Neuropatología de la COVID-19: qué sabemos y qué podemos esperar a largo plazo.

Alberto Rábano

Fundación CIEN, Instituto de Salud Carlos III

Madrid

Seminario, Fundación CIEN
Marzo 2021

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WHO Coronavirus (COVID-19) Dashboard

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Situation by WHO Region

Daily | Weekly | Cases | Deaths | Count

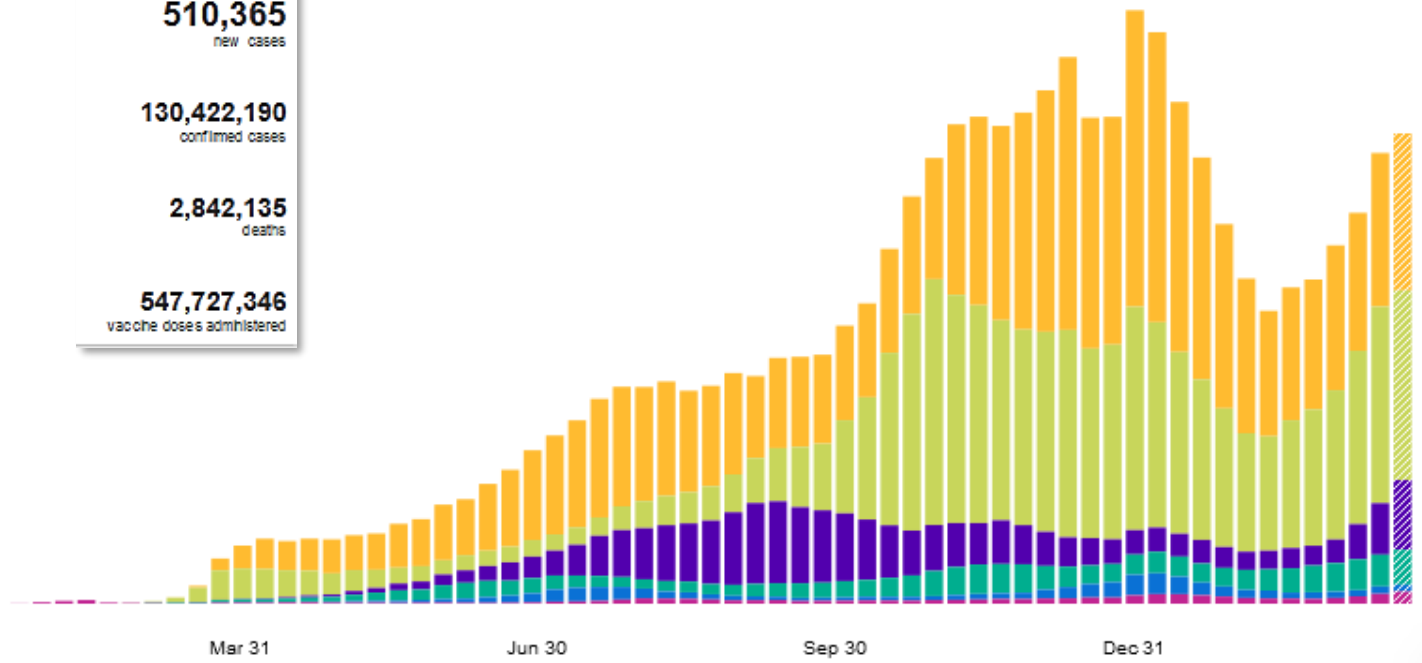
Americas	56,580,222 confirmed
Europe	45,852,597 confirmed
South-East Asia	15,212,235 confirmed
Eastern Mediterranean	7,693,094 confirmed
Africa	3,120,296 confirmed
Western Pacific	1,963,001 confirmed

510,365 new cases

130,422,190 confirmed cases

2,842,135 deaths

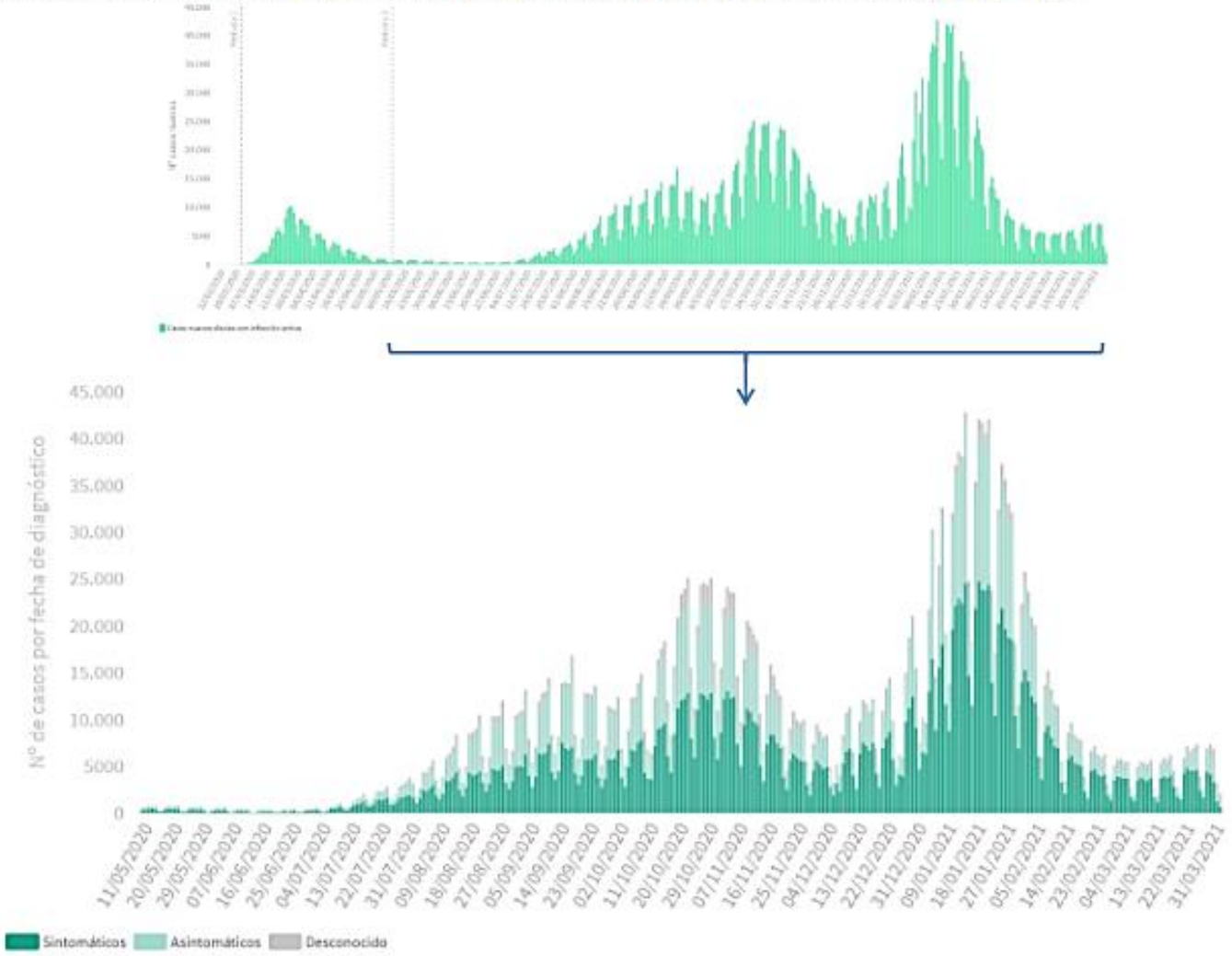
547,727,346 vaccine doses administered



Source: World Health Organization

Data may be incomplete for the current day or week.

Figura 1. Casos diarios confirmados y sospechosos de COVID-19 en España a 02.04.2021 (datos consolidados a las 14:00 horas del 03.04.2021).

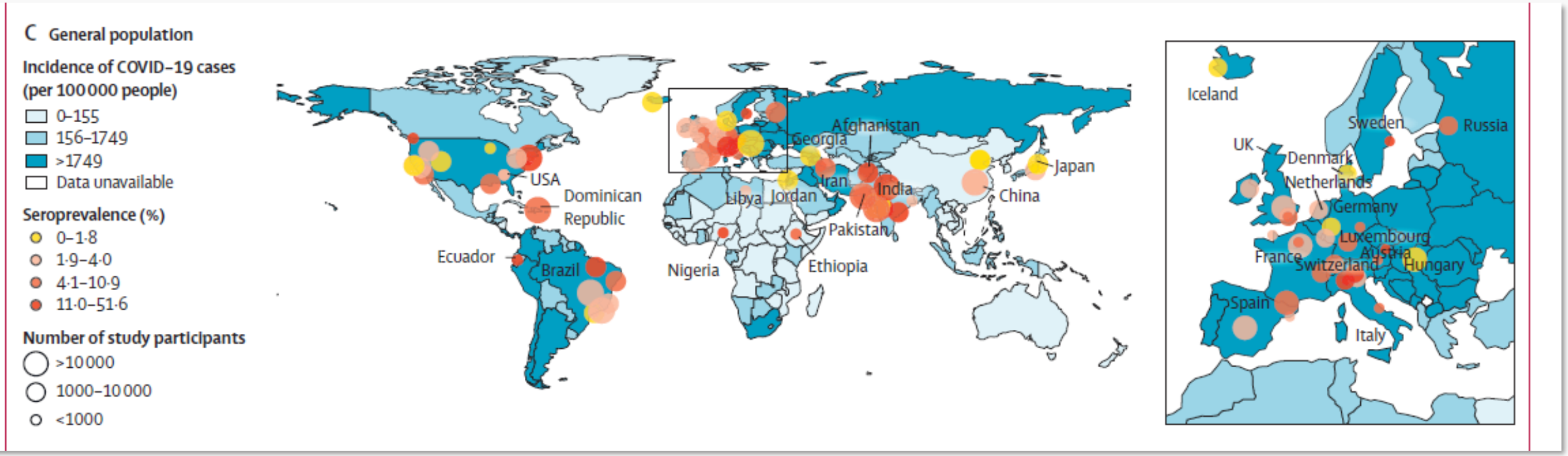


Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis

Xinhua Chen, Zhiyuan Chen*, Andrew S Azman*, Xiaowei Deng, Ruijia Sun, Zeyao Zhao, Nan Zheng, Xinghui Chen, Wanying Lu, Tingyu Zhuang, Juan Yang, Cecile Viboud, Marco Ajelli, Daniel T Leung†, Hongjie Yu†*

Lancet Glob Health 2021

Published Online
March 8, 2021



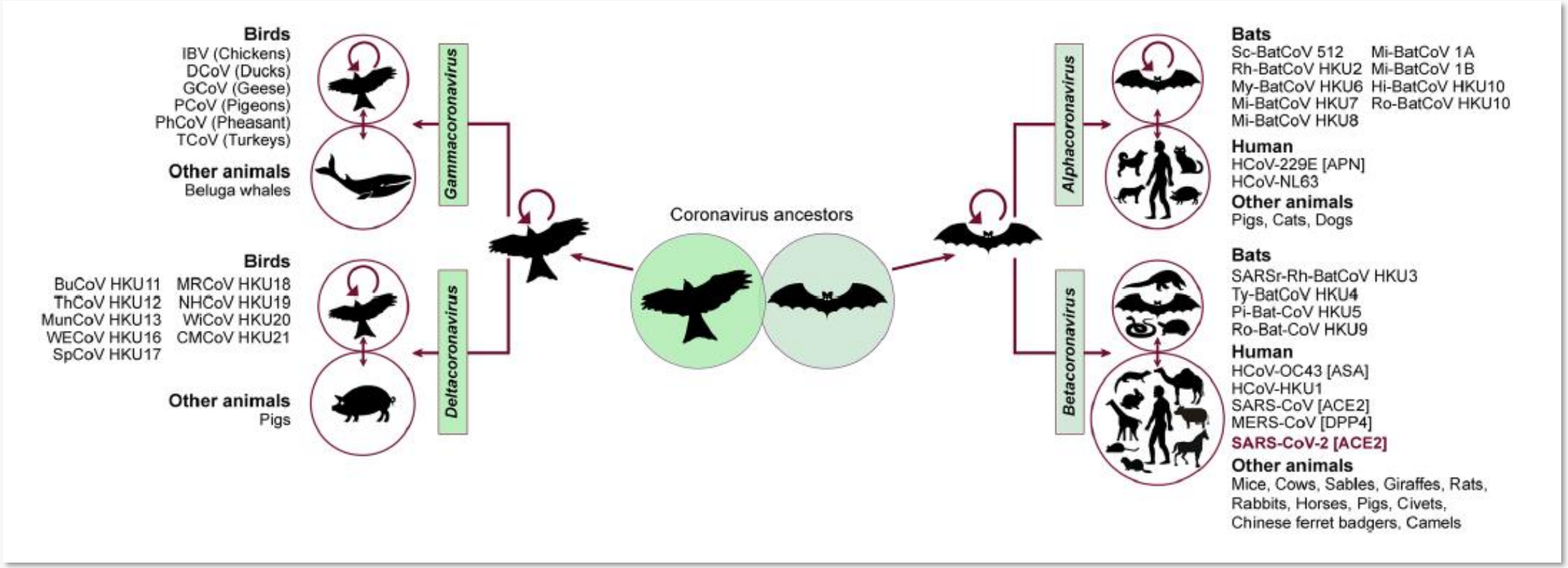
Current Microbiology
https://doi.org/10.1007/s00284-021-02396-x

REVIEW ARTICLE

The Inclusive Review on SARS-CoV-2 Biology, Epidemiology, Diagnosis, and Potential Management Options

Arezoo Beig Parikhani[1] · Masoume Bazaz[1] · Hadi Bamehr[1] · Sepideh Fereshteh[2] · Shahin Amiri[1] · Mostafa Salehi-Vaziri[3,5] · Arash Arashkia[4,5] · Kayhan Azadmanesh[4,5]

Received: 14 September 2020 / Accepted: 7 February 2021



Current Microbiology
https://doi.org/10.1007/s00284-021-02396-x

REVIEW ARTICLE

The Inclusive Review on SARS-CoV-2 Biology, Epidemiology, Diagnosis, and Potential Management Options

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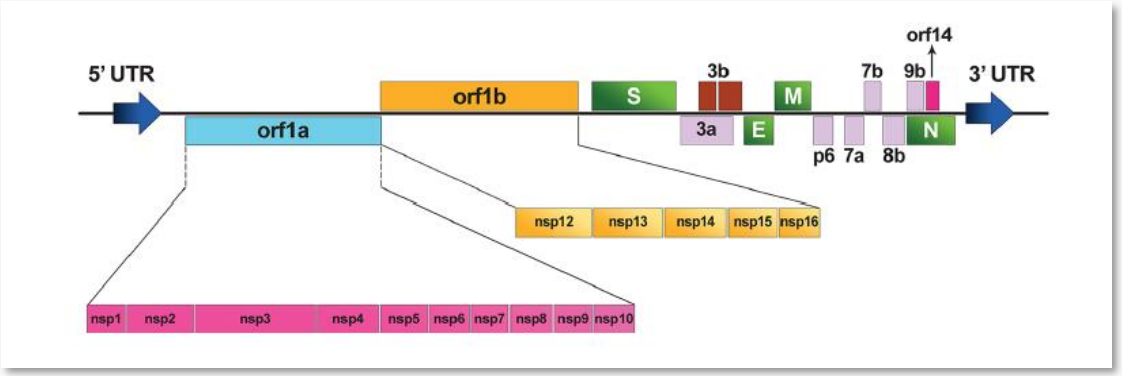
Received: 14 September 2020 / Accepted: 7 February 2021



