FAMILIAL RENAL INSUFFICIENCY

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 5, 1951)

The picture of chronic renal insufficiency in childhood is not common, and instances of more than one member of a family with this picture are comparatively rare. Mitchell (1930), in an exhaustive review of the literature of chronic interstitial nephritis in childhood, quotes 14 instances in which more than one child in the family was affected. Graham and Hutchinson (1941) have described a family in which three or probably four out of eight children suffered from this condition. Rinkoff, Stern, and Schumer (1939) reported the death from renal failure in early adult life of three brothers: necropsy on two of them confirmed the presence of chronic glomerulo-nephritis, but death apparently occurred in all three cases soon after the symptoms appeared, and there is no evidence indicating the time of onset. Hawkins (1950) has recently described the occurrence of chronic nephritis in association with a variety of congenital defects in two brothers and in one daughter of each of them. In this family the renal lesion appears to have been relatively benign, as two of the affected members were over 40 years of age, and all of them were alive.

In view of the comparative rarity of reports on familial nephro-sclerosis, it may be of interest to report the histories of a family of six children, of whom one was found at necropsy to have a hypoplastic horseshoe kidney, and two others subsequently died of chronic renal failure.

Family History

Both parents, who are not related to one another, were healthy at the relevant period in the history, though the mother has now (1950) developed diabetes mellitus. Both were in their early twenties when their first child was born. The father was one of seven brothers of whom two died aged 9 years and 7 years, one of meningitis, and one of ulcers of the stomach. The father is unable to amplify this description. The mother has six sisters and two brothers, all alive and healthy. Neither parent knows of the occurrence of kidney disease among members of previous generations of their families.

Eleanor S., the eldest child, was born in 1927. She was admitted to this hospital at the age of 5 years suffering from enuresis, but no evidence of organic disease was found. She was married at the age of 17, and was admitted to Aberdeen Maternity Hospital in the sixteenth week of pregnancy with albuminuria. This cleared up with rest, and she was discharged, but readmitted one month later with pyelitis. An intravenous pyelogram at this time showed normal concentration and renal outlines. The pyelitis settled rapidly under treatment with alkalies. She is now said to be healthy, but she refused to be examined. Her child was examined at the age of 17 months, and no abnormality was found. He is said to be excessively thirsty, and to pass much urine, but a specimen examined had a specific gravity of 1022, and was free from albumin and abnormal deposit.

Case 1. William S. was born in 1928. This boy died in this hospital on December 18, 1930, at the age of 2 years and 9 months of bronchopneumonia following tonsillec- tomy. His case notes and necropsy report are now missing, but from entries in the notes of the subsequent children it appears that at necropsy he was found to have a hypoplastic horseshoe kidney with pyelo-nephritis. Although pus had been found in the urine on one occasion, serious renal disease was not suspected before his death. Professor J. Craig, under whose care the child was, confirms these details from memory.

Alice S. (Case 2) was born in 1930. James S. was born in 1933. He was admitted to this hospital at the age of 2 months with pyelitis, at 4 years with enuresis, and again at 11 years with pyelitis. His urinary output and specific gravity were normal during each admission, and the two infections cleared up rapidly. Physical examination at the age of 13 years was negative apart from the finding of a blood pressure of 132/96, and a suggestion of palpable sclerosis of the brachial arteries. The urine was normal, though of low specific gravity at the first examination. A subsequent morning specimen had a specific gravity of 1019, and contained scanty hyaline casts. The blood urea was 38 mg. %, and a skiagram of the abdomen showed renal shadows of normal size.
Gordon S. was born in 1935, and is the only member of the family who has no history of disease of the urinary tract. On examination at the age of 11 years, no abnormality was found, apart from a slightly raised blood pressure (135/90). A morning specimen of urine had a specific gravity of 1014, and contained scanty hyaline casts. His blood urea was 32 mg. %.

Kathleen S. (Case 3) was born in 1940.

Mrs. S. has had one subsequent pregnancy which was artificially terminated.

