Childhood onset autosomal dominant polycystic kidney disease in sibs: clinical picture and recurrence risk

K Zerres, S Rudnik-Schöneborn, F Deget, and members of the German working group on paediatric nephrology (Arbeitsgemeinschaft für Pädiatrische Nephrologie*)

Abstract

In a systematic study on the clinical picture and genetics of cystic kidneys in children, in association with the German working group on paediatric nephrology (Arbeitsgemeinschaft für Pädiatrische Nephrologie), we have investigated 79 children with early manifestation of autosomal dominant polycystic kidney disease (ADPKD). They belonged to 64 families (64 index patients and 15 affected sibs). Early manifestation was defined in this study as clinical symptoms (hypertension, proteinuria, impaired renal function, palpably enlarged kidneys) occurring before the age of 15 years.

In order to estimate the recurrence risk to sibs of a previously diagnosed patient with early manifesting ADPKD, we found that 15 out of a total of 65 sibs of the 64 index patients (45% of the theoretically expected 32.5 gene carriers) showed comparable early manifestation. Another 10 symptom free children were diagnosed sonographically as having ADPKD before the age of 18 years, so that the total number of affected sibs was 25/65 in the study group, representing 76% of the gene carriers. Although the gene in childhood manifesting ADPKD can be transmitted through both sexes, a statistically significant ($p < 0.05$) maternal predominance was observed (M:F = 23:41). In affected sibs ages of onset, initial presentation, and the development of complications appeared to be similar in the majority of families.

Our data indicate a high recurrence risk to sibs for early manifestation of ADPKD which has important implications for genetic counselling and clinical care of affected families and gives clues to the underlying genetic mechanism of childhood onset ADPKD.

(J Med Genet 1993;30:583-8)

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common dominantly inherited conditions with an estimated incidence of 1 in 1000.¹ It is a major cause of chronic renal failure in adults and has gained increasing importance in paediatric nephrology. Although the age of clinical onset of this

disorder is typically in the third to fifth decade of life, early manifestations of ADPKD are now well known,² and some cases with prenatal onset have even been reported.³ At a rough estimate, about 2% of gene carriers present with severe early manifestation in childhood.^{4,5} In clinical practice, ADPKD is as common as autosomal recessive polycystic kidney disease in children.

These cases with early clinical manifestation, however, have to be differentiated from those with a typical onset in adulthood which can already be identified by ultrasound in childhood. Bear *et al*⁶ recently reported that in about 30% of persons at risk the diagnosis of ADPKD can be established sonographically before the age of 10 years, while Coto *et al*⁷ were unable to detect renal cysts on ultrasound in 40% of disease carriers younger than 30 years. Within the past 10 to 15 years a greater awareness of the disease in affected families has been achieved, facilitated by earlier detection of symptom free patients by ultrasonography and genetic testing.

Numerous reports on early manifestations of ADPKD exist, including a considerable number of cases mainly published because of a high incidence of pre- and postnatal complications. The mechanism of early manifestation is still unclear and different theories have been suggested.^{8,9} Affected sibs have either been described as single case reports or as a part of a more general analysis of ADPKD (table 1).^{2,4,5,8,10-22} Although a higher than expected recurrence risk of early onset ADPKD has been postulated before,^{15,17} no larger study exists concentrating on the intrafamilial variability and the risk to sibs for early manifestation of ADPKD.

Material and methods

Since 1987 clinical and genetic data on children with different types of cystic kidney disorders have been recorded in a prospective multicentre study associated with the German working group on paediatric nephrology (Arbeitsgemeinschaft für Pädiatrische Nephrologie). At least once a year the children underwent clinical examination, when weight, height, blood pressure, laboratory values, pathoanatomical data, findings from imaging techniques, as well as a detailed family history, were recorded on case report forms. All first degree relatives were examined sonographically.

Up to February 1992, a total of 79 patients

Institut für
Humangenetik der
Universität Bonn,
Wilhelmstrasse 31,
D-5300 Bonn 1,
Germany.
K Zerres
S Rudnik-Schöneborn
F Deget

Correspondence to
Professor Zerres.

