Spectrum, risk factors, and outcomes of neurological and psychiatric complications of COVID-19: A UK-wide cross-sectional surveillance study

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A MODERN 2020 CENTENARY PERSPECTIVE ON TRAIL BLAZING PAPERS FROM THE JNNP ARCHIVE

Standing on the shoulders of giants: 100 years of neurology and epidemic infections

Harriett Van Den Tooren, 1,2 Mark A Ellul, 1,3,4 Nicholas WS Davies, 5 Ava Easton, 4,6 Angela Vincent, 7,8 Tom Solomon, 1,3,4 Benedict Daniel Michael 1,3,4 On behalf of the CoroNerve Studies Group
H1N1 Influenza Pandemic

- Prospective, 2 years, UK
- 25 cases, 21 children
- PCR+ve respiratory, none in CSF
- Children
  - 12 encephalopathy
  - 9 encephalitis
- Adults
  - 2 encephalopathy/movement dis
  - 1 encephalitis
  - 1GBS

Neurological Manifestations of Influenza Infection in Children and Adults: Results of a National British Surveillance Study

Anu Goenka,^1 Benedict D. Michael,^1 Elizabeth Ledger,^2 Ian J. Hart,^3 Michael Absoud,^4 Gabriel Chow,^5 James Lilleker,^6 Michael Lunn,^7 David McKee,^8 Deirdre Peake,^9 Karen Pysden,^10 Mark Roberts,^11 Enitan D. Carroll,^12 Ming Lin,^4 Shiveram Arul,^11 Tom Solomon,^1 and Rachel Koen^1
70-80% symptoms
≤10% syndrome
<1% hospitalised
Fig. 1. Hierarchy of diagnostic tests for defining causal relationship between a microbe and the syndrome encephalitis. * This hierarchy is not relevant for all bacteria and viruses, e.g. rabies virus. † Normally sterile site = blood, CSF, joint, pleural, or pericardial fluid.

REVIEW ARTICLE
Causality in acute encephalitis: defining aetiologies

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FOR
- Consistency
- Temporality
- Biological plausibility
- Coherence
- Experimental evidence
- Analogy

AGAINST
- Strength
- Specific
- Biological gradient
- Experimental evidence

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Phase 1: Notification (2-3 mins)

Phase 2: Case Report Form (10-15 mins)

Link to NIHR database emailed to clinicians
Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

Aravinthan Varatharaj MRCP a, b, Naomi Thomas MRCPCH c, d, Mark A Ellul MRCP e, f, g, Nicholas W S Davies PhD h, Thomas A Pollak MRCP i, Elizabeth L Tenorio PhD k, l, Mustafa Sultan c, Ava Easton PhD f, m, Prof Gerome Breen PhD j, Michael Zandi PhD n, Prof Jonathan P Coles PhD o, Hadi Manji FRCP n, Prof Rustam Al-Shahi Salman PhD f, Prof David K Menon PhD q, Timothy R Nicholson PhD i, Laura A Benjamin PhD f, n, Prof Alan Carson PhD f, Prof Craig Smith MD s, Prof Martin R Turner PhD t, Prof Tom Solomon PhD e, f, g, Rachel Kneen MRCPCH e, f, u, Prof Sarah L Pett PhD o, p, Ian Galea PhD a, b, x, Rhys H Thomas PhD c, v, x, Benedict D Michael PhD e, f, g, d, x, on behalf of the CoroNerve Study Group
Coronerve National Surveillance:
Neurological and Neuropsychiatric Complications of SARS-CoV-2 in the UK

Heatmaps Comparing Reported Neurological and Neuropsychiatric Complications of SARS-CoV-2 (left) with Total SARS-CoV-2 Cases (right)
153 rapid reports (3-week period)

28 (18%) excluded as complete case details unavailable

125 (82%) patients included for clinical case definitions
314 (91%) confirmed cases
  6 (5%) probable cases
  5 (4%) possible cases

77 (62%) with cerebrovascular event
  74 (96%) confirmed cases
  2 (3%) probable cases
  1 (1%) possible case

39 (31%) with altered mental status
  24 (88%) confirmed cases
  1 (3%) probable case
  4 (9%) possible cases

6 (5%) with peripheral disorder
  4 (67%) confirmed cases
  2 (33%) probable cases

3 (2%) with other neurological disorder
  2 (67%) confirmed cases
  1 (33%) probable case

