COVID-19 Impact on Stroke Admissions during France’s First Epidemic Peak: An Exhaustive, Nationwide, Observational Study

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic continues to have great impacts on the care of non-COVID-19 patients. This was especially true during the first epidemic peak in France, which coincided with the national lockdown. The aim of this study was to identify whether a decrease in stroke admissions occurred in spring 2020, by analyzing the evolution of all stroke admissions in France from January 2019 to June 2020.

Methods: We conducted a nationwide cohort study using the French national database of hospital admissions (Information Systems Medicalization Program) to extract exhaustive data on all hospitalizations in France with at least one stroke diagnosis between January 1, 2019, and June 30, 2020. The primary endpoint was the difference in the slope gradients of stroke hospitalizations between pre-epidemic, epidemic peak, and post-epidemic peak phases. Modeling was carried out using Bayesian techniques. Results: Stroke hospitalizations dropped from March 10, 2020 (slope gradient: −11.70), and began to rise again from March 22 (slope gradient: 2.090) to May 7. In total, there were 23,873 stroke admissions during the period March–April 2020, compared to 29,263 at the same period in 2019, representing a decrease of 18.42%. The percentage change was −15.63%, −25.19%, −18.62% for ischemic strokes, transient ischemic attacks, and hemorrhagic strokes, respectively. Discussion/Conclusion: Stroke hospitalizations in France experienced a decline during the first lockdown period, which cannot be explained by a sudden change in stroke incidence. This decline is therefore likely to be a direct, or indirect, result of the COVID-19 pandemic.

Introduction

Because of the coronavirus disease 2019 (COVID-19) pandemic, healthcare providers have been forced to mobilize their resources in order to cope. The care of non-COVID patients has certainly been impacted [1–4]. France faced a shortage of medical resources during the first epidemic peak, in spring 2020, despite undertaking a national lockdown (March 17–May 10, 2020) [5, 6]. On the final day of this lockdown, 16,820 COVID-19 related hospital deaths were recorded [7]. The pressure experienced by the healthcare system may have resulted in collateral damage with regard to other patients, particularly for those with serious or urgent diseases [1, 8]. Moreover,
many patients have been hesitant to seek healthcare, a phenomenon described in the literature regarding the severe acute respiratory syndrome (SARS) epidemics [9, 10]. To date, several works have described the decrease in hospital admissions for non-COVID-19 diseases, but rarely on a national level [11, 12]. The aim of this study was to determine whether the number of hospital admissions for stroke in France decreased during the COVID-19 epidemic peak and lockdown period, by analyzing the evolution in the number of all stroke hospitalizations from January 2019 to June 2020. The secondary objectives were to observe the evolution of different types of stroke; to compare selected hospitalization characteristics between the epidemic peak period March–April 2020 and March–April 2019; to study the correlation between the incidence of hospital admission for COVID-19 and the evolution in stroke admissions between March–April 2020 and March–April 2019 by French administrative department.

Materials and Methods

Study Design and Setting

Anonymized data were extracted from the French national “Information Systems Medicalization Program” (PMSI) database, which includes all public and private hospitalization data in France. Diagnoses are coded using the International Classification of Diseases, 10th Revision. A stroke diagnosis is defined by the French national agency for hospitalization data as follows: subarachnoid hemorrhage (I60.-), intracerebral hemorrhage (I61.-), other nontraumatic intracranial hemorrhage (I62.-), cerebral infarction (I63.-), stroke not specified as hemorrhage or infarction (I64.-), transient cerebral ischemic attacks and related syndromes (G45.-). We defined three categories of stroke: “haemorrhagic” (I60, I61, I62), “ischaemic” (I63), and “transient” (G45). The procedures performed during hospitalization are coded according to the Common French Classification of Medical Acts. The database request, made on October 13, 2020, included all hospital admissions, pediatric ages included, between January 1, 2019, and June 30, 2020, with at least one main diagnosis of stroke among the different medical units. While IV thrombolysis data were not available, thrombectomy data were available in this database and were identified by one of the following Common French Classification of Medical Acts codes: EAFA001, EAIF341, EANF002. In order to avoid counting the same episode twice, only one admission was counted if two admissions for the same patient were separated by 1 day or less. The study size was therefore defined by the relevant entries extracted from the database. The location of hospital stay was determined at initial admission.

