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Review of nephronophthisis and a report of one case

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A REVIEW OF NEPHRONOPHTHISIS

AND A REPORT OF ONE CASE

By

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Medullary cystic disease of the kidney was first described in 1945 by Smith and Graham[35]. Their patient was an eight year old boy with an obscure anemia of insidious onset, severe azotemia, normal urine sediment, no proteinuria, and no personal or family history of antecedent renal disease. At autopsy, the kidneys contained numerous cysts, one millimeter to one centimeter in diameter, mainly at the corticomedullary junction, but also in the pyramids and occasionally in the thinned cortices. There was generalized fibrosis and some areas of chronic inflammatory cell infiltrate. Many glomeruli were hyalinized, but the remainder were either normal or hypertrophied. There was widespread tubular atrophy and dilatation.

A number of similar cases have been reported[4,5,14,15,17,25,41,43]. In 1962 and 1963, Strauss[37,38] reviewed the available literature and reported two new cases of his own plus seven other unpublished cases. In 1966, Goldman et al[9] reported fourteen cases in a single family.

In 1951, Fanconi et al[6] described a renal disease that they called familial juvenile nephronophthisis. The disease was characterized as consisting of anemia and azotemia of insidious onset, polyuria, isosthenuria, a relative paucity of other clinical findings, early onset usually at the age of two to three years, and familial occurance. The pathological findings were:

contracted kidneys, wide-spread atrophy of tubules with focal hyperplasia, wide-spread hyalinization of glomeruli, and interstitial round cell infiltrates. Cysts were not consistantly present.

A limited number of cases of this disease were reported, mainly in the european literature[2,11,12,18,20,24,34,42]. In 1964, Winberg[44] noted the similarity between medullary cystic disease and familial juvenile nephronophthisis. In 1966, in an editorial in the New England Journal of Medicine[3], attention was again called to the similarity between these two described disease entities. In 1967, Mongeau and Worthen[26], Strauss and Sommers[39], and Herdman et al[14], and in 1968, Axelsson and Ödland[1], and Pedreira et al[32] reported further cases and concluded that the reported cases of these two diseases could not be separated by reliable criteria.

Combining data published on both diseases, and recently for the two combined, there have been one hundred and seven well documented cases of this disease reported in the world literature.

Priority favors usage of the term medullary cystic disease, but this term is misleading in the light of recent findings and a great deal of confusion exists concerning it's application[7,8,10,23,27]. Familial juvenile nephronophthisis is also somewhat misleading, but is distinctive. The abandonment of the modifiers

familial and juvenile would remove the objections to this term. Therefore, I will refer to the herein described disease as nephronophthisis.

CASE PRESENTATION

C. C., a negro female, was born on December 11, 1966 following a thirty-eight week normal pregnancy, uneventful labor, and a low forceps delivery. The one minute apgar rating was eight. No abnormalities were noted, but an electrocardiogram was taken because of a family history of congenital heart disease. This was normal and she was discharged at the age of three days.

The family history was as follows: the mother, age thirty-two, and father, age thirty-three, were stated to be in good health with no evidence of heart or renal disease, or diabetes in themselves or in their families. The mother had previously delivered three children who died at the ages of two days, two weeks, and six months. D. C. was a negro male born in September, 1962. At the age of four months he was noted to be anemic with a hemoglobin of 5.3 gm%. He was treated with transfusions. Bleeding difficulties developed. Laboratory investigation revealed Stuart factor deficiency in Stages I and II and primaquine sensitivity. He was noted to have a cardiac murmur, developed congestive heart failure, and was treated with digoxin. He died at another hospital on

March 29, 1963, at the age of six months. An autopsy was performed. A report of light microscopy performed on sections of kidney showed numerous dilated cystic structures lined with a low cuboidal epithelium. These were noted throughout the cortex and medulla. Many contained an amorphous, pink-staining material.

Female C. was born on December 10, 1963, weighing five pounds, three ounces, following a thirty-eight week pregnancy. The child was noted to be cyanotic, with a loud murmur and the cardiac impulse on the right side of the chest. The child died at the age of two days. An autopsy showed dextrocardia, atresia of the pulmonary valve, hypoplasia of the main pulmonary artery, a ventricular septal defect, and "multicystic" kidneys. The kidneys weighed four grams each and showed normal lobular markings. Microscopic examination revealed scattered cystic dilatation of distal and collecting tubules. The glomeruli were predominantly normal with occasional fibrosis of Bowman's capsule that obliterated portions of some glomeruli.

