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Review Article

Acute Ischemic Stroke and Coronavirus Disease of 2019 (Covid-19): Evidence for an Association and Causality

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Abstract

Stroke is a debilitating neurological emergency with high morbidity and mortality causing serious disabilities among survivors. It is a largely preventable condition, primarily with modifications of risk factors. Post-stroke dementia is a clinical entity that includes any form of dementia which occurs following stroke. It comprises of vascular, degenerative or mixed dementia affecting about one-third of stroke survivors. However, no effective therapeutic strategies thus far exist to prevent the development of stroke or post-stroke dementia. The primary means of reducing the burden is through control of vascular risk factors and prevention of recurrent stroke, best achieved through a health promotion intervention which involve actions enabling people to improve and have a control upon their health. In this article, we have reviewed Health Promotion Interventions and their roles in the prevention of stroke and post-stroke dementia, discussed the policies and practices that are currently employed in the prevention of the menace as well as potential barriers to the prevention.

Key Words: stroke; post-stroke dementia; health promotion; stroke prevention; risk factor modification; lifestyle intervention; vascular risk factors; health literacy; public health policy; community-based prevention

Introduction

Exploring the cause-effect relationship between corona virus disease of the 2019 (COVID-19) and Ischemic stroke could be a daunting task as the disease is relatively new whose spectrum is yet to be fully understood. However, many epidemiological studies have demonstrated the association between Covid-19 and Ischemic stroke. The burden of stroke, of which 80-85% is Ischemic type, when associated with Covid-19 was shown to be high. In one of the earliest United Kingdom (UK) descriptive study in a cohort of 95 hospitalized patients, a high fatality rate was observed in Covid-19 patients associated with cerebrovascular diseases, of which stroke constitute the major part of the disease spectrum where 48% of the patients died [1]. The incidence of Ischemic stroke (IS) in the UK was estimated to be about 2.0 (95% confidence interval [CI]: 1.8–2.2) per 1,000 population per year, with prevalence estimated at between 14.7 per 1,000 and 17.5 (95% CI: 17.0 to 18.0) per 1,000 of which 30% die and 35% remained permanently disabled [2]. It is one of the major causes of physical inactivity in the UK. In 2002, physical inactivity was found to be directly responsible for 3% of disability adjusted life years lost in the UK with estimated direct cost to the National Health Service of £1.06 billion. In UK, IS causes about 10.6% of all mortality due to physical inactivity and 5.1% of total DALYs lost [3]. The socioeconomic impact of Ischemic stroke in UK is enormous with mean health and social costs per patient estimated to be £20,121 within one year and £41,432 within five years of established ischemic stroke [3]. This high economic burden is directly related to the increased morbidity and mortality secondary to ischemic stroke posing public health concerns.

On the other hand, Covid-19 is one of the three deadly outbreaks caused by novel corona virus. It impacted every part and regions of the world that resulted in health, lives, and economic losses with tremendous burden on social and economic life of the survivors. By 12th August, 2020, a UK-wide Covid-19 cases and deaths were found to be 313,798 and 46,706 respectively (472 cases and 70 deaths per 100,000 population) with regional and ethnic variation [4]. In UK, Covid-19 affected every subgroup of population but mortality data from the Office of National Statistics (ONS) has indicated increased deaths among Black, Asian and Minority Ethnicity group (BAME) with death rates of 4.2 and 4.3 times higher in black males and females respectively as compared to white ethnicity[5]. One of the major impacts of Covid-19 in UK is the implementation of the series of lockdown restrictions, which were intended to slow the spread and the progression of the disease. Although, it has helped carved out the outbreak but posed serious mental disturbance and psychological instability due to isolation and reduced social interaction which have positive effects on health and wellbeing of population. In a cross-sectional study of about 600 UK adults, self-isolation and lack of social interaction coupled with Covid-19-related livelihood concerns were associated with poorer mental health, well-being and quality of life [6]. In a UK household longitudinal study, the prevalence of psychological distress increases from 18.3% to 28.3%

between Wave 9 and April 2020 [7]. In Wales multicentre retrospective observational study of 2518 hospitalized adults, the inpatients mortality rate of nosocomial Covid-19 infections ranges from 38% to 42%, a slightly higher than mortality from the community acquired infection of 31% to 35% [8]. The disease has serious economic impact on the population especially following the series of lockdown restrictions which mostly affected trade, arts, entertainment and recreation, accommodation and food services sectors with about 53.6% lower turnover of business. The people claiming universal credit was 5.6 million on July 9th 2020 with total trade exports fell by £26.7 billion and imports fell by £35.2 billion leading to total trade widening by £8.6 billion to 8.6 billion [4]. The purpose of this study, therefore, is to assess the causality association between Covid-19 and Ischemic stroke.