Case Reports

Case 2. Alice S. was first admitted to this hospital on November 24, 1931, at the age of 18 months with a history of excessive thirst, polyuria, constipation, and occasional vomiting from the age of 9 months. Her previous history was not significant. On examination she weighed only 94 lb., but was in good general condition and there were no abnormal findings. Her blood pressure was 85/75.

The following investigations were made:

Urine. Specific gravity 1010: no albumin; deposit of pus cells and occasional red blood cells. On culture a scanty growth of haemolytic streptococci was seen. On daily examination during the next three weeks the specific gravity never rose above 1010, and scanty pus cells were seen occasionally. The 24-hour output varied between 19 and 42 oz.

Blood urea was 43 mg. %. A urea concentration test gave the following results:

- Initial specimen: urea 0.7%
- After 5 g. urea after 1 hour: 0.5%
- 2 hours: 1.5%
- 3 hours: 1.0%

Cystoscopy and cystography showed no abnormality. She was next admitted in April, 1934, complaining of occasional attacks of frontal headache and dizziness during the previous year. She was then a small child weighing only 30 lb. at the age of 4 years, but was still in fairly good general condition. Her blood pressure was 115/95. Her urine specific gravity varied between 1005 and 1012, and her output between 20 and 56 oz. in 24 hours. The urine was consistently free from albumin, and the only significant deposit seen was an occasional hyaline cast. The blood urea was 69 mg. %, and the Wassermann reaction was negative. Intravenous pyelography with 10 ml. of 'uroselectan' showed no abnormality in shape or size of the right kidney, but marked delay in secretion, the maximum concentration being seen at 1 hour and 20 minutes. The left kidney was obscured by gas throughout the examination.

The child was subsequently readmitted in November, 1934, November, 1935, May, 1936, September, 1936, May, 1939, November, 1940, January, 1941, and September, 1941. The usual reason given for admission before 1940 was recurrent attacks of colicky abdominal pain sometimes accompanied by diarrhoea and vomiting; subsequent admissions followed periods of generalized convulsions. Polyuria and thirst were constant symptoms throughout. Radiological evidence of renal rickets was first seen in April, 1937, when she was 7 years old. The optic fundi remained normal until January, 1941, when it was noted that both optic discs were pale, that there was marked exposure of the choroidal vessels, and that the arteries appeared narrow: there were no haemorrhages nor exudates. The details of her progress during these admissions can most easily be followed in tabular form (Table 1).

Her final admission was on January 13, 1942, following a series of convulsions during the preceding two days. On examination she appeared pale and drowsy and showed marked air hunger. She vomited persistently, passed no urine, and died within 12 hours of admission.

Necropsy. Necropsy was performed 12 hours after death. Both kidneys were greatly reduced in size, the right weighing 15 g. and the left 40 g. (average weight of normal kidney at age 11 years, 95 g.). The capsules could be stripped, and the subcapsular surfaces were pale and coarsely granular. The kidneys were studded with small, pearly white nodules, each about 0.5 cm. in diameter. There was no gross dilatation of the renal pelves or ureters. There was marked cloudy swelling of the liver. The heart showed slight left ventricular hypertrophy. The epiphyseal lines in the femur were wide and slightly irregular. No other abnormalities were noted.

The histology is discussed under case 3.

Case 3. Kathleen S. was first admitted to this hospital on February 11, 1942, at the age of 16 months with a history of excessive thirst, polyuria, constipation, and failure to thrive for several months. She had been born three weeks prematurely, and her birth weight was 4 lb. Her development at first appeared normal. Since weaning, she had been unwilling to eat solid foods, but had always appeared thirsty. On examination she was seen to be an irritable child with a rather waxy skin, but no other abnormality was found. Her height was 26 in., and her weight 21 lb. Twelve successive 24-hour specimens of urine were examined: the specific gravity ranged from 1006 to 1012; traces of albumin were present in two specimens, and no casts or cellular deposits were seen.

Her further progress during the next four years can again most easily be summarized (Table 2).