The third child died at the age of two weeks; other information is not available.

The clinical course was one of an inexorable progression of renal failure. She was first admitted to the University Hospital on April 26, 1967, at the age of six months for vomiting, diarrhea, and six grand mal seizures since the age of one month. Physical examination

revealed a lethargic child with no evident abnormalities. Laboratory examination revealed severe metabolic acidosis, anemia, BUN of 76 mg%, calcium of 2.3 mEq/L, and PO_4 of 15.5 mg%. Urinalysis showed low specific gravity and 2+ protein. A urine culture and colony count showed 30,000,000 colonies of Escherichia coli. A chest X-ray showed cardiomegaly with predominantly right-sided enlargement. A skull series was interpreted as normal. An intravenous pyelogram with a double dose of contrast media showed normal position, but function was too poor to allow detail to be seen. A continuous infusion IVP produced bilateral nephrograms of normal size, but again visualization of the collecting system was poor. An electrocardiogram was interpreted as evidence of sinus tachycardia and left ventricular hypertrophy. An electroencephalogram was normal. A percutaneous kidney biopsy showed predominantly hyalinized glomeruli with with a thickened basement membrane of Bowman's capsule and periglomerular fibrosis. The tubules were atrophic with thick basement membranes. There was extensive interstitial fibrosis and a moderate chronic inflammatory cell infiltrate. Electron microscopic examination the glomerular capillary basement membrane to be focally swollen on the endothelial side with focal epithelial cell foot process obliteration. Wrinkling of the membrane was common. Some glomeruli had lobular scarring. The tubules were largely atrophic

and some contained cast material. This histologic appearance was interpreted to be compatible with, but not diagnostic of, nephronophthisis.

She was treated with oral and intravenous fluid and electrolyte replacement, peritoneal dialysis, antibiotics, transfusion, and a low protein diet. She was discharged on June 6, 1967.

The patient was admitted on June 21, 1967, at the age of six months, with an upper respiratory tract infection, anemia, and acidosis. Her hemoglobin was 6.7 gm% and her BUN was 48 mg%. She was treated with fluid and electrolyte replacement and transfusion and discharged on June 28.

She was seen in the emergency room later on June 28 with hypocalcemic tetany which was treated with calcium gluconate.

Her third admission was from July 19 until September 29, 1967, for cellulitis of the right hand and arm and electrolyte imbalance. She was accidently given an overload pf packed red cells on August 3 and became anuric but returned to her previous level of function following several days of phlebotomy and careful fluid and electrolyte regulation. On September 4, she had an unexplained episode of acute pulmonary edema which subsided in three days.

The patient was next admitted from January 8, 1968, until January 10,1968, for transfusion.

Her fifth admission was from February 8 until February 12, 1968, when she was transfused and an aneurism of the right temporal artery was excised. Her BUN was 98 mg%.

On February 14, 1968, the patient was admitted with acute dehydration, severe acidosis, respiratory embarrassment, and cardiovascular collapse. She was repeatedly transfused because of uncontrolled bleeding from intravenous infusion sites. She was given a platlet concentrate infusion. Peritoneal dialysis was repeatedly performed. Oliguria of about one milliliter per minute was noted. She was discharged on March 5, 1968, at the request of her parents with knowledge of her extremely poor prognosis.

Her seventh and last admission commenced on March 11, 1968, when she was found to have anuria, anemia, edema, azotemia, a large ulcer in the right temporal area, and several infected intravenous infusion sites. Her laboratory findings were: BUN 90 mg%, creatinine 10.5 mg%, potassium 2.2 mEq/L, and hemoglogin 7.1 gm%. Following repeated peritoneal dialysis, Pseudomonas aerurinosa and Klebsiella pneumoniae were cultured from dialysate fluid, wound dressings, and macerated groin skin. She was treated with appropriate antibiotics.

