

Atypical Presentations of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, emerged in Wuhan, China in December 2019. It has now spread to all parts of the world and as of 26th July 2020, more than 16 million cases and over 600,000 deaths have been reported. The commonest presentation is respiratory in nature with non-productive cough, fever and shortness of breath. Some COVID-19 patients have had atypical or unusual presentations involving the neurological, metabolic, gastrointestinal, renal, haematological, cutaneous and cardiovascular systems. In this mini-review, we have outlined the main atypical or unusual clinical presentations of COVID-19.

Keywords

COVID-19, SARS-CoV-2, Atypical Presentation

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus erupted in Wuhan, China in December 2019. The COVID-19 global pandemic has led to adverse health outcomes worldwide [1]. As of 26th July 2020, more than 16 million cases have been reported with over 600,000 deaths. The more commonly seen symptoms includes: fever, a non-productive cough and fatigue. Complications such as respiratory distress and respiratory failure are seen among the severe COVID-19 patients [1]. However, non-pulmonary/atypical presentations such as neurological, metabolic, gastrointestinal, hepatic, renal, haematological and cardiac manifestations, have been observed in a number of patients. The SARS-CoV-2 virus enters human cells by binding to the ACE-2 receptor [2]. There is strong binding affini-

ity of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein to human ACE-2 [3]. ACE-2 is primarily expressed on Type-2 alveolar cells of the lung. However, cells from the brain, gastrointestinal tract, kidney, heart and testes also express this receptor thus making them susceptible for SARS-CoV-2 infection [4]. In this review, we discuss some aspects of the involvement of systems other than respiratory system and its importance in prognosis and treatment of COVID-19.

2. Literature Search

A literature search was performed in PubMed and Google Scholar to identify studies published on atypical manifestations of COVID-19. The keywords used in the search were: SARS-CoV-2, COVID-19, neurological, gastrointestinal, hepatic, renal, haematological, dermatological and cardiovascular manifestations. Articles published from January to July 2020 were included. The initial selection was based on the article title and abstract, following which the full-text article was read. The reference lists in the full text articles were scanned to obtain additional citations. Important findings affecting the different organ systems were included under the different presentation subheadings.

3. Atypical Presentations

Neurological Presentations

The neurological manifestations of COVID-19 have been described in a few studies [5]. Of 214 patients with confirmed Covid-19, 36.4% had neurologic manifestations [5]. Among the patients with more severe infection, acute cerebrovascular disease, impaired consciousness and skeletal muscle injury were more common [5]. Non-convulsive status epilepticus (NCSE), may occur due to metabolic abnormalities, hypoxia and/or multi-organ failure. Like the other human coronaviruses, SARS-CoV-2 may spread from the respiratory system to the CNS through hematogenous or transneuronal routes [6]. SARS-CoV-2 has been detected in the cerebrospinal fluid of a patient, suggesting the possibility of direct involvement of the nervous system by the virus [7]. Detailed pathophysiological mechanisms for the neurological manifestations of COVID-19 still remain uncertain. Discerning these mechanisms may help with identifying possible therapeutic options and prognosis.

Metabolic Presentations

The metabolic syndrome, diabetes mellitus (DM) and obesity are major risk factors for hospitalization and mortality in COVID-19. Of 173 severe and 140 hospitalised COVID-19 patients, 16.2% and 12% had DM [8] [9]. Among COVID-19 patients needing admission to an intensive care unit (ICU), DM was noted in 22% of the non-survivors [10]. Among COVID-19 patients, the risk of ICU admission was higher in those who had DM. In China, mortality rates were threefold higher in diabetic COVID-19 patients when compared with non-diabetics [8] [10]. At present, it is uncertain if DM per se or the cardiovascular and renal comor-

bidities associated with it, increases the susceptibility to the worst outcome. Uncontrolled glycaemia has been considered a significant predictor of severity and mortality in other viral infections (H1N1, MERS-CoV and SARS-CoV). Data on the development of acute complications of DM in COVID-19 patients remain scarce. Zhou and colleagues found 10% of patients with Type 2 DM and COVID-19, suffered at least one episode of hypoglycaemia [11]. Both hyper and hypoglycaemia play a role in pro-inflammatory mechanisms such as recruitment of monocytes, inducing cytokine release and upregulation of adhesion molecules. Hyper-inflammation, immune dysregulation and cytokine storms play important roles in COVID-19 related mortality.

Gastrointestinal and Hepatic Presentations

A range of gastrointestinal (GI) manifestations have been described in COVID-19. These include: anorexia, nausea, vomiting abdominal pain, diarrhoea, and gastrointestinal bleeding. These are more frequent in patients with severe symptoms compared to the non-severe group. Some present with GI symptoms prior to the appearance of typical respiratory symptoms. Thus a high degree of suspicion is needed at all times and appropriate testing undertaken. Liver damage has also been observed in some COVID-19 patients and is more common in the severely affected group [12]. Increased ALT and AST levels are noted in a high proportion of patients. In cohorts of 82 and 36 patients who died of COVID-19, liver injury was noted in 78% and 58% respectively [12]. The mechanisms leading to GI and liver damage in COVID-19 are not fully elucidated. Postulated mechanisms include: direct virus-induced effects, immune mediated damage and drug-induced injury. ACE-2 receptors are expressed on gastrointestinal epithelial cells, thus SARS-CoV-2 may infect and damage them. The virus is found in faeces and rectal swabs and the possibility of faeco-oral transmission needs to be considered. Molecular assays are able to detect SARS-Cov-2 for longer periods in the GI tract compared to the respiratory system. Thus, reinfection in the recovered patient is possible and clinicians need to be aware of this.

