Nephronophthisis related to homozygous NPHP1 gene deletion as a cause of chronic renal failure in adults

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Introduction

Nephronophthisis (NPH) is an autosomal recessive nephropathy with chronic tubulointerstitial involvement, which represents the leading cause of end-stage renal disease (ESRD) in children and adolescents. According to the age at onset of ESRD, three forms of NPH have been described: infantile, juvenile (the most frequent) and adolescent.

In the juvenile form, polyuro-polydipsia starts at 4–6 years, and precedes progressive renal failure, with ESRD occurring around 13 years of age [1]. Main histological findings are tubular atrophy with irregularly thickened tubular basement membranes appearing at an early stage, interstitial fibrosis and cysts at the corticomedullary junction and in the medulla [2]. The clinical and histological presentation is similar in the adolescent form, with a later occurrence of ESRD (median age: 19 years). Extra-renal disorders may be present in the juvenile form of NPH and include mainly retinal impairment of variable severity. The clinical and histological features of the infantile form differ sharply from the two others: ESRD occurs in the first 2 years of life, and patients usually present with enlarged kidneys and widespread cyst development [2,3]. To date, four genes implicated in juvenile or adolescent forms of NPH have been identified: NPHP1, NPHP3, NPHP4 and NPHP5. The most frequent genetic abnormality found in NPH is a large homozygous deletion of the NPHP1 gene [4,5]. These four genes encode proteins named nephrocystins, which have various subcellular localization, including the primary apical cilia, focal adhesion and adherens junction, suggesting that they play a role in the integrity and architecture of renal tubular epithelial cells [6]. NPHP3 mutations are responsible for the adolescent form of NPH. However, mutations in the five known genes are found in only 50–60% of NPH cases, indicating that other genes remain to be discovered [7].

NPH is a very rare cause of ESRD in adults. We report four cases of NPH diagnosed in adulthood, in which molecular study revealed homozygous deletion of NPHP1 gene.

Cases

Clinical, biological and radiological features of the four patients at the time of diagnosis are summarized in Table 1. Patient 3 was the sister of Patient 4. No patient had a familial history of renal or extra-renal disease, except for Patient 4, in whom NPH was diagnosed after the evaluation of his sister (Patient 3). There was no history of consanguinity in any family. The four patients were, respectively, 19, 22, 22 and 25 years old at the time of diagnosis of NPH. In Patients 1, 2 and 3, nephropathy was discovered at an advanced stage (stage 4 of K/DOQI classification); serum creatinine at diagnosis was, respectively, 261, 225 and 442 μmol/l, corresponding to calculated creatinine clearance of 29, 25 and 12 ml/min.

Patient 4 had a history of vesical impairment diagnosed in early childhood, with pollakiuria, imperiosity and enuresis. These urinary abnormalities
had been related to neurological bladder with unexplained sphincter hypertonia; the patient had required repeated self-catheterization since adolescence. At the age of 15, serum creatinine was 96 μmol/l, corresponding to an estimated creatinine clearance of 100 ml/min/1.73 m² by Schwartz formula. In the following years, serum creatinine increased progressively, reaching 419 μmol/l [estimated creatinine clearance using the modification of diet in renal disease (MDRD) formula: 16 ml/min] at the age of 25. Renal failure was attributed to chronic renal obstruction, and once the disease had been diagnosed in his sister (Patient 3), NPH diagnosis was not made until he was 25.

Blood pressure level was normal at diagnosis in Patients 2, 3 and 4, but was elevated in Patient 1, reaching 150/90 mmHg. Proteinuria was mild, ranging from 0.2 to 1.6 g/24 h, and haematuria was not detected in the four patients.

No patient had mental retardation, and clinical examination revealed no particular disorder in any of them. Despite the absence of visual symptoms, ophthalmological examination was performed in all patients. In Patient 1, eye examination revealed macular drusens; electroretinogram showed mild retinal impairment of cone system function. Standard ophthalmological evaluation demonstrated similar findings in Patient 4, but electroretinogram was not performed. In the other patients, ophthalmological examination was unremarkable; however, electroretinogram was not performed.

Radiological findings were not specific and included a reduced kidney size (Patient 3) and cortical cysts (Patients 2 and 3). Patients 1, 2 and 3 underwent renal biopsy; histological findings were characteristic tubular changes in all cases (netlike transformation, thinning, splitting into thin or fine lamellae, disintegration, collapse or complete disappearance), diffuse inflammatory interstitial fibrosis, medullary cysts in one case (Patient 2) and sclerosis of 30–50% of glomeruli in all cases (Figure 1A and B).

Molecular study using polymerase chain reaction technique identified large homozygous deletion of NPHP1 gene in all patients, confirming the diagnosis of NPH (Figure 2).

In Patient 1, estimated creatinine clearance declined from 29 to 19 ml/min over 1 year of follow-up. For Patients 2, 3 and 4, mean estimated creatinine clearance declines were, respectively, 9, 2 and 3 ml/min per year; ESRD was reached at the age of 24, 22 and 25 years, respectively.

