Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Short Communication

COVID-19 in a Hemorrhagic Neurovascular Disease, Cerebral Cavernous Malformation

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Background and hypotheses

Novel coronavirus disease 2019 (COVID-19) has caused confirmed infections in more than 30 million Americans by April 2021, and 130 million worldwide, with a case fatality rate of up to 2-10% (https://ourworldindata.org/coronavirus/). It can cause ischemic and hemorrhagic strokes secondary to coagulopathy and endothelial injury.[1] These same factors play a role in Cerebral Cavernous Malformation (CCM), an uncommon hemorrhagic neurovascular disease characterized by grossly dilated vascular "caverns" lined by a single layer of dysfunctional endothelium.[2] We sought hypothesis-generating observations whether CCM patients contracting COVID-19 have a more severe illness, including a potentially higher risk of hemorrhagic events.

Patients and methods

A self-reporting CCM-COVID-19 registry was launched in March 2020 via the Angioma Alliance CCM patient advocacy group (www.angioma.org). An initial announcement was sent to approximately 2,000 CCM patients registered with the Angioma Alliance, and the registry was featured on the Alliance homepage website, as a pinned announcement in its Facebook group (5,500 members), and in newsletter mailed to 800 homes and emailed to 4,000 recipients. The registry was further featured in three webinars in August 2020 (850 views), October 20 (350 views) and February 2021 (671 views). Patients 18 years or older were sought, with at least one non-resected CCM brain lesion, who had a positive laboratory diagnosis of COVID-19. Ninety-one CCM patients registered personally or through a designated healthcare surrogate between March 25, 2020 and April 5, 2021. Per University of Chicago Medicine Investigational Review Board approved protocol (#20-0619), the 91 registered patients were contacted approximately 1 month after their declared COVID-19 diagnosis for screening and consent. Thirty were not reachable, 9 had no confirmed COVID-19 infection, and the remaining 52 subjects were enrolled with data related to their demographics, CCM disease features and COVID-19 illness collected.

Course of COVID-19 illness

Forty-one U.S. and 11 international CCM patients (39 females, 13 males) were enrolled, 21-72 years of age (average 44.5 years). Twenty had sporadic-CCM with solitary lesion, 22 had familial-CCM with multiple lesions, and 6 an unknown genotype. Twenty-one subjects had brainstem lesions, and 9 patients had suffered a symptomatic

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CCM hemorrhage within the year prior to COVID-19 infection.

Two of the 52 patients (3.8%) were hospitalized within 1 month of COVID-19 diagnosis, one for severe pneumonia and one for a brain hemorrhage (see below). Another patient (1.9%) died of unknown cause and COVID-19 was detected post-mortem. In order to mitigate potential under-reporting of severely ill cases and deaths, a follow-up survey was sent on March 22, 2021 to the same recipients of the initial announcements, inquiring if anyone knew through their social contacts of any CCM patients that had been hospitalized or died from COVID-19. We received 1,893 responses identifying no additional cases of hospitalization and 3 deaths among previously unregistered cases (one from severe pre-existing condition, one with unknown cause of death at a skilled nursing facility, and one anonymous).

Of the 51 survivors in the registry, 3 (5.8%) reported an exacerbation or pre-existing CCM related symptoms (1 new seizures, 2 worsening of pre-existing headaches and blurred vision). Twenty-two (43%) reported new headaches, unclear if attributable to CCM or COVID-19. One month after the illness, 29 survivors (56%) reported persistent symptoms not present before the illness (mostly headaches and loss of smell or taste). Nine of of the 52 registrants (17.3%, including the one death) had a self-reported worsened functional state with an increase of modified Rankin scale by 1 point or more.

CCM hemorrhage during COVID-19 illness

Five of the 52 (9.6%) registry subjects reported a new CCM hemorrhage as communicated to them by their physician within 30 days of COVID-19 diagnosis. These included 3 cases among 12 who all reported in the CCM COVID-19 registry and were evaluated by senior author IAA at the University of Chicago CCM Center of Excellence (www.uchicagomedicine.org/ccm), with full access to their imaging and healthcare information. All three new CCM bleeds with verified healthcare information harbored sporadic/solitary lesions with an associated developmental venous anomaly (DVA),[3] and an acute hemorrhage signal in the CCM lesion on magnetic resonance imaging (MRI) of the brain. Two had new neurologic symptoms while 1 case had exacerbation of prior headaches (Fig. 1).

Because of the potential reporting bias and lack of adjudication of new hemorrhage in the CCM COVID-19 registry outside the Chicago center, the 25% rate (3 of 12) within one month of COVID-19 diagnosis among Chicago center registrants was compared to 30 prospectively logged bleeds among 110 patients followed during the same 12 months period at the same center without diagnosed COVID-19 illness (2.3% rate of new adjudicated bleeds per month in the absence of COVID-19, Chi square $p<0.001$).

