Presentation by Dr. Alireza Atri on the neurological issues emerging as a public health matter, due to the COVID-19 pandemic

Selected articles and studies relating to SARS-CoV-2, COVID-19 and the Brain

1. The **Nalbandian et al Review from Nature Medicine on "Long-COVID" (PACS) – it is really a multi-organ disorder** (can download pdf at top right of the page) https://www.nature.com/articles/s41591-021-01283-z

2. **The Lancet Neurology, editorial, April 2021**
"The concept of so-called long COVID has gained prominence in recent months, with some patients reporting persistent neurological manifestations, from **milder symptoms such as headaches, hyposmia, hypogeusia, and fatigue** to **more severe conditions including sleep disorders, pain, cognitive impairment, and (in very rare cases) Guillain-Barré syndrome**. WHO updated their living guidance for the clinical management of COVID-19 in January, 2021, which now incorporates a new practice statement on caring for patients with persistent, new, or changing symptoms after suspected or confirmed COVID-19. The guidance notes that **clinical characterization of long COVID is inadequate** and, therefore, **further research on long-term sequelae is warranted**.
People with neurodegenerative diseases are at particular risk for a poorer outcome after SARS-CoV-2 infection, since pre-existing comorbidity and older age are risk factors." https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(21)00059-4/fulltext

3. **Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized patients with Long-Covid (Graham et al. Ann Clin Transl Neurol May 2021)**; prospective study in 100 patients. Results: **Mean age was 43.2 ± 11.3 years, 70% were female**, and 48%. The most frequent comorbidities were depression/anxiety (42%) and autoimmune disease (16%). The main neurologic manifestations were: "brain fog" (81%), headache (68%), numbness/tingling (60%), dysgeusia (59%), anosmia (55%), and myalgias (55%), with only anosmia being more frequent in SARS-CoV-2+ than SARS-CoV-2- patients (37/50 [74%] vs. 18/50 [36%]; $p < 0.001$). Moreover, 85% also experienced fatigue. Both groups exhibited impaired quality of life in cognitive and fatigue domains. **SARS-CoV-2+ patients performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population** (T-score 41.5 [37, 48.25] and 43 [37.5, 48.75], respectively; both $p < 0.01$).Interpretation: **Non-hospitalized Covid-19 "long haulers" experience prominent and persistent "brain fog" and fatigue that affect their cognition and quality of life.**
https://pubmed.ncbi.nlm.nih.gov/33755344/

4. The recent publication by **Taquet et al.(Lancet Psychiatry 2021;8(5):416–427) supports that the incidence risk of dementia (and neuropsychiatric disorders) is substantially increased and at about 6 months after COVID-19** illness

the **Hazard Ratio is ~2 times of the expected compared to other respiratory tract illnesses** (see Fig 1 and Table 1 – for dementia); and that **if there is encephalopathy (delirium) – which is not uncommon in hospitalized pts w/ COVID-19 – then the incidence risk is much higher (4+ times**) … here's the link to the article (it has also links to other relevant supporting articles) along w/ the abstract (see below) of the paper (which can also be downloaded free from the link). https://pubmed.ncbi.nlm.nih.gov/33836148/

5. **Hampshire el al. 2021 - Cognitive decline in people recovered from COVID-19;** from the Great British Intelligence test which shows **lower performance in those who recovered from COVID-19 whether they were hospitalized or not.** Link is below and article can be freely downloaded. https://www.thelancet.com/action/showPdf?pii=S2589-5370%2821%2900324-2

6. **Yang et al. Nature (June 21, 2021)** – abstract below – the take home and concerning message is: *"We discover microglia and astrocyte subpopulations associated with COVID-19 that share features with pathological cell states that have previously been reported in human neurodegenerative disease4,5,6. **Synaptic signaling of upper-layer excitatory neurons—which are evolutionarily expanded in humans7 and linked to cognitive function8—is preferentially affected in COVID-19. Across cell types, perturbations associated with COVID-19 overlap with those found in chronic brain disorders and reside in genetic variants associated with cognition, schizophrenia and depression. Our findings and public dataset provide a molecular framework to understand current observations of COVID-19-related neurological disease, and any such disease that may emerge at a later date.**"*

   https://www.nature.com/articles/s41586-021-03710-0

   Published: 21 June 2021 Dysregulation of brain and choroid plexus cell types in severe COVID-19 *Nature* **volume 595**, pages565–571 (2021)Cite this article

7. The link to the **Alzheimer's Association International Conference (AAIC July 2021) press release for the symposium** which also has a little overview of the presentations and the abstracts at the very bottom. The abstracts/full press release can also be downloaded (near the top of the page)
   https://www.alz.org/aaic/releases_2021/covid-19-cognitive-impact.asp

   Dr. Tom Wiesniewski's group in NY and others, including us – Dr. Tom Beach at our institute – are finding that, to various degrees, the virus is neurodestructive by direct invasion and through indirect effects (inflammation, immune-mediation, clotting and damage to microvessels in the brain – can cause small bleeds and infarcts, etc.) -- some of these findings suggest only bits of viral DNA get in and thus in some cases this may not be enough to be infectious – but may still be very inflammatory and immune-provoking – in others there is more viable virus (especially in the olfactory bulb – tract – related brain areas). There's no doubt that COVID-illness stokes brain fires and is impacting those who may be even more susceptible. Dr. Wiesniewski's data, presented

at AAIC, from blood test biomarker analyses suggest worrisome changes in pTau/abeta42 ratio (an Alzheimer's biomarker) and other biomarkers that reflect brain neural injury, including NFL and total tau.

