

Title: Ischaemic Stroke in the Time of Coronavirus Disease 2019

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Ischaemic Stroke in the Time of Coronavirus Disease 2019

Introduction

Each year, between 1.1 and 1.5 million Europeans have a stroke¹. Two to three out of 10 patients die as a consequence of it and about one third remains functionally dependent². As we know, the likelihood of a favourable outcome in this disease relies heavily on patients presenting promptly after symptoms onset and on hospitals providing immediate access to optimized stroke care^{3,4}.

Since the first reported case in early December 2019, severe acute respiratory coronavirus 2 (SARS-CoV-2) infection, known as Coronavirus Disease 2019 (COVID-19), has become pandemic so rapidly that healthcare systems are overwhelmed^{5,7}. In Spain, by April 19th, 195,944 cases and 20,453 deaths have been confirmed⁶. With our health system on the brink of collapse, there is a risk that the remaining "non-COVID-19" pathologies lag behind and, unfortunately, it seems stroke is not an exception.

Stroke assistance is facing changes and new challenges. In a survey, among 426 stroke care providers from 55 countries, only one in five reported that stroke patients are currently receiving the standard acute and post-acute care⁸. Furthermore, it seems that fewer people are coming to emergency departments or are doing it too late. However, data quantifying this is lacking.

We aim to analyze the impact of COVID-19 epidemic outbreak on hospital stroke admissions and patients baseline characteristics in our region. Aragón represents one of the 17 first-level political and administrative divisions of Spain, one of the countries with a greater

number of confirmed SARS-CoV-2 cases and deaths. It has 1,319,291 inhabitants and around 2000 cases of stroke admissions per year. According to our regional Health System (Servicio Aragonés de Salud), public hospitals are the only ones where reperfusion therapies for ischaemic stroke are available.

Methods

We reviewed the data of every patient admitted to any hospital of Servicio Aragonés de Salud (SALUD) with the diagnosis of ischaemic stroke between December 30th 2019 and April 19th 2020. Demographic and clinical data were recorded including age, sex, modified Rankin Scale score (mRS) prior to qualifying stroke, patient location, time of onset, Code Stroke activation, National Institutes of Health Stroke Scale score (NIHSS), Alberta Stroke Program Early CT Score (ASPECTS), intravenous thrombolysis (IVT) and/or endovascular therapy (EVT), onset-to-door time (ODT), door-to-needle time (DNT), door-to-puncture time (DTP) and COVID-19 diagnostic test results. The number of stroke patients and confirmed COVID-19 cases were quantified per week (depicted according to ISO 8601:2019 standards). Weekly national policies carried out on the COVID-19 pandemic were taken into account.

We used descriptive statistics to compare the incidence of stroke admissions before and after the setting of the state of emergency in our country (March 14th 2020) expressed in strokes per week and the differences between the baseline characteristics and demographics of patients attended in those periods. Quantitative variables were reported as medians with interquartile ranges (IQR) and tested for differences with the Mann-Whitney U and Kruskal-Wallis tests. Chi-square tests were used to test for differences in dichotomous variables.

Ethical approval for this study was obtained from the regional Research Ethics Committee, "Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón" (CEICA).

Results

In total, 354 patients with ischaemic stroke (male 185, 52.3%); median of age 79, (IQR 68-86), were admitted to a hospital at SALUD between December 30th 2019 and April 19th 2020. There was a weekly average of 27.5 cases before the setting of the state of emergency against 12 afterwards ($p < 0,001$). This drop in stroke cases occurred progressively from week eleven (W11, March 9-15th), persisting in time despite the

decrease in confirmed cases of COVID-19 (Figure 1). This also happened in the number of patients who received reperfusion therapies, IVT and/or EVT, per week (8.5 vs 4, $p = 0.011$).

There were no differences in the proportion of IVT (21.1% vs 21.5%, $p = 0.935$) or EVT (12.4% vs 15.2%, $p = 0.510$) of the total amount of ischaemic stroke of each period, nor in the other demographic or clinical characteristics except for median ODT (102 vs 183 minutes, $p = 0.015$) (Table 1). Only 28 stroke patients were tested for COVID-19 according to clinical suspicion, six of them were positive (21.4%).

Discussion

Aragón is the fourth largest administrative division in Spain and the 11th most populated. Among its major demographic characteristics are the dispersion and elderly population (285,599 people older than 65 years, which represents 21.65%). The population is very unevenly distributed, with the main province gathering 964,693 inhabitants (Zaragoza), but an average population-density for the rest of the territory fewer than 20 inhabitants/km². SALUD is the entity responsible for health care in the region, assisting 97% of its citizens. The entire territory is covered by 8 district health boards, each one with a referral hospital. Three of the districts correspond to the city of Zaragoza, while the rest provide care for less inhabited areas. There is one tertiary referral hospital for stroke EVT in the whole region, and all the other hospitals can offer IVT. The whole SALUD uses the same electronic medical record and has common stroke entry/discharge reports, allowing exploitation of stroke hospital data from all over Aragón in real-time.