Received 12 August 1992.
Revised version accepted
29 January 1993

* R Beetz (Mainz), J Brodehl (Hannover), E Kuwertz-Bröking (Münster), D Müller-Wiefel (Hamburg), W Rascher (Essen), H Ruder (Erlangen), K Schärer (Heidelberg), H P Weber (Lüdenscheid).

Table 1 Published reports of sibs with manifestations of ADPKD in childhood.

Author (year)	Case No	Sex	Age at diagnosis	Initial presentation	Actual age/age at death (*)	Clinical features at present age	Affected parent	Healthy sibs	Comment
Kaplan <i>et al</i> ² (1977)		M	7 y	Haematuria	?	?	Father	3	
		F	9 y	Haematuria, enlarged kidney	?	?			
		M	5 y	Haematuria	?	?			
		M	9 y	Family history	?	?			
Loh <i>et al</i> ¹⁰ (1977)		M	18 d	Feeding problems, abdominal masses	6 mth	None	Father	1	Fraternal twins
		M	10 d	Abdominal masses	6 mth	None			
Eulderink and Hogewind ¹¹ (1978)		F	Birth	Preterm birth (27 wk)	Postnatal*	—	Mother	—	
		F	Birth	Preterm birth (29 wk)	Postnatal*	—			
Fryns and Van den Berghe ¹² (1978)		M	Birth (?)	Family history	1 y	?	Father	5	Diagnosis confirmed at necropsy
		M	Birth	Stillbirth	Postnatal*	—			
		M	Birth	Stillbirth	Postnatal*	—			
		M	Birth	Stillbirth	Postnatal*	—			
		M	Birth	Stillbirth	Postnatal*	—			
Proesmans <i>et al</i> ¹³ (1982)		F	24 y	Family history	24 y	None	Father	1	
		M	Birth	Preterm birth (28 wk)	Postnatal*	—			
		M	Birth	Abdominal masses, hypertension	8 y	Spastic paresis, mental retardation owing to intracerebral haematoma			
Farrell <i>et al</i> ¹⁴ (1984)		M	3 d	Abdominal masses	?	None	Mother	—	
		?	15 mth	Family history	15 mth	None			
Zerres <i>et al</i> ¹⁵ (1985)		?	5 y	Family history	5 y	None	Mother	1	
		F	Prenatal (32 wk)	Kidneys echogenic	Postnatal*	Potter sequence			
Fryns <i>et al</i> ¹⁶ (1986)		M	Birth	Stillbirth	Postnatal*	Potter sequence	Father	—	
		M	Birth	Stillbirth, abdominal masses	Postnatal*	—			
Kääriäinen ¹⁷ (1987)	1	?	Prenatal (16 wk)	Kidneys enlarged, echogenic	Abortion	—	Mother	—	Half brother of the other sibs
		F	Birth	Stillbirth	Postnatal*	—			
		M	Birth	Stillbirth	Postnatal*	—			
		F	Birth	Family history (?)	3 y	?			
		M	Birth	Stillbirth	Postnatal*	—			
		M	8 y	Family history	10 y	?			
Pretorius <i>et al</i> ¹⁸ (1987)	2	M	Birth	?	8 y	?	Mother	—	
		F	Birth	Family history	2 y	?			
		M	Birth	Stillbirth	Postnatal*	—			
		F	Birth	?	14 y	?			
		M	Birth	Stillbirth	Postnatal*	—			
		M	Birth	?	14 y	?			
Sedman <i>et al</i> ⁴ (1987)		?	Prenatal (36 wk)	Kidney enlarged, echogenic	4-8 y	Blood pressure upper normal limit	Mother	1	
		?	Prenatal (23-5 wk)	Kidneys enlarged, echogenic	Abortion	—			
Taitz <i>et al</i> ⁶ (1987)		?	Prenatal	Kidneys enlarged	5 y	Hypertension	Mother	?	
		?	Prenatal	Kidneys enlarged, oligohydramnios	Abortion	—			
Ceccherini <i>et al</i> ¹⁹ (1989)		?	13 y	Family history	13 y	None	?	?	
		a/b	14 y	Family history	14 y	None			
		?	Birth	Renal masses, hypertension	6 y	None			
		a/b	Birth	Renal masses	1 y	None			
Gal <i>et al</i> ²⁰ (1989)	4	F	Prenatal (29 wk)	Stillbirth	Postnatal*	Potter sequence	Mother	1	
		F	Prenatal (14 wk)	Kidneys enlarged, echogenic	Abortion	—			
		M	Birth	Kidneys enlarged	?	?			
		M	12 y	Renal insufficiency	Postnatal*	—			
		F	9 y	Family history	12 y	None			
		M	9 y	Family history	9 y	None			
		F	10 y	Renal insufficiency	?	Dialysis from 11 y			
		M	15 y	Family history	?	Dialysis from 16 y			
		M	5-5 y	?	?	?			
Guérin and Lucotte ²¹ (1989)		F	11 y	Family history	?	None	Father	—	
		F	14 y	Family history	14 y	None			
		M	13 y	Family history	13 y	None			

