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Unit No.3

SARS COV-2: CROSSING ITS RESPIRATORY BORDERS

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ABSTRACT

COVID-19 as a respiratory virus caused in excess of 7 million deaths. But a greater burden of illness comes from the extra-pulmonary manifestations. The disease was associated with thromboembolic, cerebrovascular, cardiovascular, autoimmune disease complications as well as the poorly understood long Covid or post-acute sequelae of covid (PASC). After an infection, children and adults, including pregnant women, are at a higher risk of developing diabetes mellitus with hazard ratios of 1.1-1.6; adults are at a higher risk of stroke at 2.6 percent more; new onset risk of dementia or neurodegenerative diseases increases in recovered patients, with cognitive impairment in 65 percent of patients >65 years of age; long covid strikes at about 6-7 percent of adults and 1 percent of children. And these risks persist and reoccur as individuals are repeatedly infected. Preventive measures are still effective in reducing Covid infection risks. Non-pharmaceutical measures such as mask, safe distancing, and adequate ventilation work hand in hand with vaccinations to reduce potential infection and hence complications.

Keywords: COVID-19; SARS-COV-2; Diabetes Mellitus; Cerebrovascular Disease; Dementia; Long covid

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INTRODUCTION

COVID-19 began in China in late 2019 and within months, evolved into a global pandemic. To date, the World Health Organization (WHO) records an excess of 7 million deaths on its website. However, the true death toll is expected to
be much higher, with WHO estimating the death rates at nearly three times higher.[1]

However, mortality rates do not reflect the true burden
of COVID-19. This enigmatic virus causes a wide array
of systemic illnesses beyond those typically associated with respiratory viruses. The first indication of systemic involvement came from reports of thromboembolic events in Wuhan, China. Thereafter, other complications, such as cerebrovascular, cardiovascular, and autoimmune diseases were also reported.

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And yet the virus continues to mutate. As of the time of writing, scientists warned of a new variant XEC that came just hot off the heels of JN.1, KP.1 and KP.2. XEC is a combination strain of KP.3.3 and KS.1.1 in the Omicron family. Despite more than four years of ongoing mutations, there is no indication that the virus will stop adapting. And predictions are that they will not. Fortuitously, the Omicron variant turned out to be a less virulent "variant" compared to the earlier Alpha to Delta variants. However, with continued mutations, the burden of illness on patients, especially the at-risk population continues.

This paper attempts to review some of the intriguing and unusual complications of COVID-19, which we have just beginning to understand. I will explore the virus's association with COVID-19, cerebrovascular disease, dementia and long covid or post-acute sequelae of Covid (PASC). This list is not exhaustive, and I would urge the reader to explore COVID-19 relationship with other systems.

DIABETES MELLITUS

Case reports of children developing Type 1 Diabetes Mellitus surfaced early in the COVID-19 pandemic.[2] Large case control studies subsequently showed the risk of diabetes mellitus developing in children[3] and thereafter in adults post COVID-19 infection. D'Souza et al performed a meta-analysis that involved 102,984 incident diabetes cases and found higher incidence rate during the first year of the pandemic compared to the pre-pandemic period (IRR 1.14, 95% CI 1.08-1.21). this risk increased in months 13-24 of the pandemic (IRR 1.27,95% CI 1.18-1.37) along with a higher rate of diabetes ketoacidosis (DKA) incidence (IRR 1.26, 95% CI, 1.17-1.36). The authors further commented that this rising cases on the limited resources in paediatric diabetes care could put a strain on the healthcare system.

In adults, we saw a similar increased risk of diabetes mellitus. Wong et al[4] performed an excellent review. Incident diabetes risk increased by approximately 60% compared to patients without a COVID-19 infection.

In Hong Kong, they studied the risk of diabetes following a COVID-19 infection in a population-based cohort study consisting of three groups of individuals.[5] Individuals who had received the COVID-19 vaccination (CoronaVac or BNT1626b); individuals who have had a COVID-19 infection; individuals who had no COVID-19 infection up till March 2022. Among the vaccinated group, there was no increased risk of diabetes mellitus after a year of follow-up. However, with a median follow-up of 164 days, they

noticed that the group with SARS-CoV-2 infection was associated with significantly higher risk of incident diabetes (9.04 vs 7.38, HR=1.225 [1.150 to 1.305]). This risk was statistically significantly lower with Omicron variants (p=0.009). The calculated "number needed to harm" was 406 for 1 additional diabetes case. Interestingly, the subgroup analysis revealed no evidence of increased risk of incident diabetes among fully vaccinated COVID-19 survivors, suggesting vaccination may have ameliorated the risk of diabetes mellitus in these individuals. The risk factors for incident diabetes were older age (HR=1.292 [95% CI 1.199 to 1.393], p<0.001), unvaccinated people (HR=1.694 [95% CI 1.484 to 1.933], p<0.001) and people without prediabetes (HR=1.598 [95% CI 1.326 to 1.926].

