2019-NCoV: What Every Neurologist Should Know?

Nitika Mahajan, Monika Singla, Balveen Singh, Venkatesh Sajja, Parth Bansal, Birinder Paul, Parveen Goel, Rahul Midha, Rajinder Bansal, Gagandeep Singh

Department of Neurology, Dayanand Medical College, Ludhiana, Punjab, India

Abstract

The 2019 novel Corona Virus pandemic beginning from Wuhan, China primarily affects the respiratory tract but its has impacted clinical practice across a range of specialities including neurology. We review the bearing of the 2019 NCoV infection on neurological practice. Neurological manifestations are less common than respiratory manifestations, yet conspicuous, affecting nearly over a third of hospitalized individuals. These may be classified in to early – headache, dizziness, hyposmia and hypogeusia and late – encephalopathy. Rarely but surely, a very small proportion of infected individuals might present with stroke. Certain neurological conditions, including cerebrovascular disease in both China and Italy and dementia in Italy predispose to infection and more severe manifestations, requiring intensive care unit admission. There is no convincing evidence that the manifestations, course and outcome of various neurological disorders is impacted by 2019 nCoV infection. Concerns of an increased risk of febrile seizures offset by a reduced frequency of infection in the paediatric age group. Individuals with multiple sclerosis might potentially experience both true and pseudorelapses. Besides a direct effect, 2019 nCoV has tremendously affected neurological care by disrupting the continuity of care and the availability of neurological medicines worldwide. Neurologists should respond to this challenge by developing and sustaining innovative methods of providing care as well as alerting the society at large to adopt measures to contain the spread of 2019 nCoV.

Keywords: Epilepsy, headache, multiple sclerosis, 2019 novel Corona Virus, neurological manifestations, stroke

INTRODUCTION

In early December 2019, several unexplained cases of febrile illness with upper and lower respiratory symptoms including pneumonia were reported from Wuhan, China.[1] The epidemic has since spread to much of the world, having been labelled as a pandemic with over 1.3 million confirmed cases and 74,000 deaths worldwide (as on April 07, 2020). The agent responsible for this outbreak has been confirmed to be a novel coronavirus (2019 novel coronavirus, 2019-nCoV).[2] Similar coronaviruses have been reported to be responsible for symptoms resembling Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndromes (MERS) in 2003.[3,4] Much of the pathophysiology of manifestations of 2019-nCoV infection has been attributed to interaction with the angiotensin-converting enzyme 2 (ACE2) receptor, ubiquitously distributed across many human tissues including the nervous and musculoskeletal systems.[5,6] A report from Wuhan in China described fever in over two-thirds, dry cough in half and anorexia in over a third of the 214 hospitalized patients of 2019-nCoV infection.[7] Coronaviruses can however cause multiple systemic infections in animals.[8,9] The brunt of the 2019-nCoV disease is borne by the respiratory system but reports of the epidemic from China distinctly bring out nervous and musculoskeletal symptoms and signs in a fair proportion.[7,10-13] This, added to the scale of the pandemic, invariably means that the neurological practice is likely to be severely impacted as a result of 2019-nCoV infection. An overwhelming of intensive care units and of intensive care health workers as well as efforts to contain the pandemic have obligated of neurologists from curtailing routine health care facility visits of their patients, thereby disrupting their continuity of care to even redeployment in other departments to make up for the shortage of intensivists. Neurologists should therefore be apprised appropriately of 2019-nCoV infection for the benefit of the patient community as well as their own professional advantage. Here, we review aspects of 2019-nCoV that might be relevant to neurological practice.