with early manifestation of ADPKD was registered. Early manifestation of ADPKD was defined as the occurrence of clinical symptoms of ADPKD (enlarged kidneys, hypertension, proteinuria, impaired renal function, end stage renal failure) before the age of 15 years. Palpably enlarged kidneys presenting as abdominal tumours and thus leading to the diagnosis of ADPKD were regarded as a clinically relevant symptom in our study.

The patients were ascertained through their attending paediatric department and 64 index patients and 15 sibs were eligible for evaluation. ADPKD was confirmed in all cases by the presence of the disease in one of the parents. The number of unaffected children was taken from the family histories and each child in a sibship underwent an ultrasound and clinical examination.

The mode of ascertainment differed in the study group (table 2), since 12 index patients

were diagnosed only because of a positive family history and did not show any symptoms before the first investigation (19%), whereas 52 index patients (81%) presented with problems related to ADPKD leading to the diagnosis of ADPKD.

The clinical data on 38 affected sibs out of 17 families were analysed in detail to show the intrafamilial variability of early manifesting ADPKD.

Segregation analysis was performed according to the formula of single incomplete ascertainment,²³ whereby separate calculations were done for sibs with early manifestation of ADPKD and those with a so far asymptomatic course who showed cystic kidneys on ultrasound.

We used the χ^2 test to test homogeneity of risk according to the sex of the carrier parent under the assumption of a binomial distribution.

Table 2 Details of the study group including mode of ascertainment of 64 index patients with early manifestation of ADPKD (symptoms before the age of 15 years).

Cause of clinical investigation of index patients	No of index patients	No of affected sibs with clinical features before the age of 15 years	No of sibs with ADPKD diagnosed before the age of 18 years without symptoms	No of sibs without signs of ADPKD on ultrasound
Clinical symptoms	52	12	8	33
Family history alone	12	3	2	7
Total	64	15	10	40

Results

SEGREGATION ANALYSIS

For the segregation analysis 64 families with at least one child with ADPKD were included. The 64 index patients had 65 sibs of whom 25 were affected and 40 were unaffected so far. Fifteen out of the 25 sibs with the disease had early manifestation of ADPKD as well and 10 were symptom free so far but were diagnosed sonographically as having ADPKD before the age of 18 years.

According to autosomal dominant inheritance, where statistically 50% of the offspring of an affected parent will inherit the mutation, 32.5 of the 65 sibs of the 64 index patients theoretically should be considered as gene carriers. We found that 45% (15/32.5) of the affected sibs also showed early manifestation of ADPKD, whereas the overall percentage of affected children detected before the age of 18 years was 76% (25/32.5) in this group.

PARENTAL GENDER

The diagnosis of ADPKD was established by ultrasound in most of the children. In order to confirm the diagnosis, the parents were also

examined. In the study group 23 fathers and 41 mothers had polycystic kidneys, which shows a statistically significant deviation from the assumption of an equal sex ratio among the affected parents. The ratio of affected fathers to mothers was 1:1.78 resulting in a χ^2 value of 5.06 that exceeded the critical value of 3.84 ($p = 0.05$, $df = 1$). Thus, we found a significant excess of transmitting mothers in early manifesting ADPKD. In four families in which severely affected newborns died soon after birth, the mutated gene was transmitted by the mother in three families and only in one case by the father.

