BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Post COVID: Neurology

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Disclosure

I have no financial disclosure or conflicts of interest with the presented material in this presentation.

Learning Objectives:

1) List the neurological symptoms most frequently seen in post-COVID patients

2) Understand the methodological challenges with multiple phenotypes of neurologic dysfunction in post-COVID patients

3) Discuss the overlap between post-COVID syndrome and chronic fatigue syndrome (CFS) in diagnosis and treatment

4) Discuss how to assess for and manage (a) post-COVID headache and (b) concentration difficulties (brain fog)

5) Discuss the role of an interdisciplinary approach (e.g. physical therapy, occupational therapy, as available) for addressing post-COVID symptoms and functional difficulties

Definitions

“Long COVID”

“Long-Haul COVID-19”

“Post-COVID syndrome”

“Chronic COVID syndrome”

“Post-Acute Sequelae of SARS-COV-2 Infection (PASC)”

Defining Syndromes

COVID-RELATED NEUROLOGIC SYNDROME

Encephalitis (limbic, brainstem)

ADEM (Acute disseminated encephalomyelitis)

CNS vasculitis

Guillain-Barre Syndrome (Miller Fisher)

Ophthalmoplegia, CN abnormalities

Stroke (ischemic, hemorrhagic)

Central Venous Sinus Thrombosis

CRITICAL ILLNESS SEQUELAE

Affective disorders

PTSD/Adjustment disorders

Critical illness myopathy

Dyspnea/hypoxia

Pressure nerve injuries related to prone positioning

Weight loss

Toxic/metabolic encephalopathy

LONG HAUL COVID

Brain Fog

Headache

Numbness/tingling

Dysgeusia

Anosmia

Myalgias

Anxiety

Dysphoria

Fatigue

Neurologic Complications of COVID

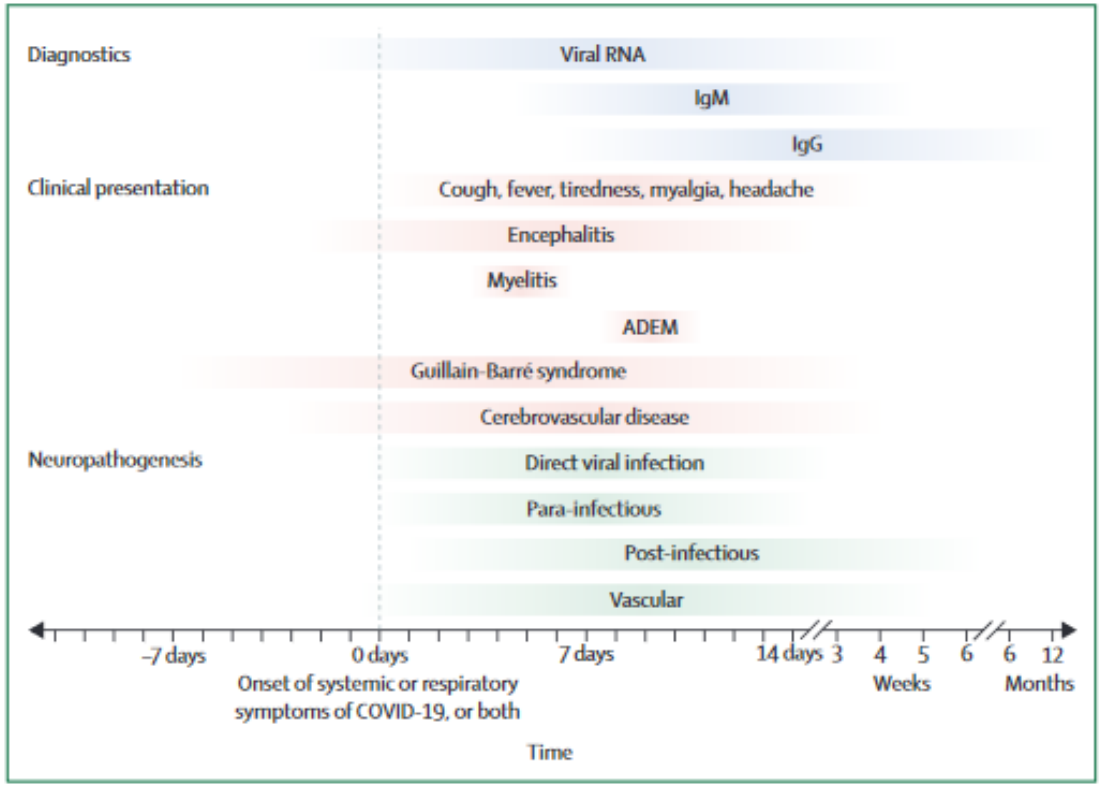
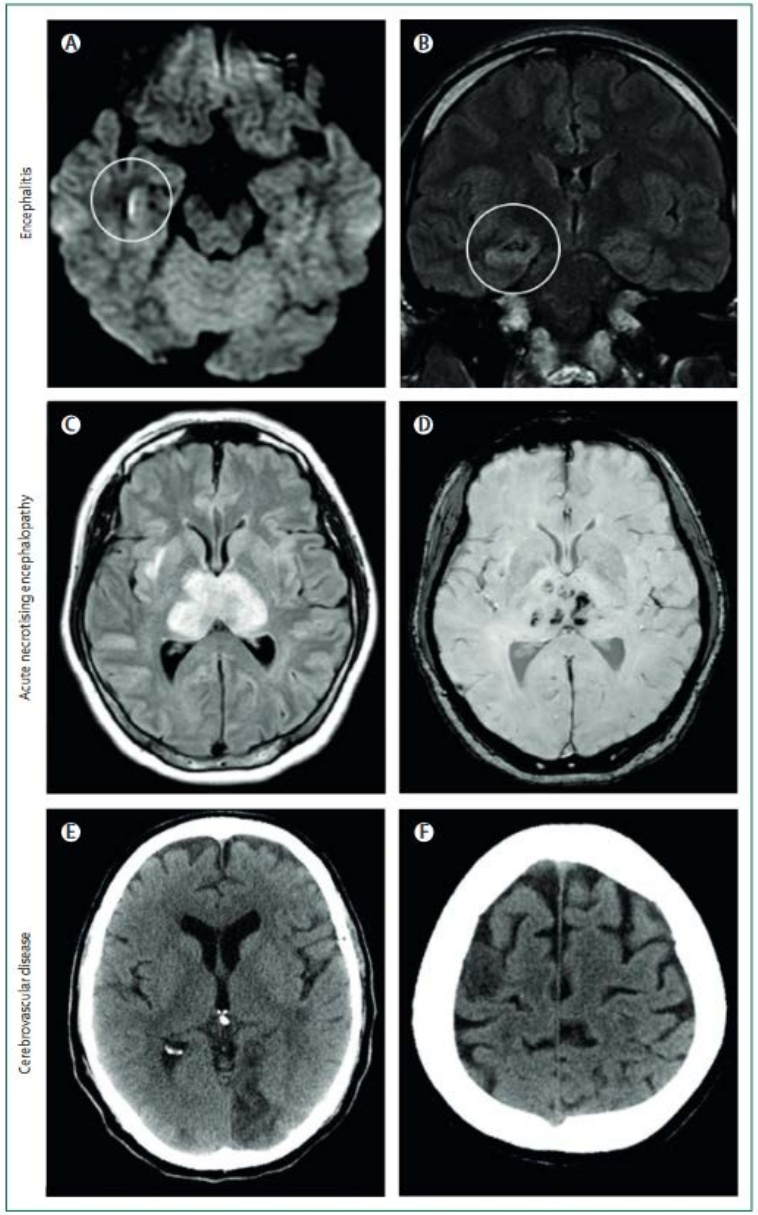


Figure 1: **Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease**



Ellul et al, 2020

First Longitudinal Studies:

- 6 month follow up for 1733 hospitalized patients (Jin Yin-tan Hospital) cohort study (Huang et al, 2021)
- Fatigue/myalgia in 63%
- Sleep difficulties 26%
- Anxiety/depression in 23%