The mechanism of this apparent increased incidence of hemorrhage among the CCM patients who contracted COVID-19 remains speculative. Remarkably, there were

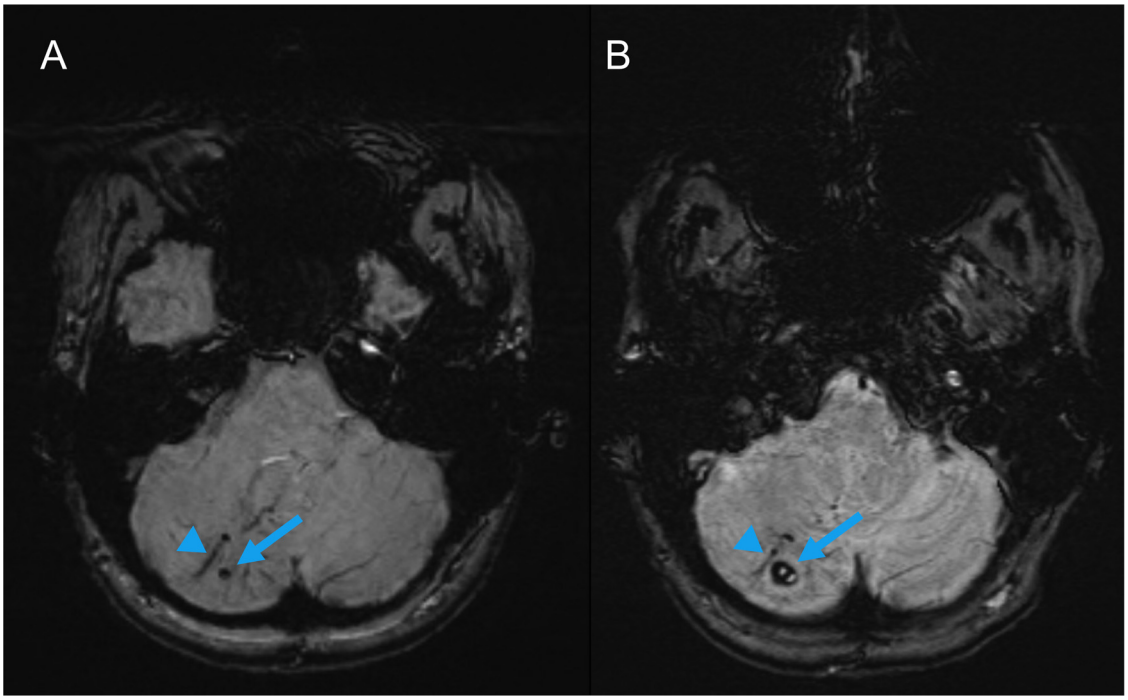

Fig. 1. *Susceptibility weighted MRI showing sporadic cerebral cavernous malformation (CCM) lesion with associated developmental venous anomaly (DVA). (**A**) Prior to COVID-19, CCM lesion (blue arrow) with associated DVA (blue arrowhead). (**B**) One month post COVID-19 diagnosis, CCM lesion (blue arrow) with signs of acute hemorrhage and peri-lesional edema.*

no new bleeds in familial cases without associated DVA in this cohort, despite their multiple lesions, nor specifically among brainstem lesions or CCM lesions that had bled in the year prior to COVID-19. This is different from the natural history of the disease where there is no greater hemorrhage risk in CCM lesions specifically associated with DVA.[4] Possible thrombosis due to hypercoagulability observed in COVID-19 could obstruct a venous branch outflow in associated DVA and destabilize the cavernoma, causing hemorrhage. This hypothesis is supported by a recent study showing decreased hemorrhagic presentation among CCM patients taking aspirin.[5] Our team has also linked CCM bleeding to lesional perfusion skewness and entropy as measured by dynamic contrast enhanced quantitative perfusion on magnetic resonance imaging.[6] We cannot comment about the presence or absence of virus in CCM lesion endothelium, as none of the hemorrhaged lesions required surgery or led to postmortem study during the acute phase of the illness.

Limitations

The voluntary reporting methodology and potential reporting and detection biases seriously limit our conclusions. Patients with persistent or new symptoms were potentially more likely to self-report. However, none of the cases with new adjudicated CCM bleeds had been referred to the Chicago center team after hemorrhage diagnosis, essentially excluding referral bias in the main finding of our study regarding a potential greater incidence of new CCM bleeds.

Conclusions

Measuring the impact of a pandemic on a rare disease can be difficult and late to recognize. Although the sample size is limited, the results herein are the first systematic analysis of disease association in a representative CCM cohort. There was no signal of more severe COVID-19 illness in CCM patients, nor greater mortality than that observed in the general population. Many of the associated symptoms and their persistence after one month of COVID-19 diagnosis could be attributed to viral illness alone, and not specifically to the association with CCM. An apparent higher incidence of new CCM bleed within a month of COVID-19 diagnosis was documented in patients with solitary lesions and associated DVAs. This is considered hypothesis generating. Independent reports and more robust studies are needed to validate these observations and motivate mechanistic explanations and improved therapies in this setting.

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Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

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