METHODS

One of the authors searched PubMed on March 22, 2020 for titles with the search terms, “COVID-19” OR “Corona virus” AND (later added) encephalitis, paediatric encephalitis, seizures, epilepsy, demyelination. Abstracts of all unduplicated papers were reviewed. Abstracts describing neurological and musculoskeletal manifestations, comorbidities, complications and investigations were segregated. Full papers of all such abstracts were retrieved and reviewed [Figure 1].
Results

Neurological manifestations of 2019-nCoV infection

There were 13 abstracts with reports of neurological manifestations. In these abstracts, neurological manifestations could involve the central nervous system, the peripheral nervous system and musculoskeletal system (Table 1).[7,10-13] Broadly, some of the central nervous system manifestations, e.g. headache and dizziness and peripheral nervous system manifestations, e.g. hyposmia and hypogeusia occurred early, while encephalopathy with varying grades of altered sensorium and irritability occurred later, and in more severe illness, perhaps as a feature of multiorgan dysfunction. Some recent reports have emphasized hyposmia as a presenting manifestation of COVID-19 infection.[7,10-13]

Overall, neurological manifestations were observed in 36% of the large series of 214 hospitalized patients from Wuhan, China.[7]

The occurrence of myalgia indicative of muscle inflammation and perhaps necrosis was emphasized in many reports.[7] Infected individuals with evidence of muscle injury had higher neutrophil counts, lower lymphocyte counts and higher C-reactive protein levels and D-dimer levels. In addition, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels and serum creatinine levels were increased in the subgroup with muscle injury.[7,10-13] Another report drew attention to the occurrence of stroke during the acute phase of illness.[14] Among 221 infected individuals from an admission facility, 11 suffered from an occlusive stroke, and one each from cerebral venous sinus thrombosis and haemorrhagic stroke.[14] Taken as a group, infected individuals experiencing stroke were older, more likely to have cardiovascular risk factors and to present with serum inflammatory and coagulation markers (e.g. C-reactive protein). Lastly, isolated case reports describe an encephalopathic presentation of 2019-CoV infection.[15]
**Late-breaking Note:** Since the original submission of this manuscript, a case of acute necrotising encephalitis in confirmed 2019-nCoV infection has been reported. Lay reports from Italy describe a range of neurological manifestations, though other experts believe that these are cases of neurological comorbidity. Cases of Gullian Barre Syndrome, post-infection have been seen in Italy (Perrucca E., Italy, personal communication) and worsening of clinical status in people with myasthenia gravis, leading to myasthenic crisis have been abundantly encountered (Sethi, N., New York, USA, personal communication) but no formal reports can be found in published literature.

**Evidence for direct CNS involvement**

During clinical illness, the 2019 nCoV agent has been isolated using reverse transcriptase polymerase chain reaction from nasopharyngeal swabs. Other samples include bronchoalveolar lavage specimens and stool samples. So far, the virus has not been isolated from cerebrospinal fluid. Of note, however, is the fact that other coronaviruses have been isolated from nervous tissue in animals. It remains conjectured at this point, however, whether the virus would enter the cerebrospinal fluid compartment in an individual with nasopharyngeal skull base defect and acute 2019 nCoV infection.

**Premorbid neurological conditions**

The presence of premorbid neurological conditions are relevant to 2019 nCoV infections in two ways: (1) Certain premorbid neurological conditions might predispose to 2019 nCoV infection or in individuals with 2019 nCoV to more severe manifestations; (2) The occurrence of 2019 nCoV infection modifies the manifestations, course or outcome of the premorbid neurological illness. Although 2019 nCoV infection can occur in any age group, people over 50 years are most often affected with the majority of hospitalized cases being over 60 years of age. Stroke along with other cardiovascular conditions were identified as premorbid conditions predisposing to 2019 nCoV infection. Moreover, 2019 nCoV-infected individuals with premorbid cerebrovascular disease are predisposed to more severe illness, requiring admission to the intensive care unit. Conversely, we did not find any evidence to suggest that 2019 nCoV illness modifies the manifestations, course and outcome of pre-existing neurological conditions.

