COVID-19에서의 뇌병증

이 순 태
서울의대

Encephalopathy in COVID-19

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SARS-CoV-2

- Coronavirus: Child URI since 1965 (1~35% of URI)
- SARS (SARS-CoV-1), SARS-CoV-2 → ACE2/TMPRSS2
- MERS → DPP4
- ACE2 expression
  - Lung, oral mucosa, heart, vascular endothelium
  - Brain: normally-negative except the periventricular area and vessels

ACE2 expression in brain (proteinatlas.org)

Neurologic diseases in other major Coronavirus

- SARS
  - Seizures
  - (Autoimmune) Encephalitis
  - Ischemic stroke
  - Guillain-Barre syndrome
- MERS
  - Seizures
  - Psychosis
  - Bickerstaff encephalitis
  - ADEM
  - GBS

Experience in MERS

- Four in 23 MERS patients (admitted)
  - Bickerstaff encephalitis+GBS
  - Intensive-care-unit-acquired weakness
  - Neuropathies
- Infection-Neurologic complication: 2-3 weeks interval

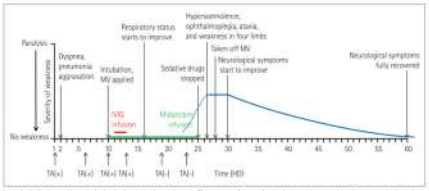
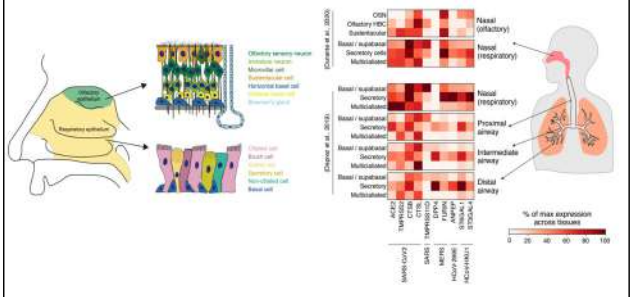


Fig. 1. Timeline of clinical events and virological results in patient 1. The onset of neurological symptoms and their course during the sedative state were uncertain, and are indicated by the dotted lines. HD: hospital day, IVIG: intravenous immunoglobulin, MV: mechanical ventilator, TA: tracheal aspirate.

Kim JE et al., JCN, 2017

Anosmia: non-neuronal pathology

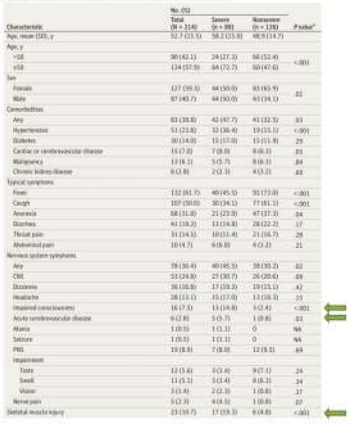


Brann et al., MedRxiv, 2020

Direct vs Indirect

- Direct invasion
  - Olfactory bulb: anosmia
  - Meningitis
  - Brain vasculopathy
  - Myositis
- Indirect effects
  - Hypoxia
  - Brain vasculopathy, Hypercoagulable stroke
  - Cytokine storm
  - Metabolic encephalopathy (sepsis, hepatic, uremic, drug)
  - Post-infectious: autoimmune encephalitis, ADEM, GBS

Neurologic symptoms in COVID-19 patients

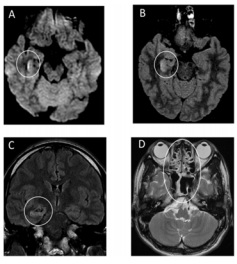


Mao et al., Lancet Neurol, 2020

Direct invasion of SARS-CoV-2

SARS-CoV-2 (Moriguchi et al., Int J Inf, 2020)

- 24-year-old man
- Stupor and seizure at day 9 of fever
- SARS-CoV-2 (+) in CSF (12 cells), not in NP swab



Other coronavirus

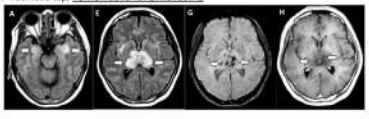
- HCoV-OC43 (+): direct fatal encephalitis in a SCID child (Morfopoulou et al., NEJM, 2016)

