Retrospective Study

Exploring kidney biopsy findings in congenital heart diseases:
Insights beyond cyanotic nephropathy

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Abstract

BACKGROUND

The association between congenital heart disease and chronic kidney disease is well known. Various mechanisms of kidney damage associated with congenital heart disease have been established. The etiology of kidney disease has commonly been considered to be secondary to focal segmental glomerulosclerosis (FSGS), however, this has only been demonstrated in case reports and not in observational or clinical trials.

AIM

To identify baseline and clinical characteristics, as well as the findings in kidney biopsies of patients with congenital heart disease in our hospital.

METHODS

This is a retrospective observational study conducted at the Nephrology Department of the National Institute of Cardiology “Ignacio Chávez”. All patients over 16 years old who underwent percutaneous kidney biopsy from January 2000 to January 2023 with congenital heart disease were included in the study.

RESULTS

Ten patients with congenital heart disease and kidney biopsy were found. The average age was 29.00 years ± 15.87 years with pre-biopsy proteinuria of 6193 mg/24 h ± 6165 mg/24 h. The most common congenital heart disease was Fallot’s...
tetralogy with 2 cases (20%) and ventricular septal defect with 2 (20%) cases. Among the 10 cases, one case of IgA nephropathy and one case of membranoproliferative glomerulonephritis associated with immune complexes were found, receiving specific treatment after histopathological diagnosis, delaying the initiation of kidney replacement therapy. Among remaining 8 cases (80%), one case of FSGS with perihilar variety was found, while the other 7 cases were non-specific FSGS.

CONCLUSION
Determining the cause of chronic kidney disease can help in delaying the need for kidney replacement therapy. In 2 out of 10 patients in our study, interventions were performed, and initiation of kidney replacement therapy was delayed. Prospective studies are needed to determine the usefulness of kidney biopsy in patients with congenital heart disease.

Key Words: Renal biopsy; Congenital heart disease; Chronic kidney disease; Focal segmental glomerulosclerosis

INTRODUCTION
The association between congenital heart disease and chronic kidney disease is well known, although its prevalence is not known. Dimopoulos et al[1] reported that 15.8% of adults with cyanotic congenital heart disease and 8% of patients with non-cyanotic heart disease have some degree of chronic kidney disease, and Rajpal et al[2] reported that 1 in 6 adults with congenital heart disease have albuminuria.

These patients are subjected to various insults associated with the disease, including pathophysiological changes such as polycythemia, cyanosis, chronic hypoxia, and alterations in renal blood flow that affect glomerular hemodynamics, as well as complex surgical interventions and prolonged stays in intensive care units, all of which can cause repeated episodes of acute kidney injury[3-7].

While there have been significant advances in understanding the pathophysiology behind the decline in kidney function in these patients, glomerular alterations associated with congenital heart disease have been reported historically since 1960[8-11]. However, over the years, there have only been a few isolated case reports and autopsy records with histopathological descriptions of glomerular changes[12].

Among the histological findings in kidney biopsies, the most common pathological features found are glomerulomegaly, mesangial hypercellularity, glomerular capillary congestion, and segmental sclerosis[13]. The most frequently observed pattern of glomerular damage is focal segmental glomerulosclerosis (FSGS), all of these changes commonly found in maladaptive glomerulopathies[14-16], as reported in a documented case by Hida et al[13]. Other authors propose the term "cyanotic nephropathy" to describe the maladaptive histological manifestation of hyperfiltration due to the previously mentioned risk factors[17-19].

Nowadays, there are more tools to increase the survival of patients with cyanotic congenital heart disease. However, it is important to keep in mind that these patients still have a high risk of developing cyanotic nephropathy, even after undergoing corrective cardiovascular surgery.

The objective of this study is to determine the baseline and clinical characteristics, as well as the findings in kidney biopsies of patients with congenital heart disease.

MATERIALS AND METHODS
This is a retrospective and observational study carried out at the Nephrology Department of the National Institute of Cardiology “Ignacio Chávez”. All patients over 16 years old who underwent percutaneous renal biopsy from January
2000 to January 2023 with congenital heart disease were included in the study. Patients with incomplete medical records were excluded.

The kidney biopsy was performed based on the indication and consideration of the attending nephrologist for each patient. The technique was guided by real-time ultrasound, and the approach as well as the number of needles used were determined by the responsible nephrologist.

