Neurological associations of COVID-19

Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767-83.

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Neurological associations of COVID-19

1. Historical background
2. Estimation of future neurological CoV-19 complications
3. Definition of COVID-19-associated neurological disease
4. Evidence from clinical investigations
5. Discussion: Disease mechanisms and further directions

1. Historical Background

A grim reminder: Encephalitis lethargica

- **1917–1930:**

An estimated number of **more than one million patients** worldwide were affect by a mysterious neurological disease of unknown etiology:

Very variable acute presentation:

excessive sleepiness, disorders of ocular motility, other nerve palsies, fever, and movement disorders (brady- as well as hyperkinetic).

-> **permanent neurological sequelae near total akinesia.**

From the Movie: *Awakenings (1990)*

Spanish flu: 1918 – 1919

-> Encepahlitis lethargica has been associated with the Influenza pandemia of the 1920s.

Should we fear for our brains?

Leslie A Hoffman, Joel A Vilensky, Encephalitis lethargica: 100 years after the epidemic, *Brain*, Volume 140, Issue 8, August 2017, Pages 2246–2251

2. Estimation of future neurological CoV-19 complications

Lessons from previous CoV associated epidemics:

SARS CoV: (RT-PCR and or Antibodies in Serum and/or CSF)

-> **3** cases of Encephalopathy, **4** cases: myopathy and peripheral neuropathy

(Total number of SARS-CoV1 patients (2002-2004)>8,000, at least 774 died worldwide)

MERS CoV: (Mostly RT-PCR confirmed)

-> **5** encephalopathies (2 acute disseminated encephalomyelitis, 2 cerebrovascular disease, 1 Bickerstaff's brainstem encephalitis), **3** peripheral neuropathy cases (GBS-like).

(Total of 2519 MERS cases, at least 866 deaths)

Extrapolation of estimated neurological case numbers

	SARS case count (n=8096)	MERS case count (n=2228)	COVID-19 worldwide minimum case count (n=4 872 308)		COVID-19 minimum case count in China (n=84 500)		COVID-19 minimum case count in USA (n=1 464 232)		COVID-19 minimum case count in UK (n=246 410)	
			Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)	Extrapolated from SARS (95% CI)	Extrapolated from MERS (95% CI)
Patients with CNS disease (proportion of total coronavirus cases [95% CI])	3 (0·04% [0·01–0·10])	5 (0·20% [0·06–0·50])	1805 (370–5277)	9671 (3143–22539)	31 (6–92)	168 (55–391)	543 (111–1586)	2906 (944–6774)	91 (19–267)	489 (159–1140)
Patients with PNS disease (proportion of total coronavirus cases [95% CI])	4 (0·05% [0·01–0·13])	4 (0·16% [0·04–0·41])	2407 (658–6163)	7737 (2110–19786)	42 (11–107)	134 (37–343)	723 (198–1852)	2325 (634–5946)	122 (33–312)	391 (107–1001)
Total patients with neurological disease (proportion of total coronavirus cases [95% CI])	7 (0·09% [0·03–0·18])	9 (0·36% [0·16–0·68])	4213 (1028–11440)	17 408 (5252–42326)	73 (18–198)	302 (91–734)	1266 (309–3438)	5231 (1578–12720)	213 (52–579)	880 (266–2141)

Calculated using data available up to May 19, 2020. COVID-19 cases based on Johns Hopkins COVID-19 Dashboard. 95% CI calculated with Clopper-Pearson exact method[24] for proportions using Ausvet Epitools. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. PNS=peripheral nervous system.

Table 1: **Estimated neurological disease case numbers associated with COVID-19, extrapolated from SARS and MERS data**

- The authors calculated a projected minimal prevalence of 1850-9671 patients with CNS symptoms and 2407-7737 with PNS complications, given a 4.8 Million total CoV-19 case number. (x10 as of November 2020)

3. Definition of COVID-19-associated neurological disease

Definition of COVID-19-associated neurological disease

WHO COV-19 case definition

Confirmed: RT-PCR or Validated antibody test

Probable: Suspected with inconclusive lab study or lab study not possible

Suspected: Clinical symptoms fitting CoV-19 + residency in location of community spread or contact to probable or confirmed case in the last 14 days leading to symptom onset , (patient with sever respiratory illness lacking other explanation)

SARS-CoV-2 meningitis, encephalitis, myelitis or CNS vasculitis

- **Confirmed:** Confirmation of SARS-CoV 2 or AB in CSF or brain tissue AND no other explenatory cause
- **Probable:** SARS-CoV-2 or AB detected in respiratory or other non-CNS sample AND no other explanatory pathogen or cause found
- (Possible): At least WHO class “suspected” + neurological clinical presentation

Acute disseminated encephalomyelitis associated with SARS-CoV-2 infection, Guillain-Barré syndrome, and other acute neuropathies associated with SARS-CoV-2 infection and CoV 19 associated stroke

- **Probable association**

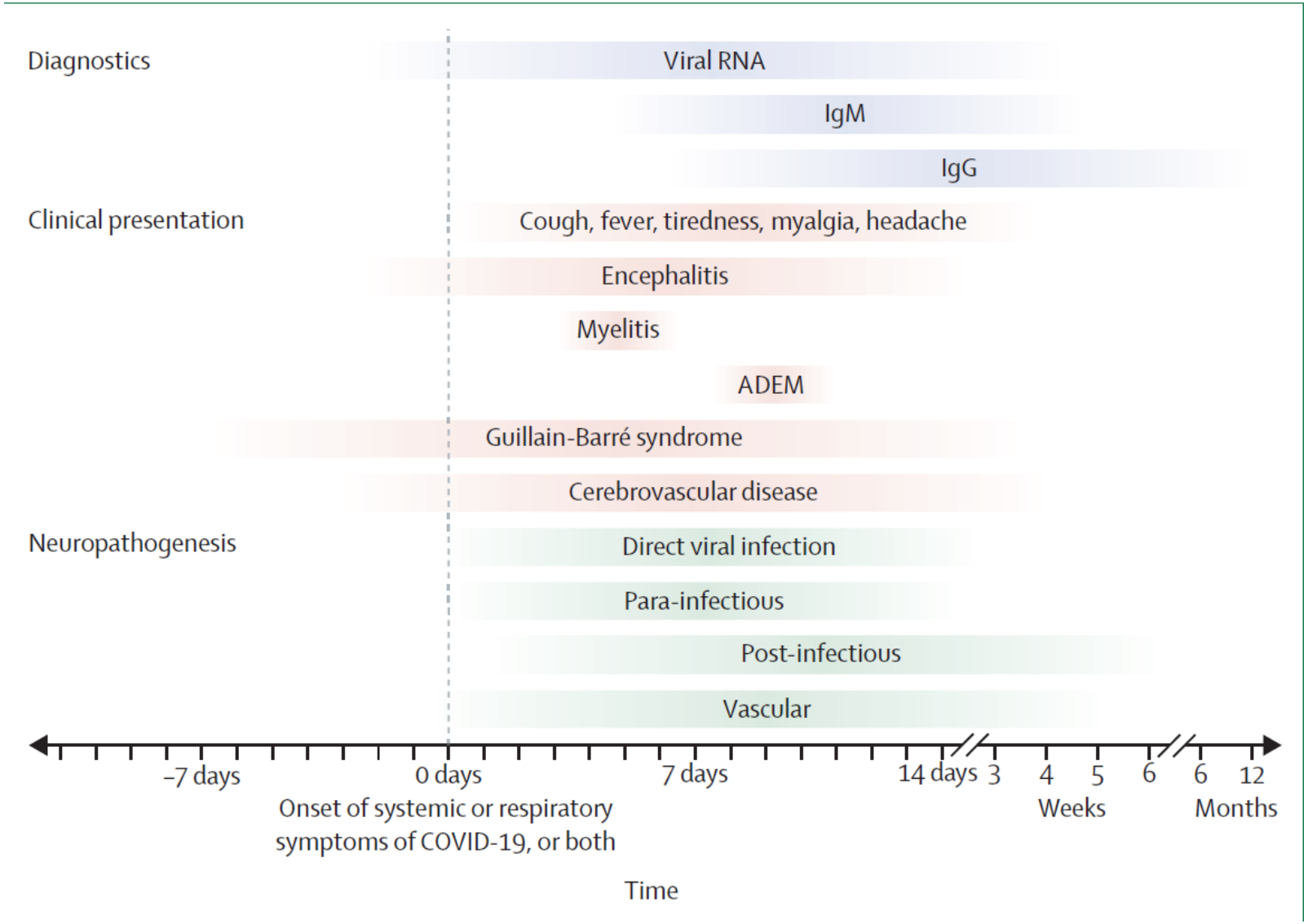
Neurological disease onset within 6 weeks of acute infection AND Lab confirmation AND no evidence of other commonly associated causes risk factors

