

# The Baffling Case of Ischemic Stroke Disappearance from the Casualty Department in the COVID-19 Era

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Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rapidly spreading worldwide, and the WHO declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic on March 11, 2020 [1]. The outbreak has hit Europe and, as of March 27, 2020, Italy has the second largest number of confirmed cases, that is, a total of 86,498 cases according to the *Istituto Superiore di Sanità* and 9,134 deaths [2]. This health emergency issue has plunged the Italian health system into an unprecedented state of emergency, and many hospitals are now dedicated exclusively to COVID-19 assistance.

We work at the *Guglielmo da Saliceto Hospital* in Piacenza, a city in northern Italy near Milan. Despite being a relatively small city, Piacenza and its province (about 280,000 inhabitants) are one of the epicenters of the Italian epidemic, listing 2,276 cases at the time of writing. This health emergency has revolutionized the hospital organization, and everything has changed for practicing clinicians in just a few weeks. For example, neurologists also contribute to the management and care of COVID-19 patients or have been “converted back” to operating as emergency physicians, as numerous colleagues have been infected.

*The question is: what can we say about the remaining non-COVID-19 pathologies?*

Let us take the ischemic stroke as an example: it seems to have almost disappeared from the Casualty Department! Over the past 5 years (2015–2019), the city of Piacenza has recorded an annual average of 612 new cases of ischemic stroke, with a monthly average of 51 cases, and 21% of them are large vessel occlusion (LVO). We investigated the monthly variance of ischemic stroke using the ANOVA test. Surprisingly, between February 21, 2020 (first SARS-CoV-2 patient recorded in Italy – in Codogno, a nearby city), and March 25, 2020, there were only 6 admissions from the Casualty Department for ischemic stroke (2 transient ischemic attacks, 1 cardioembolic LVO, and 3 lacunar stroke).

*What could we hypothesize for this observation?*

On March 8, 2020, the Italian government implemented extraordinary measures to limit viral transmission, including restricting the mobility of the general population. This strict measure was aimed at minimizing the likeli-

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hood that people who were already infected came into contact with noninfected ones. Moreover, the population was asked to refer to the Casualty Department only if really necessary. It is true that the significant reduction in currently registered strokes may well be attributable to fewer people going to the Casualty Department for fear of being infected. However, this can be true only for minor, non-disabling strokes. LVO strokes are always disabling (i.e., aphasia and/or hemiplegia), and it is impossible to avoid hospitalization in such a serious condition. Moreover, the point is that there may be an underestimation of the number of stroke, as when patients arrive in a Casualty Department with fever and respiratory distress, they take priority and the neurological deficit may, therefore, be overlooked.

*We wonder why these patients have almost disappeared.*

It is known that viral infections are associated with an increased risk of stroke, as described in influenza pneumonia [3], which is exactly the opposite of what we are currently observing. Could then the seasonal pattern of stroke occurrence and/or cytokine storm described in COVID-19 patients play a role in explaining these observations? It does not seem so.

*First*, data on seasonal differences in stroke incidence are conflicting. Some studies have reported that ischemic stroke occurrence was significantly higher during spring and autumn than in summer [4, 5]. However, another study stated that there was a fairly even distribution of ischemic stroke over all 4 seasons [6] and a recent meta-analysis showed very little seasonal variation [7]. Also, our analysis of variance of the monthly number of ischemic stroke between 2015 and 2019 was *not significant*.

*Second*, in COVID-19 affected patients, high levels of thrombosis and inflammation serum markers, such as D-dimer, fibrinogen, and C-reactive protein, have been reported, as well as increased levels of inflammatory cytokines (i.e., tumor necrosis factor- $\alpha$ , interleukin [IL]-2R, and IL-6) [8]. All these laboratory findings, including the rise of IL-6, seem to be present also in patients with mild or moderate SARS-CoV-2 clinical manifestations, with no need for hospitalization [9].

*So, why do COVID-19 patients not have an increased risk of developing ischemic stroke?*

One hypothesis could be related to the controversial role IL-6 plays in stroke. Indeed, although high IL-6 levels have been reported to have a negative effect on brain infarct volume and long-term outcome [10], conversely, in

ischemic stroke, there is also experimental evidence that IL-6 has a protective effect and helps in the improvement of poststroke angiogenesis [11].

According to these observations, should a beneficial role of IL-6 in patients without other systemic complications be considered? Another interesting possible explanation is related to the presence of thrombocytopenia in COVID-19 patients, also in patients with mild symptoms [12]. Could the decreased platelet levels be involved in the reduction of LVO strokes? Furthermore, based on previous evidence, the burden of chronic persistent infections and/or past infections, rather than one single current infectious disease, seems to be associated with stroke risk [13]. Moreover, the extraordinary measures taken by the Italian government might have reduced the spread of seasonal flu and its unfavorable effect upon stroke incidence.

Indeed, what may be true for influenza pneumonia (i.e., increased stroke risk) may not be true for SARS-CoV-2. The main limit of our remark is certainly the short observation period of just 1 month. *The baffling case of ischemic stroke disappearance from the Casualty Department* has yet to be resolved.

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