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COVID, uncertainty and clinical trials

Joaquim J. Ferreira

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Common challenge

To be as close to the “truth” as possible

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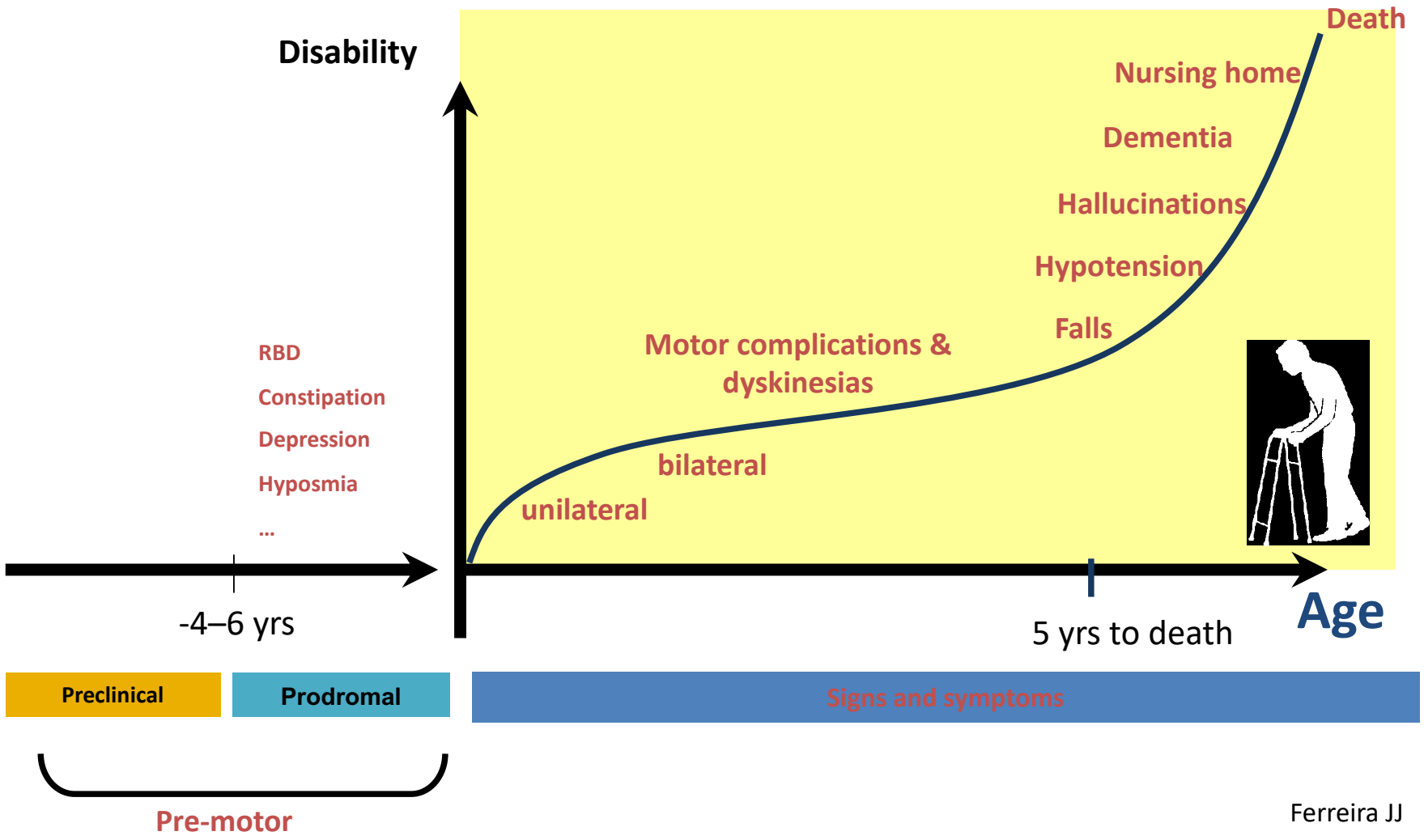
PD PROGRESSION

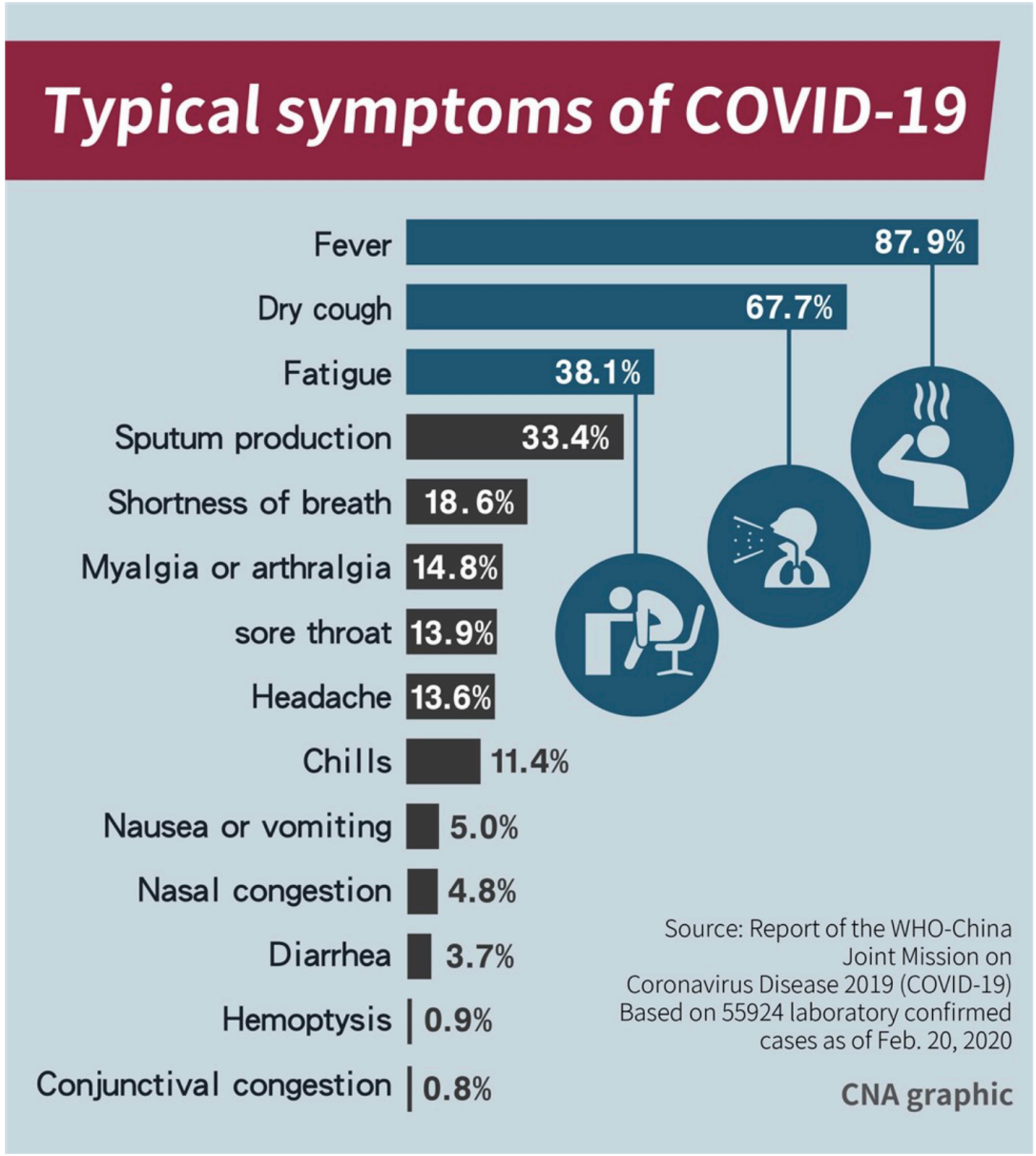


Ferreira JJ

HYPOSMIA

- Well documented in PD patients
- Very sensitive for PD but not specific:
  - Alzheimer's disease, Multi-system atrophy, ALS
  - Not PSP, restless legs syndrome, vascular parkinsonism, and essential tremor

