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SARS-CoV-2 Infection: Associated Disorders and Post-COVID-19 Clinical Sequelae

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Abstract

Three years after beginning of the COVID pandemic, SARS-CoV-2 infection still poses a multifaceted health problem in terms of acute infections or reinfections and associated disorders, including thrombotic complications, kidney diseases and endocrine disorders. Another important aspect of COVID-19 is the emergence of viral variants, each having unique and overlapping amino acid substitutions that affect transmissibility, disease severity and susceptibility to natural or vaccine-induced immune responses.

After COVID-19, 5-15% of patients suffer from postinfectious sequelae, involving multiple organ systems, grouped together as 'long COVID' or 'postacute sequelae of SARS-CoV-2 (PASC)'. Long COVID is defined by one or multiple signs or symptoms persisting or occurring more than 4 weeks after the onset of acute SARS-CoV-2 infection, including shortness of breath, fatigue with or without exertion, postural orthostatic tachycardia, myalgia, peripheral neuropathy, endocrine and kidney disorders, thrombotic complications, multisystem inflammatory syndrome and others.

The pathophysiology of acute COVID-19, of viral variants as well as of long COVID remains elusive. In addition, to date there are few or no treatment options available that have been rigorously evaluated in clinical trials. Last but not least, patients with long COVID are subject to stigmatization because of perceived simulation or psychosomatization of symptoms, in view of the lack of specific diagnostic parameters.

Keywords: *Anticoagulants, Dialysis, Endocrine system, Kidney diseases, Long COVID, Obesity, Post-COVID-19 condition, Thrombosis, Viral variants*

Abbreviations

BMI: Body Mass Index; COVID-19: Coronavirus Disease 2019; ESKD; End-Stage Kidney Disease; mAB: Monoclonal Antibody; RCT: Randomized Controlled Trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; VITT: Vaccine-induced Thrombotic Thrombocytopenia

Introduction

Globally, the pandemic of COVID-19 is caused by the RNA virus SARS-CoV-2 and has claimed more than six million lives globally. Basic research has addressed the mechanisms of viral entry and viral spreading, involving among others the angiotensin converting enzyme 2 (ACE2) receptor and the transmembrane protease/serine subfamily 2 (TMPRSS2). Further, host immune responses and pathological effects of SARS-CoV-2 infection in different tissues and organs have been described and risk factors for adverse outcomes of COVID-19 have been identified [1].

Shortly after the emergence of COVID-19 in late 2019, clinicians recognized an apparent association between SARS-CoV-2 and both arterial and venous thrombosis [2,3]. Further, it was apparent that COVID-19 can cause acute kidney injury and may cause or exacerbate chronic renal diseases [4-6]. Last but not least, the interaction between SARS-CoV-2 infection and the endocrine system has been an area of recent scientific and clinical research. Endocrine disorders, including obesity and diabetes mellitus were recognized as risk factors for poor COVID-19 outcomes [7-10].

Another important aspect of COVID-19 was the emergence of several viral variants, each having unique and overlapping amino acid substitutions. The five major variants have been designated by WHO and CDC as alpha, beta, gamma, delta and Omicron BA.1 and BA.2.They vary in terms of transmission efficiency, pathogenicity/disease severity and susceptibility to natural or vaccine-induced immune responses as well as resistance to monoclonal antibodies [11].

Finally, more recently postinfectious sequelae of SARS-CoV-2 infection have been recognized and have been termed, among others, post-acute COVID-19 syndrome, long COVID or long-haul COVID [12-14].

In the following some interesting some basic and clinical aspects of SARS-CoV-2 infection and COVID-19 will be presented in more detail to add to the understanding of the virological characteristics and the clinical sequelae of this infection.

SARS-CoV-2 Infection and Associated Clinical Diseases

Thrombotic Complications

In late 2019, shortly after the emergence of COVID 19 clinicians recognized an association between the infection and both arterial (myocardial infarction, stroke, acute limb and mesenteric ischemia,

coronary stent thrombosis) and venous thromboses. Cohort studies revealed thrombotic events in 17-47% in critically ill patients and in 3-11% in noncritically ill patients. Later, multicenter prospective studies failed to confirm this very high burden of thrombotic complications [15-17].