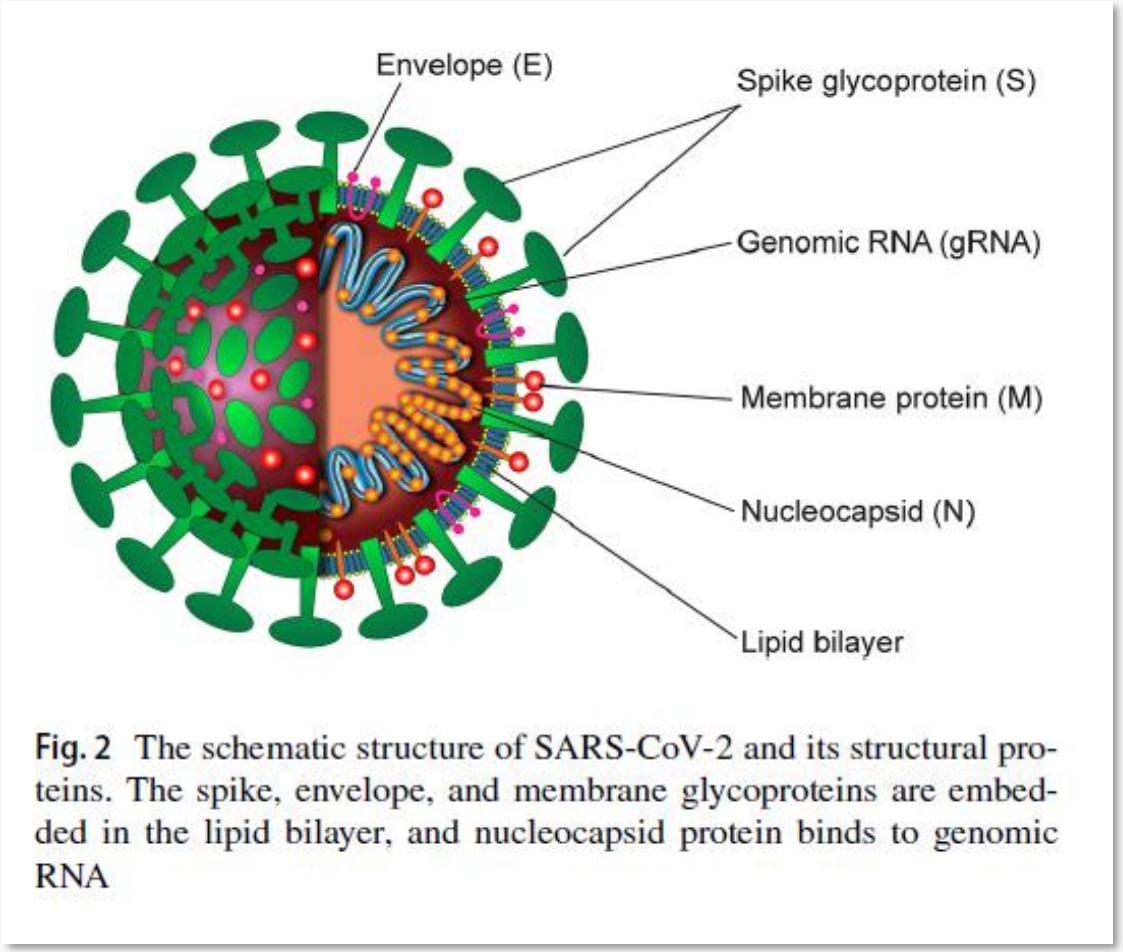


Fig. 2 The schematic structure of SARS-CoV-2 and its structural proteins. The spike, envelope, and membrane glycoproteins are embedded in the lipid bilayer, and nucleocapsid protein binds to genomic RNA

BMJ: first published as 10.1136/bmj.n436 on 10 March 2021

Severe covid-19 pneumonia: pathogenesis and clinical management

Amy H Attaway,[1] Rachel G Scheraga,[1,2] Adarsh Bhimraj,[1] Michelle Biehl,[1] Umur Hatipoğlu[1]

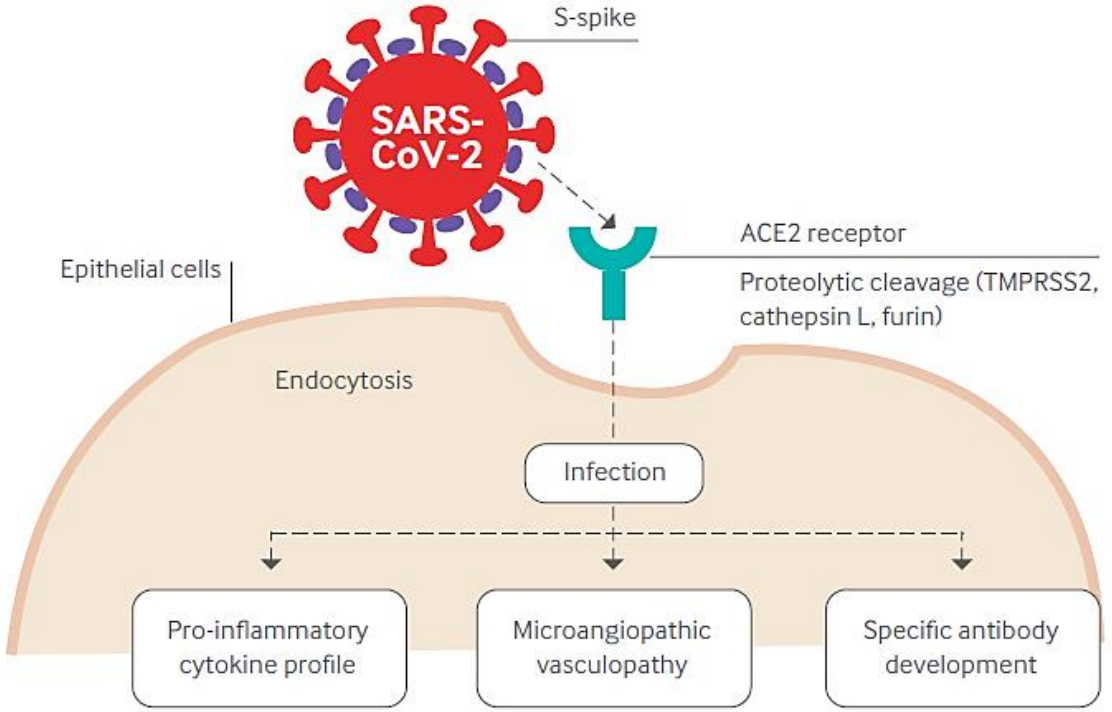


Fig 1 | SARS-CoV-2 S spike protein binds to the ACE2 receptor, which leads to proteolytic cleavage by TMPRSS2, cathepsin L, and furin in the epithelial cell of the respiratory tract. The virus undergoes endocytosis, viral maturation, replication, and release of more virus within the cytoplasm infecting the host cell. Consequences of infected cells include pro-inflammatory cytokine secretion, microangiopathic vasculopathy, and B cell secretion of specific SARS-CoV-2 antibodies

JAMA Neurology | Original Investigation

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Ling Mao; Huijuan Jin; Mengdie Wang; Yu Hu; Shengcai Chen; Quanwei He; Jiang Chang; Candong Hong; Yifan Zhou; David Wang; Xiaoping Miao; Yanan Li, MD, PhD; Bo Hu, MD, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2020.1127
Published online April 10, 2020.

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001

Journal of Neurology
https://doi.org/10.1007/s00415-020-10251-5

ORIGINAL COMMUNICATION

Neurologic manifestations in 1760 COVID-19 patients admitted to Papa Giovanni XXIII Hospital, Bergamo, Italy

Nicola Rifino[1] · Bruno Censori[2,4] · Emanuela Agazzi[2] · Dario Alimonti[1,2] · Virginio Bonito[2] · Giorgia Camera[2] · Marta Zaffira Conti[2] · Camillo Foresti[2] · Barbara Frigeni[2] · Simonetta Gerevini[3] · Maria Grimoldi[2] · Sara La Gioia[2] · Tania Partziguian[2] · Stefano Quadri[2] · Riccardo Riva[2] · Maria Cristina Servalli[2] · Manlio Sgarzi[2] · Benedetta Storti[1] · Marcella Vedovello[2] · Elisabetta Venturelli[2] · Martina Viganò[1] · Annapaola Callegaro[5] · Marco Arosio[5] · Maria Sessa[2]

Received: 21 July 2020 / Revised: 22 September 2020 / Accepted: 29 September 2020

Neurological complications	*N* (%)			
	All patients (*N* = 137)	*N* of females (%)	Average age	Average *n* of comorbidities
Cerebrovascular diseases	53 (38.7%)	20 (37.7%)	68.6	3.1
Ischemic stroke	37 (27.0%)	15 (40.5%)	70.3	3
Haemorrhagic stroke	11 (8%)	4 (36.3%)	65.9	3.5
Transient ischemic attacks	4 (2.9%)	1 (25%)	63.5	3.4
Cerebral venous thrombosis	1 (0.7%)	0 (0%)	55	3
Peripheral neuropathies	31 (22.6%)	6 (19.3%)	56.3	2.1
Guillain–Barrè syndrome	17 (12.4%)	4 (23.5%)	55.6	2.2
Critical illness polyneuropathy	9 (6.6%)	1 (1.1%)	60.7	1.7
Others	5 (3.6%)	1 (20.0%)	54.2	3.6
Altered mental status	49 (35.8%)	17 (34.7%)	65.6	2.7
Encephalitis	5 (3.6%)	1 (40%)	66	2.4
Myelitis	2 (1.4%)	0 (0%)	64.5	3.5
Headache	3 (2.2%)	1 (33.3%)	61.5	0.7
Seizures	10 (7.3%)	3 (30.0%)	64.4	2.9
Syncope	3 (2.2%)	2 (66.7%)	72.6	3.7
Movement disorders	7 (5%)	3 (42.8%)	70.3	3.8
Other	5 (3.6%)	1 (20.0%)	61.2	4.6

Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

Lancet Neurol 2020; 19: 767–83

Published Online
July 2, 2020

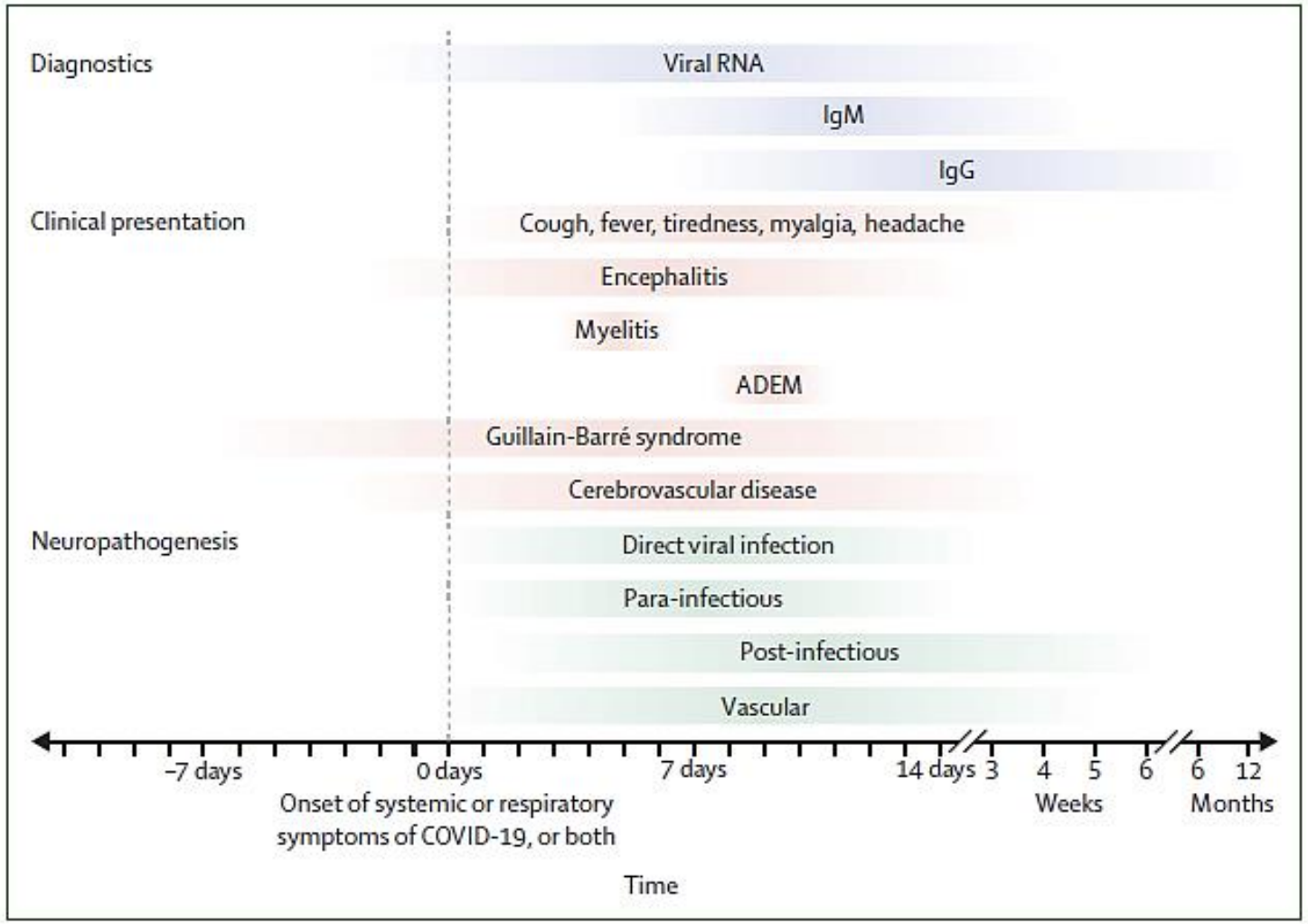


Figure 1: **Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease**

doi:10.1093/brain/awaa240 BRAIN 2020: 143; 3104–3120 | 3104

BRAIN
A JOURNAL OF NEUROLOGY

The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings

Ross W. Paterson,[1,2,3,*] Rachel L. Brown,[1,4,*] Laura Benjamin,[5,6] Ross Nortley,[1,7]

Advance access publication July 8, 2020

Table 1 Summary of clinical features of 43 patients with neurological complications of COVID-19

Cases	Age, median [range]; %male	Days of COVID-19 infection before neurological presentation, median [range]	Main clinical features	Results of note	% Naso-pharyhgeal SARS-CoV-2 PCR +	CSF or brain SARS-CoV-2 PCR + (x/number tested)	Treatment	Clinical outcome
Encephalopathy (delirium/psychosis) (n = 10)[a]	57.5 [39–72]; 40	4.5 [–4 to +21]	Delirium; psychosis	Acellular CSF (6/6); non-specific MRI changes (3/10)	80 (8/10)	(0/0)	Supportive (9/10); steroids 1/10	Complete recovery (7/10); partial (2/10)
Inflammatory CNS syndromes (para-/post-infectious) (n = 12)[a]	53 [27–66]; 33	9 [–6 to +27]	Reduced consciousness (7/12); UMN signs (10/12)	Abnormal CSF (6/11) Abnormal MRI (11/12)	67 (8/12)	(0/7)	Corticosteroids (10/12); IVIG (3/12)	Recovery: complete (1/12); partial (10/12); none (death 1/12)
Stroke (n = 8)[a]	62.5 [27–85]; 75	8[–2 to +22]	Large vessel ischaemic stroke	4/8 PE 6/6 High D–dimer	75 (6/8)	NA	Low molecular weight heparin (7/8); apixaban (1/8)	Incomplete recovery (7/8); death (1/8)
Peripheral syndromes (n = 8)								
GBS (n = 7)	57 [20–63]; 100	13 [–1 to +21]	Cranial and peripheral neuropathy		43 (3/7)	NT	IVIG (7/7)	Incomplete recovery (5/7 GBSDS 2)
Plexopathy (n = 1)	60; 100	14	Painless weakness		100 (1/1)	NT	IV steroids (1/1)	Incomplete recovery (1/1)
Miscellaneous and uncharacterized (n = 5)	20 [16–40]; 40	10 [+6 to +26]	Raised ICP; seizures; myelitis	Abnormal CSF (2/4) Abnormal MRI brain (4/5)	60 (3/5)	(0/1)	Varied (AED; steroids (1/5); tLP)	Recovery complete (1/5); partial (3/5); nil (1/5)

AED = anti-epileptic drug; GBSDS = Guillain Barré disability score; ICP = intracranial pressure; tLP = therapeutic lumbar puncture; NT = not tested; PE = pulmonary thromboembolism; UMN = upper motor neuron.
aFeatures of eight individual patients for encephalopathy (delirium/psychosis), inflammatory CNS syndromes (para/post-infectious) and stroke described in Tables 2–4. All patient details are available in the Supplementary material.

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Neurological presentations of COVID-19: Findings from the Spanish Society of Neurology neuroCOVID-19 registry

David García-Azorín [a,*], María José Abenza Abildúa [b], María Elena Erro Aguirre [c], Santiago Fernández Fernández [d], Juan Carlos García Moncó [e], Cristina Guijarro-Castro [f], Montserrat González Platas [g], Fernando Romero Delgado [h,i], José Miguel Láinez Andrés [j], David Ezpeleta [k], Spanish neuroCOVID registry group

Available online 19 December 2020

n = 233

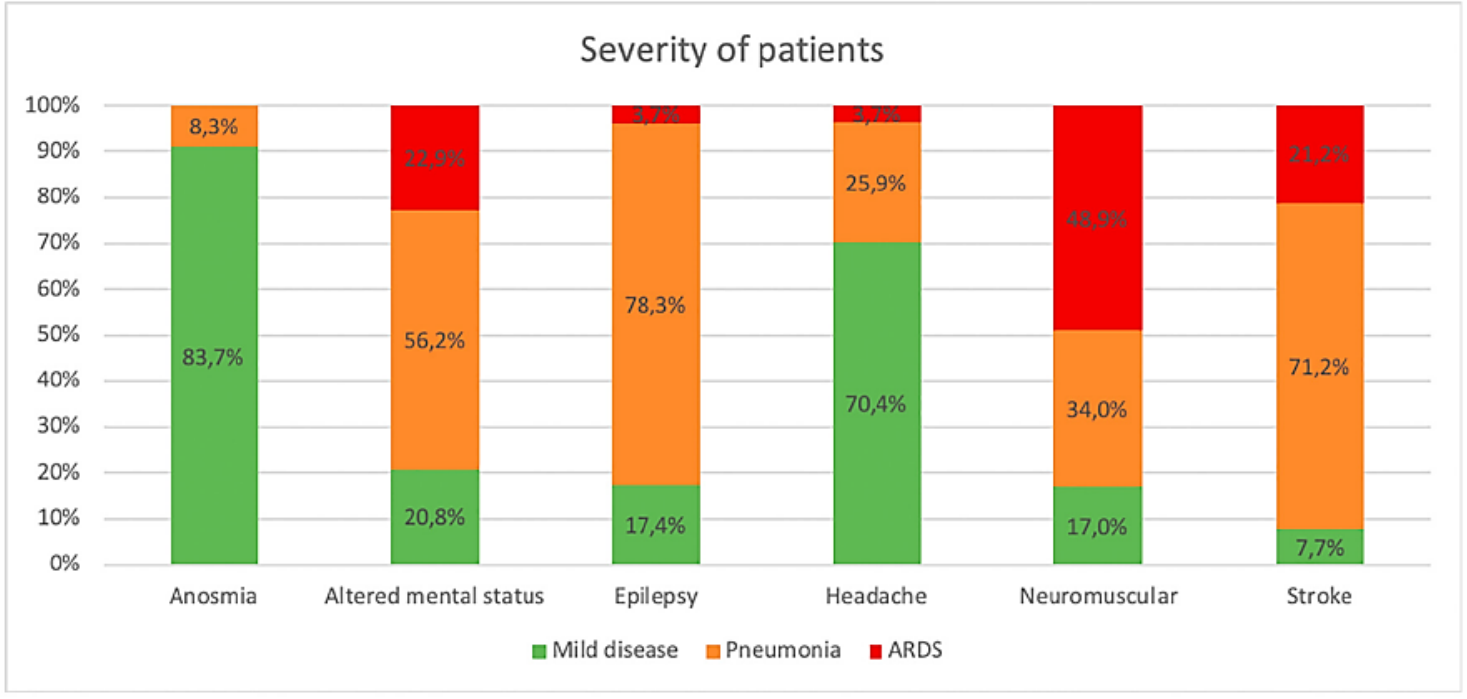


Fig. 3. Severity of COVID-19 in patients with the most frequently represented neurological complications.

