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ORIGINAL ARTICLE

SARS-CoV-2 infection in hospitalized pediatric patients with kidney disease

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Abstract

Objectives: This study aims to present the confirmed cases of SARS-CoV-2 infection in pediatric patients with chronic and acute kidney diseases admitted to a tertiary pediatric hospital. **Methods:** Descriptive and retrospective observational study with all children hospitalized between March and June 2020 who had, simultaneously, SARS-CoV-2 infection and renal pathologies. Of this total of patients, those who had another underlying disease besides the renal disease were excluded. **Results:** During the period, nine children with kidney disease were admitted to the hospital and had infection confirmed by the new coronavirus through positive RT-PCR. Regarding the underlying disease, seven had only kidney disease, three of whom had stage 5 chronic kidney disease; one, with stage 1 chronic kidney disease; one, with cortic-sensitive nephrotic syndrome; and two, with acute kidney injury. Two patients in this study had already undergone kidney transplantation, used immunosuppressants and had their doses reduced due to the infectious condition. Only one required oxygen therapy and transfer to the intensive care unit, but was not intubated and returned to the ward within 24 hours. **Conclusions:** According to the cases described, the pediatric population with kidney disease, including those using immunosuppressants due to acute transplant rejection, seems to evolve without severe COVID-19, therefore there is no great divergence in relation to the population of the same healthy age group.

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INTRODUCTION

Since December 2019 we have seen the COVID-19 pandemic, a condition caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), unfold before our eyes. Scientists from all over the world have looked into the different forms of involvement associated with the novel coronavirus and therapeutic possibilities to tackle COVID-19.

As of June 14, 2020, Brazil had a total of 867,624 confirmed cases of the disease, with a mortality rate of about 5%. Some 105,000 individuals with the disease required hospitalization, 2,250 (2%) of which in the pediatric age range. The deaths of individuals in this age range by COVID-19 have amounted to 303, or 13% of the population requiring hospitalization.[1,2]

Although most studies have described mild symptoms in children with the disease,[3,4] preexisting conditions may increase the risk of severe SARS-Cov-2 infection of individuals in this age range. Suspicion is based partly on reports about adult patients[3] and partly on data from the Brazilian Epidemiologic Surveillance Information System, in which 88% of the individuals of all ages killed by COVID-19 had at least one important preexisting comorbidity, including the likes of heart disease, diabetes, and kidney disease.[1]

More studies about patients with chronic disease and SARS-CoV-2 infection are needed to define the best clinical and therapeutic approaches for this population.

This study describes the progress of pediatric patients with acute or chronic kidney disease and SARS-CoV-2 infection treated at a tertiary pediatric hospital.

METHODS

This observational descriptive retrospective study enrolled every child with acute or chronic kidney disease and SARS-CoV-2 infection confirmed via RT-PCR testing admitted between March 15 and June 15, 2020. RT-PCR testing was prescribed based on the following criteria: presence of respiratory symptoms within the last 14 days; contact with individuals with COVID-19; having undergone transplantation. Patients with non-kidney underlying conditions were excluded.

The following information was extracted from the charts of the patients included in the study: sex; age; early COVID-19 symptoms; reason for hospitalization; preexisting kidney disease; type of renal replacement therapy; prescription of immunosuppressants for underlying disease; specific treatment for COVID-19; and patient progress (need to refer to intensive care unit and death).

RESULTS

Nine children with kidney disease and positive RT-PCR tests for COVID-19 were admitted from March 15 to June 15, 2020. Seven were males and two were females, with ages ranging from two to 15 years.

In regards to underlying disease, three patients had end-stage renal disease (ESRD); one had stage 1 chronic kidney disease (CKD); one had steroid-sensitive nephrotic syndrome; and two had acute kidney injury (AKI). In addition to kidney disease, the other patients had cancer (acute lymphoblastic leukemia and a metastatic ovarian tumor) and were on chemotherapy, which led to their exclusion from the study.

The conditions causing CKD were steroid-resistant nephrotic syndrome (two patients); C3 glomerulopathy (one patient); and atypical hemolytic-uremic syndrome (one patient). And the conditions causing AKI were post-infectious glomerulonephritis (one patient) and hemolytic-uremic syndrome secondary to colitis (one patient). One child did not have impaired kidney function and was admitted for decompensation from steroid-sensitive nephrotic syndrome and urinary tract infection.

Three of the four patients with CKD had ESRD and were on hemodialysis; the other patient had stage 1 CKD and had normal-range creatinine clearance.

Only one of the patients with AKI – the subject with hemolytic-uremic syndrome secondary to colitis – required hemodialysis.

All seven children were hospitalized for complications tied to their underlying conditions and were tested for COVID-19 for presenting respiratory symptoms within the last 14 days (four patients), being in contact with individuals with COVID-19 (one patient), or having undergone kidney transplantation (two patients).

The most common symptoms were fever (60%); coughing (60%); dyspnea (40%); diarrhea (20%); and coryza (20%). Two patients were asymptomatic; one was tested for having been in contact with a family member with COVID-19 and the other was tested prior to undergoing graft removal by the kidney transplantation team.

