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Neuropsychiatric aspects of COVID-19 pandemic: A selective review

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ABSTRACT

Corona virus disease (COVID-19) has been declared as a controllable pandemic by the World Health Organization (WHO). COVID-19 though is a predominantly respiratory illness; it can also affect brain and other organs like kidneys, heart and liver. Neuropsychiatric manifestations are common during viral pandemics but are not effectively addressed. Fever and cough are common symptoms only in infected individuals but headache and sleep disturbances are common even in uninfected general public. In this selective review, the authors report the available evidence of neuropsychiatric morbidity during the current COVID-19 crisis. The authors also discuss the postulated neuronal mechanisms of the corona virus infection sequelae.

1. Introduction

China had reported to the World Health organization (WHO) on 31st December 2019 about the outbreak of a novel corona virus (n-CoV) causing pneumonia in adults in the city of Wuhan in Hubei province. Since then the virus had spread to various countries across the globe including India and WHO had declared the illness as a controllable Pandemic. The identified virus is named as SARS-CoV-2 and the illness caused by the virus is named corona virus disease 2019 (COVID-19). As on 8th May 2020, more than 4 million + laboratory confirmed cases are reported across the world and more than 270,000+ persons had succumbed to the illness. On the same date, India had reported around 60,000+ confirmed cases and 1800+ deaths (www.mohfw.gov.in).

A meta-analysis conducted on the studies from the current outbreak had suggested that fever (88 %) and cough (58 %) are predominant complaints and overall 20 % of the infected individuals needed intensive care unit admission (Rodriguez-Morales et al., 2020). Hypertension (17 %), diabetes (8%) and cardiovascular diseases (5%) were common co-morbidities (Yang et al., 2020a). Bilateral pneumonia on chest radiograph (ground glass pattern) (73 %), decreased albumin (78 %), High C-reactive pattern (58 %), high lactate dehydrogenase (57 %) and lymphopenia (43 %) were the prevalent laboratory findings (Rodriguez-Morales et al., 2020). Early reports on case fatality rates varies widely between 0.15 % and 5 % (Yang et al., 2020b). Though emerging reports are reassuring, it is important to note that not all the countries across the world are adequately enabled to provide effective responses against the virus (Kandel et al., 2020; Tandon, 2020). Global coordination is important to provide a coherent response to this

challenge (Tandon, 2020). It is essential to understand the varied presentation of this illness to equip oneself to handle the potential crisis. In this selective review, the authors present the neuropsychiatric manifestations and postulated mechanisms of COVID-19.

2. Methodology

The authors searched PUBMED and EBSCO independently with the following search terms “COVID-19” “AND”, “Neurology”, “Mental health”, “Neuropsychiatry”, “Delirium” and “Psychosis”. The authors identified 188 manuscripts. The search was restricted to manuscripts in English language and time (till May 8th 2020). After removing duplications, review articles, commentaries, opinion letters and manuscripts not relevant to neuropsychiatry, animal studies, and other newer manuscripts from cross-references were added and the total unique manuscripts identified for the final review were “12”. Synthesis of information from these manuscripts is provided below.

3. Postulated mechanisms

Neurological manifestations could be secondary to direct neuroinvasion by the corona virus. Similar to many respiratory viruses, Corona viruses are observed to have direct effects on neuronal systems (Desforges et al., 2014, 2019; Natoli et al., 2020). The spread could happen through haematogenous route but most commonly reported entry is through the olfactory neural pathway (Wu et al., 2020). This invasion could result in meningitis, encephalopathy or at minor instances seizures (Desforges et al., 2019; Zhou et al., 2020). Direct

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invasion might be possible through the activation of Angiotensin Converting Enzyme 2 (ACE-2) receptor expressed in both capillary and neuronal endothelium (Wu et al., 2020; Hamming et al., 2004). Secondary immune alterations are hypothesized to underlie the chronic neuropsychiatric sequelae (Severance et al., 2011; Qin et al., 2020; Needham et al., 2020). Dysregulated immune response that might result in excessive inflammation is postulated to play an important role in the severity of the infection (Qin et al., 2020; Toljan, 2020). Possible direct medullary neuron destruction might precipitate respiratory failure in severely ill patients (Li et al., 2020a; Tassorelli et al., 2020). Altered sensorium or delirium might be secondary to direct neuroinvasion by virus, central immune activation, secondary to multi organ failure, hypoxia, metabolic derangements and treatment related (Wu et al., 2020; Kotfis et al., 2020). Additionally, patients also exhibit increased prothrombin time and coagulopathy that ultimately might contribute to thrombosis or hemorrhage (Wang et al., 2020).

