Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Diagnostic challenges posed by intersections between post-acute covid syndrome and neurocognitive disorders

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1. Introduction

COVID-19 initially was considered an acute respiratory illness. Its severity was classified on the basis of symptoms of respiratory distress for example, tachypnoea and hypoxia. Accordingly, 80% cases reported asymptomatic or mild illness, about 5–15% being moderate severity and the last 5% requiring hospital-based care (COVID, 2021). Almost everyone was expected to tide over the infection in a couple of weeks. In the acute phase of the illness, central nervous system (CNS) involvement manifests as headaches, confusion, cerebrovascular events like strokes, dizziness and seizures (Wang et al., 2020–Pezzini et al., 2020). Infecting cells bearing the ACE- 2 receptor, it involves multiple organ systems, some of which are now known to run a chronic course. Its understanding as an acute infection has changed as more and more persons now report persistent symptoms running over months (Revised Guidelines on Clinical Management, 2021).

Studies report that between 30% and 40% of those recovered from COVID-19 infections report of lasting symptoms (Chopra et al., 2021). Accurate estimates of persons suffering from Post Acute Covid Syndrome (PACS) are unreliable as yet considering ongoing community transmissions and limitations in health care access. With over 215 million reported cases (coronavirus.jhu.edu, 2021), numbers of those with PACS can overrun any health system. Symptoms persisting beyond 4 weeks after recovery from acute infection range from chest pain and palpitations, shortness of breath, muscle and joint aches and pains, headaches, neuropathy and paraesthesia, fatigue, anosmia, ageusia, myalgia, cardiopulmonary insufficiency, increased propensity for thromboembolic phenomena, micro vascular coagulopathies, demyelinating conditions, cognitive dysfunctions, psychological distress and even sleep and mood disturbances. Collectively, these neuropsychiatric symptoms are sometimes referred to as “brain fog” and can be incapacitating. It is also unclear how long these symptoms will last.

Pathophysiology of COVID-19 related complications is largely unknown. Current research suggests that the chronic inflammation and aberrant immune responses in the host can be a cause of chronic inflammation, resulting in long-term neuropsychiatric symptoms (weeks – months post-acute infection) (Bechter, 2013). Inflammatory markers take much longer to return to pre morbid levels: correlations with PACS are however unclear. Data from the National Survey of Residential Care Facilities in the United States showed that 70% of individuals in these facilities had some cognitive issues, out of which 29% had mild and 19% had severe cognitive impairment (Zimmerman et al., 2014). Coronavirus infection outbreaks in the past like for Severe Acute Respiratory Syndrome (2002–04) and Middle East Respiratory Syndrome (2012) have also had neuropsychiatric symptoms: depressed mood, anxiety, insomnia, irritability, and memory impairments were noted. Psychological factors may also contribute to the development of some long term neuropsychiatric symptoms.

Roughly, 10% of the current global population is aged 65 or older (United Nations, 2021). Estimates of people living with neurocognitive disorder (NCDs) hover around 50 million worldwide with 10 million new cases added yearly. Globally, 80% of the deaths attributable to COVID-19 infections have occurred amongst persons 65 or older: however, age disaggregated data for COVID-19 infection, survival, lasting morbidity and mortality are unavailable.

2. Complex Interplay

CNS infections, inflammation or hypoxic changes have been long known causes of neurocognitive decline. We note here a shared complex interplay of factors that increase the risk amongst elders for neurocognitive disorders and cognitive dysfunction post COVID-19.

2.1. Shared risk factors

Risk factors such as elderly age, comorbid diabetes, comorbid hypertension and obesity predispose persons to develop more severe COVID-19. Similarly, lifestyle behavior such as smoking and excessive alcohol consumption too contribute to such risks. These risk factors also provide elders an increased predilection for developing neurocognitive disorders.

2.2. Increased risk for COVID-19

Challenges in following distancing and hygiene norms contributes to increased risk of acquiring COVID-19 infection. Oftentimes, elders may be apathetic or depressed while not practicing distancing and hygiene.

NCDs are a robust indicator of COVID-19 related deaths and severe

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morbidity. Studies have shown that disproportionately higher hospitalization occurred for elders with COVID-19: those with NCDs were at greatest risk (Bianchetti et al., 2020).

2.3. Likelihood of being dependent or in a congregate setting

People with NCDs are at increased risk of hospitalizations, severe infections. Most are dependent on carers for routine and instrumental activities of daily living. Many live in close proximity in congregate settings which have seen alarmingly high case fatality rates (ltccovid.org, 2021). People with NCDs are prone to understimulation and loss of day structure, worsening the cognitive decline as care personnel are less available during COVID 19.

2.4. Illness and course related factors

COVID-19 infection can result in pulmonary insult that can result in pneumonia, acute respiratory distress syndrome and hypoxemia (Calabrese et al., 2020). During the acute phase, development of dysautonomia, cytokine storm and vascular coagulopathy are likely to be associated with cognitive decline. Those requiring intensive care/ critical care are also likely to develop cognitive dysfunction commonly referred to as post intensive care syndrome (PICS).

2.5. Frailty

Frailty can be considered a manifestation of aging and/or chronic illness. There are two ways of defining frailty. One approach is to define frailty as the presence of any three of the following five: weight loss, exhaustion, slowness, low activity level, and/or weakness. The other approach identifies frailty as the acquisition of multiple unrelated health conditions. Covid 19 also causes severe catabolic stress leading on to weight loss. Confounding post acute covid symptoms may include exhaustion, slowed physical and mental activities and even general malaise. Altogether, COVID-19 increases frailty, worsening elderly persons' health.