An open renal biopsy was attempted on March 13, but no renal tissue could be identified in the specimen submitted. Large bladder clots were noted and bleeding persisted. She died on March 21, 1968, at the age of

fifteen months. An autopsy was performed.

AUTOPSY FINDINGS

Generalized cachexia was noted. The immediate cause of death was probably Pseudomonas aeruginosa septicemia secondary to generalized peritonitis.

The right kidney weighed thirty-two grams, the left, twenty-nine grams. The renal vessels were normal. The calyceal systems were somewhat dilated. The capsules were slightly thickened and stripped with difficulty. The cortices were thinned; the maximal thickness being three millimeters. The corticomedullary markings were indistinct on the right, distinct on the left. There were numerous homogeneous orange-colored areas up to one centimeter in diameter. No cysts were noted.

Microscopic examination revealed numerous fibrosed and partially fibrosed glomeruli, marked periglomerular fibrosis, and a very significant increase in interstitial fibrous tissue with focal collections of chronic inflammatory cells. The medullae contained numerous cystic tubules lined with a low flattened epithelial cells. Throughout the parenchyma, in both interstitial tissue and within tubules, there were numerous refractile crystalline foreign objects. Chemical analysis showed these to be calcium oxylate crystals. The vasculature was congested. Periodic acid-Schiff staining of

sections showed thickening of the basement membranes of both glomeruli and tubules. This was minimal in some areas, but in other areas produced a wide, wavy band.

CLINICAL FEATURES

Nephronophthisis may present in a variety of ways. Most commonly, anemia of insidious onset and obscure etiology brings these patients to a physician.[4,9,10,26,32,33,35,37,38,42] They may also present as an addisonian-like salt-wasting syndrome,[37,41] as osteitis fibrosa cystica in children and adolescents,[37,42] or as hypocalcemia with or without tetany.[42] These patients progress to death within a few months to a few years following diagnosis.

Nephronophthisis has occured in patients rangeing in age from two[2,6,20] to fifty-six years.[37] Possibly because of bias introduced by usage of the term, those cases reported as familial juvenile nephronophthisis have with two exceptions been less than ten years of age at the onset of their disease. Cases reported as medullary cystic disease have ranged from eight to fifty-six years.[37] Age incidence is thus difficult to assess, but there seems to be peaks of incidence in childhood and in adolescence and young adulthood. Only five cases have been reported in patients over the age of fourty years.[1,14,38] The case reported here was younger at onset and at death than any previously

reported.

Approximately equal numbers of males and females are included among the reported cases. Only one instance of the occurance of nephronophthisis in a negro has been previously reported.[43]

A family history of renal disease has been more commonly present in those cases described as familial juvenile nephronophthisis, 83%, than in those characterized as medullary cystic disease, 47%. Consanguineous parents have been reported by two authors.[18,42]

Azotemia is usually well advanced by the time the diagnosis is established. Often the blood urea nitrogen is greater than 100 mg%, and has been greater than 200 mg% at the time of the original investigation.

Proteinuria is not uncommonly present in small amounts and becomes more common in the terminal phases of the disease. Occasional glucosuria has been reported.[2, 6] The urinary sediment is usually within normal limits.

Polyuria, with hyposthenuria, is a frequent symptom of this disease, especially in younger patients. It may have been present throughout life, but more commonly has appeared during the year or two preceeding discovery of the disease. Maximum urinary specific gravity is only rarly greater than 1.010 to 1.012. These patients are unable to concentrate their urine during a twelve hour water deprivation test or upon administration

of pitressin.[17,18,24,32,38] Water intake is generally in the range of two to four liters of water per day, considerably less than would be expected in true diabetes insipidus.[2]

Renal salt-wasting may be marked in this disease, in some cases sufficiently so that a diagnosis of adrenal insufficiency may be entertained.[36,41] This sodium and chloride loss does not respond to adrenocortical extract,[30,40,41] desoxycorticosterone acetate,[19,22,28,38,40,41] 9-alpha-flourohydrocortisone,[38] or adrenocorticotropic hormone.[28,30,40] Urinary aldosterone excretion studies, reported in two cases, have been normal to slightly elevated.[14,24] They have also been found to be elevated in relatives of affected patients.[14] The response of aldosterone excretion to salt loading has been reported as normal.[24]