The primary endpoint is the difference in slopes of stroke hospitalizations between the different periods (pre-epidemic, epidemic peak, post-epidemic peak) estimated by the model. The same model estimates the 3 knots (the number of knots being arbitrarily defined), the 4 segments, and the slopes. The secondary endpoints were the difference in the number of stroke admissions between March–April 2019 and March–April 2020: number of strokes, number of each stroke subtype, the proportion of men, the proportion of deaths.

Statistical Methods

We considered the change in the number of stroke admissions as centered 7-day rolling means. We modeled the evolution of stroke hospitalizations in four segments of lines (stability, fall, rise, return to baseline) joined by three estimated knots. Disregarding possible seasonality effects, we assumed relative stability of hospitalizations, including during the summer of 2019, before a sudden change in 2020. Modeling was carried out using Bayesian techniques with a 95% credibility interval. Probability of superiority is rounded at both extremities to <0.0001 and >0.9999. The prior distributions are assumed to be very uninformative except for the position of each of the 3 knots, which is assumed to be uniformly distributed over the time interval between February 15, 2020, and June 30, 2020.

A spatial correlation study was carried out by graphically representing, by French administrative department, the incidence rates of COVID-19 hospitalizations in March–April 2020, and the ratio between the number of stroke admissions in March–April 2020 and those in March–April 2019. The incidence rates of COVID-19 hospitalizations were standardized by age and sex, using the official data estimates of French administrative department populations by quinquennial ages and gender in 2020 [13]; if two COVID-19 stays for the same patient were separated by 1 day or less, only one was counted. An ecological normal regression was fitted to data from metropolitan France between the ratio of stroke hospitalizations and standardized incidence of COVID-19 hospitalizations, and a quadratic spatial trend was established in order to adjust for spatial effects. We used SAS Enterprise Guide 8.3 for selecting the database, and R 4.0.2, R Core Team (2020) for the analyses.

Results

From January 1, 2019, to June 30, 2020, there were 249,013 hospitalizations for stroke in France. There were 29,263 cases over the period March–April 2019, compared to 23,873 in March–April 2020. With the exception of a slight decrease in the summer of 2019, the number of strokes remains constant over the study period until a drop in March 2020 (shown in Fig. 1).

The posterior medians for three knots were estimated on: March 10, 2020, March 22, 2020, and May 7, 2020 (K3), with small credibility intervals (Table 1). After March 10, 2020, the slope of the second “fall” segment was negative (~11.70). At K3, i.e., after the “rise” period, the mean number of hospital admissions is still ~37.26 per day compared to the number calculated if the slopes of all segments had remained the same as that of the first segment. After K3, the slope of the fourth segment remains higher than that of the first segment (posterior median
COVID-19 Impact on Strokes in France

As shown in Figure 2a, the number of stroke admissions decreased between March–April 2019 and March–April 2020 for 89 out of 96 administrative departments in metropolitan France. The greatest decrease is observed in the region of Paris, the northeast and the southeast, whereas standardized incidence rates of COVID-19 hospitalization by administrative department are higher in the northeast and the Parisian region (shown in Fig. 2b). Spatial models showed that the incidence of COVID-19 hospitalizations explains the ratio of stroke admissions (as the zero line is outside of the credible interval of the smoothed effect), whether the spatial trend is included in the model or not (shown in Fig. 2c, d).

The decrease in hospital admissions concerns all three types of stroke during the period March–April 2020 (shown in Fig. 1b–d). Decrease in hospitalizations is common to all subtypes of hemorrhagic stroke. Stroke hospitalizations with at least one thrombectomy procedure decreased by 18.69% between March–April 2019 and March–April 2020 (Table 2).

Hospital stays were shorter in March–April 2020 than in March–April 2019, while the age and the proportion of men were comparable (Table 2). The death rate was slightly higher in 2020. In March–April 2020, 2.26% of hospitalizations for stroke were associated with a COVID-19 diagnosis.

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Table 1. Quantitative results were obtained by modeling the evolution of hospital admission numbers for stroke