Post-viral autoimmune phenomenon

- Gullain-Barre syndrome (Toscano et al., NEJM, 2020; Zhao et al., Lancet Neurol, 2020)
- Transverse myelitis (Munz et al., J Neurol, 2020)
- Acute disseminated encephalomyelitis (Zhang et al., Lancet Neurol, 2020)
- Acute hemorrhagic (necrotizing) encephalomyelitis (Poyiadji et al., Radiology, 2020)

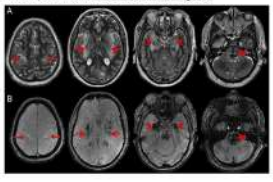
Acute necrotizing encephalopathy

- After infection and cytokine storm (Influenza, HHV6)
- [Case#1, Poyiadji et al., Radiology, 2020] Late 50s-female, Altered mentality at day 3 of fever.
- CSF: Traumatic tap, no PCR done for SARS-CoV-2



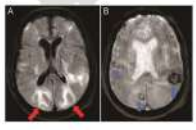
MRI from ANE after HHV6

- [Case#2, Dixon et al., N2, 2020] 59-year-old female, Seizure at day 10 of fever
- CSF: wbc 4, protein 230, PCR-SARS-CoV-2=negative



PRES, Autoimmune encephalitis

- Posterior reversible encephalopathy syndrome (PRES):
  - 64-yr-old male, coma after extubation



- Autoimmune encephalitis
  - 57-yr-old female, acute aphasia during asymptomatic COVID-19, CSF PCR(-)

Remero-Sanchez et al., Neurology, 2020

Disease-modifying treatments in MS and risk of COVID-19

- DMTs block severe immune response in COVID-19 ?

Table DMTs and risk of COVID-19

Agent	MOA	Risk of infectious disease	Potential beneficial effect by limiting immune responses mediating severe COVID-19 complication (e.g., ARDS)	Predicted potential to increase the risk of severe COVID-19 complication (e.g., ARDS)
Interferon β-1a and β-1b	Decreases immune cell activation through IFN receptor binding; decreased trafficking	No increased risk of infection[11]	Downregulation of proinflammatory cytokines	None
Glatiramer acetate	Promotes Th1→Th2 shift; induces suppressor T cells and anti-inflammatory myeloid cells	No increased risk of infection[11]	Shift from Th1 and M1 (proinflammatory) to Th2 and M2 (anti-inflammatory)	None
Dimethyl fumarate	Promotes Th1-Th2 shift; induces mild apoptosis of memory T cells and B cells; neuroprotective effect by upregulation of Nrf2-dependent antioxidant response	Potential risk of PML[11]	Block proinflammatory cytokine production[11] and inhibit macrophage function	Probably low
Teriflunomide	Inhibits proliferation of activated T and B lymphocytes by inhibiting DHODH	Potential reactivation of tuberculosis	Downregulation of IL-1, IL-6, and TNFα from activated macrophage	Probably low
S1P modulators	Prevent lymphocyte egress from lymph nodes by binding S1P receptor	Potential increased risk of some opportunistic infections (PML, Cryptococcus, VZV, and HPV); slight increased risk of lower respiratory infections	Block recruitment of monocytes and macrophages via S1P3 receptor modulation (only with nonspecific S1P modulators)	Probably low
Cladribine	Sustained reduction of T and B cells by interfering with DNA synthesis and repair	Slight increased risk of herpes infections with grade 3 or 4 lymphopenia	Uncertain, main effects on lymphocytes	Probably low
Natalizumab	Prevents entry of T cells and others into the brain	Potential risk of PML[11]	Uncertain, probably none	Probably low
Anti-CD20 monoclonal antibodies	Binds CD20 resulting in B-cell cytotoxicity	Potential increased risk of URI; reactivation of chronic hepatitis B	Uncertain; main effects on B cells/de novo plasmablasts	Probably low
Alemtuzumab	Depletes B and T cells by binding to CD52	Reactivated herpes infection (HSV and VZV), listeria, HPV	Uncertain	Probably low except during the first months after infusion

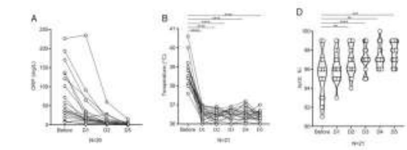
Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus 2019; DHODH = dihydroorotate dehydrogenase; DMT = disease-modifying therapy; HPV = human papillomavirus; PML = progressive multifocal leukoencephalopathy; URI = upper respiratory infection; VZV = varicella zoster virus.

