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Polycystic Kidneys Associated with Malformations of the Brain, Polydactyly, and Other Birth Defects in Newborn Sibs

A Lethal Syndrome Showing the Autosomal-recessive Pattern of Inheritance

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In 1967, Simopolous *et al* and Walbaum, Dehaene, and Duthoit reported independently in several sibs a syndrome consisting of polycystic kidneys, internal hydrocephalus, polydactyly, and other developmental abnormalities. Following our observation of this inherited syndrome in three sibs in one family a systematic search of necropsy records in two departments of pathology,* was made for similar cases. This led to the detection of 7 cases occurring in 3 other families with the same syndrome.

The Families

Family A. The propositus (II.5, Fig. 1 and the Table) was born after a prolonged pregnancy to a 30-year-old healthy mother and a 40-year-old healthy father. The parents were both Iraqi Jews, born in Bagdad. They were first cousins (the grandmothers were sisters). The mother had received injections of progesterone in the early stage of the pregnancy, but otherwise the pregnancy was uncomplicated. The infant was stillborn. The karyotype of the infant was normal. The first pregnancy resulted in the delivery of a male infant (II.1) born with tetralogy of Fallot, who died at the age of one and a half years. The second son (II.2) is now six years old and healthy. The third and fourth pregnancies resulted in the birth of two infants (II.3 and II.4) affected by similar malformations as the propositus (II.5).

Family B. The parents (I.1 and I.2, Fig. 1) were both Yemenite Jews, but were not known to be related. Their first born son (II.1) was delivered by breech presentation and birth weight was 2040 g. The father was

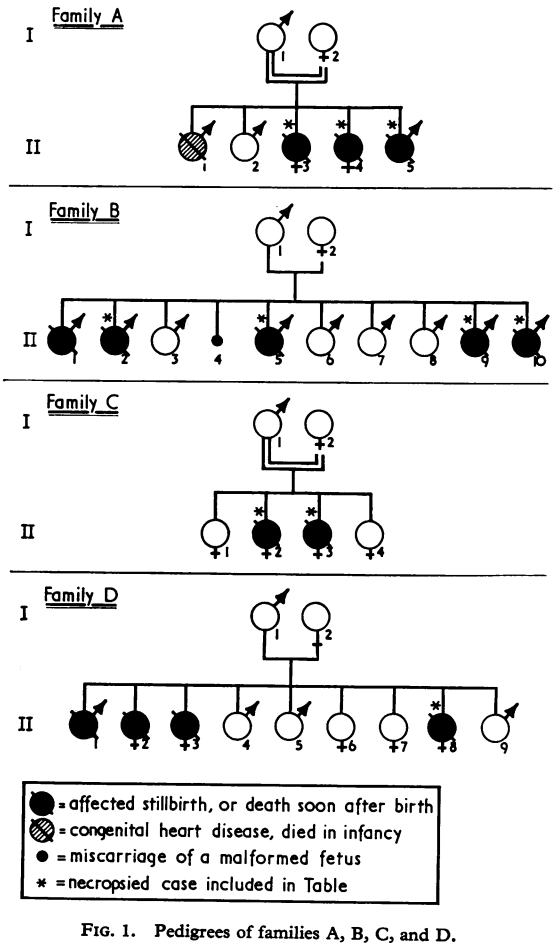

FIG. 1. Pedigrees of families A, B, C, and D.

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TABLE
SUMMARY OF PATHOLOGICAL FINDINGS

Case	Delivery	Sex	Length (cm) and Weight (g)	Brain	Polydactyly	Kidneys
Family A						
II.3	Died immediately after birth	F	2650	Occipital meningocoele; agenesis of cerebellum	6 fingers on hands and feet	Polycystic (110 g)
II.4	Stillbirth; breech presentation	F	3200	Anencephalus	6 fingers on hands and feet	Polycystic (365 g)
II.5	Breech presentation; stillbirth	M	49 3400	Anencephalus	6 fingers on feet and one hand, 7 fingers on other hand	Polycystic (277 g)
Family B						
II.2	Stillbirth; premature	M	35 2520	Occipital meningoencephalocoele; hypoplasia of cerebellum; absence of corpus callosum	Not recorded (missed ?)	Polycystic (140 g)
II.5	Stillbirth	M	38 2120	Occipital meningocoele; craniochisis; hypoplasia of cerebellum	6 fingers on hands and feet	Polycystic (8·5 × 5 × 2·5 cm)
II.9	Stillbirth	M	48 3800	Occipital meningocoele; microcephaly	6 fingers on hands and feet	Polycystic (150 g)
II.10	Breech presentation; stillbirth	M	37 2100	Occipital meningocoele; microcephaly	6 fingers on hands and feet	Polycystic (260 g)
Family C						
II.2	Stillbirth; breech presentation; premature	F	37 1640	Occipital meningoencephalocoele; microcephaly; fusion of cerebral hemispheres; absence of corpus callosum	6 fingers on hands only	Polycystic (5 × 4·5 × 3·5 cm)
II.3	Died several minutes after delivery	F		Occipital meningocoele	Polydactyly	Polycystic (35 g)
Family D						
II.8	Died immediately after birth	M	49 3000	Occipital meningoencephalocoele	6 fingers on hands and feet	Polycystic