They further noticed a difference where non-Omicron infected individuals had a higher risk of diabetes mellitus versus Omicron infected individuals.

In a UK study, they described the risk of diabetes mellitus in the first 12 months after a COVID-19 infection. The risk increases in the first four weeks post-infection (adjusted rate ratio, RR 1.81, 95% CI 1.51- 2.19) and remained elevated from 5-12 weeks (RR 1.27, 95%CI 1.11-1.46) and reduces from 13 to 52 weeks overall (1.07, 0.99 to 1.16).[6]

In a very recent study, Rincon-Guevara et. al. assessed the risk of gestational diabetes mellitus after a COVID-19 infection during pregnancy from a claims-based cohort study.[7] COVID-19 infected pregnant women up to the 21 weeks gestation were matched to controls; pregnant women without COVID-19. Gestational diabetes risk was higher among those with COVID-19 during pregnancy compared to those without (adjusted risk ratio [aRR] = 1.12; 95% confidence interval [CI], 1.08–1.15). The study also reported racial differences with Hispanics and Blacks having higher incidence, compared to the Whites and the Asians.

PATHOPHYSIOLOGY

The pathophysiology of incident diabetes after COVID-19 has been postulated to be from preferential ACE2 expression in human pancreatic tissue, and potentially for a direct effect of the virus on β-cells and the pancreatic microvasculature or ductal cells. On the balance, the risk of development of diabetes mellitus after any viral infection has been well described and documented. It has been postulated as an increase in autoimmunity in pancreas's β-cells.[8] Viral infections appear to trigger autoimmune insulitis and progressive pancreatic β-cell destruction by various mechanisms. These destruction by viral structures can lead to an exaggerated immune response, leading to fulminant Type 1 Diabetes mellitus.[9] Another popular hypothesis is the formation of reactive autoantibodies with the molecular mimicry hypothesis.[10]

CEREBROVASCULAR DISEASES

Never before has a respiratory virus been implicated in causing such extensive cerebrovascular disease. While influenza, other respiratory viruses, and even HIV have been associated with strokes, the degree and extent of cerebrovascular involvement seen with SARS-CoV-2 is unprecedented.

A meta-analysis by Menezes et. al. showed an estimated the risk of strokes as 2.6% (95% CI: 2.0-3.3; P<0.001) and an estimated the incidence of acute cardiovascular disease (CVD) in COVID-19 vs non-COVID-19 patients was 1.16 (95% CI: 0.43-3.14; P=0.77) in their pooled analysis.[11]

The risk factors for stroke incident after COVID-19 infection were seen with diabetes mellitus (OR=2.46, 95% CI: 1.36 to 4.44, P=0.003), hypertension (OR=3.65, 95% CI: 1.69 to 7.90, P=0.005), coronary artery disease (OR=2.24, 95% CI: 1.38 to 3.61, P=0.0010), and atrial fibrillation (OR=2.60, 95% CI: 1.15 to 5.87, P=0.02). The risk was not statistically significant surprisingly for kidney injury (acute or chronic) (OR=1.48, 95% CI: 0.70 to 3.15, P=0.35), chronic obstructive pulmonary disease (COPD) (OR=0.71, 95% CI: 0.31 to 1.67, P=0.40), or smoking (OR=2.14, 95% CI: 0.63 to 7.26, P=0.28). Females had equal risk of develop strokes as males.

Reviewing the aetiological causes of the stroke, the only significant risk in those with strokes after COVID-19 were those from cardioembolic or cryptogenic aetiologies. This likely reflects the association of thromboembolic risk with the SARS-CoV-2 virus. Traditional atherosclerosis, large and small vessel disease were not associated as risk factors after a COVID-19 infection.

The authors concluded that COVID-19 positivity is a significant risk factor for stroke, and there may be a biological plausibility of coronavirus itself being an independent risk factor. They further recommended screening for COVID-19 in individuals presenting with stroke.

