Perspectives

Uncommon Presentations of COVID-19

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Abstract

A Novel Corona virus, SARS-CoV-2 causing COVID-19 disease has become a global public health problem with varied presentations. The common clinical presentations include pneumonia, myocarditis, gastroenteritis, delirium, though few uncommon cases also came into light showing features of spontaneous pneumothorax, pneumomediastinum, encephalopathy, stroke, psychosis, bowel ischemia, pancreatitis, thrombosis and adrenal insufficiency. These features were more often seen in critically unwell patients with high morbidity and mortality; presented either late in the disease course or early prior to even common symptoms. Our aim of the article is to summarize 'Uncommon Presentations' which might get misdiagnosed, possibly leading to further transmission or delayed diagnosis resulting in poor outcome.

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Key words: SARS-CoV-2, COVID-19 disease, pneumothorax and pneumomediastinum, PRES, ANE, CRVO, CRAO, AI, GBS, psychosis, pancreatitis.

Introduction

National Health Commission, China CDC and WHO were warned by Wuhan health commission about unknown etiology pneumonia (27 cases) on 31st December 2019. China CDC identified the responsible infectious agent called SARS-CoV-2 on 7th January 2020 causing corona virus disease 2019 (C-OVID-19) and WHO declared it to be a pandemic on 11th March 2020 because of its rapid expansion causing worldwide spread[1]. Infected patients presented with the common symptoms including fever, dry cough, dyspnea, myalgia, fatigue and infrequent symptoms like abdominal pain, nausea, vomiting, diarrhea, headache and dizziness[2]. A subset of patients also presented with sore throat, rhinorrhea and sneezing[2].

Along with the common symptoms rare cases of uncommon presentations included pulmonary (pneumothorax and pneumomediastinum), neurological (encephalitis, encephalopathy, stroke and psychosis), gastrointestinal (bowel ischemia, bleeding and pancreatitis), thrombotic (retinal vein and gonadal vein) and endocrine (adrenal insufficiency) manifestations.

Methods

Literature review was done regarding uncommon presentations of COVID-19 disease based on publication of online media like PUBMED and Google Scholar ranging from 31st December 2019 to 15th November 2020. Main terms used include 'uncommon presentations of COVID-19 disease', 'COVID-19 patients with pneumomediastinum and pneumothorax', 'COVID-19 patients with GBS', 'COVID-19 patients with ANE', 'COVID-19 patients with PRES', 'COVID-19 patients with stroke',

'COVID-19 patients with psychosis', 'COVID-19 patients with adrenal insufficiency', 'COVID-19 patients with bowel ischemia', 'COVID-19 patients with pancreatitis.

Discussion

Common Presentations

WHO-China broadly discussed symptomatology of COVID-19 (n = 55,924) in a joint report and found that COVID-19 patients present with pyrexia in 85%, cough in 67.7%, sputum in 33.4% dyspnea in 18.6%, sore throat in 13.9% and nasal congestion in 4.8% of the cases[3]. Constitutional symptoms i.e., muscle or bone aches in 14.8%, chills in 11.4%, and headache in 13.6% of the cases are also seen.[3] GIT symptoms like nausea or vomiting and diarrhea are observed in 5% and 3.7% of the cases, respectively. There were alike clinical manifestations in other similar conducted studies.[2,4] Anosmia and ageusia were also the common presentations in COVID-19 patients.[5]

Salehi et al reported study of 919 COVID-19 cases with predominant pattern of lung abnormality was ground glass opacification (GGO) in 88.0%, bilateral involvement in 87.5%, peripheral distribution in 76.0 % and multi-lobar in 78.8% of the COVID-19 patients with pneumonia.[6] Subpleural involvement, pleural thickening, bronchiectasis, and Interlobular septal thickening were also noted.[6]

Uncommon Presentations

Pulmonary

Pneumothorax and Pneumomediastinum are known complications of intubated patients due to mechanical ventilation. Recent evidence suggests that they can occur without any barotrauma involved in the context of COVID-19 Pneumonia. Lopez. et al describes a case reports summary of patients with SARS-CoV-2 presented with pneumothorax or pneumomediastinum or both[7]. Six out of twenty patients were reported dead. Majority were males and had comorbidities. Fever was the most common symptom on presentation. Management was variable including con-serveative management, chest tube drainage, needle aspiration, thoracoscopy or even bleb resection. Eperjesiova. et al presents 7 spontaneous air leak (2 with Pneumothorax and 5 with Pneumomediastinum) out of 976 COVID-19cases[8]. 5 out of 7 patients had forceful coughs and 3 had asthma or emphysema as previous medical history.1 out of 7 died. Cough and steroids use have been postulated to the development of spontaneous air leak.[9]Clinicians should consider spontaneous air leak in the differential diagnosis of newonset pleuritic chest pain or unexpected respireatory deterioration after 2 weeks of illness in COV-ID-19 patients.[9]

