COVID, uncertainty and clinical trials

Joaquim J. Ferreira
Common challenge

To be as close to the “truth” as possible
PD PROGRESSION

Disability

Motor complications &
dyskinesias

Motor complications &
dyskinesias

Motor complications &
dyskinesias

Falls

Hallucinations

Hypotension

Dementia

Nursing home

-4–6 yrs

5 yrs to death

Age

Disability

RBD

Constipation

Depression

Hyposmia

...
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
Typical symptoms of COVID-19

- Fever 87.9%
- Dry cough 67.7%
- Fatigue 38.1%
- Sputum production 33.4%
- Shortness of breath 18.6%
- Myalgia or arthralgia 14.8%
- Sore throat 13.9%
- Headache 13.6%
- Chills 11.4%
- Nausea or vomiting 5.0%
- Nasal congestion 4.8%
- Diarrhea 3.7%
- Hemoptysis 0.9%
- Conjunctival congestion 0.8%

Source: Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) Based on 55924 laboratory confirmed cases as of Feb, 20, 2020

CNA graphic
The Majority of Infections are Mild

Seriousness of symptoms

80.9%

MILD
Like flu, stay at home

13.8%
SEVERE
Hospitalization

4.7%
CRITICAL
Intensive care

study of 44,672 confirmed cases in Mainland China
sources: China Centre for Disease Control & Prevention, Statista
### Table 1. Clinical Characteristics of Patients With COVID-19

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Severe (n = 88)</th>
<th>Nonsevere (n = 126)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (N = 214)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>52.7 (15.5)</td>
<td>58.2 (15.0)</td>
<td>48.9 (14.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>78 (36.4)</td>
<td>40 (45.5)</td>
<td>38 (30.2)</td>
<td>.02</td>
</tr>
<tr>
<td>CNS</td>
<td>53 (24.8)</td>
<td>27 (30.7)</td>
<td>26 (20.6)</td>
<td>.09</td>
</tr>
<tr>
<td>Dizziness</td>
<td>36 (16.8)</td>
<td>17 (19.3)</td>
<td>19 (15.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (13.1)</td>
<td>15 (17.0)</td>
<td>13 (10.3)</td>
<td>.15</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>16 (7.5)</td>
<td>13 (14.8)</td>
<td>3 (2.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute cerebrovascular disease</td>
<td>6 (2.8)</td>
<td>5 (5.7)</td>
<td>1 (0.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>PNS</td>
<td>19 (8.9)</td>
<td>7 (8.0)</td>
<td>12 (9.5)</td>
<td>.69</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste</td>
<td>12 (5.6)</td>
<td>3 (3.4)</td>
<td>9 (7.1)</td>
<td>.24</td>
</tr>
<tr>
<td>Smell</td>
<td>11 (5.1)</td>
<td>3 (3.4)</td>
<td>8 (6.3)</td>
<td>.34</td>
</tr>
<tr>
<td>Vision</td>
<td>3 (1.4)</td>
<td>2 (2.3)</td>
<td>1 (0.8)</td>
<td>.37</td>
</tr>
<tr>
<td>Nerve pain</td>
<td>5 (2.3)</td>
<td>4 (4.5)</td>
<td>1 (0.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Skeletal muscle injury</td>
<td>23 (10.7)</td>
<td>17 (19.3)</td>
<td>6 (4.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
“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

Spanish flu, influenza epidemic
1917 to 1920

Encephalitis lethargica, "sleeping sickness", "sleepy sickness" or von Economo Encephalitis
1917 to 1930

Post-encephalitic Parkinsonism
1917 -
ENCEPHALITIS LETHARGICA
ITS SEQUELAE AND TREATMENT