BRAIN
A JOURNAL OF NEUROLOGY

Volume 143, Issue 10
October 2020

EDITOR'S CHOICE

Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description

FREE

Francisco Hernández-Fernández ✉, Hernán Sandoval Valencia, Rosa Angélica Barbella-Aponte, Rosa Collado-Jiménez, Óscar Ayo-Martín, Cristina Barrena, Juan David Molina-Nuevo, Jorge García-García, Elena Lozano-Setién, Cristian Alcahut-Rodriguez ... Show more

Article Contents

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SHARE August 11, 2020; 95 (6) ARTICLE

Generalized myoclonus in COVID-19

Pablo Rábano-Suárez, Laura Bermejo-Guerrero, Antonio Méndez-Guerrero, Javier Parra-Serrano, Daniel Toledo-Alfocea, Daniel Sánchez-Tejerina, Teresa Santos-Fernández, María Dolores Folgueira-López, Judit Gutiérrez-Gutiérrez, Blanca Ayuso-García, Jesús González de la Aleja, Julián Benito-León

First published May 21, 2020, DOI: https://doi.org/10.1212/WNL.0000000000009829

EDITOR'S CHOICE

Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description

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Francisco Hernández-Fernández ✉, Hernán Sandoval Valencia, Rosa Angélica Barbella-Aponte, Rosa Collado-Jiménez, Óscar Ayo-Martín, Cristina Barrena, Juan David Molina-Nuevo, Jorge García-García, Elena Lozano-Setién, Cristian Alcahut-Rodriguez ... Show more

Author Notes

Brain, Volume 143, Issue 10, October 2020, Pages 3089–3103, https://doi.org/10.1093/brain/awaa239

Published: 09 July 2020 **Article history** ▾

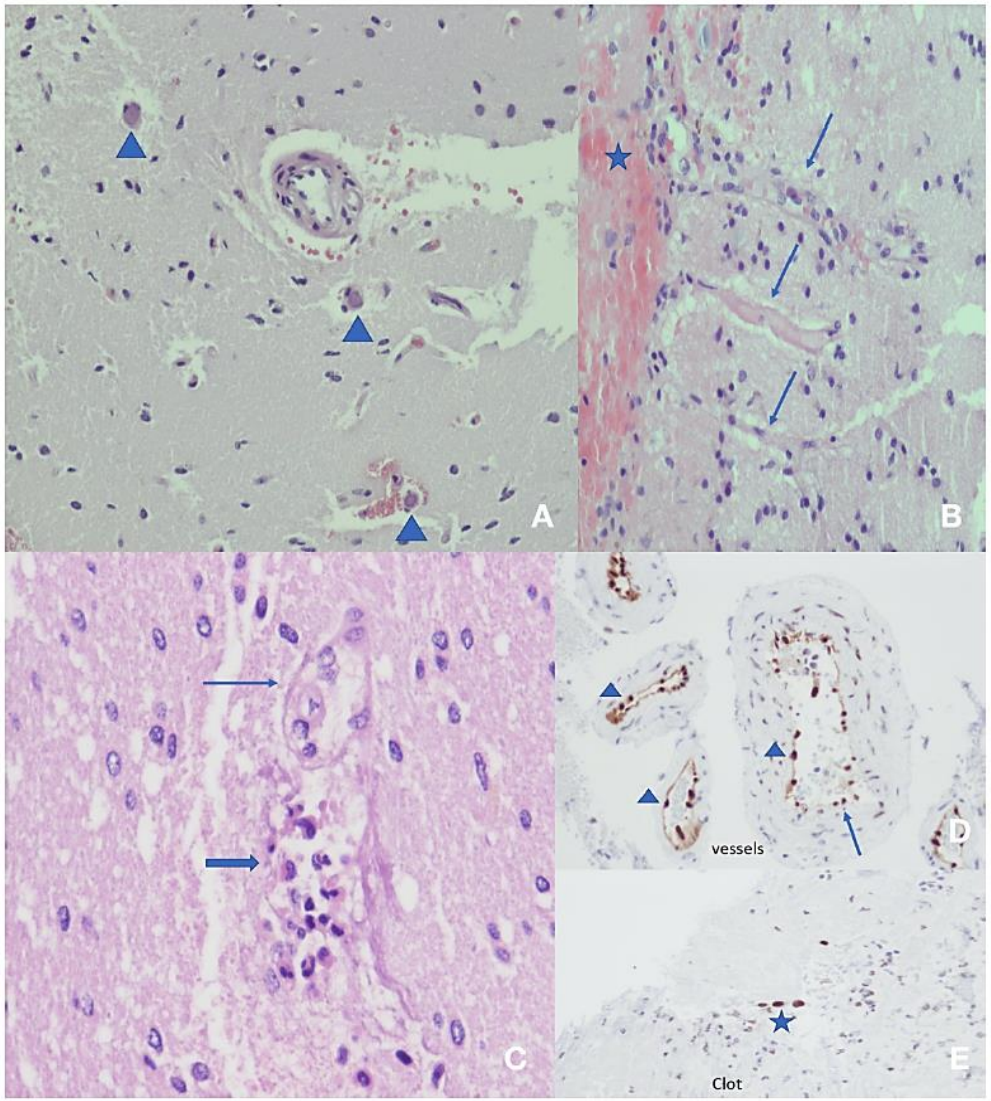


Figure 7. Patient 19 (A-D). Brain biopsy. HEx20 staining. A: Three microthrombi are observed (arrowhead). B: Image with 3 vessels (arrows): the upper one preserved with endothelial reactivity, intermediate vessel with preserved structure without viable cellularity. The lower one shows loss of endothelial cells. C: Capillary with evident alteration of endothelial cells and loss of adhesion (fine arrow). Extravasation of inflammatory cells with atypical lymphocytes in the perivascular space. D: Image of arteries and arterioles with reactive endothelial cells (arrowhead), some in the vessel lumen (small arrow) and normal endothelium (large arrow). E: Patient 3. Thrombotic material from a MT. Some endothelial cells (star) are observed.

Neurological Sciences
https://doi.org/10.1007/s10072-021-05068-7

COVID-19

Neuropathologic findings of patients with COVID-19: a systematic review

Azalea T. Pajo[1] · Adrian I. Espiritu[1,2] · Almira Doreen Abigail O. Apor[1] · Roland Dominic G. Jamora[1,3]

Received: 18 December 2020 / Accepted: 16 January 2021

Table 1 Characteristics of the included studies and population, and quality assessment

Author	Setting	Sample (*n*)	Study design	Study duration	Age/age range (mean)	Sex (F:M)	Quality assessment
Younger, 2020	USA	50	Case series	NI	NI	NI	Good
Keller et al., 2020	Switzerland	8+	Case series	March 9 to April 3, 2020	(67.6)	1:7	Good
Matschke et al., 2020	Germany	43	Case series	March 13–April 24, 2020	51–94	16:27	Good
Jensen et al., 2020	UK	2	Case series	NI	66–71	0:2	Good
Kantonen et al., 2020	Finland	4	Case series	April 14–May 18, 2020	38–90	1:3	Good
Conklin et al., 2020	USA	1	Retrospective cohort	March 12–May 14, 2020	57	0:1	Good
Reichard et al., 2020	USA	1	Case report	NI	71	NI	Good
Patel et al., 2020	USA	1	Case report	NI	48	NI	Good
Fabbri et al., 2020	Italy	10	Case series	NI	51–74	3:7	Good
Barton et al., 2020	USA	2	Case series	March 1–31, 2020	42, 77	0:2	Good
von Weyhern et al., 2020	Germany	6	Case series	April 1–30, 2020	58–82	1:2	Good
Bradley et al., 2020	USA	14	Case series	February–March 2020	42–84	4:3	Good
Jaunmuktane et al., 2020	UK	2	Case series	NI	50–60	1:1	Good
Schurink et al., 2020	Netherlands	21†	Prospective cohort	March 9 and May 18, 2020	41–78	5:16	Good

N, not indicated

† Only 9 patients consented to autopsy

+ Only 1 patient consented to autopsy

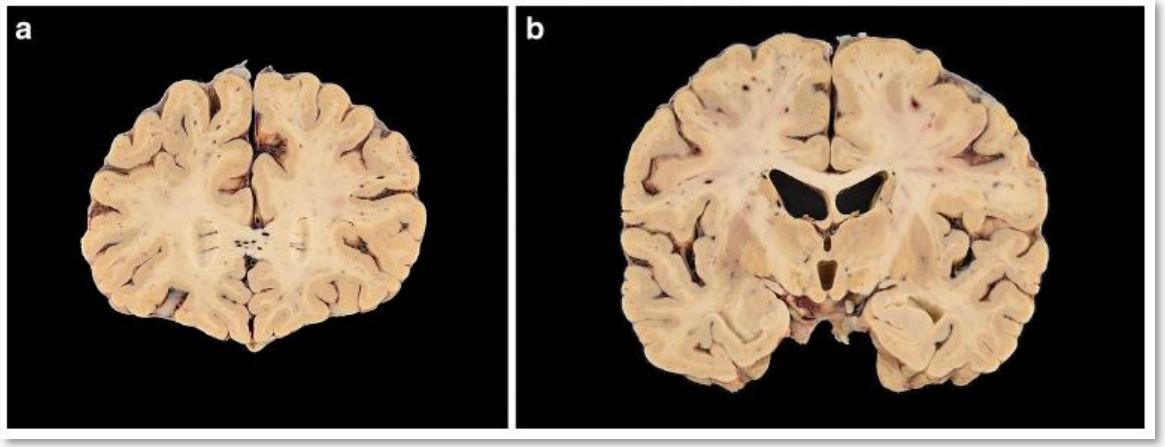
Acta Neuropathologica
https://doi.org/10.1007/s00401-020-02166-2

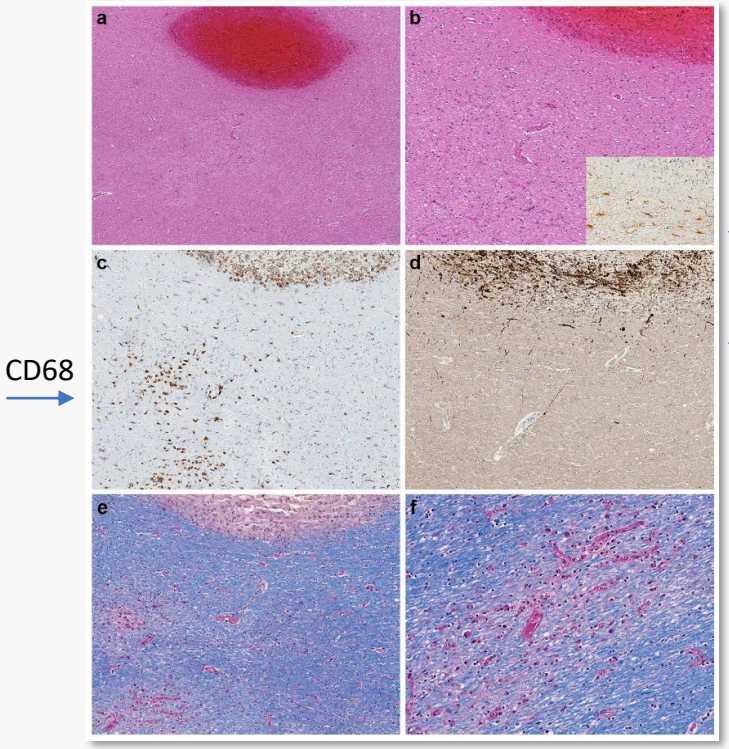
CASE REPORT

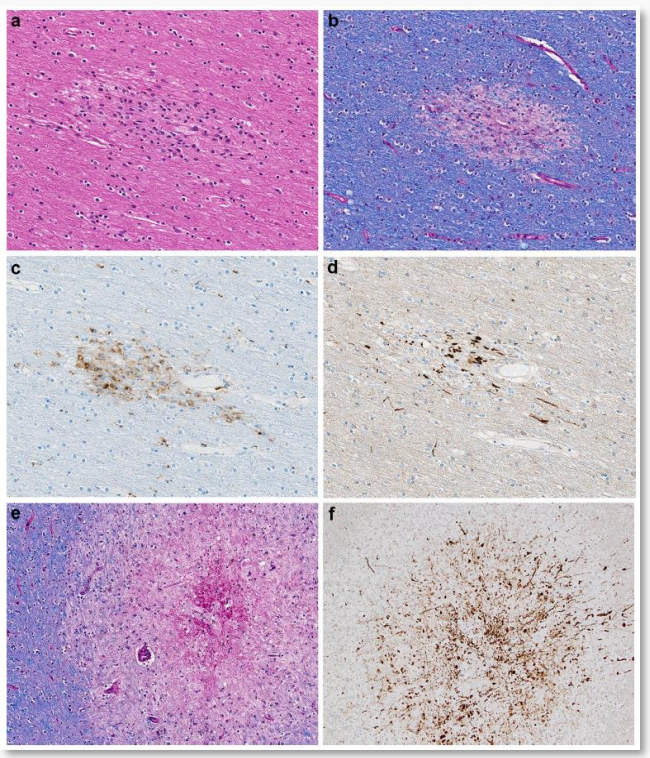
Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology

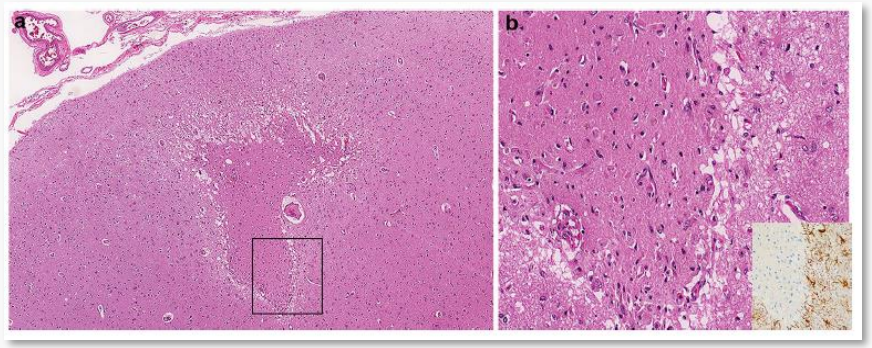
R. Ross Reichard[1] · Kianoush B. Kashani[2] · Nicholas A. Boire[1] · Eleni Constantopoulos[1] · Yong Guo[3] · Claudia F. Lucchinetti[3]

Received: 10 May 2020 / Revised: 21 May 2020 / Accepted: 21 May 2020









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DOI: 10.1111/nan.12677

Neuropathology and Applied Neurobiology WILEY

SCIENTIFIC CORRESPONDENCE

Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19

Daniel Kirschenbaum[1] | Lukas L. Imbach[2] | Elisabeth J. Rushing[1] | Katrin B. M. Frauenknecht[1] | Dominic Gascho[3] | Benjamin V. Ineichen[4] | Emanuela Keller[5] | Sibylle Kohler[6] | Mona Lichtblau[7] | Regina R. Reimann[1] | Katharina Schreib[6] | Silvia Ulrich[7] | Peter Steiger[8] | Adriano Aguzzi[1] | Karl Frontzek[1]