57 (74%) had ischaemic stroke
  56 (98%) confirmed cases
  1 (2%) probable case

9 (12%) had intracerebral haemorrhage
  8 (89%) confirmed cases
  1 (11%) probable case

1 (1%) had cerebral vasculitis
  1 (100%) confirmed case

10 (13%) other cerebrovascular event
  9 (90%) confirmed cases
  1 (10%) probable case

7 (18%) with encephalitis
  7 (100%) confirmed cases

9 (22%) with unspecified encephalopathy
  8 (89%) confirmed cases
  1 (11%) probable case

23 (53%) with neuropsychiatric disorder
  39 (83%) confirmed cases
  3 (75%) probable cases
  1 (25%) possible case

4 (67%) with Guillain-Barre syndrome and variants
  3 (75%) confirmed cases
  1 (25%) probable case

2 (33%) with other peripheral disorders
  1 (50%) confirmed case
  1 (50%) probable case

10 (43%) with psychosis
  10 (100%) confirmed cases

6 (26%) with neurocognitive disorder
  4 (67%) confirmed cases
  2 (33%) probable cases

7 (30%) with other psychiatric disorder
  5 (71%) confirmed cases
  2 (29%) possible case
511 notifications

274 (54%) cerebrovascular
- 221 (80%) ischaemic
  - 38 (14%) ICH
  - 8 (3%) other
- 7 (3%) SAH
- 8 (3%) other

179 (35%) altered mental status

42 (8%) peripheral
- 18 (43%) GBS/MFS
- 2 (0.5%) NMJ
- 22 (53%) other

16 (3%) central other
- 4 (25%) ADEM
- 5 (31%) myelitis
- 7 (44%) other

96 (53%) encephalopathy / delirium

27 (15%) encephalitis / meningitis

5 (3%) seizure

51 (28%) psychiatric
- 25 (49%) psychosis
- 8 (16%) affective disorders
- 6 (12%) neurocognitive
- 4 (8%) mania
- 2 (4%) catatonia
- 6 (12%) other

THE LANCET
Neurology
CORRESPONDENCE | VOLUME 20, ISSUE 3, P172, MARCH 01, 2021
An extraordinary World Encephalitis Day
Ava Easton + Benedict D Michael
Spectrum, risk factors, and outcomes of neurological and psychiatric complications of COVID-19: a UK-wide cross-sectional surveillance study

Amy L Ross Russell¹,², #, Marc Hardwick²,³, #, Athavan Jeyanantham³, Laura M White⁴, Saumitro Deb⁵, Girvan Burnside⁶, Harriet M Joy⁷, Craig J Smith⁸,⁹, Thomas A Pollak¹⁰, Timothy R Nicholson¹⁰, Nicholas WS Davies¹¹, Hadi Manji¹²,¹³, Ava Easton¹⁴,¹⁵, Stephen Ray¹⁴,¹⁶, Michael S Zandi¹³, Jonathan P Coles¹⁷, David K Menon¹⁷, Aravindhan Varatharaj²,³, Beth McCausland²,³,¹⁸, Mark A Ellul¹⁴,¹⁶,¹⁹, Naomi Thomas²⁰,²¹, Gerome Breen²², Stephen Keddie²³,²⁴, Michael P Lunn¹²,¹³, Rustam Al-Shahi Salman²⁵, Alan Carson²⁵, Eileen Joyce¹³, Martin R Turner²⁶, Laura A Benjamin¹³,¹⁵, Tom Solomon¹⁴,¹⁷,²⁰, Rachel Kneen¹⁴,¹⁷,²⁸, Sarah Pett²⁹,³⁰, Rhys H Thomas²¹,²²,³¹, #, Benedict D Michael¹⁴,¹⁷,²⁰, #, Ian Galea²,³, #, on behalf of the CoroNerve Studies Group* *Joint Senior Author

To access paper:


Or scan here:
Characteristics

- 267 cases
  - 95 (36%) female
  - 44 (18%) from Black, Asian and Minority ethnic groups
  - 113 (42%) below 60 years
  - COVID-19 was confirmed or probable in 239 (90%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>139 (67)</td>
</tr>
<tr>
<td>Fever</td>
<td>172 (73)</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>24 (13)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>37 (22)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>26 (14)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>134 (61)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>124 (68)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (27)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>34 (18)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (21)</td>
</tr>
</tbody>
</table>
Case classification

1. Neuroanatomical
2. Pathophysiological

- 267 Cases
  - 226 Central cases
  - 41 Peripheral cases
    - 131 Cerebrovascular
    - 25 Inflammatory
    - 28 Delirium
    - 25 Primary psychiatric
    - 17 Other CNS