VARIABILITY OF ADPKD IN AFFECTED SIBS

The intrafamilial variability of ADPKD in 38 affected sibs from 17 families with more than one affected child was analysed. The clinical data of the sib pairs are summarised in table 3 and a graphic illustration of the main clinical features is presented in the figure.

The age of diagnosis ranged from prenatal detection to 15 years with a mean age of 4.2 years. The most frequent reason for clinical examination was a positive family history in 10

Table 3 Clinical data of 38 affected sibs from 17 families with early manifestations of ADPKD.

Case ID	Sex	Age at diagnosis	Initial presentation	Actual age (y)	Start of antihypertensive therapy (y)	Start of creatinine > 100 μ mol/l (y)	Affected parent	Healthy sibs	Comments
1.1.	F	Prenatal	Prenatal	9	1-7	—	Mother	1	
1.2.	F	1 wk	Abdominal tumour	5	2-5	—			
2.1.	F	Postnatal	Abdominal tumour	7	—	—	Mother	—	
2.2.	F	Postnatal	Abdominal tumour	4	—	—			
3.1.	F	11 y	?	16	—	—	Mother	—	
3.2.	M	9 y	Enuresis, headache	10	—	—			
4.1.	M	8 mth	?	4	—	—			
4.2.	M	Prenatal	Prenatal	1	—	—	Mother	—	
5.1.	M	15 y	Family history	16	—	—	Father	—	5.1: sec enuresis, UTI (6 y), backpain
5.2.	F	12 y	Family history	17	—	—			
6.1.	F	8 y	Family history	14	9-14	—			
6.2.	M	4 y	Family history	11	4-11	—	Mother	—	Twins
6.3.	M	4 y	Family history	11	—	—			
7.1.	F	Prenatal	Prenatal	4	—	—			
7.2.	M	Postnatal	Respiratory failure	8 d*	—	—	Mother	—	Twins, CD: respiratory failure, preterm birth
7.3.	M	Postnatal	Respiratory failure	1 d*	—	—			
8.1.	M	9 y	Hypertension	10	10	—	Father	1	
8.2.	M	4 y	Enuresis	5	5	—			
9.1.	M	9 y	Family history	19	—	—			9.1: half brother of 9.2, 9.3, haematuria (10 y)
9.2.	F	3 y	?	14	—	—	Father	1	
9.3.	F	10 mth	Haematuria	10	1-2	—			
10.1.	M	Prenatal	Prenatal	1	—	—	Father	—	
10.2.	M	Prenatal	Prenatal	3 mth	—	—			
11.1.	M	Postnatal	?	Postnatal*	—	—			CD: unknown
11.2.	F	Postnatal	Paleness, atonia	10	1 mth	1	Mother	—	
12.1.	M	?	?	?	?	?			Kidney transplantation
12.2.	F	5 y	Raised creatinine	11	—	5	Mother	2	Dialysis and kidney transplantation at 10 y
13.1.	M	Postnatal	Respiratory failure	Postnatal*	—	—			CD: respiratory failure
13.2.	F	Postnatal	Abdominal tumour	11	3mth-9	—	Mother	—	
14.1.	M	6 y	?	?	?	?			Half brother of 14.2
14.2.	F	7 y	Enuresis, UTI, abdominal pain	12	—	—	Mother	2	
15.1.	M	Postnatal	Respiratory failure	Postnatal*	—	—			CD: respiratory failure
15.2.	F	Postnatal	Abdominal tumour	5	3	—	Father	2	
15.3.	F	Postnatal	Abdominal tumour	5	3	—			Twins
16.1.	F	14 y	Family history	18	14	—	Father	—	
16.2.	M	14 y	Family history	14	—	—			Haematuria
17.1.	M	13 y	Family history	26	16	—	Father	1	17.1: polydipsia, pollakiuria
17.2.	F	11 y	Family history	17	—	—			17.2: polydipsia, abdominal pain

* = age at death. CD = cause of death. UTI = urinary tract infection.

children. Abdominal tumours were discovered by physical examination in six cases and pre-natal diagnoses by ultrasound were made in five patients. Other initial symptoms mentioned included respiratory failure (four patients), enuresis (three patients), and one each of urinary tract infections, hypertension, abdominal pain, haematuria, postnatal failure to thrive, and raised creatinine levels.

