Medical Research & COVID-19: Updates from NIH's National Institute of Neurological Disorders and Stroke (NINDS)

Walter Koroshetz, MD, Director, NINDS
May 4, 2021
How to address an emerging problem: recovery from SARS-CoV-2 infection?
COVID-19 Affects Multiple Organs

The Scientist, April 2020
Is SARS-CoV-2 in the brain?

- Post-mortem study of brains of individuals who had COVID-19
- No evidence of viral infection in brain
- Widespread evidence of inflammation and damage, including:
  - Multifocal breakdown of the blood brain barrier, small infarcts, microhemorrhages, inflammatory infiltrates, and microglial nodules,
  - Infection can lead to blood clots $\rightarrow$ stroke

Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from COVID-19

Nath et al, NEJM, NINDS
COVID-19 NEURO DATABANK/BIOBANK

PIs Andrea Troxel, Sc.D.; Eva Petkova, Ph.D.

Data repository
Documented COVID-19 inpatients & outpatients with new or worsened neurological conditions
Infants born to mothers with COVID-19 during pregnancy

Objectives:
Rapidly collect high-quality data and linked biospecimens
Accelerate pace of research
Leverage talent, commitment, experience of all collaborators
Data and biospecimens available for sharing

Participation from Academic medical centers and individual medical practitioners
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.
# The Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

*High variability in symptoms and symptom severity*

*PASC can affect individuals who had severe, mild, or asymptomatic primary infection*

*Preliminary studies indicate 10-60% of COVID infections result in PASC*

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Cardio/Pulmonary</th>
<th>Gastrointestinal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
<td>• Shortness of breath</td>
<td>• Diarrhea</td>
<td>• Elevated temperature</td>
</tr>
<tr>
<td>• Memory/word finding difficulites</td>
<td>• Dry cough</td>
<td>• Decreased appetite</td>
<td>• Chills, flushing sweats</td>
</tr>
<tr>
<td>• Concentration difficulties, e.g., “brain fog”</td>
<td>• Chest pain</td>
<td>• Nausea</td>
<td>• Sore throat</td>
</tr>
<tr>
<td>• Executive function difficulites</td>
<td>• Exercise intolerance/ Post-exercise malaise</td>
<td>• Abdominal pain</td>
<td>• Extreme thirst</td>
</tr>
<tr>
<td>• Sleep disorders</td>
<td>• Postural Orthostatic Tachycardia</td>
<td></td>
<td>• Skin changes</td>
</tr>
<tr>
<td>• Pain syndromes - muscle, joint</td>
<td>• Palpitations/ Fast heart rate</td>
<td></td>
<td>• Menstrual changes</td>
</tr>
<tr>
<td>• Abnormal sensations - tingling</td>
<td>• Myocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Headache</td>
<td>• Pulmonary fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Postural Orthostatic Tachycardia</td>
<td>• Dizziness/balance problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abnormal smell/taste</td>
<td>• Confused state/psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Visual abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mental Health**

- Post traumatic stress disorder
- Anxiety
- Depression

See Davis HE et. al. (2021) Characterizing Long Covid in an International Cohort: 7 months of symptoms and their impact. medRxiv preprint

High-dimensional characterization of post-acute sequelae of COVID-19

Veterans Administration Study of incident diagnoses 1-6 months post COVID-19 infection

Fig. 3 | Risks and burdens of incident pre-specified high resolution post-acute COVID-19 outcomes at 6 months in mutually exclusive cohorts of people with non-hospitalized COVID-19 (green), people hospitalized for COVID-19 (orange), and people admitted to intensive care for COVID-19 (blue) during the acute phase (first 30 days) of the infection.
New diagnoses of anxiety, insomnia, dementia and mood disorders as well as psychiatric disorders in general, were increased after COVID-19 illness
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?
NIH PASC Research: Toward Recovery from SARS-CoV-2 Infection

**Goal**

Rapidly improve our understanding of and ability to treat and prevent PASC

**Key Scientific Questions**

1. What are the clinical spectrum of and biology underlying recovery from infection over time?

2. What are the incidence/prevalence, natural history, clinical spectrum, underlying biology, and subtypes of PASC?

3. Does infection promote delayed organ dysfunction or increase the risk of developing other disorders?
PASC Characterization Strategy

SARS-CoV-2 Recovery Clinical Study

- Acute Cohort
- Acute Cohort
- Acute Cohort
- Acute Cohort
- Post-Acute Cohort
- Post-Acute Cohort
- Post-Acute Cohort
- Post-Acute Cohort

Enrolled at time of COVID+ dx

Enrolled when present with Post-Acute sx

Clinical Characterization/Phenotyping

Streamlined core protocol elements (exam, labs, functional tests, imaging) to capture spectrum of PASC

Examples of assessments could include:
- Imaging (CT, MRI, Echo)
- Functional Assessments (PFTs, 6MW, ETT)
- Neuropsychiatric assessments (screening, questionnaires, testing)
- Psychosocial Factors, SDoH
- Immunophenotyping
- Biospecimens (Biomarkers, Multi-omics)
- More in-depth assessments as indicated (e.g., fpgPET)

Notes:
- Includes Peds Cohorts Studies
- Includes new and leveraged ongoing studies
- Broad Spectrum of Recovery Phenotypes

SARS-CoV-2 Recovery Cohort
What are the clinical spectrum of and biology underlying recovery from infection over time?

Does infection lead to later organ dysfunction or increase the risk of developing other disorders?

Autopsy studies of tissue injury and persistent viral effects.

NIH SARS-CoV-2 Recovery Cohort

PASC Recovery Cohorts—“Meta-cohort”
Leverage existing cohorts/Establish new cohorts/Engage long COVID community

EHR- and Other Real-World Data-Based Studies
PASC Initiative Components

**SARS-CoV-2 Recovery Meta-Cohort**

- Clinical Recovery Cohort
- Autopsy Cohort (Acute and PASC)
- EHR-/ Other Real-World Data-Based Studies

**Investigator Consortium**

- In this innovative approach, all study investigators will work together to achieve **speed and scale**:
  - Develop a streamlined set of common core protocol elements (specific hypotheses, design elements, screening evaluations, exams, lab tests, functional assessments, imaging, etc.)
  - Conduct rapid systematic screening and follow-up evaluations of infected individuals, to provide a resource for in-depth multi-disciplinary phenotyping, and to pool data and share biospecimens and data from across studies

The goals of the Recovery Cohort and Investigator Consortium will be supported by **administrative coordination and oversight** as well as **three cores**:

- Clinical Science Core
- Data Resource Core
- PASC Biorepository Core
**Key Milestones and Timeline**

**February**
- OTA approved
- NOITP issued
- ACC Launched
- Website and listserv Launched
- Research Opportunity Announcements issued for Cores and Research Studies

**March**
- Technical Assistance Workshop
- 273 PASC Applications Received
- Screened >600 potential reviewers to secure 210 SEP and 170 SMEs for review of PASC Applications
- Posted 112 FAQs in response to >700 questions received

**April**
- 273 PASC Applications Reviewed
- NOITP issued for Mobile Health Platform and Data Repositories
- Cores Award Recommendations
- Draft Common Screening Assessment and Protocol
- PASC listening sessions launch

**May**
- PASC Awards made
- PASC Cores launch
- PASC Consortium convenes and studies launch
- ROAs issue for Mobile Health Platform and Data Repositories
The public may direct questions about the program to: PASCinfo@nih.gov.
Questions