World Health Organization

Expanding our understanding of Post COVID-19 condition

1st webinar
9 February 2021, 13.00 CET

Immunology and pathophysiology of long Covid – what do we know, what do we need to know?

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Altmann has received remuneration for consultancy work from Oxford Immunotec

“limited understanding of the clinical characterization during the recovery period and associated pathophysiology have limited progress in treatment and management”

We may dream of meaningful clinical support from dedicated long Covid clinics, but consider:

1. How will you get referred there?
2. Which clinical specialties will staff them?
3. What expertise and specialist equipment and tests will they need?
4. How will they deal with the fact that a person's symptoms may move between needing support from neuro, rheumatology, cardiology, endocrinology, respiratory teams..?
5. What type of management, therapeutics will they offer?
6. How many years will we need these clinics for?


CLINICAL OPINION

Decoding the unknowns in long covid

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CPD READING
0.5 HOURS

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This article is adapted from a piece published on BMJ

Manifesto - A call to arms:

- Like other features of the disease, this is a story narrated in real-time, making it currently unknowable whether long Covid will come to be seen as a condition typically lasting months, years, or lifelong
- Many come from that large, hidden iceberg of those who self-isolated unwell at home, did not access a PCR and so have no formal health record evidence of COVID-19 – ***the need for immunity data***
- These points highlight an uncharted pathophysiology, demanding a better answer than 'post-viral syndrome' or the notion that people are 'bound to feel a bit rough coming out of hospital'
- Recognised criteria for a working diagnosis are needed, not least to facilitate access to ***appropriate*** services
- **Moving forward our goals must move beyond the observational to the interventional**
- If 10-20% of the globe's COVID-19 infections lead to long Covid, we face a legacy of 10-20 million long-term cases to manage. This has massive ramifications for the lives of the affected and for healthcare planning
- Unless we move rapidly towards resolving mechanism, how to offer any rational therapeutics?

Some (non-mutually exclusive) working hypotheses for current investigations

- Residual damage to ACE2-positive infected tissue (though might this not be expected to make long Covid a condition correlated with severity of the acute infection)?
- Ongoing immune stimulation from reservoirs (gut) of persistent infection (-meriting greater focus on anti-virals..?)
- Acute infection causes chronic perturbation of immune subsets
- Acute infection causes activation of an autoimmune response

Some things we know

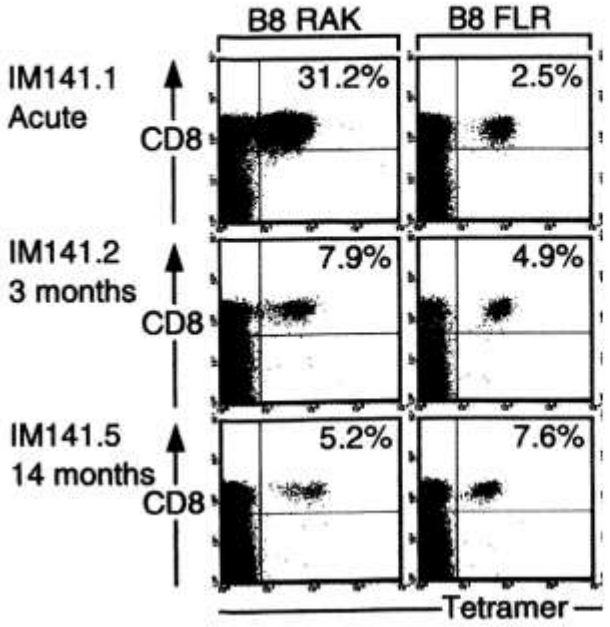
- Since the earliest reports even of asymptomatic cases, it's been clear that infection can leave a lingering trail of lung CT changes
- ACE-2 positive cells within the lung, heart, kidney and elsewhere are susceptible to direct SARS-Cov-2 infection, leaving the potential for a legacy of fibrosis
- Initial reporting of the COVERSCAN MRI study of >200 LongCovid individuals at around 4-months after infection shows multi-organ involvement, especially heart and lungs
- While the notion of long-term, virus persistence is not one that had previously been considered for coronaviruses, this seems to be another textbook chapter to be re-written: gastrointestinal biopsies taken some 4-months after acute disease show persistent live virus in about a third of cases (Nussenzweig lab)

‘Acute viral infection can be like throwing a hand-grenade at normal immune subsets..’