On March 14th 2020, the Government of Spain implemented extraordinary measures to control viral transmission, restricting free mobility over the entire country. This was reinforced from March 31st to April 11th, being essential workers the only ones allowed to leave their homes. Until now, the state of emergency is still on. We believe the significant reduction in current stroke admissions might be related to fewer people going to the Emergency Department due to fear of being infected and in response to the measures previously described. This might make sense in minor non-disabling strokes. However, it is hard to assume that a severely disabling stroke, such as those secondary to large-vessel occlusion, did not come to the hospital, even if it was late for reperfusion treatments. Having said that, although there was a decrease in the number of patients who received reperfusion therapies per week, we did not find changes in the proportion of IVT and EVT patients in our region, if we compared it with the total amount of ischaemic strokes for each period. There was also a similar number of low ASPECTS or high NIHSS scores and the same proportion of patients

with strokes of more than 24 hours of evolution or those with unknown time of symptom onset.

It seems unlikely that COVID-19 is directly related to the decrease in the influx of ischaemic stroke patients to our emergency departments. Furthermore, possible mechanisms by which SARS-CoV-2 may increase the risk of stroke have been described: angiotensin-converting enzyme 2 (ACE2) receptor may act as an entry for SARS-CoV-2 causing neurological complications such stroke through direct and indirect mechanisms¹⁰. The high level of D-dimer, low platelet count and production of antiphospholipid antibodies predispose to a hypercoagulative state¹¹⁻¹³. Besides, SARS-CoV-2 is reported to cause cytokine storm syndromes, which could contribute to stroke. Hypoxia in the central nervous system derived from alveolar gas exchange disorder, cardioembolism due to virus-related cardiac injury, or direct virus nervous system invasion are other proposed mechanisms. Nevertheless, these associations remain to be determined¹⁴.

Considering frailty and strict social isolation, older patients could be at higher risk of dying at home from this or other diseases if they do not seek emergency services. In fact, it is the age group with higher mortality from COVID-19 and also the one with more ischaemic stroke rates. However, this would have increased the proportion of strokes in young adults, which did not happen. Another hypothesis is that some stroke patients could be in a different in-patient area and would have not been transferred to the Neurology ward. Considering the actual hospital organization derived from COVID-19, patients hospitalized with other diseases could either be in isolation units where stroke might not be the major issue or not being paid enough attention to make the diagnosis, which would be a serious inconvenience. As a result, some patients might not be receiving the necessary stroke standard of care.

On the other hand, it seems that around 29% of the global burden of stroke may be attributed to air pollution¹⁵. The measures adopted to control viral transmission in Spain have led to a drastic and general reduction in urban transportation, industrial activity and other sources of environmental pollution. There has been a 77% decrease in road traffic in main Spanish cities, with a maximum near 90% on weekends. In Zaragoza, this reduction has contributed to a 45% decrease in the NO₂ levels registered in the city¹⁶. It would be tempting to assume that isolation might have contributed to better control of some modifiable stroke risk factors, making it plausible that the decrease in stroke admissions in this period might reflect a real reduction in stroke incidence. However, more studies are needed to make this statement.

Questions might arise whether the seasonal pattern of stroke occurrence may play a role in our results, but evidence about it is conflicting. Some studies report that ischaemic stroke events are significantly higher during spring and autumn than in summer^{17,18} and, in our case, the drop in stroke admissions has occurred during the beginning of spring. However, another study stated that there was a fairly even distribution of ischaemic stroke over all four seasons¹⁹ and a recent meta-analysis showed very little seasonal variation²⁰.

The higher ODT observed in our sample could be secondary to the collapse of the emergency services, focused on the transfers of COVID-19 patients. On the other hand, we think that fear could also delay stroke activation by patients or their families.

To the best of our knowledge, this is the first study that quantifies the impact of COVID-19 outbreak in stroke hospital admissions in an entire region. However, some limitations should be noted. First, the way records were obtained from the SALUD database limits stroke events to the ones which cerebrovascular disease was among the main diagnosis during hospitalization. This did not allow us to thoroughly assess the characteristics of the whole COVID-19 population suffering from ischaemic stroke, but other series analyzing these aspects found that the incidence of acute ischaemic stroke in this population is no more than 5%²¹. Second, the time frame to analyze how SARS-CoV-2 infection and policies affect stroke care is short, but due to the urge for some advice to other countries which are in a previous phase of the epidemic, we considered this registered month significant enough to obtain interesting data that could help stroke centres.