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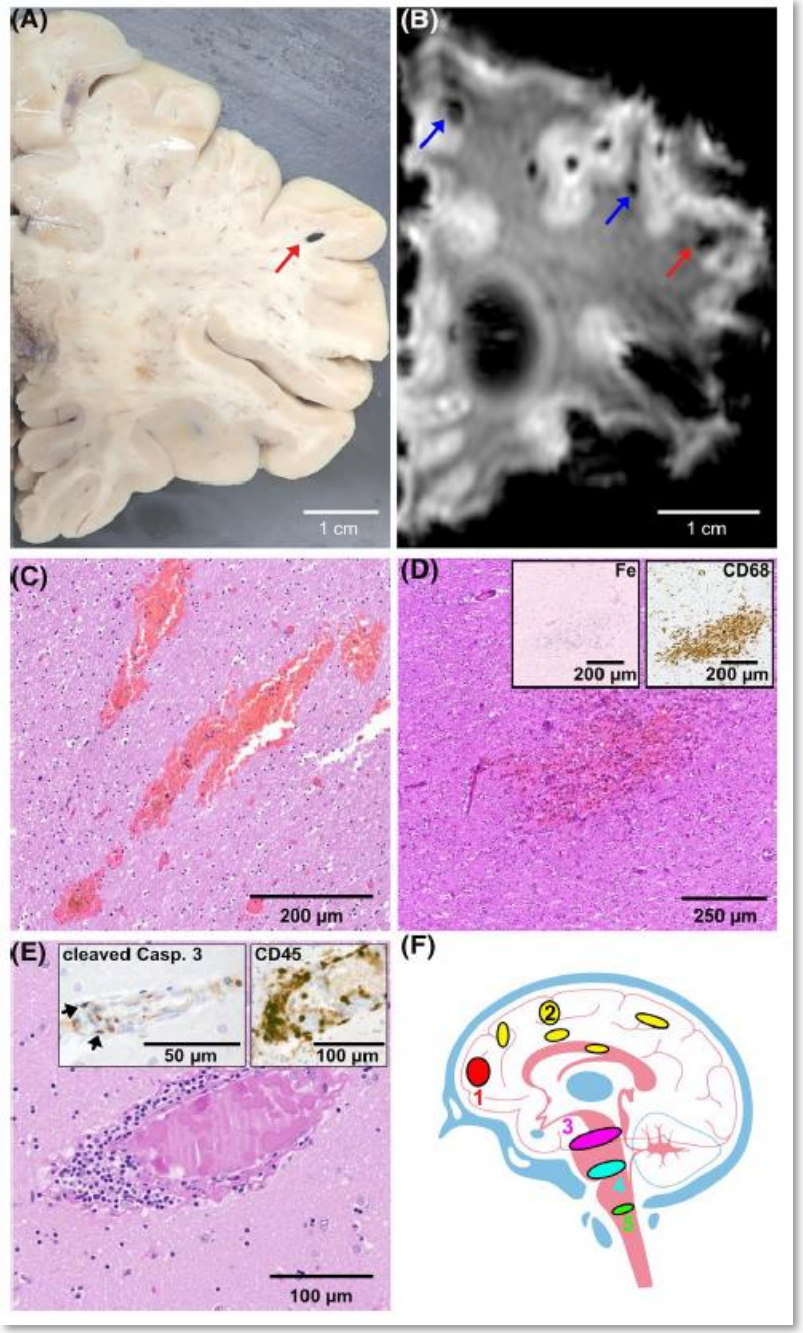
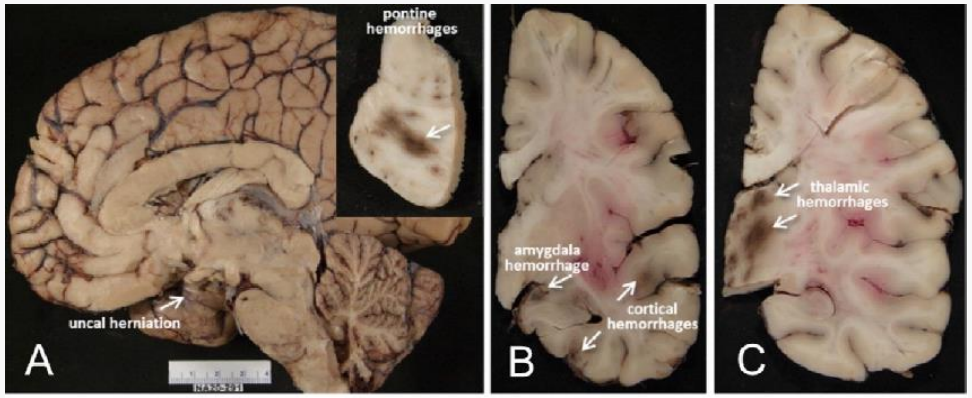
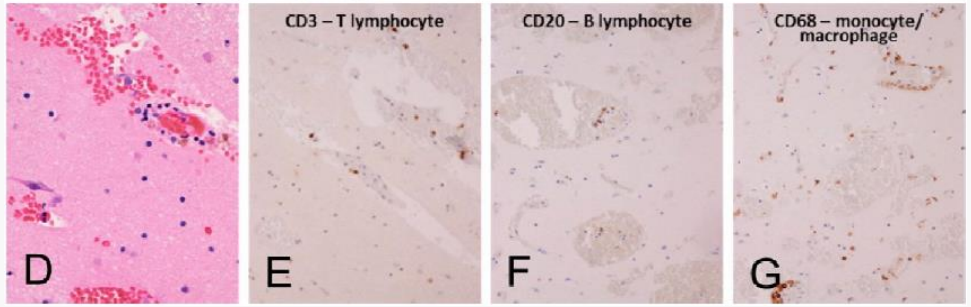
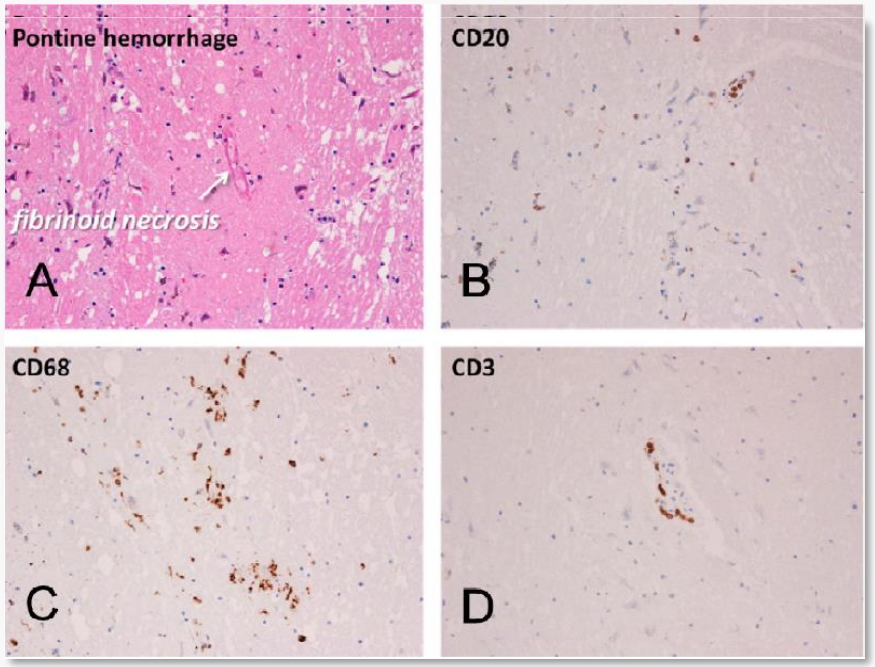




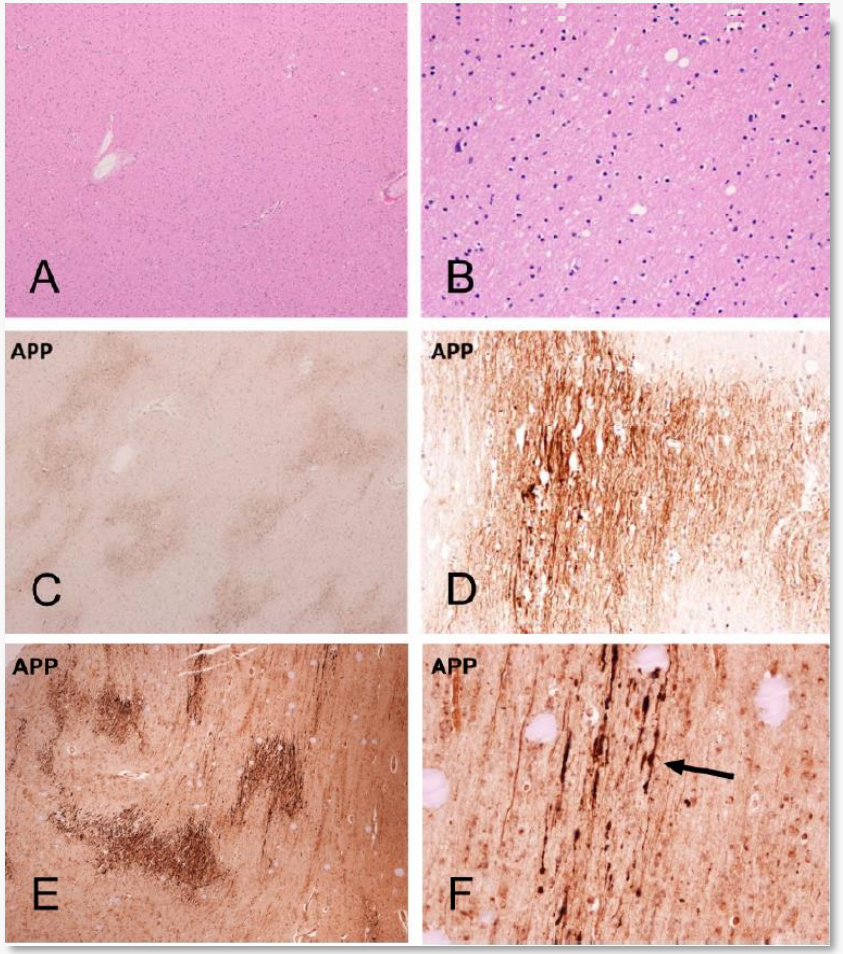




n = 20

Mapping of SARS-CoV-2 Brain Invasion and Histopathology in COVID-19 Disease

Geidy E. Serrano[a*], Jessica E. Walker[a*], Richard Arce[a], Michael J. Glass[a], Daisy Vargas[a], Lucia I. Sue[a], Anthony J. Intorcia[a], Courtney M. Nelson[a], Javon Oliver[a], Jaclyn Papa[a], Aryck Russell[a], Katsuko E. Suszczewicz[a], Claryssa I. Borja[a], Christine Belden[a], Danielle Goldfarb[a], David Shprecher[a], Alireza Atri[a,b], Charles H. Adler[c], Holly A. Shill[d], Erika Driver-Dunckley[c], Shyamal H. Mehta[c], Benjamin Readhead[e], Matthew J. Huentelman[f], Joseph L. Peters[g], Ellie Alevritis[g], Christian Bimi[h], Joseph P. Mizgerd[i], Eric M. Reiman[j], Thomas J. Montine[k], Marc Desforges[l], James L. Zehnder[k], Malaya K. Sahoo[k], Haiyu Zhang[k], Daniel Solis[k], Benjamin A. Pinsky[m], Michael Deture[n*], Dennis W. Dickson[n*] and Thomas G. Beach[a*]



Neuropathology of patients with COVID-19 in Germany: a post-mortem case series

Jakob Matschke, Marc Lütgehetmann, Christian Hagel, Jan P Sperhake, Ann Sophie Schröder, Carolin Edler, Herbert Mushumba, Antonia Fitzek, Lena Allweiss, Maura Dandri, Matthias Dottermusch, Axel Heinemann, Susanne Pfefferle, Marius Schwabenland, Daniel Sumner Magruder, Stefan Bonn, Marco Prinz, Christian Gerloff, Klaus Püschel, Susanne Krasemann, Martin Aepfelbacher, Markus Glatzel

Lancet Neurol 2020; 19: 919–29

Published Online
October 5, 2020

n = 43

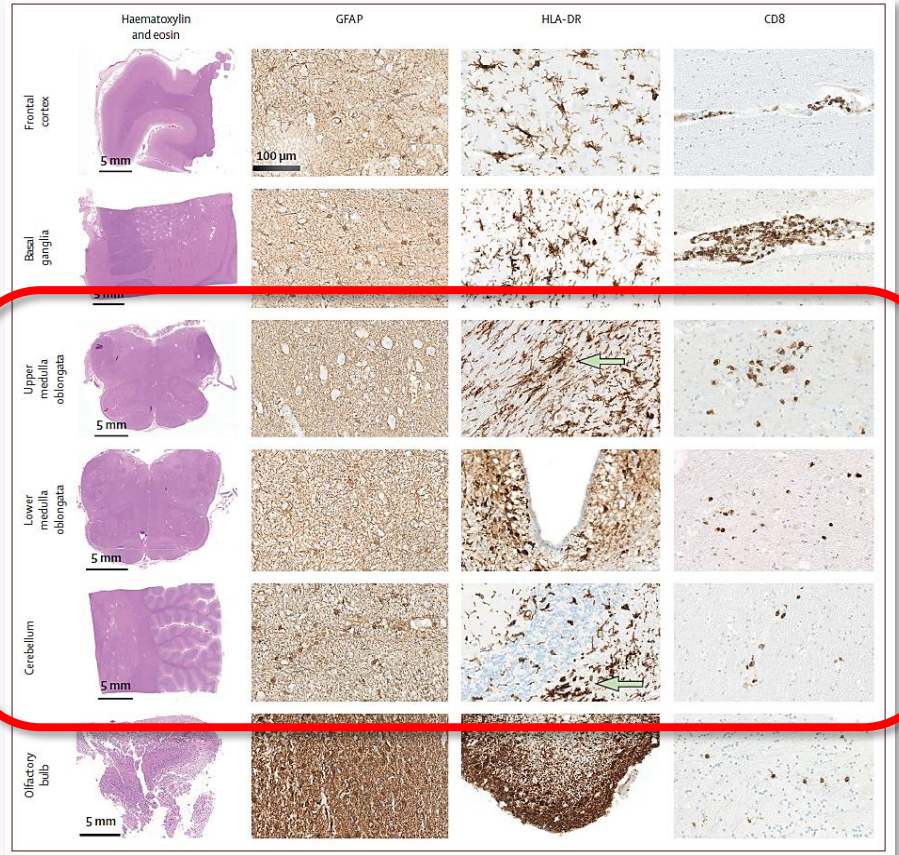


Figure 1: **Common neuropathological findings in the brains of patients who died from COVID-19**
An overview of each brain region with haematoxylin and eosin staining is shown in the first column. Immunohistochemical staining for the astrocytic marker GFAP showed variable degrees of reactive astrogliosis. Immunohistochemical staining for the microglia marker HLA-DR showed reactive activation of the microglia with occasional microglial nodules in the medulla oblongata and cerebellum (green arrows). Staining for the cytotoxic T lymphocyte marker CD8 (brown) revealed perivascular and parenchymal infiltration with CD8-positive cells. GFAP=glial fibrillary acidic protein.

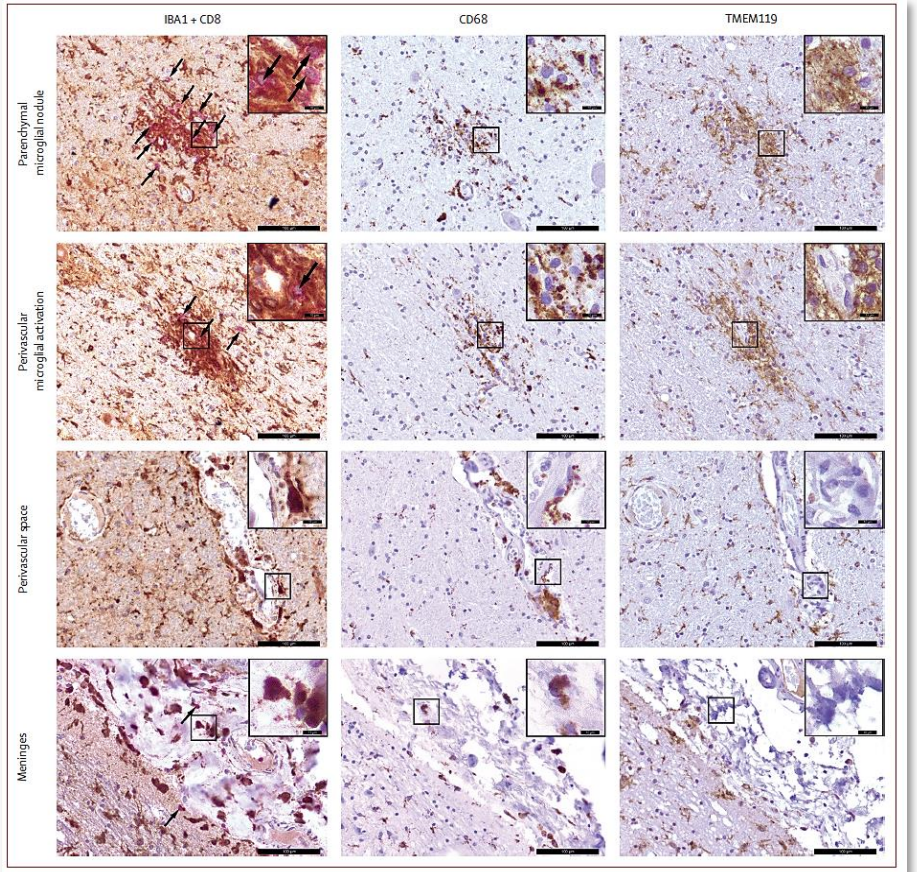


Figure 2: **Concomitant activation of the adaptive and innate immune systems in the brain of one patient (case 2) who died from COVID-19**
Representative images of double-chromogenic immunohistochemical labelling for IBA1 (brown) and CD8 (pink), as well as immunohistochemical staining for CD68 (brown), and TMEM119 (brown) at different CNS interfaces in the upper medulla oblongata. Counterstaining was done with haematoxylin (blue). Scale bars represent 100 µm (10 µm in the inset images). Arrows indicate CD8-positive T cells.

