COVID-Neuro Network

COVID Neuro systematic review and individual patient data meta-analysis

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Neurological Associations of COVID-19
Narrative Review

Recent review paper - accepted by The Lancet Neurology
• Descriptive review of neurological manifestations/ syndromes reported in patients with COVID-19
  • Meningitis, encephalitis and encephalopathy, myelitis, ADEM, Stroke, GBS and variants
  • Many individual case reports, some larger studies
  • Some reports with high level of detail, others less so
  • Outcome data frequently not reported
  • Heterogeneity

How can we better describe and compare these patients?
Meta-analysis

- Statistical technique for combining sources of quantitative evidence
- **Meta-analyses are traditionally performed with aggregate data (AD)**
  - Summary statistics (mean differences, event counts, odds ratios, hazard ratios etc.) extracted from published journal articles, conference abstracts, trial registries
  - Unpublished documentation also used, such as protocols, statistical analysis plans, clinical study reports
  - Numbers of events and relative effects overall
What others are doing....

• Systematic reviews and meta-analysis in neurological disease and COVID-19

• Some will review neurological disease, some looking at stroke, GBS, meningoencephalitis

• Prospero (international systematic review register)- 92 studies registered, none that describe analysis of individual patient data, studies as unit of analysis
Alternative: Individual patient data (IPD) approach

• Original patient level data is requested and re-analysed
• Regarded as the ‘gold-standard’ approach to meta-analysis
• Many advantages
  • Allows a more flexible and complex analysis approach
  • May be the only option if summary data is not available
• Often used to guide diagnosis (e.g. imaging modalities) and treatment decisions (steroids, chemotherapy, antibiotics, anti-malaria, stroke)
• Also focus on epi and clinical description in specific disease

Lancet Neuro 2010
Data from 2029 patients from five trials

Lancet Psych 2018 - 24 patients from 333 studies
Alternative: Individual patient data (IPD) approach

• Inclusion of published or unpublished data in analysis

• Aim to involve many partners globally

• Inclusion of those who contribute data as named co-authors
COVID Neuro Meta-analysis

Investigation of neurological associations of COVID-19 by analysing pooled individual patient data in a meta-analysis to:

• Characterise the spectrum of neurological associations of COVID-19

• Determine factors that impact on outcome in cases with neurological features

• Look at risk factors for development of neurological disease in COVID-19
Research questions to be answered

In patients with neurological disease and COVID-19 (principal focus)
• To characterise the spectrum of neurological disease reported to be associated with COVID-19: proportions of total patients with each syndrome.
• To identify if there are factors associated with outcome in neurological disease linked with COVID-19, including admission to critical care, mortality and sequelae at discharge.

In all COVID-19 patients (if possible)
• To estimate the proportion of patients who had an acute neurological presentation in COVID-19 - out of all COVID-19 patients
• To identify if there are factors associated with presence of neurological disease in patients with COVID-19
Conducting the meta-analysis

- Systematic search of the literature
- Approach authors of published studies on COVID-19 and neurological disease and other prominent researchers in relevant areas
- Invite them to register their interest to participate & contribute data
- Sending and signing of data sharing agreement
- Inputting of collected data into COVID Neuro Network data collection tool
- Login and password to secure server for upload of data
- Data cleaning and harmonization
- Analysis
- Write up
Conducting the meta-analysis

- Registration of interest:
  https://www.surveymonkey.co.uk/r/GPY5RH3

- Data sharing
  All variables of interest included in the COVID Neuro Network Case Record Form
Conducting the meta-analysis - Case definitions

Neurological disease syndromes

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<th>WHO COVID-19 Definitions, adapted</th>
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<tr>
<th>Confirmed</th>
<th>Probable</th>
<th>Suspected</th>
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<tr>
<td>A person with laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical presentation, which may include a nucleic acid amplification test (e.g., RT-PCR) or validated antibody test.</td>
<td>A suspected case, for whom testing for the COVID-19 virus is inconclusive.</td>
<td>A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory distress) AND having been in contact with a confirmed or probable case in the last 14 days prior to symptom onset. OR A suspected case, for whom testing could not be performed for any reason. OR A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory distress) AND in the absence of an alternative explanation that fully explains the clinical presentation.</td>
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**Encephalitis**

- Suspected encephalopathy with no other diagnosis apparent, but does not fulfil level 3 criteria
- Acute or sub acute (<4 weeks) alteration in consciousness, cognition, personality or behaviour persisting for more than 24 hours
- Absence of an alternative diagnosis for symptoms

- New onset seizure
- New focal neurological signs
- FEVER (≤ 38°C)
- Movement disorder (includes: Parkinsonism, oromotor dysfunction etc.)
- EEG consistent with focal abnormalities
- CSF total white cell count > 5 cells/mm³
- Confirmation of brain inflammation on brain biopsy

- Level 1 Encephalitis
- Level 2 Possible encephalitis
- Level 3 Encephalopathy
- Suspected encephalopathy

Provisional Timeline (up for discussion)

- Data sharing by 24\textsuperscript{th} June 2020
- Window open until 1\textsuperscript{st} July
- Data cleaning and analysis – July
- Publication!
Thank you for attending

sign up here: https://www.surveymonkey.co.uk/r/GPY5RH3