Dear Sirs,

Increasing evidence supports the association between the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of the coronavirus disease 2019 (COVID-19), and neurological complications, including encephalopathy, encephalitis, Guillain–Barré syndrome, and cerebrovascular disease [1, 2]. In particular, both ischemic and hemorrhagic strokes have been linked to COVID-19 [3–5]. Since a substantial proportion of these reported patients had associated vascular risk factors, it is crucial to determine whether this association is causal or coincidental [1, 3, 6]. In an effort to systematically assess this issue, Shtaya et al. proposed to classify cases of COVID-19-related stroke in three major groups: (1) hospital acquired; (2) community acquired; (3) stroke as direct complications of COVID-19 [7]. Most of the cases of our report [3] and other series [4, 5] fulfill the criteria for the latter group as defined by the authors. Conversely, we did not encounter hospital-acquired COVID-19 infections in patients hospitalized for stroke, since protective measures were readily implemented in our institutions. Although we believe that this proposed classification is valuable in highlighting a relevant clinical problem, these definitions are based on both epidemiological data (location of infection, as for pneumonia, difficult to ascertain in real-life settings) and pathogenetic aspects (as in group 3, for which few information is available at the moment), making their use impractical. Moreover, we believe that it is possible that some patients can fit two of the proposed categories (e.g., patients with community-acquired COVID-19 can develop stroke as direct complication of SARS-CoV-2). Ellul et al. suggested an alternative classification, subdividing cases with “probable” (SARS-CoV-2 identified, lack of vascular risk factors) and “possible” (when vascular risk factors are present) association [1]. We suggest some adaptations of the latter case definition as emerging data have shown distinct stroke patterns in COVID-19 infection [3–5, 8]. These features (clinical, laboratory, and pathological characteristics, shown in the Table 1) can provide supporting evidence in favor of a link in doubtful cases.

We propose a revised definition of CAS, with three degrees of certainty (possible, probable, and confirmed, as illustrated in the Table 1). Even if the World Health Organization (WHO) has provided definition for suspected, probable, and confirmed COVID-19 cases, we believe that only patients with laboratory-confirmed SARS-CoV-2 should enter in the classification, in addition to clinic-radiological evidence of acute stroke (ischemic...
or hemorrhagic). These two represent the major criteria of this revised definition. Minor criteria were designed to capture additional evidence of a causal and biologically plausible association: (1) onset of stroke few days to 3 weeks after COVID-19 symptoms [3–5], (2) lack of cardiovascular risk factors [1, 8], (3) D-dimer and/or LDH elevation [3–5]. The presence of at least one of these features is required for “possible CAS”, and two for “probable CAS”, while confirmed CAS requires pathological evidence of disappearance of endothelial cells in the affected arterioles, capillaries and venules. These findings reflect the pathogenesis of CAS, which involves a thrombotic microangiopathy caused by endotheliopathy [4, 9]. Some additional features, such as the detection of SARS-CoV-2 in the cerebrospinal fluid (CSF), can possibly provide additional evidence of a causal association, although cases with negative CSF have been described [10]. Therefore, we do not believe that this represents a necessary feature.

It is important to notice that the absence of the typical clinical patterns of CAS should question the diagnosis. Typical clinical features of COVID-19-related stroke include large vessel occlusion, multi-territory involvement, and posterior circulation predisposition (Fig. 1a–g) [3–5, 8]. In addition, less frequent presentations were also observed: onset with seizures and/or encephalopathy [3, 4], extra-cranial dissection [4, 11, 12], including bilateral carotid artery dissection [12] (Fig. 1h–j), and posterior reversible encephalopathy (PRES) [4] or laminar cortical damage [13].

Interestingly, if we retrospectively apply the CAS criteria to the 12 patients with community-acquired COVID-19 reported by Shtaya et al. [7], 3 of their cases do not fulfill the major criteria (neuroimaging not performed). Among the other nine patients, stroke developed few days to 3 weeks later in all cases (criteria for possible CAS fulfilled) and in two, there were no known vascular risk factors (criteria for probable CAS fulfilled). In particular, case 12 was a previously healthy 50-year-old man who developed a posterior circulation stroke 3 days after the onset of COVID-19 symptoms in the context of vertebral artery dissection [7], consistent with our proposed definition. This example suggests that the CAS criteria can be useful in identifying stroke cases more likely to be causally linked to COVID-19, irrespective of where the infection was acquired.

Development of a standardized case definition for stroke of presumed infectious etiology related to SARS-CoV-2 is important for epidemiological surveillance, clinical research, outbreak investigations, as well as for allocation of healthcare resources. As the understanding of this novel disease is expanding rapidly, the proposed definition will likely need refining as more data emerge. Nevertheless, this proposal represents a first step into harmonization of research studies into the topic of CAS.
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Compliance with ethical standards

Conflicts of interest  None reported.

Ethical standards  All procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

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