Five children died postnatally from respiratory failure as a result of ADPKD. During the study period 13 children developed hypertension requiring antihypertensive therapy, three children developed renal insufficiency, and two children from one family had already undergone kidney transplantation.

With regard to intrafamilial variability, in the majority of families great clinical similarity between sibs was observed in terms of age of onset, initial presentation, and the development of complications (figure).

Discussion

Kaplan *et al*² were the first authors to report on a large number (eight) of children with ADPKD, including two sib pairs. They stressed that the few descriptions of early onset ADPKD led to the erroneous conclusion that

the condition rarely presents in children. Later published reports of early manifesting ADPKD showed that the disease can very often be detected clinically in the first decade of life.

Diagnosis of ADPKD in sib pairs with onset in early childhood has been established by intrauterine detection of enlarged, echogenic kidneys,^{4 15 16 18 19} in several cases combined with Potter sequence. Unspecified stillbirths or pre-term births in families with ADPKD, in whom the diagnosis was generally confirmed at necropsy, were reported by Eulerink and Hogewind,¹¹ Fryns and Van den Berghe,¹² Proesmans *et al*,¹³ Fryns *et al*,¹⁶ Kääriäinen,^{5 17} and Gal *et al*.²⁰ Some authors observed severe complications of ADPKD in childhood and infancy as the presenting symptom,^{2 5 8 10 13 14 17 20} whereas a large number of affected sibs were diagnosed by ultrasound in childhood or young adulthood merely because of their family history without showing clinical symptoms initially.^{8 14 17 20-22}

Taitz *et al*⁸ found a bimodal onset distribution in their study group and subdivided their cases into those detected by ultrasound aged 1 to 14 years because of a positive family history (group 1, n=6) and those presenting with renal masses at birth (group 2, n=4) who had a bad prognosis. They claimed that these were different entities and discussed several possible explanations. The gender of the parent might determine the newborn manifestation of ADPKD but this seemed to be ruled out because of the equal distribution of affected fathers and mothers in the reported cases. Homozygosity for the ADPKD mutation in children with the rare neonatal presentation (estimated incidence 6 to 12 per million)¹⁸ appeared to be unlikely, since no case had been reported where both parents were affected. Ultimately, the authors suggested that these severely affected children might be heterozygous for both the autosomal dominant and recessive types of polycystic kidney disease, which would be consistent with the apparent frequency of renal masses at birth as a result of ADPKD. Meanwhile, there have been several reports showing that the neonatal form defined by Taitz *et al*⁸ and the mild form of ADPKD detected later in childhood or adulthood may occur in the same sibship.^{12 14 17} This does not exclude double heterozygosity, a hypothesis based on the findings of a bimodal age distribution, but, as far as our results are concerned, heterozygosity for both the dominant and recessive types seems unlikely considering the continuous age spectrum of affected sibs in our study.

Nevertheless, the ages at initial presentation in the reported families and in our series of patients show a striking similarity in affected sibs, regardless of the age of onset in the parents which was generally in adult life.

Our observation has important implications for the explanation of the underlying genetic mechanisms. In autosomal recessive disorders, intrafamilial variability has often been explained by the existence of multiple alleles causing compound situations in the affected

Graphical illustration of the clinical course of 38 affected sibs from 17 families with early manifestation of ADPKD.

offspring. The situation in autosomal dominant conditions, however, is different. One parental gene is passed on and the clinical variability in gene carriers can be determined, for example, by the polygenic background, modifying environmental factors, or by changes in the transmitted mutation itself. The latter hypothesis has come into focus with the recent molecular biological findings in other genetic disorders such as myotonic dystrophy or fragile X syndrome. In these diseases variable insertions of DNA fragments have been detected which determine the clinical severity in affected subjects. The number of trinucleotide repeats were found to correlate closely with the phenotype. Recently, considerable attention has been paid to the hypothesis of an heritable unstable repeat element in ADPKD²⁴ explaining severely affected children. Reenders²⁴ suggested a germline repeat instability in these families as one possible explanation because classical anticipation does not occur in ADPKD. One argument in favour of similar mechanisms in ADPKD is the fact that severely affected offspring (stillbirths, Potter sequences) were observed in half sibs or other branches of the pedigree.^{15 17}

