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Invited review

Glomerulocystic kidney disease – nosological considerations

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Abstract. Glomerulocystic kidneys can be categorized into three major groups: (1) glomerulocystic kidney disease, comprising nonsyndromal heritable and sporadic forms of severely cystic kidneys in children and adults, (2) glomerulocystic kidneys in heritable malformation syndromes, and (3) glomerular cysts in dysplastic kidneys. The first category includes diffusely glomerulocystic kidneys in newborns and young children, many of whom have family histories positive for classical polycystic kidney disease. No differences between familial and sporadic cases have been identified, apart from the family histories. The sporadic cases are conceivably new mutations of the same disease. The first category also includes sporadic and familial disease in older children and adults. The inheritance in adult familial disease, as in childhood familial disease, has been dominant. An apparently distinct entity is hypoplastic glomerulocystic kidney disease, a dominant reported in only a few families. These kidneys, apart from being glomerulocystic, are small, and imaging studies show abnormal pyelocaliceal anatomy. The second category includes glomerulocystic kidneys as major components of heritable syndromes such as tuberous sclerosis, orofaciodigital syndrome, brachymesomelia-renal syndrome, trisomy 13, and the short rib-polydactyly syndromes. The category also includes glomerular cysts in several syndromes, namely Jeune syndrome and familial juvenile nephronophthisis, better known for chronic progressive tubulointerstitial disease. Glomerular cysts occur as a minor component, i.e., scattered cortical cysts, in several other syndromes, among them Zellweger's, in which the cysts are typically present and are usually inconsequential, only occasionally serious enough to affect renal function. In all of these syndromes, the cysts are inconsistently expressed. The third category includes a number of dysplastic kidneys, some of which, as in Meckel syndrome and glutaric aciduria type 2, are also syndromal. The glomerular cysts are minor in comparison with the dysplastic components of the abnormality, although they may be present in sufficient numbers to create confusion with other glomerulocystic conditions.

Key words: Glomerulocystic kidney disease – Dominant polycystic kidney disease – Malformation syndromes – Tuberous sclerosis

Introduction

The literature on glomerulocystic kidneys is largely anecdotal, with reports of glomerular cysts in both syndromal and nonsyndromal renal disorders. Descriptions of glomerular cysts go back to the last century, usually with no attempt to delineate glomerulocystic kidneys from other forms of cystic kidney disease [1]. In the 1960s, Bialestock [2], Baxter [3], and Vlachos and Tsakraklidis [4] demonstrated glomerular cysts histologically and by microdissection in a miscellany of children's kidneys. Others found glomerular cysts in trisomy 13 [5] and Zellweger syndrome [6, 7]. The report by Taxy and Filmer in 1976 [8] brought the term *glomerulocystic kidneys* into the literature, and the authors emphasized that the renal abnormality is associated with a large number of other conditions. This obvious heterogeneity tends to confuse the casual reader. An orderly approach, however, and categorization of glomerulocystic kidneys by associated conditions, even without a formal classification, dispels much of the confusion [9, 10].

The term *glomerulocystic* is widely used descriptively, without quantitative definition. Glomerulocystic kidneys are defined histopathologically merely as containing glomerular cysts. Baxter [3] described glomerular cysts as varying from slightly dilated to colossal, commenting that a twofold increase in diameter reflects an eightfold increase in volume. Verani et al. [11] defined cysts as dilatations exceeding 0.1 mm. We thought that even mild degrees of dilatation in glomeruli, which normally have a snug fit, are obvious to the microscopist [10], and I believe that Bowman spaces dilated 2–3 times in the plane of section are cystic. A more difficult question concerns the number of identifiable glomerular cysts required for diag-