|                       | Posterior median | 95% credible interval | Probability of superiority |
|-----------------------|------------------|------------------------|-----------------------------|
| Slope segment 1       | 0.02012          | [0.004876; 0.03655]    | 0.9953                      |
| Slope segment 2       | −11.70           | [−16.25; −8.552]       | <0.0001                     |
| Slope segment 3       | 2.090            | [1.772; 2.470]         | >0.9999                     |
| Slope segment 4       | 0.4863           | [0.1883; 0.7784]       | 0.9991                      |
| Difference between slopes 4 and 1 | 0.4663          | [0.16594; 0.7585]     | 0.9984                      |
| Difference between slopes 3 and 4 | −1.611         | [−2.132; −1.105]      | <0.0001                     |
| Knot 1*               | 429.9            | [427.4; 431.7]         |                             |
| Knot 2*               | 441.2            | [439.4; 443.3]         |                             |
| Knot 3*               | 487.8            | [479.7; 491.5]         |                             |
| Delay between knot 2 and knot 1, days | 11.34          | [8.253; 15.28]        | >0.9999                     |
| Delay between knot 3 and knot 2, days | 46.64           | [38.30; 49.84]        | >0.9999                     |
| Difference in mean number of hospitalizations at knot 3 | −37.26         | [−51.09; −26.78]      | <0.0001                     |

* K1, K2, K3: in days since January 4, 2021.

Table 2. Characteristics of stroke hospital admissions

|                        | March–April 2019 | March–April 2020 | Evolution 2020/2019, % |
|------------------------|------------------|------------------|-------------------------|
| Age, years             |                  |                  |                         |
| Median (Q1, Q3)        | 75 (64, 85)      | 75 (64, 85)      | 0                       |
| Mean (SD)              | 72.77 (15.52)    | 72.77 (15.33)    | 0                       |
| Duration of hospital stay, days |                  |                  |                         |
| Median (Q1, Q3)        | 7 (3, 13)        | 6 (3, 11)        | −14.29                  |
| Mean (SD)              | 10.24 (13.07)    | 9.090 (10.50)    | −11.23                  |
| Proportion of men      |                  |                  |                         |
| Men, n (% of total)    | 15,059 (51.46)   | 12,355 (51.75)   | 0.56                    |
| Admissions ending in death |                |                  |                         |
| Deaths, n (% of total) | 3,032 (10.36)    | 2,661 (11.15)    | 7.63                    |
| Admissions by stroke subtype, n |          |                  |                         |
| All                    | 29,263           | 23,873           | −18.42                  |
| Ischemic               | 16,776           | 14,154           | −15.63                  |
| TIA                    | 6,978            | 5,220            | −25.19                  |
| Hemorrhagic            | 5,509            | 4,483            | −18.62                  |
| Stroke not specified as hemorrhage or infarction | 1,050         | 773              | −26.38                  |
| Hemorrhagic strokes by subtype, n |                  |                  |                         |
| Subarachnoid hemorrhage | 1,148           | 942              | −17.94                  |
| Intracerebral hemorrhage | 3,472           | 2,847            | −18.00                  |
| Other nontraumatic intracranial hemorrhages | 1,145         | 918              | −19.83                  |
| Mechanical thrombectomy, n |                |                  |                         |
| Patients undergoing thrombectomy | 1,118       | 909              | −18.69                  |

SD, standard deviation; Q1, lower quartile; Q3, upper quartile.
Discussion/Conclusion

The number of admissions for stroke decreased significantly in France during the first COVID-19 epidemic peak, and this decrease is seen across all stroke subtypes. Proportions between the sexes did not change. Differences in the duration of hospital stay and the mortality rate are difficult to interpret because some long-term hospital stays in 2020 may have ended after data extraction, and/or relevant data may have been updated at a later date.
This sudden decrease of hospitalizations cannot be explained by seasonality, nor by a change of hospital facility, because our study is national. The comparable spatial distribution of COVID-19 and decreased stroke admissions seems to reflect causality because the link between them persists when a spatial trend is modeled.

This phenomenon was described in the literature for emergency department visits during the 2003 SARS outbreak in Taipei [10] and Toronto [14]. More recently, the authors described the impact of lockdown on emergency department visits in Lebanon [15]. Equally, in a tertiary pediatric emergency department in Cincinnati, USA, the volume of patients decreased at a daily rate of 19.4% after the launch of public health interventions against COVID-19 [16]. Few works focused on the decrease in stroke admissions during the pandemic, concentrating mainly on emergency departments, or on limited geographical areas [11, 12]. In 2021, Daniel et al. [17] showed a nationwide decrease of strokes in Germany, and a worldwide study by Nogueira et al. [18] on 457 stroke centers found an 11.5% decline in stroke admissions during the pandemic [17, 18]. Siegler et al. [11] hypothesize that this decrease is a consequence of patients presenting milder symptoms, therefore less likely to seek healthcare. The lack of interaction and communication during lockdown could also have increased under-recognition of stroke signs and limited encouragement by relatives to seek care [19–21]. Due to this crisis situation, the quality of care and patient follow-up may have deteriorated as COVID-19 activity increased, with a higher probability of caregivers underdiagnosing stroke. It may also have resulted from healthcare providers redirecting a higher proportion of patients out of hospital. In support of these hypotheses, our study found a greater decline in stroke admissions in several administrative departments experiencing a higher incidence of COVID-19 hospitalization. It is also possible that the epidemic context and the lockdown measures could have influenced stroke risk factors on the short term, although this is not our main hypothesis.