Defective hydrogen ion excretion by the kidneys may be great enough to produce a marked metabolic acidosis, generally in the terminal phases of the disease.[9,26,38,42]

Renal calcium loss may be marked enough to produce renal osteodystrophy[32,37,42] or tetany.[26,32] Either of theseconditions may be early and severe enough to produce the presenting complaints. Slipped femoral capital epiphyses have complicated renal osteodystrophy to the point that the patient was unable to walk.[37]

Anemia is an almost universal concomitant of nephronophthisis. This anemia is usually of the normocytic, normochromic variety, but may be hypochromic.[2,26,32,37] Two patients have been reported with a low serum iron,[2,32] whereas this was noted to be normal in others.[2,4] The anemia is often severe enough to require repeated transfusion,[26,32,37] as was the case with C. C.

Hypertension has been an unusual finding in patients with nephronophthisis until the terminal stages, when both systolic and diasolic pressures may show moderate elevation.[9,26,32,37]

An elevated erythrocyte sedimentation rate has been noted by some authors,[2,14,24] while others have found this parameter to be within normal limits.[26]

Associated abnormalities have not commonly been found with nephronophthisis. Small stature and growth retardation are found with some frequency in young patients. Pedreira et al[32] suggest that this may be genetically determined, but this finding is not noted among older patients. Three families have been reported in which retinitis pigmentosa coincided with nephronophthisis in several siblings.[14,25,34] Another family has been reported in which cataracts and retinal changes coexist with polycystic disease, medullary sponge kidney, and nephronophthisis in three siblings respectively.[5]

One of the families reported by Fanconi et al[6] had a high incidence of hare-lip and cleft palate, but neither of these abnormalities was present in the reported cases. One patient with a club foot was reported by Mongeau and Worthen.[26] No auditory abnormalities have been found in conjunction with nephronophthisis. Neither have any previous cases been reported coexistant with congenital heart disease.

A variety of diagnostic procedures have been performed on these patients. As has been noted previously, they do not respond to water deprivation, pitressin, desoxycorticosterone acetate, or 9-alpha-flourohydrocortisone. Amino acid excretion studies have been unrewarding except in two patients who showed increased excretion of proline.[2,26]

Radiographic procedures are also generally unrewarding except to demonstrate decreased renal function, and often small kidneys. Intravenous pyelography often shows only delayed or absent appearance of the contrast media.[32] Retrograde pyelography is usually normal, but may reveal small kidneys.[8,10,26,32,38] Selective renal arteriograms have either been normal[14] or shown a small kidney with a very thin cortex, distended medullary vessels, and lucencies suggesting the presence of cysts.[26] Renal scans with Hg^{203} and I^{131}-Hippuran were normal in the single case in which they were reported.[14]

The most helpful diagnostic procedure has been renal biopsy. Both the percutaneous needle technique[14, 24,26] and open surgical biopsy[9,26] have been performed.

PATHOLOGICAL FEATURES

Grossly, the kidneys from a case of nephronophthisis are usually small, firm, and pale. Their average weight has been from eighty-five to ninty grams,[9,14] with a range of from forty-three and forty-five grams[14] to one hundred and forty grams each.[41] Rarely has the difference in weight between the two kidneys been greater than ten grams.[1,37,38] The kidney sizes reported for C. C. and female C. are considerably smaller than any repprted previously. This may be due to the extremly young age at which they were examined.

The capsule usually strips easily[32,38] to reveal a smooth,[38] granular,[9,32] or slightly nodular surface.[1, 38] On cut section, the cortex is thinned, usually to two to four millimeters in thickness, the cortico-medullary junction blurred, and the calyceal and pelvic regeons smooth and not thickened. Often numerous cysts are present, varying from pinpoint to two centimeters in size.[9] They are located predominantly along the corticomedullary junction, but may also be numerous down into the pyramids. Frequently occasional cysts are found throughout the cortex. Macroscopic cysts have been present in eighty-five percent of

those cases reported as medullary cystic disease and in forty percent of those reported as familial juvenile nephronophthisis.[26]

By light microscopy, a majority of the glomeruli are hyalinized, but the remainder are either normal or hypertrophied. Thickening of Bowman's capsule and periglomerular fibrosis are present. Strauss and Sommers[39] report that some glomeruli are abnormally small, about half normal size. They suggest that this reflects a process that began in the perinatal period.