[Image of CoroNerve Studies Group logo]
Onset of neurological symptoms relative to first COVID symptom

66 (25%) after respiratory improvement
69 (26%) predated respiratory symptoms
Traditional diagnostic flowchart

267 Cases

226 Central cases
41 Peripheral cases

131 Cerebrovascular
25 Inflammatory
25 Primary psychiatric
17 Other CNS

105 Ischaemic event/s
21 Haemorrhagic event/s
5 Cerebral Venous sinus thrombosis
28 Delirium
19 New psychiatric diagnosis*
6 Exacerbation of psychiatric condition
4 PRES
13 Severe encephalopathy
35 Peripheral inflammatory
6 Other peripheral

5 Vasculitis
1 Meningitis
3 Encephalitis
13 Leukoencephalopathy/demyelination
3 Opsoclonus-Myoclonus syndrome/Brainstem encephalitis

4 Transient Ischaemic Attacks
54 Large vessel infarctions
8 Small vessel infarctions
20 Multivessel infarctions
7 Clinical strokes with no imaging evidence of acute infarct
12 Ischaemic strokes where imaging reports were not available.
17 Isolated haemorrhage
4 Multifocal haemorrhage
5 Cerebral Venous Sinus Thromboses

* New psychiatric diagnoses

9 Psychosis
4 Depression
2 Anxiety
4 Miscellaneous diagnoses (catatonia, mania, functional illness, and neurocognitive syndrome)
Intensive care
(65% vs 26%, p < 0.001)

Ventilation
(71% vs 28%, p < 0.001)

Neuropsychiatric complications of covid-19
From acute delirium to long term fatigue, covid-19 has serious neuropsychiatric effects
Matthew Butler, 1 Thomas A Pollok, 1 Alasdair G Rooney, 2 Benedict D Michael, 3 Timothy R Nicholson
5) Altered neurodevelopment - maternal immune activation

1) Direct viral infection - via the blood brain barrier, infected leukocytes or neuronal transport

2) Parainfectious - cytokine storm

4) Post-infectious - cell or antibody mediated

3) Acute stress response to pandemic anxiety

THE LANCET Neurology

RAPID REVIEW | VOLUME 19, ISSUE 9, P767-783, SEPTEMBER 01, 2020

Neurological associations of COVID-19

Mark A Ellul, MRCP ▪ Laura Benjamin, PhD ▪ Bhagteshwar Singh, MRCP ▪ Suzannah Lant, MBChB ▪ Benedict Daniel Michael, PhD ▪ Ava Easton, PhD ▪ Rachel Kneen, FRCPCH ▪ Sylviane Defres, MRCP ▪ Jim Sejvar, MD

Prof Tom Solomon, FRCP

Contents lists available at ScienceDirect

journals Elsevier

Minireviews

COVID-19 and psychosis risk: Real or delusional concern?

Cameron J. Watson a, b, Rhys H. Thomas c, d, Tom Solomon e, f, Benedict Daniel Michael e, f, g, Timothy R. Nicholson a, Thomas A. Pollak a

Journal homepage: www.elsevier.com/locate/neulet
13 cases of severe encephalopathy, not meeting delirium criteria

With severely reduced level of arousal

• cardiac and renal complications including cardiac arrest in adults

• seizures in older adults with significant pre-existing neurological comorbidities

• seizures and status epilepticus in younger patients with no premorbid conditions

These patients were younger and had higher in-hospital resource utilization (duration of ventilation, intensive care)
Leukoencephalopathy, or encephalitis

Pearls & Oy-sters: Leukoencephalopathy in critically ill patients with COVID-19

Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2–Related Encephalitis: The ENCOVID Multicenter Study
CVA

- 35 (27%) aged <60 years
- 10 (0-18) vs 0 (-7 to 7) days p<0.001
- Co-morbidities (67% vs 88%)
- Multi-vessel (31% vs 15%)
- Non-CNS thrombosis (18% vs 8%)
Cerebrovascular cases: younger but with similar risk factors vs historical control

Non-CNS thrombotic complications 11% vs 5%

Pulmonary, cardiac, renal artery
# Recovery: Premorbid health and age predominate