- The immune perturbation hypothesis – consider the long-term impacts of infectious mononucleosis.
- Some epitope responses persist as 8% of total CD8 repertoire

From: **Epitope-specific Evolution of Human CD8⁺ T Cell Responses from Primary to Persistent Phases of Epstein-Barr Virus Infection. A.D Hislop et al**

J Exp Med. 2002;195(7):893-905. doi:10.1084/jem.20011692



We are familiar with the concept of acute viral infection triggering autoimmune sequelae

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N Engl J Med. 2019 March 07; 380(10): 924–934. doi:10.1056/NEJMoa1805435.

A Longitudinal Study of Ebola Sequelae in Liberia

The PREVAIL III Study Group*

- **Background:** Multiple health problems have been reported in survivors of Ebola virus disease (EVD).
- **Methods:** We enrolled a cohort of EVD survivors and their close contacts and prospectively collected data on symptoms, physical examination findings, and laboratory results. A subset of participants underwent ophthalmologic examinations.
- **Results:** A total of 966 EBOV antibody-positive survivors and 2350 antibody-negative close contacts (controls) were enrolled, and 90% of these participants were followed for 12 months. At enrolment (median time to baseline visit, 358 days after symptom onset), six symptoms were reported significantly more often among survivors than among controls: urinary frequency (14.7% vs. 3.4%), headache (47.6% vs. 35.6%), fatigue (18.4% vs. 6.3%), muscle pain (23.1% vs. 10.1%), memory loss (29.2% vs. 4.8%), and joint pain (47.5% vs. 17.5%). On examination, more survivors than controls had abnormal abdominal, chest, neurologic, and musculoskeletal findings and uveitis. Other than uveitis (prevalence at enrollment, 26.4% vs. 12.1%; at year 1, 33.3% vs. 15.4%), the prevalence of these conditions declined during follow-up in both groups. The incidence of most symptoms, neurologic findings, and uveitis was greater among survivors than among controls.
- **Conclusions:** A relatively high burden of symptoms was seen in all participants, but certain symptoms and examination findings were more common among survivors. With the exception of uveitis, these conditions declined in prevalence during follow-up in both groups.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

EMERGING INFECTIONS

Fingolimod treatment abrogates chikungunya virus–induced arthralgia

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Chikungunya virus (CHIKV) is one of the many rheumatic arthropod-borne alphaviruses responsible for debilitating joint inflammation in humans. Despite the severity in many endemic regions, clinically approved intervention targeting the virus remains unavailable. $CD4^+$ T cells have been shown to mediate CHIKV-induced joint inflammation in mice. We demonstrate here that transfer of splenic $CD4^+$ T cells from virus-infected C57BL/6 mice into virus-infected T cell receptor–deficient ($TCR^{-/-}$) mice recapitulated severe joint pathology including inflammation, vascular leakages, subcutaneous edema, and skeletal muscle necrosis. Proteome-wide screening identified dominant $CD4^+$ T cell epitopes in nsP1 and E2 viral antigens. Transfer of nsP1- or E2-specific primary $CD4^+$ T cell lines into CHIKV-infected $TCR^{-/-}$ recipients led to severe joint inflammation and vascular leakage. This pathogenic role of virus-specific $CD4^+$ T cells in CHIKV infections led to the assessment of clinically approved T cell–suppressive drugs for disease intervention. Although drugs targeting interleukin-2 pathway were ineffective, treatment with fingolimod, an agonist of sphingosine 1-phosphate receptor, successfully abrogated joint pathology in CHIKV-infected animals by blocking the migration of $CD4^+$ T cells into the joints without any effect on viral replication. These results set the stage for further clinical evaluation of fingolimod in the treatment of CHIKV-induced joint pathologies.

