Nephronophthisis
Report of 8 Cases from Britain

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Gibson, A. A. M., and Arneil, G. C. (1972). Archives of Disease in Childhood, 47, 84. Nephronophthisis: report of 8 cases from Britain. Eight Scottish children with nephronophthisis are described. The typical clinical picture is thirst and polyuria associated with severe anaemia, progressive impairment of renal function, and dwarfism. Isosthenuria and gross enlargement of the bladder are usually present. Systemic hypertension is usually absent until the terminal stages.

Five of these children are dead and the kidneys have been examined at necropsy. Percutaneous renal biopsy has been carried out on the remainder. The typical morbid anatomical feature is the presence of medullary cysts in small uniformly contracted kidneys. Histologically, the kidney is diffusely affected with extensive sclerosis of glomeruli, periglomerular fibrosis, and obvious hyaline thickening of the tubular basement membrane.

The disease progresses inexorably and renal transplantation offers the only long-term solution.

'Die familiäre Juvenile Nephronophthise' described by Fanconi et al. in 1951 was soon recognized in several European countries (Enell, 1952; Hackzell, 1952; Hooft, Roels, and Herpol, 1959; Broberger, Winberg, and Zetterström, 1960; Royer, Mathieu, and Habib, 1963). Apart from the family reported from Ireland in 1970 (Alexander and Campbell), the condition has received little attention in the United Kingdom.

During the period 1934–1970, 8 children with clinical and histological evidence of nephronophthisis have been investigated at this hospital; details of these children are given in Tables I–IV.

This series of 8 children included 2 sibships. There were a sister and brother (Cases 7 and 8) and 2 sisters (Cases 3 and 4). The remaining 4 children had a total of 10 healthy sibs. The age of recognized onset of the disease varied from 3½ to 11 years. Death occurred at the age of 10 or 11 years in the 5 fatal cases. 3 children, aged 10, 12, and 17 years, are still alive but in progressive renal failure.

** Presenting Features

Thirst and polyuria were the presenting features in 7 of the 8 children. Hb ranged from 6.8 g–10.0 g/100 ml in the 7 children for whom this value was recorded on first attendance. Each of the 8 affected children was dwarfed, some severely. The bladder size was noted to be large on first attendance in 4 of the 5 children for whom this observation was recorded. Systemic hypertension was noted in only 1 child on first attendance at hospital (150/105 mmHg in Case 6); the remainder were normotensive. 4 of the 8 children had reverted to enuresis nocturnally.

The urinary and biochemical findings on first admission to hospital are recorded in Table II.

The paucity of red cells, leucocytes, and casts in the urine is a striking feature. The pattern of high urinary output of low specific gravity, poor urea concentration, and progressively poorer corrected creatinine clearance is reflected in the abnormal biochemical findings in the serum. There was clear evidence of azotaemia on presentation with hypokalaemia in 3 patients and hypocalcaemia in 1. The level of serum sodium was almost normal. With progression of the disease, the hypocalcaemia tended to increase and to produce radiological changes as shown in Table III.

This constant renal osteodystrophy of varying severity is non-specific and presumably due to secondary hyperparathyroidism. Radiological investigation confirmed the very large bladder in each child in whom it had been detected clinically, while infusion urography showed poor concentration of dye due to poor renal function.

** Pathology

Necropsy was carried out in all 5 children who died. The kidneys in every case were less than half of the normal size but the weight made no difference between the two sides. The external surface was uniformly granular and finely scarred with an adherent capsule. Loss of

Received 23 June 1971.
### TABLE I

**Sex, Age at Onset, Diagnosis, and Death; and Number of Sibs of 8 Children with Nephronophthisis**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At Onset of Symptoms</td>
<td>At Hospitalization</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>8½</td>
<td>8½</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>3½</td>
<td>3½</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>8</td>
<td>8½</td>
</tr>
</tbody>
</table>

### TABLE II

**Urinary and Biochemical Findings**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Urine</th>
<th>Renal Function Tests</th>
<th>Plasma Level (mg/100 ml)</th>
<th>Serum Level (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBC</td>
<td>Protein</td>
<td>Casts</td>
<td>SG</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>Trace</td>
<td>Few granular</td>
<td>1008</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>Trace</td>
<td>Few granular</td>
<td>1007</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>Trace</td>
<td>0</td>
<td>1005</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1004</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>+</td>
<td>Few granular</td>
<td>1005</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>1005</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1004</td>
</tr>
</tbody>
</table>

RBC, red blood corpuscles; SG, maximum specific gravity; NPN, non-protein nitrogen.

*Maclean and de Wesselow's method.

†Figures in parentheses are serum creatinine levels (mg/100 ml).