Stress during virus outbreak is postulated to activate hypothalamo-pituitary-adrenal axis releasing increased levels of steroids. Steroids released impairs the immune system functioning and might precipitate the infection or worsen the severity. Viral infection further leads to neurasthenia and chronic fatigue. Psychiatric symptoms could also manifest secondary to side effects of drugs used to treat COVID-19 like oseltamivir, corticosteroids and interferons (Russell et al., 2020; Ueda et al., 2015; Haque and Nizami, 2017). A pharmacovigilance study had reported significant neuropsychiatric adverse effects like amnesia, delirium, hallucinations, depression and loss of consciousness associated with exposure to chloroquine (Sato et al., 2020). Chloroquine and other antiviral drugs can cause toxic neuropathy and myopathy (Cortegiani et al., 2020; Guidon and Amato, 2020).

4. Neurological manifestations

SARS-CoV-2 virus is primarily a respiratory virus that has a predilection towards lower respiratory tract. Though the most common presentation is a self limiting viral illness with fever and dry cough, severe infection is reported in 15–20 % of the affected population (Wu and McGoogan, 2020). Lungs are involved in more than two-thirds of patients with severe infection. Pneumonia with ground glass opacities in middle and lower lobes of lungs are reportedly characteristic of the infection. In about 5% of the severely ill patients, Acute Respiratory Distress Syndrome (ARDS), Multi organ involvement and septic shock leads to further clinical deterioration. Case fatality rate ranges between 2–3 % and elderly individuals with medical co-morbidities are more vulnerable to develop fatal illness (Wu and McGoogan, 2020). Other organs involved include but not limited to kidneys, liver and heart. These organs are involved in about 15–30 % of severely ill patients (Yang et al., 2020c).

Headache and myalgia are commonly noted in COVID-19. In mild to moderate infection, headache, altered smell and taste, cough, asthenia and myalgia are the most common symptoms (Lechien et al., 2020a). There are reports of encephalopathy (Filatov et al., 2020), encephalitis (Wong et al., 2020), meningitis (Yin et al., 2020), stroke (Gonzalez-Pinto et al., 2020; Beyroufi et al., 2020; Avula et al., 2020; Li et al., 2020b), seizures, dysexecutive syndrome, neuromuscular disorders, Guillain Barre syndrome and other neuropathies. Neurological manifestations are reported in one hospital based study from China (Mao et al., 2020). 78 out of 214 admitted patients (36 %) were identified to exhibit one or more neurological symptoms. Such presentations were analyzed broadly under illness effects on central nervous system, peripheral nervous system and musculo-skeletal system. Central nervous system symptoms include dizziness (16 %), headache (13 %), altered sensorium (8 %) and cerebro vascular events (3 %). Reduced taste (5 %) and reduced smell (5 %) perceptions are peripheral nervous system manifestations. Myalgia with significant muscle injury happened in 12 % of admitted patients (Mao et al., 2020).

A multicentre European study had reported olfactory and gustatory

dysfunction in 85 % and 88 % of mild/moderately ill patients respectively (Lechien et al., 2020b). Smell and taste disorders were reportedly more common in COVID-19 patients than in influenza (Beltran-Corbellini et al., 2020). Acute brainstem dysfunction has been reported during the 2nd week of COVID-19 illness (Wong et al., 2020). Aberrant immune response to COVID-19 might lead to neuro-ophthalmological manifestations like Miller-Fisher Syndrome and polyneuritis cranialis (Gutierrez-Ortiz et al., 2020; Dinkin et al., 2020). Acute polyradiculopathy (Guillain Barre Syndrome –GBS) has been reported related to SARS-CoV-2 infection (Padroni et al., 2020; Alberti et al., 2020; El Otmani et al., 2020; Camdessañe et al., 2020; Zhao et al., 2020; Sedaghat and Karimi, 2020). Another study from China had showed that among the deceased patients, 22 % had altered sensorium and 20 % exhibited features of hypoxic encephalopathy (Chen et al., 2020).