In the literature, the incidence of neurological symptoms in COVID-19 patients is between 1.6% and 2.5% [22–26]. A bicenter study in New York City found a higher probability of stroke with SARS coronavirus 2 infections than with influenza (OR 7.6), after adjustment for age, sex, and race [26]. It appears that COVID-19 is likely to increase the incidence of stroke, probably because of its pathophysiology, involving inflammation and hypercoagulability [24, 26–28]. Although COVID-19 may be responsible for neurological symptoms, it may also have been a concurrent cause of death [27].

Our study also pointed to a decrease in thrombectomy procedures, which indicates a global decrease in stroke therapies, as suggested in the literature [21]. However, we were unable to assess the evolution in the number of thrombolysis, as this information is unavailable in the PMSI database.

To our knowledge, this is the first nationwide study in France, a country with a relatively high incidence rate of stroke, to describe the evolution of stroke admissions during the first COVID-19 epidemic peak. We have been able to highlight the decline in stroke admissions while taking into account its evolution over the entire year. These results alert us to the need for ensuring appropriate care for non-COVID-19 patients during the epidemic. The impact of the epidemic on cerebrovascular diseases may be seen in the months and years to come.

A first limitation of using the PMSI national database is the possible delay between patient discharge and coding. However, the extent of this bias is limited, because diagnoses made during hospitalization have to be sent to the national database during the month following discharge. Second, this database has been designed for funding allocation, and not for epidemiological purposes. Therefore, there may be a variation in the quality of the medical information, according to the relation between coding and funding. However, homogeneity of coding is provided by strict, national rules with regular checks carried out by the funding body, thus limiting misclassification bias.

This study has determined a nationwide decrease in stroke hospital admissions at the time of the first COVID-19 wave in France. The drastic lockdown measures and unprecedented epidemic context have most likely impacted the probability of patients seeking hospital assistance in France, particularly in those regions most affected by COVID-19. In light of these findings, the care provided for stroke should be reconsidered in order to prevent underdiagnosis, to improve outpatient medical care, and to facilitate health provider decision-making during the crisis.

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Statement of Ethics

This study adheres to French legislation regarding the reuse of anonymized data (MR-005 of Commission Nationale de l’Informatique et des Libertés) and is registered at Strasbourg University Hospital under the reference 21-2019. Relevant data files
are deposited on the Health Data Hub (reference: CE-2021-14). Participants’ informed consent is not required. The Strasbourg University Hospital Ethics Committee has approved this study (reference: CE-2021-14).

