Renal involvement in epidermolysis bullosa patients: a case series study

Case series

Epidermolysis bullosa (EB) is a group of heritable diseases characterized by trauma-induced excessive skin and mucosal fragility. Beside the skin manifestations, different EB types have a different risk to develop extracutaneous complications. It has been described that a small but clinically significant portion of EB patients develops major nephro-urological complications, affecting mainly Junctional EB (JEB) and Recessive Dystrophic EB patients (RDEB). These complications have a strong influence on patient's quality of life and in the most severe cases, are their principal cause of death. DEBRA Chile is the only referral unit for EB patients in Chile, and currently their registry contains 225 patients from all EB types. From these 225 patients, eight are JEB and 64 are RDEB, with age range from 3 to 22 years old for JEB and from 0 to 76 years old for RDEB. Patients are periodically evaluated for cutaneous and extracutaneous manifestations, including renal function. Laboratory tests (blood and urine) are performed in patients with suspicion of renal involvement, specifically looking at renal dysfunction (urinary nitrogen/plasmatic creatinine, serum amyloid A and electrolytes in plasma), hematuria (urinalysis) and proteinuria (micro albuminuria). When a urological cause is discarded, a renal biopsy is highly advice to obtain a specific diagnosis, treatment and prognosis. The biopsy is afterwards sent for histopathology analysis, which includes light microscopy, immune fluorescence and electron microscopy.

In the last 6 years, eight patients have been diagnosed with renal disease; all classified as recessive dystrophic EB patients by skin biopsy (Table 1). From these 8 cases, 6 underwent a renal biopsy, and the procedure was performed without complications. In the other 2 cases, families declined a renal biopsy because of the invasiveness of the procedure; however, in both cases, the clinical characteristics suggest an IgA nephropathy. The mean age for patients with renal involvement suspicion was 16 years old (ranging from 13 to 28 years old), with a slight over representation of male over female patients (5/8). Diagnoses were highly variable, 5 different diagnoses were observed (2/8 confirmed and 2/8 highly suspected). Interestingly, patients from our case series were mainly carrying mutations predicting to cause absent type VII collagen protein (6/8). This observation could be interpreted, as the absence of this protein in the most severe cases, are their principal cause of death. As our results showed, hematuria was the most common renal phenotype observed on EB patients (6/8).

No JEB patients were diagnosed with renal involvement, although 16 patients were alive at some point of this period. A possible explanation is a lower life expectancy when compared with other populations. It has been observed that more than 70% of our JEB patients die before the age of 10, and mainly due to sepsis and respiratory failure. Patients with a biopsy-confirmed IgA nephropathy were treated with oral corticosteroids for 12 weeks, one of them showed a good clinical response. Two patients develop renal terminal failure managed initially with peritoneal dialysis and are currently on hemo dialysis. The patient with renal amyloidosis was treated with colchicine for 3 months, but died of sepsis with multiple organ failure, at the age of 22 years. The patient with MCG I, did not require treatment.

The pathogenesis of renal damage is complex and several factors are involved:

A. Frequent antibiotic therapies based on amino glycocides, notoriously nephotoxic, used to treat renal and skin infections.

B. Cytokine release, particular amyloid A protein, which, in EB patients, may lead to renal failure.

C. Immuno complexes, deposited in glomerular capillary basement membranes, or in the mesangium, resulting in post-infectious glomerulonephritis, IgA glomerulo nephritis, or mesangio proliferative glomerulonephritis; besides the renal damage secondary to urinary tract stenosis/obstruction and associated infections.

All these conditions can lead to chronic renal failure, although it is a rare cause of death in pediatric population. For EB patients, some of the long-term renal consequences can be avoided by a routine symptom screening followed by a diagnosed-specific clinical management. As our results showed, hematuria was the most common renal phenotype observed on EB patients (6/8). This phenotype can be caused by glomerular or extra glomerular damage, the latter being easily discarded by performing urine tests and a renal/bladder ultrasound. However, if a kidney insult cannot be excluded by laboratory and image tests, a renal biopsy should be advice for obtaining a specific diagnosis. Renal involvement monitoring should be included in the standard of care, starting as early as an EB diagnosis is made. In this sense, there are currently no published guidelines on how to monitor these patients. Almahiai and Mellerio recommend a 6-monthly serum urea and electrolytes, blood pressure, and urinalysis be performed in all patients belonging to the most severe EB types; RDEB gen sev and JEB gen sev. We also proposed a kidney and bladder ultra sound annually, even without signs of abnormalities.

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Table 1 Overview of patients with nephro-urological complications

<table>
<thead>
<tr>
<th>Patient nº</th>
<th>Gender</th>
<th>Type of EB</th>
<th>Mutations</th>
<th>Protein consequence</th>
<th>Age at clinical diagnosis (years)</th>
<th>Clinical signs for renal failure</th>
<th>Biopsy result</th>
<th>Treatment</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>RDEB gen sev</td>
<td>c.[7708delG] + [7708delG]</td>
<td>Absent protein</td>
<td>13</td>
<td>Persistent macroscopic hematocrit</td>
<td>IgA nephropathy</td>
<td>Steroids$</td>
<td>Regression of Hematuria</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>RDEB gen sev</td>
<td>c.[7532+1G&gt;T] + [8245G&gt;A]</td>
<td>Absent protein</td>
<td>13</td>
<td>Renal Insufficiency Stage 3</td>
<td>Chronic interstitial nephritis</td>
<td>Dialysis</td>
<td>ESRD in dialysis#</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>RDEB gen sev</td>
<td>ND</td>
<td>Absent protein</td>
<td>19</td>
<td>Nephrotic syndrome</td>
<td>PIGN with crescents</td>
<td>Dialysis</td>
<td>ESRD in dialysis#</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>RDEB gen intermed</td>
<td>ND</td>
<td>Slightly different protein</td>
<td>28</td>
<td>Macroscopic hematocrit in the context of hospitalization for convulsive syndrome</td>
<td>MCG type I</td>
<td>NT</td>
<td>Regression of Hematuria</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>RDEB gen sev</td>
<td>c.[6527insC] + [7708delG]</td>
<td>Absent protein</td>
<td>16</td>
<td>Macroscopic hematuria + Proteinuria</td>
<td>IgA nephropathy</td>
<td>Steroids$</td>
<td>Stable / untreated hematuria</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>RDEB gen sev</td>
<td>c.[7708delG] + [7708delG]</td>
<td>Absent protein</td>
<td>21</td>
<td>Persistent macroscopic hematuria + Proteinuria</td>
<td>Renal amyloidosis</td>
<td>NT</td>
<td>Stable / untreated hematuria</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>RDEB gen sev</td>
<td>c.[6527insC] + [6527insC]</td>
<td>Absent protein</td>
<td>17</td>
<td>Macroscopic hematuria + Proteinuria</td>
<td>ND</td>
<td>NT</td>
<td>Stable / untreated hematuria</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>RDEB gen sev</td>
<td>ND</td>
<td>Absent protein</td>
<td>16</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Stable / untreated hematuria</td>
</tr>
</tbody>
</table>

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Conflicts of interest

None declared.

References