

## In Reply: Dismantling the Apocalypse Narrative: The Myth of the COVID-19 Stroke

To the Editor:

We read “Letter: Dismantling the Apocalypse Narrative: The Myth of the COVID-19 Stroke”<sup>1</sup> with surprise and disappointment. The letter has major fallacies, misinterpretations, and attributing conclusions not implied by us.<sup>2</sup> With the prolific and growing literature on COVID-19 and stroke,<sup>2-29</sup> it is clearly not a myth. We advise the authors to reconsider this fundamental feature of the current pandemic, and we strongly recommend them to get themselves familiar with the cited manuscripts that describe the pathophysiology of cerebrovascular events in COVID-19 patients.<sup>3-14,30-40</sup> It is a moral imperative in a pandemic for clinicians to raise awareness about associations even when proof of causation is pending.

The authors<sup>1</sup> repeatedly made subjective false claims characterizing our honest observations as scientifically unfounded, and then themselves add their subjective baseless opinion “*that this information exacerbates anxiety among the youth.*”<sup>1</sup>

It is never one’s intent to raise public fear. Instead, it is to promptly increase awareness among the public and healthcare community, mainly that COVID-19 is a new virus, and we do not have a full grasp on its manifestations yet. The disease has been devastating, leading to more than 32 million cases and close to one million casualties. Our responsibility is to promptly report any noteworthy trends and be vocal in the media to reach the most massive audience to spread awareness.

Neurointerventionalists from cities hit hard by the pandemic and working in comprehensive stroke centers were able to identify unusual trends that prompted further investigations, an observation that the senior author R. Rahme may not have experienced at his primary stroke center (SBH health system). Based on the data presented in their table, it seems that they are a low volume primary stroke center suggested by the sole case of LVO during March-April 2018 and 2019. Philadelphia was not hit as hard as New York. However, in early April, we encountered many cases of COVID-19 positive patients that required mechanical thrombectomies in addition to sinus thrombosis. We published numerous papers on our experience,<sup>2,25-29, 41-45</sup> and we implemented a joint effort collaboration with other institutions in the U.S. and outside to better understand this phenomenon.

Only a fraction of patients acquiring COVID-19 are at risk of stroke (1%-6%).<sup>17,46,47</sup> As such, other institutions, that have not experienced a peak in COVID-19 cases, may miss such a trend. Therefore, during a pandemic, it is the duty of healthcare providers practicing in busy centers to raise awareness if they notice anything unusual. Such efforts may push the population to take the disease seriously and follow the guidelines to decrease their risk of getting the disease and its complications. In addition, reporting of such observations allows other healthcare practi-

tioners to evaluate this phenomenon in their patient populations. Given the narrow time window of stroke intervention and outcomes being related to early intervention, it is vital to overemphasize stroke symptoms within the community to allow patients to gain from the current therapies.

To help pinpoint and clarify the inaccuracies as presented by the authors,<sup>1</sup> we provide the following responses to the statements made in their letter:

1- *“In fact, during the pandemic, stroke centers, including ours (Table), have experienced significant reductions, rather than increases in the rates of strokes, large vessel occlusions (LVOs), and thrombectomies.”*

We, and other centers, have experienced a similar phenomenon,<sup>25</sup> except for the decrease in thrombectomies for large vessel occlusion. Even the data presented in table 1 showed that the numbers of LVOs quadrupled at their hospital.<sup>25,48</sup> In fact, the reduction in telestroke consults and total stroke admission started before releasing the 2 publications.<sup>2,23</sup> Patients were delaying presentation to the hospitals due to fear of the contagion. The rationale is that patients with mild and moderate symptoms might delay presentation, where some may improve, and others may worsen and either present to the hospital late or possibly pass away at home. In fact, the Fire Department of the City of New York reported an almost 4-times normal rate of patients being dead on emergency medical service arrival during the pandemic period.<sup>48</sup> The authors appear to be confusing the quarantine effect on stroke broadly (which has also been well documented) in the literature with the actual scientific pathophysiology of the disease.<sup>49,50</sup> COVID-19 is been overwhelmingly demonstrated to be pro-thrombotic and causes clots to form in a wide range of organ systems... whether fractures in systems of care, changed referral patterns, ED resource reallocation, social distancing, or self-isolation result in decreased stroke presentation to hospitals, the pro-thrombotic reality of COVID-19 is scientifically unarguable. It belies logic that such a disease would not affect stroke presentation and it is unclear to us why the authors would seek to conflate the broad societal “shut down” with scientific discussion of the disease pathophysiology.