Table 1. Categorization of glomerulocystic kidneys

Glomerulocystic kidney disease
Autosomal dominant polycystic kidney disease in young infants
Dominant glomerulocystic kidney disease in older patients
Sporadic nonsyndromal glomerulocystic kidney disease
Familial hypoplastic glomerulocystic kidney disease
Glomerulocystic kidneys in heritable malformation syndromes
Tuberous sclerosis
Orofaciodigital syndrome, type 1
Brachymesomelia-renal syndrome
Trisomy 13
Short rib-polydactyly syndromes
Jeune asphyxiating thoracic dystrophy syndrome
Zellweger cerebrohepatorenal syndrome
Familial juvenile nephronophthisis
Glomerular cysts in dysplastic kidneys
Diffuse cystic dysplasia
Renal-hepatic-pancreatic dysplasia

nosis. The number of cysts containing glomerular tufts in random sections is often surprisingly high, some illustrations showing proportions approaching 40% [1], but the "hits" on tufts drop as the cysts enlarge; glomerular tufts are more numerous in sections of small cysts. On the basis of my own counts, and in the absence of other established criteria, I believe that the occurrence, in random sections, of glomerular tufts within at least 5% of otherwise identical cysts identifies the kidneys as glomerulocystic. In many specimens, of course, the glomerular cysts are accompanied by tubular cysts, necessitating careful histopathological evaluation.

I use the term *glomerulocystic kidneys* for the entire heterogeneous group (Table 1), reserving the term *glomerulocystic kidney disease* (GCKD) for those nonsyndromal cases with severely cystic kidneys. Syndromal cases are diagnosed by their principal syndromes. A small number of essentially dysplastic kidneys, some of them heritable and others sporadic, also contain glomerular cysts as relatively minor components of major renal maldevelopment.

Glomerulocystic kidney disease

The group of glomerulocystic kidneys that can properly be called GCKD comprises both sporadic and familial cases, the latter usually with autosomal dominant transmission. The great majority of reported cases, both sporadic and familial, are in newborns and young children, a smaller number in adolescents and adults. Whether the sporadic and familial forms are different diseases remains uncertain. Whether the childhood, adolescent, and adult forms are different diseases is equally uncertain.

The affected adult relatives of babies having GCKD and positive family histories with vertical transmission have for the most part had classical polycystic kidney disease (PKD) [12–16]. The babies' kidneys were large and diffusely cystic; descriptions and illustrations of the histopathological findings emphasize the glomerular cysts. In some babies with dominant PKD by family history, the kidneys contained more tubular than glomerular cysts [17, 18]. In one instance, the father's renal biopsy showed PKD with some glomerular cysts and the baby had extensive glomerular cysts [19].

It may be asked first whether the disease in these families differs from that in classical PKD and second whether there is any explanation for the new appearance of early infantile onset in a family with a history of typical adult onset. Reeders et al. [20] and Novelli et al. [21] reported linkage to the short arm of chromosome 16 in PKD families with fetuses that had cystic kidneys containing glomerular cysts, and Gal et al. [22] reported the same linkage in several newborns with dominant PKD, although without details of histopathological studies. The unexpected appearance of infantile-onset disease in a family with a previous history of adult-onset classical PKD has no satisfactory explanation. Although some degree of intrafamilial variation may be expected, this much of a break with family tradition seems extreme.

Two other observations relate dominant familial GCKD and classical PKD [19]. First, even though glomerular tufts are unlikely to show up in random sections of large cysts, we found some glomerular cysts in 8 of 20 cases of classical adult PKD by examining 2–3 random sections per case (J. Bernstein, unpublished data). Glomerular cysts appear, therefore, to be a common expression of dominant PKD, easily identified when the cysts are relatively small. Glomerular cysts in recessive PKD are, on the other hand, quite rare; I have been shown only one case, in a somewhat older child. Second, dominant GCKD may have a strongly asymmetrical onset [15, 16], much like that in children with typical dominant PKD [23–26].

