Characterizing Long COVID in an International Cohort

Hannah Davis
Patient-Led Research Collaborative
Who we are

- Long COVID patients, all onset in March 2020, all still symptomatic
- Met in Body Politic Support Group’s data channel
- Previously researchers:
  - Survey design & participatory design
  - Qualitative research
  - Public policy
  - Research engineering
  - Data science & machine learning
  - Psychiatry (NY Presbyterian/Weill Cornell Medicine)
  - Neuroscience (University College London)
- IRB from University College London
Survey

● First report on Long COVID May 2020
● Second report December 2020:
  ○ “Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact”
● 205 symptoms in total over 7 months
● Impact on work/life, antibody testing, diagnostics, medical support, coping
● 250+ questions, average time 70 minutes
● 9 languages:
  ○ English, French, Spanish, Portuguese, Arabic, Russian, Indonesian, Italian, Dutch
● Survey questions are open sourced, translations are available at PatientResearchCOVID19.com
Demographics

- Total data: 6,500+ respondents from 84 countries
- First paper only on “first wavers” (onset between December-May):
  - 3,762 respondents from 56 countries
  - Symptoms > 28 days
  - 92% not hospitalized!
  - Wide age range:
    - 31.5% age 18-39
    - 31% age 40-49
    - 37.7% age 50+
  - 18% healthcare workers
  - 6.8% recovered
Recovery

- Recovered: 91 days of symptoms
- Unrecovered: 144 days at time of survey

- Recovered <90 days: symptoms peaked in week 2 (11 symptoms)
- Not recovered <90 days: symptoms peaked in month 2 (17 symptoms)

- Those not recovered by month 7 experienced 14 symptoms on average in month 7
- 21%: severe or very severe after month 6
10 categories

1. Systemic
2. Neurological*
3. Gastrointestinal
4. Pulmonary
5. Dermatologic
6. Immunologic/Autoimmune
7. Cardiovascular
8. Musculoskeletal
9. Reproductive/Genitourinary/Endocrine
10. HEENT (Head, Ears, Eyes, Nose, Throat)
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Top 10 symptoms by category:

**Systemic**
- Breathlessness
- Dry cough
- Breathing difficulty (normal O2 level)
- Cough with mucus production
- Sneezing
- Rattling of breath
- Other Respiratory and Sinus
- Coughing up blood

**Pulmonary**
- Tightness of chest
- Muscle aches
- Joint pain
- Stiff neck
- Muscle spasms
- Bone ache or burning

* Neurological symptoms may include headache, confusion, numbness or weakness in the arms or legs, blurred vision, difficulty with speech or trouble understanding speech, and loss of balance or coordination.
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Neuro: 9 subsections

1. Sensorimotor
2. Cognitive Functioning
3. Sleep
4. Taste and Smell
5. Speech and Language
6. Headaches
7. Memory
8. Hallucinations
9. Mood
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Top symptoms at Month 6
Symptom timecourse

a. Systemic
- Chills, flushing, sweats
- Elevated temp (98.8-100.4°F)
- Fatigue
- Fever (≥100.4°F)
- Low temperature
- Other temperature issues
- Post-Exertional Malaise

b. Reproductive, Genitourinary and Endocrine
- All menstrual, period issues
- Bladder control issues

c. Cardiovascular
- Bradycardia
- Palpitations
- Pain/burning in chest
- Tachycardia
- Visibly bulging veins

d. Musculoskeletal
- Bone aches
- Joint pain
- Muscle aches
- Muscle spasms
- Tightness of chest

e. Immunologic and Autoimmune
- New allergies
- New anaphylaxis reactions

f. Head, Ear, Eye, Nose, Throat (HEENT)
- Hearing loss
- Other ear, hearing issues
- Other eye issues
- Runny nose
- Sore throat
- Tinnitus
- Vision symptoms

- Acute confusion
- Brain fog
- Memory issues
- Slurring words
- Speech and language issues
Symptom timecourse
Symptom onset (mean)
a. 164 participants experienced break in their symptom timecourse

Symptom Breaks

b. Probability of temporary break in symptoms across all subjects

Time (since illness onset)
Neuro: 9 subsections

1. Sensorimotor
2. **Cognitive Functioning**
3. Sleep
4. Taste and Smell
5. Speech and Language
6. Headaches
7. Memory
8. Hallucinations
9. Mood
Cognitive Dysfunction & Memory

d. Impact of memory and cognitive dysfunction on daily life

- Able
- Unable - mild to severe

- Percentage of patients

- Work
- Make serious decisions
- Communicate your thoughts
- Conversations with others
- Drive
- Remember medication
- Follow simple instructions
- Watch children
- Cook or use hot items
- Shower or bath regularly
- Remember month or year
- Feed yourself
- Return home without getting lost
Cognitive Dysfunction & Memory

