Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

UNIVERSITÀ DI TRENTO
Dipartimento di Biologia Cellulare, Computazionale e Integrata
CIBIO

CSF autoimmunity in Neuro-COVID patients

"Neuro-COVID: complicanze neurologiche dell'infezione da SARS-CoV-2"

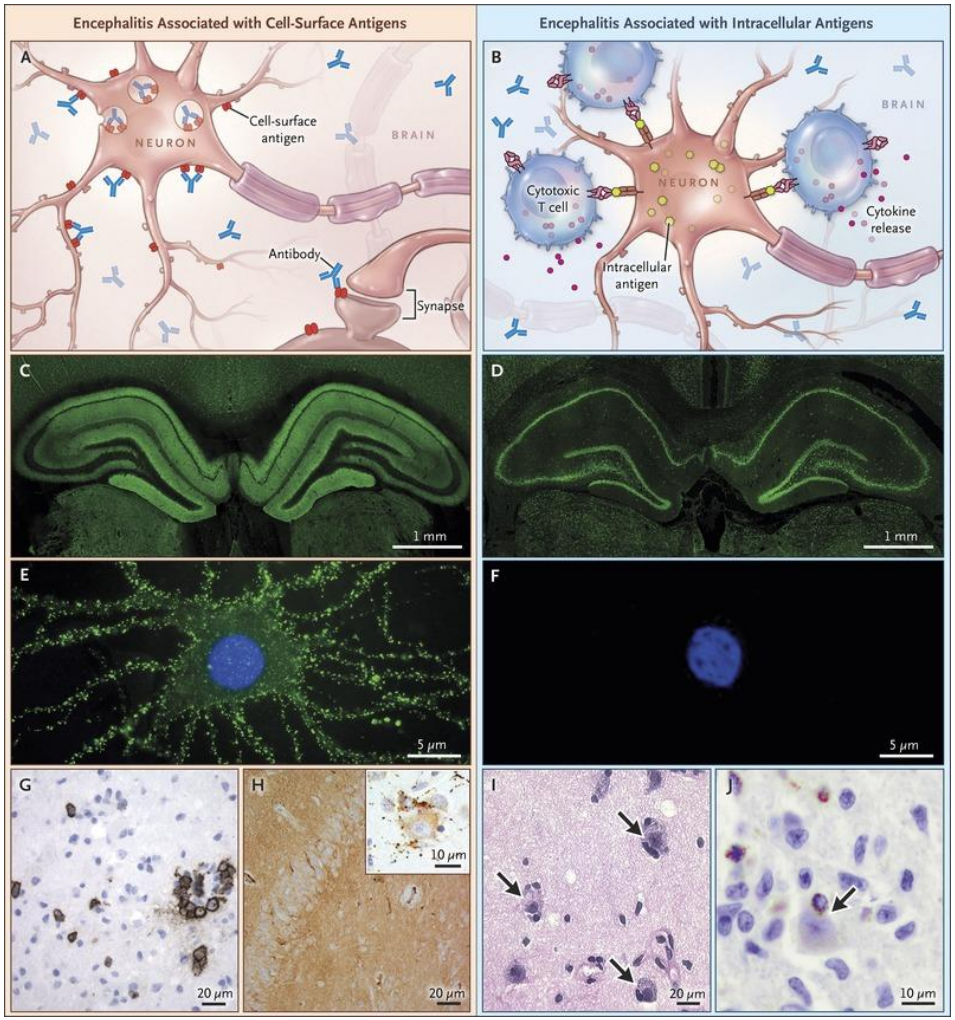
Trento, 9th September 2021 - F.Boso

Illustration components: Profile, Jake Olimb; COVID, Big Blue/ Both Istock

Neuroimmunology

Autoimmunity has been increasingly acknowledged as a cause of a **wide array of neurological syndromes** in recent years.

- An increasing array of **pathogenic neuronal autoantibodies** are being identified and thought to cause specific clinical syndromes, but they are now associated also with different phenotypes beyond encephalitis (cognitive impairment, movement disorders, seizures,…).
- Their relevance **beyond the encephalitis spectrum** is still not clear, but the **possibility of specific immunotherapies** warrants evaluation.



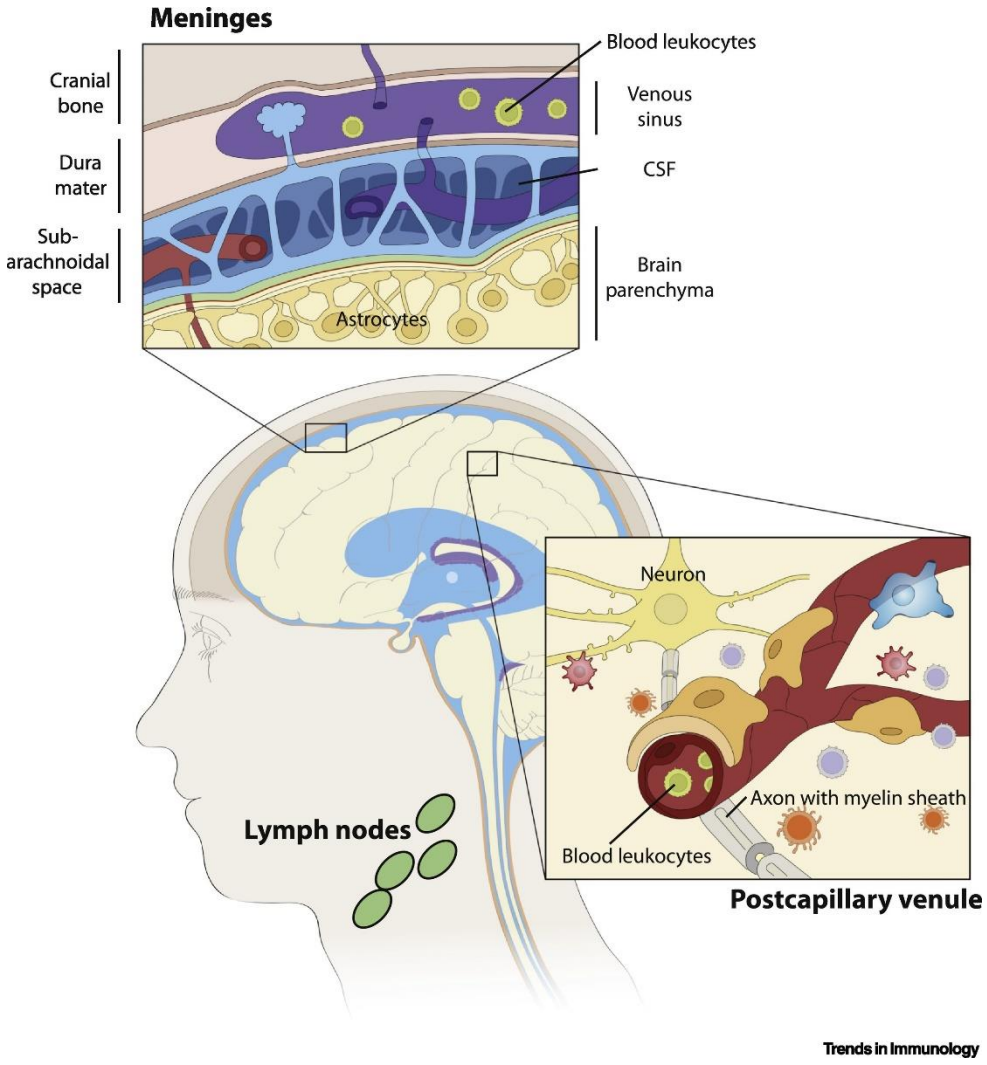
Dalmau et al, 2018

Immune privilege or privileged immunity?

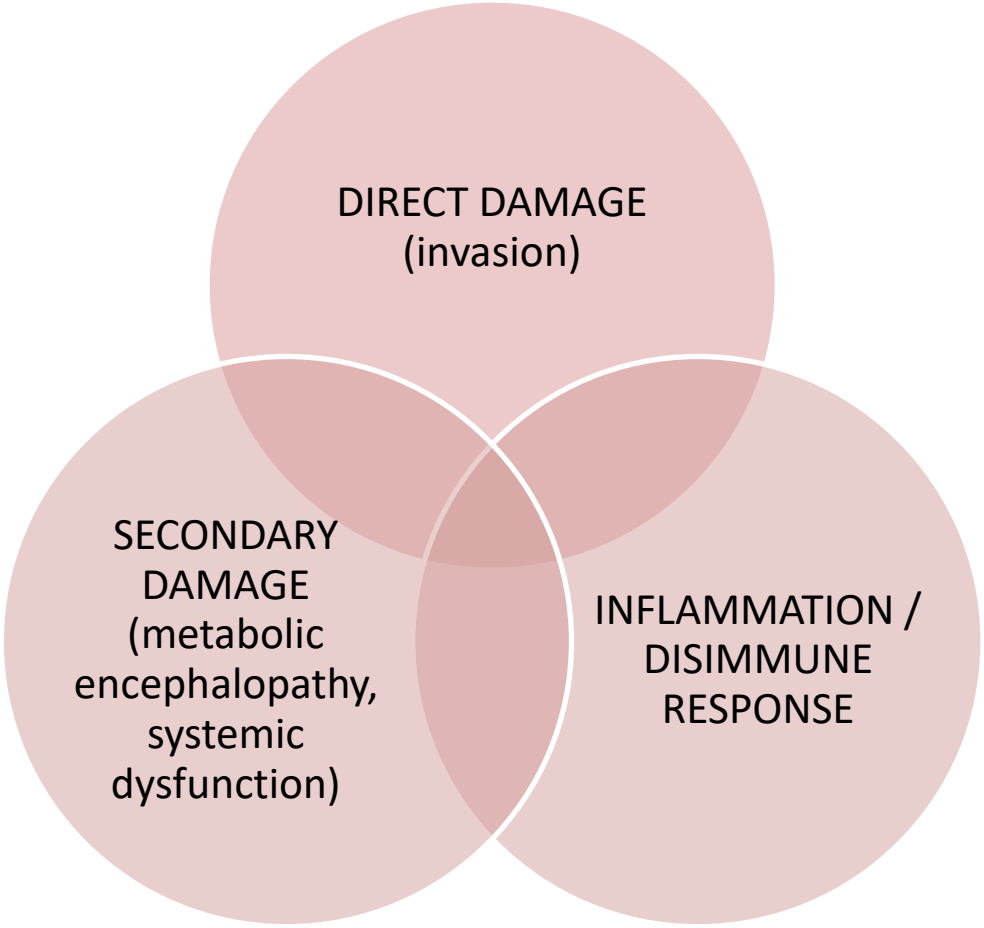
As an immune privileged site, CNS is **vulnerable to autoimmune attack**, as demonstrated by various neurological and psychiatric diseases