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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References
1. Akiyama Y, Morioka S, Wakinoto Y, Kawashima A, Kanda K, Ohkuma A, et al. COVID-19 patients with life-threatening diseases who visited a fever clinic: a single-center, observational study in Tokyo, Japan. Intern Med. 2020 Dec;59(24):3131–3.
2. Gouabchand R, Clarét PG, Lattuca B. What if the worst consequences of COVID-19 concerned non-COVID patients? J Infect Public Health. 2020 Sep;13(9):1217–9.
3. Abraham DA, Vijayakumar TM, Rajanandh MG. Challenges of non-COVID-19 patients with chronic illness during the pandemic. J Res Pharm Pract. 2020 Oct;9(4):155–7.
4. Ojetti V, Covino M, Petruzzellio C, Saviano A, Migneco A, et al. Non-COVID diseases during the pandemic: where have all other emergencies gone? Medicina. 2020 Oct;56(10):512.
5. Salje H, Tran Kiem C, Lefrançais N, Courtejoie N, Bosetti P, Painier J, et al. Estimating the burden of SARS-Cov-2 in France. Science. 2020 Jul;369(6500):208–11.
6. Di Domenico L, Pullano G, Sabbatini CE, Di Santo G, Colizzi V. Impact of lockdown on COVID-19 epidemic in Île-de-France and possible exit strategies. BMC Med. 2020 Jul;18(1):240.
7. Ministère des Solidarités et de la Santé. Données relatives à l’épidémie de COVID-19 en France vue d’ensemble – data.gouv.fr [Internet]. Ministère des Solidarités et de la Santé; 2021 [cited 2021 Jan 23]. Available from: http://fr/datasets/donnees-relatives-a-lepidemie-de-covid-19-en-france-vue-densemble/.
8. Persiano A, Kraemer M, Touze E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. Eur J Neurol. 2020 Sep;27(9):1799–804.
9. Markus HS, Brainin M. COVID-19 and stroke: A Global World Stroke Organization perspective. Int J Stroke. 2020 Jun;15(4):361–4.
10. Huang HH, Yen DH, Wang LM, Huang CI, Lee CH. Declining emergency department visits and costs during the severe acute respiratory syndrome (SARS) outbreak. J Formos Med Assoc. 2006;105(1):31–7.
11. Siegler JE, Haslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. J Stroke Cerebrovasc Dis. 2020 Aug;29(8):104953.
12. Mariet AS, Giroud M, Benzenine E, Cottenet J, Roussot A, Aho- Glélé LS, et al. Hospitalizations for stroke in France during the COVID-19 pandemic before, during, and after the national lockdown. Stroke. 2021 Apr;52(4):1362–7.
13. Insee. Estimation de la population au 1er janvier 2022 [Internet]. Insee; 2022 [cited 2021 Feb 20]. Available from: https://www.insee.fr/fr/statistiques/1893198.
14. Heiber M, Lou WF. Effect of the SARS outbreak on visits to a community hospital emergency department. CJEM. 2006 Sep;8(05):323–8.
15. Mahmassani D, Tamim H, Hitti E. The impact of COVID-19 lockdown measures on ED visits in Lebanon. Am J Emerg Med. 2021 Aug;46:634–9.
16. Dean P, Zhang Y, Frey M, Shah A, Edmunds K, Boyd S, et al. The impact of public health interventions on critical illness in the pediatric emergency department during the COVID-19 pandemic. J Am Coll Emerg Physicians. 2020 Aug;16(6):5142–51.
17. Daniel R, Jens E, Weber R, Dirk B, Grau A, Werner H, et al. Analysis of nationwide stroke patient care in times of COVID-19 pandemic in Germany. Stroke. 2020 Feb;52(2):716–21.
18. Nogueira RG, Qureshi MM, Abdalkader M, Ivens KO, Yamagami H, Qiu Z, et al. Global impact of COVID-19 on stroke care and intravenous thrombolysis. Neurology. 2021;96(23):e2824–38.
19. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmünzer B, Barlín K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. Stroke. 2020 Jul;51(7):2224–7.
20. Diegoli H, Magalhães PSC, Martins SCO, Moraes HC, Brasil PH, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. Stroke. 2020 Aug;51(8):2315–21.
21. Hajdu SD, Piette V, Puccinelli F, Ben Hassen W, Ben Maacha M, Blanc R, et al. Acute stroke management during the COVID-19 pandemic. Stroke. 2020 Aug;51(8):2593–6.
22. Helms J, Kremer S, Merdji H, Clerc-Jehl R, Schenk M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020 Jun;382(23):2268–70.
23. Shahjouei S, Naderi S, Li J, Khan A, Chaudhary D, Farahmand G, et al. Risk of stroke in hospitalized SARS-CoV-2 infected patients: a multinational study. EBioMedicine. 2020 Sep;59:102939.
24. Yaghil S, Ishida K, Torres J, Mac Groy R, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020 Jul;51(7):2002–11.
25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus: infected pneumonia in Wuhan, China. JAMA. 2020 Mar;323(11):1061–9.
26. Mekler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. JAMA Neurol. 2020 Jul;77(11):1–7.
27. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, et al. Neurological manifestations and implications of COVID-19 pandemic. Ther Adv Neurol Disord. 2020;13:1771628620932036.
28. Rouyer O, Pierre-Paul IN, Balde AT, Jupiter D, Binndla D, Geny B, et al. High prevalence of deep venous thrombosis in non-severe COVID-19 patients hospitalized for a neurovascular disease. Cerebrovasc Dis Extra. 2020;10(3):174–80.

Author Contributions
C.R., V.W., and E.-A.S. designed the study; P.T.B.L. and C.R. extracted the data; C.R., P.T.B.L., E.-A.S., V.W., F.B.-F., H.L., and C.S. analyzed the data; E.-A.S., C.R., T.F., and P.T.B.L. performed the statistical analysis; C.R. wrote the manuscript; all authors reviewed, revised, and approved the final report. Manuscript edition was provided by Dr. Kate Dunning (Strasbourg University Hospital).

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