Her tonsils and adenoids were removed in February, 1945, on account of recurrent attacks of tonsillitis. Radiological evidence of rickets was first detected in February, 1946, and by June of that year knock-knee was apparent. About this time she began to complain of pain in her legs and became unwilling to walk.

By July, 1946, she was having frequent attacks of vomiting, and on July 31, she was finally admitted with a history of constant nausea and drowsiness, and occasional convulsions during the preceding two weeks. On admission she appeared pale and drowsy; no oedema was present; the optic fundi were normal; her blood pressure was 120/80. Urine specimens were difficult to collect owing to continual incontinence, but on one occasion the specific gravity was 1010; no albumin was present but there were considerable numbers of pus cells.

Blood chemistry

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea</td>
<td>392 mg.%</td>
</tr>
<tr>
<td>Plasma cholesterol</td>
<td>184 mg.%</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>6.4 mg.%</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>8.0 mg.%</td>
</tr>
<tr>
<td>Serum phosphatase</td>
<td>33 units</td>
</tr>
</tbody>
</table>
### TABLE 1
#### SUMMARY OF CASE 2 DURING ADMISSIONS BETWEEN 1934 AND 1941

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Height (in.)</th>
<th>Weight (lb.)</th>
<th>Blood Pressure</th>
<th>24-hr. Urine Output (oz.)</th>
<th>Urine Specific Gravity*</th>
<th>Blood Urea (mg. %)</th>
<th>Other Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov., 1935</td>
<td>5½</td>
<td>31½</td>
<td>108/62</td>
<td>50–90</td>
<td>1002–1010</td>
<td>120</td>
<td></td>
<td>Urine: occasional trace albumin; day and night volumes approximately equal. Blood Ca 10·2 mg. % Phosph. 5·9 mg. %</td>
</tr>
<tr>
<td>May, 1936</td>
<td>6</td>
<td>33½</td>
<td>132/96</td>
<td>44–70</td>
<td>1005–1010</td>
<td></td>
<td></td>
<td>Urea clearance 9%</td>
</tr>
<tr>
<td>May, 1939</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>1002</td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov., 1940</td>
<td>10½</td>
<td>45½</td>
<td>120/82</td>
<td></td>
<td>1004</td>
<td>220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan., 1941</td>
<td>10½</td>
<td>46½</td>
<td>46</td>
<td>145/90</td>
<td>40–92</td>
<td>1003</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Sept., 1941</td>
<td>11½</td>
<td>46½</td>
<td>50</td>
<td>140/90</td>
<td>30–50</td>
<td>1003</td>
<td>192</td>
<td></td>
</tr>
</tbody>
</table>

* The very low figures quoted were confirmed on several occasions during the later admissions by the Natural Philosophy Department, Aberdeen University.

### TABLE 2
#### SUMMARY OF CASE 3 DURING ADMISSIONS BETWEEN 1943 AND 1946

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Height (in.)</th>
<th>Weight (lb.)</th>
<th>Blood Pressure</th>
<th>24-hr. Urine Output (oz.)</th>
<th>Urine Specific Gravity</th>
<th>Blood Urea (mg. %)</th>
<th>Other Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept., 1943</td>
<td>3</td>
<td>34½</td>
<td>28½</td>
<td></td>
<td>1004–1018</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sept., 1944</td>
<td>4</td>
<td>28</td>
<td>140/110</td>
<td>23–43</td>
<td>1002–1008</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb., 1945</td>
<td>4½</td>
<td></td>
<td>128/92</td>
<td>18–26</td>
<td>1011</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb., 1946</td>
<td>5½</td>
<td></td>
<td></td>
<td></td>
<td>1003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June, 1946</td>
<td>5½</td>
<td></td>
<td>135/100</td>
<td></td>
<td>1005</td>
<td>358</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
following intermittent convulsions, the child died on August 4, 1946.

Necropsy. Necropsy was performed 24 hours after death. The kidneys were the only organs showing significant abnormality. The combined weight of the two kidneys was 70 g. (normal at this age 130 g.). The capsules stripped readily leaving a smooth but pale surface; the cut surface showed a loss of definition between the cortex and the medulla, and some small, scattered cysts. The blood vessels appeared normal.