clinical uncertainty



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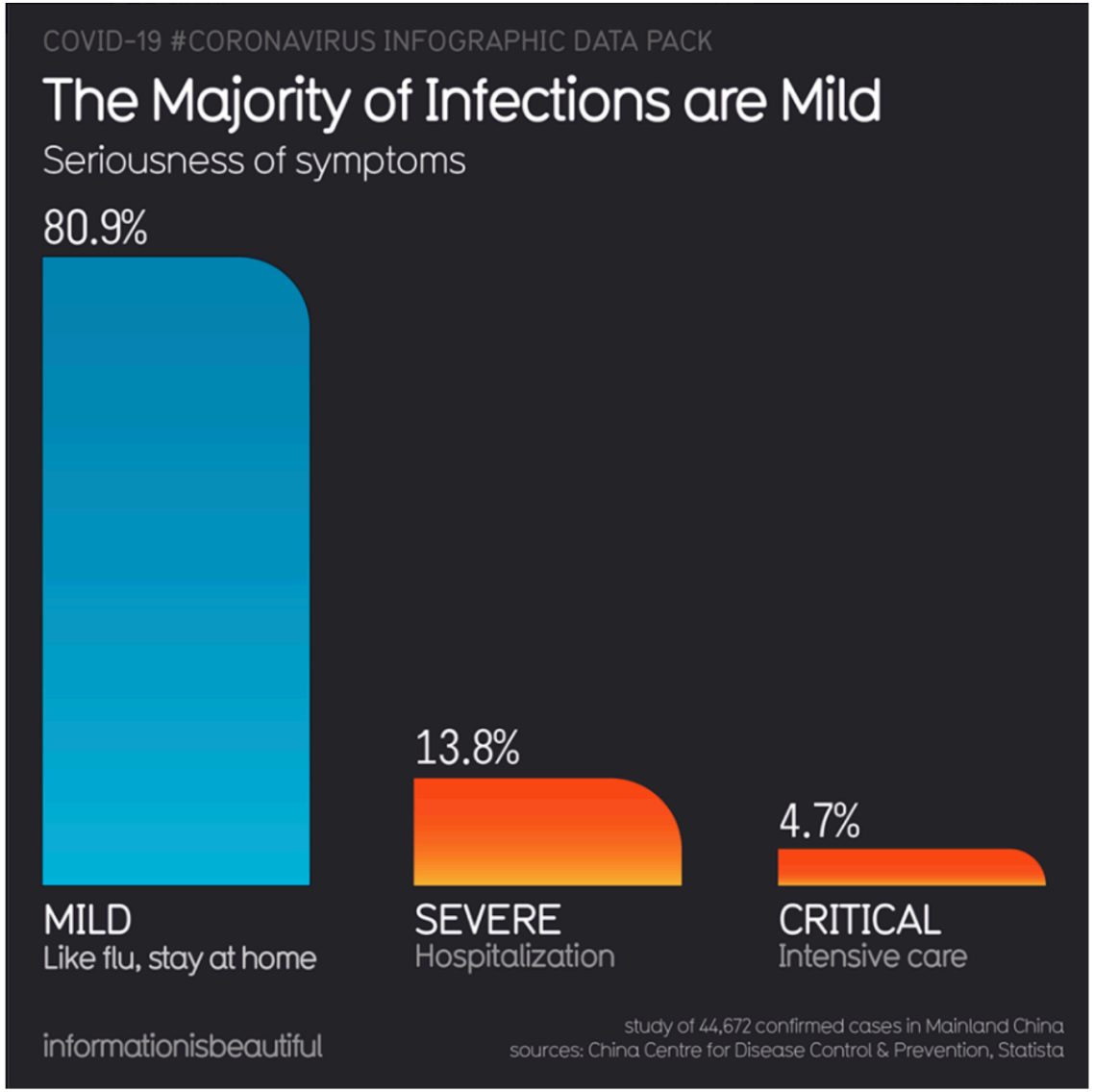
clinical uncertainty



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clinical uncertainty

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

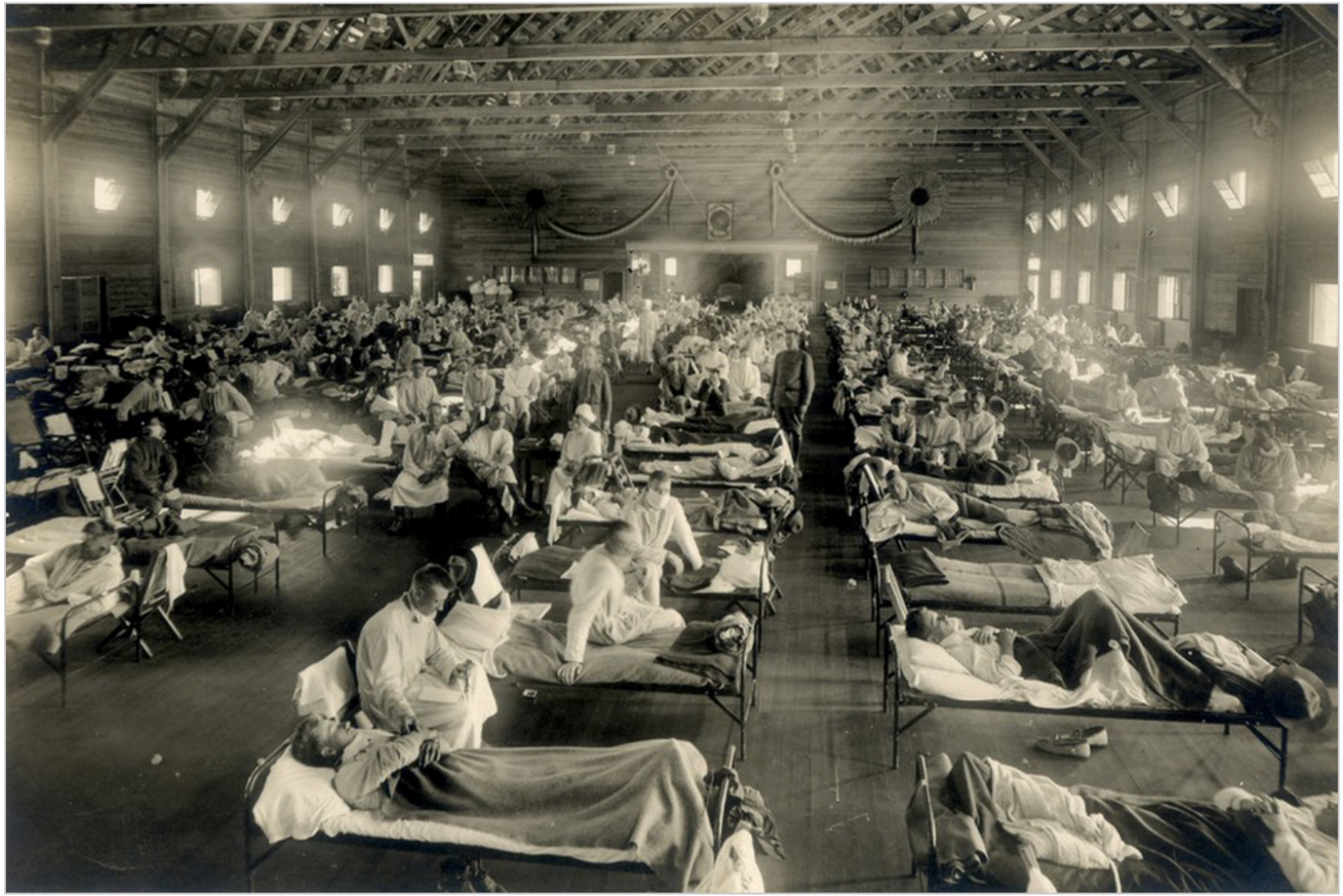
Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
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