2- *“While the authors try to make a similar claim, the vast majority of their patients (12/14) were older than 50 yr and, of the 2 patients younger than 50, 1 had cerebral venous thrombosis.”*

Can the authors point where did we claim that our population is younger than 50 yr? The result section clearly shows the average age of the 14 patients, 60.1 ± 11.1 yr. Second, the discussion mentions that 42% were 55 yr or younger. Do the authors believe that this is not worthy of sharing? There are now multiple publications from many different geographies that all demonstrate

COVID-19 positive ELVO populations are statistically younger than non-COVID-19 populations.<sup>20,21,41,48,51</sup>

3- *“Overall, the vast majority of their patients (12/14) had cardiovascular risk factors (8/14)?”*

Does the author mean 12/14 or 8/14 had no cardiovascular risk factors? We mentioned that 42% (8/14) had no traditional risk factors in the result section and discussion. We do not understand what the authors are implying here. Furthermore, statistically significant differences in traditional stroke risk factors have been well demonstrated between COVID-19 ELVO patients and non-COVID-19 ELVO patients.<sup>48</sup>

4- *“While 50% (7/14) had pneumonia and/or adult respiratory distress syndrome, suggesting severe COVID-19.”*

This is incorrect and demonstrates that the authors misunderstood our letter. The data presented represents patients without regard for nonspecific terminology, such as severe or mild. In fact, the publications simply point out that COVID-19 puts patients at risk of stroke. Additionally, our data alerts people to the fact that stroke can be the presenting symptom of a COVID-19 infection. The authors should be aware that SARS-CoV-2 positivity has since been demonstrated to be an independent risk factor for imaging confirmed stroke and for ELVO in specific.<sup>52,53</sup>

5- *“Most importantly, there was no mention whatsoever of any etiologic stroke workup in those patients.”*

Those patients were admitted to a comprehensive stroke center and underwent standard complete stroke workups. By stating that some of the patients did not have any risk factors for stroke, we clearly had to have performed an etiologic stroke workup which did not show any other etiology. Otherwise, we couldn't claim that there were no risk factors for stroke.

6- *“Therefore, the suggestion of a causal relationship between COVID-19 and stroke remains unfounded.”*

It may be beneficial for the authors to read the conclusion one more time; **“Unusual trends have been seen in AIS patients who are COVID-19 positive; while it is too early to establish direct causality, our preliminary data can be used to raise awareness in the population. We are seeing younger patients with no risk factors presenting with AIS and MT procedures are more challenging to deal with. It is crucial in pandemic times to watch and follow closely noteworthy trends and investigate and report new findings.”**

Currently, there is more than anecdotal evidence linking COVID-19 to stroke. The incidence of stroke in COVID-19 hospitalized patients ranges from 0.9%-2%,<sup>17,46,47</sup> increasing to 5.7% in severe disease.<sup>17</sup> COVID-19 has been reported to be an independent predictor of stroke (OR, 3.9; 95% CI, 1.7-8.9; P0.001),<sup>52</sup> and compared to influenza; it has a 7.5-fold higher rate of ischemic stroke.<sup>47</sup> Moreover, a study by Yaghi et al<sup>51</sup>

reported a 65.6% incidence of cryptogenic stroke in COVID-19 patients compared to contemporary (30.4%) and historical controls (25.0%). Histological analysis of lung tissue in patients with Covid-19 showed a distinctive severe endothelial injury characterized by widespread thrombosis and microangiopathy. Compared to influenza, COVID-19 patients were nine times more likely to have alveolar microthrombi.<sup>54</sup> Several recent publications reported a similar experience to Oxley et al<sup>23</sup> in terms of stroke occurrence in the young.<sup>2,21-26</sup> Two extensive multicenter studies reviewing large vessel occlusion in COVID-19 under review have observed that among a group of patients undergoing a mechanical thrombectomy, 19% were under 50 yr, and 34% under 55 (12 centers from the USA and Europe). Moreover, a recent comparative analysis depicting the experience from New York corroborated such early findings.<sup>48</sup>

Finally, we appreciate the dialogue as this is necessary for advancement of science and better care for our patient populations but we stand by the integrity, value and importance of the data we shared. We believe that raising awareness about an association between the COVID-19 pandemic and stroke is not only beneficial for the population and practitioners but it is a moral imperative. We respectfully disagree with Dr Rahme and coauthors<sup>1</sup> and invite them to be more precise and scientific in their criticism and to join us in raising awareness about the association of stroke and COVID-19.


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