Histology. Both cases alike presented the histological characteristics of chronic pyelo-nephritis (Fig. 1 and 2). Both showed hyalinization of many glomeruli accompanied by atrophy of the related tubules. In case 2 the proportion of hyalinized glomeruli was greater, and all the surviving glomeruli were considerably hypertrophied, while their capsules were distended as in hydronephrosis (Fig. 3); arteriosclerosis and arteriolosclerosis were prominent features (Fig. 4); no tubular cysts were present. In case 3 numerous small cysts lined by moderately hyperplastic cubical epithelium were noted (Fig. 5): the majority of the surviving glomeruli were normal in size, and only a small number of them showed a conspicuous degree of hypertrophy (Fig. 6); neither arteriosclerosis nor arteriolosclerosis was a prominent feature. It is emphasized that, in both cases alike, all the surviving glomeruli, whether hypertrophied or not, showed no stigmata of an antecedent glomerulo-nephritis.

Discussion

The clinical picture of renal sclerosis in childhood is an uncommon one. It may result from chronic glomerulo-nephritis or from chronic pyelo-nephritis; it may be associated with congenital cystic disease; it is probably very rarely secondary to essential hypertension; in a considerable proportion of cases it appears insidiously, often at a very early age, without any history suggestive of previous renal disease.

In the two children of this family about whom detailed information is available, there was no definite evidence of the nature of the original disease process. In both, the history of thirst and polyuria indicated the onset of renal failure before the end of the first year of life. In neither was there any history suggestive of an acute attack of glomerulo-nephritis, nor does the histological picture support this diagnosis. Moreover, when glomerulo-nephritis does occur at this age, it tends, in my experience, to be severe and unlikely to pass unnoticed. The histological appearances would support a diagnosis of pyelo-nephritis, and indeed establish its presence in both cases at the time of death, but the clinical evidence suggested that this was not the primary condition. In the course of a very large number of urine examinations in both cases, pus cells in significant numbers were reported on isolated occasions only. In neither case was there any evidence at necropsy of congenital or other conditions predisposing to urinary stasis which is associated with chronic urinary infection in such a large proportion of cases in childhood. Furthermore, pyelo-nephritis is usually known to have been present for a number of years in those cases in which it ultimately leads to renal sclerosis. While it seems improbable that it could produce symptoms of renal failure before the end of the first year of life, this possibility cannot be absolutely excluded; but, even if it be admitted that the essential pathological process is a pyelo-nephritis, the fact that this condition has occurred in three members of one family in the absence of gross urinary stasis surely suggests that the kidneys in the first place must have been in some way abnormal. The clinical evidence seemed to indicate that the pyelo-nephritis was a secondary condition.

Arteriosclerosis and arteriolosclerosis were prominent on histological examination only in case 2 (Fig. 4), but in neither case was anything more than a very moderate degree of hypertension observed even in the terminal stages, while in case 2 the blood pressure was certainly normal after the picture of renal failure was established. This is in keeping with the usual finding in cases presenting the picture of this type of renal failure in the first few years of life (Spence and Davison, 1949). Ellis (1942), in his survey of the natural history of Bright’s disease, has suggested that “chronic interstitial nephritis, as we have known it in the past, is merely the result of hypertension.” This may well be true of those cases seen in adult life or later childhood in which the blood pressure is usually found to be significantly raised whatever the nature of the primary disease. In infancy and early childhood, however, it seems that some other factor must be capable of producing the clinical and histological picture of chronic interstitial nephritis.