### TABLE III

**Radiological Findings**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Excretion Urography</th>
<th>Other Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unsuccessful</td>
<td>Renal osteodystrophy terminally</td>
</tr>
<tr>
<td>2</td>
<td>Not done</td>
<td>Renal osteodystrophy terminally</td>
</tr>
<tr>
<td>3</td>
<td>Not done</td>
<td>Renal osteodystrophy terminally</td>
</tr>
<tr>
<td>4</td>
<td>Two small kidneys with smooth outline</td>
<td>Micturating cystograph shows no vesicoureteric reflux; renal osteodystrophy present</td>
</tr>
<tr>
<td>5</td>
<td>Both kidneys small and smooth; gross impairment of function</td>
<td>Renal osteodystrophy present</td>
</tr>
<tr>
<td>6</td>
<td>Both kidneys small and smooth; both sides show hydrenephrosis</td>
<td>Renal osteodystrophy terminally</td>
</tr>
<tr>
<td>7</td>
<td>Both kidneys small; very poor renal function; slight irregularity of outline</td>
<td>Renal osteodystrophy terminally</td>
</tr>
<tr>
<td>8</td>
<td>Both kidneys smooth and of average size, very poor renal function</td>
<td>Renal osteodystrophy present</td>
</tr>
</tbody>
</table>
TABLE IV
Pathological Features

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Death (yr)</th>
<th>Source of Tissue</th>
<th>Findings in Kidney</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight (g)</td>
<td>Medullary Cysts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>Necropsy</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Necropsy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>Necropsy</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>Biopsy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Necropsy</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>Necropsy</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>Biopsy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>Biopsy</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

The normal corticomedullary markings and small medullary cysts up to 8 mm in diameter were constant features of the cut surface (Fig. 1). The histological changes were similar in each case and noticeably diffuse in distribution. In the cortex there was extensive sclerosis of glomeruli and hypertrophy of surviving glomeruli with periglomerular fibrosis. Tubular atrophy was marked in both cortex and medulla, with interstitial fibrosis and cellular infiltration by lymphocytes and occasional plasma cells. In the medulla there was usually alternation of groups of surviving dilated tubules and atrophic tubules in a characteristic radial distribution. The great thickening of the tubular basement membrane, particularly in the distal portion of the nephron, was a prominent feature in all cases. These broad hyaline bands sheathing atrophic tubules were seen in sections stained by haematoxylin and eosin, but were seen most clearly with the periodic acid Schiff (PAS) technique (Fig. 2). The medullary cysts were lined by cubical or flattened epithelial cells. In one case only there was mild chronic inflammation of the pelvis. Hypertensive arteriolar changes of varying severity were present in every case.

In the material from the 3 renal biopsies similar but less severe histological changes were present, though medullary cysts were not identified. Basement membrane thickening associated with atrophic tubules supported the diagnosis of nephronophthisis.

The pathological findings which are of value in diagnosis are summarized in Table IV.

Discussion

The diagnosis of chronic renal failure associated with small contracted kidneys is seldom difficult, but the classification by cause in the individual patient within this group presents a continuing problem. The original cases described in 1951 by Fanconi et al. recorded a form of chronic nephropathy in 2 unrelated families in whom all 5 sibs in one family and 3 out of the 5 sibs in the other
Nephronophthisis

FIG. 2.—Renal medulla (Case 3) to demonstrate marked thickening of the tubular basement membrane, tubular atrophy, and interstitial fibrosis. (P.A.S. × 125.)

were affected. The clinical picture was characterized as polyuria, polydipsia, diminished renal concentrating power, raised blood urea, and anaemia. The onset of the disease was usually before 4 years of age, with a progressive course ending in death usually before 10 years of age. The pathological features in the late stages were small contracted kidneys with a loss of differentiation of the renal parenchyma, hyaline degeneration of the glomeruli and the tubular basement membrane, and interstitial fibrosis. Fanconi and his colleagues considered that the condition was primarily a degenerative process rather than the result of inflammation, and they gave it the name of 'familial juvenile nephronophthisis'. Reports from other European centres have confirmed the existence of this new variety of familial nephropathy in children. von Sydow and Ranström (1962) tabulated the details of the cases of nephronophthisis and their sibs from 13 families described in the literature, including their report of a family in which at least 6 of the 11 sibs were affected. Senior, Friedmann, and Braudo (1961) in South Africa described a family of 13 sibs, of whom 6 suffered from nephronophthisis and tapetoretinal degeneration. The first report of familial nephronophthisis in America was described by Mangos et al. (1964).

During this same period a number of reports appeared in the American literature, starting with that of Smith and Graham (1945), of a disease characterized by progressive renal insufficiency and anaemia in which cysts in the renal medulla were a prominent pathological feature. The term 'medullary cystic disease' was applied to this renal condition which became accepted as a clinical and pathological syndrome. It was not until 1964
that Winberg drew attention to the similarities
between medullary cystic disease and familial
juvenile nephronophthisis.