Both astrocytes and microglia contribute to CNS autoimmunity and clinical manifestations result from a **complex interplay** between CNS and the immune system

Autoimmune responses can be triggered by infectious pathogens, possibly through molecular mimicry and breakdown of physiological barriers

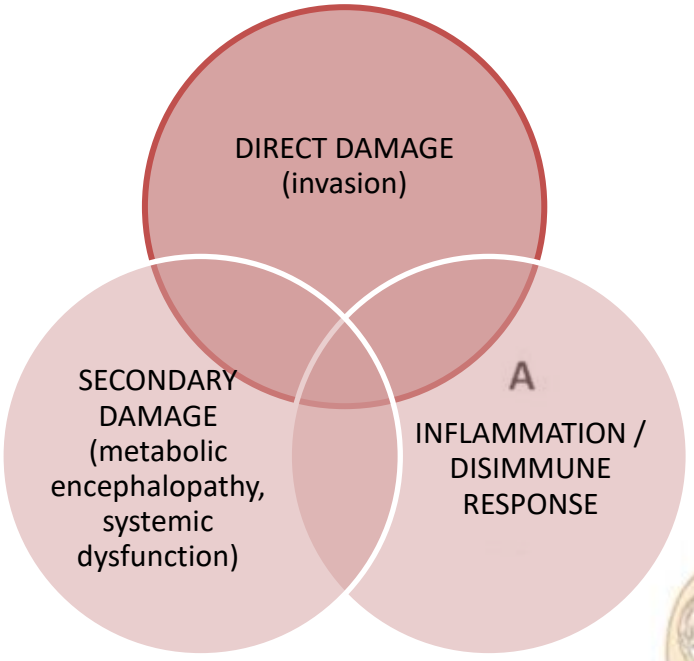


Putative mechanisms of neurological damage

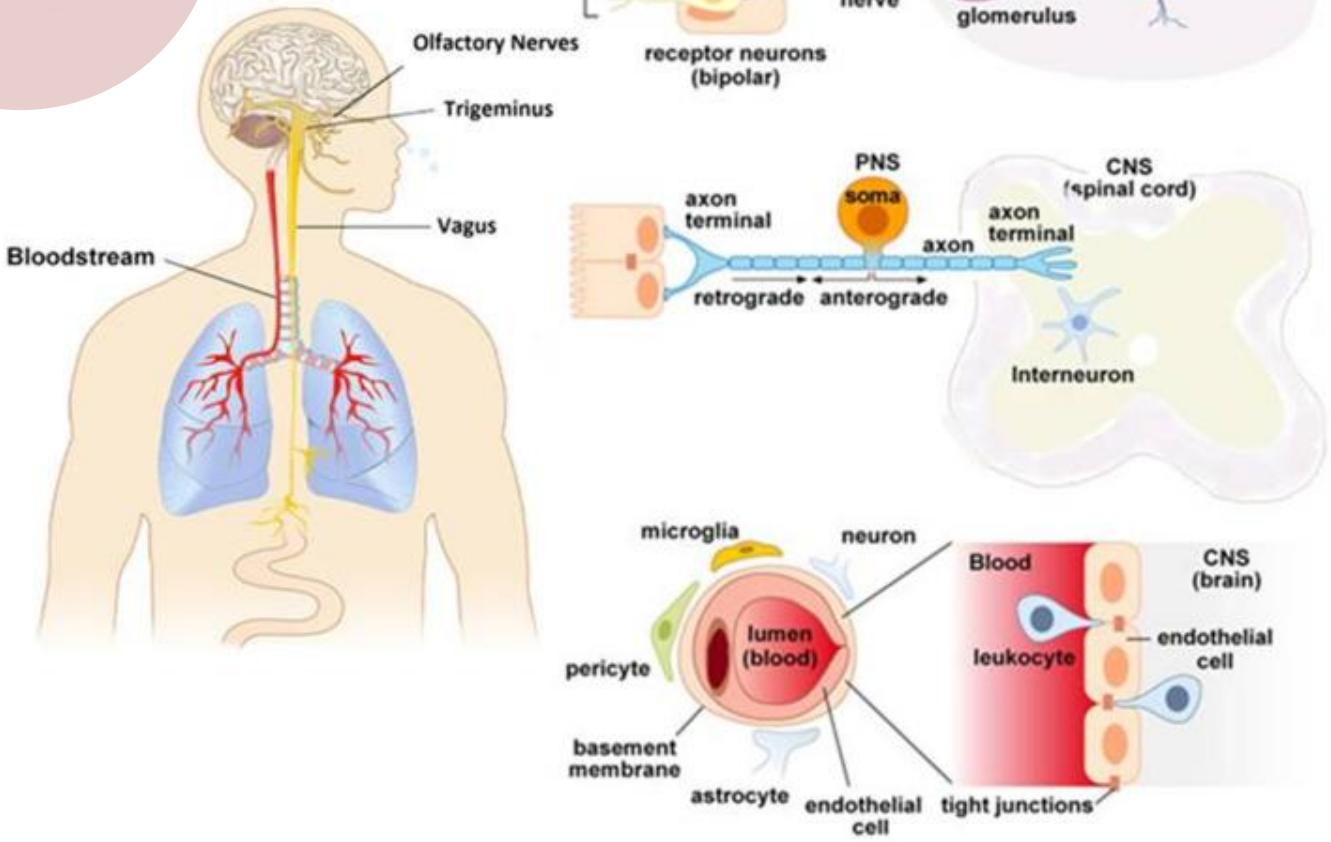


What about COVID-19?

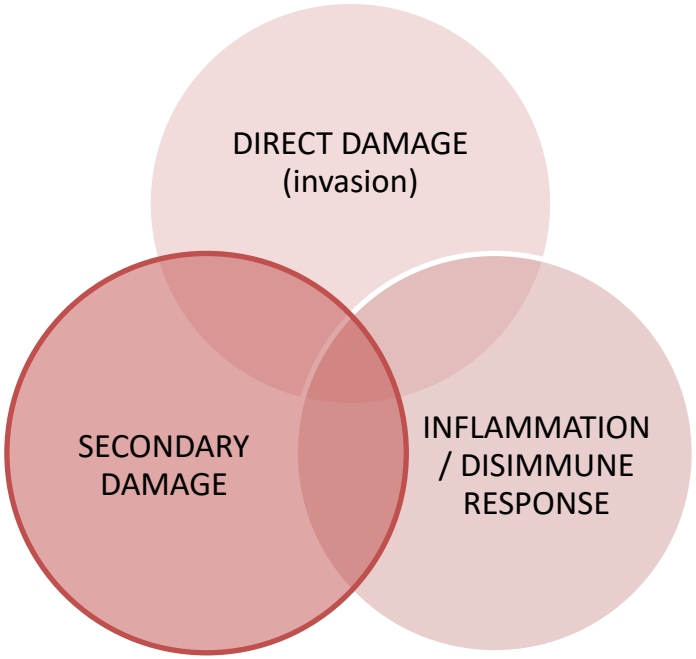
Gettyimages

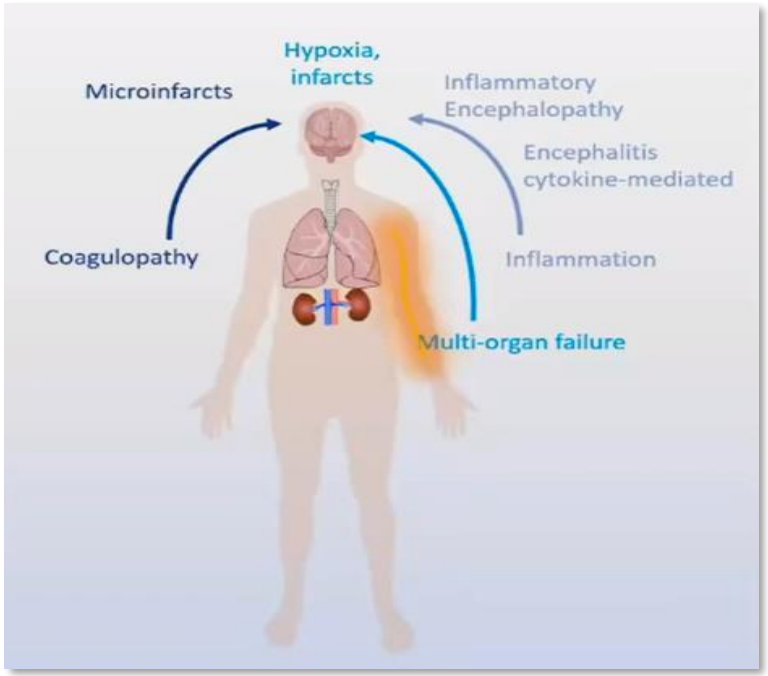


Alleged neurotropic pathways of SARS-CoV-2 (via olfactory bulb, blood circulation, lymphatic vessels, retrograde and trans-synaptic transmission)