Sporadic GCKD in young infants is in my experience indistinguishable from PKD-related GCKD in every way other than the family history. Sporadic and familial forms are present in approximately equal proportions in my series of consultation cases. The kidneys in both the familial and sporadic forms of infantile GCKD are variably enlarged, sometimes weighing more than 400 g each. The degree of renal enlargement seems to relate to the degree of cyst formation. The cysts in both groups may be diffuse or clustered. Uneven development of cysts may be responsible for asymmetrical and even asynchronous onsets of what is essentially bilateral disease. Diffuse involvement is associated with interstitial edema, just as in recessive PKD, whereas patchy involvement is associated with better preservation of renal function (Fig. 1). Some cysts in both forms of GCKD are identified as tubular or ductal by histological characteristics of their epithelial linings. Severe epithelial hyperplasia of glomerular capsular epithelium, with piling up of epithelium into glomeruloid structures [8], has so far been observed in only a few cases of sporadic GCKD and not in familial GCKD. The cysts in both forms are present throughout the cortex. Simply put, sporadic GCKD is for the most part indistinguishable from familial GCKD on the basis of histopathological findings.

The kidneys in both forms of GCKD often contain abnormally differentiated medullary pyramids, a type of medullary dysplasia (Fig. 2). The pyramids are narrow and poorly demarcated from the renal sinus; they contain dilated collecting ducts lined with incompletely differen-

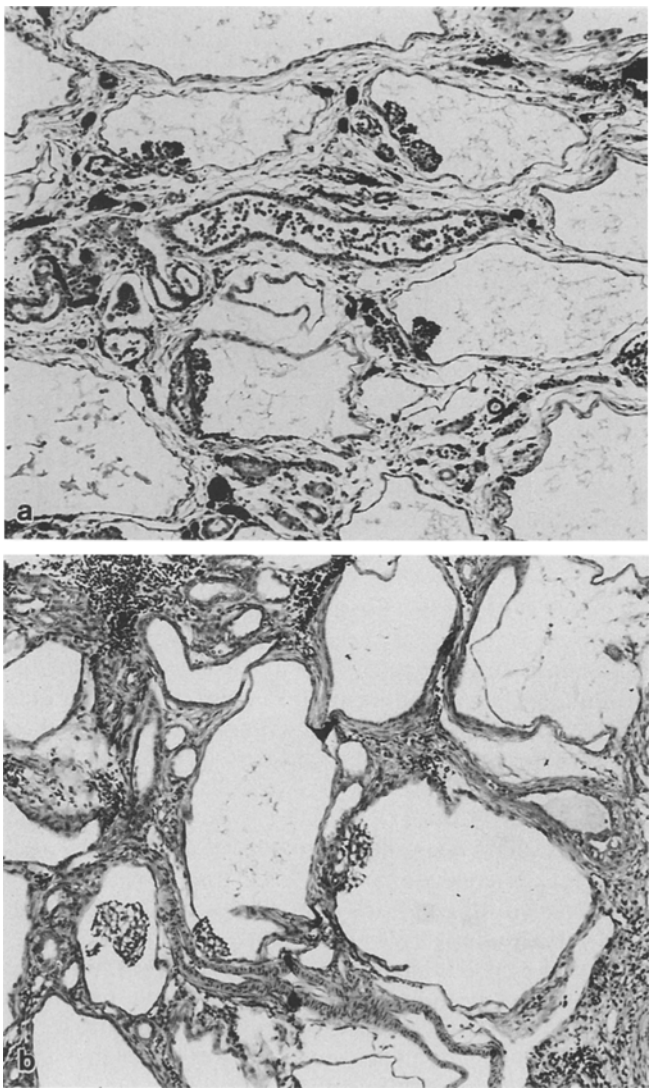

Fig. 1. Glomerulocystic kidney disease (GCKD) **A** A diffuse, very severe abnormality in an oliguric newborn is associated with interstitial edema and the appearance of reduced numbers of convoluted tubules. The family history was positive for classical polycystic kidney disease (PKD) in the father, and an older sibling had died of PKD. **B** A less severe abnormality in a young infant with a negative family history is associated with less interstitial edema and with uneven distribution of the glomerular cysts. These two patterns occur in both the familial and sporadic forms of GCKD. Both sections stained with hematoxylin and eosin, ×80