Almost all the cortical tubules, except for a few proximal convolutions, have an atrophic or unspeciallized epithelium. Many are dilated and nearly all appear engulfed in fibrous tissue.[39] Ivemark et al[20] describe thickening of the tubular basement membrane in all segments, especially the ascending limb of Henle's loop and the distal convoluted tubule. There is extensive, diffuse interstitial fibrosis[39] and patchy infiltrates of lymphocytes, plasma cells, and occasional histiocytes.[9,32,37,38,39] Strauss and Sommers[39] also note occasional dense, focal scars and calcific foci, as were found in the present case. In the series of Goldman et al[9] no calcific foci were found.

When cysts are present, They are lined by a single layer of cuboidal[9] or flattened epithelium.[38] They may

contain scanty amorphous eosinophilic material.[38] Ivemark et al[20] report that all the cortical cysts examined through serial sections were found to contain glomerular tufts of varying degrees of atrophy. They also note that the histologic structure of the large medullary cysts was indistinguishable from that of the ectatic papillary ducts they found, but that small cysts, up to two millimeters in diameter, often had one ascending and one descending limb of Henle's loop opening into their cortical aspects. This finding has been confirmed by other authors.[14,26] Strauss[38] noted structures resembling atrophic smooth muscle fibers in the wall of an occasional medullary cyst. Medullary tubules and cysts are surrounded by an acellular hyaline material, or collar,[38] that took a collagen stain.[37]

Renal vessels have only shown changes in older patients.[32,37,38]

This histologic appearance is nonspecific and is indistinguishable from that of chronic pyelonephritis.[9,26,32,39,43] This might commonly lead to misdiagnosis,[26] especially in sporadic cases and in patients seen late in the course of their disease. Voth,[43] Mongeau and Worthen,[26] and Strauss[37] argue against pyelonephritis playing a significant role in the pathogenesis of this disease on the basis of the absence of clinical evidence of infection, the bilaterally symmetrical involvement

of the kidneys, the uniform involvement throughout each kidney, and the absence of the usual pyelonephritic scars. Strauss[35] has since reported the presence of scars in some affected kidneys. The present case deviates from the usual pattern of nephronophthisis in that clinical evidence of pyelonephritis was present. This may account for some of the variations in pathological findings, such as kidney size and capsule stripping.

Florescence microscopy has failed to reveal the presence of either immune globulin or compliment on the glomeruli.[14,15]

Microangiographic studies reported by Ivemark et al,[20] in a case described as familial juvenile nephronophthisis, noted a striking hyperplasia of the descending limb of the loop of Henle. However, Herdman et al,[14] reporting microdissection studies in one of their cases, found the loops of Henle to be normal.

Electron microscopic examination has been reported in only three cases. Pedreira et al[32] noted thickening of the basement membranes of both glomeruli and tubules. Goldman et al[9] reported irregular thickening and loss of distinct boundaries in the basement membrane of the cysts and dilated tubules. Herdman et al[14] reported interstitial fibrosis and greatly thickened basement membranes of all tubules with either lamination or scalloped irregular extensions which projected into

the cytoplasm of the tubular cells. Cyst formation was associated with extreme thinning of the tubular cytoplasm and extreme thickening of the basement membrane. The cysts contained material that was presumed to be casts. They also noted dilated, protein-filled lymphatic vessels.

The electron microscopic findings in the present case are essentially in accord with the previous studies.

Other pathologic findings at autopsy have been parathyroid hyperplasia,[32,37] hypoplasia of the bone marrow,[38] and renal osteodystrophy.[26] Adrenal hyperplasia has been common among patients with severe salt-wasting.[38] In one of Fanconi's[6] cases, dense eosinophilia of the cells of the anterior pituitary was noted, and a pituitary adenoma was present in the case reported by Fairly et al.[5]

The only cystic changes noted in other organs in the reported cases of nephronophthisis was cystic dysplasia of the mucosa of the colon.[4]

Several conjecture have been made concerning the pathologic physiology in patients afflicted with nephronophthisis. Strauss[38] suggests that the absence proteinuria and formed elements in the sediment reflects the relative intregrity of the remaining glomeruli. He further speculates that the hyposthenuria may be caused by an osmotic diuresis due to the great urea load

presented to the tubules, by a disruption of the countercurrent multipier mechanism in the disorganized medulla, or by an inhibition of osmotic equilibrium between the tubular lumens and the medullary interstitium by the large amount of fibrous tissue surrounding the collecting tubules. The last mentioned hypothesis might also explain the previously noted unresponsiveness to antidiuretic hormone.