The gene for ADPKD has not been identified yet, although a series of genomic clones has been isolated spanning the entire PKD1 region. There is no evidence of genetic heterogeneity in childhood and adult onset ADPKD, since linkage of early onset ADPKD has been confirmed by chromosome 16 markers.²⁰

Although transmission of the responsible mutation through both mothers and fathers of affected children has been observed, and no definite genetic imprinting effect for early manifesting ADPKD has been described yet, a predominance of transmitting mothers was noted in our study group. The father:mother ratio of 1:1.78 (23:41) in this study group with early manifestation of ADPKD suggests a maternal effect with increasing severity of ADPKD in the affected offspring. Owing to the mode of ascertainment, however, some form of bias cannot be completely excluded. Kääriäinen¹⁷ made a similar observation in 11 families with ADPKD in children, as the mother was affected in seven families and the father in only four. Further investigations are therefore required in order to clarify the role of parental gender in the expression of the gene for ADPKD.

The results of our study are important for genetic counselling of families in whom the first child with early onset ADPKD is born. The probability that a gene carrier whose sibs showed early manifestation of ADPKD will suffer from a similar form of ADPKD is 45% at least. If the index patient shows clinical features early in life, sometimes even before the disease is diagnosed in one of his parents, the results of our study indicate that about 2/3 of all expected gene carriers can be detected in childhood. It has to be taken into account that these figures are most likely an underestimate because of as yet unaffected sibs who are still too young for their status to be defined. Another reason is the mode of ascertainment,

as the proportion of affected sibs has been calculated according to the method of single incomplete ascertainment. Under the more realistic assumption of multiple incomplete ascertainment, the ratio of affected sibs would be much higher. The design of our study, however, did not allow us to define the exact mode of ascertainment of all affected children retrospectively.

Although childhood manifestation of ADPKD is rare, we believe that our results are important for the clinical management of ADPKD families. A considerable proportion of affected offspring who are diagnosed only because of their family history may already show treatable complications of ADPKD, such as hypertension, urinary tract infections, and impaired renal function.^{25 26} Regular ultrasound screening of subjects at risk, especially in families with early onset ADPKD, would help to detect so far undiagnosed children with ADPKD who require medical treatment. Parents and attending clinicians should be aware of the high recurrence risk of early manifesting ADPKD which may affect family planning and clinical care. With an early diagnosis, however, the majority of children with manifesting ADPKD have a favourable long term prognosis without being markedly handicapped by their disease, if sufficient medical care is provided.

We thank U Weingarten for his technical assistance. The study was supported by the Bundesministerium für Forschung und Technologie.

