Neuro-COVID: an infectious and non-infectious nervous system disease

David García Azorín MD, PhD, MSci
Headache Unit. Hospital Clínico Universitario de Valladolid, Spain
Secondary Headache, Special Interest Group, International Headache Society
Infectious diseases panel, European Academy of Neurology
International Area, Spanish Society of Neurology
# Disclosure

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Speaker honoraria</th>
<th>Events and travel support</th>
<th>Research projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva, Eli Lilly, Amgen, Novartis, Allergan, Lundbeck</td>
<td>Teva, Novartis, Allergan, Chiesi, Eli Lilly</td>
<td>European Academy of Neurology, Teva, Allergan, Novartis, Eli Lilly</td>
<td>World Health Organization, International headache Society, Regional Health Administration Castilla y Leon, Spanish Society of Neurology</td>
</tr>
</tbody>
</table>
Outline: 4 questions – 10 statements

• Is SARS-CoV-2 a respiratory virus?

• Why are neurological symptoms so diverse?

• Which symptoms can be considered as non-infectious?

• How can we treat/prevent COVID?
Is SARS-CoV-2 a respiratory virus?

Murphy. Radiology. 2020 Sep;296(3):E166-E172
Case #1:

- 45 year-old male with new—onset headache AND anosmia
  - Headache fulfilled the International Classification of Headache Disorders criteria for tension-type headache
1. SARS-CoV-2 is **not only** a respiratory virus\(^1, 2\)

- Severe acute **respiratory** syndrome coronavirus-2

---

2. Neurological manifestations are frequent

- >50% of patients\(^1\)
- Prevalence varies from manifestation to manifestation\(^2, 3\)
- Non-specific (anosmia, headache, myalgia, altered mental status) > frequent tan specific\(^2, 3\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of studies (N)</th>
<th>Summary estimate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small disturbances</td>
<td>17</td>
<td>35.8</td>
<td>(21.4, 50.2)</td>
</tr>
<tr>
<td>Taste disturbances</td>
<td>14</td>
<td>38.5</td>
<td>(24.0, 53.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>54</td>
<td>14.7</td>
<td>(10.4, 18.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>38</td>
<td>19.3</td>
<td>(15.1, 23.6)</td>
</tr>
<tr>
<td>Disturbances in consciousness/ altered mental status</td>
<td>9</td>
<td>9.6</td>
<td>(4.9, 14.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>6.1</td>
<td>(3.1, 9.2)</td>
</tr>
<tr>
<td>Acute cerebrovascular disease</td>
<td>8</td>
<td>2.3</td>
<td>(1.0, 3.6)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>7</td>
<td>2.1</td>
<td>(0.9, 3.3)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>7</td>
<td>0.4</td>
<td>(0.2, 0.6)</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>2</td>
<td>0.3</td>
<td>(0.1, 0.6)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3</td>
<td>1.8</td>
<td>(0.9, 4.6)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>0.3</td>
<td>(0.1, 0.7)</td>
</tr>
<tr>
<td>Seizure</td>
<td>5</td>
<td>0.9</td>
<td>(0.5, 1.3)</td>
</tr>
</tbody>
</table>

3. Neurological manifestations are diverse\(^1\), and in most cases accompanied by other symptoms\(^2\)

Case #2:

- 49 year-old female.
- No vascular risk factors, including smoking.
- Regular physical activity.
- 25 days after COVID-19, which had a mild course (no pneumonia, no need of hospitalization) left MCA stroke.
- Delayed diagnosis due to ED collapse / lack of PPE.
- Complete work-up of stroke in a young patient: unremarkable.
3. Neurological manifestations are diverse in nature but also in timing.\textsuperscript{1, 2}

Days between the symptom onset and the neurological manifestation

Why are neurological symptoms so diverse?
4. Neurological symptoms can be caused by the virus, the immune response or by organ dysfunction\textsuperscript{1-3}

5. Some manifestations (headache, anosmia) may reflect a more efficient immune response

- **Lower adjusted mortality**\(^1\)
- **Related with the phenotype**\(^2\)

---

6. But the immune response may cause also neurological complications (e.g., Guillain-Barré, myelitis, encephalitis)


Which symptoms can be considered as non-infectious?