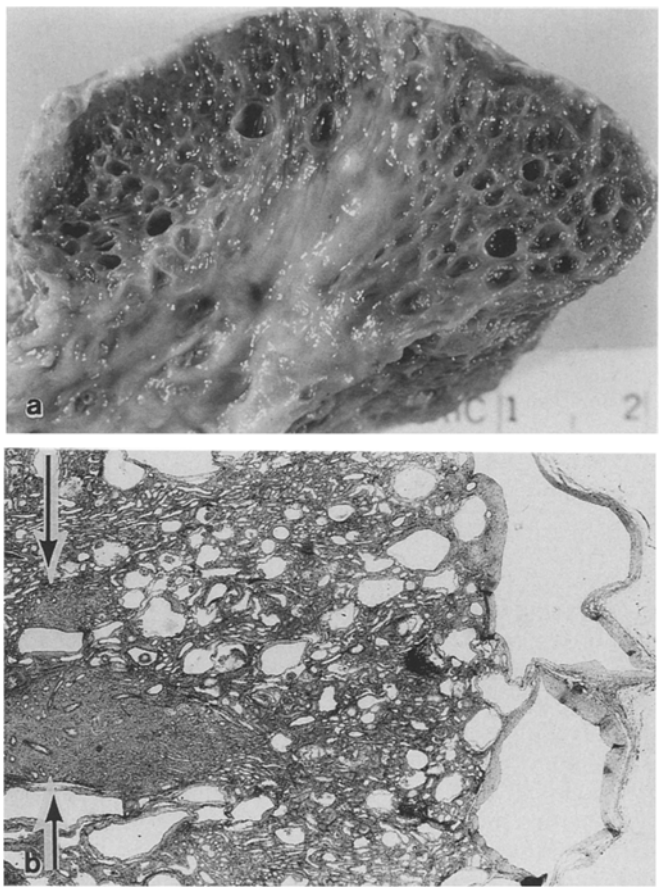

Fig. 2. Abnormal medullary development in GCKD. **A** The gross photograph shows a fibrotic medulla poorly demarcated from the renal sinus and lacking the usual gross appearance. **B** Microscopic examination in another case shows a very small medullary pyramid (*arrows*), poorly demarcated and lacking the normal arrangement of vasa recta and recurrent loops. Hematoxylin and eosin stain, ×6

tiated epithelium, and periductal fibrosis is associated with a paucity of vasa recta and recurrent loops [10, 27]. This abnormality, not present in neonatal recessive PKD, suggests that the cystic abnormality in GCKD began early enough in renal morphogenesis to interfere with medullary differentiation. The earliest notice of oligohydramnios I know of in dominant PKD is at 16 weeks [28], but most descriptions mention deficient amniotic fluid well after the 20th week [29]. The medullary abnormality is associated with severe overlying cyst formation, and it is not necessarily present in all pyramids. Incidentally, the dilated ducts may be visualized be excretory urography, creating confusion by its resemblance to the medullary ectasia of recessive PKD. Both forms of GCKD are associated with abnormalities of the intrahepatic bile ducts in about 10% of cases. The biliary abnormality is histopathologically similar to the biliary dysgenesis ("ductal plate malformation") present in virtually all cases of recessive PKD, but not as severe (J. Bernstein, unpublished data).

The clinical characteristics are also the same, sometimes with long-term stabilization of renal function in both groups. More often, GCKD leads to chronic renal failure and hypertension. The imaging characteristics are the same by both sonography and computed tomography, that is, hyperechoic kidneys with occasional macrocysts. With this much similarity – basically the same phenotype – questions arise about the genotype. Is sporadic GCKD a new mutation for classical PKD or is it a different disease? The questions are currently unanswerable.