Only one of the patients developed severe symptoms with blood oxygen level decreases requiring the use of a non-rebreather mask and the placement of an oxygen nasal cannula. This case had an associated confounding factor, as the patient presented with Gram-positive bacteremia caused by a dialysis catheter-related infection. At the time of decompensation the patient had a sudden-onset fever, a significant decrease in oxygen saturation levels, mild dyspnea, peripheral perfusion impairment, and hypotension. The protocol for sepsis was initiated with antibiotics, placement of a non-rebreather mask, and fluid replacement. The patient tested positive for SARS-CoV-2 in RT-PCR and had catheter tip, peripheral blood, and central blood cultures positive for *S. aureus*.

Regarding complementary examination, the child with severe disease progression had alterations in chest X-ray images; chest computed tomography (CT) scans revealed bands of laminar atelectases in the posterior basal segments of the two inferior lobes, ground-glass nodules in the central portion of the left superior lobe, signs consistent with bronchopneumonia, and minimal bilateral pleural effusion. Mild pleural

effusion is explained by the decompensation stemmed from the patient's underlying condition (C3 glomerulopathy). However, the other imaging findings, particularly when associated with severely low oxygen saturation levels without significant dyspnea, were consistent with SARS-CoV-2 pneumonia. The patient developed well with non-invasive oxygen therapy and treatment for bacteremia, and did not present other clinical repercussions from COVID-19. The presence of infection prevented the continuation of immunosuppressant therapy for the decompensation by C3 glomerulopathy.

Five patients were on hemodialysis when they were diagnosed with coronavirus infection. Three had been on renal replacement therapy. The other two needed hemodialysis during hospitalization, one for AKI secondary to hemolytic-uremic syndrome and the other for decompensation by C3 glomerulopathy.

Two patients included in the study had undergone kidney transplants. One had been hospitalized for two months to treat acute graft rejection and was on dialysis when diagnosed with novel coronavirus infection; the patient was not responding to graft rejection therapy, developed numerous infections and macroscopic hematuria, and was prescribed graft removal. An RT-PCR test for COVID-19 was ordered as part of preparation for surgery, and the patient progressed without symptoms or imaging signs of acute infection by SARS-CoV-2. The other transplant patient presented concomitantly with coronavirus infection and acute graft rejection, and had diarrhea as the only symptom. Graft rejection therapy could not be initiated on account of the presence of infection.

The two children were on immunosuppressants (tacrolimus and steroids) and were placed on low dose therapy during the course of infection. None had severe symptoms.

One patient required oxygen therapy and referral to an intensive care unit for staphylococcal infection; the patient was not intubated and was sent back to the pediatric ward within 24 hours. As this manuscript was finalized, four patients had been discharged and three remained in hospital. None died. The children still in hospital were tested again and their RT-PCR tests came back negative.

DISCUSSION

SARS-CoV-2 is an RNA virus of the *Coronaviridae* family, which comprises a diverse group of viruses divided into four genera associated with diseases ranging from mild respiratory conditions with influenza-like symptoms to severe acute respiratory syndrome.[5] Transmission occurs primarily via respiratory droplets produced by individuals carrying the virus and asymptomatic subjects in the infection incubation period. Although children apparently develop milder disease, more severe levels of involvement are also possible.[6]

Significant progress has been made in attaining knowledge about the disease, despite the short time elapsed since the start of the pandemic. However, epidemiologic and clinical data about children with SARS-CoV-2 infection are still scarce.

The incidence of the disease in children has been lower than the numbers reported for adults. In Brazil, at the end of Epidemiological Week 21, only 0.3% of the cases of severe acute respiratory syndrome by COVID-19 affected children and adolescents aged 0-19 years, a proportion lower than the numbers reported in Italy (1.2%) and the USA (1.7%).[7]

A Chinese study looked into the test results of 1,391 children with symptoms or prior contact with symptomatic individuals with COVID-19 and reported that only 171 had positive PCR tests for the disease. Children with the disease were aged 6.7 years on average and the most common symptoms were fever, coughing, and sore throat. Of the subjects tested positive for COVID-19, 15.8% were asymptomatic and were tested for having been in contact with symptomatic individuals. The three patients in the series requiring referral to an intensive care unit and invasive mechanical ventilation had other underlying conditions (hydronephrosis, leukemia, intussusception). A child with a history of intussusception died four weeks into hospitalization.[8]

In China, although clinical manifestations of the disease have been generally less severe in children than in adults, small children and babies in particular were reportedly more vulnerable to COVID-19.[4] In Brazil, a third (33%) of the children killed by COVID-19 were aged one year or less.[1]

Although most scientific publications about the disease describe cases of adult patients, the risk factors associated with severe novel coronavirus infection in children have gained increased attention. A meta-analysis comprising four studies about COVID-19 and CKD in adults found that the latter appears to predispose patients to developing more severe infection by SARS-CoV-2. Seemingly, the presence of CKD in patients with COVID-19 has been associated with greater risk of pneumonia and a 14-fold increase in the chance of dying of pneumonia.[9]