These two conditions have been reappraised
and there is general agreement that the terminal
histology is identical (Strauss and Sommers, 1967;
Mongeau and Worthen, 1967). This does not mean
that the two names are interchangeable. The term ‘medullary cystic disease’ is non-specific
and probably has a variety of causes. It is mis-
leading in the present context because nephronoph-
thisis affects both cortex and medulla, and the
glomerular destruction is probably critical to
prognosis. It, therefore, seems to us that the
typical clinical appearance in children should be
termed juvenile nephronophthisis and modified to
familial juvenile nephronophthisis if another sib or
relative is similarly affected. Familial incidence
was a constant feature of the earlier reports, and
there is now general agreement that the condition
is inherited as an autosomal recessive character.
However, when the family size is limited, as in the
present series, the chance of single cases of the
disease occurring in a family becomes much greater.

The typical clinical picture is of a dwarfed
child aged 4 to 10 years who presents with a story
of thirst, polyuria, and a return of nocturnal
enuresis. A large bladder is palpable and severe
normochromic anaemia present. Haematuria, cast-
uria, and proteinuria are not usually present, and
systemic hypertension is a late feature. Renal
function is extremely poor and azotaemia with
eventual renal osteodystrophy are constant. Hypo-
kalaemia may be present or tapetoretinal degenera-
tion. The various tests of renal function, such as
intravenous pyelography and creatinine clearance,
reveal in the early stages normal-sized kidneys
with a progressive loss of ability to clear and to
concentrate. The isosthenic urine is of low
specific gravity and osmolality. Tomography will
show normal-sized, smooth kidneys in the early
stages, and these usually progress to small smooth
kidneys with only very fine scarring.

The contracted kidneys associated with chronic
renal disease share many pathological features
whatever the underlying aetiology, and juvenile
nephronophthisis is no exception. Certain points
may be of value in distinguishing this particular
variety of chronic nephropathy. The appearance
of uniformly contracted kidneys with fine scarring of
the subcapsular surface reflects the diffuse
nature of the disease, and contrasts with the focal
involvement of the renal parenchyma and irregular
scars which characterize the kidneys in chronic
pyelonephritis. The absence of inflammation of
the renal pelvis distinguishes nephronophthisis
from chronic pyelonephritis. The small medullary
cysts, which are a constant finding in our post-
mortem material and which are present, though not
necessarily emphasized, in many of the previous
reports of juvenile nephronophthisis, are not a
feature of either chronic pyelonephritis or chronic
glomerulonephritis, the two conditions with which
nephronophthisis is most likely to be confused.

The histological picture of glomerular sclerosis,
tubular atrophy, chronic inflammatory infiltration,
interstitial fibrosis, and hypertensive arteriolar
change is, of course, common to several varieties
of chronic renal disease. In nephronophthisis the
sclerosis of the glomerular tufts is not associated
with much intracapillary or extracapillary prolifera-
tion, and in addition periglomerular fibrosis is always
prominent in the remaining glomeruli. Tubular
atrophy is extensive, but the important feature is
the degree of thickening of the basement membrane
which is associated with both atrophic and dilated
tubules. Though this change is present in the
cortex, the distal part of the nephron, particularly
the limbs of Henle, is most severely affected.
Thickening of the tubular basement membrane is
not specific, but if unusually prominent it should
suggest the diagnosis of nephronophthisis. The
exact nature of the eosinophilic hyaline material
which surrounds the tubules is not yet clear; it
does not stain for amyloid. The interstitial
inflammatory infiltrate is diffuse, mainly lympho-
cytic in nature, and it is usually mild.

With a typical clinical history, particularly if
there is familial involvement, a renal biopsy may
provide pathological support for the diagnosis of
nephronophthisis. Necropsy will establish it
beyond doubt. Four children in this series were
diagnosed retrospectively in this way without
knowledge of the clinical details.

Little has been added to the understanding of
the condition since the original description by
Fanconi et al. (1951). There is general acceptance
that it is a degenerative rather than an inflamma-
tory process, but there is little information about
the histological changes in the early stages of the
disease.

The observations of Fetterman, Fabrizio, and
Studnicki (1967), employing the technique of
microdissection of tubules, may help to throw light
on the pathogenesis of the disease. They demon-
strated abnormalities in all portions of the nephron,
but the most striking finding was the presence of
multiple diverticula in approximately 15% of the
descending limbs, which were isolated. This is
probably the same lesion which Ivemark, Ljunqvist,
and Barry (1960) demonstrated when nephrons
were filled with radio-opaque material, but which they interpreted as elongation and coiling of the tubule.

We thank our colleagues Professor J. H. Hutchison, and Drs. J. Inall, R. A. Shanks, A. M. MacDonald, and J. D. Briggs for permitting us access to their patients.

REFERENCES


Correspondence to Dr. A. A. M. Gibson, Department of Pathology, Royal Hospital for Sick Children, Yorkhill, Glasgow C.3.
Nephronophthisis: Report of 8 Cases from Britain

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Arch Dis Child 1972 47: 84-89
doi: 10.1136/adc.47.251.84

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