Cataldi et al, 2020





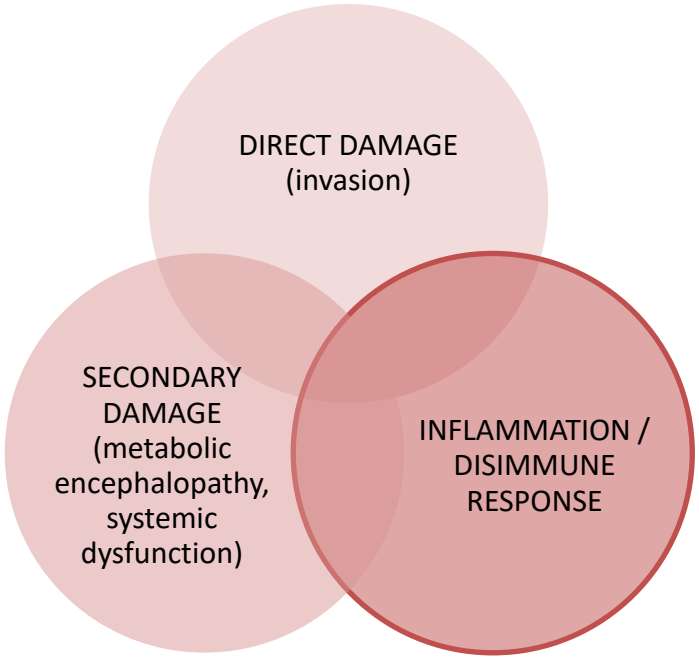
Hypoxia

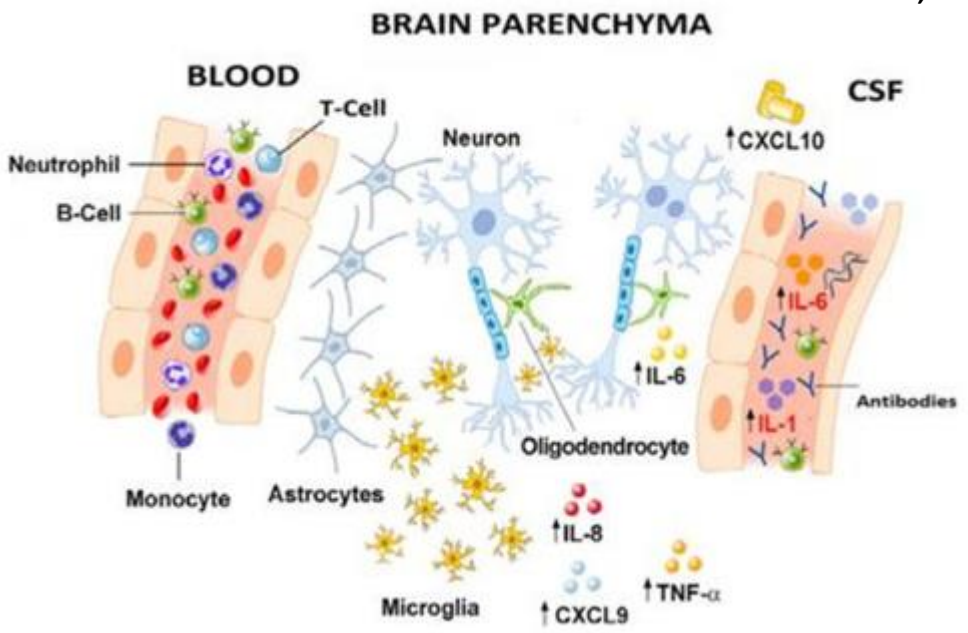
Multiorgan failure

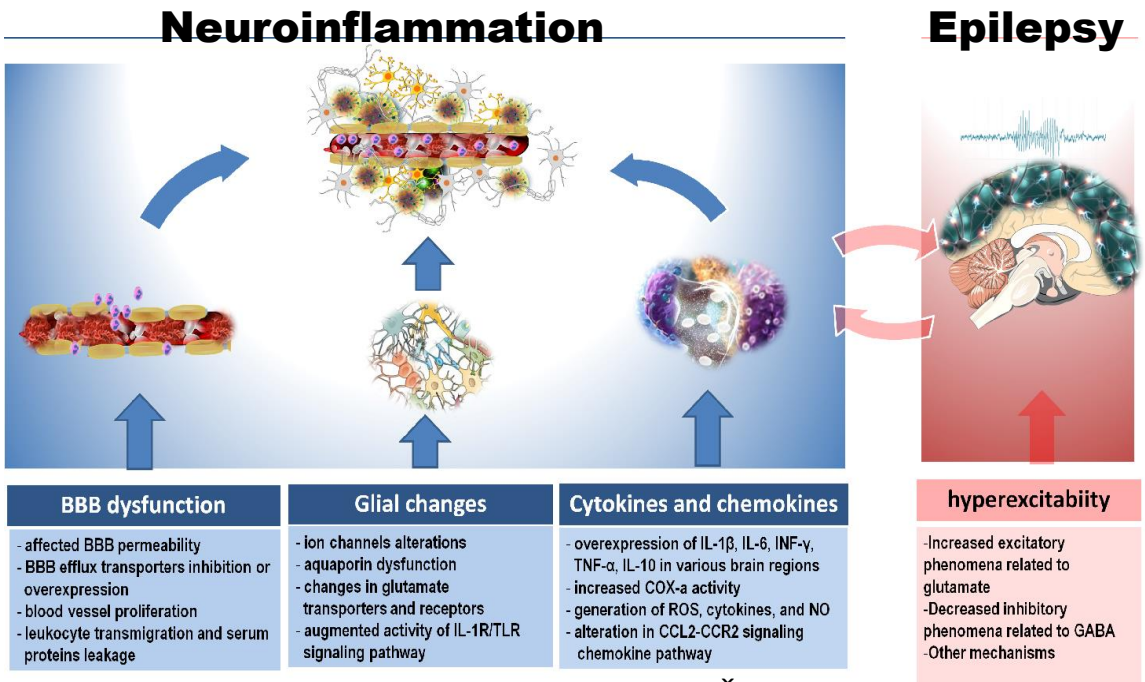
Thrombotic complications

Dysregulated blood pressure

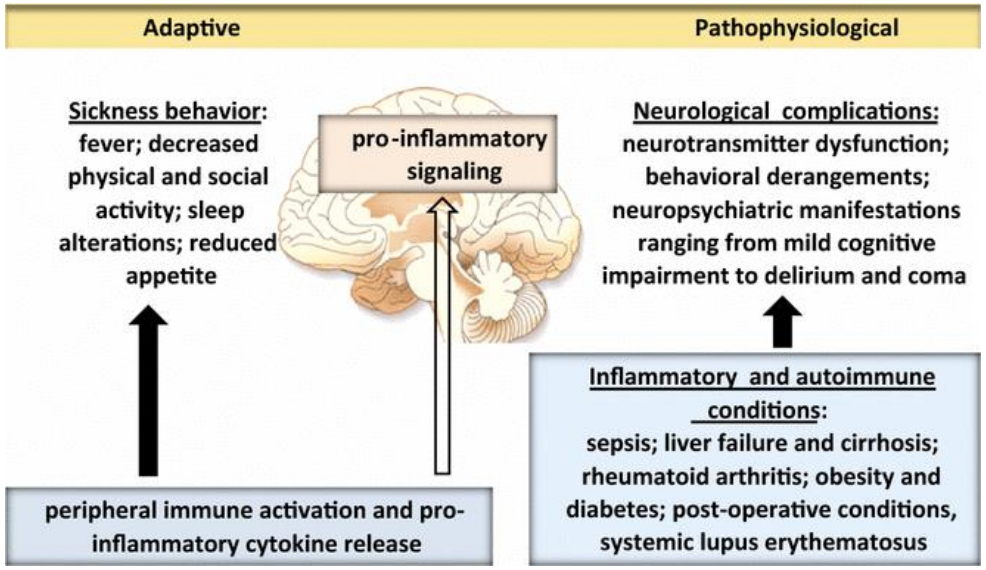
Cataldi et al, 2020



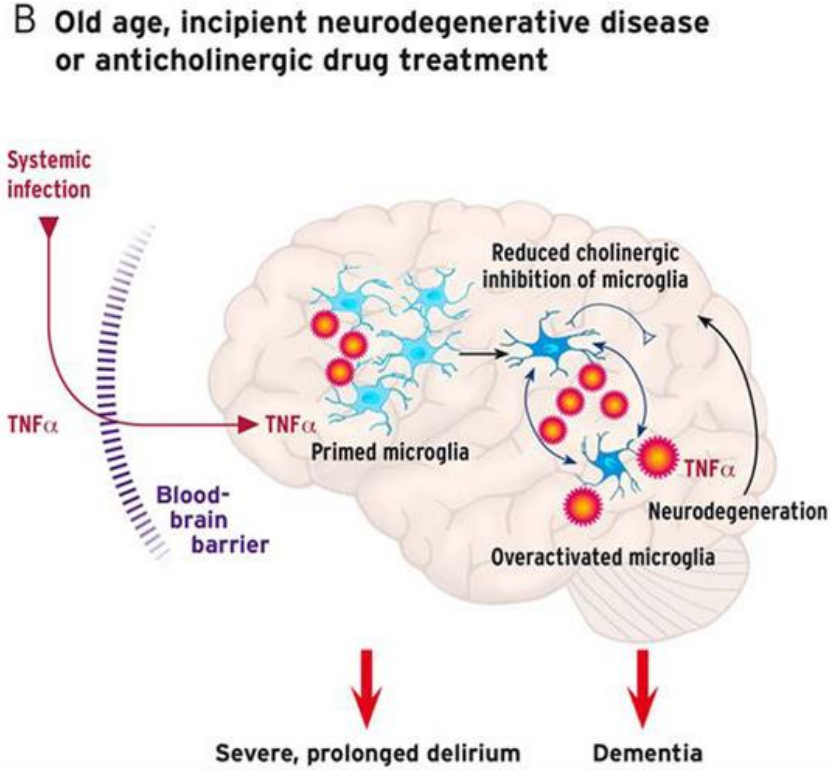




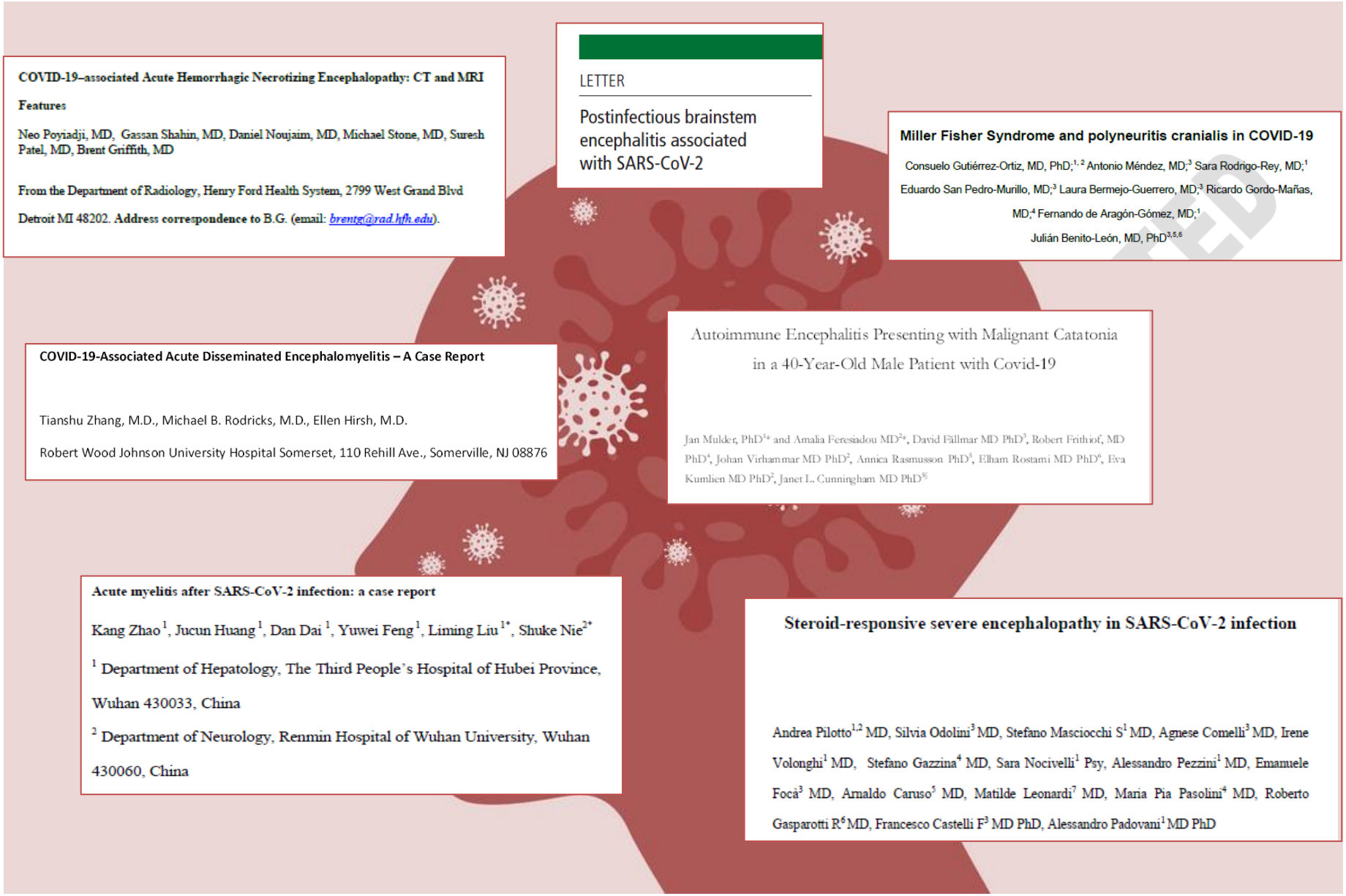
Šutulović et al, 2018



Pavlov et al, 2015



Van Gool et al, 2010



COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features

Neo Poyiadji, MD, Gassan Shahin, MD, Daniel Noujaim, MD, Michael Stone, MD, Suresh Patel, MD, Brent Griffith, MD

From the Department of Radiology, Henry Ford Health System, 2799 West Grand Blvd Detroit MI 48202. Address correspondence to B.G. (email: brentg@rad.hfh.edu).

LETTER

Postinfectious brainstem encephalitis associated with SARS-CoV-2

Miller Fisher Syndrome and polyneuritis cranialis in COVID-19

Consuelo Gutiérrez-Ortiz, MD, PhD;[1,2] Antonio Méndez, MD;[3] Sara Rodrigo-Rey, MD;[1] Eduardo San Pedro-Murillo, MD;[3] Laura Bermejo-Guerrero, MD;[3] Ricardo Gordo-Mañas, MD;[4] Fernando de Aragón-Gómez, MD;[1] Julián Benito-León, MD, PhD[3,5,6]

COVID-19-Associated Acute Disseminated Encephalomyelitis – A Case Report

Tianshu Zhang, M.D., Michael B. Rodricks, M.D., Ellen Hirsh, M.D.

Robert Wood Johnson University Hospital Somerset, 110 Rehill Ave., Somerville, NJ 08876