clinical uncertainty

"Anosmia, in particular, has been seen in patients ultimately testing positive for the coronavirus with no other symptoms... anosmia, hyposmia, and dysgeusia in the absence of other respiratory disease such as allergic rhinitis, acute rhinosinusitis, or chronic rhinosinusitis should alert physicians to the possibility of COVID-19 infection and warrant serious consideration for self-isolation and testing of these individuals," the AAO-HNS said in a statement on the proposal.

100 years medical mystery



Patients fill an emergency hospital in Camp Funston, Kan., during the 1918 influenza epidemic. OTIS HISTORICAL ARCHIVES NAT'L MUSEUM OF HEALTH & MEDICINE

Spanish flu, influenza epidemic

1917 to 1920

Encephalitis lethargica, "sleeping sickness", "sleepy sickness" or von Economo Encephalitis

1917 to 1930

Post-encephalitic Parkinsonism

1917 -

clinical uncertainty

OXFORD MEDICAL PUBLICATIONS

ENCEPHALITIS LETHARGICA
ITS SEQUELAE AND TREATMENT

BY

CONSTANTIN von ECONOMO

PROFESSOR OF PSYCHIATRY AND NEUROLOGY
IN THE UNIVERSITY OF VIENNA

TRANSLATED AND ADAPTED BY

K. O. NEWMAN, M.D.

PATHOLOGIST TO THE OXFORD COUNTY
AND CITY MENTAL HOSPITAL
OXFORD

With 21 Illustrations

OXFORD UNIVERSITY PRESS
LONDON : HUMPHREY MILFORD
1931

clinical uncertainty

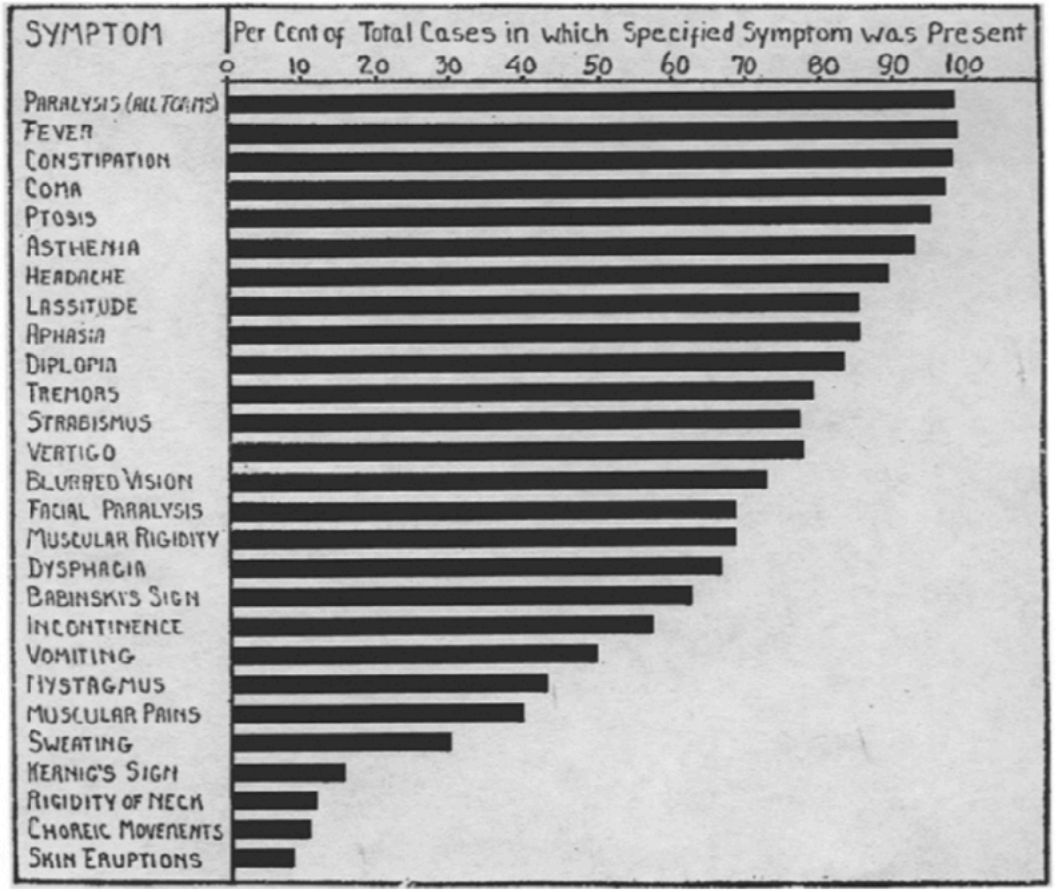


Fig. 37.2. Enacephalitis lethargica symptomatology. (Reproduced from Smith, 1921.)

von Economo classified acute encephalitis lethargica into 3 forms:

somnolent-ophthalmoplegic
hyperkinetic
amyostatic-akinetic

psychiatric manifestations
changes in mood, feelings of euphoria, increased sexual drive, hallucinations, and excessive puns, joviality, and silliness

Smith HF (1921). Epidemic encephalitis (encephalitis lethargica, Nona): report of studies conducted in the United States. Public Health Rep 36: 207–242.

clinical uncertainty

clinical uncertainty

Experimental studies of the influenza hypothesis for encephalitis lethargica (EL)

Study	Conclusions
Gamboa et al. (1974)	Influenza antigens detected in hypothalamus and midbrain in 6 PEP but no PD patients
Marttila et al. (1977a)	No difference between 23 PEP and 421 PD controls for antibodies to influenza strain PR/8/34
Marttila et al. (1977b)	No difference between 20 PEP and 55 PD and controls in antibodies to strains PR/8/24 and Sw/1976
Elizan et al. (1989)	Negative immunostains for several flu strains in 1 acute EL and 1 PEP brain
Isocson et al. (1995)	No influenza RNA in 7 PEP patients
McCall et al. (2001)	mRNA of β_2-microglobulin but not influenza in brains of EL and PEP patients
Lo et al. (2003)	mRNA of β-actin but not influenza in 8 EL brains

Modified from McCall et al. (2008).

aetiologies:

H1N1 cause / trigger / susceptibility ?