ETIOLOGY AND PATHOGENESIS

The most commonly proposed etiologic mechanism of nephronophthisis has been genetic transmission.[1,2,3,6,9,14,15,24,26,32,42] Two patterns of inheritance have been described.[14] Usually, the familial pattern is most consistant with an autosomal recessive transmission,[1,2,14,24,26,32,42] however, the pattern in some families is more consistant with a dominant type of inheritance,[9,29,34] and may be X-linked.[9]

In the families in which autosomal recessive transmission is most compatible with the observed genealogical pattern, the ratio of affected to healthy siblings is close to 1:1. On theoretical grounds this ratio should be 1:3. Since most of these families have been reported as familial juvenile nephronophthisis, ascertainment bias due to exclusion of sporadic cases may account for this discrepancy, although, as Mangos et al[24] show statistically, this does not fully explain

the disparity between the expected and observed ratios.

Decreased concentrating ability of the kidney in several otherwise healthy relatives of affected patients has been reported in three families.[2,24] The pedigrees of these families have otherwise been consistent with autosomal recessive transmission. This finding has been considered by several authors to indicate an heterozygous "carrier" state.[2,24,26,32] Careful studies of other families have not documented this finding.[14]

Several authors suggest that nephronophthisis represents a primary tubular disease, with interstitial and glomerular changes secondary to tubular malfunction.[2,6,14,20,26] Herdman et al[14] propose that some inborn error of metabolism causes functional and ultimately structural changes in the distal nephron leading to cyst formation and secondarily to glomerular changes and scarring.

Mongeau and Worthen,[26] noting the histological and clinical features of this disease to be very similar to those of toxic nephropathies, propose that nephronophthisis results from the action of a nephrotoxic substance on the kidney. Because of the probable genetic nature of the disease, they further postulate that it is a metabolic error that either allows a toxic substance to accumulate or deprives the kidneys of an essential substance. As support for this proposition, they site the demonstration by Kline et al[21] that the

chronic administration of diphenylamine to rats leads to a disease resembling polycystic disease. They further speculate that some cases of nephronophthisis may be due to exposure to an exogenous toxin.

TREATMENT

No definitive treatment, other than renal homotransplantation, has been proposed. In most reported cases of the disease, treatment has been limited to supportive measures aimed at correcting the metabolic defects secondary to renal failure. Sodium, calcium, and potassium deficiencies may be corrected by oral or intravenous fluid and electrolyte replacement. Mineralocorticoids have not been successful in the management of renal salt-wasting. Transfusion, as was so often necessary for the patient reported here, has commonly been required to maintain hemodynamic homeostasis. Peritoneal dialysis has been temporarily successful in decreaseing the azotemia. The employment of hemodialysis has not been reported in the management of this disease.

Renal homotransplantation has been performed on two patients suffering from nephronophthisis.[9,14] Herdman et al[14] reported an open renal biopsy of the kidney transplanted to one of their patients two years following the procedure. They found no histologic alterations similar to those found in the patient's

own kidneys.

CONCLUSIONS

Following a review of the literature published on both medullary cystic disease and familial juvenile nephronophthisis, I concur with those who have equated the two. With future research and findings, this disease may be found to be comprised of more than one etiological and pathological entity.

I beleive that the diagnosis is well established in C. C., D. C., and female C.. The fact that all the children born of these parents have died, at least three with nephronophthisis, leads one to consider a dominant inheritance pattern. But the absence of renal disease in either parent makes this conclusion untenable unless mosaicism were present in one parent. At present this cannot be established since no gross chromosomal abnormality has been demonstrated in this disease. The reason for the early appearance of the disease in these children is obscure.

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