Autoimmune Encephalitis Presenting with Malignant Catatonia in a 40-Year-Old Male Patient with Covid-19

Jan Mulder, PhD[1]* and Amalia Feresiadou MD[2]*, David Fällmar MD PhD[3], Robert Frithiof, MD PhD[4], Johan Virhammar MD PhD[2], Annica Rasmusson PhD[5], Elham Rostami MD PhD[6], Eva Kumlien MD PhD[2], Janet L. Cunningham MD PhD[5]

Acute myelitis after SARS-CoV-2 infection: a case report

Kang Zhao [1], Jucun Huang [1], Dan Dai [1], Yuwei Feng [1], Liming Liu [1*], Shuke Nie[2*]

[1] Department of Hepatology, The Third People's Hospital of Hubei Province, Wuhan 430033, China

[2] Department of Neurology, Renmin Hospital of Wuhan University, Wuhan 430060, China

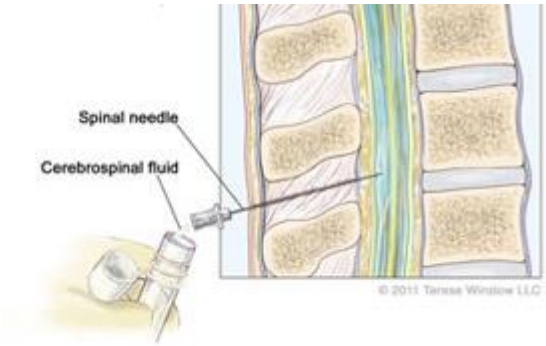
Steroid-responsive severe encephalopathy in SARS-CoV-2 infection

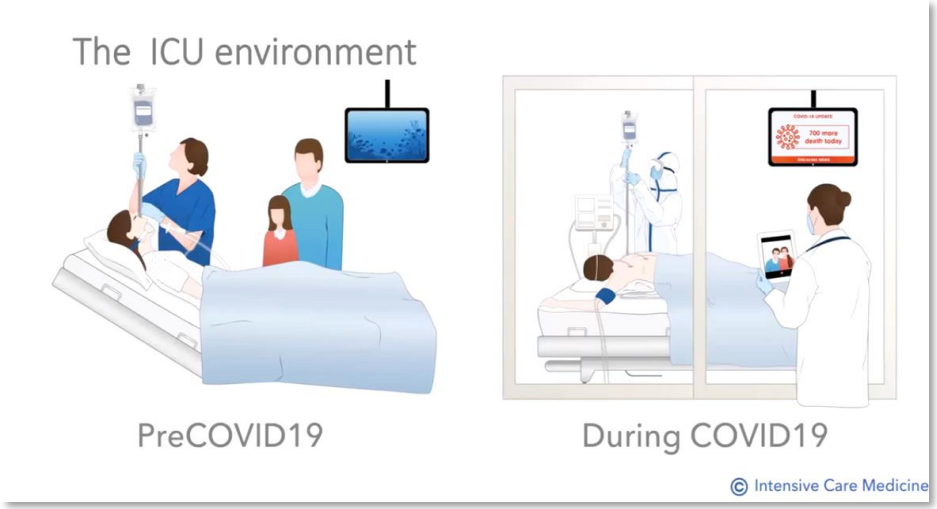
Andrea Pilotto[1,2] MD, Silvia Odolini[3] MD, Stefano Masciocchi S[1] MD, Agnese Comelli[3] MD, Irene Volonghi[1] MD, Stefano Gazzina[4] MD, Sara Nocivelli[1] Psy, Alessandro Pezzini[1] MD, Emanuele Focà[3] MD, Arnaldo Caruso[5] MD, Matilde Leonardi[7] MD, Maria Pia Pasolini[4] MD, Roberto Gasparotti R[6] MD, Francesco Castelli F[3] MD PhD, Alessandro Padovani[1] MD PhD

CSF analysis

Lumbar puncture as a **key tool** in the diagnostic workup, especially considering:

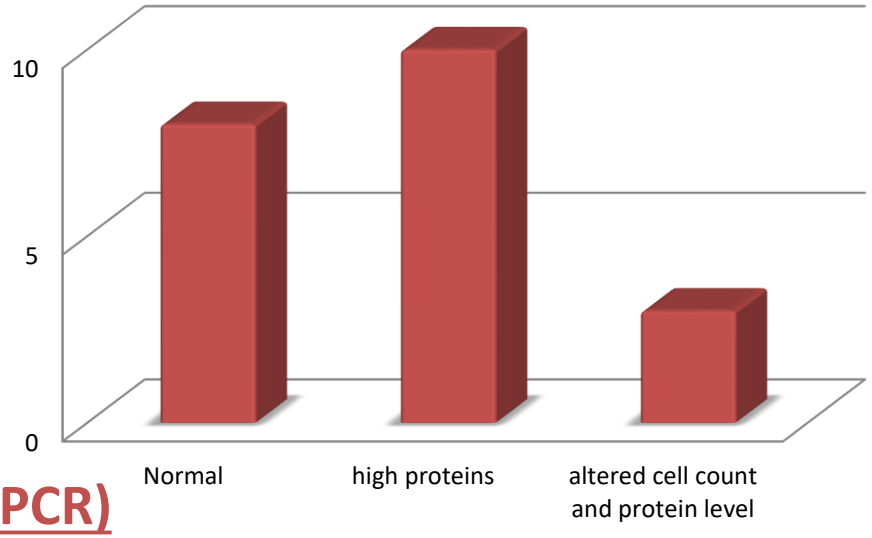
- the astounding number of *confounding factors*
- the *paucity of radiological clues*
- the *new work environment*