- 1 Dalgaard OZ. Bilateral polycystic disease of the kidneys. A follow-up of two hundred eighty-four patients and their families. *Acta Med Scand* 1957;158(suppl 328):1-255.
- 2 Kaplan BS, Rabin I, Nogrady MB, Drummond KN. Autosomal dominant polycystic renal disease in children. *J Pediatr* 1977;90:782-3.
- 3 Zerres K, Weiss H, Bulla M, Roth B. Prenatal diagnosis of an early manifestation of autosomal dominant adult-type polycystic kidney disease. *Lancet* 1982;ii:988.
- 4 Sedman A, Bell P, Manco-Johnson M, et al. Autosomal dominant polycystic kidney disease in childhood: a longitudinal study. *Kidney Int* 1987;31:1000-5.
- 5 Kääriäinen H. Polycystic kidney disease in children: differential diagnosis between the dominantly and recessively inherited forms. Medical thesis, University of Helsinki, 1988.
- 6 Bear JC, Parfrey PS, Morgan JM, Martin CJ, Cramer BC. Autosomal dominant polycystic kidney disease: new information for genetic counselling. *Am J Med Genet* 1992;43:548-53.
- 7 Coto E, Aguado S, Alvarez J, Menéndez Diaz MJ, López-Larrea C. Genetic and clinical studies in autosomal dominant polycystic kidney disease type 1 (ADPKD1). *J Med Genet* 1992;29:243-6.
- 8 Taitz LS, Brown CB, Blank CE, Steiner GM. Screening for polycystic kidney disease: importance of clinical presentation in the newborn. *Arch Dis Child* 1987;62:45-9.
- 9 Zerres K, Propping P. Autosomal dominant polycystic kidney disease in children. *Arch Dis Child* 1987;62:870-1.
- 10 Loh JP, Haller JO, Kassner EG, Aloni A, Glassberg K. Dominantly-inherited polycystic kidneys in infants: association with hypertrophic pyloric stenosis. *Pediatr Radiol* 1977;6:27-31.
- 11 Eulderink F, Hogewind BL. Renal cysts in premature children. Occurrence in a family with polycystic kidney disease. *Arch Pathol Lab Med* 1978;102:592-5.
- 12 Fryns JP, Van Den Berghe H. 'Adult' form of polycystic kidney disease in neonates. *Clin Genet* 1978;14:205-6.
- 13 Proesmans W, Van Damme B, Casaer P, Marchal G. Autosomal dominant polycystic kidney disease in the neonatal period: association with a cerebral arteriovenous malformation. *Pediatrics* 1982;70:971-5.
- 14 Farrell TP, Boal DK, Wood BP, Dagen JE, Rabinowitz R. Unilateral abdominal mass: an unusual presentation of autosomal dominant polycystic kidney disease in children. *Pediatr Radiol* 1984;14:349-352.
- 15 Zerres K, Hansmann M, Knöpfle G, Stephan M. Prenatal diagnosis of genetically determined early manifestation of autosomal dominant polycystic kidney disease? *Hum Genet* 1985;17:368-9.
- 16 Fryns JP, Vandenbergh K, Moerman F. Mid-trimester ultrasonographic diagnosis of early manifesting 'adult'

- form of polycystic kidney disease. *Hum Genet* 1986; 74:461.
- 17 Kääriäinen H. Polycystic kidney disease in children: a genetic and epidemiological study of 82 Finnish patients. *J Med Genet* 1987;24:474-81.
 - 18 Pretorius DH, Lee ME, Manco-Johnson ML, Weingast GR, Sedman AB, Gabow PA. Diagnosis of autosomal dominant polycystic kidney disease in utero and in the young infant. *J Ultrasound Med* 1987;6:249-55.
 - 19 Ceccherini I, Lituania M, Cordone MS, et al. Autosomal dominant polycystic kidney disease: prenatal diagnosis by DNA analysis and sonography at 14 weeks. *Prenat Diagn* 1989;9:751-8.
 - 20 Gal A, Wirth B, Kääriäinen H, et al. Childhood manifestation of autosomal dominant polycystic kidney disease: no evidence for genetic heterogeneity. *Clin Genet* 1989; 35:13-19.
 - 21 Guérin P, Lucotte G. Pas d'évidence d'hétérogénéité génétique dans une famille de polykystose rénale adulte (dominante autosomique) particulière à manifestation précoce. *Nephrologie* 1989;10:201-3.
 - 22 Kuwertz-Bröking E, Rabe H, Grande B, Bulla M. Autosomal dominante polyzystische Nierenerkrankung im Säuglingsalter. *Klin Padiatr* 1991;203:381-3.
 - 23 Emery AEH. *Methodology in medical genetics*. Edinburgh: Churchill Livingstone, 1986.
 - 24 Reeders S. Multilocus polycystic disease. *Nature Genet* 1992;1:235-7.
 - 25 Ravine D, Walker RG, Gibson RN, Sheffield LJ, Kincaid-Smith P, Danks DM. Treatable complications in undiagnosed cases of autosomal dominant polycystic kidney disease. *Lancet* 1991;337:1356-7.
 - 26 Zerres K, Rudnik-Schöneborn S, Deget F. Routine examination of children at risk of autosomal dominant kidney disease. *Lancet* 1992;339:1356-7.