Defining causality in COVID-19 and neurological disorders

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When faced with acute neurological presentations in a patient with COVID-19, how confident can one be that SARS-CoV2 is causal?

Introduction

Clinicians are increasingly recognising neurological presentations occur in some patients.[1] A case series from Wuhan described associated neurological syndromes (eg, 'dizziness' and 'impaired consciousness'), but with little detail regarding symptomatology, and cerebrospinal fluid (CSF) and neuroimaging findings.[2] The extent to which these disorders were caused by the virus per se, rather than being complications of critical illness, unmasking of degenerative disease, or iatrogenic effects of repurposed medications is not clear.

Numerous case reports have since emerged and, at the time of writing, published cases include encephalopathy,[3] encephalitis,[4] Guillain-Barré syndrome (GBS)[5] and stroke.[6] In most of these cases, the virus has been identified in respiratory samples, and in a small number in CSF. So far, the reporting of clinical features has been extremely variable, for example, several cases have claimed to report encephalitis without clear evidence of central nervous system (CNS) inflammation, which would not meet established definitions of the disease.[7]

Whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is associated with neurological manifestations is of critical importance as this may result in substantial morbidity and mortality.

Defining causality

It is crucial that neurologists and neuropsychiatrists apply a systematic strategy to determine whether there is evidence that SARS-CoV2 is causing these manifestations, whether they are a consequence of severe systemic disease alone, or simply coincidence. In 1965, Hill proposed criteria on which to build an argument for disease causation, which can be applied to COVID-19.[8]

What is the *strength* of the association? So far, it appears fairly weak. >2.5 million people have been infected with SARS-CoV2 and to date (to the authors' knowledge) there have been only 93 published cases of neurological manifestations (about 5/100 000). However, reported cases are an underestimate of the real incidence, and this underscores the need for proper epidemiological study.

What is the *consistency* of the association? So far, there have been published reports of neurological manifestations across the globe, including from China, Japan, Italy, France, the USA and the UK. Although the numbers are low, these are not isolated incidences and have occurred throughout the evolution of the pandemic.

To what extent is the relationship *specific*? The range of neurological manifestations reported in association with SARS-CoV2 is wide, from the CNS through to peripheral nerves. However, in previous pandemics, similar central and peripheral associations have been well recognised.[9]

What can *temporality* tell us about the association? The delay between infection and the neurological presentation may give a clue to mechanisms. Direct CNS infection might be expected to be contemporaneous with, or shortly after, fever and respiratory symptoms. Parainfectious disease, owing to innate immune responses, such as acute necrotising encephalopathy, usually occurs in the days following infection. Post-infectious syndromes, due to adaptive immune responses, such as GBS, are typically in the few weeks following infection. In most reported cases, respiratory disease has occurred a few days prior to the onset of the neurological syndrome although significant delays between a neurological presentation and COVID-19 diagnosis in some raise the possibility of nosocomial infection.

Hill asks us to look for a *biological gradient*. In general, those with neurological manifestations have had severe COVID-19 respiratory disease suggesting the possibility that higher viral loads and/or more fulminant inflammatory responses may be accountable for both.

Is there *biological plausibility*? Many human viruses can enter the CNS and some coronaviruses exhibit neurotropism in animal models.[10] The syndromes described so far could plausibly be related to primary infection with SARS-CoV2, although improved understanding of host responses is needed.

Hill asks us to consider the *coherence* of the evidence. Perhaps our best sources of coherent data are the SARS and Middle East respiratory syndrome (MERS) epidemics: coronaviruses with about 80% and 50% homology to SARS-CoV2, respectively. Neurological syndromes were reported in association with both, including acute disseminated encephalomyelitis-like presentations with MERS and encephalopathy/encephalitis with SARS.[11]

Is there any possibility of *experimental evidence*? The ideal investigational vehicle would be a case control study, but this presents design challenges as exposure is high and we do not yet have validated widespread antibody testing to ascertain seroprevalence.

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Can we learn by *analogy* with other similar scenarios? Other respiratory viruses, most notably influenza, are well-established triggers of CNS damage. During the H1N1 pandemic, neurological syndromes were well described, including acute necrotising encephalopathy bearing striking resemblance to the case recently described with COVID-19.[9] So, the emergence of neurological disorders associated with pandemic viral infections is less the exception, and more the norm.

Conclusions

As always, our evidence must be founded on clear and systematic assessment of the clinical syndromes, supported by well-designed laboratory studies. Cases must be reported in line with clear clinical case definitions, both systematically and transparently, and with honesty about negative or missing results.

These aims are best served by standardisation and centralisation of case reporting, which calls for a truly collaborative approach between neurologists, neuropsychiatrists and allied colleagues.

To address this, we have established the CoroNerve Studies Group as a collaboration between professional bodies in the UK (CoroNerve.com), and similar studies are underway in other countries. However, a joined-up international approach is necessary. To begin this process, a complimentary initiative, the COVID-Neuro Network, through Brain Infections Global, is supporting collaboration among several lower and middle-income countries.

We all must learn the lessons from previous pandemics, and the principles of Bradford Hill if we are to translate these rapidly growing datasets into meaningful advances in our understanding of the neurological complications of COVID-19.

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