**Definitions**

Complications after the biopsy were classified as major or minor complications. A major complication was defined as an event that required therapeutic intervention for resolution (e.g., blood transfusion, placement of a foley catheter, cystoclysis, angiography, nephrostomy, or nephrectomy). In addition, death was also considered a major complication. A minor complication, on the other hand, was defined as an event that did not require any intervention for resolution, regardless of symptoms (e.g., pain on a visual analog scale greater than 5 out of 10, need for hospitalization for further monitoring).

Minor complications included macroscopic and microscopic hematuria, hematoma regardless of size, pain, arteriovenous fistula, infection, subcapsular hemorrhage, and retroperitoneal hemorrhage. All of the above-mentioned complications were elevated to major if they required any therapeutic intervention. The need for hospitalization for monitoring a complication was not included as a second complication.

As for late complications, all patients were scheduled for a follow-up consultation one month after the biopsy to evaluate the histopathological outcome. This consultation served to rule out any late complications and to ensure that patients did not visit the emergency department during this period.

The indication for kidney biopsy was a 50% increase in proteinuria and/or a ≥ 50% increase in serum creatinine compared to the previous consultation and/or active sediment defined by erythrocyturia or leucocyturia, without a clinical event justifying the deterioration of proteinuria or increase in serum creatinine.

**Statistical analysis**

The normal distribution of variables was evaluated using the Shapiro-Wilk test. Quantitative variables were described using means and SD or medians and interquartile ranges (IQR), depending on their distribution. Categorical variables were described using frequencies and proportions.

**RESULTS**

A total of 10 cases were found from January 2000 to January 2023, of which 3 (30%) patients were female. The average age was 29 years ± 15.87 years with a body mass index of 20.11 kg/m² ± 7.90 kg/m². The time from diagnosis of congenital heart disease to biopsy was 60 (39.60) months. Among the 10 patients, only 5 (50%) had a history of hypertension. Pre-biopsy proteinuria was 4843 (4079-6490) mg/24 h with a blood urea nitrogen level of 37.25 mg/dL ± 4.74 mg/dL.

Regarding ultrasonographic findings, kidney length was 9.16 centimeters ± 1.01 centimeters, 6 (60%) patients had lobulated borders, and only 2 (20%) patients had a preserved cortex to medulla ratio. In the kidney biopsy, 4 (40%) patients had insufficient samples for diagnosis; in all cases, a 16-gauge needle was used, and a transverse approach technique was employed. The number of glomeruli obtained was 13.00 ± 6.55. There were only minor complications in 3 (30%) patients, including 2 perirenal hematomas and a patient with hematuria. The rest of the baseline characteristics are presented in Tables 1 and 2.

Histopathological findings included one case of IgA nephropathy and one case of membranoproliferative glomerulonephritis due to immune complexes. Among the remaining 8 (80%) cases, one case of FSGS with perihilar variety was found, while the other 7 cases were non-specific FSGS. The findings and diagnoses of congenital heart disease are shown in Table 3.

**DISCUSSION**

Research on cardio-renal syndrome has made great strides in recent times; however, there is limited evidence on kidney disease in patients with congenital heart diseases. As life expectancy in this population has increased due to therapeutic advances, a higher percentage of adults living with congenital heart diseases is expected.[13-19]

The mechanisms of kidney injury in these patients include chronic hypoxia, intraglomerular hemodynamic changes, neurohormonal alterations, and even cardiac surgeries for the correction of congenital defects. These mechanisms are difficult to modify and consequently result in a significant increase in the prevalence of kidney disease in these patients[3-19].

Another significant obstacle is the identification of more accurate and sensitive diagnostic tools, as well as biomarkers for kidney function in this population. The international literature recommends requesting serum creatinine and cystatin C for the estimation of glomerular filtration rate from the first contact, given the biases in isolated creatinine measurement in these patients due to the presence of sarcopenia associated with decreased physical activity. Additionally, evaluating the presence of albuminuria as a prognostic factor is recommended. However, the role of renal biopsy in these patients is a crucial point to evaluate[20-22].
Table 1 Baseline and clinical characteristics, n (%)  

<table>
<thead>
<tr>
<th>Initial variables</th>
<th>Results, n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29.00 ± 15.87</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.23 ± 27.17</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.62 ± 0.08</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.11 ± 7.90</td>
</tr>
<tr>
<td>Diagnosis-biopsy time (months)</td>
<td>60 (39-60)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Use loop of Henle diuretics</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Spironolactone use</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Use of ACE inhibitors</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Surgery prior to kidney biopsy</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.73 ± 2.10</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>30.57 ± 29.32</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>4843 (4079-6490)</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>15.33 ± 4.45</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>48.07 ± 17.32</td>
</tr>
<tr>
<td>Platelets × 10⁹/L</td>
<td>288.00 ± 82.00</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

ACE: Angiotensin-converting enzyme; BUN: Blood urea nitrogen.