5. Neuropsychiatric sequelae

The neuropsychiatric sequelae of currently evolving COVID-19 pandemic are still unclear. However, there is a growing concern about a crashing wave of neuropsychiatric burden (Troyer et al., 2020). Such neuropsychiatric manifestations include encephalopathy (Ye et al., 2020), delirium (Moriguchi et al., 2020; Poyiadji et al., 2020; Alkeridy et al., 2020; Duong et al., 2020), mild cognitive impairment (Helm et al., 2020), mood swings (Yin et al., 2020), insomnia (Hao et al., 2020a, 2020b), suicide (Valdes-Flórido et al., 2020) and psychosis (Troyer et al., 2020; Valdes-Flórido et al., 2020; Huaraya-Victoria et al., 2020). Existing evidence suggest 0.9–4 % of infected individuals develop psychotic spectrum disorders. Psychosis may be secondary to viral illness, treatment provided and increased psychosocial stress during pandemics (Brown et al., 2020). Neuropsychiatric sequelae of COVID-19 are discussed in Table 1.

6. Psychotropic drugs usage

Patients with pre-existing mental illness who develop COVID-19 and individuals developing mental health concerns during the pandemic are advised to be treated with psychotropic drugs along with the standard treatment for the viral illness. The following drugs are suggested as safe considering the tolerability and minimal drug interactions: Benzodiazepines (oxazepam and lorazepam), antidepressants (citalopram and escitalopram), antipsychotics (olanzapine) and mood stabilizer (valproate) (Zhang et al., 2020). Delirium is one of the atypical presentations of the COVID-19 illness (Alkeridy et al., 2020). In most instances, delirium is poorly assessed and inadequately intervened (Kotfis et al., 2020; O'Hanlon and Inouye, 2020). Assessment using a standard tool and identifying the precipitating factors are essential in delirium management (di Giacomo et al., 2020). Benzodiazepines are to be avoided and among antipsychotics, quetiapine is preferred especially in elderly (di Giacomo et al., 2020) and oral haloperidol (0.5–1 mg) otherwise (“Managing COVID-19 symptoms including at the end of life in the community: summary of NICE guidelines,” 2020). Additionally, melatonin is suggested for sleep wake rhythm and consciousness disturbances and in severely ill individuals (Zambrelli et al., 2020).

7. Conclusion

The COVID-19 pandemic is still evolving and the medical fraternity is posed with huge challenge. Neurological manifestations are common. Immune alterations, hypoxic brain injury, available treatment options and psychosocial stress might potentially lead to a wave of neuropsychiatric sequelae. Improved attention to the possible neuropsychiatric consequences of SARS-CoV-2 viral infection might aid in early identification and better management.

Table 1
: Neuropsychiatric sequelae of COVID-19.