**DISCUSSION**

Although the major focus of 2019 nCoV infection is on respiratory manifestations with both the earliest and most severe symptoms being referred to the respiratory system. Neurological manifestations, however, are by no means insignificant, substantiated by thorough analyses of large numbers of patients from China. Perusal of literature reveals that neurological manifestations might be classified in to early and late. Awareness of these neurological features should be useful not only for neurologists but also for general physicians, internists, intensivists and respiratory physicians, who are likely to encounter atypical cases. More pertinent, however, is the predisposition to 2019 nCoV infection in people with premorbid cerebrovascular disorders. The latter in conjunction with hypertension, diabetes and immunologically compromising conditions increase the risk to acquire 2019 nCoV infection. Not only are premorbid cerebrovascular disorders risk factors for infection, these are associated with more severe infections, and also predict the need for intensive care. Poor general health associated with neurological premorbidity might be one of the reasons for the predispositions. Another reason might be the altered interaction with angiotensin converting enzyme receptors induced by various antihypertensive medications, so often administered in people with cerebrovascular disease that might lead to more severe manifestation of 2019 nCoV infection. Very recent data from a subsample of 335 individuals infected in Northern Italy, nearly 7% had pre-existing dementia and 10% had a prior stroke. 2019 nCoV infection might potentially alter the manifestations of comorbid chronic neurological disorders. Neurologists should be mindful of these potential disease-disease interactions. A compilation of such interactions, each specific for different neurological disorders and based on expert opinion alone for want of documented evidence is provided below.

**Multiple sclerosis**

No reports of concomitant or subsequent acute demyelinating disorders or precipitation of multiple sclerosis relapses surfaced from China in the aftermath of the Wuhan epidemic. The precipitation of acute disseminated encephalomyelitis or similar illnesses, however still remains a concern. Also pertinent to consider is the temporary worsening during fever, of neurological status in individuals with multiple sclerosis with residual deficits or progressive forms of multiple sclerosis. Patients with multiple sclerosis may be warned of these phenomena, known as pseudo-relapses, and should perhaps be reassured that the neurological worsening would resolve as fever lessens. Another concern expressed by experts is the potential worsening of fatigue and muscular weakness because of myalgias and muscle necrosis associated with 2019 nCoV infection.

**Epilepsy**

Until now, there is no evidence of a direct effect of 2019 nCoV on seizures and epilepsy. Personal communication to one of the authors from neurologists in China confirms that, apart from rare seizures, there was no apparent worsening of seizure control in people with epilepsy during the Wuhan epidemic (Ding Ding, personal communication). The occurrence of febrile seizures in association with related viruses, Cov-HKU1, HCoV-NL63 and HCoV-OC43 has been previously reported. One redeeming aspect of the 2019-nCoV infection is that does not seem to considerably affect the paediatric population. In both Wuhan, China and Italy, about or less than one percent in published reports were in the paediatric age group. Hence, the occurrence of febrile seizures might not be a concerning aspect of 2019-nCoV.
infection. Of potential concern though is the worsening of seizure control with fever and systemic illness in certain types of epilepsies, or due to drug interactions, stress or simply due to the unavailability of anti-seizure medications. People with epilepsy are required to be counselled on all the above aspects.

**Stroke**

Other aspects of stroke care might be impacted during a 2019 nCoV infection epidemic. As routine consultations and care are reduced or stopped, there is a possibility of worsening of neurological status due to lack of physical therapy and ongoing rehabilitation services. The unavailability of routine anticoagulation assay testing during the epidemic might lead to increased risk of stroke, both haemorrhagic and occlusive due to inappropriate dosing without INR guidance.

**Neurodegenerative disorders**

How intercurrent 2019 nCoV illness would affect the course and outcome of several neurodegenerative disorders, including Alzheimer’s disease, Parkinson’s Disease or Motor Neurone Disease is not known but an area for future research among survivors of the 2019 nCoV epidemic.