Association and Causality

Association

There are many studies that reported the association between Covid-19 and Ischemic stroke. The current available literatures that reported the association are basically case reports and series, cohort studies and case control studies with no clinical trial found. In the first category (case reports/series), five case series [9–13], and two case reports [14,15] were identified. The total sample size was 42 patients with 61 years as the mean age. The participants were 32 males (76.2%) and 10 females (23.8%). The average duration from the onset of Covid-19 symptoms to development of neurological symptoms of Ischemic stroke was 8 days. In all the cases, diagnosis of both Covid-19 and Ischemic stroke were made by standard confirmatory diagnostic methods. There were only thirteen patients (31%) who had no significant prior medical history or vascular risk factors in the entire sample size, but the remaining 29 patients (69%) have had both modifiable and non-modifiable risk factors including diabetes mellitus, hypertension, smoking, advancing age, atrial fibrillation, ischemic heart disease, dyslipidemia and prior stroke history implying that association seen in these cases might be just coincidental. To minimize the effect of random error, systematic error, confounding and reverse causality to determine true association, the thirteen patients were only considered as the only cases of IS secondary to Covid-19 infection. Therefore, the cumulative incidence of the ischemic stroke was deduced as 3 per 1000 persons. It will therefore be convenient to infer that, there was a potential association between Covid-19 and Ischemic stroke among these cohort of patients.

The second category of studies observed were five cohort studies, three of the studies[16–18] do not have comparative groups. The total sample size of the studies was 10785 patients, out of which 83 patients were confirmed to have ischemic stroke. However, 67 patients out of the 83 patients had significant prior medical history and/or vascular risk factors and the remaining 16 patients had no any significant medical or vascular risk factors. To minimize the effects of random error, systematic error, confounding and reverse causality in order to determine true association, the 16 patients were only involved in the analysis. The average age of the participants was 51 years and the average duration from the onset of Covid-19 symptoms to development of neurological symptoms of Ischemic stroke was 12 days. Therefore, cumulative incidence (primary attack rate) was calculated as 0.0015 per 1000 population (equivalent to incidence rate of 1.5%). This incidence is in keeping with reported incidence of ischemic stroke among Covid-19 patients from other literatures, and it indicates that Covid-19 infection is most likely associated with the development of Ischemic stroke. The remaining two cohort studies[19,20] have comparative groups. The first study consisted of 1916 patients with confirmed diagnosis of Covid-19 as experimental group and 1486 patients with confirmed diagnosis of influenza as control group. Ischemic stroke was diagnosed among 31 patients of the experimental group and 3 patients of the control group. Therefore, relative risk (RR) was found to be 8. In the second study, there were 27 patients with confirmed diagnosis of Covid-19 as experimental group and 303 patients without Covid-19 as control group. Ischemic stroke was diagnosed among 20 patients of the experimental group and 222 patients of the control group. Therefore, the relative risk (RR) was calculated to be 1.01. In both studies the relative risks are suggestive that there was an association between exposure to Covid-19 and development of ischemic stroke.

The last category of the studies observed was single case control study[21] with the total number of the study population as 1507 stroke patients. Out of these, 123 patients have Covid-19 and the remaining 1384 patients do not have the infection. The 123 patients will serve as cases and the 1384 patients will serve as controls. Eighty-one (81) patients out of the 123 patients developed Ischemic stroke with evidence of Covid-19 at the time of stroke onset and 1193 patients out of the 1384 patients have Ischemic stroke but no evidence of Covid-19. So, to find the relationship between the Covid-19 infection and the development of Ischemic stroke, the odds among the cases and controls were calculated and finally odds ratio was deduced as follows: Odds of Covid-19 patients developing IS = 81/42 = 1.93; odds of controls developing IS = 1193/191 = 6.25; odd ratio = 1.93/6.25 = 0.31 (or 31%). This clearly indicates some level of association between the infection and development of Ischemic stroke.