Lancet Neurol 2020; 19: 919–29
Published Online
October 5, 2020

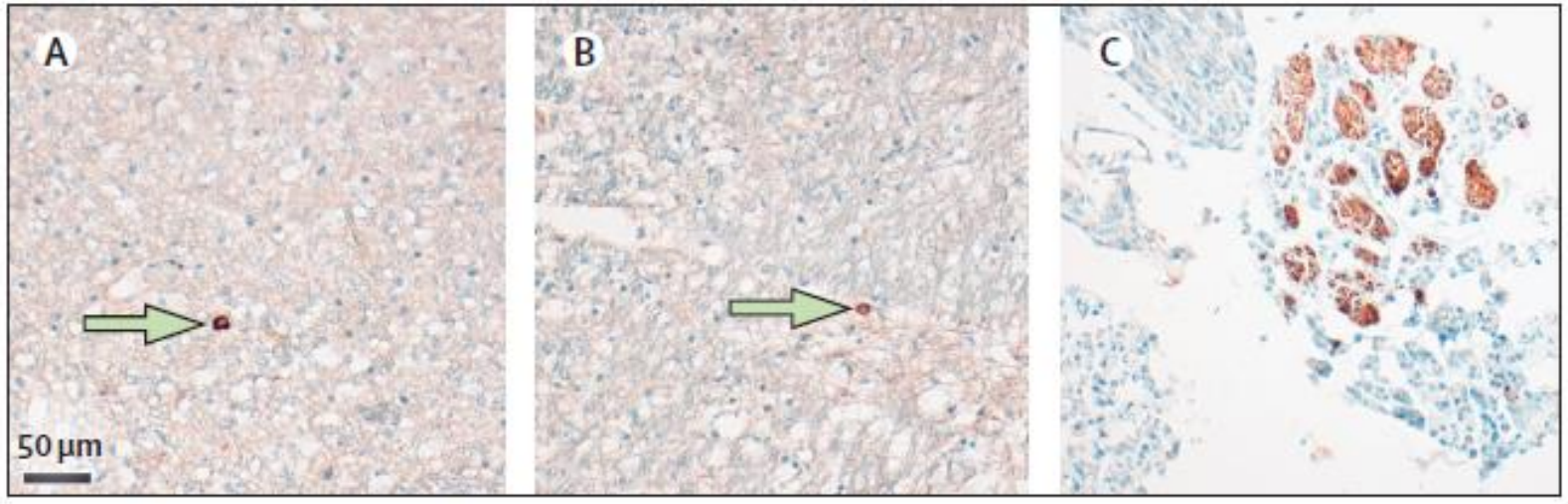


Figure 5: **Distribution of SARS-CoV-2 within the CNS**
Representative images of viral protein-positive cells (green arrows) in the medulla oblongata detected by anti-nucleocapsid protein antibody (A) or anti-spike protein antibody (B). (C) SARS-CoV-2 nucleoprotein (brown staining) could also be detected in subsets of cranial nerves originating from the lower brainstem. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

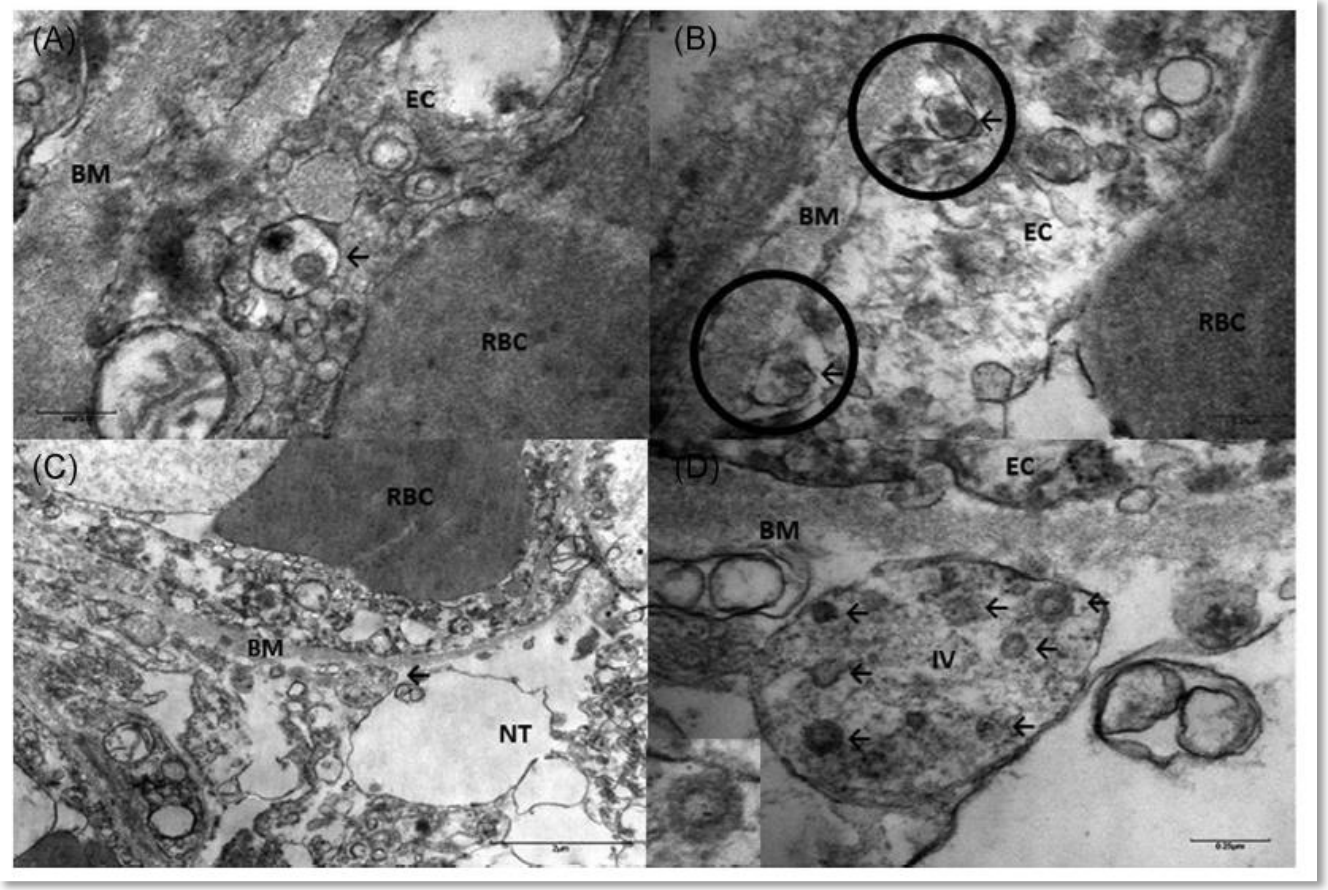
JOURNAL OF
MEDICAL VIROLOGY

COMMENTARY | Free Access

Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

Alberto Paniz-Mondolfi, Clare Bryce, Zachary Grimes, Ronald E. Gordon, Jason Reidy, John Lednicky, Emilia Mia Sordillo, Mary Fowkes

First published: 21 April 2020 | https://doi.org/10.1002/jmv.25915 | Citations: 190



Neuropathology and Applied Neurobiology (2021), 47, 3–16 doi: 10.1111/nan.12667

Invited Review: The spectrum of neuropathology in COVID-19

S. Al-Sarraj*† , C. Troakes† , B. Hanley‡, M. Osborn‡, M. P. Richardson§ , M. Hotopf§¶ , E. Bullmore** and I. P. Everall§

Principle mechanisms of SARS-CoV-2 CNS infection:

The virus attaches to cells in the CNS through interaction between the spike (S) glycoprotein and the host ACE2 receptors, which are reported to be present in neurons as well as endothelial cells.

Potential modes of CNS involvement by SARS-CoV-2

(1) Through the olfactory nerve and/or the hypoglossal, facial, glossopharyngeal and vagus cranial nerves with trans-synaptic neuronal spread to other brain regions. Supported by frequent initial presentation of hyposmia and hypogeusia.
(2) Haematogenous route via endothelial cell infection, utilizing ACE2 receptors in the endothelial cells followed by gaining access through the BBB with viral budding via interaction with ACE2 receptors in the neurons.
(3) Immune cell route. The virus first infects the epithelial cells of the trachea, bronchi and alveolar cells of the lung. Then it infects the resident immune cells, which carry the virus to other organs including the brain.
(4) An auto-immune mechanism

Neurological manifestations in COVID-19 patients

- Dizziness, headache, nausea, impaired consciousness (non-specific neurological manifestation)
- Hypogeusia and hyposmia
- Cerebrovascular accident (infarction, intra cerebral bleeding, venous thrombosis)
- Acute necrotizing encephalopathy
- Meningo-encephalitis
- Guillain–Barre syndrome
- Myalgia, elevated creatine kinase and lactate dehydrogenase levels (non-specific muscular disease features)
- Anxiety, depression, insomnia, distress, mental confusion (non-specific psychiatric symptoms)

Expected COVID-19 pathology in the CNS

(1) Ischaemic/hypoxic encephalopathy
(2) Increase activated microglial cells and variable perivascular T lymphocyte infiltration
(3) Cerebrovascular disease
- Haemorrhagic infarction
- Ischaemic infarction
- Intracerebral haemorrhage
- Acute multiple necrotizing encephalopathy

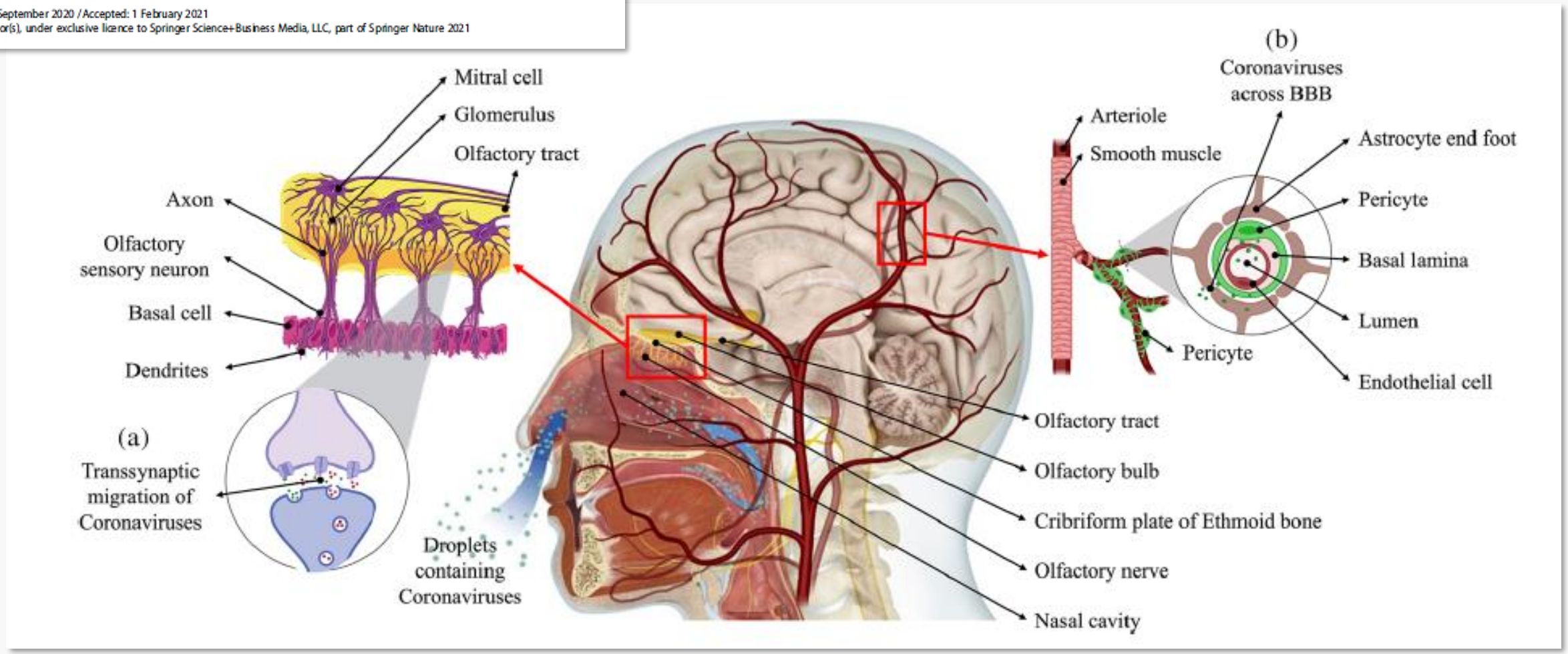
(4) Opportunistic infection
(5) Encephalitis/meningitis
(6) Acute myelitis
(7) Guillain–Barre syndrome
(8) Demyelinating diseases

Molecular Neurobiology
https://doi.org/10.1007/s12035-021-02318-9

Neurological Manifestation of SARS-CoV-2 Induced Inflammation and Possible Therapeutic Strategies Against COVID-19

Dipak Kumar[1] · Sadaf Jahan[2] · Andleeb Khan[3] · Arif Jamal Siddiqui[4] · Neeru Singh Redhu[5] · Wahajuddin[6] · Johra Khan[2] · Saeed Banwas[2,7,8] · Bader Alshehri[2,7] · Mohammed Alaidarous[2,7]

Received: 3 September 2020 / Accepted: 1 February 2021



SCIENCE ADVANCES | RESEARCH ARTICLE

Brann *et al.*, *Sci. Adv.* 2020; **6** : eabc5801 31 July 2020

CORONAVIRUS

Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19–associated anosmia

David H. Brann[1]*, Tatsuya Tsukahara[1]*, Caleb Weinreb[1]*, Marcela Lipovsek[2], Koen Van den Berge[3,4], Boying Gong[5], Rebecca Chance[6], Iain C. Macaulay[7], Hsin-Jung Chou[6], Russell B. Fletcher[6†], Diya Das[6,8‡], Kelly Street[9,10], Hector Roux de Bezieux[5,11], Yoon Gi Choi[12], Davide Risso[13], Sandrine Dudoit[3,5], Elizabeth Purdom[3], Jonathan Mill[14], Ralph Abi Hachem[15], Hiroaki Matsunami[16], Darren W. Logan[17], Bradley J. Goldstein[15], Matthew S. Grubb[2], John Ngai[6,12,18§], Sandeep Robert Datta[1‖]

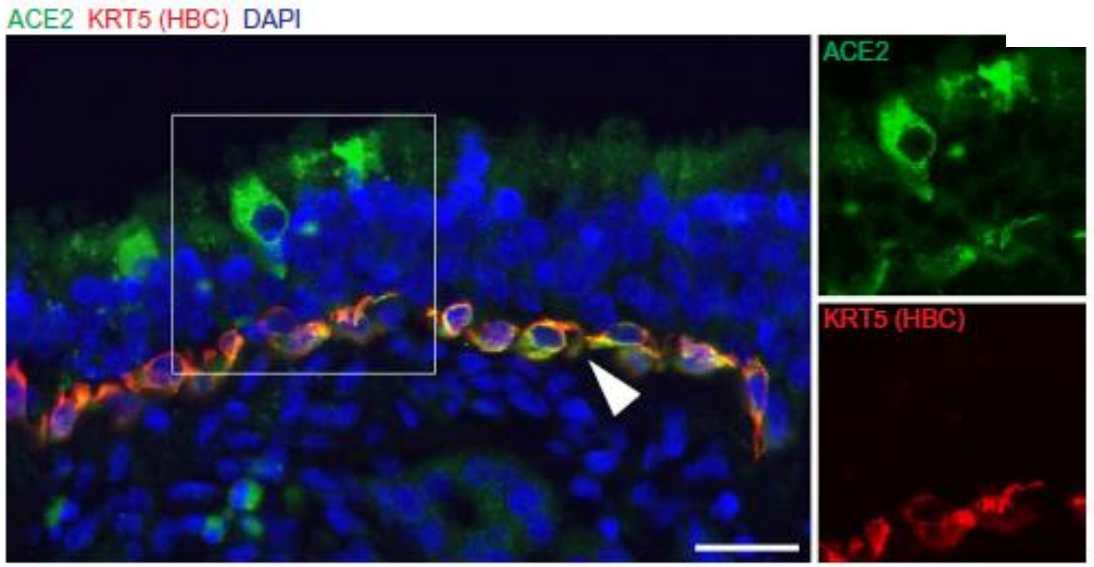


Fig. 2. Coronavirus cell entry–related genes are expressed in human RE and OE but are not detected in human OSNs.