- **Possible association**

As above + possible other cause: (e.g. Campylobacter jejuni, Mycoplasma pneumoniae, Cytomegalovirus, Epstein–Barr virus, hepatitis E virus, Zika virus, or HIV; or vaccination in the last 6 weeks…) (for stroke traditional cardiovascular risk factors).

4. Evidence from clinical investigations

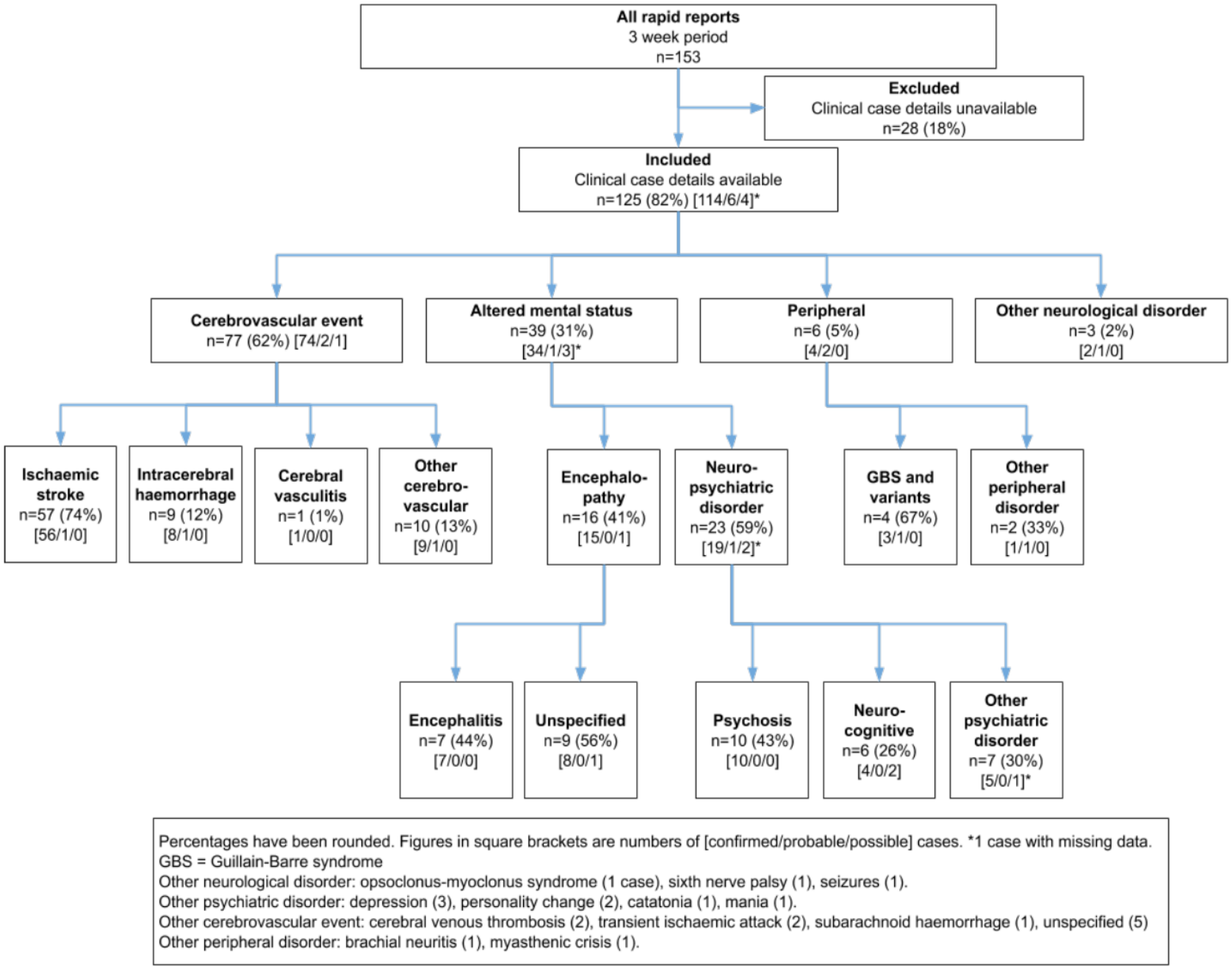
Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease



A total of 901 case studies have been included in this review.

