Heterogeneous Phenotypes of Congenital Nephrotic Syndrome related to NPHS1 mutation

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Introduction

Congenital nephrotic syndrome (CNS) is a rare disease predominantly caused by genetic conditions. Mutations in NPHS1, which encodes nephrin on the cell surface of podocytes, are the most common cause of primary CNS. Though being more often associated with early death and/or end stage kidney disease (ESKD), milder courses with later onset have also been reported.

Method

We retrospectively reviewed all children with genetically confirmed NPHS1-related CNS who presented between 2000 and 2018.

Results

Four patients were identified (Pakistani, 10/F; Pakistani, 16/M; Pakistani, 3/F; Thai/Chinese, 8/M). They all presented at a mean age of 1.5 months old with generalized oedema or poor weight gain. All patients required medical therapies and two required nephrectomies to reduce proteinuria and oedema. Three patients progressed to ESKD and required renal replacement therapy. Time to ESKD ranged from 2.1 to 10 years (mean time to ESRD 5 years). The remaining one patient improved subsequently and only developed stage II chronic kidney disease in early adulthood. He was a cousin of one of the CNS patients with ESKD. Both children inherited the same mutation but experienced different renal outcomes. Details of clinical characteristics, genetic findings, treatments and outcomes are presented in Table 1.

Conclusion

Our findings suggest that genotype to phenotype correlation is poor and highlight the importance of individualized management in patient care.

Table 1. Clinical characteristics of the 4 patients with NPHS1-related Congenital Nephrotic Syndrome (CNS)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Sex</th>
<th>Age at diagnosis (m)</th>
<th>Mutation Site</th>
<th>Nature</th>
<th>Nucleotide change</th>
<th>Treatments</th>
<th>Outcomes</th>
<th>Age at ESRD (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>0.6</td>
<td>Homozygous exon 27</td>
<td>Nonsense</td>
<td>c.3478C&gt;T p.(Arg1160*)</td>
<td>Conservative</td>
<td>No nephrectomy</td>
<td>No HD</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2.5</td>
<td>Homozygous exon 27</td>
<td>Nonsense</td>
<td>c.3478C&gt;T p.(Arg1160*)</td>
<td>No albumin infusions</td>
<td>Diuretics</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>Homozygous exon 27</td>
<td>Frame shift</td>
<td>c.2944dupA p.(Thr982Asnfs*36)</td>
<td>ACEI</td>
<td>Indomethacin</td>
<td>Unilateral HD</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>2</td>
<td>Heterozygous intron 6 exon 7</td>
<td>Splice site frame shift</td>
<td>c.712+2T&gt;A c.809dupG</td>
<td>Bilateral, sequential</td>
<td>PD followed by KTX</td>
<td>3</td>
</tr>
</tbody>
</table>

ACEI: ACE inhibitor; CKD: Chronic kidney disease; ESRD: End stage renal disease; SRNS: Steroid resistant nephrotic syndrome; PD: Peritoneal dialysis; KTX: Kidney transplant.