Renal Presentations

Acute renal injury has been reported in COVID-19 patients. Early studies from China and New York found that up to 30% of hospitalized COVID-19 patients, developed moderate or severe acute kidney injury (AKI) and that this was associated with higher mortality [13] [14]. Proteinuria and haematuria have been observed. Renal damage could be due to: direct virus-related effects (as the ACE-2 receptor is expressed on renal tubular epithelial cells), hypoxic damage, macrothrombi in the renal vessels and cytokine mediated injury. Some common medical conditions (DM and hypertension) cause renal damage and thus may increase the risk of COVID-19 complications. Some elderly and poorly controlled Type 1 and Type 2 DM patients with COVID-19, present with Diabetic ketoacidosis, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia) and acid-base imbalance. There is inadequate reabsorption of electrolytes in the proximal renal tubules. COVID-19 patients with

acute renal failure benefit from CRRP (Continuous renal replacement therapy) compared to regular hemodialysis. CRRP is the preferred method of renal replacement, as it does not require 1:1 hemodialysis nursing support.

Hematological Presentations

Coagulation abnormalities and thrombosis have become increasingly recognised in COVID-19 patients. Elevated D-Dimer levels are consistently reported. A gradual increase of D-dimer levels during the course of the illness, is associated with poorer outcomes. There is a high prevalence of venous thromboembolism (VTE) in hospitalized COVID-19 patients. One-third of ICU patients were found to have pulmonary embolism in spite of receiving prophylactic anticoagulation. Among 28% of 2773 hospitalized COVID-19 patients who received systemic anticoagulation, there was improved in-hospital survival in those receiving (71%) versus those not receiving anticoagulants (37%) [15]. Bleeding events were similar in both groups. A cytokine storm and hyper-inflammation are seen in patients with severe and critical COVID-19. The hyper-inflammatory state in turn affects several haematological parameters. Lymphopenia, a high neutrophil to lymphocyte ratio, thrombocytopenia, elevated IL-6, procalcitonin, ferritin and CRP levels have been found to be poor prognostic factors [16]. Regular measurements of these markers may allow the early identification of those who may develop severe disease. Recently, a Kawasaki-like syndrome has been described in some children and is suspected to be a manifestation of post-COVID vasculitis [17]. Positive anti-phospholipid antibodies have also been noted in some COVID-19 patients [18].

Cardiovascular presentations

SARS-CoV-2 is able to cause ischemic and non-ischemic myocardial damage. Infection may decrease the stability of an atherosclerotic plaque and lead to coronary ischaemia [19]. Non-ischemic myocardial damage may lead to myocarditis, pericarditis, cardiomyopathy and arrhythmia. The possibility of fulminant myocarditis needs to be considered when the following are observed: increased respiratory rate, low blood pressure and even shock, prolonged QRS interval on an electrocardiogram (ECG) and frequent premature beats, abnormal increase in creatine kinase isoenzyme (CK-MB) and troponin, or reduced left ventricular ejection fraction (LVEF) and decreased diffuse wall motion on echocardiogram [20]. The mechanisms of acute myocardial injury include: direct viral infection via the ACE-2 receptor (that is expressed on various cardiovascular cells), effects due to a dysregulated cytokine storm and hypoxaemia secondary to respiratory dysfunction. Several studies have found that patients with an underlying cardiovascular disorder to have worse outcomes following SARS-CoV-2 infection [21] [22].

Dermatological presentations

A variety of skin rashes have been reported in around 20% of COVID-19 patients. These include macular or varicella-like or urticarial rashes [23]. Among 375 Spanish patients, the cutaneous manifestations were classified as: acral areas of erythema with vesicles or pustules (pseudo = chilblain)—19%, other vesicular

eruptions—9%, urticarial lesions—19%, maculopapular eruptions (47%) and livedo or necrosis—6%. The vesicular eruptions appeared early in the course of the disease, whilst the pseudo-chilbain pattern tended to appear later on [24].

4. Conclusion

SARS-CoV-2 is able to infect several organ systems in addition to the respiratory system. Thus atypical clinical manifestations may occur and clinicians need to be aware of these to facilitate earlier diagnosis and to avoid misdiagnosis. Some atypical symptoms and signs may even occur before the development of respiratory symptoms. Further studies are needed to better understand the pathophysiological mechanisms of different organ involvement in COVID-19, as they may provide insights into novel diagnostic and treatment options. Studies on the more long term effects of COVID-19, on the different organs should also be systematically ascertained. The timely recognition of the different atypical manifestations of COVID-19, should allow more targeted treatment to be instituted with a view to preserving the function of the affected organ or system.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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