nature neuroscience

ARTICLES

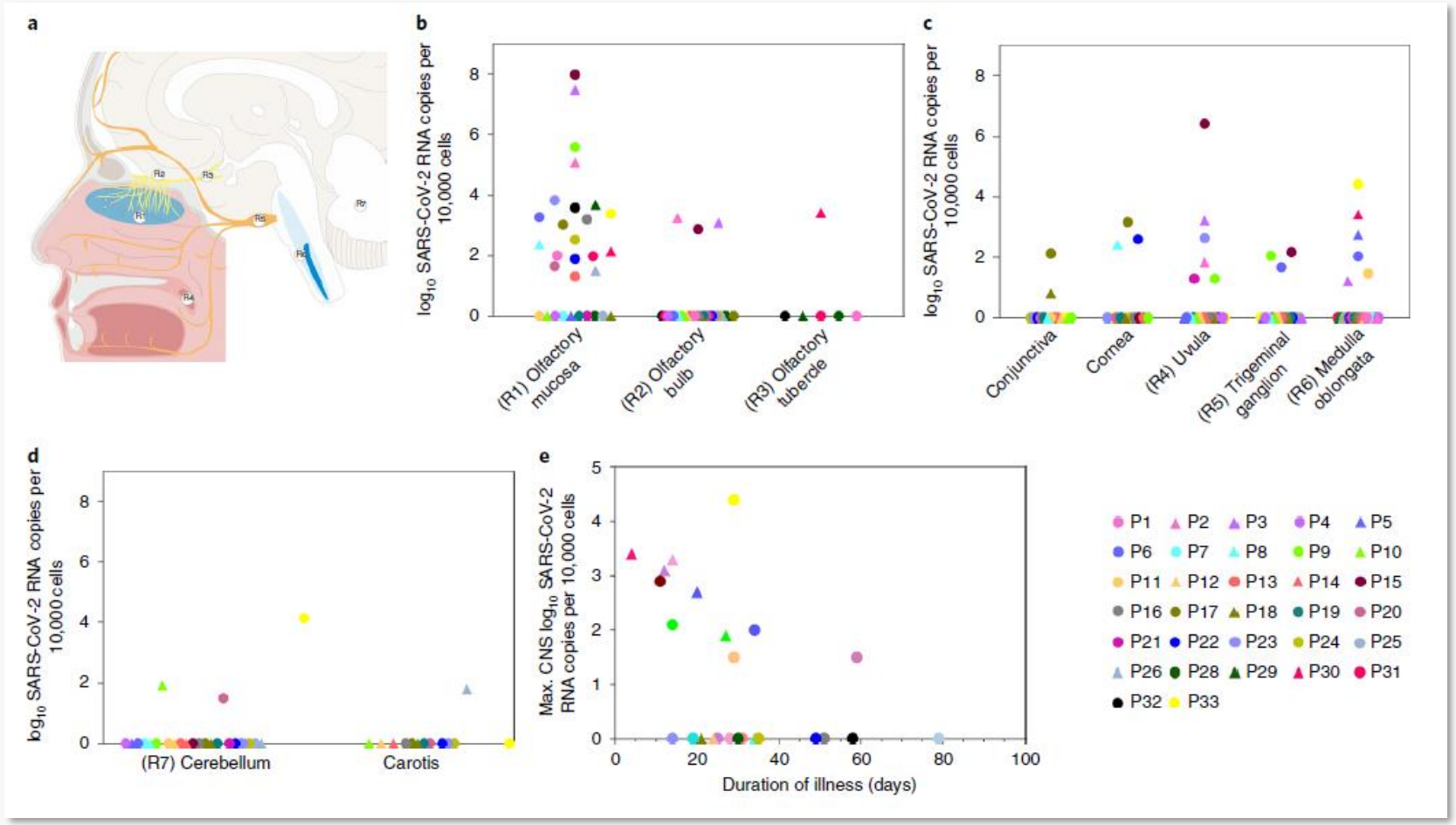
https://doi.org/10.1038/s41593-020-00758-5

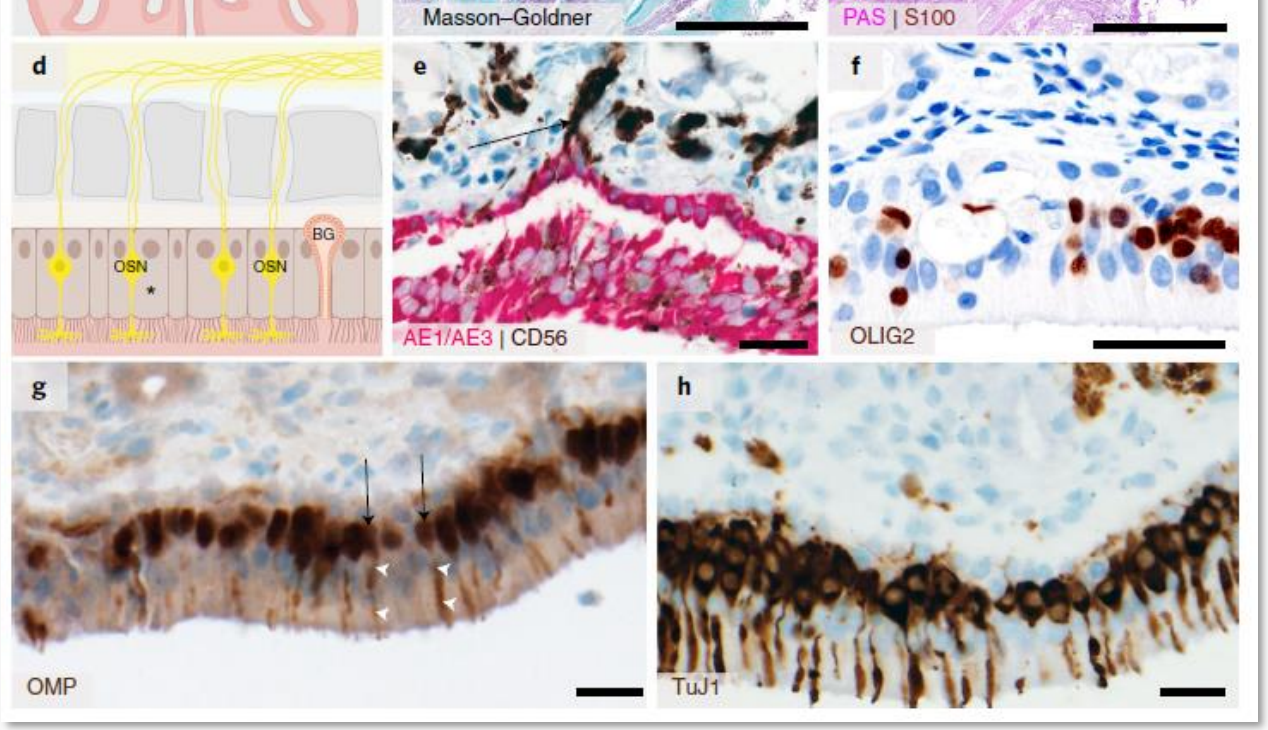
Check for updates

Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19

Jenny Meinhardt[1,25], Josefine Radke[1,2,3,25], Carsten Dittmayer[1,25], Jonas Franz[4,5,6], Carolina Thomas[4,6],

Received: 13 June 2020; Accepted: 12 November 2020;
Published online: 30 November 2020




Masson–Goldner
PAS | S100
d
e
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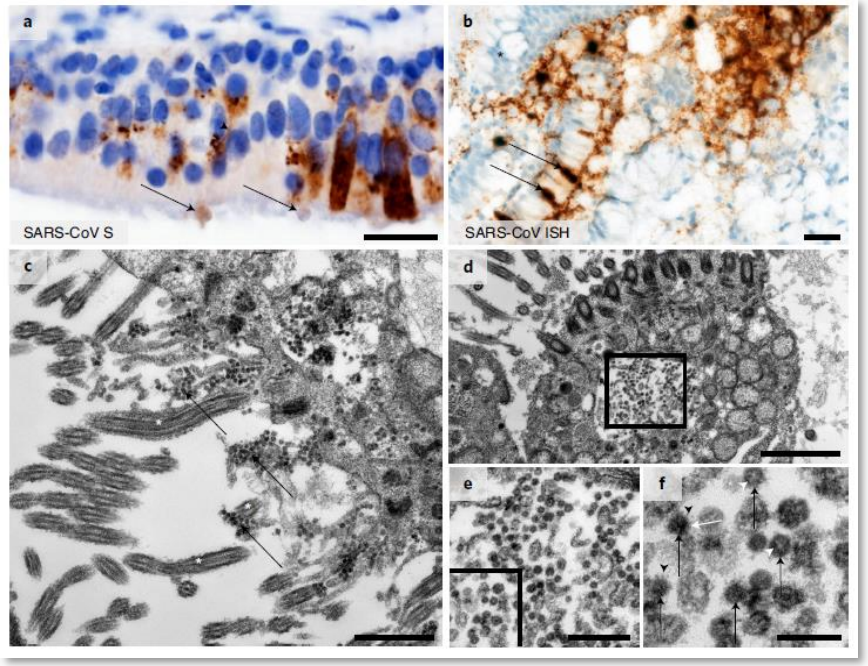
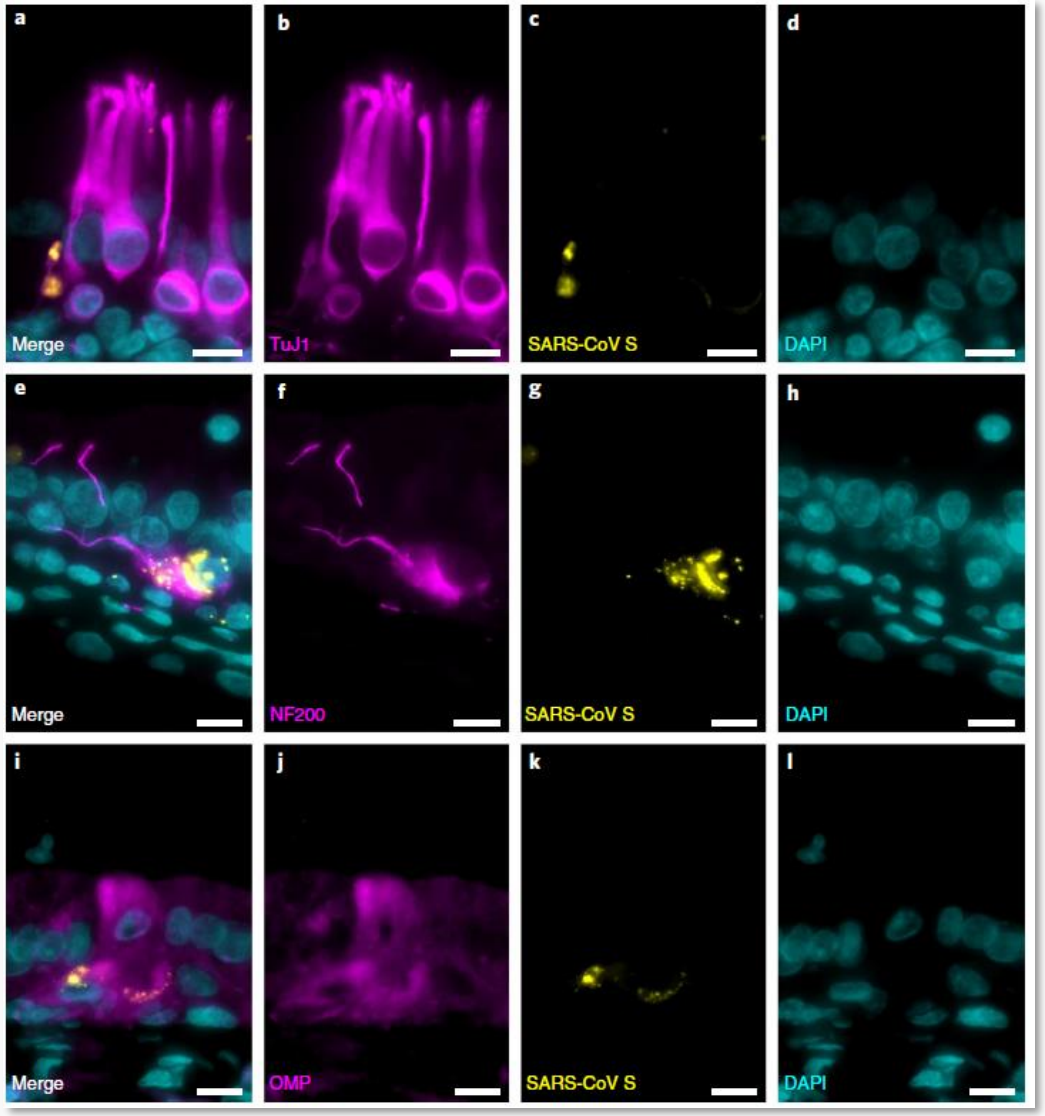
OSN
AE1/AE3 | CD56
OLIG2
g
h
OMP
TuJ1


a
b
SARS-CoV S
SARS-CoV ISH
c
d
e
f


a
b
c
d
Merge
TuJ1
SARS-CoV S
DAPI
e
f
g
h
Merge
NF200
SARS-CoV S
DAPI
i
j
k
l
Merge
OMP
SARS-CoV S
DAPI

Movement Disorders, 2020

LETTERS: NEW OBSERVATIONS

A Post-COVID-19 Parkinsonism in the Future?

Aliaksandr V. Boika, MD, PhD
Department of Neurology and Neurosurgery, Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus

www.thelancet.com/neurology Vol 19 July 2020

Focal Point

COVID-19: can we learn from encephalitis lethargica?

Antonino Giordano, Ghil Schwarz, Laura Cacciaguerra, Federica Esposito, Massimo Filippi

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

EMERGING INFECTIOUS DISEASES®

EID Journal > Volume 12 > Number 1—January 2006 > Main Article

PERSPECTIVE

1918 Influenza: the Mother of All Pandemics

Jeffery K. Taubenberger* and David M. Morens†

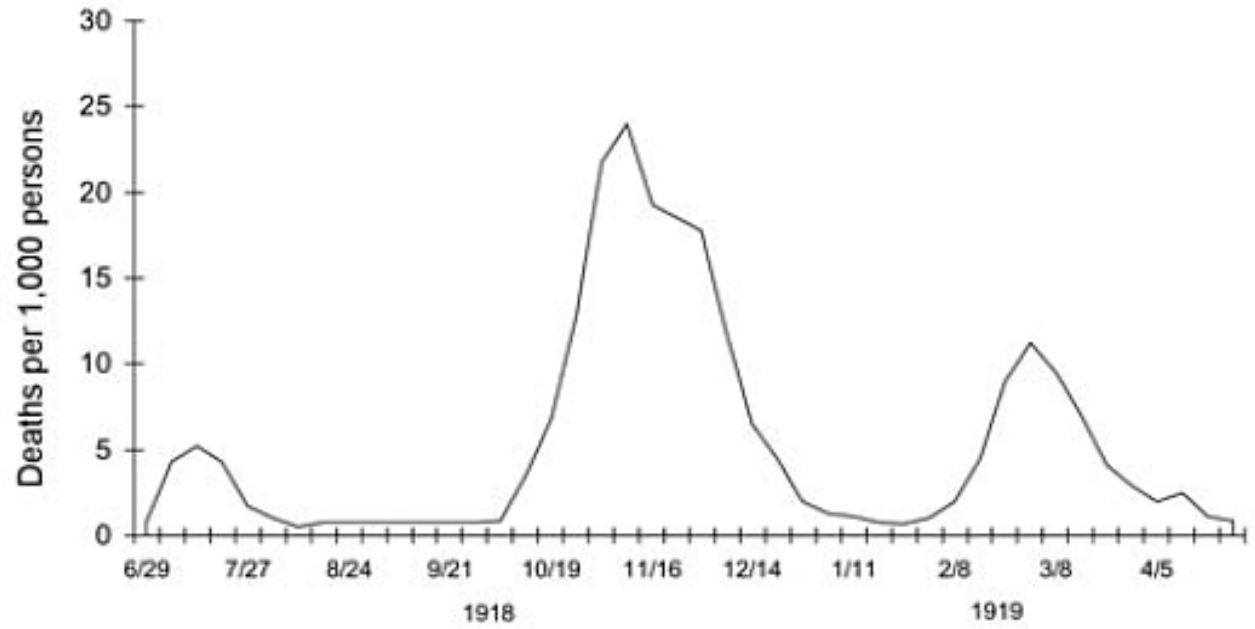


Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919 (*21*).

HISTORICAL NEUROLOGY

The centennial lesson of encephalitis lethargica

Bart Lutters, BSc, Paul Foley, PhD, and Peter J. Koehler, MD, PhD

Neurology® 2018;90:563-567. doi:10.1212/WNL.0000000000005176

Correspondence
Dr. Koehler
pkoehler@neurohistory.nl

Constantin von Economo,
Wiener Klinische Wochenschrift, 1917

7 pacientes, 2 autopsias

Histo-pathologic examination revealed acute inflammation of the brainstem, marked by small cell infiltration of the gray matter around the third ventricle and cerebral aqueduct, the area of the oculomotor nuclei, and the floor of the fourth ventricle.