Rovereto COVID-Hospital experience

LP: 24% pts that were referred to the neurologist (2020)



- Cell count: 1 / uL (0-87)
- Protein level: 65 mg/dl (33-608)
- Glucose level: normal

Microbiological assays:

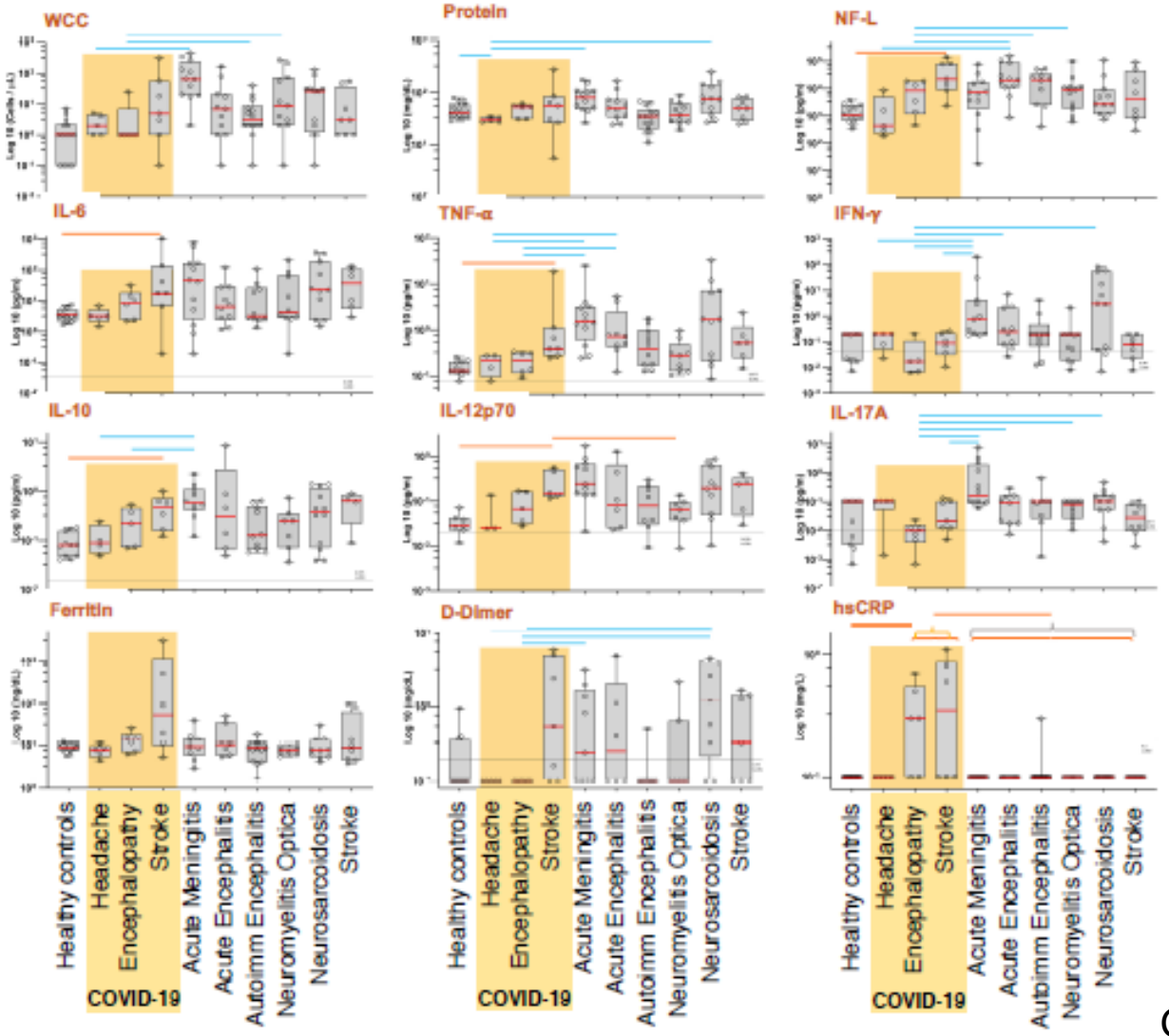
SARS-CoV-2 was never identified (RT-PCR)

No sovrainfections (culture, PCR and antibody testing for common neurotropic pathogens)

Few data about serum/CSF comparison:

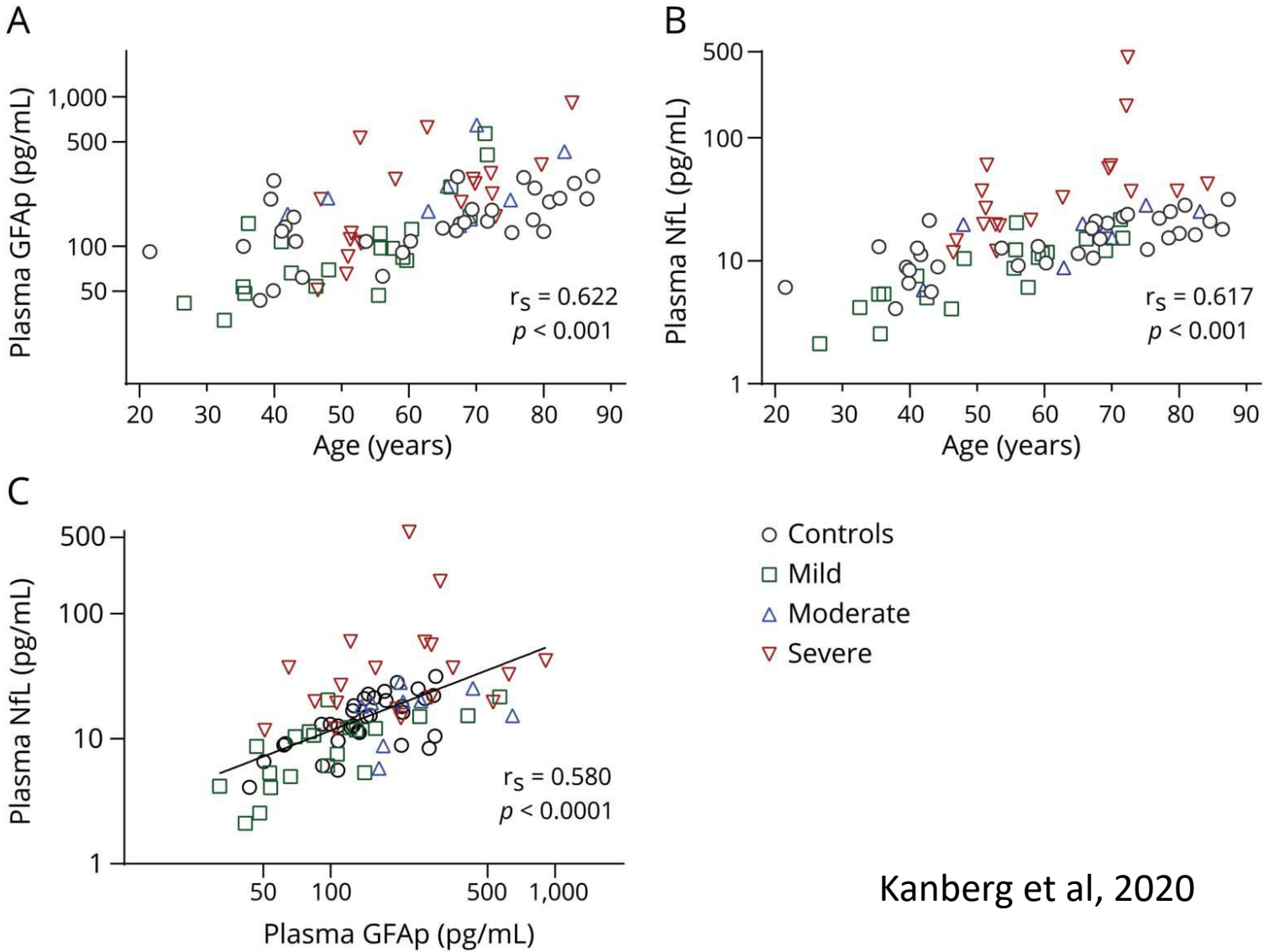
- Albumin ratio: extreme variability
- IgG index: negative - borderline
- Oligoclonal bands (rare patients): type 1 – type 4

