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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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Clinical Implications

Severe acute respiratory syndrome coronavirus 2 infection and coronavirus disease 2019 vaccination can trigger severe relapse of systemic capillary leak syndrome (Clarkson disease).

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

The coronavirus disease 2019 (COVID-19) and its preventive vaccines have been recently reported to trigger first episodes and relapses of Clarkson disease.[6,7] We aimed to describe the outcome of European patients with Clarkson disease from the EurêClark registry during the COVID-19 pandemic. All patients with a diagnosis of monoclonal gammopathy–associated SCLS included in the EurêClark registry and alive at the start of COVID-19 pandemic (February 1, 2020) were included and evaluated until July 10, 2021 (Table I). Thirty patients were included, with a female-to-male ratio of 1.3 and a mean ± standard deviation age of 58 ± 14 years. Every patient had an IgG gammopathy with kappa (n = 24) or lambda light chain (n = 7). Most patients were under long-term treatment with IVIg (n = 27, 90%). Five patients (17%) experienced a relapse related to a proven (n = 3) or highly probable (see footnotes in Table I) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a fatal outcome in 4 patients. None had evidence of COVID-19 pneumonia, and all experienced typical flare of Clarkson's disease with severe hypovolemic shock and refractory multiple-organ failure. Twenty patients underwent COVID-19 vaccination with BNT162b2 (Pfizer-BioNTech, Pfizer Inc, New York City, NY), n = 17; Ad26.COV2.S (Janssen Pharmaceuticals, Beerse, Belgium), n = 1; and mRNA-1273 (Moderna Inc, Cambridge, MA), n = 2. Vaccination was uneventful in 18 patients, including 2 not receiving IVIg. Two patients treated with IVIg had a relapse after a second dose of mRNA vaccine, with a favorable outcome in both cases. During the time of the study, 5 patients had a new diagnosis of Clarkson disease and were reported to the EurêClark registry (Table II). All required intensive care unit management, and 1 died during this opening episode. Four had their first flare triggered by a polymerase chain reaction–confirmed COVID-19 infection. The last patient, previously known to have a monoclonal gammopathy, had a typical opening flare of SCLS 3 days after the first injection of ChAdOx1 (AstraZeneca).

Our results highlight the burden of the COVID-19 pandemic for patients with Clarkson disease. They face the threat of both the infection and its preventive vaccine. Moreover, IVIg seems to protect them imperfectly against these foes. Several lessons can be drawn from our results jointly with previous reports. First, COVID-19 infection seems to induce very frequently a relapse of Clarkson disease. Every patient from our cohort with a proven or suspected SARS-CoV-2 infection had a severe flare, fatal in 80% of cases. To the best of our knowledge and in the published literature, there is no report of uneventful SARS-CoV-2 infection in these patients. As previously reported, viral infection frequently elicits relapse in patients with Clarkson disease. However, vascular leakage seems to play a major role in COVID-19 pathophysiology and may explain the high relapse risk during SARS-CoV-2 infection. Although IVIg have been shown to prevent severe episodes[8] and to improve survival,[5] they failed to prevent the COVID-19-related relapses in 4 of our patients, including 1 treated with full dose (2 g/kg/4 weeks). The tapered dose in the 3 others might have lowered their preventive effect. The lack of SARS-CoV-2 specific immunoglobulins in available preparations of IVIg could explain this lower efficacy.[6] A recent study revealed the apparition of anti-SARS-CoV-2 nucleocapsid protein and spike protein receptor binding domain antibodies in IVIg preparation containing plasma collected in Italy after March 2020.[9] Yet, it cannot be denied that some patients from our cohort might have had asymptomatic COVID-19 during the time of the study. Second, although the incidence of Clarkson disease is unknown, being probably very low, this pandemic has been associated with an elevated number of new diagnoses in a short period of time. This finding highlights the critical role of viral triggers in the onset of SCLS. Third, although we usually recommended vaccination in our patients (especially against influenza virus), COVID-19 vaccines have been shown to trigger Clarkson disease episodes. All 4 vaccines authorized by the European Medicines Agency (EMA, BNT162b2, Ad26.COV2.S, mRNA-1273, and ChAdOx1) have been incriminated and not solely ChAdOx1 (AstraZeneca) for which this adverse effect was