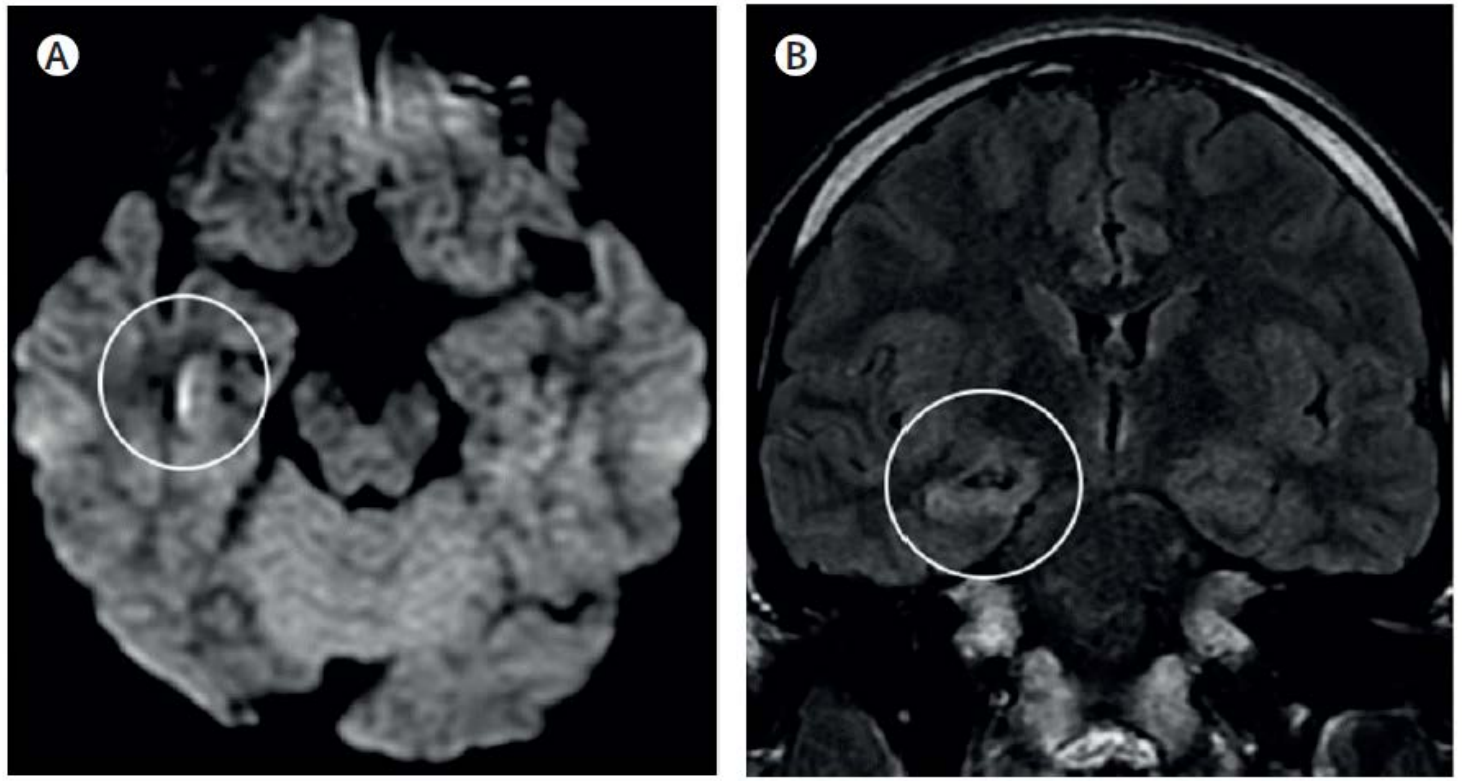
-> First systematic overview

Clinical features of CoV-19-associated neurological disease



- One of the first registry studies (UK) - CoroNerve Studies Group:
- **153** patients with COVID-19.
- -> High prevalence of altered mental status and cerebrovasculat events!
- However median age 71, preexisting conditions

Encephalitis



Encephalitis

Encephalitis defined as the typical EEG, MRI, CSF (e.g. pleocytosis) presentation -> clincial diagnosis of ongoing CNS inflammation

The studies reported vary greatly in the laboratory and radiological Investigations reported!

- As of May 19 2020: **8** adults (24-78y)
- Highly variable symptoms from respiratory onset to 17days afterwards:

Irritability, confusion, reduced conciousness, seizures, neck stiffnes, psychotic symptoms, ataxia, oscilliopsia, hiccups, nerve palsy.

Other Encephalopathies

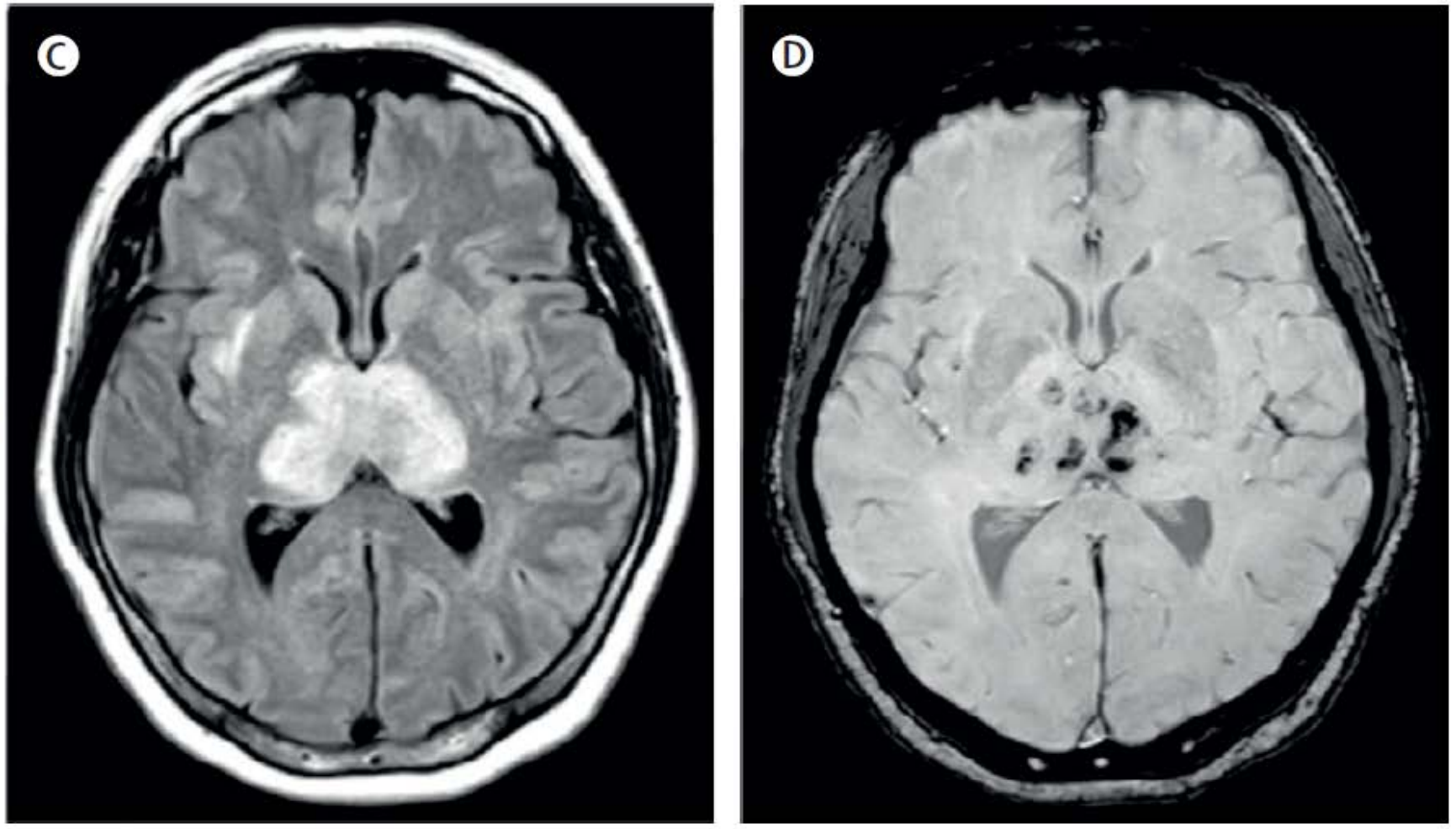
Wuhan study	**Total of 214** CoV 19 patients (all hospitalized)	**53 (25%) with CNS symptoms** Dizziness (17%) Headache (13%) Impaired Conciousness (7%) Overlap to severe course (51%)
French intensive care series	**Total of 58** CoV 19 patients (all ICU)	**49 (84%) neurological complications:** **40 (69%) encphalopathy** **39 (67%) corticospinal tract signs** -> MRI 8 out of 13 patients showed leptomeningeal enhancement, 2 x acute ischaemic change -> CSF examination for seven patients showed no pleiocytosis. -> 15 (33%) of 45 patients who had been discharged had a dysexecutive syndrome

- Wider category of neuro/psychiatric impairment, does not require proof of brain inflammation.