Sporadic GCKD is not necessarily more heterogeneous in adults than in children. Reports of occasional, questionable syndromal associations in patients of both age groups continue to appear in the literature, possibly because the association of abnormalities justifies the report. Individual reports of GCKD in adults with nephrotic syndrome [30] and hypothyroidism [31], for example, do not establish a syndromal basis of the glomerular cysts. Similarly, oc-

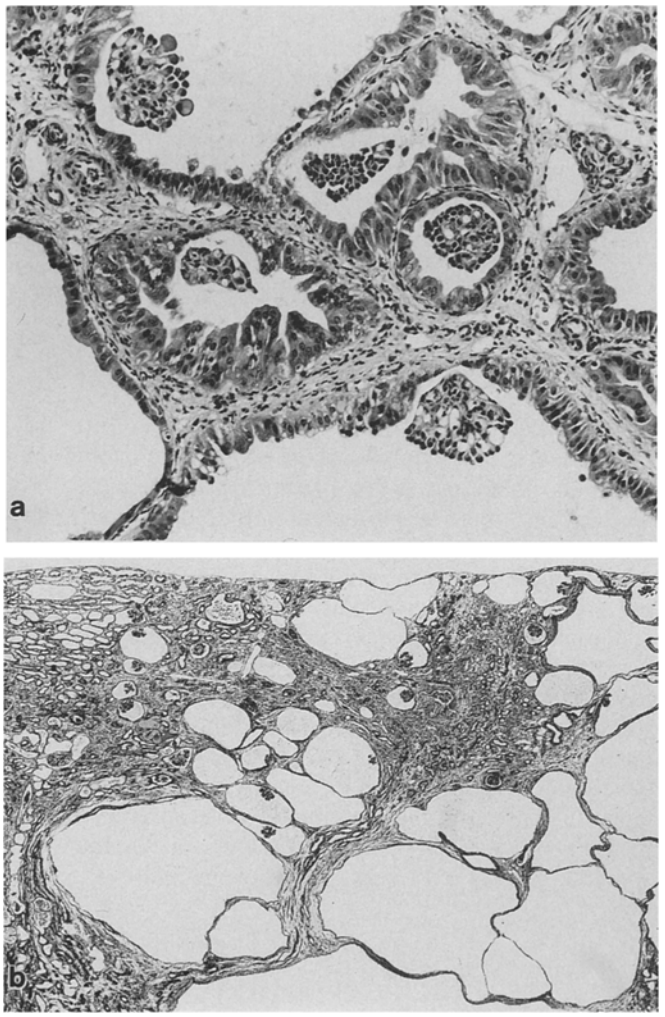

Fig. 3. Glomerulocystic kidneys in heritable syndromes. **A** The renal abnormality in a newborn with tuberous sclerosis and unilateral renal enlargement is marked by extraordinary epithelial hypertrophy and hyperplasia in Bowman's epithelium, glomerular podocytes, and tubular epithelium. Hematoxylin and eosin stain, ×100 **B** Glomerular cysts in the orofaciodigital syndrome, type 1 often predominate in the inner cortex. Hematoxylin and eosin stain, ×15

casional reports of children with GCKD and common congenital malformations [2, 3] or hepatoblastoma [32] do not adequately establish syndromal associations. More consistent associations will be discussed in the section on syndromal GCKD. Reports of isolated GCKD in adults [33–36] and older children [37, 38] provide no morphological basis for separating the condition from GCKD in newborns and young infants.

As in infants, familial GCKD in adults and older children is a dominant trait. Melnick et al. [39] reported GCKD and renal failure in a father and three children. The kidneys were of normal size. Carson et al. [40] reported six siblings with GCKD. The proband had lupus nephritis, but the other five, 15–22 years old, were asymptomatic with normal renal function. The mother had died of renal failure, cause unknown, 5 years earlier.

A probably different disease is hypoplastic GCKD. Baxter [3] described glomerular cysts in a 4-year-old child's kidneys that weighted only 19 g each, considerably less than two standard deviations below the expected mean weight. Rizzoni et al. [41] described as *familial hypoplastic GCKD* glomerulocystic kidneys is two pairs of female siblings and their mothers with chronic renal failure. Excretory urograms showed small kidneys, as much as three standard deviations below normal, that had coarse or absent calyces and lacked papillae. The patients (mother and son) reported by Kaplan et al. [42] also had abnormal calyces and chronic renal failure. The structural abnormalities visualized radiographically in the last two studies [41, 42] seem to constitute important differences from usual GCKD.