Neurological

a. PRES: Posterior Reversible Encephalopathy Syndrome

PRES appears to be a combination of radiological and clinical presentations characterized by acute delirium, seizures, or focal neurological deficits with associated cerebral vasogenic edema.[10] Hypertension, uremia, toxemia of pregnancy, chemotherapy, sepsis[11] or viral infection (Varicella zoster, influenza and parainfluenza) can be a cause of its manifestation.[13] PRES reported in older age, critically ill COVID-19 patients with[10,12] or without acute kidney injury presented later in disease course.[10,12,13,14] Supposed pathogenesis is found to be massive inflammatory reaction[13] and endothelial dysfunction.[10,12, 13,14] Subcortical parieto-occipital white matter exhibit confluent hypoattenuation on non-contrast CT Scan of head[10,11,13] and confluent T2 hyperintensity is found on MRI in the same parieto-occipital regionns[10,12,13,15] without diffusion restriction in most of PRES patients.[10,13,14] T2 hyperintensity with diffuseon restricted was associated with worst prognosis.[10] MRI demonstrating superimposed hemorrhages either micro or extensive hemorrhages in the parieto-occipital region[13, 14] are associated with poor outcome.[13] EEG may show epileptic state or non-epileptic state.[10,14] Most of the COVID-19 patients with PRES had elevated blood pressure in common and symptoms got improved on tight regulation of blood pressure.[10, 12, 14]

b. ANE: Acute Necrotizing Encephalopathy

It is a rare CNS disease having rapid onset of neurological symptoms with or without hemorrhage,

usually seen in children, rarely in adult, as a result of viral infection most notably influenza and herpes virus.[15,16], COVID-19 critically unwell patients developed ANE with altered mental status such as delirium, difficulty in tracking conversation, confusion or seizures.[15,16] CT and MRI findings include symmetrical, multifocal lesions with necrosis and edema in the thalamus, medial temporal lobes and sub insular regions with hemorrhagic component sometimees. [15,16,17] These features were mainly due to the demyelination and neuronal injury mediated by COVID-19 virus.[15]The resulting necrosis of brain cells was of coagulative type indicating that it was due to neurotropic effect of COVID-19 virus and olfactory or trigeminal nerve could be entry route.[15, 17]ANE is associated with poor outcome of COVID-19 critically ill patients.

c. GBS: Guillain-Barre Syndrome

Guillain-Barre Syndrome comprise a spectrum of polyneuropathies primarily expressed as gradually, ascending, bilateral flaccid paralysis of limbs, along with either absence of reflexes or diminished reflexes and cranial nerves may and may not be involved.[18] GBS has been associated with viral(CMV, EBV, HSV or HIV) and bacterial infections.[19] Case reports of COVID-19 patients showing GBS symptoms have been documented in the literature[19,20] and among those, findings of ageusia, anosmia, lymphocytopenia and thrombocytopenia were consistent.[19]

Electrophysiology showed demyelinating GBS and caudal nerve roots enhancement is found on MRI.[19] Caress. et al reviewed published cases (n = 37) of COVID-19 patients having GBS with mean age of 59 years, male gender in 65% and symptoms appeared on average 11 days from COVID-19 symptoms.[20] CSF proteins were elevated but virus was not detected in CSF suggesting GBS to an autoimmune phenomenon resulting from molecular mimicry.[18]Most patients were given single dose of IV immunoglobulin and improved within 8 weeks.[20]

d. Stroke

Stroke is not an uncommon presentation of COVID-19 infection. Merkler et al reported that as compared to influenza virus, there is a 7.6-fold rise in the probability of stroke in COVID-19.[21] Possible implycated explanation behind increased incidence could be endothelial injury, vigorous inflammatory and pro-thrombotic state in COVID-19 cases.[21] Patients presenting with COVID-19 and stroke tend to be older, more critically ill, have more comorbidities and higher level of inflammatory markers.[21,22] Large vessel and cryptogenic stroke incidence is noted to be increased during COVID-19 pandemic. A multicenter study of COVID-19 patients (n = 26) with stroke reported one fourth patients younger than 50 years[23]. Nearly 2/3rd had large vessel occlusion (LVO) with 50% mortality. Low GCS and high dimers on admission indicate poor prognosis.[23]

e. Psychosis

Psychosis is a condition mainly manifested by delusions, hallucinations, and severe disconnection from reality.[24] Rogers et al reported acute and post-illness psychiatric features of COVID-19 and compared with SARS and MERS infections.[25] They described delirium and agitation being the most common symptoms in acute illness while post illness phase mainly exhibits post-traumatic stress disorder, anxiety, depression, and fatigue.[25] Various factors contribute to its etiology including the direct effect of the virus, hypoxia, and immunological response. Other reasons include pandemic social impact, physical distancing measures and quarantine causing social isolation, unemployment, and financial difficulties, concerns about infecting others and about the outcome of their illness.[24, 25, 26, 27] Dexamethasone has become a standard care for COVID-19 patients requiring oxygen after publication of results of RECOVERY trial and is another important cause of psychosis receiving this treatment. Psychosis can present as acute manifestation of COVID-19 infection or reactive psychosis. Since their ability to make a decision, think and conceptualize is disturbed, psychotic patients are considered to be of high risk for rapid COVID-19 spr-ead.[24] Delusions of prejudice, persecutory, referential beliefs were most common complaints among COV-ID-19 patients[26] and some had even suicidal beha-vior.[27] Although larger prospective cohort study is re-quired, a UK wide surveillance study on 153