- No difference in memory by age
- No difference in cognitive dysfunction by age
- No difference in impact on life by age
Cognitive Dysfunction and Memory Loss

"mother has started to help me take the medications I’m on because I can’t remember if I’ve taken them immediately after having the bottle in my hand"

"was trying to fill out a mortgage application form and couldn’t remember our rent. I put £3750 a month. My partner said, no it’s £1375. So I put £13750. My partner said no, so I tried several more times - I was just guessing numbers"

"sitting on the toilet to pee and had to stop for a second to think if I was really there and not about to pee myself or the bed"

"don’t remember what I did in March or April up until the last week of April. I had almost nothing on my schedule. I don’t know what I did"

"put food on the gas stove and walked away for over an hour, only noticing when they were smoking/burning"

"forget how to do normal routines like running a meeting at work"

"felt lost driving and had to stop and find my position in a GPS to be able to drive back home. It’s a route I have done hundreds of times"

"have trouble comprehending new ideas"

"can’t hold multiple trains of thought […] If I tell myself I have to water my plants, I must do it before another thought comes into my mind because otherwise I will forget"

"can’t follow plots in movies or tv shows, have to write everything down, have to remember to look at notes"

"had to terminate many phone calls because I could no longer comprehend the speakers nor communicate clearly with them"

"used to do the New York Times crossword puzzle every single day and I can’t even manage the mini ones now"

"can’t focus on reading complex texts, and it makes me feel very tired to do that"

"Found that I had become dyslexic - and knew it was happening at the time, could not remember how to spell words - also found I was missing words from sentences and sometimes writing things that did not make sense"
Post-Exertional Malaise

a. When does PEM start?

b. How long does PEM last?

c. How severe is PEM?
Immunologic/Allergies

- 20%: change in sensitivity (in both directions) to medications
- 12.1%: heightened reaction to old allergies
- 9.3%: new allergies
- 4%: new/unexpected anaphylaxis reactions
- Disappearing allergies (shellfish, medications, seasonal allergies)
- Post-COVID Reactivations of EBV, CMV, Shingles, Lyme reported
  - Occipital and trigeminal neuralgias
Other serious symptoms

- 1% vision loss
- 9% hearing loss
- 3% facial paralysis
- 12% suicidality

Reproductive Health

- 15% of men, 8% of women: sexual dysfunction
- 11% of cis men: pain in testicles
- 3% of cis men: decrease in genital size
- Post-menopausal bleeding/spotting: 4.5% of cis women over age 49
- Early menopause: 3% of cis women in their 40s
- Abnormal periods: 26%
Relapses, Triggers, Recovery

d. Triggers of relapses

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>60%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>40%</td>
</tr>
<tr>
<td>Caffeine</td>
<td>20%</td>
</tr>
<tr>
<td>Heat</td>
<td>30%</td>
</tr>
<tr>
<td>Exercise</td>
<td>50%</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>40%</td>
</tr>
<tr>
<td>Mental Activity</td>
<td>30%</td>
</tr>
<tr>
<td>Menstruation</td>
<td>20%</td>
</tr>
<tr>
<td>Week before menstruation</td>
<td>10%</td>
</tr>
<tr>
<td>Others</td>
<td>10%</td>
</tr>
</tbody>
</table>

e. Experiences with relapses and symptom course

<table>
<thead>
<tr>
<th>Experience</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relapse</td>
<td>10%</td>
</tr>
<tr>
<td>Regular pattern</td>
<td>20%</td>
</tr>
<tr>
<td>Irregular pattern</td>
<td>30%</td>
</tr>
<tr>
<td>In response to trigger</td>
<td>40%</td>
</tr>
<tr>
<td>Shorter/easier (relapses)</td>
<td>50%</td>
</tr>
<tr>
<td>Longer/harder (relapses)</td>
<td>60%</td>
</tr>
<tr>
<td>Stayed the same (relapses)</td>
<td>70%</td>
</tr>
<tr>
<td>Gradually better (symptoms)</td>
<td>80%</td>
</tr>
<tr>
<td>Gradually worse (symptoms)</td>
<td>90%</td>
</tr>
<tr>
<td>Stayed the same (symptoms)</td>
<td>10%</td>
</tr>
<tr>
<td>Rapidly got worse</td>
<td>20%</td>
</tr>
<tr>
<td>Rapidly got better</td>
<td>30%</td>
</tr>
<tr>
<td>Others</td>
<td>10%</td>
</tr>
</tbody>
</table>
Impact on work

