POST-ACUTE COVID-19 SYNDROME (PACS)

Advisory Council to the Director
Dec 10, 2020

Walter J. Koroshetz, MD
Director, National Institute of Neurological Disorders and Stroke
1) Problem statement
2) Clinical manifestations and knowledge gaps
3) Leveraging our assets and strengths
Post-Acute COVID-19 Syndrome

From ‘Brain Fog’ to Heart Damage, COVID-19’s Lingering Problems Alarm Scientists
J Couzin-Frankel

Long After the Fire of a COVID-19 Infection, Mental and Neurological Effects Can Still Smolder
E Cooney
Long-Term Effects of Covid-19 Infection

COVID-19 Affects Multiple Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cell Type</th>
</tr>
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<tbody>
<tr>
<td>nasal</td>
<td>goblet/ basal/ciliated</td>
</tr>
<tr>
<td>lung</td>
<td>secretory/ basal/multiciliated</td>
</tr>
<tr>
<td>ileum</td>
<td>epithelial enterocytes</td>
</tr>
<tr>
<td>heart</td>
<td>endothelial</td>
</tr>
<tr>
<td>eye</td>
<td>myocyte</td>
</tr>
<tr>
<td>liver</td>
<td>corneal epithelium</td>
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<tr>
<td>bladder</td>
<td>cholangiocytes</td>
</tr>
<tr>
<td>kidney</td>
<td>fibroblast</td>
</tr>
<tr>
<td>pancreas</td>
<td>proximal tubule</td>
</tr>
<tr>
<td>brain</td>
<td>ductal epithelium</td>
</tr>
<tr>
<td>prostate &amp; testis</td>
<td>oligodendrocyte</td>
</tr>
<tr>
<td>placenta</td>
<td>epithelial</td>
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</tbody>
</table>

SARS-CoV-2 interacts with ACE2 and TMPRSS2 to internalise the virus into an endosome, activating CTSL to further infect the cell.
CLINICAL MANIFESTATIONS AND KNOWLEDGE GAPS
COVID-19: Persistent Symptoms in Hospitalized Patients
A Multi-Organ, Multi-System Clinical Presentation

120 patients (mean = 111 days post admission)

**Persistent symptoms**

- Fatigue 55%
- Difficulty breathing 42%
- Memory loss 34%
- Sleep disorder 32%
- Attention disorder 27%
- Significant hair loss 20%
- Cough 17%
- Loss of smell 13%
- Chest pain 11%
- Loss of taste 11%

https://doi.org/10.1016/j.jinf.2020.08.029

143 patients (mean 60 days post onset)

COVID-19: Persistent Symptoms and Health-related Quality of Life

A Multi-Organ, Multi-System Clinical Presentation

120 patients (mean = 111 days after admission for COVID-19)

Professional and physical activities

- Not yet resumed to sports (engaged regularly pre-COVID) 28%
- Slower walking 29%
- Not yet returned to work (worked pre-COVID) 32%

Among symptomatic non hospitalized patients with positive test for SARS-CoV-2, 35% not returned to baseline health 2-3 weeks after testing

- Older age and comorbidities associated with lack of return to baseline health
- 19% of young adults (18-34) with no comorbidities had not returned to baseline health
- In contrast 90% of influenza outpatients recover within 2 weeks
New diagnoses of anxiety, insomnia, dementia, and mood disorders, as well as psychiatric disorders in general, were increased after COVID-19 illness.
Cross-talk among injured organs might explain post-acute COVID syndrome
cMRI revealed cardiac abnormalities in 78%, and gadolinium enhancement in 60%, (N-100), median 72d p dx.

- Independent of preexisting conditions, severity, and overall course of acute illness, and time from original diagnosis
- Lower EF, Higher LV volume, Higher hsTroponin
- 3 patients biopsied, demonstrate inflammatory infiltrates, no virus

15% of Ohio State University athletes had myocarditis after mild COVID-19, and fully half had CMR abnormalities
Autopsy reports suggest direct cardiac involvement
- Lindner showed virus in myocardium in majority of 39 autopsy cases with evidence of viral replication:
  - Direct viral infection leading to myocardial injury??
- Other reports have also shown myocardium infiltration of both innate and adaptive immune cells:
  - Potential for cardiac fibrosis and decrease cardiac function in the long term??