BY
CONSTANTIN VON ECONOMO

PROFESSOR OF NEUROLOGY AND PSYCHIATRY
IN THE UNIVERSITY OF VIEUXNA

TRANSLATED AND ADAPTED BY
K. O. NEWMAN, M.D.
INTERNE IN THE ELY COUNTY AND CITY MENTAL HOSPITAL
Oxford

With 21 Illustrations

OXFORD UNIVERSITY PRESS
LONDON: HUMPHREY MILFORD
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

ACUTE ENCEPHALITIS LETHARGICA

BY

F. H. LEWY
Experimental studies of the influenza hypothesis for encephalitis lethargica (EL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamboa et al. (1974)</td>
<td>Influenza antigens detected in hypothalamus and midbrain in 6 PEP but no PD patients</td>
</tr>
<tr>
<td>Marttila et al. (1977a)</td>
<td>No difference between 23 PEP and 421 PD controls for antibodies to influenza strain PR/8/34</td>
</tr>
<tr>
<td>Marttila et al. (1977b)</td>
<td>No difference between 20 PEP and 55 PD and controls in antibodies to strains PR/8/24 and Sw/1976</td>
</tr>
<tr>
<td>Elizan et al. (1989)</td>
<td>Negative immunostains for several flu strains in 1 acute EL and 1 PEP brain</td>
</tr>
<tr>
<td>Isocson et al. (1995)</td>
<td>No influenza RNA in 7 PEP patients</td>
</tr>
<tr>
<td>McCall et al. (2001)</td>
<td>mRNA of β2-microglobulin but not influenza in brains of EL and PEP patients</td>
</tr>
<tr>
<td>Lo et al. (2003)</td>
<td>mRNA of β-actin but not influenza in 8 EL brains</td>
</tr>
</tbody>
</table>

Modified from McCall et al. (2008).


**Clinical uncertainty**

aetiologies:

- H1N1 cause / trigger / susceptibility?

environmental (toxicological)

infectious (viral, bacterial, etc.)

auto-immunity

post-infectious autoimmune disorder

Sydenham’s chorea

anti-NMDA receptor encephalitis
von Economo clinicopathologic findings

+++ upper midbrain and substantia nigra subcortical sleep-regulating center

10% insomnia
von Economo clinicopathologic findings

+++ upper midbrain and substantia nigra
chronic phase of encephalitis lethargica

developed 1 to 5 years after the acute phase

one case 45 years
Awakenings, Oliver Sacks’ 1973 book
Movie 1990

kinesia paradoxical
clinical uncertainty
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.
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 I. Jayaseelan, Guru Kumar, Rhian E Raftopoulos, Laura Zambrenau ... 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

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

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

Ja Liu¹, Ruyuan Cao², Mingyue Xu¹,³, Xi Wang⁴, Huanyu Zhang¹,³, Hengrui Hu⁴,³, Yufeng Li¹,³, Zhikong Hu⁴, Wu Zhong⁵ and Weili Wang⁶

Fig. 3 (See legend on next page)
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,b, Philippe Parola a,b, Van Thuan Hoang a,b, Lise Meddeb 1, Morgane Mailhe a, Barbara Doudier a, Johan Courjon a,b,c, Valérie Giordanengo a, Vera Estaves Vieira a, Hervé Tissot Dupont a,b, Stéphane Honoré d, Philippe Colson a,b, Eric Chabrière a,b, Bernard La Scola a,b, Jean-Marc Rolain a,b, Philippe Brouqui a,b, Didier Raoult a,b,c

**Outcome**

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

6 hydroxychloroquine- treated patients were lost during the follow-up (23%)
methodological uncertainty
Ongoing trials on COVID-19

- 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 ($n=331$)

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of Trials</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy</td>
<td>163 (49)</td>
<td></td>
</tr>
<tr>
<td>Traditional Chinese Medicine</td>
<td>89 (27)</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal stem cells and NK cells</td>
<td>24 (7)</td>
<td></td>
</tr>
<tr>
<td>Advanced life-support strategies</td>
<td>13 (4)</td>
<td></td>
</tr>
<tr>
<td>Convalescent plasma and immunoglobulins</td>
<td>12 (4)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>30 (9)</td>
<td></td>
</tr>
</tbody>
</table>

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**
  - Nº **trials powered** to detect a difference ≥50% between treatment groups
- 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
so little time, so much work, so much waste

João Costa
be a humble researcher

After 100 years standard of treatment is the same

Leaflets to the people
Rio de Janeiro, 1918

quinine for prevention!
We need pragmatic trials feasible to be conducted in difficult clinical circumstances

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 ...
COVID, uncertainty and clinical trials

Joaquim J. Ferreira