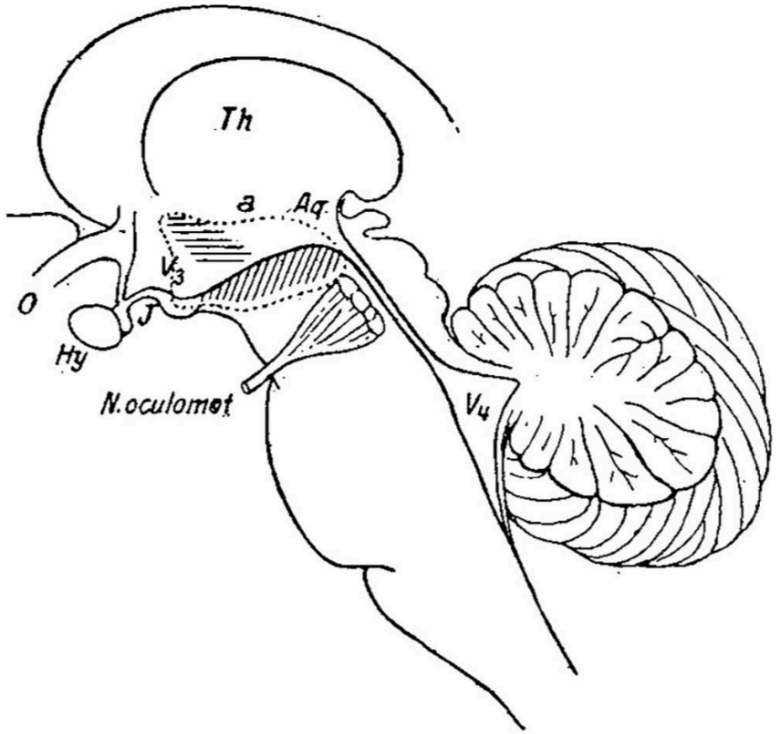
environmental (toxicological)
infectious (viral, bacterial, etc.)
auto-immunity

post-infectious autoimmune disorder
Sydenham's chorea
anti-NMDA receptor encephalitis

McCall S, Vilensky JA, Gilman S et al. (2008). The relation- ship between encephalitis lethargica and influenza: a crit- ical analysis. J Neurovirol 14: 177–185.

clinical uncertainty

Figure von Economo's sleep-regulating center: First published in 1926



[28]The sleep-regulating center is located at the transition between the diencephalon and mesencephalon (dotted line). The horizontal lines indicate the location of lesions resulting in somnolence. The diagonal lines denote the location of lesions resulting in insomnia.

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

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von Economo clinicopathologic findings