The risk of thromboembolic complications of patients with COVID-19 is highest in hospitalized critically ill patients, Iower in hospitalized not critically ill patients and moderate in discharged post-COVID-19 patients and low in stable outpatients [17]. From this it follows that hospitalized critically ill patients should be treated with prophylactic-dose heparin or low molecular weight heparin (LMWH), i.e., daily 40 mg enoxiparin, 4,500 units tinzaparin, 5,000 units dalteparin or 2 x daily 5,000 units heparin. Hospitalized not critically ill patients should receive treatment-dose heparin or LMWH, i.e., 2 x daily enoxiparin 1 mg/kg, daily 175 units tinzaparin, 2 x daily 100 units/kg dalteparin or continuous i.v. heparin. Discharged post-COVID-19 patients should be treated with a prophylactic-dose oral anticoagulant, e.g., 10 mg rivaroxaban daily for 35 days. In view of the low risk of thromboembolic complications in stable COVID-19 outpatients no anticoagulation is recommended. As ongoing RCTs are completed, emerging new data need to be incorporated into updated evidence-based guidelines.

Kidney Injury

COVID-19 can cause acute kidney injury and may cause or exacerbate chronic renal diseases [4-6]. The causes of renal impairment in patients with COVID-19 are thought to be an impaired renal perfusion and immune dysregulation [18]. While renal parenchymal cells, in particular proximal tubular cells, express high levels of ACE2 and TMPRSS2 as well as other proteases, suggesting that the kidney may be susceptible to SARS-CoV-2 infection [19]. To date, it is controversial, however, whether the kidney is a target for SARS-CoV-2 infection [20].

Numerous glomerular diseases were found to be associated with COVID-19 and/or with vaccination against SARS-CoV-2: podocytopathies, focal segmental glomerulosclerosis, minimal change disease and membranous nephropathy. Several antiviral medications, including molnupiravir (inhibitor of viral RNA replication), ritonavir-boosted nirmatrelvir (inhibitor of SARS-CoV-2 MPRO protease) and remdesevir (inhibitor of viral RNA polymerase) have been approved for the treatment of patients with COVID-19 and kidney disease. In addition several anti-Spike monoclonal antibody formulations and immunomodulatory medications, including tocilizumab (an inhibitor of the interleukin-6 receptor) and baricitinib (an oral JAK1/JAK2 inhibitor) are recommended in selected patients with COVID-19 [21] Further studies are needed, however, to define the optimal strategies for prevention and treatment of COVID-19 in patients with kidney diseases.

Endocrine Disorders

The interaction between COVID-19 and the endocrine system has recently become a major area of scientific and clinical interest. In this context several endocrine disorders, including obesity and diabetes mellitus have been recognized among significant risk factors for COVID-19 severity [1,7-10]. In addition to body mass index, increased visceral adipose tissue appears to predict COVID-19 severity but not mortality [22]. In the course of the pandemic and adjusting for comorbidities, obesity was recognized as an independent risk factor for COVID-19 severity and mortality in women and men [7]. In addition, obesity-related comorbities were shown to be associated with poor COVID-19 outcomes [8,9]. Male sex appears to be associated with a greater COVID-19 severity and mortality, but not susceptibility [23].

The available data regarding the long-term effects of SARS-CoV-2 infection on thyroid, adrenal and male gonadal functions are too limited to draw scientific or clinical conclusions.

SARS-CoV-2 Variants

An important aspect of COVID-19 is the emergence of viral variants, each having unique and overlapping amino acid substitutions. The five major variants, designated by WHO and CDC as alpha, beta, gamma, delta and Omicron BA.1 and BA.2 vary in terms of transmission efficiency, pathogenicity/disease severity and susceptibility to natural or vaccine-induced immune responses and monoclonal antibodies. In general, RNA viruses display significant plasticity based on the low fidelity of the RNA-dependent RNA polymerases and the lack of genomic repair mechanisms such as proofreading and mismatch repair [24]. The phylogenetic evidence suggests that this plasticity may have allowed SARS-CoV-2 to jump from bats to humans [25].