The findings from previous studies suggest a clinical association between FSGS and heart disease in pediatric patients, which may be speculated to be associated with an immune mechanism responsible for the development of FSGS that can also affect the heart. An important point to note is that these studies were performed with biopsies in the pediatric population, without studying the impact of these glomerulopathies in adulthood, both in renal and cardiac prognosis. Another disadvantage is that the prevalence of other glomerulopathies other than FSGS is unknown, as they are associated with maladaptive changes, and the biopsy result is often ignored in favor of empirical treatment. In our center, within the congenital heart disease department, there is a registry of 3500 patients with congenital heart disease. We do not have the exact prevalence of chronic kidney disease in this population, but unpublished information indicates an approximate 13%. In our study, we are one of the first to describe the long-term behavior of patients with congenital heart diseases who reach adulthood and evaluate the impact of renal damage on morbidity and mortality. One of the included patients, who had ventricular septal defect as the underlying heart disease and whose biopsy reported membranoproliferative glomerulonephritis, received treatment with steroids and calcineurin inhibitors, delaying the initiation of renal replacement therapy by 3 years. Another one of our patients with ventricular septal defect who underwent successful closure of the defect had IgA nephropathy as a finding in the kidney biopsy, and received immunosuppressive treatment with steroids, delaying the initiation of kidney replacement therapy by 24 years. In both cases, these treatments would not have been given without a histopathological report justifying these interventions. Furthermore, another important point to highlight is the prognostic information provided by these renal biopsies, as they establish a percentage of tubulointerstitial damage or fibrosis, which gives us an idea of the likelihood of recovery. Another advantage of the study is the low prevalence of minor complications in only one-third of the population and the absence of major complications, indicating the safety of the kidney biopsy procedure in this patient population. Our study has limitations such as: (1) The retrospective nature of the study and small number of cases, with only 10 patients included; and (2) the study did not focus on the medical treatment instituted to modify the decline in kidney function, as this was determined by each attending physician for each patient. However, these findings motivate the need for a prospective study with the possibility of implementing interventions that could improve the renal and cardiac prognosis in these patients.
### Table 2 Baseline and clinical characteristics

<table>
<thead>
<tr>
<th>Variables prior to performing the renal biopsy</th>
<th>Results, n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.17 ± 1.88</td>
</tr>
<tr>
<td>Pre-biopsy BUN (mg/dL)</td>
<td>37.25 ± 4.74</td>
</tr>
<tr>
<td>Proteinuria prior to biopsy (mg/24 h)</td>
<td>6193.00 ± 6165.00</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.10 ± 3.76</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.90 ± 12.96</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Platelets × 10^9/L</td>
<td>281.00 ± 78.15</td>
</tr>
<tr>
<td>Skin-kidney distance (cm)</td>
<td>2.100 ± 0.264</td>
</tr>
<tr>
<td>Renal length (cm)</td>
<td>9.160 ± 1.011</td>
</tr>
<tr>
<td>Renal width (cm)</td>
<td>3.86 ± 0.64</td>
</tr>
<tr>
<td>Lobulated borders</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Ratio Cortex Medulla preserved</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Transverse biopsy technique</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Insufficient sample</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Number passes</td>
<td>1</td>
</tr>
<tr>
<td>Glomeruli</td>
<td>13.00 ± 6.55</td>
</tr>
<tr>
<td>Interstitial fibrosis (%)</td>
<td>46.67 (45.00-50.00)</td>
</tr>
<tr>
<td>Complications</td>
<td>3 (30%)</td>
</tr>
</tbody>
</table>

BUN: Blood urea nitrogen.