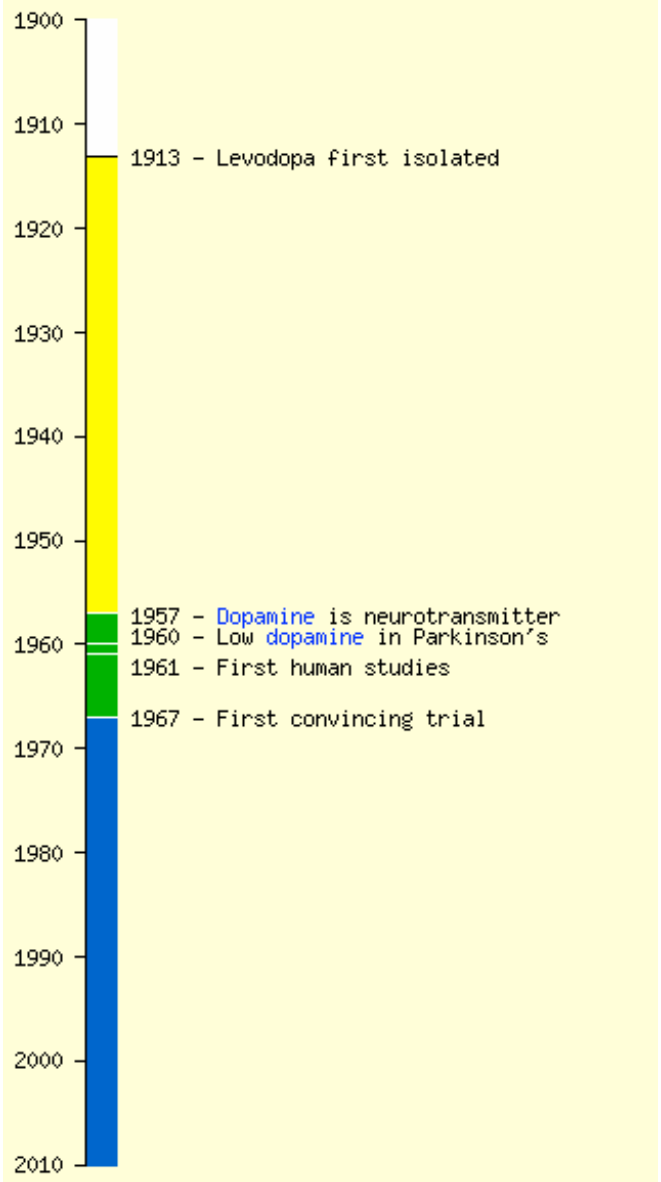
+++ upper midbrain and substantia nigra

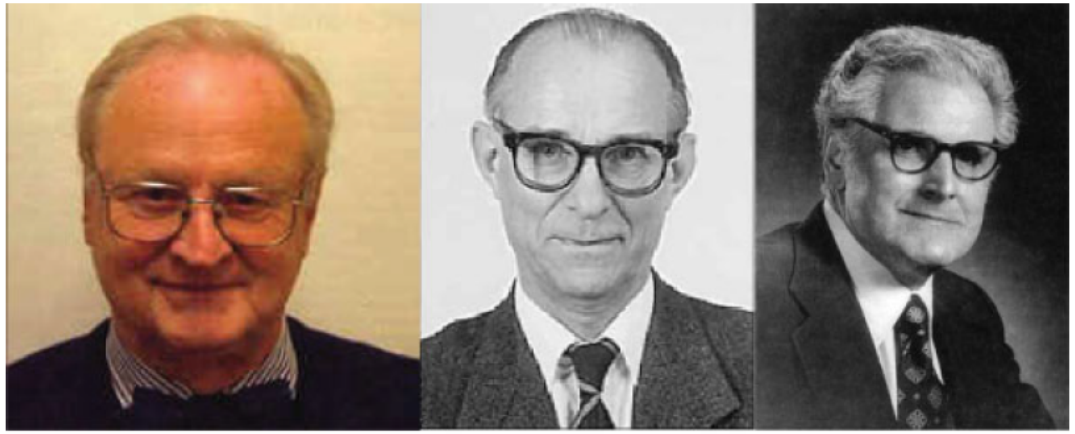
subcortical sleep-regulating center

10% insomnia

von Economo clinicopathologic findings

+++ upper midbrain and **substantia nigra**





Arvid Carlsson | Oleh Hornykiewicz | George Cotzias

clinical uncertainty

chronic phase of encephalitis lethargica

developed 1 to 5 years after the acute phase

one case 45 years

clinical uncertainty

Awakenings, Oliver Sacks' 1973 book
Movie 1990

kinesia paradoxical

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clinical uncertainty

2:00

clinical uncertainty

Case Report

A first case of meningitis/encephalitis associated with SARS-Coronavirus-2

Takeshi Moriguchi[a,*], Norikazu Harii[b], Junko Goto[a], Daiki Harada[a], Hisanori Sugawara[a], Junichi Takamino[a], Masateru Ueno[a], Hiroki Sakata[a], Kengo Kondo[a], Natsuhiko Myose[a], Atsuhito Nakao[c], Masayuki Takeda[d], Hirotaka Haro[e], Osamu Inoue[f], Katsue Suzuki-Inoue[g], Kayo Kubokawa[h], Shinji Ogihara[i], Tomoyuki Sasaki[g], Hiroyuki Kinouchi[j], Hiroyuki Kojin[k], Masami Ito[k], Hiroshi Onishi[l], Tatsuya Shimizu[l], Yu Sasaki[l], Nobuyuki Enomoto[m], Hiroshi Ishihara[n], Shiomi Furuya[k], Tomoko Yamamoto[k], Shinji Shimada[o]

coronaviruses (OC-43, 229E, MERS and SARS) can invade the central nervous system and cause neurological pathologies

SARS-CoV-2 infection causes

headache, dizziness, myalgia and anosmia

cases encephalopathy, encephalitis, necrotising haemorrhagic encephalopathy, stroke, epileptic seizures, rhabdomyolysis and Guillain-Barre syndrome

ACCEPTED MANUSCRIPT

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

Ross W Paterson, Rachel L Brown, Laura Benjamin, Ross Nortley, Sarah Wiethoff, Tehmina Bharucha, Dipa L Jayaseelan, Guru Kumar, Rhian E Raftopoulos, Laura Zambreanu ... Show more

Author Notes

Brain, awaa240, https://doi.org/10.1093/brain/awaa240

Published: 08 July 2020 **Article history** ▾

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 [−1–21]	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 [6–26]	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)

clinical uncertainty

Why is important to recognize the unknown / uncertainty?

6 months of data is short

delayed onset manifestations?

post-infectious neurologic disorders ?

association hyposmia + sleep + behaviour !

reasons to be prudent

methodological uncertainty

Hydroxychloroquine story?

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methodological uncertainty

Liu et al. *Cell Discovery* (2020)6:16
https://doi.org/10.1038/s41421-020-0156-0

Cell Discovery
www.nature.com/celldisc

CORRESPONDENCE Open Access

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

Jia Liu[1], Ruiyuan Cao[2], Mingyue Xu[1,3], Xi Wang[1], Huanyu Zhang[1,3], Hengrui Hu[1,3], Yufeng Li[1,3], Zhihong Hu[1], Wu Zhong[2] and Manli Wang[1]

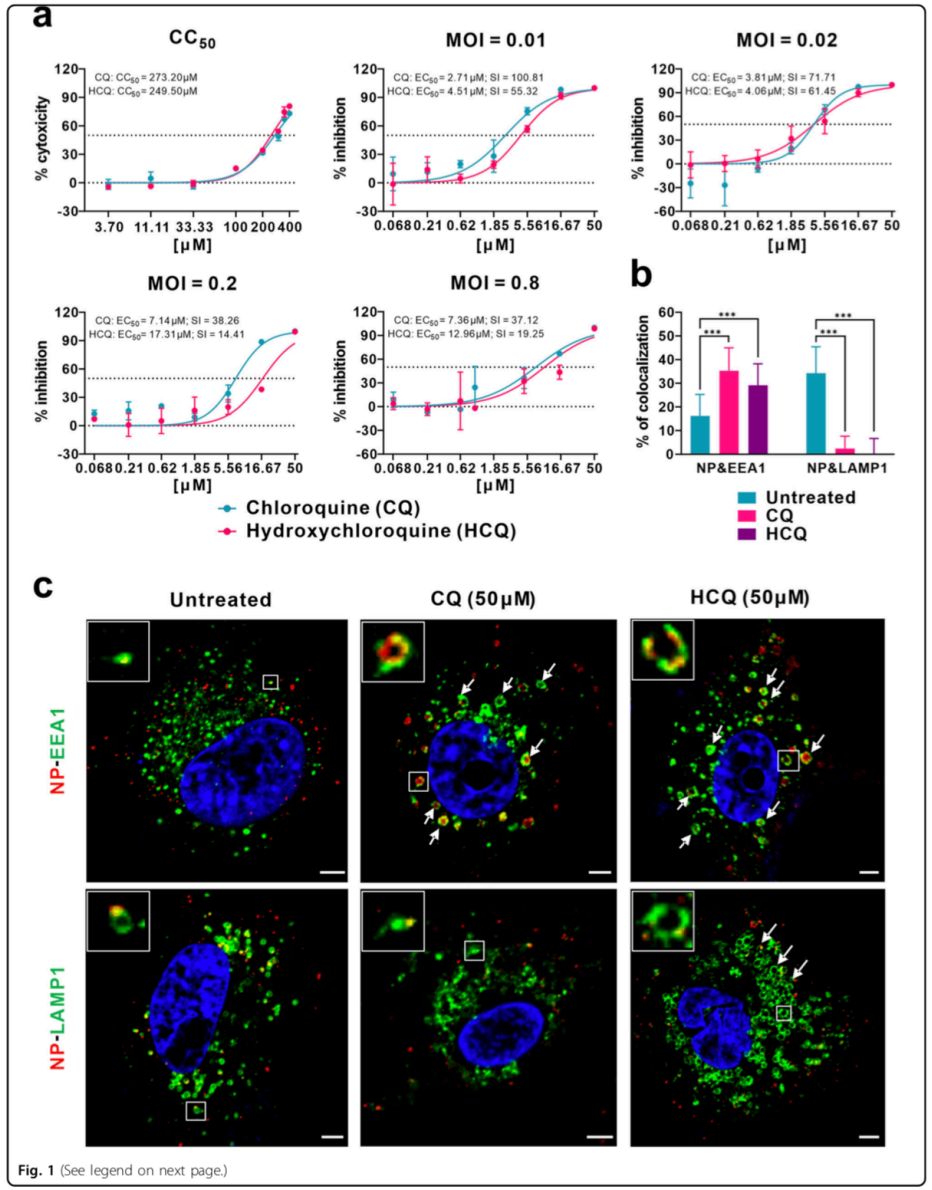

Fig. 1 (See legend on next page.)

methodological uncertainty

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial ☆

Philippe Gautret[a,b,$], Jean-Christophe Lagier[a,c,$], Philippe Parola[a,b], Van Thuan Hoang[a,b,d], Line Meddeb[a], Morgane Mailhe[a], Barbara Doudier[a], Johan Courjon[e,f,g], Valérie Giordanengo[h], Vera Esteves Vieira[a], Hervé Tissot Dupont[a,c], Stéphane Honoré[i,j], Philippe Colson[a,c], Eric Chabrière[a,c], Bernard La Scola[a,c], Jean-Marc Rolain[a,c], Philippe Brouqui[a,c], Didier Raoult[a,c,*]

Outcome

Primary endpoint was virological clearance at day-6 post-inclusion.