Berger et al., N2, 2020

"You can't eat your cake and have it" ?

Drugs	COVID-19	Effects in neurologic diseases	Dose in COVID
Immunoglobulin	Possible antiviral?	GBS, ADEM	2g/kg
Tocilizumab	Attenuates cytokine storm	Autoimmune encephalitis, New-onset refractory status epilepticus, ADEM, NMO	4~8mg/kg
Dexamethasone	Attenuates mortality (RECOVERY trial: unpublished)	Steroid-necessary diseases	6mg/day for 10 days

Tocilizumab in COVID-19

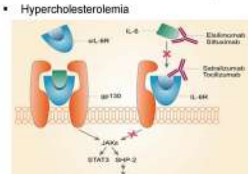


Xu et al., PNAS, 2020

Tocilizumab (Actemra®)

- IL-6 receptor blocker
- Rheumatoid arthritis: 4mg/kg infusion q4weeks → 8mg/kg infusion q4weeks
- Cytokine storm: 4~8mg/kg (divided in 1 or 2 shots)
- **Autoimmune encephalitis: initial 4mg/kg infusion → another 2~4mg/kg after 1~14 days, depending on the clinical response and ANC (absolute neutrophil counts)**
- Subcutaneous form is available (fixed to 162mg)

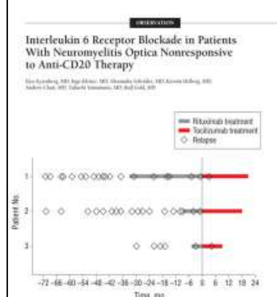
- Major side effects in AE
  - Increased risk of bacterial infection: tocilizumab can mask fever and CRP
  - Neutropenia (>6mg/kg) after several days
  - Hypercholesterolemia



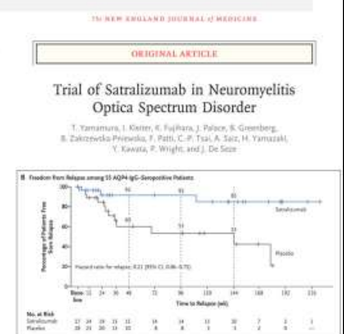
FDA Health news, 2020

Satralizumab= the engineered tocilizumab, rapidly dissociating from IL-6R within the acidic environment of the endosome

Tocilizumab and Satralizumab in NMO



Ayzenberg et al., JAMA Neurol, 2013


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder
T. Yamamura, I. Kleiter, K. Fujihara, J. Palace, B. Greenberg, B. Zakrzewska-Pniewska, F. Patti, C.-P. Tsai, A. Saiz, H. Yamazaki, Y. Kawata, P. Wright, and J. De Seze
Satralizumab
Placebo
Time to Relapse (wk)
No. at Risk

Yamamura et al., NEJM, 2019

Readiness for pandemic in Korea ?

- In case of an overwhelming number of patients, the issues are
  - Keeping COVID-free in neurological facilities (ward, MRI, electro-physiologic labs)
  - Continuing patients care for urgent neurologic diseases
  - Protecting patients with chronic neurological illness from COVID-19 in daycare, rehabilitation centers, and nursing hospitals.
  - Safety protocols for COVID-19 with neurological problems: CSF tapping, EMG, neurologic exams
  - Subspecialty issue: if your neurology patients get COVID-19, are you ready for a prompt decision ?
    i.e., immune-suppressing agents in autoimmune, neuromuscular patients in risk of respiratory failure

Summary

- Neurological manifestation is common
- Direct involvement of SARS-CoV-2 is very rare, but possible
- Indirect encephalitis is the major: hypoxia, cytokine, autoimmune
- Get ready for your own clinical protocols amid COVID-19 pandemic
- Long-term neurologic consequences?
  - Late parkinsonism in 1918-1920 influenza