8. Here's a link to our study on PubMed (paper is attached – Serrano et al. Feb 2021; Dr. Tom Beach is the senior author; I've copied and pasted the abstract at the very bottom of this email) which is notable and novel not just because it's a brain autopsy study but because it involved a comprehensive, detailed and very rigorous survey of many brain regions.

   Mapping of SARS-CoV-2 Brain Invasion and Histopathology in COVID-19 Disease
   https://pubmed.ncbi.nlm.nih.gov/33619496/

   As stated in our study: "Like other human coronaviruses, SCV2 can inflict acute neuropathology in susceptible patients. Much remains to be understood, including what viral and host factors influence SCV2 brain invasion and whether it is cleared from the brain subsequent to the acute illness".

9. **Antonelli et al. study in 1.2 million+ in UK users of the COVID symptoms app (Lancet Infectious Dis** from 2 days ago – and related links, including an earlier version on medrix)
   https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00460-6/fulltext
   https://plu.mx/plum/a/?doi=10.1016/S1473-3099(21)00460-6
   https://www.medrxiv.org/content/10.1101/2021.05.24.21257738v1

   Findings
   Between Dec 8, 2020, and July 4, 2021, 1 240 009 COVID Symptom Study app users reported a first vaccine dose, of whom 6030 (0·5%) subsequently tested positive for SARS-CoV-2 (cases 1), and 971 504 reported a second dose, of whom 2370 (0·2%) subsequently tested positive for SARS-CoV-2 (cases 2). In the risk factor analysis, frailty was associated with post-vaccination infection in older adults (≥60 years) after their first vaccine dose (odds ratio [OR] 1·93, 95% CI 1·50–2·48; p<0·0001), and individuals living in highly deprived areas had increased odds of post-vaccination infection following their first vaccine dose (OR 1·11, 95% CI 1·01–1·23; p=0·039). Individuals without obesity (BMI <30 kg/m^2) had lower odds of infection following their first vaccine dose (OR 0·84, 95% CI 0·75–0·94; p=0·0030). For the disease profile analysis, 3825 users from cases 1 were included in cases 3 and 906 users from cases 2 were included in cases 4. **Vaccination (compared with no vaccination) was associated with reduced odds of hospitalization or having more than five symptoms in the first week of illness following the first or second dose, and long-duration** (≥28 days) symptoms following the second dose. **Almost all symptoms were reported less frequently in infected vaccinated individuals than in infected unvaccinated individuals, and vaccinated participants were more likely to be completely asymptomatic, especially if they were 60 years or older**.
   Interpretation**: To minimize SARS-CoV-2 infection, at-risk populations must be targeted in efforts to boost vaccine effectiveness and infection control**

measures. Our findings might support caution around relaxing physical distancing and other personal protective measures in the post-vaccination era, particularly around frail older adults and individuals living in more deprived areas, even if these individuals are vaccinated, and might have implications for strategies such as booster vaccinations.

10. The **VA study on kidney function being lowered after COVD-19** –
Ziyad Al-Aly, et al. *Journal of the American Society of Nephrology*, online, Sept. 1, 2021
https://jasn.asnjournals.org/content/early/2021/08/25/ASN.2021060734

11. **de Erausiquin et al**: https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12255 *The Alzheimer's Association and representatives from more than 30 countries—with technical guidance from the World Health Organization—have formed an international consortium to study the short- and long-term consequences of SARS-CoV-2 on the CNS—including the underlying biology that may contribute to AD and other dementias. This consortium will link teams from around the world covering more than 22 million COVID-19 cases to enroll two groups of individuals including people with disease, to be evaluated for follow-up evaluations at 6, 9, and 18 months, and people who are already enrolled in existing international research studies to add additional measures and markers of their underlying biology.*

12. A paper we published in 2019 – led by me and including an international group of renowned academicians and organizations (the journal had a press release on it – link the Eureka Alert that provides an overview is also below)
Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer's Disease and Related Dementias and Strategic Implications for Stakeholders

https://pubmed.ncbi.nlm.nih.gov/31256142/
https://www.eurekalert.org/news-releases/619041

which is even more pertinent now, since the socioeconomic costs and burden of having an earlier wave of cognitive disability and dementia that could impact not just 70+ year old retirees but those who are working in their 50-60's (and who are likely developing AD and ADRD disease changes but were previously not showing symptoms) but who could burn through their cognitive reserve and become disable and suffer from cognitive impairment and dementia can substantially impact our public health and systems, employers and the economy. Just like in AD/ADRD there are many economic costs that seem "hidden" but rise as individuals experience the decline cognition and function (including savings, missed payments, lower credit scores, lost days and work productivity, etc.).