Table 1
Characteristics of the study population.

	Age (years)			Male gender		Clinical status				Time between onset of symptoms and inclusion (days)		
	Mean ± SD	t	p-value	n (%)	p-value	Asymptomatic	URTI	LRTI	p-value	Mean ± SD	t	p-value
Hydroxychloroquine treated patients (N=20)	51.2 ± 18.7	-1.95	0.06	9 (45.0)	0.65	2 (10.0)	12 (60.0)	6 (30.0)	0.30	4.1 ± 2.6	-0.15	0.88
Control patients (N=16)	37.3 ± 24.0			6 (37.5)		4 (25.0)	10 (62.5)	2 (12.5)		3.9 ± 2.8		
All patients (36)	45.1 ± 22.0			15 (41.7)		6 (16.7)	22 (61.1)	8 (22.2)		4.0 ± 2.6		

URTI: upper tract respiratory infection, LRTI: lower tract respiratory infection

6 hydroxychloroquine- treated patients were lost during the follow-up (23%)

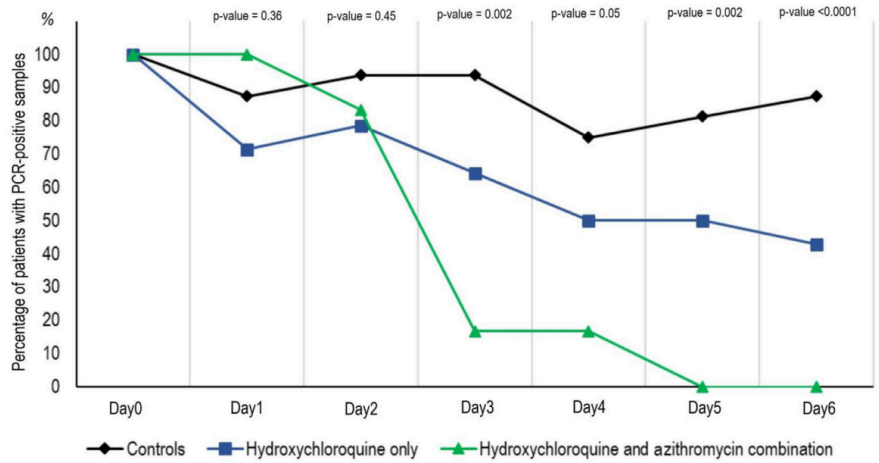

Fig. 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithromycin combination, and in COVID-19 control patients.

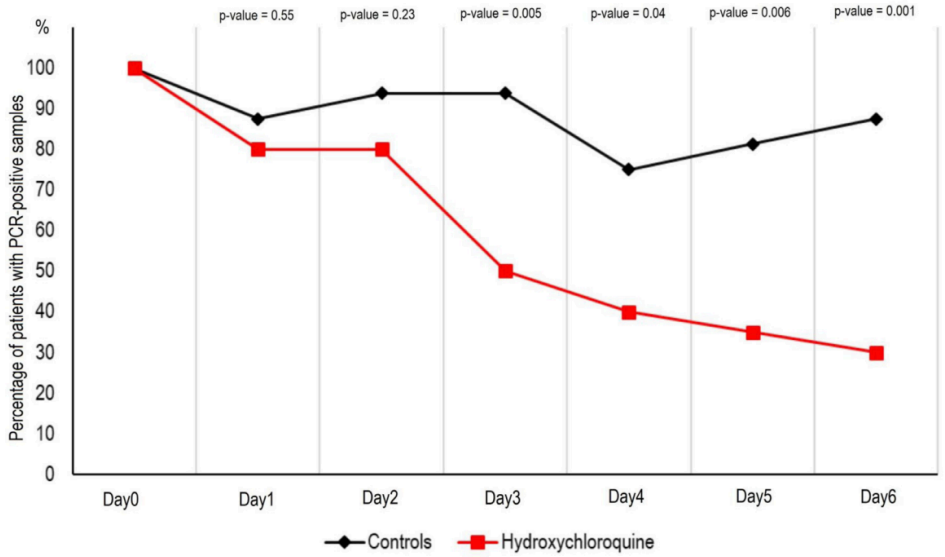

Fig. 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.

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methodological uncertainty

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation m[illegible]ide, are b[illegible] widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Althoug[illegible]nerall[illegible]fe whe[illegible] used for approved indications such as autoimmune disease or malaria, the safety and bene[illegible]f th[illegible]treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine [illegible]oquine with[illegible]thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hospi[illegible]s in s[illegible]ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory t[illegible]g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn[illegible]e included in [illegible]f four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor[illegible]ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed [illegible] control gr[illegible]. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o[illegible]ile they w[illegible]on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc[illegible]of int[illegible]t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias ([illegible]tained o[illegible]ed ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) [illegible]OVID-19 were hospitalised during the study period and met the inclusion criteria. Of the[illegible] patie[illegible]were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with [illegible]macro[illegible]e, 3016 [illegible]eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and [illegible] pati[illegible]in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple c[illegible]four[illegible]ctors ([illegible] sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac[illegible] diabetes, [illegible]derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), w[illegible]mpared wi[illegible]ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% [illegible] 1·22[illegible]457), hydro[illegible]ychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), [illegible]chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated [illegible]n an increased r[illegible]f in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6[illegible]; 2·36[illegible]·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; [illegible]1, 2[illegible]0–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate[illegible] an incr[illegible]d risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati[illegible] We w[illegible] unable[illegible]nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macro[illegible] on in[illegible]spital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospita[illegible]vi[illegible]reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding William[illegible]vey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

P[illegible]d Online
[illegible] 22, 2020
https://doi.org/10.1016/S0140-6736(20)31180-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 29, 2020

See Online/Comment
https://doi.org/10.1016/S0140-6736(20)31174-0

Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA (Prof M R Mehra MD); **Surgisphere Corporation, Chicago, IL, USA** (S S Desai MD); **University Heart Center, University Hospital Zurich, Zurich, Switzerland** (Prof F Ruschitzka MD); **Department of Biomedical Engineering, University of Utah, Salt Lake City, UT, USA** (A N Patel MD); **and HCA Research Institute, Nashville, TN, USA** (A N Patel)

Correspondence to:
Prof Mandeep R Mehra, Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA 02115, USA
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RETRACTED