Discussion

Diagnosis of NPH in adult patients is very uncommon. In the juvenile form of NPH, ESRD usually occurs during childhood or adolescence (median age of 13 years), but exceptionally in adulthood [1]. Omran et al. [5] report on 24 patients with NPHP3 mutation, with late onset of ESRD at a median age of 19 years (quartile borders 16 and 25 years). Clinical symptoms and histopathological features observed in these patients were identical to those of juvenile NPH.

Other cases of NPH diagnosed in adults have been rarely reported, but no definitive diagnosis was established in the absence of mutation identified despite molecular studies [8,9]. In our four cases, NPH diagnosis was established through the identification of NPHP1 gene deletion. Our data indicate that, in some cases, NPH may be revealed by renal failure occurring in adulthood.

Because of the paucity of specific clinical symptoms, diagnosis of NPH may be very difficult in adults. Polyuria and polydipsia, or late enuresis, related to an impaired urinary concentrating ability and urine salt wasting, may be helpful. However, only two of our four patients had secondary enuresis, and two patients had discrete polyuria and polydipsia. Moreover, radiological findings were aspecific and inconclusive in our patients. Renal biopsy may be useful, as tubular atrophy with irregularly thickened tubular basement

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age (years)</th>
<th>Serum creatinine rate (μmol/l)</th>
<th>Calculated glomerular filtration rate (ml/min)</th>
<th>Proteinuria (g/day)</th>
<th>Haematuria</th>
<th>Blood pressure (mmHg)</th>
<th>Late enuresis</th>
<th>Polyuria and polydipsia</th>
<th>Radiological features</th>
<th>Kidneys size</th>
<th>Cysts</th>
<th>Extra renal-disorders</th>
<th>NPHP1 gene deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/19</td>
<td>261</td>
<td>29</td>
<td>0.4</td>
<td>–</td>
<td>150/90</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
<td>Retinal dystrophy</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>F/22</td>
<td>225</td>
<td>25</td>
<td>0.2</td>
<td>–</td>
<td>120/75</td>
<td>–</td>
<td>–</td>
<td>Reduced</td>
<td>Reduced</td>
<td>1 cortical (1 cm)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F/22</td>
<td>442</td>
<td>12</td>
<td>0.4</td>
<td>–</td>
<td>115/70</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Reduced</td>
<td>1 cortical (1 cm)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/25</td>
<td>419</td>
<td>16</td>
<td>1.6</td>
<td>+</td>
<td>130/80</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
<td>Retinal dystrophy, neurologic bladder</td>
<td>+</td>
</tr>
</tbody>
</table>

*Creatinine clearance calculated using the MDRD formula.
membranes, interstitial fibrosis and medullary cysts are suggestive of NPH. However, these histological lesions are not specific and may be found in other tubulointerstitial nephropathies [2].

Extra-renal disorders occur in ~15% of patients suffering from NPH. The most frequent disorder is tapetoretinal degeneration [10], which may lead to early blindness (Leber’s amaurosis); the association of NPH and severe visual impairment is called Senior–Loken syndrome. Retinal involvement may be mild, causing pauci-symptomatic ocular disease. Other extra-renal manifestations have been described: oculomotor apraxia (Cogan syndrome) [11], Joubert syndrome (characterized by cerebellar vermis hypoplasia, ataxia, hypotonia, retardation, irregular respiratory patterns and abnormal eye movements), [8,12] bone anomalies with cone-shaped epiphyses [13] and hepatic fibrosis [5].

Patient 1 presented with asymptomatic retinal involvement, with macular drusens and impairment of cone system function. In Patient 3, eye examination demonstrated signs of retinal dystrophy, although he was asymptomatic too. Moreover, he had urinary troubles related to neurological bladder of undetermined cause, which had started several years before the onset of renal failure. Interestingly, ophthalmological and urinary troubles were absent in his sister (Patient 4).

Despite lack of specific treatment, diagnosis of NPH and identification of mutation are very important, allowing early detection of disease in kindred. Thus, it is important for clinicians implicated in the diagnosis of adult renal diseases to be aware that NPH must be considered in patients presenting with features of chronic tubulointerstitial nephropathy.

In all of our patients, molecular study demonstrated large homozygous deletion of NPHP1 gene, which is the commonest cause of NPH, accounting for 30–60% of the cases [7]. The molecular study was made by means of PCR technique, which can yield rapid results.

We have no clear explanation for the late occurrence of ESRD observed in our patients. Interestingly, Patients 3 and 4, who are brother and sister, had a similar evolution of renal disease, and reached ESRD at 22 and 25 years, respectively. The course of chronic renal failure in NPH may be altered by unidentified modifier genes or environmental factors.

In conclusion, diagnosis of NPH must be considered in patients presenting with renal failure secondary to chronic tubulointerstitial nephropathy, even in adulthood. Study of renal biopsy specimens may be helpful for diagnosis, showing suggestive histological lesions. Molecular study can play a very useful role in confirmation of diagnosis. Once the diagnosis of NPH has been made, complete work-up must be done in order to identify extra-renal disorders, particularly retinal involvement. Finally, kindred must be investigated for early detection of NPH.

Conflict of interest statement. None declared.

References

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