Profile of CSF inflammatory markers & plasma biomarkers of CNS injury



Garcia et al, 2021

Profile of CSF inflammatory markers & plasma biomarkers of CNS injury



Kanberg et al, 2020

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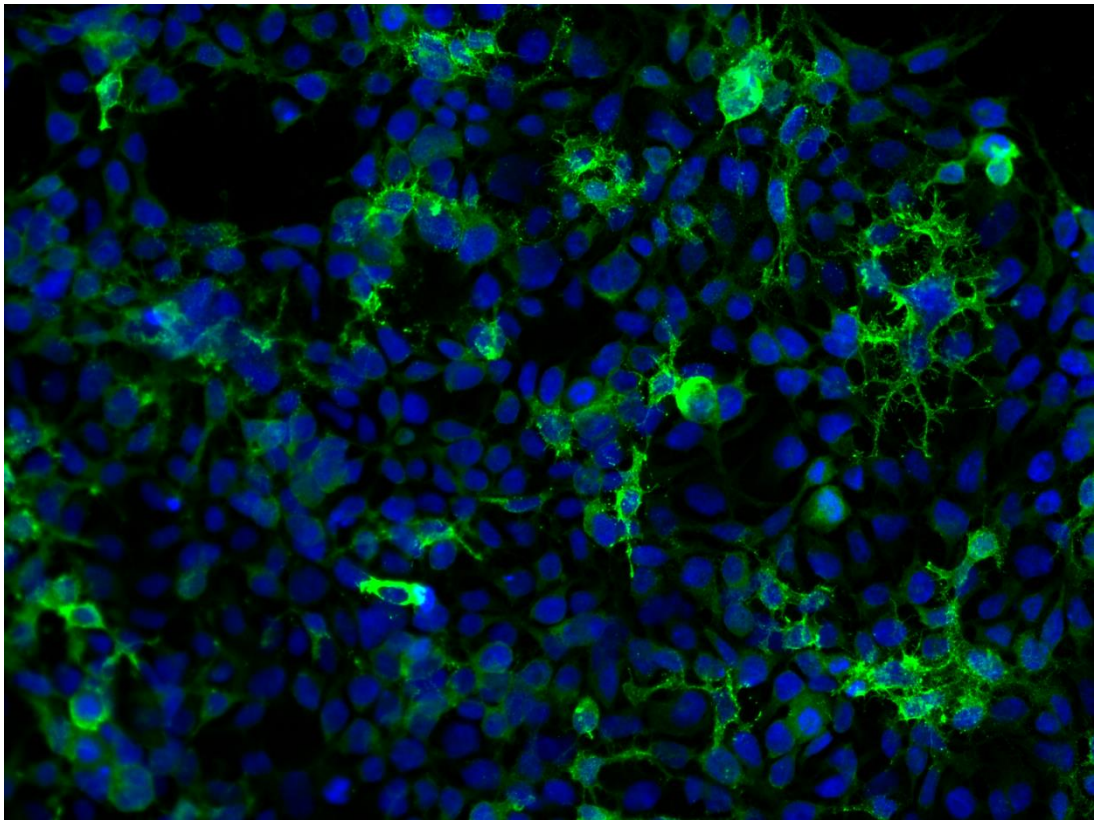
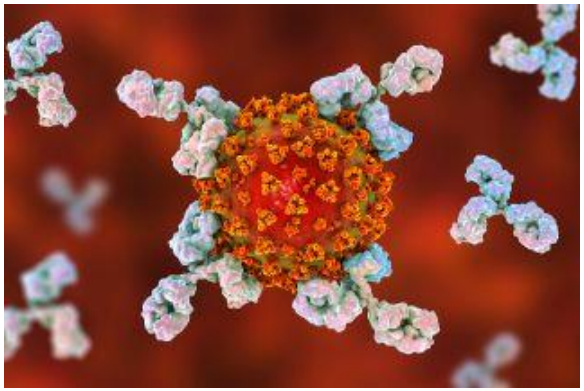
a Carattere Scientifico | IRCCS

Anti-spike antibodies



In-house CBA using HEK293 cells detected anti-spike IgGs in the CSF of most COVID patients that were referred to the neurologist.

Signs of CNS invasion?

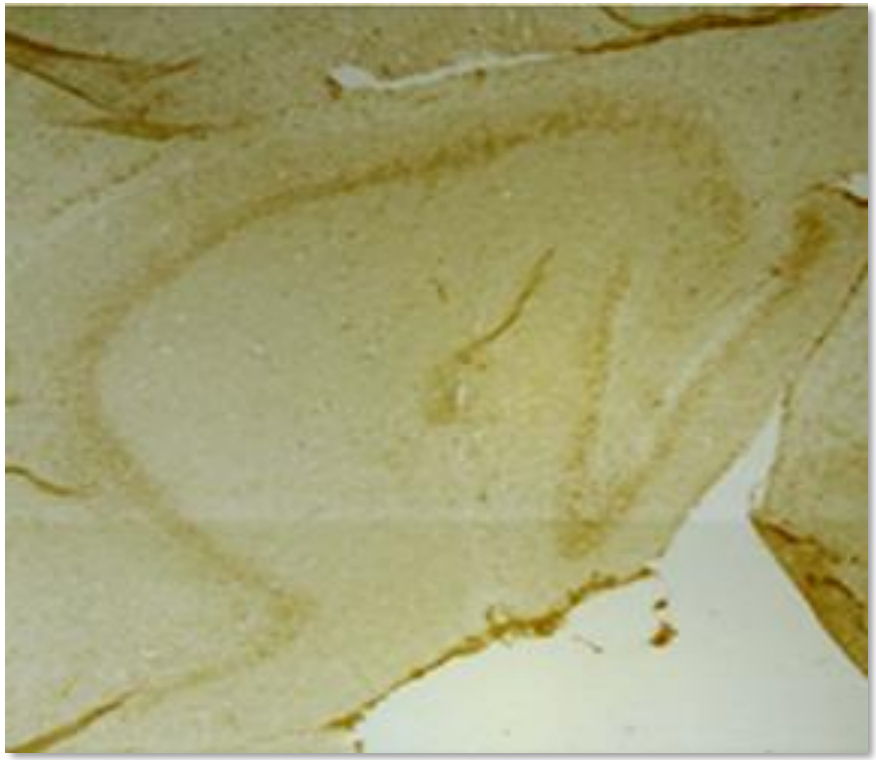


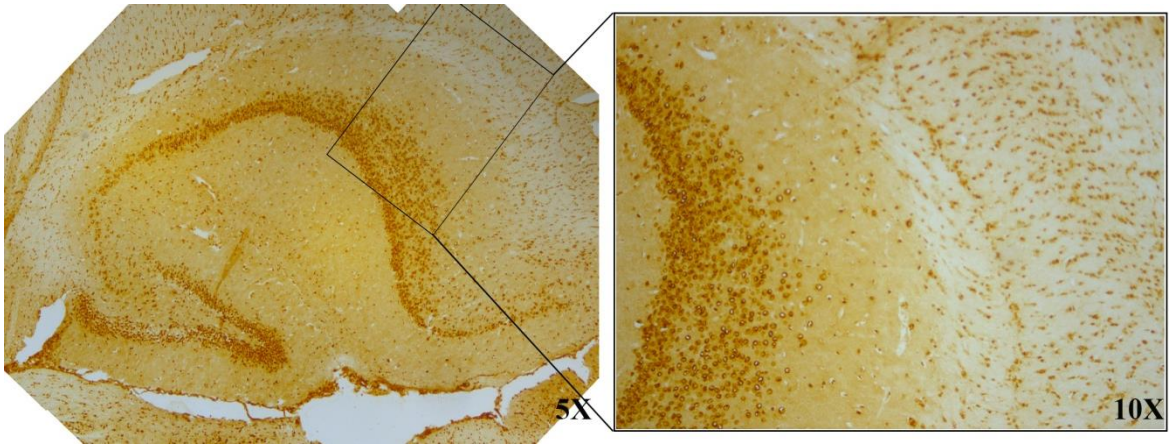
Is it just a matter of BBB disruption ?

Is there a specific intrathecal response?

(Image credit: Shutterstock)

IHC on rat brain section





69% of the samples exhibited hippocampal reactivity

Screening for known antigens

NEURONAL SURFACE ANTIBODIES

NMDAR, CASPR2, AMPA1/2, LGI1, DPPX, $GABA_BR$

(BIOCHIP FA 112d, Euroimmun, Luebeck)

ONCONEURAL ANTIBODIES

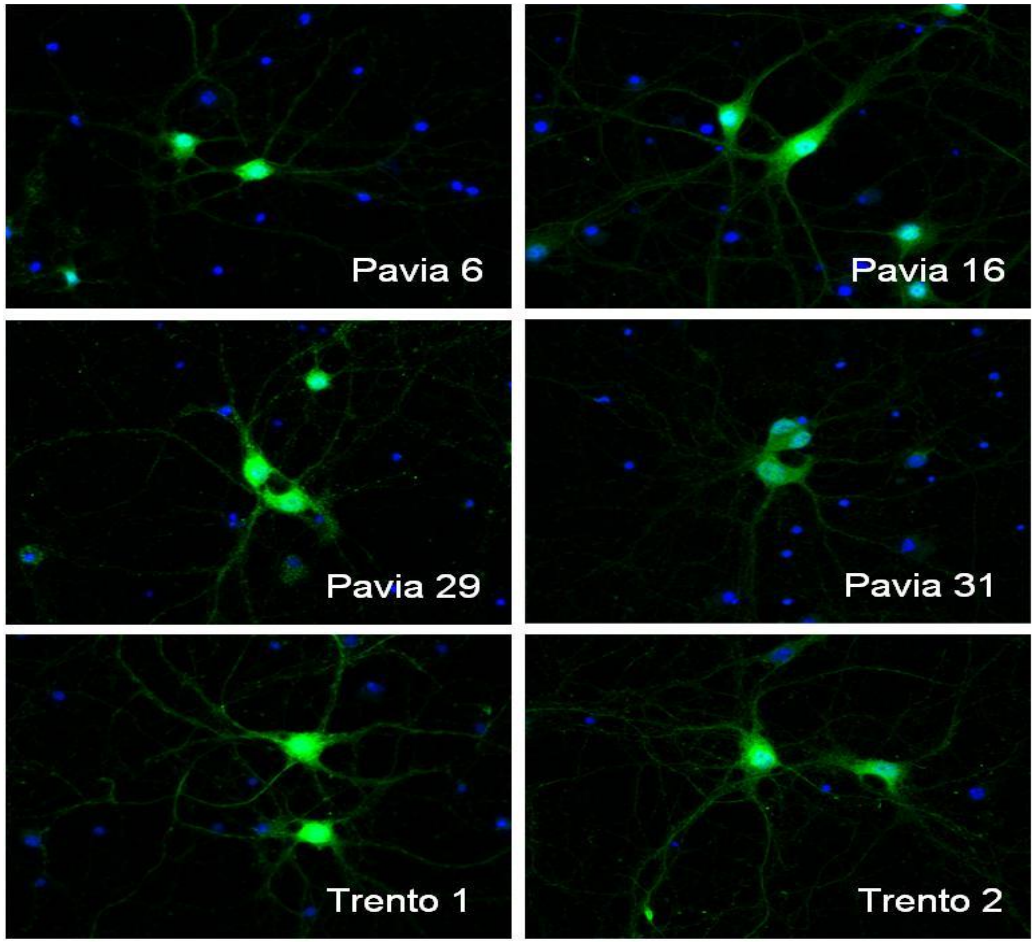
Tr, GAD65, Zic4, Titina, SOX1, Recoverina, Hu, Yo, Ri, Ma2, CV2, amfifisina