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

Patients	Sex	Age	Diagnosis	Monoclonal gammopathy	IVIg	Date	Dose	COVID-19	COVID-19 vaccine	Flare	Interval*	ICU†	Outcome
1	F	45	2013	IgG K	1	2013	0.5 g/kg/4 wk	PCR +	–	Yes	Concomitant	Yes	Dead
2	M	62	2015	IgG K	1	2015	2 g/kg/4 wk	–	BNT162 b2	No	–	–	Alive
3	M	53	2010	IgG K	1	2011	0.5 g/kg/4 wk	–	BNT162 b2	No	–	–	Alive
4	F	81	2012	IgG K and L	1	2012	0.5 g/kg/12 wk	–	BNT162b2	No	–	–	Alive
5	M	76	2004	IgG K	1	2021	1 g/kg/4 wk	–	–	No	–	–	Alive
6	M	75	2007	IgG L	1	2009	0.5 g/kg/16 wk	–	BNT162b2	No	–	–	Alive
7	M	56	2010	IgG K	1	2010	1 g/kg/4 wk	PCR +	–	Yes	Concomitant	Yes	Alive
8	F	54	2008	IgG L	1	2008	0.5 g/kg/6 wk	Probable‡	–	Yes	Concomitant	Yes	Dead
9	M	61	2011	IgG K	1	2012	0.7 g/kg/6 wk	–	BNT162b2	No	–	–	Alive
10	M	67	2003	IgG K	1	2005	2 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
11	F	81	2013	IgG K	1	2014	0.5 g/kg/6 wk	–	BNT162b2	No	–	–	Alive
12	F	80	2013	IgG K	1	2014	1 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
13	F	59	2009	IgG K	0	–	–	–	BNT162b2	No	–	–	Alive
14	F	62	2002	IgG K	1	2007	1 g/kg/8 wk	–	mRNA-1273	No	–	–	Alive
15	F	73	2011	IgG L	1	2011	2 g/kg/6 wk	–	BNT162b2	No	–	–	Alive
16	M	73	2015	IgG L	1	2015	0.5 g/kg/8 wk	–	Ad26.COV2.S	No	–	–	Alive
17	M	51	2008	IgG K	1	2008	1 g/kg/4 wk	–	–	No	–	–	Alive
18	F	68	2016	IgG L	1	2016	0.5 g/kg/4 wk	–	–	No	–	–	Alive
19	F	59	2008	IgG K	1	2008	0.5 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
20	M	59	2012	IgG K	1	2012	2 g/kg/4 wk	PCR +	–	Yes	Concomitant	Yes	Dead
21	F	40	2017	IgG K	1	2018	1 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
22	F	46	2016	IgG K	1	2019	0.5 g/kg/4 wk	–	BNT162b2	Yes	2 d after second dose	No	Alive
23	F	52	2018	IgG K	0	–	–	–	BNT162b2	No	–	–	Alive
24	F	61	2003	IgG K	0	–	–	Probable‡	–	Yes	Concomitant	Yes	Dead
25	M	43	2021	IgG L	1	2021	2 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
26	M	45	2020	IgG K	1	2021	2 g/kg/4 wk	–	BNT162b2	No	–	–	Alive
27	M	60	2019	IgG K	1	2019	1 g/kg/3 wk	–	BNT162b2	No	–	–	Alive
28	F	27	2021	IgG K	1	2021	2 g/kg/4 wk	–	–	No	–	–	Alive
29	F	37	2016	IgG K	1	2016	1 g/kg/4 wk	–	mRNA-1273	Yes	3 d after second dose	Yes	Alive
30	F	43	2011	IgG K	1	2011	1 g/kg/6 wk	–	–	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.
COVID-19, Coronavirus disease 2019; *F*, female; *g/kg/wk*, gram per kilogram of body weight delivered every x weeks; *ICU*, intensive care unit; *IgG*, immunoglobulin G; *IVIg*, intravenous immunoglobulins; *K*, kappa light chain; *L*, lambda light chain; *M*, male; *PCR*, polymerase chain reaction.
*Interval between COVID-19 infection or COVID-19 vaccination and Clarkson's disease flare.
†Admission to the ICU.
‡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 on emergency department admission that 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 II. New diagnosis of Clarkson's disease during the COVID-19 pandemic (2020-2021)

Patients	Sex	Age (y)	Monoclonal gammopathy	COVID-19	COVID-19 vaccine	Flare	Interval*	ICU†	Hb‡ (g/dL)	MV	RRT	Compartment syndrome	Outcome
A	M	44	?§	PCR +	–	Yes	Concomitant	Yes	23	Yes	Yes	4 limbs	Alive
B	F	47	?‖	PCR +	–	Yes	Concomitant	Yes	19	Yes	Yes	No	Dead
C	M	56	IgG K	–	ChAdOx1	Yes	3 d after first 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

COVID-19, Coronavirus disease 2019; *F*, female; *Hb*, hemoglobin; *ICU*, intensive care unit; *IgG*, immunoglobulin G; *K*, kappa light chain; *L*, lambda light chain; *M*, male; *MV*, mechanical ventilation; *PCR*, polymerase chain reaction; *RRT*, renal replacement therapy.
*Interval between COVID-19 infection or COVID-19 vaccination and Clarkson's disease flare.
†Admission to the ICU.
‡Hemoglobin highest value during the episode.
§Monoclonal gammopathy could not be found during the acute episode and will be tested few weeks/month after the flare.
‖Monoclonal gammopathy could not be found during the acute episode and the patient died.

recently pointed out by the EMA's safety committee. Conversely, with cases reported by Druey et al,[7] our 2 patients relapsing after vaccination were given IVIg regularly. Furthermore, 18 patients, including 2 not receiving IVIg, had no adverse event after COVID-19 vaccination.

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

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