Impact of COVID-19 on Stroke

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"We have now lived with the COVID-19 pandemic for more than a year, and throughout that time the evidence demonstrating an impact of COVID-19 on stroke has improved. From those early case series, through to case-control studies and finally larger studies combining data from earlier work, a more consistent picture is emerging."

Very early on in the COVID-19 pandemic, reports from China indicated that the virus responsible, SARS-CoV-2, was a cause of abnormal blood clotting, or coagulopathy. Indeed, it was clear that the damage to the lungs in severe COVID-19 cases could be attributed in part to thrombosis. As a result, stroke physicians were bound to wonder if COVID-19 could be a cause of stroke, or at least change the manifestation of this condition.

Small cases series started to emerge in April 2020, including one from our own centre in London, in which young patients without stroke risk factors were reported with ischaemic strokes caused by blockage of large arteries in the brain. These patients seemed to have very high D-dimers, as may be seen in coagulopathies with other causes.

It was not at all clear at the time whether this was really a new type of stroke caused by COVID-19 or just represented a reporting bias. Young patients do occasionally arrive with strokes caused by large vessel occlusions and, initially at least, no obvious cause. Perhaps these centres New York and London were seeing a few more than usual by chance. In both centres the first wave of the pandemic was in full swing in April 2020 and so it was reasonable to assume that quite a few of our stroke patients would have COVID-19 anyway.

In May and June, however, the quality of evidence was already starting to improve. Small cohort studies comparing the characteristics of ischaemic stroke patients with and without COVID-19 started to emerge from New York. These initial results appeared to be rather contradictory. A study by Yaghi and colleagues suggested that, compared with stroke patients without the infection, patients with COVID-19 at the time of their ischaemic stroke appeared to be younger, have more severe strokes and higher D-dimers, conclusions that appeared to support the earlier small case series. Another report from New York, this time by Kihira and colleagues, showed no difference in age in stroke patients with and without COVID-19, no increase in severity associated with the infection, and no difference in D-dimers between the two groups. Clearly larger studies were going to be needed to clarify these points.

In the UK we published our experience in November 2020. The advantage of our study was that we did not rely on data from a single city, but rather our study included thirteen leading stroke centres from right across England and Scotland. In our ischaemic stroke patients we found no difference at all in age between those with and without COVID-19 at the onset of their stroke. If there is a specific group of much younger patients with coagulopathy as the main cause of their stroke, this sub-group must be very small.

Why then did the study of Yaghi and colleagues from New York seem to show a significant age difference between their COVID-positive and COVID-negative patients? One difference between their study and ours is that we were looking at a very different stroke populations. Our patients were largely those that presented to stroke services with a stroke as their primary diagnosis. In the New York study this was true of fewer than half of the patients. Most were taken to hospital because of severe COVID-19 and were found to have strokes later on. Two-thirds of their patients with COVID-19 and stroke died during their hospital admission compared with only one fifth in our study.

The discrepancy may possibly be explained by an age bias between the COVID-19 positive and negative groups in the New York study. At the time that their patients were admitted, New York was a COVID-19 epicentre. A recent retrospective study by Janke and colleagues from Yale University has shown that the very severe shortage of intensive care beds in the city contributed to the mortality rate from the infection. Under these extreme circumstances it seems very likely that there was a tendency to select younger COVID-19 patients for intensive care. Among their stroke patients, those with COVID-19 may have tended to be younger simply because these were the patients that were prioritised for admission and for intensive care, a selection pressure that did not operate on stroke patients without COVID-19.

The most consistent finding in comparisons between stroke patients with and without COVID-19 is that those with the infection have more severe ischaemic strokes

with a worse outcome. In our UK study, only 14% of patients with COVID-19 at the onset of an ischaemic stroke left hospital without any disability, compared with 29% of patients without the infection. At the other end of the scale, the COVID-19 group were twice as likely to die during their hospital admission with stroke. The reasons for these poorer outcomes are not yet fully understood.

From the start of the pandemic, the expectation was that COVID-19-associated ischaemic stroke might turn out to have a different mechanism to the strokes that we normally see. In our study we found some evidence to support the idea that a coagulopathy may be playing a part. D-dimers are a useful marker of coagulopathy and in our study the D-dimer level was significantly higher in ischaemic stroke patients with COVID-19 than in those without the infection.

On the other hand the proportions of stroke patients in whom the cause appeared to be thrombus from the heart, thrombus from a diseased large artery in the neck, or intrinsic small vessel disease in the brain, appeared to be similar between patients with and without COVID-19. This observation does not appear to support the idea that there is a single unique mechanism by which COVID-19 has its impact on stroke. Our conclusion was that COVID-19 may tend to promote more severe strokes by interacting with any of these "conventional" underlying causes. There may be a whole series of mechanisms by which COVID-19 exerts its adverse influence over stroke, including various forms of pathological inflammation as well as coagulopathy.

Most of this article has been about the impact of COVID-19 on ischaemic stroke because this is much the commonest form of stroke and so is easier to study. In our study the number of patients spontaneous intracerebral haemorrhage (sometimes called haemorrhagic stroke) was too small to draw any firm conclusions and many other studies excluded this type of stroke completely. At the moment the only way of deriving good evidence about the impact of COVID-19 on this stroke type is to combine data from all of the small studies that exist in the literature.

In January we analysed data from 139 patients reported with spontaneous intracerebral haemorrhage up to that time. Unfortunately here the news was no better than it was for ischaemic strokes. More than half of intracerebral haemorrhage patients with COVID-19 died during admission.

There were a few other indicators that COVID-19 may have an influence over this type of stroke. Among patients with spontaneous intracerebral haemorrhage, those with COVID-19 appeared to be younger than expected, with a median age of only 60 years. Only about half of the patients had hypertension as a risk factor, whereas this is usually found in about 85% of patients with spontaneous intracerebral haemorrhage. Finally, the pattern of bleeding in the brain seemed to be different in patients with COVID-19, with multiple bleeds and bleeds near the surface of the brain appearing to be more common than expected from historical studies.

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The primary theme here seems to be that patients who are at risk of ischaemic stroke from the usual risk factors such as atherosclerosis, atrial fibrillation, hypertension or diabetes are likely to have more severe strokes, with a worse outcome, if they have COVID-19 at the time of their stroke onset. The data on primary intracerebral haemorrhage is more sparse but it seems clear that the onset of this condition at a time of COVID-19 infection is a particularly deadly combination, with a mortality rate of more than 50%. These results suggest an urgent need to understand the mechanisms by which COVID-19 exerts its malign influence over stroke, so that we can optimise treatment of these patients and improve their outcomes in the future.