Challenges with seropositivity/negativity

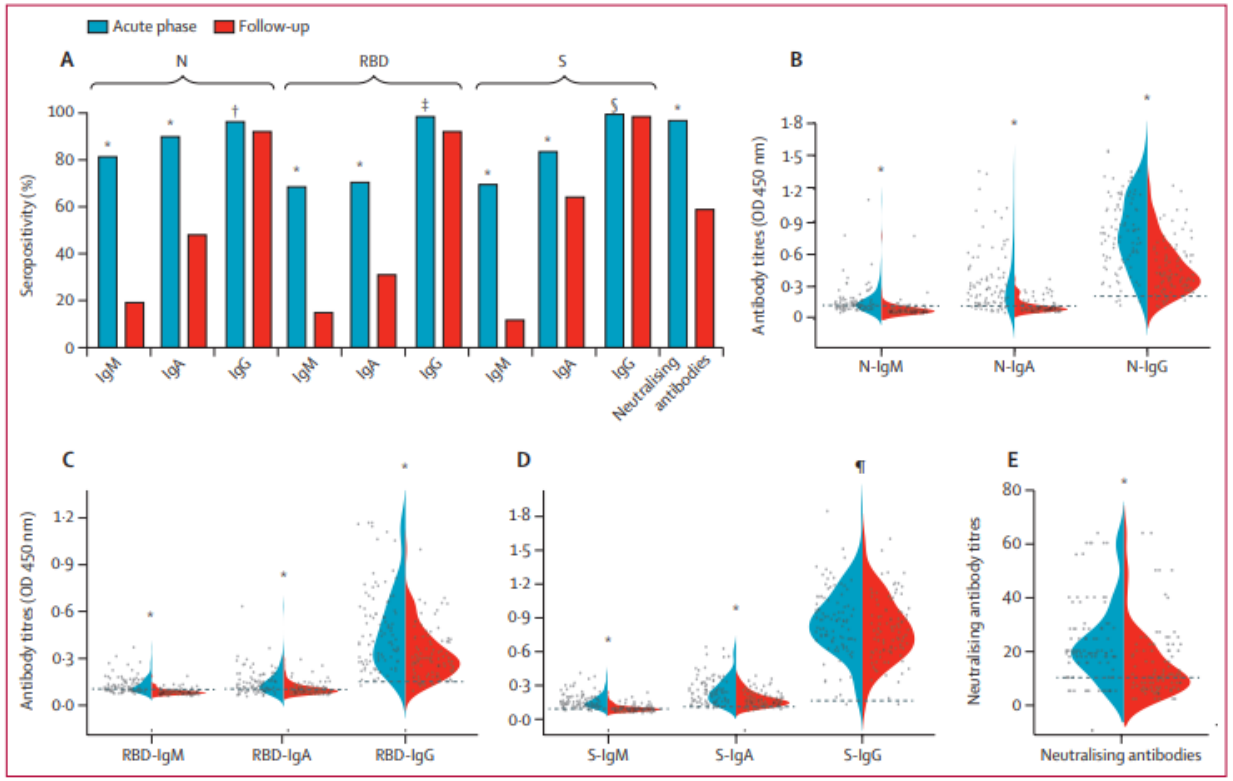


***Figure 3*: Temporal changes of seropositivity and antibody titres against SARS-CoV-2**
(A) Seropositivity of each antibody indicated by the y-axis. Violin plots show the distribution of each antibody feature N (B), RBD (C), S (D), and neutralising antibodies (E) split across baseline and follow-up plasma samples of 94 individuals. The horizontal lines are used to indicate the value used to diagnose positivity from the antibody test. The comparison of antibody test results at acute phase and follow-up was done with paired *t* tests for antibody titres and McNemar test for antibody positive rates. Plasma samples at acute phase were collected during hospital stay with a median duration of 23 (IQR 20–26) days from illness onset. OD=optical density. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. p values indicate a comparison between acute phase and follow-up. *p<0·0001. †p=0·29. ‡p=0·039. §p=1·00. ¶p=0·021.