Neuropathology and Applied Neurobiology (2009), **35**, 462–472 doi: 10.1111/j.1365-2990.2009.01024.x

Review: Neuropathology of acute phase encephalitis lethargica: a review of cases from the epidemic period

L. L. Anderson*, J. A. Vilensky* and R. C. Duvoisin†

**Department of Anatomy and Cell Biology, Indiana University School of Medicine, Fort Wayne, Indiana, and †Department of Neurology, University of Medicine and Dentistry of New Jersey (Emeritus), New Brunswick, New Jersey, USA*

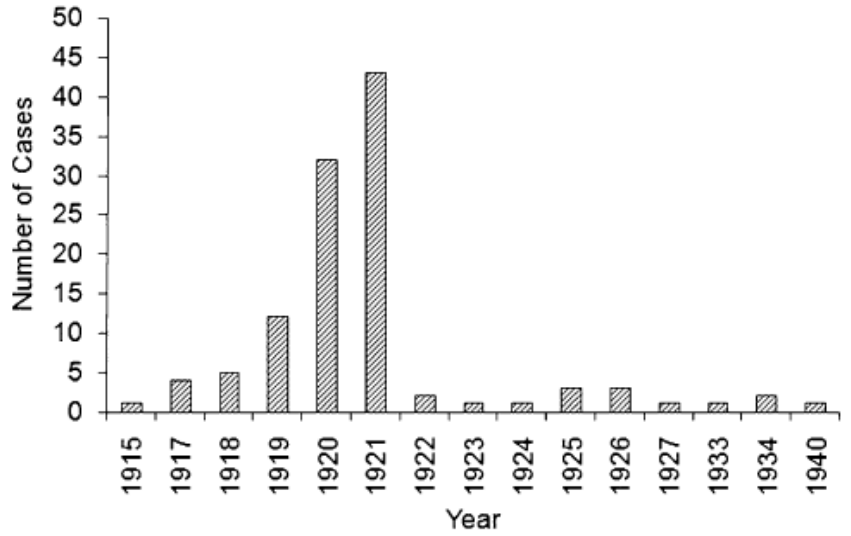


Figure 1. Number of encephalitis lethargica cases reported per year.

The fact that few patients were reported to have had influenza suggests that influenza was not the cause of EL.

Medical Hypotheses 74 (2010) 798–801

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Influenza caused epidemic encephalitis (encephalitis lethargica): The circumstantial evidence and a challenge to the nonbelievers

C.P. Maurizi *

Retired Pathologist, 103 Bartl

J Neurovirol. 2008 May ; 14(3): 177–185. doi:10.1080/13550280801995445.

The relationship between encephalitis lethargica and influenza: A critical analysis

Sherman McCall[1], **Joel**

Movement Disorders
Vol. 25, No. 9, 2010, pp. 1116–1123

Historical Review

A Historical Analysis of the Relationship Between Encephalitis Lethargica and Postencephalitic Parkinsonism: A Complex Rather than a Direct Relationship

Joel A. Vilensky, PhD,[1]* Sid Gilman, MD,[2] and Sherman McCall, MD[3]

Pathological τ Proteins in Postencephalitic Parkinsonism: Comparison with Alzheimer's Disease and Other Neurodegenerative Disorders

Valérie Buée-Scherrer, PhD,*¶ Luc Buée, PhD,*
Béatrice Leveugle, PhD,§†† Daniel P. Perl, MD,‡**
Patrick Vermersch, MD, PhD,*† Patrick R. Hof, MD,‡§‖
and André Delacourte, PhD*

Ann Neurol 1997;42:356–359

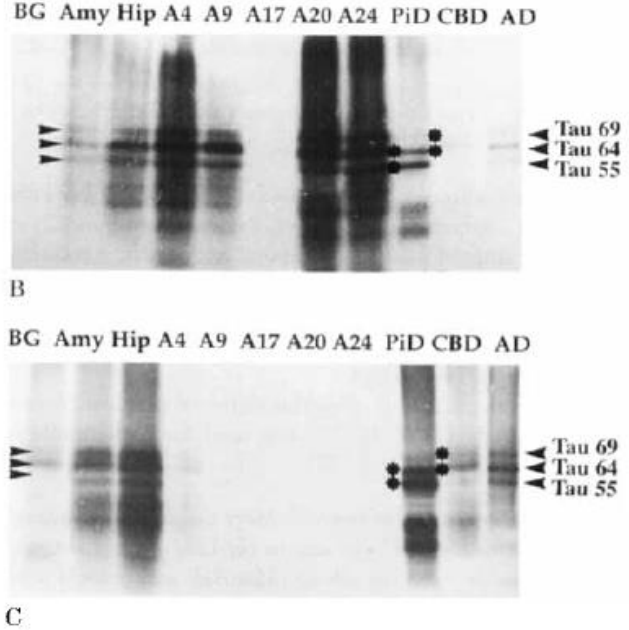
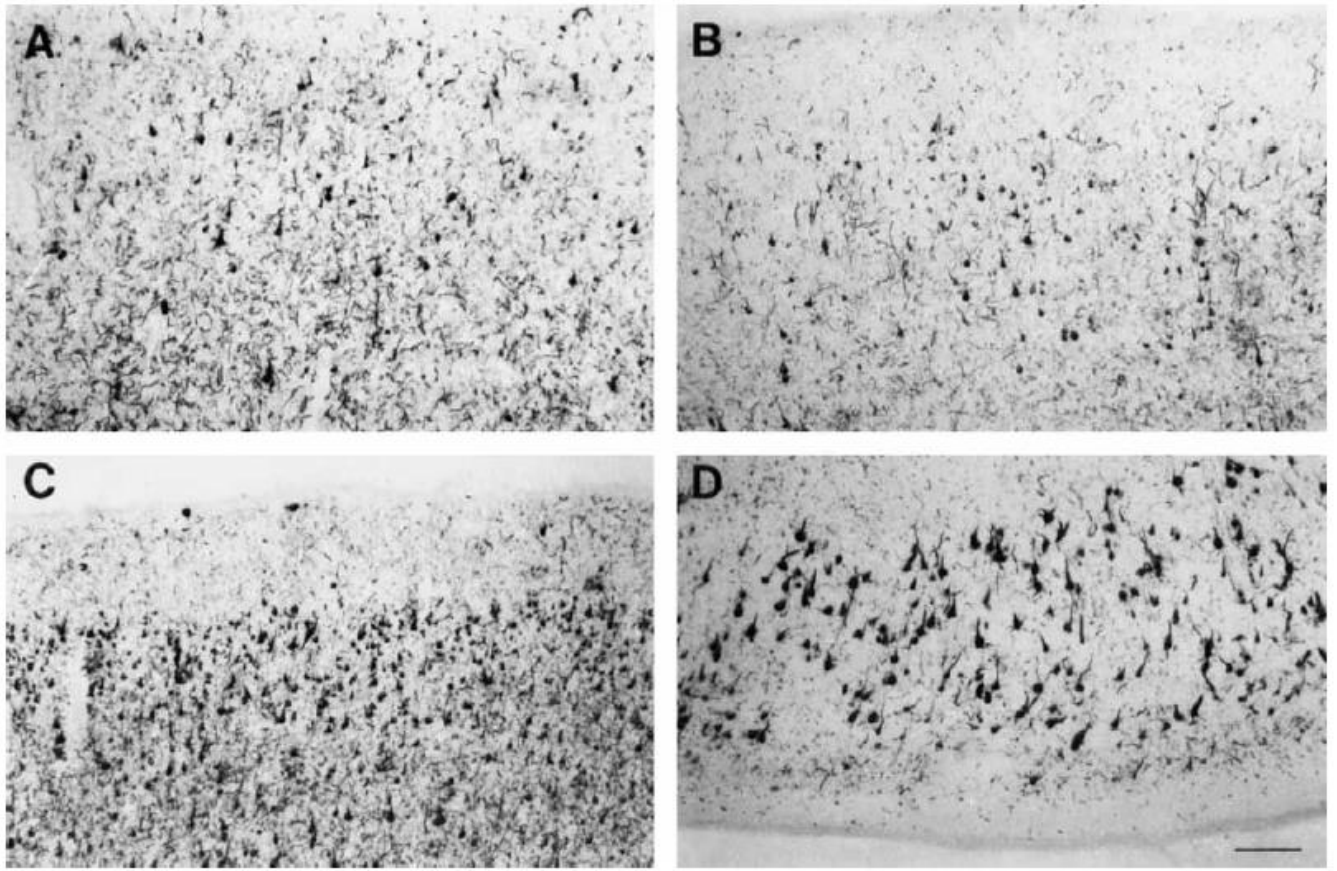
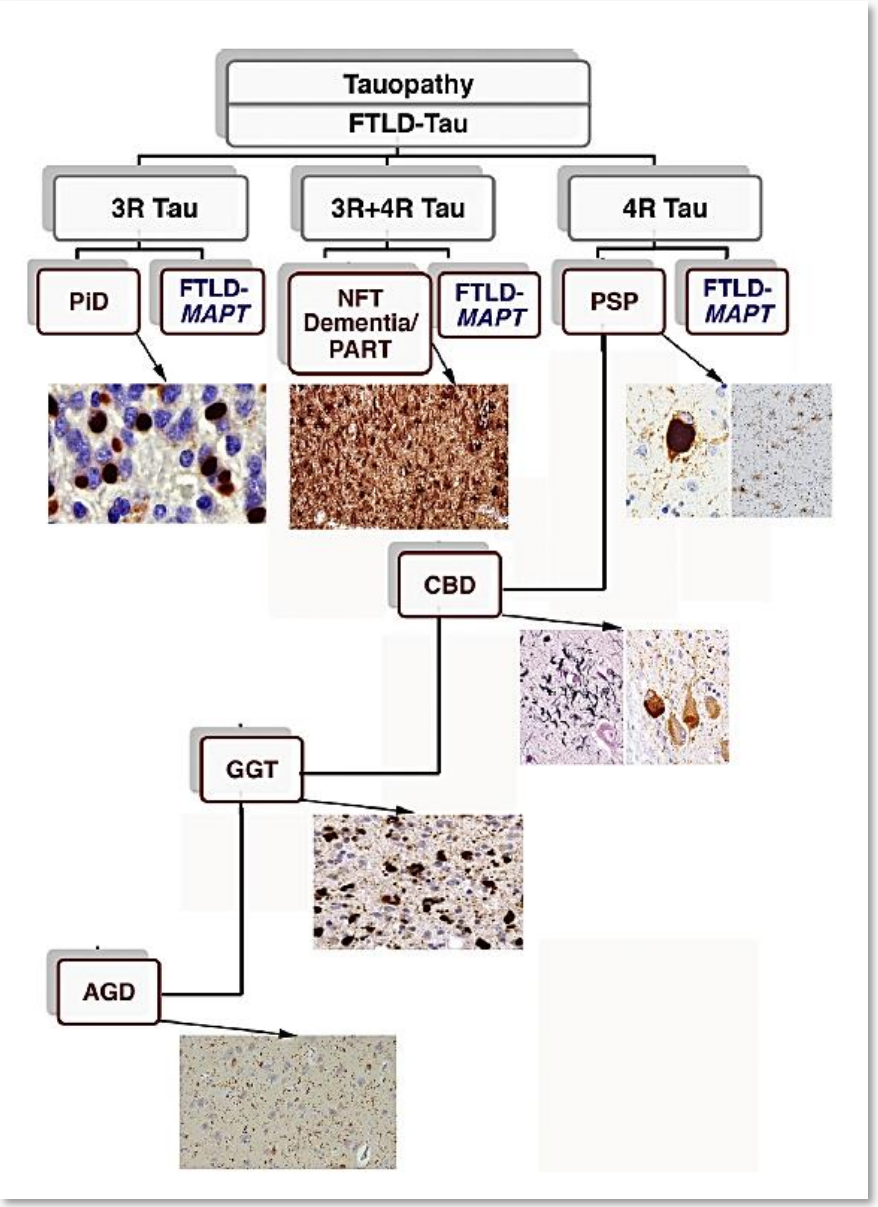


Figure 1. Distribution of neurofibrillary tangles in the supragranular layers of primary motor cortex (A), superior frontal cortex (B), inferior temporal cortex (C), and in the CA1 field of the hippocampus (D) in Case 1. All these cortical structures are severely affected by the degenerating process. Materials were stained with antibody AD2. Scale bar = 100 μm.



Taupatías primarias *vs*. secundarias



List of disorders associated with various tau pathologies (Murray et al., 2014; Kovacs, 2015; Tacik et al., 2016)

- Alzheimer disease (sporadic and hereditary: *APP*, *PSEN1*, *PSEN2*)
- Down syndrome
- Prion diseases (sCJD, vCJD, gCJD, GSS, FFI)
- Diffuse neurofibrillary tangles with calcification
- Familial British and Danish dementia
- Postencephalitic parkinsonism
- Subacute sclerosing panencephalitis
- Myotonic dystrophy (DM1) and PROMM (DM2)
- Aging-related tau astrogliopathy
- Traumatic brain injury
- Chronic traumatic encephalopathy
- IgLON5-related tauopathy
- Guadeloupean parkinsonism
- Parkinson–dementia complex of Guam
- Non-Guamanian motor neuron disease with NFTs
- Amyotrophic lateral sclerosis of Guam
- X-linked parkinsonism with spasticity
- Cerebrotendinous xanthomatosis
- Niemann–Pick disease type C
- NBIA *PANK2* and *PLA2G6*
- *SLC9A6* mental retardation
- *LRRK2*, *PRKN*, *SNCA*, *TARDBP*, *C9orf72* gene mutations

Höglinger *et al*., 2018

Taupatías asociadas a otras patologías neurodegenerativas genéticas

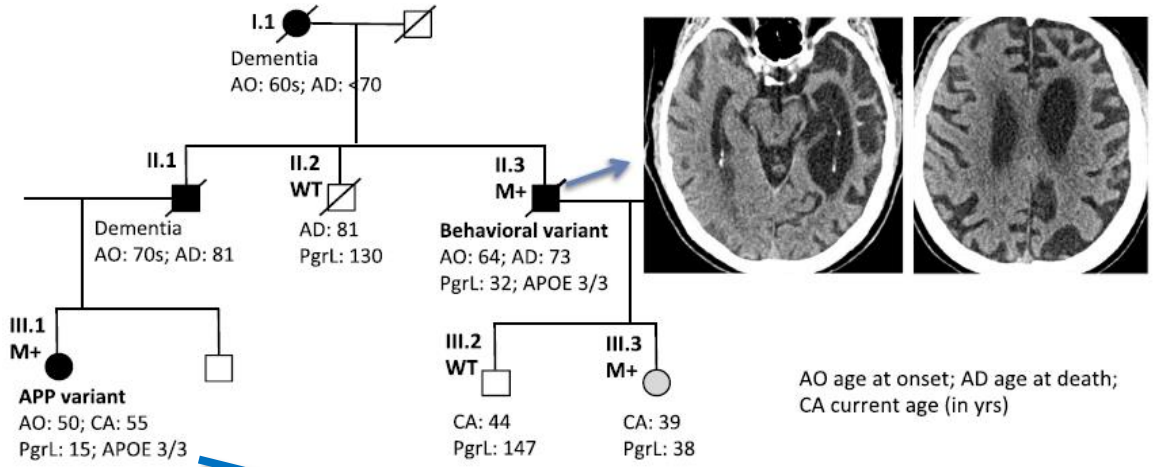
Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Presence of tau astrogliopathy in frontotemporal dementia caused by a novel *Grn* nonsense (Trp2*) mutation

Estrella Gómez-Tortosa[a,*], Yalda Baradaran-Heravi[b,c], Valentina González Alvarez[d], María José Sainz[a], Cristina Prieto-Jurczynska[e], Rosa Guerrero-López[f], Pablo Agüero Rabes[a], Christine Van Broeckhoven[b,c], Julie van der Zee[b,c], Alberto Rábano Gutiérrez[d], on behalf of the EU EOD Consortium



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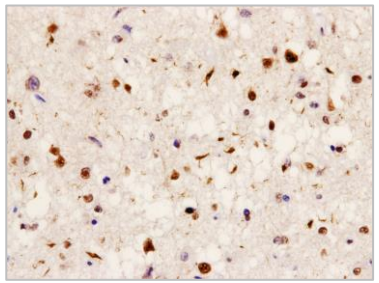
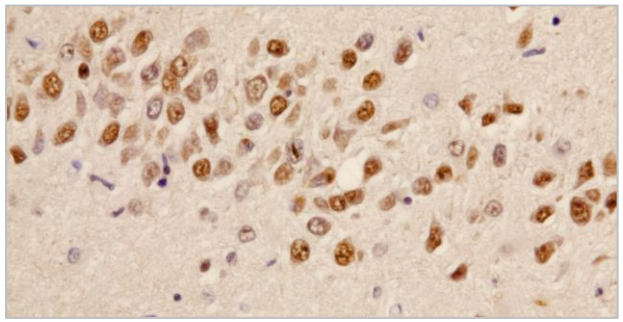
Tipo A





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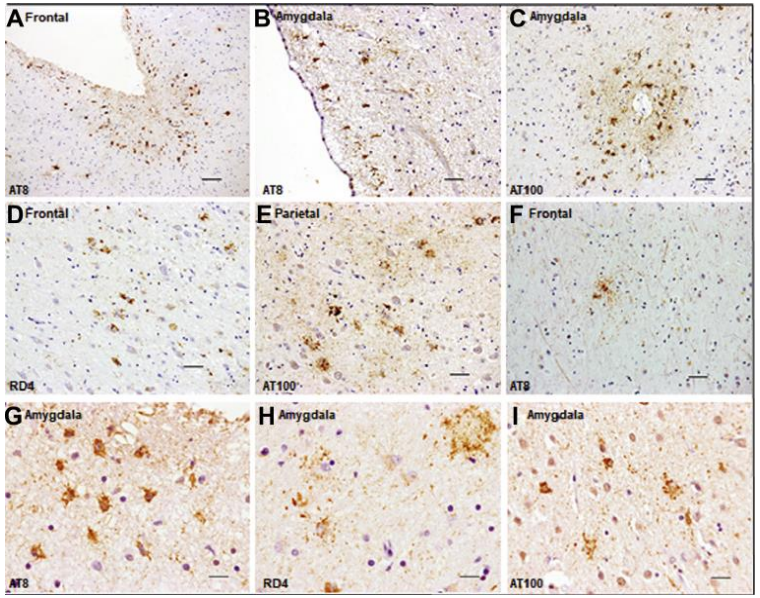
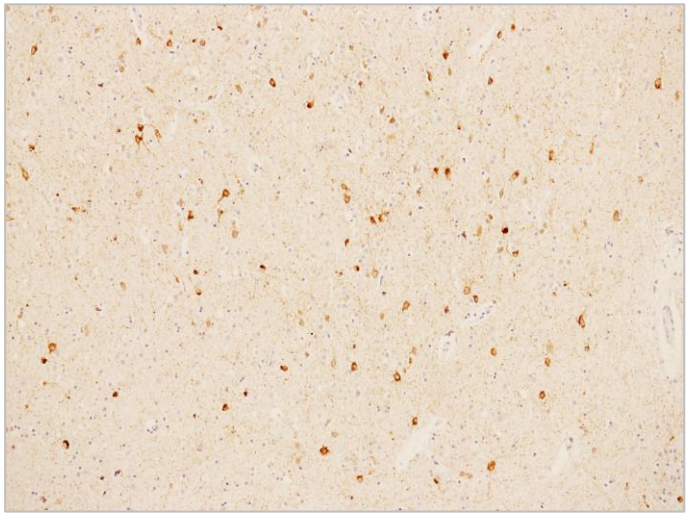