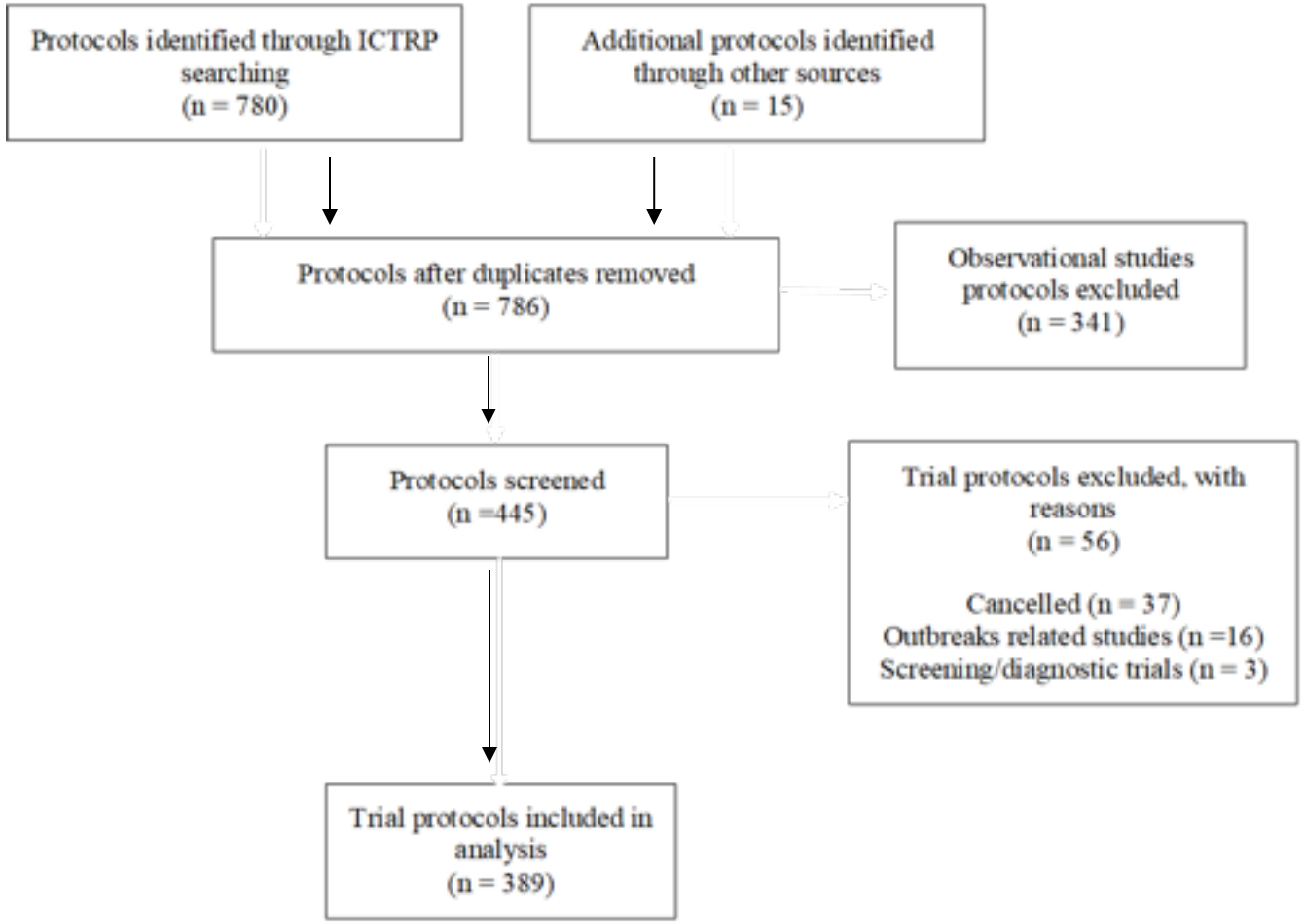
methodological uncertainty

Ongoing trials on COVID-19

Beatrice Mainoli
Tiago Machado
Gonçalo S Duarte
Luísa Prada
Nilza Gonçalves
Joaquim J Ferreira
João Costa

- 30 March 2020
  - WHO International Clinical Trials Registry Platform (ICTRP) contains the trial registration datasets provided by 17 clinical trial registries
  - National clinical trials registries
    - ClinicalTrials.gov, EU Clinical Trials Register, Chinese Clinical Trial Register
- Independent trials selection and data extraction