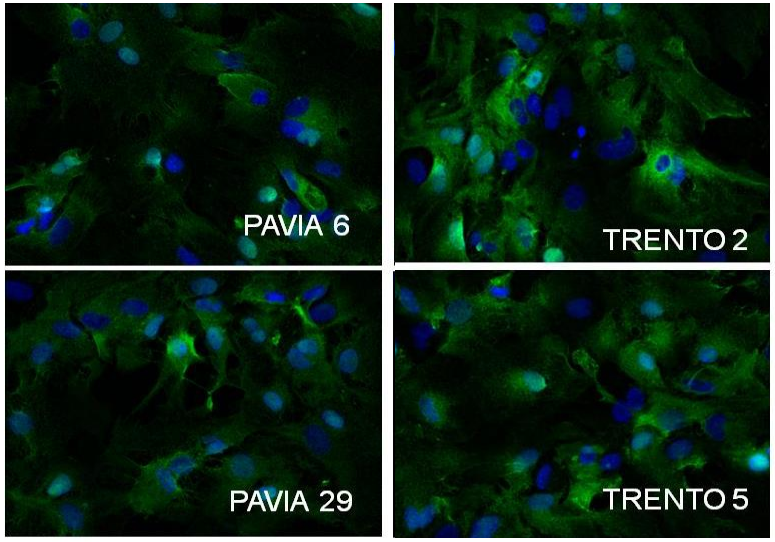
(Euroline, DL 1111-X G)

ANTI-MOG ANTIBODIES

(CBA)

Testing on neurons and astrocytes





Preliminary results

70% of the samples showed CNS reactivity with both IHC and neuronal testing.

•No clinical correlation (beside GBS)

•Female predominance

•Regardless of BBB permeability

•No significant association with plasma inflammatory biomarkers and COVID-19 severity

LIMITS

- Low number of samples
- Absence of real negative controls
- heterogeneity (different neurological features, timing of the lumbar puncture, treatments, COVID-19 severity,…)

ELSEVIER

Brain, Behavior, and Immunity
Available online 24 December 2020
In Press, Corrected Proof

Short Communication

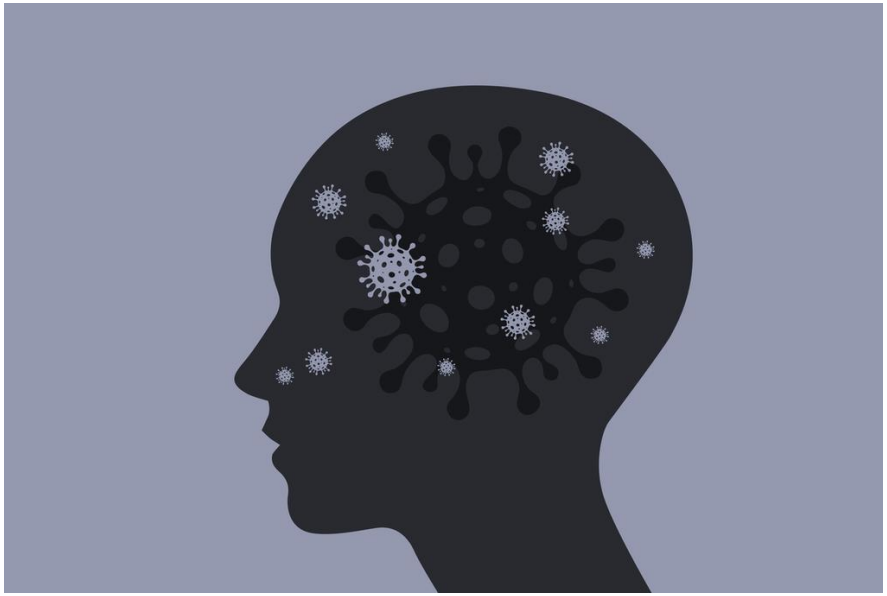
High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms

Christiana Franke [a], Caroline Ferse [c], Jakob Kreye [a, b, f], S. Momsen Reincke [a, b, k], Elisa Sanchez-Sendin [b], Andrea Rocco [d], Mirja Steinbrenner [a], Stefan Angermair [e], Sascha Treskatsch [e], Daniel Zickler [c], Kai-Uwe Eckardt [c], Rick Dersch [g], Jonas Hosp [g], Heinrich J. Audebert [a], Matthias Endres [a, b, h, i, j], J. Christoph Ploner [a], Harald Prüß [a, b]

COVID-19 encephalopathy: detection of antibodies against SARS-CoV-2 in CSF

Daniela Andriuta[1] · Pierre-Alexandre Roger[2] · William Thibault[1] · Bénédicte Toublanc[2,3] · Chloe Sauzay[4,5] · Sandrine Castelain[6,7] · Olivier Godefroy[1] · Etienne Brochot[6,7]

Received: 29 May 2020 / Accepted: 4 June 2020 / Published online: 11 June 2020



Anti–SARS-CoV-2 antibodies in the CSF, blood-brain barrier dysfunction, and neurological outcome

Studies in 8 stuporous and comatose patients

Harry Alexopoulos, PhD, Eleni Magira, MD, Kleopatra Bitzogli, MSc, Nikolitsa Kafasi, MD, Panayiotis Vlachoyiannopoulos, MD, Athanasios Tzioufas, MD, Anastasia Kotanidou, MD, and Marinos C. Dalakas, MD, FAAN

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Dr. Dalakas
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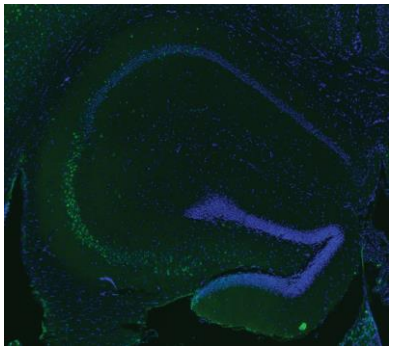
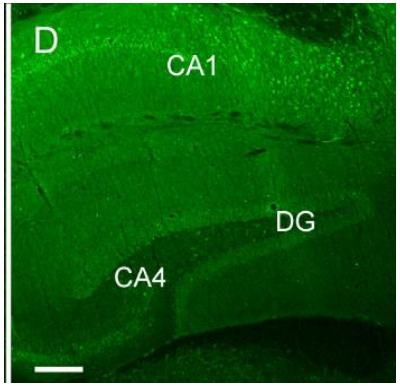
Neurol Neuroimmunol Neuroinflamm 2020;7:e893. doi:10.1212/NXI.0000000000000893

- *Garcia et al, 2021:*
- **77**% samples with anti-spike IgGs (but no viral RNA) >> anti-spike IgAs
- Titer do **not** correlate with *COVID-19 severity, neurological symptoms nor their onset*

- *Alexopoulos, et al, 2020:*
- **all** encephalopathy patients had anti-SARS-CoV-2 antibodies on ELISA testing, but **50**% of them had high CSF antibody titers and **disrupted BBB or increased intrathecal IgG synthesis**.
- there is also evidence of **ongoing neurodegeneration** in some of our encephalopathic patients (14-3-3 CSF positivity in patients with poor outcome)

Loss of tolerance & cross-reactivity





Autoimmune Encephalitis Presenting with Malignant Catatonia in a 40-Year-Old Male Patient with Covid-19

Jan Mulder, Amalia Feresiadou, David Fällmar, Robert Frithiof, Johan Virhammar, Annica Rasmusson, Elham Rostami, Eva Kumlien, Janet L. Cunningham

doi: https://doi.org/10.1101/2020.07.23.20160770

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High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms

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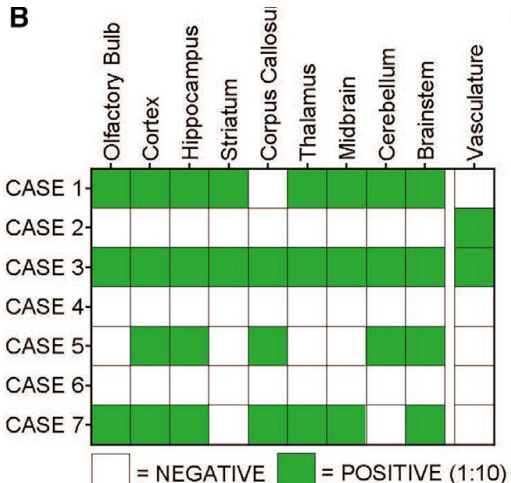
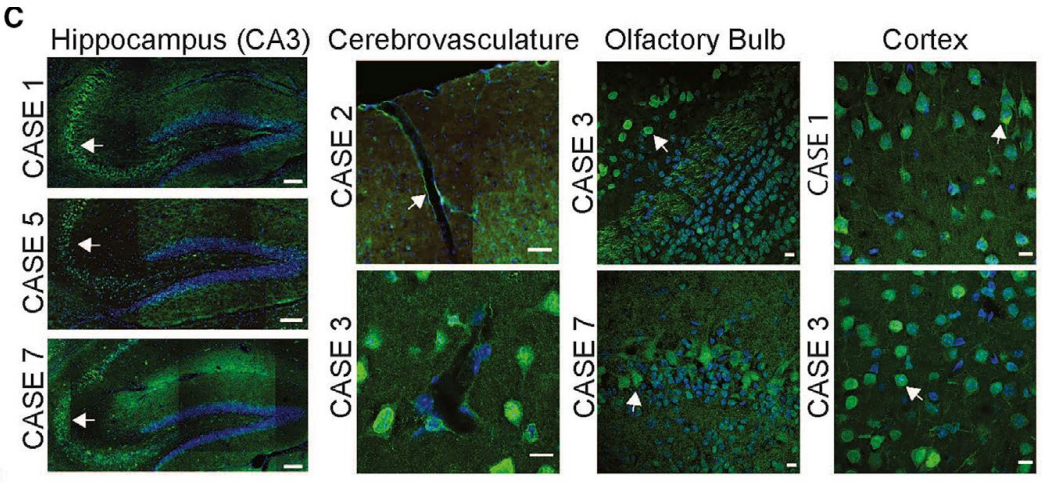
- High reactivity against **hippocampus, somatosensory cortex, thalamus, basal ganglia**
- Good response to **plasma exchange**