And an emerging dataset on autoimmunity following COVID-19

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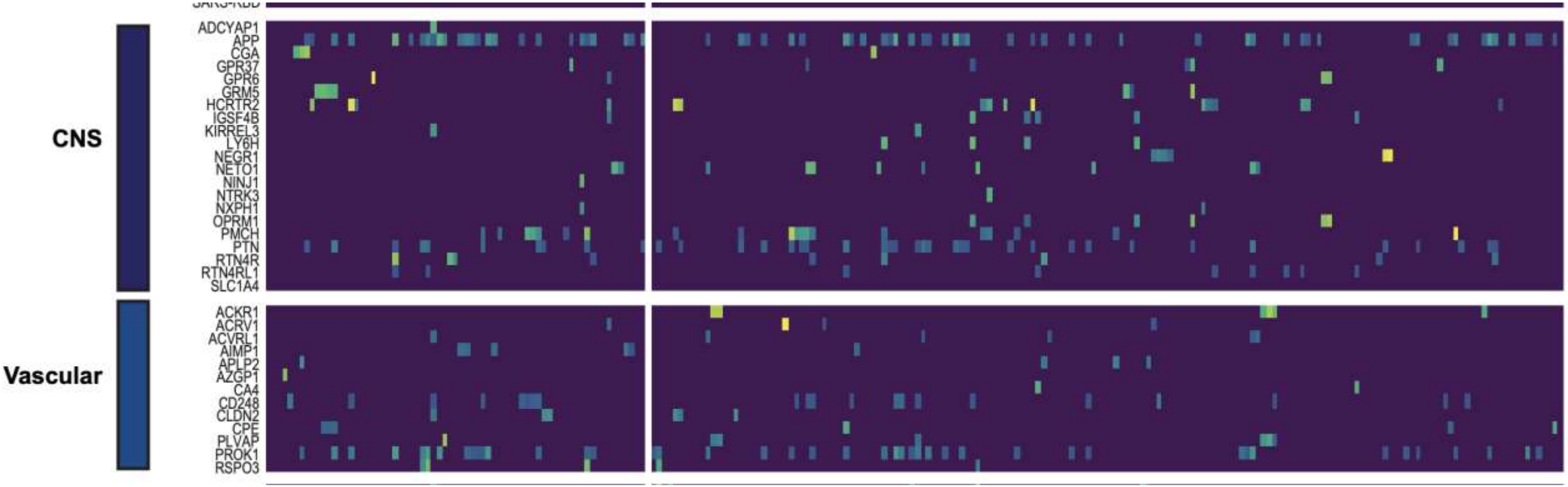
Diverse Functional Autoantibodies in Patients with COVID-19

Eric Y. Wang, Tianyang Mao, Jon Klein, Yile Dai, John D. Huck, Feimei Liu, Neil S. Zheng, Ting Zhou, Benjamin Israelow, Patrick Wong, Carolina Lucas, Julio Silva, Ji Eun Oh, Eric Song, Emily S. Perotti, Suzanne Fischer, Melissa Campbell, John B. Fournier, Anne L. Wyllie, Chantal B. F. Vogels, Isabel M. Ott, Chaney C. Kalinich, Mary E. Petrone, Anne E. Watkins, Yale IMPACT Team, Charles Dela Cruz, Shelli F. Farhadian, Wade L. Schulz, Nathan D. Grubaugh, Albert I. Ko, Akiko Iwasaki, Aaron M. Ring

doi: https://doi.org/10.1101/2020.12.10.20247205



- So, we have a new group of patients – potentially larger than the current global community of rheumatoid arthritis patients
- We don’t know how long their condition will go on for
- Patient groups are highly motivated, active and ready to team up with researchers
- How to now engage policy-makers and research funders to join us so that we can move forwards?