No	Author Publication type Sample size	Features	Remarks
1	Helms et al. (2020) Observational study n = 58	In severely ill patients, neurological findings varied 14–67% based on sedation. 60% patients exhibited confusion. Two-third of the patients had enhanced deep tendon reflexes, clonus and bilateral extensor plantar	Among discharged patients 33 % exhibited dysexecutive syndrome characterized by inattention and disorientation. 13 patients had undergone MRI brain. Majority exhibited bilateral frontotemporal hypo perfusion. CSF reported negative in all tested patients (n = 7) CT Brain – no abnormalities. CSF negative for SARS-CoV-2. Treated with Antiviral drugs, traditional Chinese medicine and symptomatic treatment. No psychotropics used.
2	Yin et al. (2020) Case report n = 1	64 year old male, with fever, myalgia and insomnia had developed lethargy, irritability, irrelevant speech on Day 14 of the illness. Ankle clonus was positive bilaterally, Babinski positive on left lower limb. Neck stiffness was noted with positive Brudzinski sign	CSF negative for the viral strain. CT head done was normal. Patient improved with supportive measures. Psychotropic drugs used not reported.
3	Ye et al. (2020) Case report n = 1	A man diagnosed positive for SARS-CoV-2, presented with altered sensorium on day 14 of the illness with meningeal irritation signs and plantar extensor. Diagnosed to have COVID-19 related encephalitis	Nasopharyngeal swab was negative but CSF sample was positive for SARS-CoV-2. MRI brain showed hyper intensity along the wall of right lateral ventricle and hyper intense signal changes in right mesial temporal lobe and hippocampus. Details of psychotropics not provided.
4	Moriguchi et al. (2020) Case report n = 1	A 24 year old man presented with unconsciousness and new onset seizures on day 9 of febrile illness despite being treated with antipyretics and antiviral (Laninamivir) from day 2. Patient had neck stiffness and confusion.	CSF not tested for the virus. MRI Brain showed hemorrhagic ring enhancing lesion within the bilateral thalami. A diagnosis of acute necrotizing encephalitis related to COVID-19 was made.
5	Poyiadji et al. (2020) Case report n = 1	A 55 year old female airline worker had presented with 3 days history of fever, cough and altered sensorium. Nasopharyngeal swab was positive for SARS-CoV-2	Atypical presentation of delirium as the first symptom of COVID-19. CT head was normal. CSF test report not available. Psychotropic use not reported.
6	Alkeridy et al. (2020) Case report n = 1	A 73 year old man presented with confusion in the absence of fever or respiratory distress. Patient developed fever and cough on day 3 of admission. Meningeal irritation signs were negative. Nasopharyngeal test – positive for the virus	Patient had fever and neuropsychiatric manifestations without any respiratory distress. COVID-19 test positive. CT head without contrast reported normal. CSF protein 100 mg glucose 120mg Details regarding psychotropic use not available.
7	Duong et al. (2020) Case report n = 1	41 year old lady presented with fever, headache and new onset generalized seizures. Initially she was diagnosed to have viral meningitis. During the course of hospital stay patient had altered sensorium, lethargy and hallucinations. Hallucinations persisted intermittently even after improved mentation	Epilepsy patients showed significantly higher psychological distress and spent more time following the COVID-19 outbreak.
8	Hao et al., 2020b Case control study n = 252	Patients with pre-existing epilepsy were compared with age and sex matched healthy controls. Psychological distress was measured using Kessler 6 item psychological distress scale	Psychiatric patients reported significantly higher anxiety, depression, insomnia and traumatic stress. More than one third patients might fulfill the criteria for PTSD
9	Hao et al., 2020a Case control study n = 76	Patients with pre-existing psychiatric (non-psychotic) illness were compared with age and sex matched healthy controls. Psychological impact was assessed with IES-R, DASS-21 and ISI scales	Patient 1 had acute left MCA territory infarct while Patient 2 had acute right MCA territory infarct. Details regarding psychotropics used for treatment not provided.
10	(Avula et al. (2020) Case series n=2	2 out of 4 reported patients had altered sensorium. Patient 1–73 year old man had presented with right sided hemi paresis and altered sensorium. Patient 2–80 year old lady had presented with left hemi paresis, hemi neglect and aphasia. Average time of onset of stroke after COVID-19 diagnosis is Day 12.	Symptoms remitted within few days of initiating treatment. All of them received antipsychotic drugs (olanzapine, risperidone and aripiprazole). Three of them received adjunct benzodiazepines.
11	Valdes-Flórida et al. (2020) Case series n = 4	Case series included 4 individuals (2 male, 2 female) presented with recent onset psychotic features attributed to the psychosocial stress associated with COVID-19. All of them received a diagnosis of Brief reactive psychotic disorder. All of them had delusions while one each had hallucinations and disorganized speech. Two of them exhibited severe suicidal behavior.	Patient improved with oral quetiapine 500 mg/day and clonazepam 1 mg/day. CT brain normal study. Tested negative for the virus.
12	Huarcaya-Victoria et al. (2020) Case report n = 1	A 38 year old woman with no past psychiatric history had presented with acute onset persecutory delusion, auditory and visual hallucinations and circumstantial speech was diagnosed to Acute psychotic disorder secondary to increased fear of contracting COVID-19	

COVID-19 – corona virus disease 2019; CSF – cerebrospinal fluid; CT-computed tomography; DASS-21- depression anxiety and stress scale 21 items version; IES-R – the impact of event scale – revised; ISI – insomnia severity index; MCA – middle cerebral artery; MRI – magnetic resonance imaging; PTSD – post traumatic stress disorder; SARS-CoV-2 – severe acute respiratory syndrome-coronavirus-2.

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Declaration of Competing Interest

None.

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