A Spanish study carried out in March and April 2020 described the cases of 16 children with kidney disease and positive PCR tests for SARS-CoV-2 infection. Three had undergone kidney transplantation, three were on hemodialysis, three had stage 2 or 3 CKD, and seven did not have glomerular filtration rate alterations. In this study, 62.5% of the children had coughing or rhinorrhea, 50% had fever, 25% had gastrointestinal symptoms, and 19% were asymptomatic. None required oxygen therapy.[10]

In our series, 28% of the children were asymptomatic; when present, symptoms consisted essentially of coughing, fever, and dyspnea. Differently from a study cited above, rhinorrhea was one of the least prevalent symptoms in our population. Only one patient with staphylococcal infection required oxygen therapy with a non-rebreather mask and a nasal cannula for about 24 hours; orotracheal intubation was not needed.

A Chinese study analyzed the cases of 701 patients aged 50-71 years and found that 14.4% of the subjects had increased serum creatinine levels on admission and 13.1% had a GFR <60ml/min/1.73m^2. The individuals with increased serum creatinine levels were generally males of advanced age

with severe involvement. They had increased leukocyte and lymphocyte levels; low platelet counts; increased D-dimer levels; high partial thromboplastin times; and increased lactate dehydrogenase and liver enzyme levels. Kidney injuries were seen in 5.1% of the patients. Overall mortality was 16.1%; the death rate of individuals with increased baseline creatinine levels was 33.7%. Increased mortality was associated with increased baseline creatinine levels, increased blood urea nitrogen levels, proteinuria, and hematuria.[11,12]

Acute kidney injury is not a common finding in pediatric patients with COVID-19, although the combination may indicate poorer clinical outcomes. Rapid loss of kidney function has been associated more often with sepsis or hemodynamic decompensation than with viral infection, although additional studies on the subject are warranted.

In the Spanish study cited above, eight of 16 children required hospitalization. Three subjects with CKD had renal flares due to poor fluid intake and one had nephrotoxicity by tacrolimus. However, all returned to baseline kidney function.[10]

The seven patients included in our study were admitted on account of symptoms related to kidney disease, not SARS-CoV-2 infection.

Two patients had acute kidney injury, one for hemolytic-uremic syndrome associated with colitis (tested for SARS-CoV-2 infection for having presented flu-like symptoms ten days before admission) and the other for post-streptococcal glomerulonephritis (tested for SARS-CoV-2 infection for presenting with fever and coughing during hospitalization).

In regards to immunosuppressant therapy, studies performed in other countries have shown that patients on immunosuppressants apparently do not have worse outcomes than their immunocompetent peers. Studies about other viral infections in transplant patients have shown that antimetabolites such as sirolimus are discontinued or tapered down, while calcineurin inhibitors are maintained if the patient does not develop severe disease.[10] Unlike other respiratory viruses, the coronaviruses do not cause more severe involvement in patients on immunosuppressants. In fact, there have been no reports of death of transplant patients or individuals on chemotherapy or immunosuppressants.[13] The reason for such finding lies within the host's immune response, which if deregulated or excessive, becomes a relevant tissue damage factor during the course of coronavirus infection.[14]

An Italian study included children and adults previously submitted to transplant procedures, with liver autoimmune disease, or on chemotherapy for hepatocellular carcinoma. None developed clinical lung disease by SARS-CoV-2. To this point, patients on immunosuppressants, regardless of age, have not been described as at risk of developing severe COVID-19.[13]

In our study, two of seven children were on tacrolimus and steroids for acute graft rejection. One had been on acute graft rejection therapy for two months before being diagnosed with novel coronavirus infection; this patient had multiple infections and was prescribed graft removal. The patient in question did not present symptoms of COVID-19 before or after the procedure. Another child presented concurrently with acute graft rejection and COVID-19; acute graft rejection therapy was contraindicated, but the patient was kept on tacrolimus and oral steroids. This child progressed favorably despite COVID-19, with short duration diarrhea as the single symptom. However, the patient lost graft function and was started on hemodialysis.

Cases of patients with concomitant acute graft rejection and COVID-19 have not been described in the literature.

In Brazil, there is no specific protocol for the treatment of pediatric patients with COVID-19. Therefore, none of the patients included in this study was given specific treatment for the disease. Although the literature indicates that patients with kidney disease might progress unfavorably if diagnosed with COVID-19, in our hospital – a referral center in pediatric nephrology – only one patient had more significant disease and developed pneumonia, without needing orotracheal intubation. However, the number of cases of multisystem inflammatory syndrome in children with COVID-19, described for the first time in late April 2020, have grown in our hospital since early June 2020, with a total of nine children diagnosed with the condition by the time this manuscript was written. However, none of these children had kidney disease.

According to the cases described in this study, pediatric patients with kidney disease, including individuals on immunosuppressants for acute graft rejection, appear not to develop severe novel coronavirus infection, similarly to their healthy peers. However, it is too early to say that the risk of developing severe complications from COVID-19 for pediatric patients with kidney disease and healthy children is similar.

More studies are needed to support the development of therapeutic guidelines for pediatric patients with kidney disease and COVID-19.

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