<table>
<thead>
<tr>
<th>OUTCOME VARIABLE: MRS SCORE AT OUTCOME &gt;2</th>
<th>Adjusting for diagnostic variables</th>
<th>No adjustment for diagnostic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (10-year age groups)</td>
<td>1.66 (1.23, 2.25)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Sex at birth (Male)</td>
<td>1.40 (0.61, 3.24)</td>
<td>0.431</td>
</tr>
<tr>
<td>Non-white ethnic group</td>
<td>1.73 (0.66, 4.55)</td>
<td>0.267</td>
</tr>
<tr>
<td>Clinical frailty scale (Rockwood)</td>
<td>1.48 (1.08, 2.03)</td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td>Pre-existing neurological disease</td>
<td>1.38 (0.47, 4.10)</td>
<td>0.560</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.75 (0.31, 1.81)</td>
<td>0.517</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.96 (0.36, 2.55)</td>
<td>0.928</td>
</tr>
<tr>
<td>Log&lt;sub&gt;10&lt;/sub&gt; white cell count at admission</td>
<td>6.56 (1.01, 42.53)</td>
<td><strong>0.049</strong></td>
</tr>
<tr>
<td>Cerebrovascular event diagnosis</td>
<td>2.84 (0.72, 11.22)</td>
<td>0.136</td>
</tr>
<tr>
<td>Central inflammatory diagnosis</td>
<td>1.68 (0.39, 7.33)</td>
<td>0.490</td>
</tr>
<tr>
<td>Delirium diagnosis</td>
<td>0.94 (0.24, 3.67)</td>
<td>0.932</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>0.65 (0.13, 3.26)</td>
<td>0.600</td>
</tr>
<tr>
<td>Other encephalopathy diagnosis</td>
<td>0.94 (0.16, 5.70)</td>
<td>0.950</td>
</tr>
<tr>
<td>Peripheral neuropathy diagnosis</td>
<td>2.45 (0.47,12.87)</td>
<td>0.289</td>
</tr>
</tbody>
</table>
Research Questions

What are the clinical characteristics & mechanisms of acute neurological complications of COVID-19?

Who is at risk?

What are the medium-term sequelae?

£2.3M
$3.3M
Research Question

What are the clinical characteristics & mechanisms of acute COVID-19 neurological complications?
Who is at risk?
What are the medium-term sequelae?

Aims

1. Establish clinical characteristics and routine biomarkers.
2. Identify the underlying pathogenesis.
3. Determine the role of biomarkers of CNS injury.
4. Determine if similar, but milder, complications exist in community cases.*

Over-arching hypothesis:

Markers of CNS inflammation, injury, and genetic risk will identify mechanisms of these acute complications and sequelae; providing targets for therapy.

*Already funded
Conclusions

• COVID-19: Broad spectrum throughout the nervous system

• Outcomes vary between disease groups and pre-COVID status
  • A severe encephalopathy associated with requiring intensive care and ventilation
  • Large and multi-vessel stroke
    • Young people; Often with non-CNS thrombotic disease and requires further study

• Conventional, modifiable risk factors
  • Potential for public health intervention

• Clinical data, biomarker, neuroimaging
  • Stratified to targeted existing or novel therapeutics

• Unanswered questions
  • Working together
Dr Laura Bricio-Moreno PhD
Post-Doctoral Research Fellow
Harvard
Chemokines in HSVE

Dr Yoshi Miyabe MD, PhD
Post-Doctoral Researcher
Nippon, Tokyo
Chemokines in HSVE and CNS Vasculitis

Dr Mark Ellul MRCP
PhD Fellow
UoL
Host Immunity in AE

Cory Hooper MSc
PhD Student
Cognitive encephalitis

Dr Harriet Van der Tooren MBChB
AFP
UoL
Outcomes in encephalitis

Dr Krishanthi (Kris) Subramaniam
Post-Doctoral Researcher
UoL
Modelling COVID

Dr James Mitchell MBChB
ACF
Seizures in encephalitis

Dr Marta Frackowiak MSc, MBChB
SHO
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Cochrane Epilepsy

Dr Ashik Babu MBChB
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BBB model of encephalitis

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Sydney Medical School
Stroke Fellow

Dr Julie Phukan MRCP
Consultant Neurologist
UCL
Public engagement

Dr Viraj Bharambe MD
SpR Neurolog
Walton Centre
Functional

Dr Dean Walton MBBS
Neurology Registrar
NW Deanery

Mr Sumirat Keshwara
MPhil Neurology student
NW Deanery
Thank you

@BenedictNeuro

The Academy of Medical Sciences

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Wellcome

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National Institute for Health Research