Amígdala, tau AT100

Neuropathology and Applied Neurobiology (2013), **40**, 654–657

Scientific correspondence

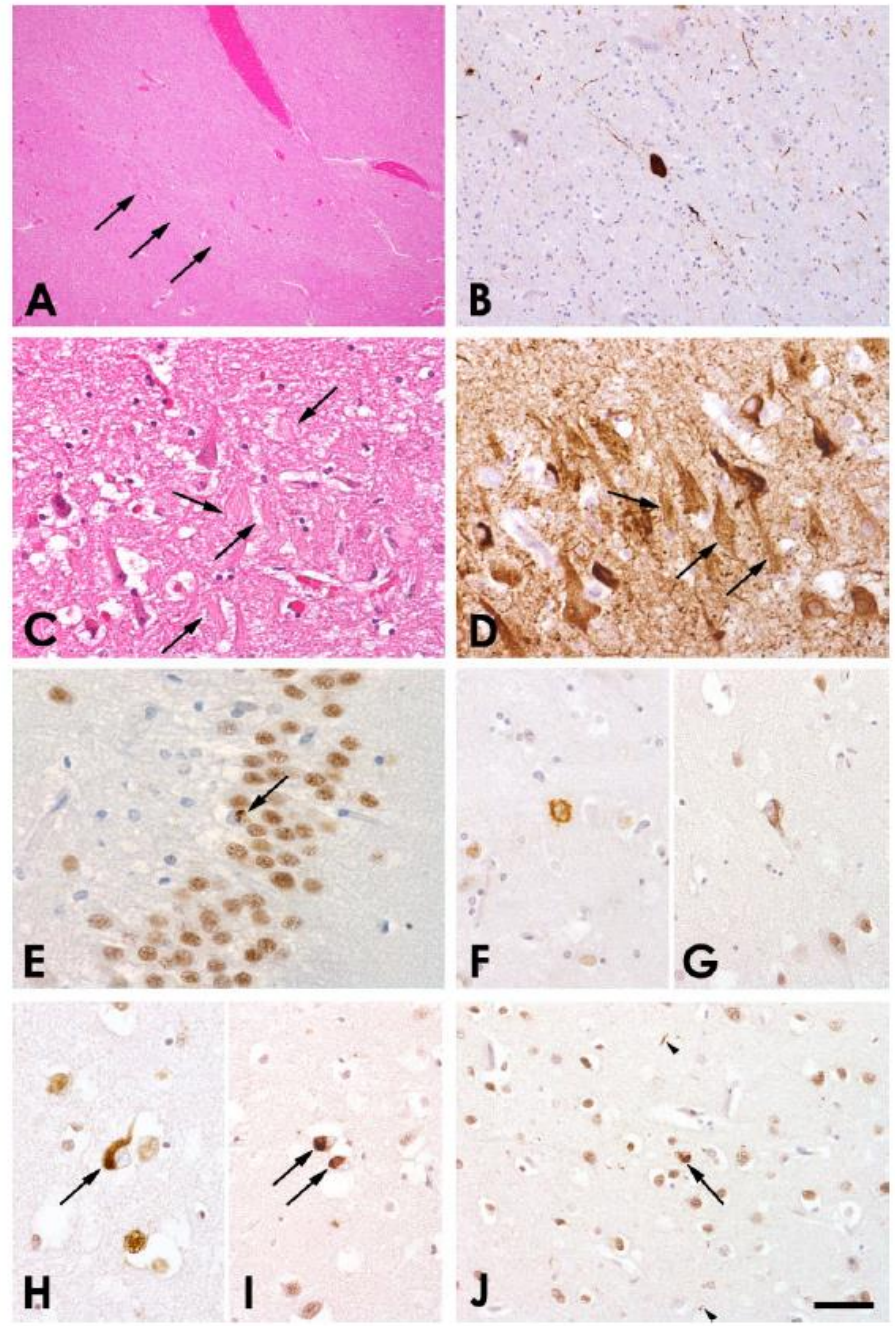
TDP-43 pathology is present in most post-encephalitic parkinsonism brains

H. Ling
J. L. Holton
A. J. Lees
T. Revesz
Reta Lila Weston Institute of Neurological Studies and Queen Square Brain Bank for Neurological Disorders, Department of Molecular Neuroscience, Institute of Neurology, University College London, London, UK

Table 1. Demographic and clinical findings of seven cases with post-encephalitic parkinsonism

Case No.	*Case No. (in paper by Geddes* et al. *[1])*	*Gender*	*Year of birth*	*History of EL*	*Age of parkinsonism onset (years)*	*Hx of OGC*	*Age at death (years)*	*Duration of parkinsonism (years)*
1	Case 2	F	1907	Yes	Unclear, 'severe' symptoms by age 35 years	No	79	>44
2	Case 3	M	1910	Yes	38	No	79	41
3	Case 4	M	1912	Possible	28	Yes	74	46
4	Case 5	M	1904	No	26 (OGC) 51 (tremor)	Yes	84	33
5	Case 7	F	1919	Possible	24	No	69	45
6	NA	F	1917	Yes	61	No	81	20
7	NA	M	1922	Yes	38	Yes	79	41

F, female; M, male; EL, encephalitis lethargica; Hx, history; NA, not applicable; OGC, oculogyric crisis.



Biochim Biophys Acta. 2009 July ; 1792(7): 714–721. doi:10.1016/j.bbadis.2008.08.001.

Viral Parkinsonism

Haeman Jang[1], **David A. Boltz**[2], **Robert G. Webster**[2], and **Richard Jay Smeyne**[1]

[1]Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis TN

[2]Department of Virology, St. Jude Children's Research Hospital, Memphis TN

Table 1

Association of Virus and Parkinsonsim

Virus	Family	Species	References
DNA	Herpesviridae	Herpes simplex virus	[159-162]
		Epstein-Barr virus	[163]
		Cytomegalovirus (CMV)	[160, 162]
		Varicella zoster virus (VZV)	[164]
RNA	Bornaviridae	Borna disease virus	[165]
	Orthomyxoviridae	Influenza virus Type A	[57, 63, 65, 135, 166-171]
	Paramyxoviridae	Measles	[172, 173]
	Picornavirisae	Coxsackie virus	[99, 100, 174, 175]
		Echo virus	[176]
		Polio Virus	[177]
	Retroviridae	Human Immunodeficiency Virus (HIV)	[178-183]
	Flaviviridae	West Nile virus	[184]
		Japanese encephalitis B virus	[110, 166, 185-192]
		St. Louis Virus	[92, 111, 193]

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Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2020, Vol. 75, No. 11, 2231–2232
doi:10.1093/gerona/glaa131
Advance Access publication May 26, 2020

OXFORD

Letter to the Editor

APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort

Chia-Ling Kuo, PhD,[1,2] Luke C. Pilling, PhD,[2,3] Janice L. Atkins, PhD,[3] Jane A. H. Masoli, MBChB,[3,4] João Delgado, PhD,[3] George A. Kuchel, MD,[2] and David Melzer, MBBCh, PhD[2,3,*]

Gerontology

Clinical Section: Research Article

Gerontology
DOI: 10.1159/000513182

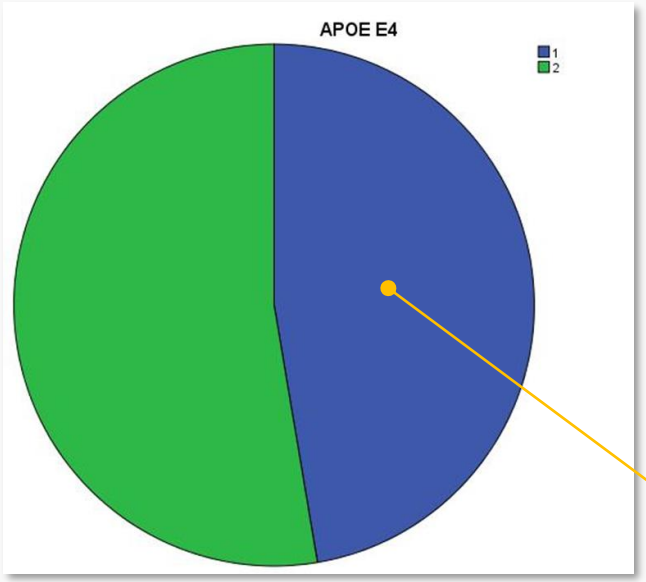
Received: July 14, 2020
Accepted: November 14, 2020
Published online: January 11, 2021

Residence, Clinical Features, and Genetic Risk Factors Associated with Symptoms of COVID-19 in a Cohort of Older People in Madrid

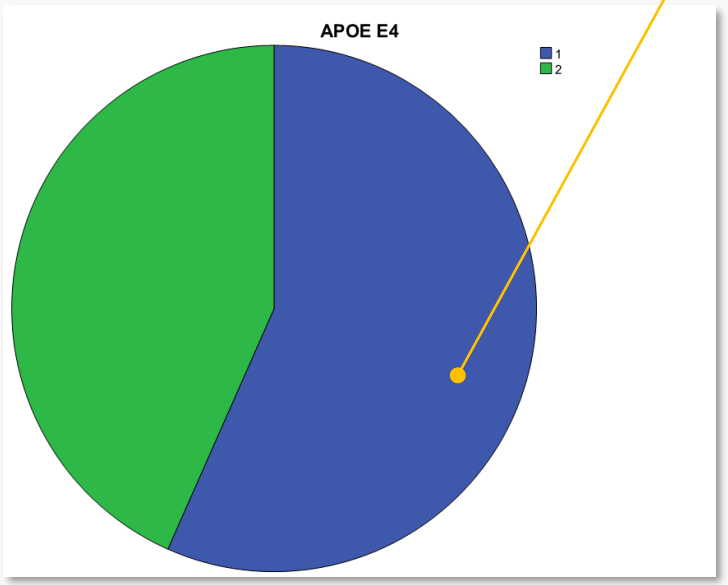
Teodoro del Ser[a] Miguel A. Fernández-Blázquez[a] Meritxell Valentí[a] María Ascensión Zea-Sevilla[a] Belén Frades[a] Eva Alfayate[a] Laura Saiz[a] Olga Calero[b, c] Fernando José García-López[d] Alberto Rábano[a] Miguel Medina[a, b] Miguel Calero[a, b, c]

[a]Alzheimer's Disease Investigation Research Unit, CIEN Foundation, Institute of Health Carlos III, Queen Sofia Foundation Alzheimer Research Center, Madrid, Spain; [b]Centro de Investigación Biomédica en Red sobre Enfermedades Degenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain; [c]Chronic Disease Program, Institute of Health Carlos III, Madrid, Spain; [d]National Epidemiology Centre, Institute of Health Carlos III, Madrid, Spain

Cohorte del CAV-FRS, cerebros post mortem (n = 165)



E4+



frontiers in Neurology

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Impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the Nervous System: Implications of COVID-19 in Neurodegeneration

Myosotys Rodriguez[1], Yemmy Soler[1], Marissa Perry[1], Jessica L. Reynolds[2] and Nazira El-Hage[1]**

Journal of Neural Transmission
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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLES

Coronaviruses: a challenge of today and a call for extended human postmortem brain analyses

Peter Riederer[1,2] · Volker ter Meulen[3]

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Nat Rev Neurol. 2021 Feb;17(2):65-66.

Neurological infection with SARS-CoV-2 — the story so far

Tom Solomon

Key advances

- Anosmia, encephalopathy and stroke are the most common neurological syndromes associated with SARS-CoV-2 infection[1], though many others have been reported.
- Analysis of human biopsy samples suggests that anosmia results predominantly from SARS-CoV-2 infection of non-neuronal cells in the olfactory epithelium and olfactory bulb[2], leading to local inflammation and neuronal malfunction.
- A high proportion of patients admitted to intensive care units with COVID-19 develop delirium, and evidence suggests that this is caused by microvascular and inflammatory mechanisms[3].
- Autopsy data show activation of astrocytes and microglia in COVID-19, particularly in the brainstem, where there is also infiltration of cytotoxic T cells[7,9].
- SARS-CoV-2 can be detected in the brain with PCR and immunohistochemistry, but the evidence to date suggests it is mostly in vascular and immune cells rather than directly infecting neurons[7,9].

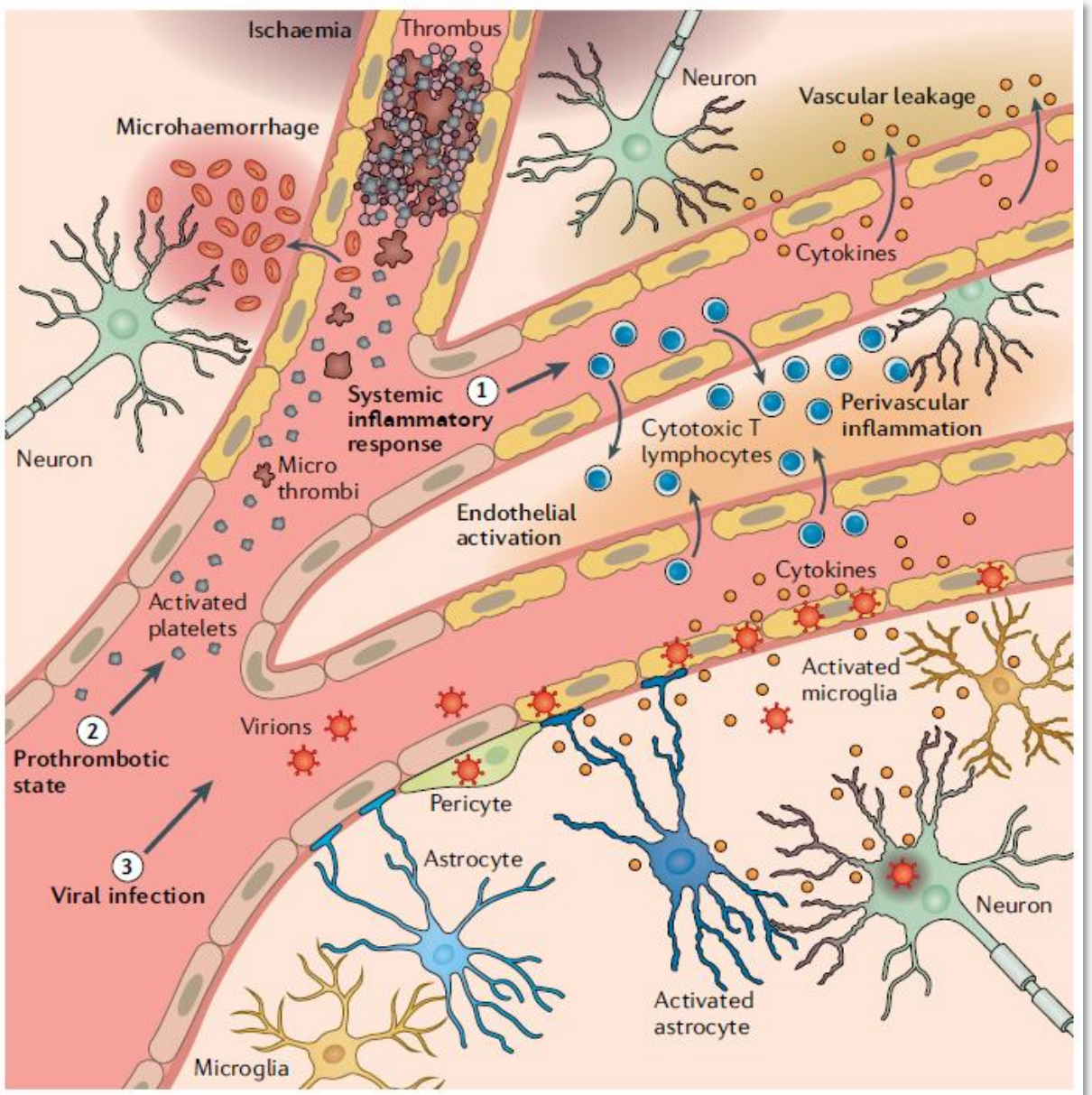

Fig. 1 | **Current understanding of predominant COVID-19 neurological disease mechanisms.** Mechanisms include a systemic inflammatory response (1), a prothrombotic state (2) and direct viral invasion (3).

Gracias!

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