- High levels of autoantibodies against **endothelial, glial and neuronal antigens**
- With **signs of BBB dysfunction and/or neuronal injury**



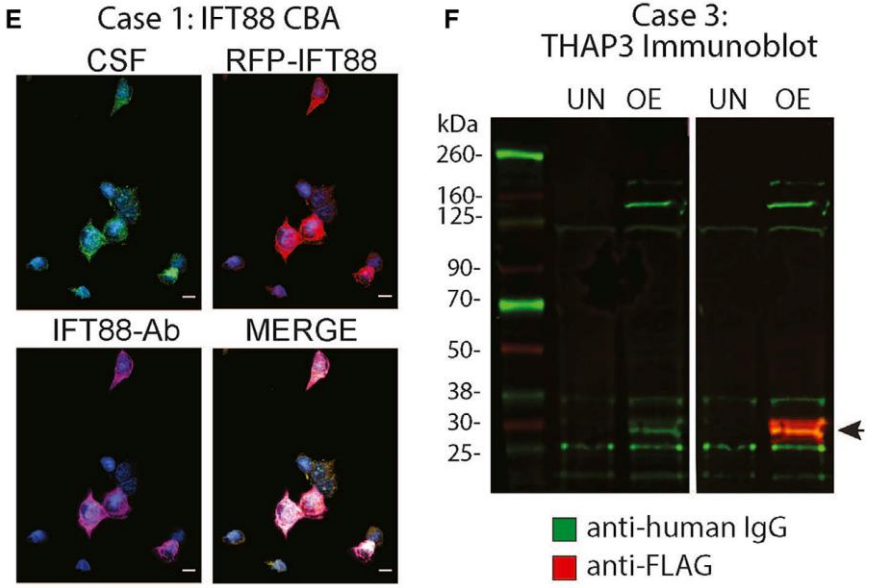


Do cross-reactive antibodies cause neuropathology in COVID-19?

Jakob Kreye[1,2], S. Momsen Reincke[1,3] and Harald Prüss[1,3]

Neurological symptoms are seen in patients with COVID-19 and can persist or re-emerge after clearance of SARS-CoV-2. Recent findings suggest that antibodies to SARS-CoV-2 can cross-react with mammalian proteins. Focusing on neurological symptoms, we discuss whether these cross-reactive antibodies could contribute to COVID-19 disease pathology and to the persistence of symptoms in patients who have cleared the initial viral infection.

- **A subset of high affinity neutralizing antibodies can recognize CNS** (Kreye et al)
- Infections can **break self-tolerance**
- Autoantibodies can be transient and without clinical correlate, but they can also trigger autoimmune diseases (post-herpetic NMDAR encephalitis)



- **Anti-Gangliosidi** (Dalakas et al, 2020; Guilmot et al, 2020): spike protein can bind gangliosides on cellular surfaces
- **IFT88** e **THAP3** as potential targets

Cell Reports
Medicine

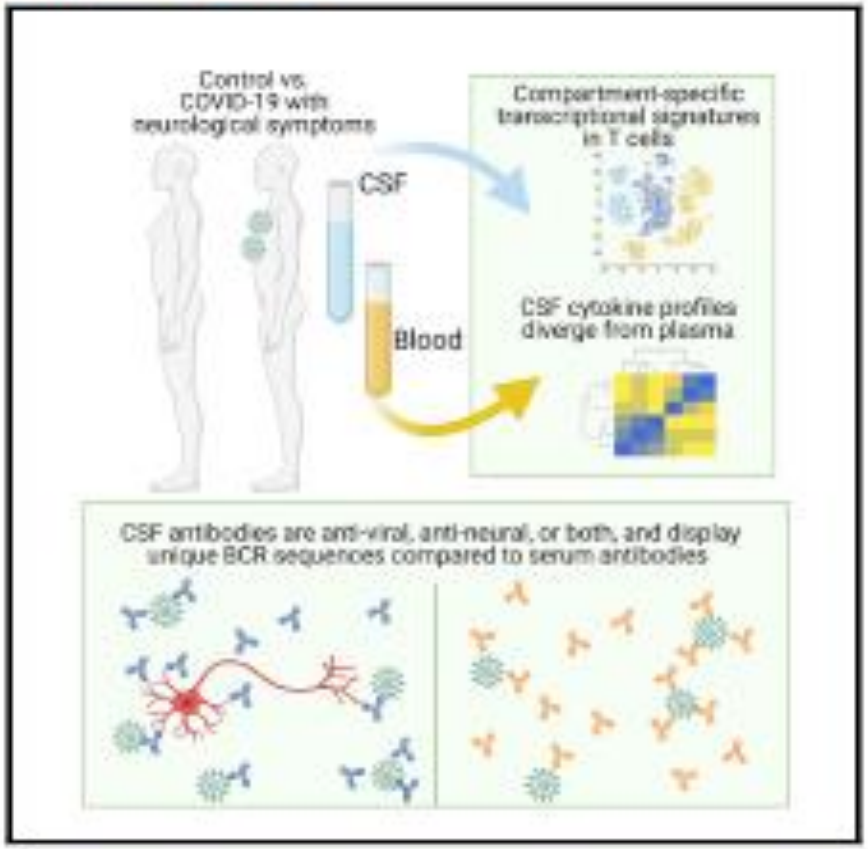
Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms

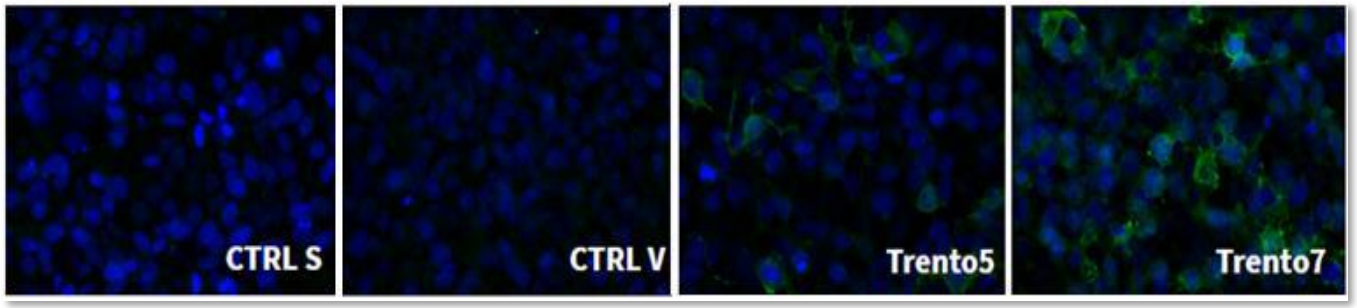
- Immune cell scRNA-seq showed **divergent T cell activation in the CNS** during COVID-19
- Individuals with COVID-19 had a **compartmentalized cytokine response** in the CNS
- **All** individuals with COVID-19 had **anti-SARS-CoV-2 antibodies in their CSF**
- **Five of seven individuals with COVID-19 had antineural autoantibodies in their CSF**

- CSF show high IL-12 and IL-1b levels
- Enrichment in CSF B cells
- CSF anti-SARS-CoV-2 antibodies recognize specific epitopes (serum antibodies have different targets); in rodent models (hACE2) mice display CSF antibodies **only after neuroinvasion**

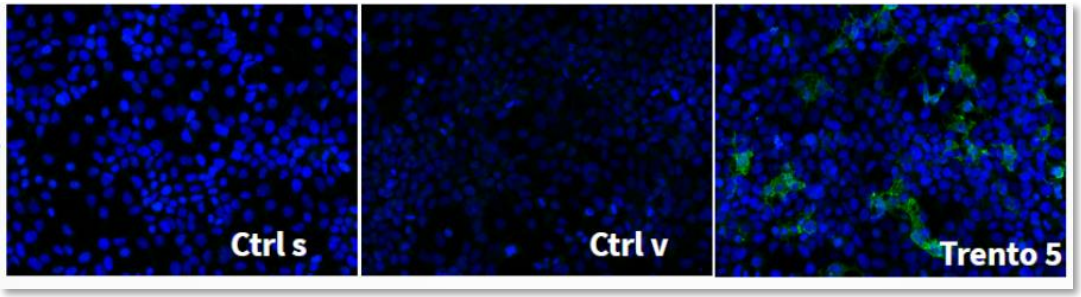
- **80% CSF antibodies exhibited CNS immunoreactivity (cortical neurons, olfactory bulb, thalamus, CA3, cerebellum, brainstem, cerebral vessels)**
- **CSF mabs were derived from a COVID-19 patient; they recognized viral (spike) and neural antigens, while serum antibodies did not react with brain tissues**

Graphical abstract





3 months later



Cognitive impact of neuronal antibodies: encephalitis and beyond

L. L. Gibson[1],

Brain imaging before and after COVID-19 in UK Biobank

Gwenaëlle Douaud[1]✉, Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L.R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Anderson M. Winkler[4], Thomas E. Nichols[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Stephen M. Smith[1]

Take home message

- Standard CSF analysis is often **fairly normal** in pts with COVID-19
- **SARS-CoV-2 has rarely been identified in the CSF** (and in autopsy case series)
- **High frequency of CSF anti-SARS-CoV-2 antibodies**
- Antibodies can be present **regardless of BBB integrity**
- This could suggest **disimmune pathogenetic mechanisms**

- *Is there a common target?*
- *Are the antibodies clinically relevant? Can they predict the so-called "Neuro-Covid"?*
- *What about pathogenetic mechanisms?*
- *Could they warrant immunological treatment?*

“The molecular biology of Neurocovid”

To be continued…

Thanks for your attention!