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Glomerulonephritis associated with SARS-CoV-2 infection

Mohsen Akhavan Sepahi¹, Bhaskar VKS Lakkakula², Bijan Roshan³, Banafsheh Yalameha⁴¹Department of Pediatric Nephrology, School of Medicine, Qom University of Medical Sciences, Qom, Iran²Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India³Division of Nephrology, Scripps Clinic, La Jolla, California, USA⁴Nickan Research Institute, Isfahan, Iran

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Implication for health policy/practice/research/medical education: Post-infectious glomerulonephritis (PIGN) can develop secondary to infections associated with bacterial, viral, fungal, protozoal, and helminthic parasites. Recently, there is a serious concern regarding the occurrence of kidney dysfunctions and subsequent acute kidney injury (AKI) among COVID-19 patients. The outcome data of COVID-19 in neonates and children demonstrated that the fatality rate is significantly higher in patients with AKI than in patients without AKI. In the current COVID-19 pandemic, few instances of glomerulonephritis (GN) in patients affected by SARS-CoV-2 have been reported. In this review, we investigated the PIGN concentrating on the COVID19-nephropathy, as well as its prevention and diagnosis strategies.

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Introduction

Post-infectious glomerulonephritis (PIGN) is one of the most common forms of glomerulonephritis (GN) (1-3). Among children, acute 'post-streptococcal glomerulonephritis' (APSGN) is the most common cause of PIGN, whereas viral infections are accounting for less common forms of PIGN (4,5). Further, viral infections can occur at any age (2,4). Recognizing the pattern of GN has paramount importance for causative diagnosis, treatment guidance, and prognostication of many GNs and thus frequently kidney biopsy is required (6,7). Typical APSGN and typical nephrotic syndrome in children are two major exceptions that can be initially managed without biopsy.

The immune system, with direct or indirect activation of the complement system, plays a substantial role in different forms of immune GNs such as lupus nephritis and many infectious related GN (8,9).

Although the exact cause is not known, different factors including environmental agents, immune dysregulation and genetic predisposition can lead to the formation and accumulation of immune complexes in the glomeruli (10-13). Furthermore, chronic GN is most often associated with other systemic diseases such as hypertension, diabetes mellitus, and hepatitis (14,15). Mild cases of GN

do not cause any clear symptoms and may not need any treatment. The most common clinical features of GN include hypertension, macroscopic hematuria, proteinuria, and edema (16), together called nephritic syndrome. In cases where the proteinuria is severe (more than 2 g/m² of body surface area), patients may develop significant edema, hypoalbuminemia and hyperlipidemia, called nephrotic syndrome. Some other common symptoms of kidney failure due to GN include fatigue, nausea and tremulousness. In severe GN cases, confusion or coma may develop (17). Glomerular disease can clinically be asymptomatic and detected as asymptomatic proteinuria or microscopic hematuria, or may be clinically detected with overt nephrotic syndrome or nephritic syndrome or mixed nephrotic-nephritic syndrome and ultimately with progressive to chronic renal failure (3, 4).

COVID-19 and kidney injury

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus. A series of publications have reported multiple organ dysfunction including acute respiratory distress syndrome (ARDS) and acute renal injury (AKI) in COVID-19. Recently, there is more concern regarding AKI among COVID-19

patients as a significant risk factor for increasing morbidity and mortality (18,19). Despite lower mortality rates of COVID-19 in neonates and children, the fatality rate is significantly higher in patients with AKI than in those without AKI (20). Hematuria, proteinuria, increased blood urea nitrogen, increased serum creatinine, and AKI are common in patients with SARS-CoV-2 infection (21). Presence of viral RNA in urine of COVID-19 patients accompanied with albuminuria and hematuria is another potential link between SARS-CoV-2 infection and renal injury (22). Interestingly, a retrospective analysis of clinical data has demonstrated that the urinalysis is better in predicting kidney impairment than blood biochemistry in COVID-19 patients (23). Hence, it is important to pay more attention to the current issue and perform early diagnostic tests for kidney damage in patients with COVID-19. Angiotensin converting enzyme 2 (ACE2) the main receptor of entry of SARS-CoV-2 infection to target cells is significantly expressed in the kidney. In fact, the expression of ACE2 in the kidney is even higher than lung tissue, making renal cells prone to direct viral injury (24). SARS-CoV-2 infection can invade proximal straight tubule cells, proximal tubule, proximal convoluted tubule, and even glomerular parietal epithelial cells by ACE2 receptors and transmembrane serine protease 2 (25).

Glomerulonephritis in COVID-19 patients

Viral infections are well known to cause glomerular diseases. Cytomegalovirus and human immunodeficiency virus (HIV) in children and Epstein-Barr virus infection in adults are associated with collapsing glomerulopathy (26). In the current COVID-19 pandemic, few instances of GN in patients affected by SARS-CoV-2 have been reported. Although kidney disease in patients with COVID-19 is primarily reported in Chinese patients, a recent case report revealed presence of collapsing glomerulopathy as well as reduced renal function in an African-American woman with COVID-19 (27). Subsequent case reports of a 63-year-old black male and 46-year-old West African man also showed collapsing glomerulopathy and acute tubular necrosis that resulting from the SARS-CoV-2 effect on podocytes (28, 29). Interestingly all three case reports documented the presence of APOL1 genotypes in their patients (27-29). Presence of *APOL1* high-risk genotype is the major genetic contributor to the risk for glomerulosclerosis and particularly to collapsing glomerulopathy among patients of African ancestry (30). The precise mechanism underlying COVID-19 related collapsing glomerulopathy is not known, but histopathological examinations have revealed the presence of viral particles in the cytoplasm of podocytes of patients with collapsing glomerulopathy. Alternatively, collapsing glomerulopathy could be the result of inflammation-induced podocyte injury due to cytokine release syndrome in COVID-19 patients (31).

In summary, renal tubular injury, and collapsing glomerulopathy are important complications of COVID-19 nephropathy. Direct viral effects on podocytes and/or virus-induced cytokine injury to podocytes are some of the known possible mechanisms of GN in COVID-19 patients. In addition, the presence of high-risk *APOL1* genotypes increases the genetic susceptibility to collapsing glomerulopathy in COVID-19 patients of African origin. Further studies are needed to understand the SARS-CoV-2 effect on the podocyte and changes occurring in the podocytes during infection.

Authors' contribution

MAS and BY prepared the primary draft. LVKSB and BR revised the manuscript. All authors read and signed the final paper.

Conflicts of interest

No conflict of interest.

Ethical considerations

Ethical issues (including data fabrication, double publication, and plagiarism) have been detected by the authors.

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