 2011 | 2g/kg/6w    | -                     | BNT162b2            | No    | -                     | -                | Alive   |

|    |   |    |      |       |   |      |            |                       |             |     |                               |     |       |
|----|---|----|------|-------|---|------|------------|-----------------------|-------------|-----|-------------------------------|-----|-------|
| 16 | M | 73 | 2015 | IgG L | 1 | 2015 | 0.5g/kg/8w | -                     | Ad26.COVS.S | No  | -                             | -   | Alive |
| 17 | M | 51 | 2008 | IgG K | 1 | 2008 | 1g/kg/4w   | -                     | -           | No  | -                             | -   | Alive |
| 18 | F | 68 | 2016 | IgG L | 1 | 2016 | 0.5g/kg/4w | -                     | -           | No  | -                             | -   | Alive |
| 19 | F | 59 | 2008 | IgG K | 1 | 2008 | 0.5g/kg/4w | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 20 | M | 59 | 2012 | IgG K | 1 | 2012 | 2g/kg/4w   | PCR +                 | -           | Yes | Concomitant                   | Yes | Dead  |
| 21 | F | 40 | 2017 | IgG K | 1 | 2018 | 1g/kg/4w   | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 22 | F | 46 | 2016 | IgG K | 1 | 2019 | 0.5g/kg/4w | -                     | BNT162b2    | Yes | 2d after 2 <sup>nd</sup> dose | No  | Alive |
| 23 | F | 52 | 2018 | IgG K | 0 | -    | -          | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 24 | F | 61 | 2003 | IgG K | 0 | -    | -          | Probable <sup>3</sup> | -           | Yes | Concomitant                   | Yes | Dead  |
| 25 | M | 43 | 2021 | IgG L | 1 | 2021 | 2g/kg/4w   | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 26 | M | 45 | 2020 | IgG K | 1 | 2021 | 2g/kg/4w   | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 27 | M | 60 | 2019 | IgG K | 1 | 2019 | 1g/kg/3w   | -                     | BNT162b2    | No  | -                             | -   | Alive |
| 28 | F | 27 | 2021 | IgG K | 1 | 2021 | 2g/kg/4w   | -                     | -           | No  | -                             | -   | Alive |
| 29 | F | 37 | 2016 | IgG K | 1 | 2016 | 1g/kg/4w   | -                     | mRNA-1273   | Yes | 3d after 2 <sup>nd</sup> dose | Yes | Alive |
| 30 | F | 43 | 2011 | IgG K | 1 | 2011 | 1g/kg/6w   | -                     | -           | No  | -                             | -   | Alive |

EurêClark Registry was approved by local review boards and by the Commission Nationale de l'Informatique et des Libertés n°1001704; no AP-HP 14 in 1997.

Abbreviation: COVID-19, the coronavirus disease 2019; M, male; F, female; IgG, G immunoglobulin; K, kappa light chain; L, lambda light chain; g/kg/w, gram per kilogram of body weight delivered every x weeks; PCR, polymerase-chain reaction; d, days; ICU, intensive care unit.

<sup>1</sup>Interval between COVID-19 infection or COVID-19 vaccination and Clarkson's disease flare.

<sup>2</sup>Admission to the ICU.

<sup>3</sup>Two patients died during severe flare of Clarkson's disease complicated by refractory cardiac arrest probably related to an undiagnosed COVID-19 infection. Both had fever and viral symptoms upon emergency department admission which happened respectively during the epidemic peak of the first wave in France (March 23, 2020) and of the third wave in Italy (March 5, 2021). As cardiac arrest occurred very early in both patients, deep airway COVID-19 PCR could not be taken.

**Table 2. New diagnosis of Clarkson’s disease during the COVID-19 pandemic (2020-2021)**

| Patients | Sex | Age, years | Monoclonal Gammopathy | Covid-19 | Covid-19 vaccine | Flare | Interval <sup>1</sup>         | ICU <sup>2</sup> | Hb <sup>3</sup> , g/dL | MV  | RRT | Compartment syndrome | Outcome |
|----------|-----|------------|-----------------------|----------|------------------|-------|-------------------------------|------------------|------------------------|-----|-----|----------------------|---------|
| A        | M   | 44         | ? <sup>4</sup>        | PCR +    | -                | Yes   | Concomitant                   | Yes              | 23                     | Yes | Yes | 4 limbs              | Alive   |
| B        | F   | 47         | ? <sup>5</sup>        | PCR +    | -                | Yes   | Concomitant                   | Yes              | 19                     | Yes | Yes | No                   | Dead    |
| C        | M   | 56         | IgG K                 | -        | ChAdOx1          | Yes   | 3d after 1 <sup>st</sup> dose | Yes              | 23                     | No  | No  | No                   | Alive   |
| D        | M   | 35         | IgG L                 | PCR +    | -                | Yes   | Concomitant                   | Yes              | 25                     | Yes | Yes | 4 limbs              | Alive   |
| E        | M   | 38         | IgG K                 | PCR +    | -                | Yes   | Concomitant                   | Yes              | 26                     | Yes | No  | Lower limbs          | Alive   |

Abbreviation: COVID-19, the coronavirus disease 2019; M, male; F, female; IgG, G immunoglobulin; K, kappa light chain; L, lambda light chain; PCR, polymerase-chain reaction; d, days; ICU, intensive care unit ; Hb, hemoglobin; MV, mechanical ventilation ; RRT, renal replacement therapy.

<sup>1</sup>Interval between COVID-19 infection or COVID-19 vaccination and Clarkson’s disease flare

<sup>2</sup>Admission to the ICU

<sup>3</sup>Hemoglobin highest value during the episode

<sup>4</sup>Monoclonal gammopathy could not be found during the acute episode and will be tested few weeks/month after the flare

<sup>5</sup>Monoclonal gammopathy could not be found during the acute episode and the patient died