Conclusion: Long-term follow-up of recovered COVID-19 patients is necessary to assess risk of heart failure and other chronic CV complications
COVID-19: Long-term lung sequelae

- Carvalho-Schneider et al. followed 150 patients with non-critical COVID-19 for 2 months after symptoms onset
  - Persistent dyspnea: 36.7% pts at 30d, 30% pts at 60d
  - Conclusion: A prolonged medical follow-up of patients with COVID-19 seems essential, whatever the initial clinical presentation (never admitted patients in this case)

- Zhao et al. analyzed 55 COVID-19 survivors (non-critical cases) 3 months after hospital discharge
  - Radiological abnormalities: 71% pts
  - Lung function abnormalities: 25% pts
  - Elevated D-dimer on admission predictive of impaired DLCO at 3 months post-d/c (in some pts, only abnormality)
  - Conclusion: It is necessary to follow up COVID-19 patients to appropriately manage persistent or emerging long-term sequelae
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361108/ July 2020
Nervous System and COVID-19

Manifestations during infection

- Stroke - large & small vessel occlusion, micro-bleeds
- Confusion and depressed level of consciousness
- Loss of smell
- Muscle/Nerve pain and weakness
- Meningitis/encephalitis
- Seizures
- Asymptomatic hypoxia

Rare Post-viral syndromes

- Delayed injury to brain and spinal cord (multiple sclerosis- like).
- Delayed injury to nerves (ie. Guillain Barre Syndrome)
- Parkinsonism
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

LR Feldstein, S Li et al., for the Overcoming COVID-19 Investigators, and the CDC COVID-19 Response Team

- 186 patients in 26 states, median age 8.3 years
- 80% required ICU care, 20% required mechanical ventilation
- 71% with involvement of at least 4 organ systems
- 73% with no underlying conditions
Health Disparities in COVID-19 Risk and Mortality

Black & Indigenous Americans experience highest death tolls from Covid-19
Cumulative actual Covid-19 mortality rates per 100,000, by race and ethnicity, April 13-Nov. 10, 2020

Predisposing Conditions
- Cancer
- Chronic Kidney Disease
- COPD
- Heart Conditions
- Obesity
- Pregnancy
- Sickle Cell Disease
- Smoking
- Type 2 Diabetes

Source: APM Research Lab. Get the data. Created with Datawrapper.

What we need to understand about recovery

• What is the spectrum of clinical “recovery” from COVID-19 infection?
  • Of those with symptoms 2-3 weeks post infection the rate of improvement is not yet known.

• What interventions might enhance or hasten recovery?
  • In the immediate post infection phase as well as in the more chronic phase

• What is the spectrum of tissue injury due to COVID-19 infection?
  • Are the various tissue injuries reversible, static, or contribute to progressive organ dysfunction
  • How to identify those with tissue injury in heart, lung, nervous system, kidney

• Will unabated symptoms lead to chronic illness(s) in a subset of people?
  • If so, what is its pathophysiology (s).
  • Is so, what are the drivers of special vulnerability or resilience across the lifespan and in special populations

• Will COVID-19 infection predispose people to other diseases in the future?
Preparing for the Possibility of a Post-COVID Storm

- Current expectation is that up to tens of thousands could suffer from sequelae of acute infection with COVID-19

- Time is of the essence - interventions are expected to have a greater effect the earlier they are employed

- The multi-organ involvement calls for a coordinated research program drawing on the expertise in multiple NIH Institutes and Centers
LEVERAGING OUR ASSETS AND STRENGTHS

A Few Examples
NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

Note: Includes existing and new assets

Evaluation of Treatment and Preventive Strategies for Post-acute COVID-19 Sequelae

Longitudinal Community-Based Cohorts
- Large Scale EHR-/Health Systems-based Cohorts
- Longitudinal Deeply Phenotyped Community-based Cohorts

Case-based Registry Cohort of Persons with hx SARs COV-2 Infection
- Individuals Enrolled in NIH COVID-19 Clinical Trials
- Individuals Enrolled in NIH COVID-19 Case Registries/Observational Studies/Clinics

Data Coordination/Harmonization and Analytics Framework
NIAID: Observational Cohorts