- ARDS
- Endothelial leakage
- Liver dysfunction
- Hypoalbuminemia
- Impaired detoxification
- Acute kidney injury
- Emergency hematopoiesis
- Thrombocytopenia
Case #3:

• 76 year-old male, with prior history of hypertension, diabetes, chronic emphysema, chronic kidney failure, insomnia and depression.
• Current treatment: Furosemide 40 mg/24h, metformin 850 mg/8h, enalapril 2,5 mg/24h, lormetazepam 1 mg/24h, venlafaxin 75 mg/24h.
• Day 1: Fever, cough, anosmia, headache
• Day 3: + Dyspnea, pleuritic chest pain
• Day 6: + somnolence, altered mental status
• Day 8: decreased level of consciousness
Case 3:

- Laboratory work-up:
  - Erythrocyte sedimentation rate: 90 mm/hour
  - C-reactive protein: 160 mg/L (normal range 0-5)
  - D-dimer: 2400 ng/mL
  - Creatinine 3.5 (Glomerular filtration rate: 27 mL/min)
  - Alanine aminotransferase: 98 Units per liter
  - Aspartate aminotransferase: 95 Units per liter
  - Arterial gasometry:
    - pO2: 55 mmHg
    - pCO2: 75 mmHg

Would you suspect a COVID-19 encephalitis?
7. While other manifestations (e.g., encephalopathy, seizures) can be associated with multiple organ failure and poor prognosis

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Systemic cause</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ failure</td>
<td>Hypercapnia/hypoxia</td>
<td>Pulse oximetry, blood gas</td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
<td>ALT, AST, GGT, ALP, ammonia</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
<td>Creatinine, urea</td>
</tr>
<tr>
<td></td>
<td>Thyroid disorders</td>
<td>TSH, T4</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
<td>ECG, Echo, clinical examination</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyper/hiponatremia</td>
<td>Plasma Na+</td>
</tr>
<tr>
<td></td>
<td>Hyper/Hypocalcemia</td>
<td>Corrected plasma ++</td>
</tr>
<tr>
<td></td>
<td>Hyper/hypoglycemia</td>
<td>Plasma / finger-prick glucose</td>
</tr>
<tr>
<td></td>
<td>Hyperpyrexia/fever/hypothermia</td>
<td>Temperature/observations</td>
</tr>
<tr>
<td></td>
<td>Cytokine release syndrome</td>
<td>IL-1, IL-6, TNF-alpha</td>
</tr>
<tr>
<td>Toxic</td>
<td>Sedatives, corticosteroids, hydroxychloroquine, lopinavir, ritonavir, tocilizumab, drugs, alcohol</td>
<td>Patient history, treatment review</td>
</tr>
<tr>
<td>Septic</td>
<td>Superinfection</td>
<td>Blood, urine, sputum cultures, serology</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hypertensive encephalopathy/Severe hypotension</td>
<td>Blood pressure monitoring</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Wernicke encephalopathy</td>
<td>Thiamine replacement, B12</td>
</tr>
</tbody>
</table>

Benedict M. Diagnosis s and management of adult patients with COVID-19 encephalopathy; consensus guidance from the Global COVID-19 Neuro Research Coalition. Submitted.
8. And other manifestations (e.g., stroke) are related with the pro-thrombotic state
How can we treat/prevent COVID?
9. The treatment is in most cases symptomatic and non-specific

- No neuro-specific RCT so far
- Solidarity and Discovery studies had negative results\(^1,2\)
- Interferon beta 1-a: Positive results in small studies and surrogate variables, not confirmed in larger studies\(^3-5\)

RCT: Randomized controlled trials

10. Vaccination may be associated with neurological manifestations

- 1 CVT per 100,000-1,000,000 non-replicant adenovirus vector-based vaccines

- 227 cases of GBS out of 51M doses of AstraZeneca vaccine

- But **COVID** is even worse:
  - RR CVT in COVID: 14.3 (95% CI: 3.9-36.8) to 1589 (95% CI: 192-5740)
  - RR Guillain-Barré syndrome in COVID: 6.30 (95% CI: 3.2-12.5)

CVT: Cerebral Venous Thrombosis, GBS: Guillain-Barre syndrome, M: Million, RR: Relative risk, CI: Confidence Interval.
WHO classification of TTS is based on the degree of certainty

WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)
Within 30 days following adenovirus vector-based immunization

WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)
Treatment of TTS

Patients should be hospitalized and closely monitored

Avoid platelet transfusions
In all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe, and platelet transfusion is required to be able to proceed with emergency surgery

Avoid heparin based anticoagulation
For individuals with TTS following vaccination with a COVID-19 vaccine