The ancestral strain of SARS-CoV-2 was sequenced in Wuhan, China in December 2019 (GenBank accession no. MN908947). The first significant mutation was detected in March 2020: a D614G substitution in the viral spike glycoprotein S [11,26-28].

Alpha Variant

The alpha or B.1.1.7 variant was identified in September 2020 in the UK and was shown to have increased transmission efficiency and pathogenicity but no resistance to monoclonal antibodies, no protection from a previous infection or no change of vaccine efficiency [11].

Beta Variant

The beta or B.1.351 variant was identified in May 2020 in South Africa. It had increased transmission efficiency and pathogenicity as well as a resistance to the mAbs bamlanivimab-etesevimab, a reduced protection from a previous infection or reduced vaccine efficiency [11].

Gamma Variant

The gamma variant was identified in November 2020 in Brazil and was shown to have similar characteristics as the beta variant [11.

Delta Variant

The delta or B.1.617.2 variant was first identified in India in October 2020 and displayed similar properties as the beta and gamma variants, respectively [11].

Omicron Variants

The omicron or B.1.1.529 variant first emerged in November 2021 and was shown to have increased transmission efficiency, a lower pathogenicity, a reduced protection from a previous infection and lower vaccine efficiency. Two significant sublineages BA.1 and BA.2 have been described with predominant substitutions in the receptor binding domain of the Spike glycoprotein and in the receptor binding motif as compared to the ancestral Wu-Hu-1 strain [11].

Variants of SARS-CoV-2 continue to be a challenge for diagnosis, treatment and prevention of COVID-19. Tracking of the known variants and the early identification of new variants and updating of COVID-19 vaccines composition for new SARS-CoV-2 variants are of paramount importance for the effective control of the SARS-CoV-2 infection and the COVID-19 pandemy. New viral variants are for example the Omicron variants XBB.1.5, **XBB.1.16.6, EG.5, FL.1.5.1** and **FE.1.**

Post-COVID Conditions

Postinfectious sequelae of SARS-CoV-2 infection have been recognized and are termed, among others, post-acute COVID-19 syndrome, long COVID or post- COVID-19 [12-14]. Common signs and symptoms of post-COVID-19 include among others pulmonary, cardiovascular and neuropsychiatric manifestations. Common manifestations are fatigue, shortness of breath, memory or cognitive disturbances, headache, smell or taste disturbances, autonomic dysfunction, anxiety and depression and a decreased functional capacity. While age and comorbidities, such as obesity and psychiatric illnesses, and the severity of the acute COVID-19 are risk factors for long COVID, long-lasting sequelae of COVID-19 can also affect young and previously healthy individuals with mild COVID-19. Symptoms may be new, persist after acute COVID-19 or may be relapsing or remitting. The duration of symptoms is variable. Most patients have a significant reduction of symptoms by one year postdiagnosis. In a cohort study from China, the proportion of patients with at least one symptom decreased from about 70% at 6 months to about 50% at 12 months, of patients with fatigue or muscle weakness from about 50% at 6 months to about 20% at 12 months. In addition, about 90% of subjects returned to their original work after 12 months [29]. Risk factors for long COVID include female sex and preexisting respiratory and psychiatric diseases. The mainstay of treatment is individualized, including supportive care to mitigate symptoms as well physical rehabilitation and mental health support.

Summary and Conclusions

Since the emergence of the COVID-19 three ago, SARS-CoV-2 is still with us. Much has been learned about the sequelae of the SARS-CoV-2 infection in terms of acute infections or reinfections, the recognition of associated complications (arterial and venous thromboses, kidney diseases and endocrine disorders), the identification and characterization of emerging viral variants and of the post-COVID-19 conditions. A major scientific achievement was the rapid development of safe and effective COVID-19 vaccines and therapies [30]. Since SARS-CoV-2 infection and its sequelae will continue to evolve and pose a challenge to our health care systems, innovative vaccines and therapies will be central to prevent or control future pandemics by SARS-CoV-2, seasonal influenza, respiratory syncytial virus and other pathogens.

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