**Obligations of the neurologist**

The 2019 nCoV pandemic being a time of great uncertainty has presented unprecedented challenges to the neurological community. Professionals in neurological care including clinicians, neuropsychologists, neurophysiotherapists and neuropsychology technicians may have to deliver care under demanding circumstances with limited resources that are vital to their effective functioning. The dire shortage of personal protective equipment is one such example. Neurologists should certainly comply with administrative directives to halt routine outpatient care, yet at the same time, be involved in the continuity of care of their patients. This will require innovative methods of care provision. Tele-medicine is a great option and in hospitals in western countries, where it has already been operational, is providing a crucial alternative to face-to-face consultations. However, tele-medicine facilities are rather underdeveloped in our country. That being said, this is a great opportunity for policy-makers to accelerate the pace of development of tele-medicine in India. In the interim, neurologists should consider carefully offering telephonic consultations and in these consultations emphasize continuity of care for people with chronic neurological disorders. Needless to add, neurologists should be committed to promote health and should heed and promote all public health recommendations for the containment of 2019 nCoV. It is also possible that neurologists might have to be redeployed to other departments for providing patient care, should the 2019 nCoV infection epidemic acquire unprecedented scale.

Lastly, there is hope that the world would be able to surmount this unprecedented challenge, and the neurological community is firmly behind the entire healthcare fraternity in the belief that “the world will emerge from the crisis as a stronger and better place to live in!”

**List of abbreviations**

nCoV = novel coronavirus  
SARS = Severe acute respiratory syndrome  
MERS = Middle-east respiratory syndrome  
ACE2 = angiotensin converting enzyme-Type 2

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Kaplan EH. Containing 2019-nCoV (Wuhan) coronavirus. Health Care Manag Sci 2020. doi: 10.1007/s10729-020-09504-6.
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-273.
3. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 2016;24:490-502.
4. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). November, 2019. Available from: https://www.who.int/ emergencies/mers-cov/en/.[Last accessed on 2020 Jan 19].
5. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. bioRxiv 2020. doi: 10.1101/2020.01.26.919985.
6. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.
7. Guan WJ, Ni ZY, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
8. Marc D, Dominique JF, Élodie B, Jessica D, Mathieu P, Helene J, et al. Human coronavirus: Respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neuroviral agents. In: Sunit KS, Daniel R, editors. Neuroviral Infections: RNA Viruses and Retroviruses. Florida Boca Raton: CRC Press; 2013. p. 93-122.
9. Arabi YM, Bakhly HH, Hayden FG, Bouchema A, Luke T, Baillie JK, et al. Middle East respiratory syndrome. N Engl J Med 2017;376:584-94.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
11. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa270.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020. doi: 10.1001/jama.2020.1585.
13. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa272.
14. Yanan Li, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study (3/3/2020). Available from: SSRN: https://ssrn.com/abstract=3550025.
15. Filatov A, Sharma P, Hindi F, Patricio S. Neurological complications of coronavirus disease (COVID-19): Encephalopathy. Cureus 2020;12:e7352.
16. Poyiadji N, Shahn G, Nourjaim D, Stone M, Patel S, Griffit B. COVID-19—associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. 2020. Available from: https://doi.org/10.1148/radiol. 2020201187.
17. Talan J. COVID-19: Neurologists in Italy to colleagues in US: Look for poorly-defined neurologic conditions in patients with the
coronavirus. Neurology Today. Available from: https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=920. [Last accessed on 2020 Apr 04].

18. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis. Int J Infect Dis 2020. doi: 10.1016/j.ijid.2020.03.017

19. Lau SKP, Woo PCY, Yip CCY, Tse H, Tsoi HW, Cheng VC, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. J Clin Microbiol 2006;44:2063-71.

20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.

21. Onder G, Rezza G, Brusaferro S. Case-Fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020. doi: 10.1001/jama.2020.4683.

22. Ling M, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: A retrospective case series study. medRxiv. doi: https://doi.org/10.1101/2020.02.22.20026500.