- Among asymptomatic, 81% had reduction in neutralizing antibody in the early convalescent phase
- Seropositivity of neutralizing antibodies, N-IgM, RBD-IgM, S-IgM, N-IgA, RBD-IgA, S-IgA RBD-IgG and neutralizing antibody titres were significantly lower compared with acute phase
- Further decline in antibody titres may occur between 3-5 months after illness

Huang et al, 2021

CSF Testing

- While case reports have confirmed meningitis/encephalitis with positive SARS-CoV-2 RNA in the CSF, several reports on CSF from hospitalized patients (LP) and post-mortem have not found evidence of frequent direct invasion of the virus
- Anosmia may be due to cytokine storm than direct invasion

Registry of Hospitalized Patients

4,491 hospitalized patients in NYC

- Excluded several groups (including negative tests, not seen by neurology, Hispanic ethnicity)
- Toxic/metabolic encephalopathy 6.8%
- Stroke 2% (ischemic 1.4%, hemorrhagic 0.6%)
- Seizure: 1.6% (half without history of seizure)
- Hypoxic/ischemic injury 1.4%
- Movement disorder 0.9%
- Neuropathy 0.8%
- Myopathy 0.5%
- Guillain-Barre syndrome 0.1%
- No encephalitis/meningitis/myelopathy/myelitis directly attributable to COVID

Of those with Neurologic Sequelae:

- 69% developed prior to hospital admission
- 2% develops symptoms prior to traditional viral symptoms
- 43% developed viral/neurologic symptoms at the same time
- 54% developed neurologic sympptoms after traditional COVID symptoms (median 12 days)
- Significantly older, male (66% vs 57%), more severely ill (higher SOFA scores, intubation rates, acute renal failure rates, ICU admission), white (63% vs 45%) with comorbidities (HTN, T2DM, afib), in-hospital death (35% vs 19%)

Frontera et al, 2021

Non-hospitalized patients

- Prospective study (Graham et al, 2021) of first 100 patients in non-hospitalized ‘long haul’ patients
- Compared 50 seropositive vs 50 seronegative patients
- Predominately female/white
- Premorbid depression/anxiety suggests neuropsychiatric vulnerability
- Fatigue
- Brain fog- abnormal complex attention/memory
- Autoimmune reaction? Lingering reservoirs of virus? Functional neurological disorder?

Review

Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology

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- Compared Long COVID with CFS: 25/29 were reported with all of the major criteria (fatigue, reduced daily activity, post-exertional malaise) were well represented

- Potentially common pathophysiologic mechanisms (immune system dysregulation, hyperinflammatory state, oxidative stress, autoimmunity)

- A particular phenotype of CFS has been liked to viral infections (EBV, HPV-B19)

- There may be overlap in the pathophysiology/treatment

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (ME/CFS) Criteria

Following Three Symptoms:

1) Impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities for >6 months. Accompanied by fatigue (new/definite onset, not lifelong) that is not due to excessive exertion and is not alleviated by rest.

2) Post-exertional malaise (>50% of the time with moderate, substantial, or severe intensity exercise)

3) Unrefreshing sleep

AND: Either

A) Cognitive Impairment

OR

B) Orthostatic intolerance

The file wasn’t able to be loaded, but it’s a short 20 second interview segment of Dr. Fauci talking about CFS from the below link

https://www.youtube.com/watch?v=wRmGj0evJGw

Diagnosis/Management

- Careful history
- Rule out other comorbid conditions (CBC, renal function, glucose, LFTs, TSH, rheumatologic disease, celiac disease, sleep apnea, etc)
- PACE trial: 5-year UK clinical trial published in LANCET found that CBT (cognitive behavioral therapy) and GET (graded exercise therapy) were helpful, though due to a variety of methodologic considerations, this has become *extremely controversial*
- These patients are vulnerable, and there may be psychologically based factors that are self-exacerbating
- There are no tests, cures, or drugs approved by the FDA for ME/CFS

Management of ME/CFS:

- Fatigue: Avoiding Post-Exertional Malaise (PEM)
  - Patients with ME/CFS **do not tolerate vigorous aerobic exercise**
  - Activity Management/'Pacing'/'Energy Envelope'
  - Rehab specialists/Exercise Physiologists/Occupational Therapists
  - May need additional devices (wheelchairs for longer distances)
  - Stimulants (Methylphenidate, Modafinil, Amantadine) may be trialed though their use is controversial
- Sleep
  - Sleep hygiene measures
  - Rule out other sleep disorders (apnea, RBD, narcolepsy)
  - Sleep pharmacotherapy (Melatonin, Trazodone, Tramadol)
  - Manage Expectations

Management of ME/CFS:

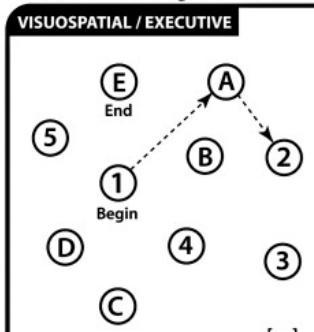
- Pain
  - Workup and evaluation of sources of pain
  - Acupuncture
  - Massage, heat packs, water therapy, acupuncture
  - Pain psychotherapy/counseling
  - Physical therapy/Occupational Therapy
- Cognitive Fog
  - Evaluation for other etiologies of memory impairment
  - Memory aids (calendars)
  - Pomodoro Method
  - Stimulants (controversial)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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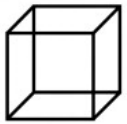


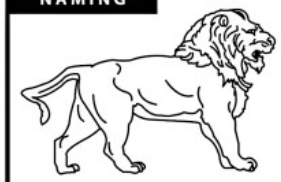
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING



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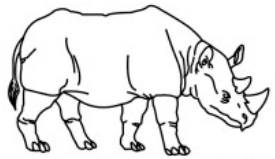

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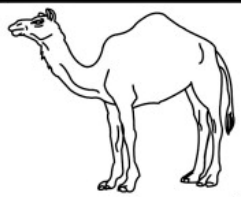

[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Management of ME/CFS:

- Depression/Anxiety- may be reactive
  - Psychotherapy
  - Movement strategies (stretching, yoga, tai chi, massage)
  - SNRI (Duloxetine or Venlafaxine)
  - Workup and evaluation of sources of pain
- Orthostatic Intolerance
  - Increase fluids, electrolytes, salts
  - Beta blockers for POTS
  - Fludrocortisone, midodrine, or pyridostigmine

Headache and COVID

- Multiple phenotypes (Migraine, Tension-type, Cough, New Daily Persistent Headache (NDPH) have all been widely reported in mild and severe (hospitalized) patients
- (Graham et al, 2021): Headache was present in 68% of non-hospitalized ‘long haul covid’ patients
- Differentiating characteristics (in a questionnaire) include:
  - Anosmia-ageusia (OR= 11.4), Bilateral pain (3.37), Analgesic-resistant (2.61), GI symptoms (2.13), Male gender (2.06), >72 hrs (OR 1.93), >48 hrs (1.63)
- Several phenotypes may be present at different times during COVID-infection
- No data to guide treatment currently:

Summary:

- COVID 19 has a variety of neurologic and neuropsychiatric sequelae
- There are likely different syndromes of COVID neurologic sequelae which methodologically complicates current studies
  - Acute infection which can cause system effects/primary CNS disease
  - Sequelae of critical illness in severe COVID patients
  - “Long haul” COVID syndrome that mimics ME/CFS
- Post-mortem and LP studies have found that direct CSF invasion to be rare
- Multidisciplinary care is vital for each of these phenotypes and may involve PT/OT/SLP, psychotherapists, and other outside specialists
- Fatigue, cognitive fog, sleep disturbance, and headache are common and may be refractory to traditional pharmacotherapy; management is largely supportive
- Anecdotal (not yet peer reviewed) evidence that some patients improve after vaccine administration
- There may be significant cross-cultural differences in the neurologic and neuropsychiatric sequelae

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