methodological uncertainty

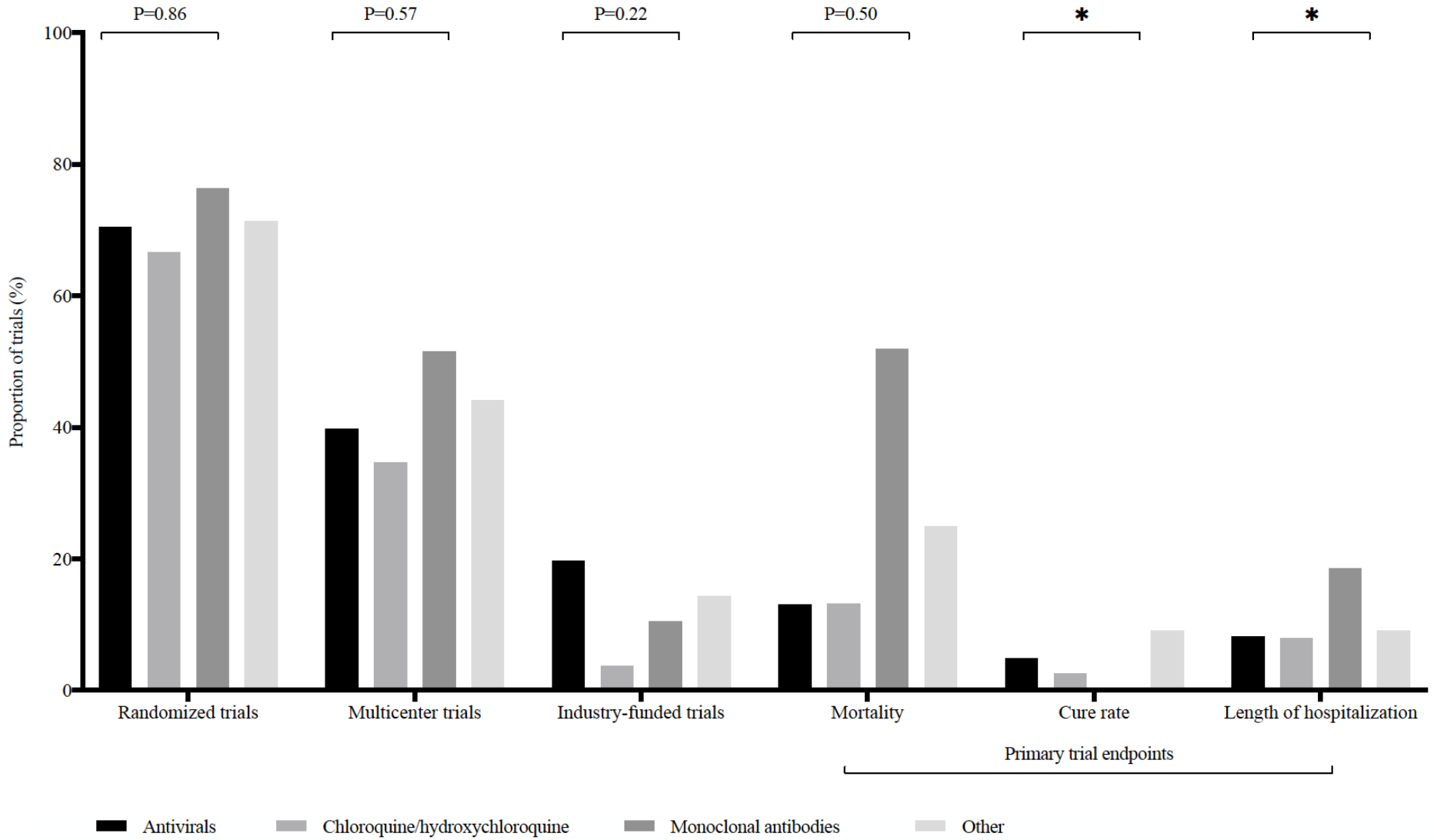


RESULTS - *COVID-19 treatment (n=331)*

	Pharmacotherapy	Traditional Chinese Medicine	Mesenchymal stem cells and NK cells	Advanced life-support strategies	Convalescent plasma and immunoglobulins	Others
Number of trials – no. (%)	**163 (49)**	**89 (27)**	**24 (7)**	**13 (4)**	**12 (4)**	**30 (9)**

methodological uncertainty

RESULTS - *COVID-19 pharmacotherapy (n=163)*



methodological uncertainty

- **Patients at largest risk** of death **are not being prioritized** in trials
  - High baseline risk means that smaller treatment effects would be more easily detected
- 15% are **single-arm**
  - CFR change considerably over time
  - Trials using historical controls will likely lead to more false-positive findings
- 59% are **not multicenter**
  - single-center trials are more prone to bias and tend to provide larger effects
    - Particularly true in the critical care setting, where many positive single-center trials have been contradicted by subsequent multicenter trials
- **Lack of hard and more pragmatic endpoints**
- **Many** treatment trials are ***a priori* already deemed to fail**
  - N° **trials powered** to detect a difference ≥50% between treatment groups

methodological uncertainty

- Persisting on the path of “futile” trials will likely only lead to no informative trials and no gain in knowledge

- Urgent need for a global high-quality COVID-19 trials and observational data registry

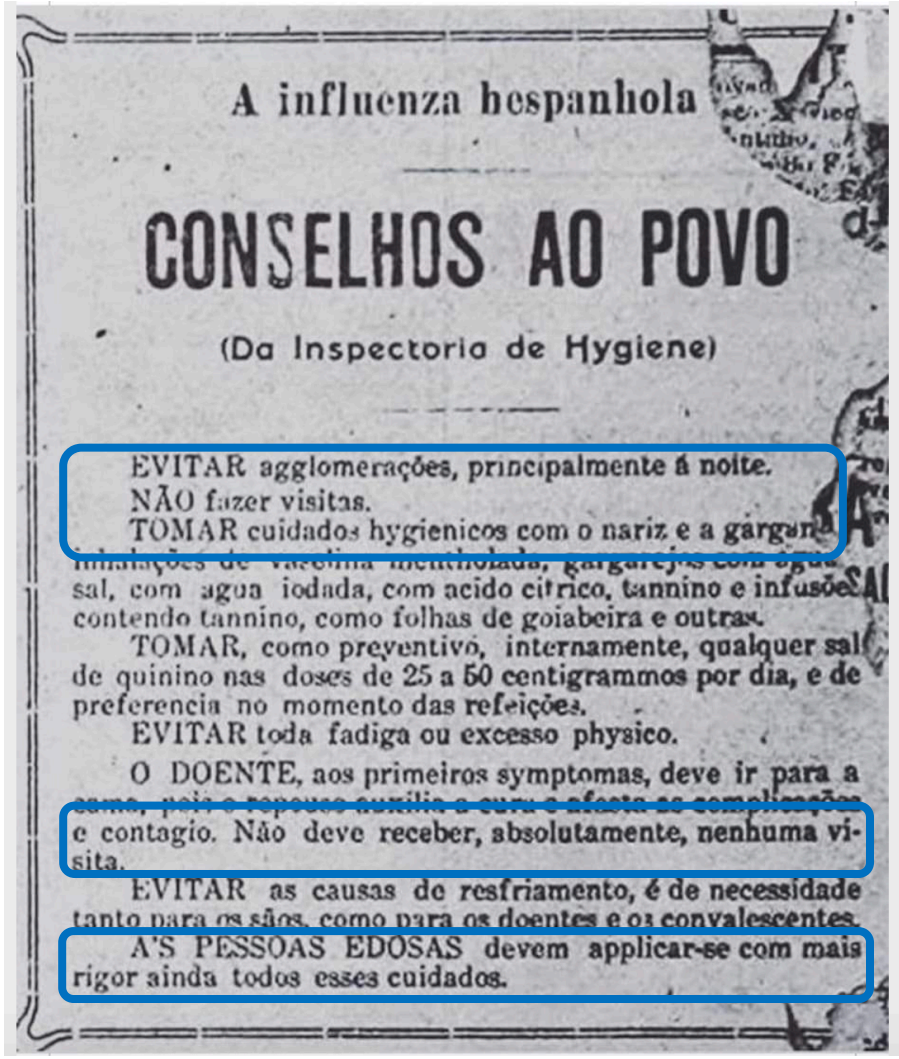
methodological uncertainty

so little time, so much work, so much waste

João Costa

be a humble researcher

After 100 years standard of treatment is the same



A influenza hespanhola

CONSELHOS AO POVO

(Da Inspectoria de Hygiene)

EVITAR agglomerações, principalmente á noite.
NÃO fazer visitas.
TOMAR cuidados hygienicos com o nariz e a garganta, inhalações de vaselina mentholada, gargarejos com agua sal, com agua iodada, com acido citrico, tannino e infusões contendo tannino, como folhas de goiabeira e outras.
TOMAR, como preventivo, internamente, qualquer sal de quinino nas doses de 25 a 50 centigrammos por dia, e de preferencia no momento das refeições.
EVITAR toda fadiga ou excesso physico.
O DOENTE, aos primeiros symptomas, deve ir para a cama, pois o repouso auxilia a cura e afasta as complicações e contagio. Não deve receber, absolutamente, nenhuma visita.
EVITAR as causas de resfriamento, é de necessidade tanto para os sãos, como para os doentes e os convalescentes.
A'S PESSOAS EDOSAS devem applicar-se com mais rigor ainda todos esses cuidados.

Leaflets to the people
Rio de Janeiro, 1918

quinine for prevention!

be a humble researcher

We need pragmatic trials feasible to be conducted in difficult clinical circunstances

Hard outcomes

Adaptive designs (therapeutic arms, dose, therapeutic associations, futility trials)

Registries of clinical trials and long term observational data

be a humble researcher

At least lets learn for the next pandemic ...

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COVID, uncertainty and clinical trials

Joaquim J. Ferreira