- BUT:

25–45% of critically ill patients who are admitted to intensive care units and at least 40-70% of sepsis patients develop some form critical illness neuropathy or myopathy, IRREGARDLESS of etiology

Particularly sever acute necrotising encephalopathy



Acute necrotising encephalopathy

2 cases, femals, middle aged, 3-7 day history of cough and fever -> altered mental status ,
Serum, CSF not suggestive of other known neurotropic pathogens

Acute disseminated encephalomyelitis and myelitis

2 ADEM cases: female, middle aged, developed during the 1-2 week after CoV 19 onset.

-> Dysphagia, dysarthria, encephalopathy

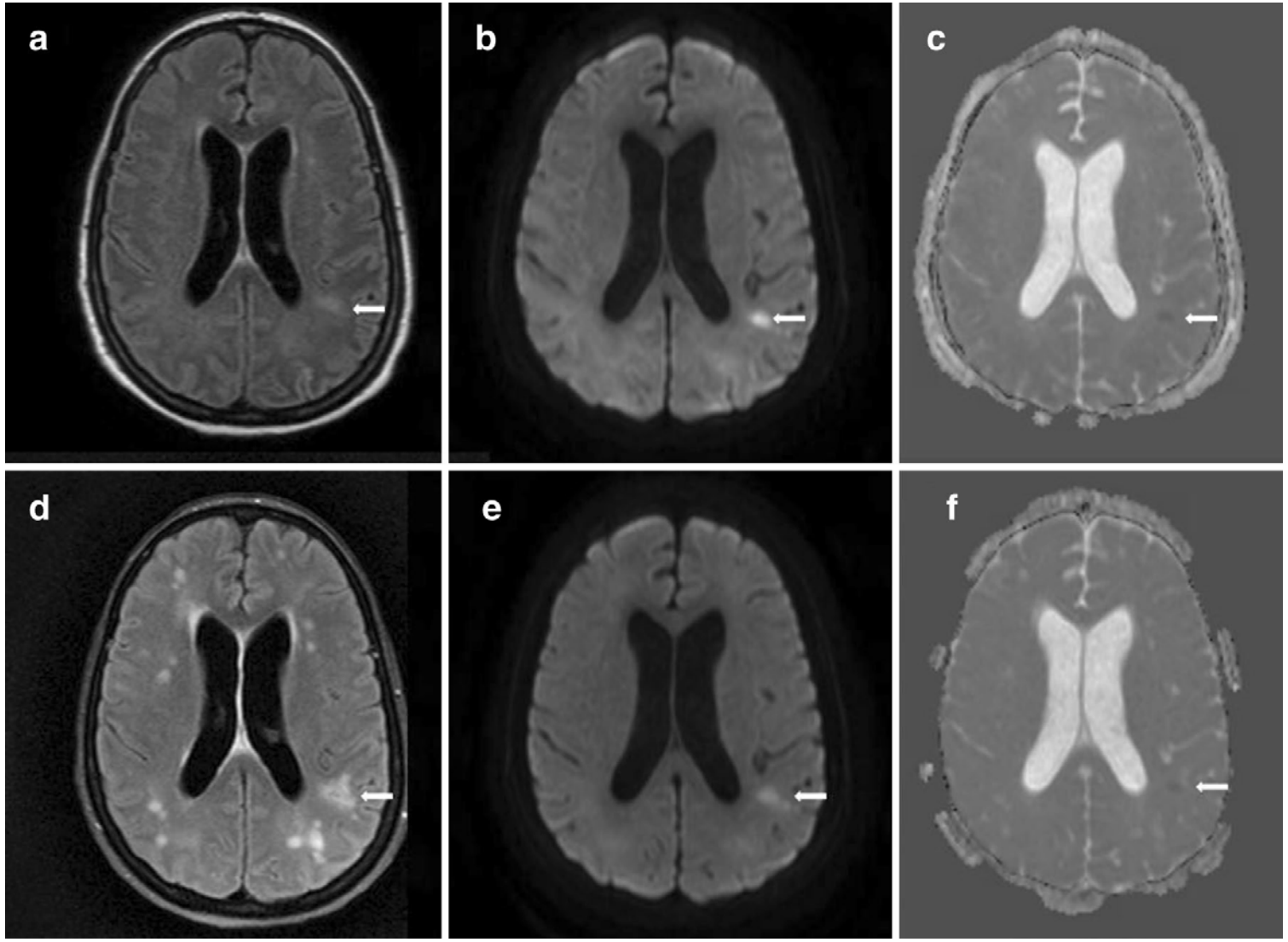
-> Seizures, reduced conciousness, severe respiratory course