- International Observational Study of Outpatients With SARS-CoV-2 Infection
- PREVAIL-XI: PREVAIL COVID-19 Observational Study
- Chasing COVID Cohort
- Immunophenotyping in a COVID-19 Cohort (IMPACC)
- Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)
- Observational study at San Antonio VA

- EHR based
  - Corona infectious virus epidemiology team (CIVETs)
  - Big Data Driven Clinical Informatics & Surveillance (BDD-CIS) project
Collaborative Cohort of Cohorts for COVID-19 Research (C4R)

• 70,000+ participants from 14+ longstanding longitudinal population- and disease-based cohorts
  • Highly diverse with multi-racial, multi-ethnic populations
  • Broad age range, national span of geographic reach
  • Enriched for at-risk populations (e.g., pre-existing lung disease)
  • Genotyped and deep phenotyping across multiple domains
    • Imaging, biomarkers, social determinants, lung function, anthropometry, vascular function, cognition, genetics and other -omics

• Leverage existing infrastructure, processes, data, and biospecimens from available cohorts/existing patient populations
  • Embed systematic protocolized assessment in existing cohorts
  • Include multiple nested sub-studies

• Collaboration with NHLBI, NINDS, and NIA
NHLBI platforms leveraged for development of COVID-19 long-term follow-up cohorts

Registry and observational cohort study (CORAL) follow-up of COVID-19 inpatients (n = 3,000) leveraging critical care network

- Clinical characteristics, Rx, biology, and outcomes using retro/prospective methods
- Deidentified repository of clinical, imaging, and biologic data and biospecimens

*Serves as a pilot for:*

Larger Scale Multicenter Prospective COVID-19 Registry Cohort

- Leveraging the diagnosis, screening, and referral cores and clinical centers
- COVID-19 enriched and diverse cohort spanning pre-hospital, hospital, and post-discharge enrollment
- Systematic and protocolized collection of health data, biospecimens, and imaging on post-COVID pts for long-term, post-infection follow-up studies; utilizing full spectrum of data (EHR mining to IPLD)
- Fully consented for data sharing and follow-up
NIAID: A Longitudinal Study of COVID-19 Sequelae and Immunity

• Adults who have recovered from COVID-19 or were in close contact with someone with COVID-19 but did not become infected
• Evaluation includes history, physical exam, mental health exam, imaging and functional tests, laboratory draws
• Study visits at NIH Clinical Center every 6 months for 3 years
• Goal enrollment: 900
Funded programs to assess long-term neurological effects of COVID-19

- **Natural History of Post-Coronavirus Disease 19 Convalescence** Avi Nath (NINDS), Brian Walitt (NINR)
  - To observe and describe the range of medical syndromes that occur following an acute COVID-19 infection in 1000 adults within six months of their convalescence from an acute COVID-19 infection

- **Observational Study of Neurologic Function after COVID-19 Infection** Avi Nath, Bryan Smith (NINDS)
  - To investigate brain MRI and components of neurologic function in those with prior SARS-CoV-2 infection and persistent neurologic symptoms

- **NIH COVID-19 NeuroDataBank and NeuroBioBank** (at NYU Langone)
  - Building a national (NeuroDatabank and BioBank) to document and study neurological complications of COVID

- **Projects (through supplements)**
  - 2 studies examining **cognitive sequelae** of the biological effects of COVID-19 on the nervous system-cognitive batteries every 3 months for one year via phone to determine cognitive trajectories over time
  - **Neurofilament light chain (NfL) protein in** predicting long term cognitive, behavioural and functional prognosis for ICU COVID patients
  - Add-on study to college student cohort (followed for post EBV **chronic fatigue** syndrome) to assess long-term health post COVID-19
<table>
<thead>
<tr>
<th>GOAL</th>
<th>To improve understanding of and develop strategies to treat and prevent post-acute manifestations of SARS-CoV-2 infection through a multi-pronged research framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand</td>
<td>COVID-19 clinical sequelae, risk factors for illness, severity, outcomes</td>
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<tr>
<td>Recognize</td>
<td>SARS-CoV-2 infected individuals at risk for post-acute manifestations</td>
</tr>
<tr>
<td>Identify</td>
<td>Pathogenic mechanisms and therapeutic targets</td>
</tr>
<tr>
<td>Develop</td>
<td>Therapeutic strategies for people with post-acute sequelae</td>
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DISCUSSION