### Table 3 Cases

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Type of heart disease</th>
<th>Diagnosis</th>
<th>Glomeruli</th>
<th>Creatinine (mg/dL)</th>
<th>Proteinuria (g/g/24 h)</th>
<th>Renal measurements (cm)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>Dextromorphism with common atrium, absence of right ventricular atrial septal defect</td>
<td>FSGS NOS</td>
<td>14</td>
<td>2.89</td>
<td>1.70</td>
<td>8.0 × 3.6</td>
<td>None</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>Acianogen VSD</td>
<td>FSGS NOS</td>
<td>19</td>
<td>1.75</td>
<td>14.69</td>
<td>9.8 × 3.4</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>Dextrocardia concordant atrioventricular and ventricular-arterial connection</td>
<td>FSGS NOS</td>
<td>6</td>
<td>1.88</td>
<td>1.91</td>
<td>9.7 × 4.6</td>
<td>None</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>ASD</td>
<td>IgA nephropathy</td>
<td>18</td>
<td>1.41</td>
<td>3.23</td>
<td>8.7 × 4.2</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>Persistent ductus arteriosus + Eisenmenger Syndrome</td>
<td>FSGS NOS</td>
<td>25</td>
<td>1.02</td>
<td>4.09</td>
<td>10.1 × 5.3</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>Pulmonary atresia</td>
<td>FSGS NOS</td>
<td>6</td>
<td>8.25</td>
<td>10.89</td>
<td>9.4 × 4.3</td>
<td>Perirenal hematoma</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>Infundibular VSD</td>
<td>GMN proliferative membrane immune complexes</td>
<td>11</td>
<td>1.98</td>
<td>8.25</td>
<td>9.9 × 4.3</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>69</td>
<td>Ebstein Anomaly</td>
<td>FSGS Perihiliar</td>
<td>13</td>
<td>4.27</td>
<td>1.58</td>
<td>9.3 × 4.3</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>Tetralogy of fallot</td>
<td>FSGS NOS</td>
<td>6</td>
<td>3.24</td>
<td>5.18</td>
<td>8.4 × 4.2</td>
<td>Perirenal hematoma</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>Tetralogy of fallot</td>
<td>FSGS NOS</td>
<td>8</td>
<td>1.93</td>
<td>3.70</td>
<td>8.96 × 4.24</td>
<td>None</td>
</tr>
</tbody>
</table>
CONCLUSION

Congenital heart disease is a growing diagnosis in the adult population and is known to be associated with chronic kidney disease. However, the etiology of chronic kidney disease in this population is not well understood. Therefore, determining the cause can help intervene in delaying the progression to kidney replacement therapy. In two out of the ten patients in our study, interventions were performed based on the renal biopsy findings, this may probably delay the initiation of renal replacement therapy.

Our study serves as an initial proposal for prospective studies to determine the importance of renal biopsy in this population. By understanding the underlying renal pathology, appropriate interventions can be implemented to improve the renal and cardiac prognosis in these patients.

ARTICLE HIGHLIGHTS

Research background
There is limited information available about the etiology of chronic kidney disease in patients with congenital heart disease today due to advanced surgeries providing an increased life expectancy, therefore it’s truly important to delay the onset of kidney replacement therapy.

Research motivation
There is a growing population of patients with congenital heart disease and chronic kidney disease which is an area of opportunity to evaluate the causes of this pathology and the impact on it’s treatment.

Research objectives
To determine that there may be other glomerulopathies in this population and treating them may possibly delay the onset of kidney replacement therapy.

Research methods
We conducted a retrospective analysis of information from patients with congenital heart disease who underwent kidney biopsy.

Research results
We determined that there may be other glomerulopathies in which treatment could be given. It would be appropriate to determine in a larger population if the number of other glomerulopathies different from focal segmental glomerulosclerosis (FSGS) is higher and if treatment really delays kidney replacement therapy.

Research conclusions
Chronic kidney disease in congenital heart disease is not always due to hypoxic damage that leads to FSGS.

Research perspectives
Clinical trials that can clarify who truly benefits from biopsy and enable follow-up to perform interventions that could delay renal replacement therapy.

FOOTNOTES

Author contributions: Juarez-Villa JD, Zepeda-Quiroz I, Toledo-Ramírez S, Gomez-Johnson VH, Pérez-Allende F, Garibay-Vega BR, Rodríguez Castellanos FE, Moguel-González B, García-Cruz E, and Lopez-Gil S contributed to design of the study, data analysis, drafting and critical revision and editing, and final approval of the final version.

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Informed consent statement: The need for informed consent was waived by the local Ethics Committee of The National Institute of Cardiology.

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Data sharing statement: No additional data are available.
REFERENCES