In both normal CSF, high signal intensity lesions in MRI

Responded well to IVIGs, Steroids

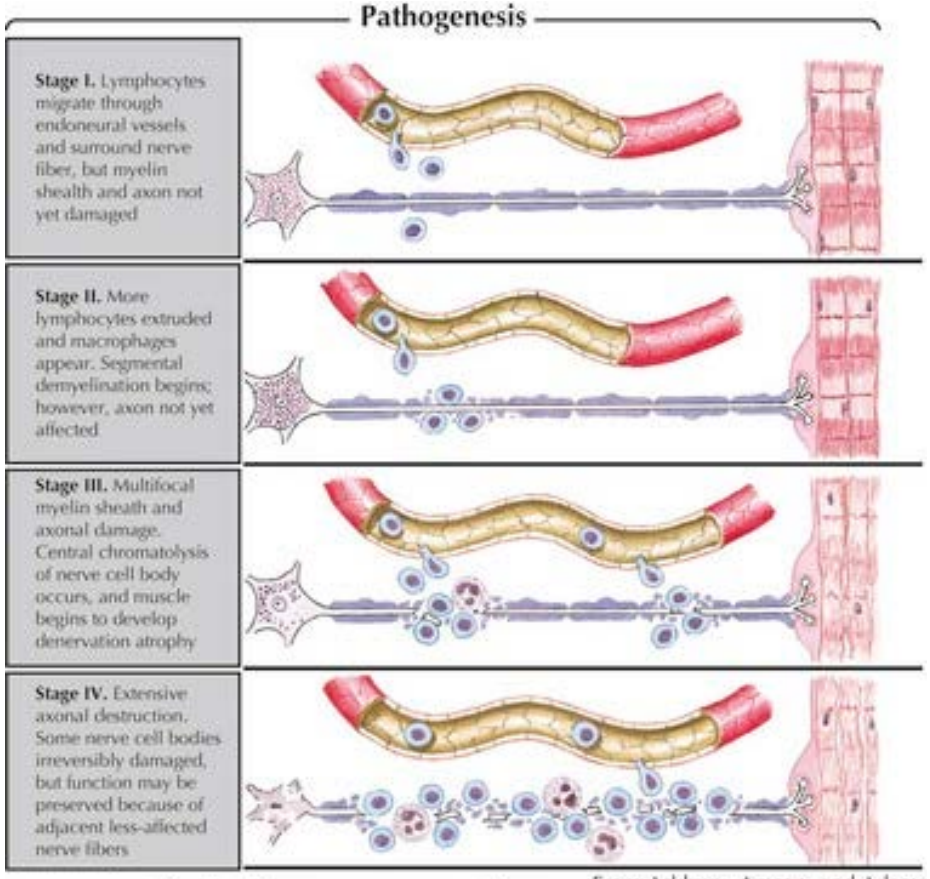
1 Myelitis case: male, 66 y, fever, fatigue, than flaccid paraparesis (Th 10 lesion) -> Responded to IVIGs, dexamethason

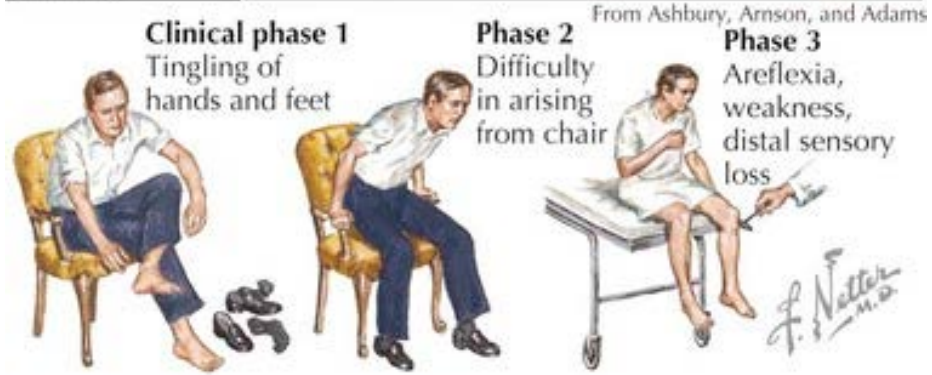
COVID-19-associated acute disseminated encephalomyelitis (ADEM) – MRI studies



Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020;267(10):2799-2802. doi:10.1007/s00415-020-09951-9

Peripheral nervous system and muscle disease





→ 19 CoV-19 associated Guillain-Barré cases:

Neurological onset median of 7 (-7 to 24) days after respiratory/systemic symptoms.

-> **16** patients with PCR confirmed CoV-19 from respiratory swab, CSF GBS-typical (albuminocytological dissociation).

0 SARS-CoV 19 PCR positive CSF samples!

Only 4 studies reported stringent testing for other GBS associated pathogens!

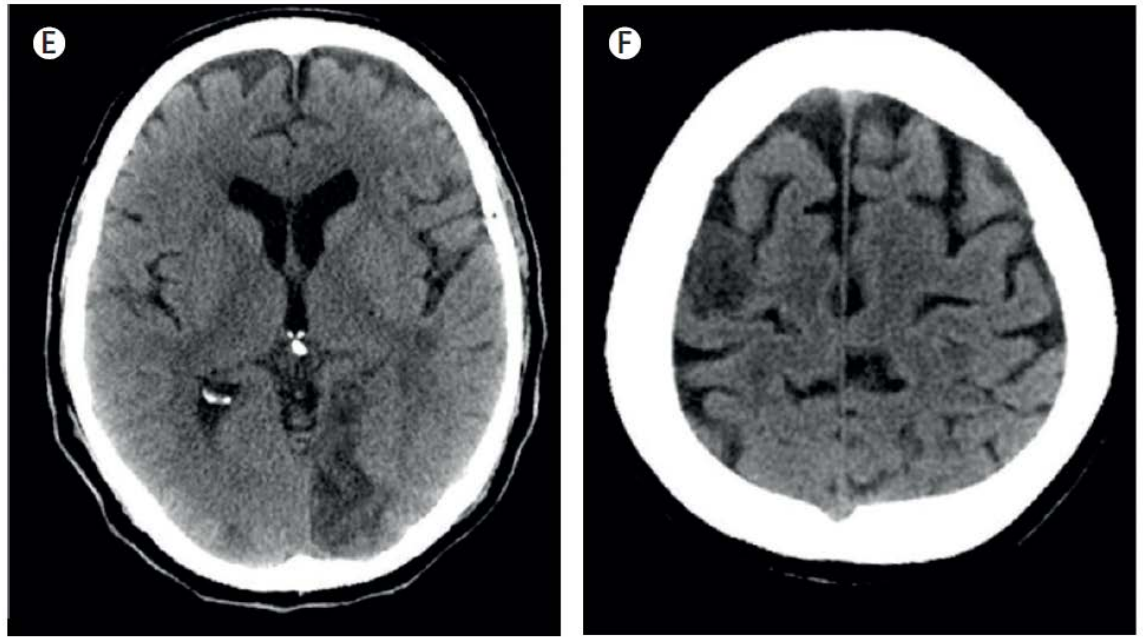
→ Raised CK and muscle injury in 11% of the Wuhan cohort, including Rhabdomylisis

Anosmia and Ageusia

- **Common!** In the biggest cited study on the issue: Olfactory disorders in 357 (86%) of 417 CoV 19 patients, gustatory disorders in 342 (82%).
- More common! than in other respiratory viruses and Influenza, also in the absence of other symptoms and before coryza.