In cases of renal sclerosis which arise insidiously without any previous history of renal disease, it is sometimes assumed that there has in fact been a preceding attack of glomerulo-nephritis with symptoms mild enough to escape detection. There seems no justification for this assumption in cases such as are the ones under discussion, for in clinically obvious cases of acute nephritis in childhood, where complete resolution does not occur, progress towards the final picture of renal sclerosis is slow, and this stage is rarely reached before the age of puberty. There seems no good reason to suppose that an attack of acute nephritis mild enough to remain undetected will result in the more rapid onset of sclerosis and, even if the possibility of an attack of acute nephritis in utero be admitted, it seems highly improbable that it will result in the
FIG. 1 (Case 2).—Pus in lumen of tubule; hyperaemia and round cell infiltration of interlobular septum (×90).

FIG. 2 (Case 3).—Chronic pyelitis. Pus in lumen of pelvis (×90).

FIG. 3 (Case 2).—Group of five glomeruli showing some dilatation of capsules and capsular fibrosis; notable absence of adhesions between tuft and capsule; interstitial fibrosis and atrophy of tubules (×90).
FIG. 4 (Case 2).—Sclerosed artery and two nearly normal glomeruli (×90).

FIG. 5 (Case 3).—Small cyst lined by hyperplastic cuboidal epithelium (×90).

FIG. 6 (Case 3).—Group of glomeruli, one of which is notably hypertrophied; other glomeruli sclerosed; related tubules atrophied (×90).
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clinical picture of renal sclerosis before the age of one year.

Where, as in this instance, the syndrome appears in two members of one family in the first year of life, and in addition another member is known to have had congenitally abnormal kidneys, it suggests either the presence of some maternal factor capable of damaging the foetal kidneys in utero, or of a genetic factor resulting in the development of inferior or abnormal renal tissue. The first possibility would seem unlikely, as there was an interval of 12 years between the birth of the first and the last of the affected children, and as, during this period, the mother herself remained in good health, and gave birth to two children with apparently normal kidneys. While it seems likely, therefore, that the defect was genetically determined, its nature remains obscure and histological examination threw no light on this aspect of the problem. It is indeed unlikely that the problem will ever be solved on the basis of necropsy findings in children dying of chronic renal failure, for the picture then is of general atrophy of renal tissue accompanied by interstitial fibrosis. Evidence as to the nature of the defect might be obtained by examination of kidney tissue from stillbirths or abortions occurring in a family where a case of renal sclerosis in early life is already known. From the family here reported, no further information can be obtained, as the mother has already been sterilized.

The occasional occurrence of several cases of renal sclerosis in one family supports the view that genetic factors may be responsible for some, at any rate, of the single cases of this syndrome declaring itself in the early years of childhood. For the present the title 'congenital hypoplastic kidneys' suggested by Spence and Davison (1949) is probably the most appropriate to describe this condition, although it is by no means certain that this is a true primary hypoplasia rather than an inflammatory or degenerative process.

Summary

The history is given of a family in which two members developed chronic renal failure in infancy, and a third died at an early age and was found to have a hypoplastic horseshoe kidney.

It is suggested that in these cases renal sclerosis is the result of some congenital defect or weakness of the kidney tissue.

I wish to express my thanks to Professor John Craig for advice and encouragement in the preparation of this report, and to Professor John S. Young for the necropsy and histological reports and for the accompanying microphotographs.

REFERENCES


ADDENDUM

Since this paper was submitted another family with a somewhat similar history has come to my notice. The parents are both alive and healthy; they have had 11 children, three boys and eight girls. Of these, numbers 4, 6, and 7 in birth order, all girls, died at the age of 7 or 8 years with symptoms of chronic uraemia. Necropsy confirmed the presence of renal sclerosis in all three. Number 9 in birth order, also a girl, has now appeared at the age of 8 years with a history of excessive thirst from the age of 18 months or earlier. She is in fair general condition; the blood pressure is 110/70, the blood urea 132 mg. %, and the serum phosphorus level 9 mg. %.

The urinary output is high and the specific gravity of the urine rarely rises above 1006. Traces of albumin are occasionally present and there is no significant deposit. A urea clearance test showed 25% of normal clearance. It has not been possible to examine the remaining members of the family but specimens of urine from three of them, including the two youngest, were of fairly high specific gravity and contained neither albumin nor abnormal deposit.