Syndromal glomerulocystic kidneys

Glomerular cysts occur in several heritable syndromes, both as major involvement with rapid progression to renal insufficiency and as minor involvement with little or no functional impairment. The information we have is based almost entirely on case reports, and the morphological description is often that of a poorly characterized cystic disease. We know, however, that glomerular cysts are present in several heritable syndromes, but we do not know the frequency of glomerulocystic kidneys in the conditions under consideration.

Severe cystic kidney disease with glomerular cysts occurs in patients having tuberous sclerosis [43]. Tubular cysts are frequently also present and lined with strikingly hyperplastic, eosinophilic cells that are practically diagnostic of tuberous sclerosis [44]. Glomerular cysts are easier to identify in newborns than in older children. As the cysts enlarge and the glomerular tufts become less frequent in random sections, the abnormality strongly resembles that of classical dominant PKD, and the diagnosis of tuberous sclerosis depends on either the recognition of the characteristic epithelial abnormalities in tubular cysts or of the characteristic skin stigmata and cerebral abnormalities. Renal involvement in tuberous sclerosis includes also angiomyolipoma, which increases in frequency and size with advancing patient age and which can be identified by computed tomography. The presence of both cysts and angiomyolipomas in a patient's kidneys strongly suggests the diagnosis of tuberous sclerosis [45]. One gene locus for tuberous sclerosis has been identified on the short arm of chromosome 16, in proximity to the PKD 1 locus [46]. Despite the possibility that a contiguous gene syndrome accounts for renal cystic disease in tuberous sclerosis, it does not explain the renal epithelial abnormalities that are characteristic of tuberous sclerosis but not present in classical PKD.

Unilateral renal enlargement has been described in some newborns with tuberous sclerosis [44, 47]. The cortices are severely cystic, and the adjacent medullary pyramids may be rudimentary and dysplastic. The cysts are small, arising in both glomeruli and tubules, where they are lined with spectacularly hypertrophic and hyperplastic epithelial cells (Fig. 3A). Glomerular podocytes are

Table 2. Occasional glomerular cysts in heritable syndromes

Congenital nephrotic syndrome
Cornelia de Lange syndrome
Down syndrome
Marden-Walker syndrome
Phocomelia syndrome
Smith-Lemli-Opitz syndrome
Trisomy 9
Trisomy 18

frequently enlarged and atypical. In one case with a unilateral onset, the other kidney became enlarged and was found to have a hamartomatous, localized, histopathologically similar abnormality [48].

Glomerular cysts are typical of renal involvement in the orofaciodigital syndrome, type 1 (Fig. 3B) [49]. The occurrence of renal cystic disease in heterozygous girls is well known; this X-linked dominant disorder is ordinarily lethal to male fetuses. The renal cystic disease, sometimes described casually as coincidental PKD, involves predominantly the inner cortex [49, 50]. Tubular and ductal cysts are also present [51], and the cysts do not get as large as those in classical PKD.

Major renal involvement with renal failure occurs in the brachymesomelia-renal syndrome [52]. The frequency of renal involvement and the clinical characterization of the renal involvement are questions unanswered by the small number of reported cases. Glomerular cysts in the short rib-polydactyly syndromes [53, 54] may be accompanied by elements of renal dysplasia [55], although the dysplasia is not a necessary accompaniment. Both the Majewski and Saldino-Noonan types may be affected. Enlarged glomerulocystic kidneys with renal failure may be present in trisomy 13 [5], but small, scattered glomerular cysts without functional significance are much more typical, present in as many as one-third of cases [9, 56].

Other heritable syndromes with variably occurring glomerular cysts, usually as minor components, are Jeune syndrome [57, 58], renal-retinal dysplasia [59], nephronophthisis [60, 61], nephronophthisis with hepatic fibrosis [62, 63], and rapidly evolving nephronophthisis [64]. In all of these conditions, patients develop progressive tubulointerstitial nephropathy, and the contribution of scattered glomerular cysts to the evolution of the nephropathy is arguable. The exception to this generalization is that diffuse cystic disease occurs in some patients with phenotypic Jeune syndrome [65, 66].