Conclusions

This observational study offers the perspective of a whole region in one of the countries more heavily stricken by the SARS-CoV-2 epidemic. It shows that the decrease of stroke events, since the beginning of COVID-19 outbreak, happened globally and without any specific patient distribution. This forces us to stay alert and make a thorough scout of ischaemic strokes. It might be useful to remind the general population and other health services that Code Stroke has not suffered from new policies and diversion of resources and to highlight the importance of alert activation in order to provide potential patients with the care that they deserve.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

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	pre-CoV (n = 275)	p-CoV (n = 79)	p
Age, median (IQR)	80 (68.0 - 86.0)	78 (67.0 - 85.0)	0.298
> 80 years, n (%)	130 (47.3)	32 (40.5)	0.287
Male, n (%)	143 (52.0)	42 (53.2)	0.855
In-hospital stroke, n (%)	15 (5.5)	5 (6.3)	0.783
Strokes per week, median (IQR)	27.5 (22.5 - 33.5)	12 (10.8-16)	<0.001
TP per week, median (IQR) [‡]	8.5 (6.3-9.3)	4 (2.5-5.3)	0.011
IVT, n (%)	58 (21.1)	17 (21.5)	0.935
EVT, n (%)	34 (12.4)	12 (15.2)	0.510
>24h from SO, n (%)	59 (21.5)	10 (12.7)	0.082
Unknown-onset stroke, n (%)	129 (46.9)	35 (44.3)	0.682
ODT in minutes, median (IQR) [^]	102 (65.3 - 196.8)	183 (80.0 - 532.0)	0.015
mRS >2, n (%)	39 (14.2)	15 (19.0)	0.295
Patients from retirement homes, n (%)	18 (6.5)	4 (5.1)	0.794
Brought in ambulance	90 (32.7)	32 (40.5)	0.200
ASPECTS, median (IQR) [*]	10 (9 - 10)	10 (9 - 10)	0.309
ASPECTS <6, n (%) [*]	9 (4.0)	4 (5.9)	0.508
NIHSS, median (IQR)	5 (2 - 11)	6 (3 - 12)	0.156
NIHSS <5, n (%)	143 (52.0)	38 (48.1)	0.541
NIHSS >15, n (%)	39 (14.2)	13 (16.5)	0.615
DNT in minutes, median (IQR)	50 (35.0 - 70.3)	64 (38.5 - 89.0)	0.112
DPT in minutes, median (IQR)	59.5 (37.3 - 108.5)	68 (41.8 - 126.8)	0.388

Abbreviations: intravenous treatment (IVT), endovascular treatment (EVT), treated patients (TP), symptoms onset (SO), onset-to-door time (ODT), door-to-needle time (DNT), door-to-puncture time (DPT).

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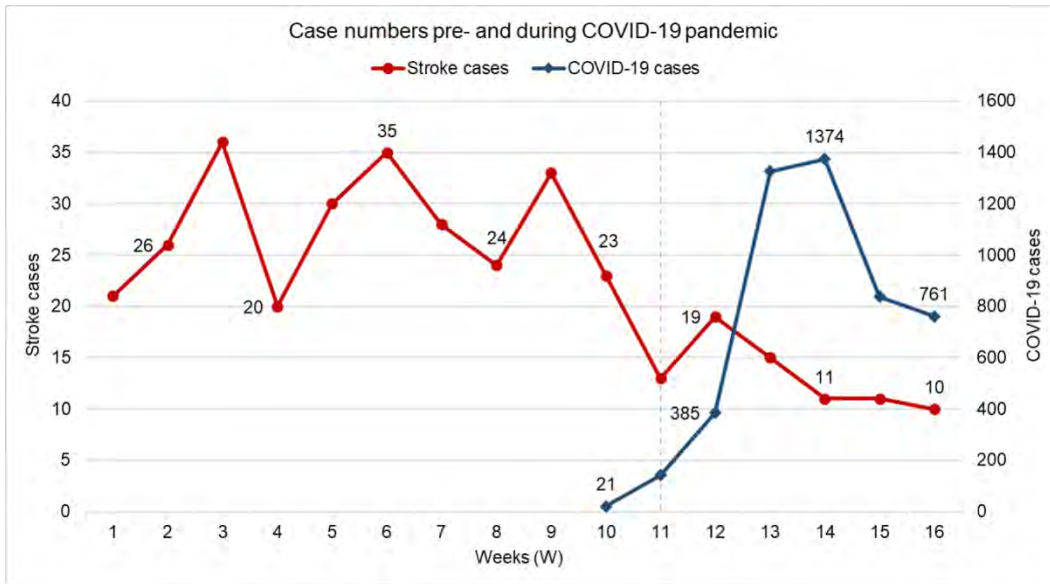
*Treated patients as the ones who recieved IVT and/or EVT

^Out-of-hospital patients with less than 24 hours from symptoms onset

*Only patients with anterior circulation strokes

Clinical characteristics of stroke admissions in Aragón before (pre-CoV) and after (p-CoV) the setting of the state of emergency in Spain

Table
1:
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