2.6. Homeostenosis and immunosenescence

Homeostenosis refers to a reduced ability to revert to or maintain homeostasis in the presence of health conditions: typically seen along with senescence. Notably, age increases vulnerability to acute and chronic inflammatory processes. Relevant to vaccinations we note immunosenescence in which there is a reduced physiological capacity to produce post vaccination antibody response 12.

Elderly individuals have changes in their immune system with age. These changes include (i) decline in neutrophil induced phagocytosis; (ii) decreased production of superoxide anion in macrophages (iii) reduced chemotactic activity of macrophages and phagocytosis; and (iv) inability to maintain peripheral pool of B and T cells, thus reducing the ability to recognize new antigens (Aiello et al., 2019). Recent reports indicate SARS CoV- 2 virus also infects astrocytes and pericytes. It may also contribute to autoantibody production against NMDA receptors (Marshall, 2021).

2.7. Other miscellaneous

Some miscellaneous factors include debility from cancer, treatments with immunosuppressants, pre-existing mental health conditions, thyroid disorders, nutritional insufficiency and any other long standing disabilities. A genetic predisposition towards developing NCD is noted with the presence of ApoE e4 alleles (Kuo et al., 2020) which are associated with both NCDs and the development of vigoral humoral responses/ cytokine storms. Other factors include socioeconomic status, general health access and environmental resources.

3. Murky Picture

Cognitive dysfunctions may worsen or alter the course and presentations of neurocognitive disorders variously. The risk for exposures to the virus may also be considered heterogeneous across NCDs of various etiologies. As countries proceed with vaccinations against Covid 19, they have included senior citizens amongst priority groups - primarily achieved using age thresholds. Consequently, those with NCD of Alzheimer's type may receive the vaccines as most cut offs are at 60 years of age and above. Possibly, for those with NCD of frontotemporal lobar degeneration (FTLD) and its variants, vaccinations are less likely to have been completed on account of earlier ages at onset. Persons with the behavioral variant of the FTLD type NCD are also at greater risks of exposure and more likely to not practice Covid appropriate behavior. Other rare, rapidly progressive NCDs see delayed identification, care access and encounter management difficulties on account of the cognitive derangement. One may speculate that NCDs of other etiologies such as Parkinson's disease might similarly be affected. One can also anticipate that encephalopathic presentations would appear to accelerate progression of minor NCDs to major NCDs. PACs may itself superimpose on the insidious development / progression of other NCDs. Notably, non neurological PACs such as cardiopulmonary insufficiency, decreased oxygenation on account of lung fibrosis/ exertional intolerance, micro vascular coagulopathies with an increased risk of vascular events. Covid-19 can itself precipitate vascular pathologies - increasing risk of dementias. The usually observed step ladder deterioration may be less evident. NCDs of mixed etiologies are even more challenging to diagnose and manage especially as healthcare systems deliver services in a pandemic. Thromboembolic phenomena also occur frequently with SARS Cov 2 infection. The multidirectional interactions between NCDs with diseases such as Diabetes Mellitus, Hypertension and SARS Cov-2 infection can alter clinical presentations in unprecedented ways. As PACs run a chronic course, the clinical wisdom of assessing for severity of NCDs after reversible and acute causes have been addressed will need modification. Management guidelines and protocols need to consider the overlaps between PACS and NCDs and appropriately alter treatment guidelines.

Encephalopathic PACS superimposing Parkinsons or Parkinsons plus syndromes might be mistaken for Lewy Body dementias. Autoimmune encephalitis may develop consequent to COVID-19 infection: superimposed chronic PACS would render identification and diagnosis more difficult. Demyelinating PACS, even Guillain Barre syndromes can confuse neurological presentations. Noteworthily, neuropsychiatric PACS presentations include hypoactive delirium, sleep wake changes, attentional disturbances and apparent fluctuating levels of alertness and activity. The impact on minor and rapidly progressing NCDs of various etiologies would require increased surveillance.

Additionally, COVID-19 has been a cause of depression, anxiety, post-traumatic disorder (PTSD), obsessive-compulsive symptoms and severe fear and anxiety pertaining to being infected with COVID-19 Click here to enter text. These may superimpose on NCD presentations too. Instances of posterior reversible encephalopathy syndrome (PRES) have also been reported amongst elders. Viral effects and drug effects may add to metabolic dysfunctions such as hyperglycemia. Elderly patients who are COVID positive also tend to present with atypically, for example as delirium and functional decline without fever or cardiorespiratory symptoms. Atypicality in presentation may impede an early and timely diagnosis of COVID-19. Dementia and delirium can be considered as age related conditions with shared inflammatory pathogenetic mechanisms. This is noted with the presence of elevated levels of cytokines in both conditions. High levels of cytokines are also associated with other cognitive dysfunctions.

4. Summary

Our understanding of the pandemic since its declaration nearly 18

months ago has transformed from an acute life threatening respiratory infection to a persistent multi system debilitating condition. Its impacts on persons with various health conditions has been disparate yet disparaging. At greatest risk are senior members of the population, especially those in communal and congregate living. PACS could confound the conversion of minor NCDs into major NCDs. PACS may be also likely responsible for "bringing forward" or precipitating major neurocognitive disorders in elderly populations. Health care providers when caring for elders must keep in mind the above considerations and the possible altered clinical presentations. In terms of management of the post acute covid symptoms, scant intervention research has been undertaken for us to be optimistic. Corticosteroid therapy may alleviate persistent pneumonitis and hence improve lung functions with possible improvements in brain profusion. Rehabilitative interventions may yet remain the mainstay for those reporting PACS: for elder persons these may need to be altered to suit the needs of those with PACS concomitant with NCDs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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