Reports of haemorrhagic stroke and cerebral venous sinus thrombosis were also recorded and described in the review by Fraiman et al.[12]

PATHOPHYSIOLOGY

Multiple mechanisms account for the unique association between SARS-CoV-2 and stroke. Some of these include increased thromboxane synthesis with associated platelet activation, rapid turnover of fibrinogen, endothelial dysfunction, and inflammation, as well as thrombus formation following cardiac dysfunction. These manifestations may occur as part of a "cytokine storm".[13]

Other hypothesis includes direct viral action, a mechanism suggested from the retrograde brain infection from the olfactory nerve[14]; or from an endothelitis process.[15]

DEMENTIA

One of the most vulnerable groups of patients for poor COVID-19 outcomes are the elderly, especially those with comorbidities. Many have pre-existing dementia, and

COVID-19 poses a risk to their lives, and their mental faculty.

Cognitive decline after an infection is well known and reported.[16,17] These infections lead to an increased risk of dementia and may persist over the long term. Individuals who are hospitalised (indicating more severe disease) were associated with higher risk. What has been lacking was interventional studies of vaccinations or anti-viral medications in reducing these risks.[18]

With COVID-19, there is increasing evidence of new onset dementia or neurodegenerative diseases in recovered patients.[19,20] Rahmati et al showed a pooled analysis, compared with control groups, COVID-19 survivors have a significant increased risk for new-onset Alzheimer's disease (HR=1.50, 95% CI 1.22-1.85), dementia (HR=1.66, 95% CI 1.42-1.94), and Parkinson's disease (HR=1.44, 95% CI 1.06-1.95, I^2=86%). Shrestha et al performed a meta-analysis consisting of 18 studies that examined cognitive impairment and dementia outcomes in individuals aged ≥65. There were 412,957 patients with a COVID-19 infection versus 411,929 patients without an infection. The overall mean Montreal Cognitive Assessment (MoCA) score in COVID-19 patients was 23.34 out of 30 (95% CI [22.24, 24.43]), indicating cognitive impairment. The surprising figure was that overall, 65% (95% CI 44-81) of patients had new onset cognitive impairment. Fortunately, subgroup analysis indicated that time since infection significantly improves MoCA score and reduced the proportion of patients with cognitive impairment.

Hampshire et al in a large online assessment of cognitive function in adults aged 18 years and older.[21] From a total of 276,840 respondents which completed the questionnaire, they found[1] those with onset early in the pandemic had greater decrements in the global cognitive score than those with later onset (P<0.001), with those infected with the alpha strain had greatest deficits[2]; greater risk of fall in global cognitive score when the illness/symptoms persists for more than 12 weeks[3]; hospitalisation or ICU admission predicted greater fall in global cognitive score. In those with persistent symptoms, memory, reasoning, and executive function tasks were associated with the largest deficits (-0.33 to -0.20 SD).

In a more relatable way, Al-Aly and Rosen[22] tried to put Hamphire's study in a more quantifiable manner in an editorial. They noted the cognitive deficit in patients (commensurate with a 3-point loss in IQ) was evident even in participants who had had mild COVID-19 with resolved symptoms. Participants with unresolved persistent symptoms had the equivalent of a 6-point loss in IQ, and those who had been admitted to the intensive care unit had the equivalent of a 9-point loss in IQ. Reinfections contributed an additional loss in IQ of nearly 2 points, as compared with no reinfection. The authors questioned the functional implications of a 3-point IQ loss, and if these deficits persist or resolve with recovery. They further asked if there was a predisposition to Alzheimer's Disease or other dementia in future. It clearly calls for even more research.

In an elegant study by Dubey et al, they studied 14 COVID-19 survivors with pre-existing dementia, of which 10 of them required hospitalisation.[23] The subjects were pre-existing patients on dementia follow-up and post-COVID-19 infection, these individuals developed more fatigue and depression. Their mean Frontal Assessment Battery and Addenbrooke's Cognitive Examination worsened. MRI revealed new findings of white matter densities that mimicked multiple sclerosis or small vessel disease. The strength of the study describes the pre-post mental cognitive assessment as well as the MRI findings in patients with COVID-19. It brings to question if SARS-CoV-2 virus is more a systemic disease than an upper respiratory tract virus.

PATHOPHYSIOLOGY

We are aware that SARS-CoV-2 virus may directly infect the brain and cerebrospinal fluid (CSF) in addition to a variety of other tissue. This can result in direct virus-induced cellular injury. In addition, as SARS-CoV-2 infects healthy cells, it decreases the bioavailability of ACE2 receptors within the renin-angiotensin-aldosterone system. This leads to a disruption of homeostatic organ function and induces an injury cascade. This ACE2 deficiency is aggravated in cytokine storm, increased vascular permeability, acute lung injury, myocardial injury.[24] Subsequent severe ACE2 deficiency leads to further disruption of the homeostatic organ function, and further injury cascade. Severe COVID-19 disease is thus associated with worse dementia outcomes.

The authors further hypothesised that the virus may induce a chronic neurovirulent state after COVID-19.[24] This is still to be determined.