Administer non-heparin based anticoagulants
Argatroban, bivalirudin, fondaparinux, danaparoid, rivaroxaban, apixaban, dabigatran

Consider IV Immunoglobulins
1 g/kg x 2 days or 0.4g/kg x 5 days

PCR test for COVID-19
Monitor platelet count
Complete examinations per patient
Report the case

WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)
11. Care of neurological patients was severely disrupted during the pandemic

Disruptions of neurological services, its causes and mitigation strategies during COVID-19: a global review

David García-Azorín¹, Katrin M. Seeher², Charles R. Newton³, Njideka U. Okubadejo⁴, Andrea Pilotto⁵, Deanna Saylor⁶, Andrea Sylvia Winkler⁷, Chahnez Charfi Triki⁹, Matilde Leonardi¹⁰

Received: 26 April 2021 / Accepted: 29 April 2021
© The Author(s) 2021
N=105 countries
N=210,419 patients

Studies included in qualitative syntesis
(n=369)
Degree of disruption per subspecialty

N refers to the number of studies addressing each subspecialty.
Which were the most affected areas and the causes for the disruption?
Disrupted areas and degree of disruption

- Emergency and acute care (n=113)
- Investigations (n=77)
- Treatment and care (n=109)
- Neurorehabilitation (n=39)
- Service delivery (n=151)
- Promotion of brain health (n=57)
- Residents training (n=12)
- Research (n=22)

- None
- Mild
- Moderate
- Severe
<table>
<thead>
<tr>
<th>Reason of the disruption</th>
<th>Number of studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel restrictions hindering access to the health facilities for patients</td>
<td>196 (81.7%)</td>
</tr>
<tr>
<td>Closure of services or consultations as per health authority directive</td>
<td>157 (65.4%)</td>
</tr>
<tr>
<td>Decrease in outpatient volume due to patients not presenting</td>
<td>135 (56.2%)</td>
</tr>
<tr>
<td>Decreased volume of patients due to cancellation of elective care</td>
<td>109 (45.4%)</td>
</tr>
<tr>
<td>Inpatient services and or hospital beds not available</td>
<td>52 (21.7%)</td>
</tr>
<tr>
<td>Clinical staff deployed to provide COVID-19 clinical management or emergency support</td>
<td>40 (16.7%)</td>
</tr>
<tr>
<td>Unavailability or stock out of essential medicines, medical diagnostics or other health products at health facilities</td>
<td>40 (16.7%)</td>
</tr>
<tr>
<td>Insufficient PPE available for health care providers to provide services</td>
<td>22 (9.2%)</td>
</tr>
<tr>
<td>Insufficient staff to provide services</td>
<td>11 (4.6%)</td>
</tr>
</tbody>
</table>
Ok, no much literature from Africa, but what do we know?
• 43 countries participated to this survey
• Covering all the 6 WHO Regions and all income levels
Disruption of services by WHO region

![Graph showing disruption levels by WHO region](image)
Take-home messages

1. COVID is polymorph: Include it in the differential diagnosis

2. Symptoms can be related with the virus, the immune response or the presence of systemic complications

3. Work-up of patients should consider metabolic, toxic, vascular, septic and nutritional causes

4. We have to work together to answer all the remaining questions
Thank you!

Headache Unit
- Ángel Guerrero
- Álvaro Sierra
- Daniel Gil
- Blanca Martínez
- María Gutiérrez

Imaging Processing Laboratory
- Álvaro Planchuelo
- Rodrigo de Luis
- Santiago Aja

Department of Neurology
- Javier Trigo
- Enrique Martínez
- Blanca Talavera
- Alba Chavarría
- Isabel Hernández
- Gonzalo Valle
- Cristina López
- Mercedes de Lera
- Paula Simón
- Elena Martínez

Department of Radiology
- Beatriz Gómez
- María Pedraza
- Juan Arenillas

Department of Emergency Medicine
- Carlos del Pozo
- Marta Celorio

Valladolid East Primary Care Area
- Ana Alberdi
- María Blanco
- Ismael Calcerrada
- Ana Cornejo
- Miguel Cubero
- Ana Gil
- Cristina García
- Ana Guiomar Lozano
- Cristina Badillo
- Carol Montilla

Spanish Society of Neurology
- David Ezpeleta
- Jesús Porta
- Miguel Láinez

Marta Mora
- Marina Paniagua
- Carolina Pérez
- María Rojas
- Marta Ruiz
- Leticia Sierra
- María Luisa Hurtado

davilink@hotmail.com