● 67.5% had their work affected due to their illness
  ○ 45.2% required a reduced work schedule
  ○ 22.3% were not working at all
  ○ Remaining respondents were retired, volunteers, or did not provide enough information.
● Of patients with brain fog, 86.2% are mildly to severely unable to work because of brain fog.
Comparing Positive & Negative Cohorts
Priority Research Questions and Methods

● Need comprehensive selection of patients:
  ○ Many/most LC patients were not hospitalized
  ○ Many didn’t experience respiratory symptoms
  ○ Many were not PCR positive/antibody positive (must include clinical diagnosis subset)
  ○ Many had mild acute cases
  ○ Many never had low oxygen levels

● Ask about right symptoms!
  ○ Often missing neurological, especially cognitive, and post-exertional malaise
  ○ Often missing questions on relapses

● Particularly when using machine learning!
  ○ Algorithms will be biased without representative patient and symptom dataset
Long COVID-specific research:

1. **F-FDG brain PET hypometabolism in patients with long COVID, Guedj et al**
   a. MRIs are normal, but hypometabolism found in PET scans with 100% classification between patients & controls
   b. Symptom severity correlates with metabolic PET severity
   c. Results: decrease in brain activity in olfactory bulb, limbic regions (memory/emotion regulation), brainstem (autonomic functions, breathing/sleeping), cerebellum (motor skills/balance)

2. **Early immune pathology and persistent dysregulation characterise severe COVID-19, Bergamaschi et al**
   a. Immunometabolic inflammatory changes & unresolved immune cell defects may contribute to Long COVID

3. **Neurologic manifestations of nonhospitalized patients with COVID-19 in Wuhan, China, Ding et al**
   a. Non-hospitalized patients more likely to have neurological symptoms
   b. Non-hospitalized patients more likely to test negative on antibody tests
   c. Non-hospitalized patients have symptoms for longer

4. **CDC study “Decline in SARS-CoV-2 Antibodies”**
   a. 28% seroreverted by 60 days
   b. 2% of PCR-positive patients seroreverted compared to 27% of PCR-negative
   c. 65% of patients with low antibody levels seroreverted (low levels more likely in women)
   d. Seroreversion more likely in 1) younger patients, 2) patients with underlying conditions
   e. Non-Hispanic Black patients and Hispanic patients less likely to serorevert
Priority Research Questions and Methods

- Validate & further investigate past post-viral research, interdisciplinarily:
  - Brain inflammation, brainstem inflammation, appropriate neuroimaging techniques (Dr. Jarred Younger, Dr. Michael VanElzakker, Dr. David Systrom, Harvard)
  - Neuroimmunology (Dr. Avindra Nath, NIH)
  - Metabolic profiling (Dr. Oystein Fluge, Dr. Ron Davis, Dr. Jarred Younger)
  - Impaired endothelial function in POTS (Dr. Alfred Gamboa, Vanderbilt)
  - Mitochondrial fragmentation, antiviral & metabolic phenotypes in ME (Dr. Bhupesh Prusty)
  - Hypoperfusion/cerebral blood flow (Dr. Peter Rowe, Johns Hopkins)
  - Two-day exercise testing & other PEM research (Workwell foundation, Dr. Leonard Jason)
  - Nanoneedle diagnostic test (Dr. Ron Davis, Stanford)
  - Overlaps with connective tissue disorders, including Ehlers-Danlos Syndrome (PolyBio Research, Dr. Peter Rowe, Johns Hopkins, Dr. Bjorn Bragee, Karolinska Institutet)
  - Autoimmunity, autoantibodies (Dr. Franziska Sotzny)
  - Viral/microbial persistence (Dr. Amy Proal, Dr. Bhupesh Prusty)
  - Intracranial hypertension, hypermobility, craniocervical obstructions (Karolinska Institutet, Dr. Bjorn Bragee, Dr. Nicolas Higgins)
  - Altered T cells and B cells, Metabolomics and Proteomics (Dr. Maureen Hanson, Cornell University)
  - Elevated blood lactate (Dr. Alaa Ghali)
  - Reactivations, difference in early vs late post-viral years (Dr. Nancy Klimas)
Treatment Options

- Pacing Regiment!
  - no exercise for people with post-exertional malaise

- Dysautonomia
  - Test for POTS
  - Compression garments (leggings, abdominal binders)
  - Salt and electrolyte tablets

- Mast Cell Activation Syndrome
  - H1 and H2 histamine antagonists (famotidine, loratadine)
  - Quercetin

- Many symptoms don’t currently have treatments
@patientled (Twitter)
PatientResearchCovid19.com

Resources for Long COVID researchers: https://patientresearchcovid19.com/resources-for-long-covid-researchers/

Thank you!