Causality

To systematically determine whether this observed statistical association between the Covid-19 and the development of Ischemic stroke is a true causal relationship, a Bradford Hill criterion was applied[22]. The criteria consisted of the following nine factors to be considered and analyze: strength of association, consistency, specificity, temporal sequence, biological gradient, biological plausibility, coherence, experiment and analogy. The ***strength*** of the association appears to be strong from the statistical information presented earlier. In the first category of studies discussed earlier [9-15], the cumulative incidence was determined to be 3 per 1000 population which is statistically strong. However, in the second category (16-20), the cumulative incidence was relatively weak (0.0015 per 1000 population) but the two relative risks are statistically strong (8 and 1.01 respectively). Similarly, the last category [21] demonstrated an odds ratio of 0.31, which is comparatively weak but, however, demonstrates some level of association though suggesting further research. The association appears to be ***consistent*** as same findings have been observed by different scientists from different places including United States, United Kingdom, China, Spain, United Arab Emirate, Turkey and Brazil using different study designs including case reports, case series, cohort studies and case a control study as demonstrated by the studies included in the association above [9-21]. The association demonstrated in the study was very specific as virtually all the included studies reported one to one relationship between the Covid-19 infection and development of Ischemic stroke because factors that might influence the association like random error, systematic error, confounding and reverse causality were eliminated from the study.

Furthermore, in all the included studies, the exposure to Covid-19 appeared to have preceded the development of Ischemic stroke indicating ***temporality*** of the association. It has been demonstrated from the included studies that the severity of the infection is directly proportional to the severity of the neurological symptoms of the Ischemic stroke. Symptomatic patients were observed and reported in almost all cases of severe Covid-19 infections with some few asymptomatic cases reported in cases of mild infections indicating the positive ***biological gradient*** [16-20]. There was a potential biological mechanism observed in virtually all the included studies which provided possible explanation for the observed association. In all the patients, some or all features of coagulability were observed including raised D-dimer and fibrinogen degradation product, raised ferritin, prothrombin time (PT), activated partial thromboplastin time (APTT) but normal platelets with evidence of some inflammatory factors such as cytokines, and interleukins. Therefore, the possible biological mechanism explaining the association was hypercoagulability indicating ***biological plausibility*** of the association. This biological

mechanism was confirmed by several studies as the potential mechanism for stroke development in patient with IS[23,24].

The ***coherence*** of the association can be explained from the natural history and/or biology of the infection, which unfortunately, is yet to be fully elucidated. However, the pathogenesis of the infection progress from the viral binding to the ACE2 receptors (which are widely spread throughout the brain) to the penetration into the host tissues, replication and biosynthesis of the viral proteins within the tissues, and finally stimulation of exaggerated host immune response by the released viral proteins, called Cytokine Storm, which damages the host tissues[25]. The exaggerated immune response can causes cerebrovascular disease through either blocking the blood vessels by the inflammatory cells or by damaging the vascular endothelium creating the cascade of thrombus formation[26]. So, from this pathogenesis it appears that the association agrees with the natural history and biology of the infection. The ***experimental evidence*** of the association appears to be strong as evidence of the association was observed from different investigational study designs including case series, cohorts and case control studies as demonstrated in the included studies [9-21]. The causality can be explained also by ***analogy*** with other respiratory viruses like influenza whose causality of cerebrovascular damage has been well established. Therefore, the relationship between Covid-19 infections, which is also caused by a respiratory virus, with cerebrovascular disease cannot be an exception.

Conclusion

Acute Ischemic stroke and COVID-19 infection are both life threatening pathologies, therefore any association between these two deadly diseases should not be taken lightly. In this essay, the public health importance of both COVID-19 and Ischemic stroke in UK was depicted by analyzing the burdens and impact of both diseases in the country. The potential association between the infection and development of Ischemic stroke was effectively demonstrated using statistical methods. Thirteen different studies from different geographical regions of the world and among various age groups have been evaluated and analyzed for the proposed association. Statistical evidence of the association was presented using cumulative incidence, relative risks and odds ratio. The causal association was clearly illustrated using Bradford Hill criteria and true causality between the infection and the development of Ischemic stroke was found according to the criteria. Finally, the public health practices in the UK were linked with the context of the association where the implications of the UK public health actions were shown to be positively associated with reduced incidence and burden of the COVID-19 associated Ischemic stroke.

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