Glomerular cysts are very common, almost constant findings in Zellweger syndrome [9]. They were recognized in the earliest studies [6, 7] as scattered, variably sized cysts of uncertain clinical significance. They are not likely to account for the occasional findings of albuminuria and aminoaciduria. They may, however, be admixed with tubular cysts [67]. The description of diffuse cystic dysplasia in patients with Zellweger phenotype [65] antedates recognition of the biochemical abnormality, and variability in the renal phenotype conceivably relates to heterogeneity of the peroxisomal abnormality. Minor renal involvement by glomerular cysts occurs in a number of other syndromes (Table 2), almost always without functional implications. Recognition of these associations serves mostly to emphasize the heterogeneity of glomerulocystic kidneys.

Although some reported associations seem to be coincidental, as noted above, hypertrophic pyloric stenosis in infants with cystic kidney disease, including dominant PKD [15, 68] and hypoplastic GCKD [42], occurs with some regularity. The nature of this association is unclear, but obviously heterogeneous.

Glomerular cysts in dysplastic kidneys

Glomerular cysts in severely dysplastic kidneys are of little consequence, and they contribute little to the evolution of the abnormality and to renal functional impairment. Glomerular cysts may be prominent in the diffuse cystic dysplasia associated with glutaric aciduria, type 2 [69], and renal-hepatic-pancreatic dysplasia [70]. They are focally present in the cystic dysplasia of Meckel and Goldston syndromes. Glomerular cysts have, as noted above, been described in the short rib-polydactyly syndromes, in which the kidneys may also be dysplastic. Glomerular cysts are sometimes present in multicystic kidneys, obviously as inconsequential components of profound renal maldevelopment. Recognition of the associations is of importance in separating these examples of dysplasia from the medullary maldevelopment that occurs in dominant and sporadic GCKD with very severe congenital cyst formation.

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Literature abstracts

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A single pediatric center experience with 1025 children with hypertension

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Between January 1982 and December 1989 1025 patients aged between one month and 18 years with increased blood pressure were referred for evaluation. Borderline hypertension was found in 389 children; 636 had sustained significant hypertension. In 351 patients, hypertension was secondary to a known disease. Renal parenchymal diseases were present in 68% of patients while renovascular and endocrine disorders were found in 10% and 11%, respectively. Of the 258 children aged less than 15 years, all but six children had known causes of hypertension, while 75% of adolescents had essential hypertension. In the 389 children with borderline hypertension. 65% developed fixed hypertension over a period of 2–3 years.

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Growth, serum lipoproteins and apoproteins in infants with congenital nephrosis

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Retarded growth and extremely high cholesterol levels have been reported in infants with congenital nephrotic syndrome of the Finnish type (CNF). In an attempt to normalize growth and lipid disturbances the high-calory diet (130 kcal/kg/d) containing protein 4 g/kg/d and supplemented with unsaturated fatty acids (mean P/S-ratio 1.40) was given to ten infants with CNF from birth. Growth, lipoprotein and apoprotein concentrations were measured. All patients exhibited normal growth, which allows renal transplantation, the only life-saving treatment in CNF; already at an early age. In spite of the diet lipid profiles at 3 and 9 months revealed marked elevation of triglyceride in all lipoproteins, especially in VLDL fraction, compared to controls. The abnormalities increased significantly with time (p for VLDL-TG 0.04). The elevation of serum cholesterol was mainly attributable to the increase of cholesterol in triglyceride-rich particles (chylomicrons, VLDL, IDL). Analysis of VLDL, LDL and HDL revealed significant triglyceride enrichment and cholesterol deficiency in all lipoproteins. The concentrations of the low-molecular weight apoproteins A-I and A-II were significantly decreased, but the concentration of high-molecular apo B was high. Urinary analysis revealed progression and decreasing selectivity of proteinuria with time. Thus the mechanisms leading to lipid abnormalities in CNF are multiple including stimulated hepatic lipoprotein synthesis, impaired conversion of VLDL and IDL to LDL, compositional changes, urinary loss of low-molecular apoproteins and presumably reduced LPL activity. The abnormalities indicate an increased risk of arteriosclerosis in CNF patients.