→ **Indicative of neuroinvasion?**

Cerebrovascular manifestations



Wuhan series (retrospective)	Total of 221 CoV-19 patients (all hospitalized)	**13 (6%)** -> 5% ischemic stroke -> 1 intracerebral hemorrhage -> 1 Venous thrombosis
Milan series (retrospective)	Total of 388 CoV-19 patients (all hospitalized)	**9 (2%)** -> Ischemic stroke
Lombardy series (retrospective)	Selected patients: 56 CoV-19 patients admitted to the Brescia Neurology unit	**43 (77%) cerebrovac. disease** **-> 35 ischemic** **-> 3 hemorrhagic stroke** **-> 5 TIA**
Netherlands series (retrospective)	Total of 184 CoV-19 patients (all ICU)	**3 (2%) -> ischemic stroke**

Often predominantly older (>60y), unclear comorbidities

Summary: Total of 88 patients with ischemic stroke 8 with hemorrhagic stroke
Overall mortality: 19%

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	33	37	39	44	49
Sex	Female	Male	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes	Mild stroke, diabetes
Medications	None	None	None	None	Aspirin (81 mg), atorvastatin (80 mg)
NIHSS score‡					
On admission	19	13	16	23	13
At 24 hr	17	11	4	19	11
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)	7 (on day 4)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit	Discharged to rehabilitation facility
Time to presentation — hr	28	16	8	2	8
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousness, global dysphasia, hemiplegia on right side, gaze preference	Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery	Right middle cerebral artery
Imaging for diagnosis	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP
Treatment for stroke	Apixaban (5 mg twice daily)	Clot retrieval, apixaban (5 mg twice daily)	Clot retrieval, aspirin (81 mg daily)	Intravenous t-PA, clot retrieval, hemicraniectomy, aspirin (81 mg daily)	Clot retrieval, stent, aspirin (325 mg daily), clopidogrel (75 mg daily)
Covid-19 symptoms	Cough, headache, chills	No symptoms; recently exposed to family member with PCR-positive Covid-19	None	Lethargy	Fever, cough, lethargy
White-cell count — per mm^3	7800	9900	5500	9000	4900
Platelet count — per mm^3	427,000	299,000	135,000	372,000	255,000
Prothrombin time — sec	13.3	13.4	14.4	12.8	15.2
Activated partial-thromboplastin time — sec	25.0	42.7	27.7	26.9	37.0
Fibrinogen — mg/dl	501	370	739	443	531
D-dimer — ng/ml	460	52	2230	13,800	1750
Ferritin — ng/ml	7	136	1564	987	596

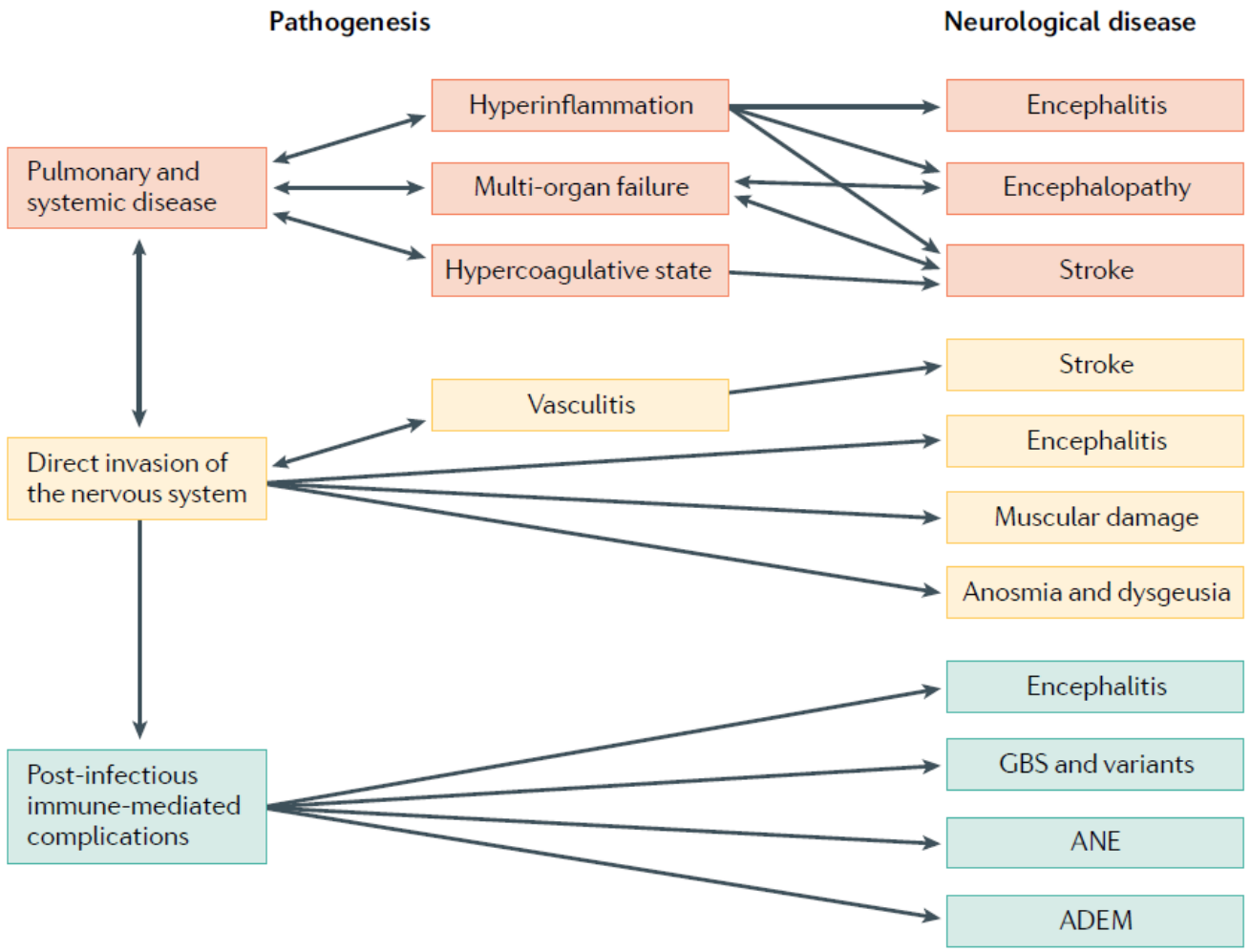
New York Series

- 5 young to middle aged CoV-19 patients, mostly otherwise healthy.

Oxley TJ, Mocco J, Majidi S, Kellner CP. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. 2020;382(20):e60.

5. Discussion: Disease mechanisms and further directions

Discussion: Putative Disease mechanisms



- Key questiones to be adressed by future research:

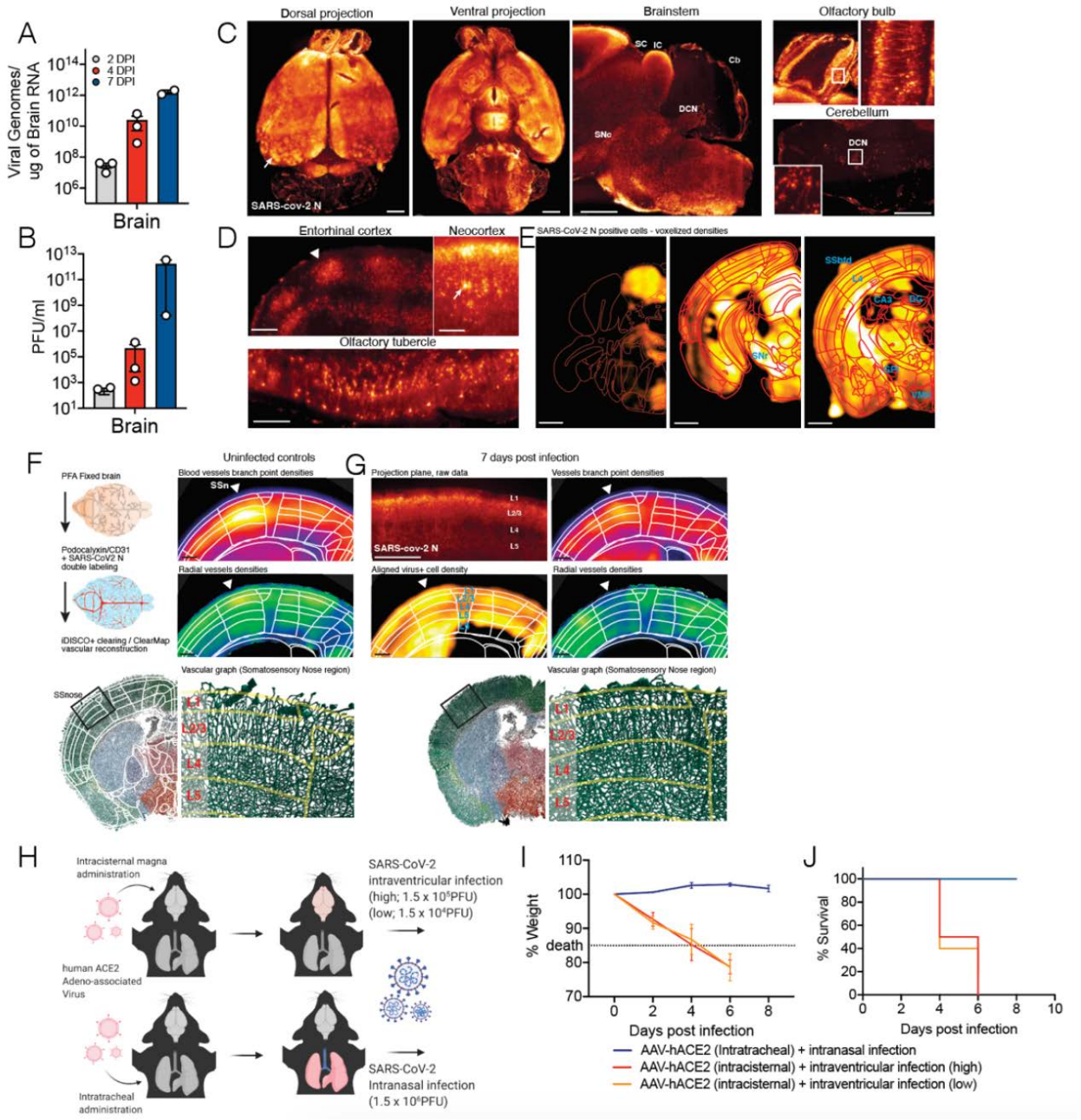
-> Contributions of neuroinvasion (if at all?)

-> Contributions of para and post infectious immune and coagulatory mechanisms (and their interplay?)

-> Which neurological complications are CoV-19 specific, which are critical illness related ?

Pezzini, A., Padovani, A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 16, 636–644 (2020). https://doi.org/10.1038/s41582-020-0398-3

Direct invasion of nervous tissue via the olfactory bulb?



- The olfactory bulb is the only part of the CNS not protected by dura

→Common entry of neurotropic viruses

Refresher from last week: Currently investigated and debated

→ IF neuroinvasion is likely, can the virus persist (similar to Herpesviridae?)

Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., Lu, P., Weizman, O. E., Liu, F., Dai, Y., Szigeti-Buck, K., Yasumoto, Y., Wang, G., Castaldi, C., Heltke, J., Ng, E., Wheeler, J., Alfajaro, M. M., Levavasseur, E., Fontes, B., … Iwasaki, A. (2020). Neuroinvasion of SARS-CoV-2 in human and mouse brain. bioRxiv : the preprint server for biology, 2020.06.25.169946. https://doi.org/10.1101/2020.06.25.169946

Alternative routes: Putative mechanisms by which the BBB can be passed or cirumvented?