COVID-19 hospitalized patients provide a glance of psychiatric or acute neurological complications.[28]

Thrombosis

Cytokine storm has been implicated in COVID-19 infection contributing to hyper inflammatory and hypercoagulability state resulting in DVT and PE. Thrombosis at unusual sites like retinal vein[29,30] and ovarian vein[31,32] has been reported with COVID-19. Case reports showed manifestations of cotton wool hemorrhages, dilated tortuous veins[29,30] optic disc edema, dot and blot hemorrhages[31] on fundoscopy indicating central retinal vein occlusion either as bilateral[29] or unilateral[30] phenomenon. Early full dose anticoagulation has been suggested for COVID-19 patients with severe infection and retinal vein occlusion.[29] A case report of post-menopausal women demonstrated left Ovarian Vein thrombosis (OVT) on CT scan, which was extended partially to left renal vein, quite different from OVT presentation in postpartum period, inflammatory disease, or recent gynecological surgery.[31] Another COVID-19 case report of 26 years old pregnant lady demonstrated thrombosis of IVC, iliac veins and left ovarian vein.[32]

Gastrointestinal

a. Bowel ischemia

10% of COVID-19 patients show mild gastrointestinal symptoms[33], though it can be worse with severe abdominal pain, loose stools, nausea, and vomiting. Norsa. et al reported 7 patients with clinical and radiological evidence of bowel ischemia among COVID-19 patients.[33] The implicated reason behind ischemic state is hypercoagulability state in COVID-19 disease further supported by elevated D-dimers.[33,34,35] Bowel ischemia in COVID-19 patient is associated with poor outcome.[33,35]

b. Pancreatitis

Acute pancreatitis is most seen in gallstones, alcohol use, hypertriglyceridemia, hypercalcemia, medications, and trauma.[36,37] Viral illnesses i.e., hepatitis A, hepatitis B, measles, EBV, and mumps have been reported to cause pancreatitis.[36,37] During COVID-19 pandemic, young, infected patients presented with worsening epigastric pain radiating to back and tenderness, nausea, and vomiting. Lab investigations demonstrated elevated amylase and lipase. Abdominal CT scan demonstrated edema of the distal pancreas with surrounding fluid.[36] The proposed pathophysiology of COVID-19 virus involvement is due to ACE2 receptors expression on islets and exocrine portion of pancreas or pancreatic injury secondary to immune mediated injury.[36, 37]

Endocrine

a. Adrenal insufficiency (AI)

AI is attributed to a failure of cortisol production by the zona fasciculata of the adrenal cortex or by a deficiency of adrenocorticotropic hormone and/or corticotrophin-releasing hormone. It has been reported in SARS infection and was implicated that virus expresses certain amino acids sequences which are molecular mimics of adrenocorticotropic hormone(ACTH) and antibodies produced as a result of viral entry could destroy ACTH knocking down the stress response.[38,39] COVID-19 patients also showed AI and pathogenic phenomenon is considered to be same.[38,39] Another reason is expression of ACE2 receptors on the hypothalamus and pituitary gland which could explain central hypocortisolism.[38] Primary adrenal insufficiency patients, when suspected of COVID-19 virus should increase corticosteroids dose on thems-elves.[38]

Conclusion

Uncommon presentations of COVID-19 were more frequently seen in critically ill patients requiring mechanical ventilation and were associated with worst prognosis. The implicated pathogenesis behind these manifestations included ACE2 receptor expressions, cytokine storm resulting in hyperinflammatory, hypercoagulability state and endothelial dysfunction. Repeat testing for COVID-19 PCR antigen test and strong clinical suspicion in the context of pandemic are essential as early false negative cases with uncommon presentations later can progress to fatal and lethal complications.

Limitations of our Article

Firstly, our article focused only on the conditions or states suggestive of uncommon presentations or complications, risk factor, confirmatory investigations and the suggestive implicated pathogenesis. Secondly, the available publications regarding uncommon presentations are mostly case reports or some case series.

Acronyms

ARDS: Acute respiratory distress syndrome, PRES: posterior reversible encephalopathy syndrome, ANE : acute necrotizing encephalopathy, GBS: Guillain Barre Syndrome, AI: adrenal insufficiency, ACE2: angiotensin converting enzyme 2, AIS: acute ischemic stroke

Funding source

This review article did not receive any specific grant from any of the funding agencies.

Conflict of interest

There is no conflict of interest.

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