LONG COVID OR POST ACUTE SEQUELAE OF COVID (PASC)

The discussion on other effects of COVID-19 will not be complete without mentioning long covid. "Long covid" was a term coined by patients themselves who experienced long-term illness after SARS-CoV-2 infection.[25]

Long COVID, also known as PASC (post-acute sequelae of COVID-19), is a complex multisystem disorder that affects nearly every organ system, including the cardiovascular, nervous, endocrine, immune, and gastrointestinal systems, among others. It does not discriminate age, races and social strata. Chief manifestations would include brain fog (or cognitive dysfunction), fatigue, dysautonomia (which may manifest as postural orthostatic tachycardia syndrome, POTS), and exceptional fatigue, which worsen with exertion.

We know very little of the condition. There is no test for it, though there have been attempts to describe the symptoms surrounding it.[26] The National Academies of Sciences, Engineering and Medicine attempted to give it a fuller definition recently and reproduced in full: "Long

Covid is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems."[27]

We know some facts about PASC.

1. Vaccines (before infection) may reduce the risk of long covid. Having had three full doses of an mRNA vaccine is superior to having 1 or 2 doses or none at all.[28]

2. Anti-virals such as nirmatrelvir / ritonavir or molnupiravir, may reduce the risk of long covid.[29]

3. The pre-omicron variants causing a higher risk of PASC.[30]

4. The more severe the illness, from hospitalisation to intensive care stay, the more likely the patient is likely to suffer from PASC.[31] Each infection predisposes the individual from getting PASC again.[32]

5. Individuals who have had mild illnesses may still develop PASC. Studies have repeatedly emphasised that severe COVID-19 infection predisposes to PASC, but the large absolute numbers of patients with mild disease contribute more to the total number of patients with PASC.[33] According to one study, 90 percent of people with PASC had mild COVID-19.[34]

The scientific world suffers from a lack of useful definition of the disease, with incomplete accounting of the manifestations of PASC, and misclassification of other disease pathology as PASC. Even publications citing the recovery figures cast doubt as the right definition of PASC may not have been used.

There is thus little doubt that given the breadth and prevalence of this disease, PASC is already a burgeoning major public health crisis. The overall prevalence of the disease is estimated at 6-7 percent in adults and 1 percent in children.[35] The fear is the continued additional new cases with each successive mutation and infection of the SARS-CoV-2 virus.

There is no effective treatment modality for PASC other than supportive care. As a result, prevention of COVID-19 infection remains the best strategy. Non-pharmaceutical interventions, such as masking and social distancing, combines with vaccinations, are essential in reducing the risk of infection and subsequently lowering the chances of developing PASC. By preventing severe disease, vaccines also help decrease the likelihood of long-term complications associated with PASC. In an infected individual, the use of anti-viral agents (nirmatrelvir-ritonavir and molnupiravir) may help. There may be some benefit for the Japanese 3CL protease inhibitor ensitrelvir in reducing PASC.[36] In a randomised trial, the use of metformin reduced the incidence of PASC by 41 percent.[37]

PATHOPHYSIOLOGY

The pathophysiology of PASC is poorly understood. In part, the disease probably has many subtypes and multiple aetiological causes, risk factors, biological mechanisms and disease trajectory. And this in turn contributes to the difficulty in treatment, each having its own treatment.[38]

Several mechanistic pathways have been described, from viral persistence, immune dysregulation, mitochondrial dysfunction, complement dysregulation, prothrombotic inflammation, and microbiome dysbiosis.

CONCLUSION

The complications and effects of SARS-CoV-2 virus extends beyond the respiratory tract, and the cost of the illness extends beyond death toll as many individuals suffer from persistent complications thereafter, from dementia to PASC to diabetes mellitus; just to name a few. Preventing an infection with an effective, and up-to-date vaccine remains the best preventive measure and consuming an anti-viral agent after falling ill seem to be best hope for most of us.

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LEARNING POINTS

- **Sars COV-2 virus has complications extending beyond pulmonary disease. This includes thromboembolic, cerebrovascular, cardiovascular, gastrointestinal, and autoimmune disease complications as well as the poorly understood long covid or post-acute sequelae of covid (PASC).**
- **Both children and adults have a higher risk of developing diabetes mellitus, with risks highest in the first three months after infection.**
- **Individuals are at an increased risk of stroke after Covid-19. It is an independent risk factor for developing stroke.**
- **New onset risk of dementia or neurodegenerative diseases increases in recovered patients, with cognitive impairment in 65 percent of patients >65 years of age**
- **Long Covid strikes at about 6-7 percent of adults and 1 percent of children.**