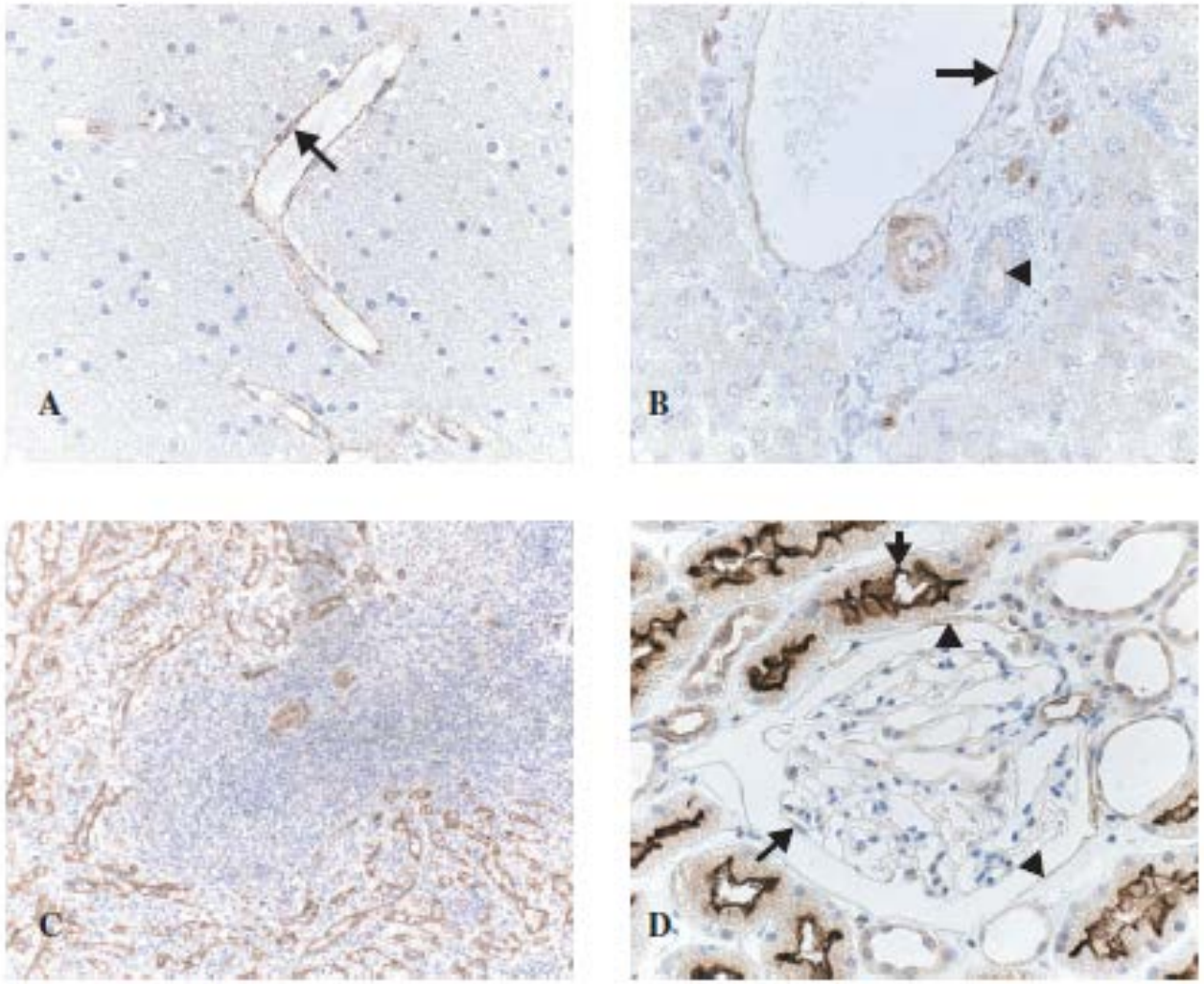


Figure 4. In the brain (A), ACE2 is expressed only in endothelium (arrow) and vascular smooth muscle cells. In the liver (B), Kupffer cells, hepatocytes, and the endothelium of sinusoids are negative. Luminal staining in bile ducts is occasionally observed (arrow-head). Vascular endothelium (arrow) and smooth muscle cells are positive. In the spleen (C), ACE2 is not expressed in cells of the immune system. Vascular and red pulp sinus endothelium is positive. In the kidney (D), ACE2 is present in glomerular visceral (arrow) and parietal (arrow-head) epithelium, in the brush border (short arrow) and cytoplasm of proximal tubular cells, and in the cytoplasm of distal tubules and collecting ducts

- Modest repliaction of SARS-CoV-2 in U-251 MG Glioblastoma Cell Line (human neuronal cell line), *in vitro*
- The main entry receptor of the virus is expressed in the human brain vasculatur
- Could immuncells act like „viral trojan horse“
- Changes of the BBB by vascular damage in the diseases course?

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-637. doi:10.1002/path.1570

Precise pathological mechanisms of tissue damage in COVID-19 Encephalitis and Encephalopathy?

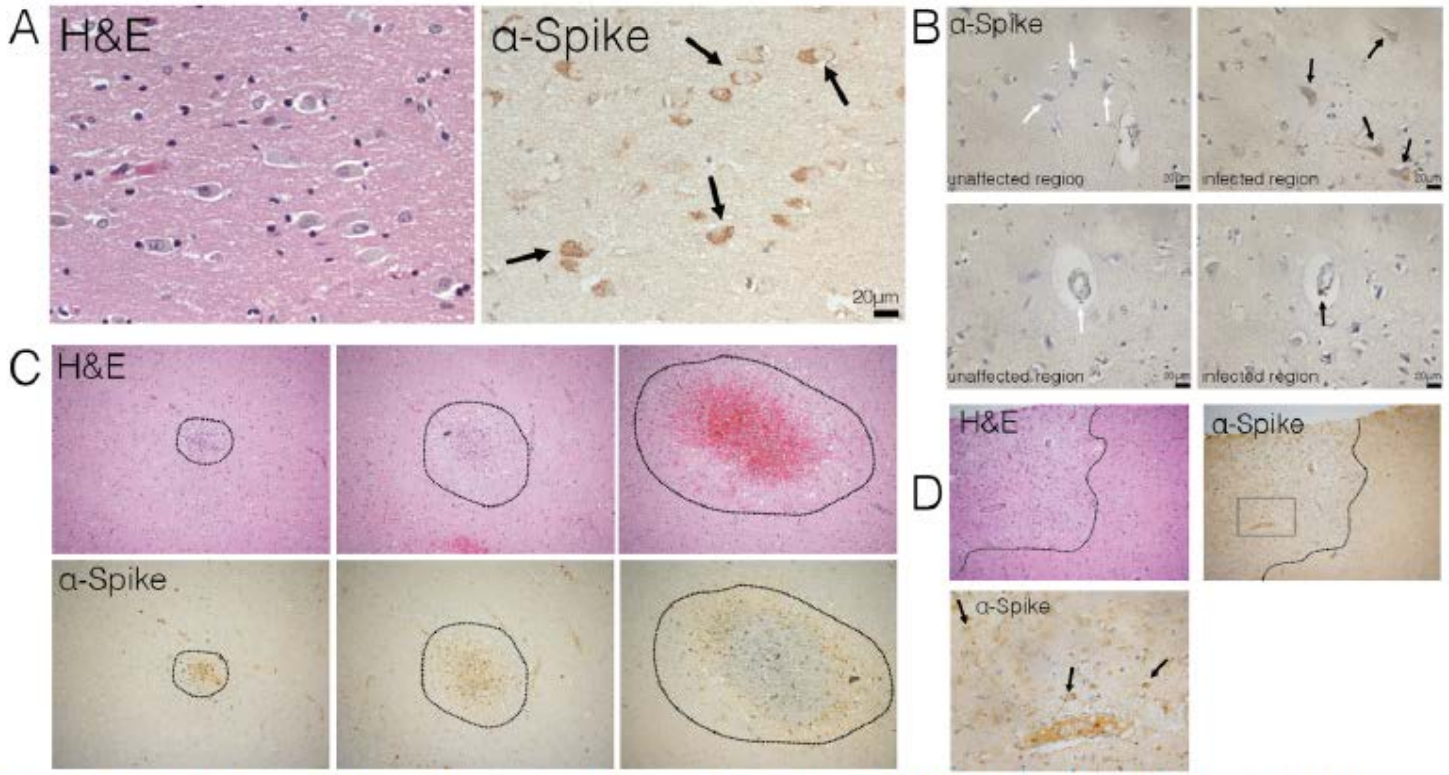


Figure 5: Evidence of neuroinvasion in post-mortem COVID-19 patient brains. FFPE sections of brain tissue from COVID-19 patients were stained using H&E and anti-SARS-CoV-2-spike antibody. (**A**) Image of cortical neurons positive for SARS-CoV-2 (black arrows). (**B**) Images of unaffected regions (left) and infected regions (right) demonstrating infection of neurons (top row) and microvasculature (bottom row). (**C**) Ischemic infarcts found at different stages stained with H&E (top row) and SARS-CoV-2-spike antibody (bottom row). (**D**) Ischemic region outlined with dotted line with positive staining focused around ischemic infarct. Bottom image shows zoomed in image indicated by dotted box in top image, and black arrows indicate infected neurons in the region.

- Coronaviridae are not thought to be highly neurovirulent.
- So far evidence of CXCL-9 elevation and local T-Cell, Monocyte and Macrophage invasion.
- Likely complex collateral damage of innate and adpative immune response

Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., Lu, P., Weizman, O. E., Liu, F., Dai, Y., Szigeti-Buck, K., Yasumoto, Y., Wang, G., Castaldi, C., Heltke, J., Ng, E., Wheeler, J., Alfajaro, M. M., Levavasseur, E., Fontes, B., … Iwasaki, A. (2020). Neuroinvasion of SARS-CoV-2 in human and mouse brain. bioRxiv : the preprint server for biology, 2020.06.25.169946. https://doi.org/10.1101/2020.06.25.169946

Cerebrovacular diseases

- Key questions:

Contributions of SARS-CoV-2 associated vascular damage and hypercoagulopathy and the interplay of these events with immunodysregulation?

-> Pleiotropy of possible mechanisms:
NETosis induced hypercoagulopathy, secondary vasculitis, influence of general cerebral hypoxia in ICU patients, plaque destabilization and rupture….

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