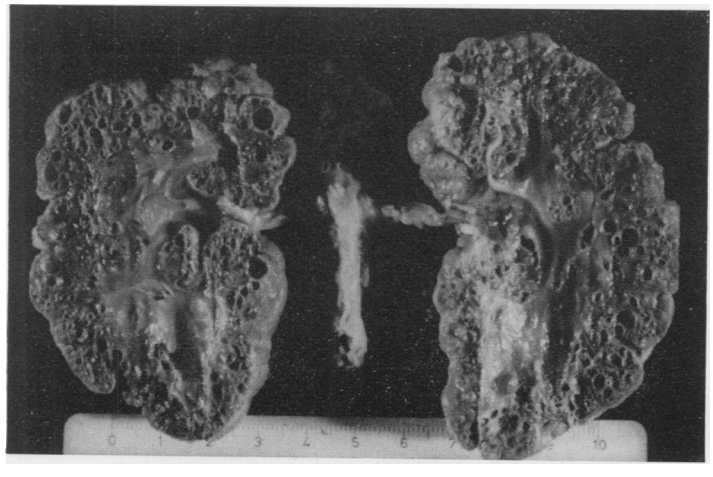

FIG. 2. Large polycystic kidneys of case II.5, family B (scale in centimetres).

23 years old and the mother 18 years old at his birth. The infant died two hours after birth. Meningocoele, pes varus, and atresia of genitalia were clinically recorded. Unfortunately no necropsy was performed. As there was no postmortem examination this case was not included in the Table. The second pregnancy resulted in a stillborn son (II.2, see Table). The third son (II.3) is normal and healthy. The fourth pregnancy

IN 10 CASES IN 4 FAMILIES

Liver	Cleft Palate	Eyes	Adrenals	Genitalia	Other malformations
165 g; fibrosis with bile duct proliferation	–		Normal size		Congenital atresia of right ureter
200 g; no histological examination	+		Hypoplastic		Ventricular septal defect cleft lip
Polycystic (115 g)	–	Anophthalmia	Right hypoplastic; left absent	Hypoplasia of penis; undescended testes	Hypoplasia of urinary bladder
130 g, fibrosis with bile duct proliferation	–	Microphthalmus (left)	Hypoplastic	Undescended testes	Hypoplasia of thymus; epiglottis bisecta
Polycystic (120 g)	+	Microphthalmus (right)		Absence of penis; undescended testes	Malformation of tongue and larynx; malrotation of intestine; hypoplasia of small intestine and bladder
Polycystic	+		Hypoplasia (0·5 g each)	Absence of corpora cavernosa of penis; undescended testes	Contracture of joints; malformation of tongue and larynx; hypoplasia of bladder
110 g; fibrosis with bile duct proliferation	+	Bilateral microphthalmia	Hypoplasia (1 g each)	Absence of penis; undescended testes	Contracture of joints; single umbilical artery; malformation of tongue and larynx
Polycystic	–				Malrotation of intestine
Polycystic (150 g)	+			Bicornuate uterus	
180 g; fibrosis with bile duct proliferation and mild cystic dilatation	–			Hypoplasia of penis; undescended testes	Malrotation of intestine; atresia of distal part of sigmoid colon

terminated in miscarriage in the fifth month of pregnancy and the mother was informed that the fetus was malformed. The fifth pregnancy ended in the birth of an affected son (II.5, see Table and Figs. 2, 3, 4, and 5. The sixth, seventh, and eighth pregnancies resulted in the birth of three healthy sons (II.6, II.7, and II.8).) The ninth and tenth pregnancies ended in the birth of two sons having similar malformations (II.9 and II.10, see Table and Figs. 1, 6, and 7).

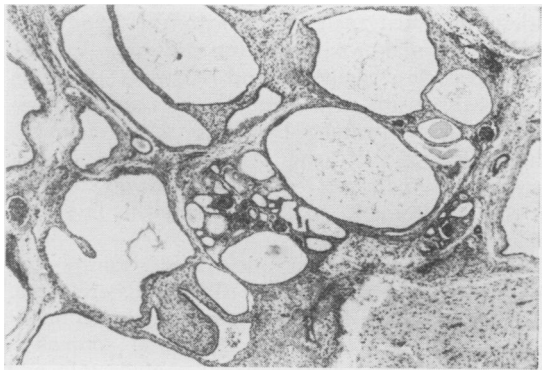

FIG. 3. Microscopic photograph of kidneys, case II.5, family B. Multiple cysts of various size of tubular origin are present. Among the cysts there are a few well preserved glomeruli. Haematoxylin and eosin, ×25.

Family C. The parents (I.1 and I.2, Fig. 1) were both Yemenite Jews. They were first cousins (the father's mother and the mother's father were sibs). The first born daughter (II.1) is normal and is living and well. The second and the third children were affected daughters (II.2 and II.3). The pathological findings are summarized in the Table. The fourth and last child, a daughter (II.4) is healthy. One nephew of the father (I.1) died at birth.

Family D. The parents (I.1 and I.2, Fig. 1) were Yeminite Jews, but were not known to be related. The first son (II.1) was born after several years of primary sterility. The father was 30 years old and the mother was 25 years old at his birth. The son died shortly after birth and the mother was told that the child was malformed. The second child was a malformed female infant (II.2) delivered at home who died shortly after birth. The mother remembered that she had a bulging in the occipital region. The third child was again a malformed daughter (II.3), who was delivered on the way to the hospital and died shortly after arrival. The next four children are living and healthy (II.4, II.5, II.6,

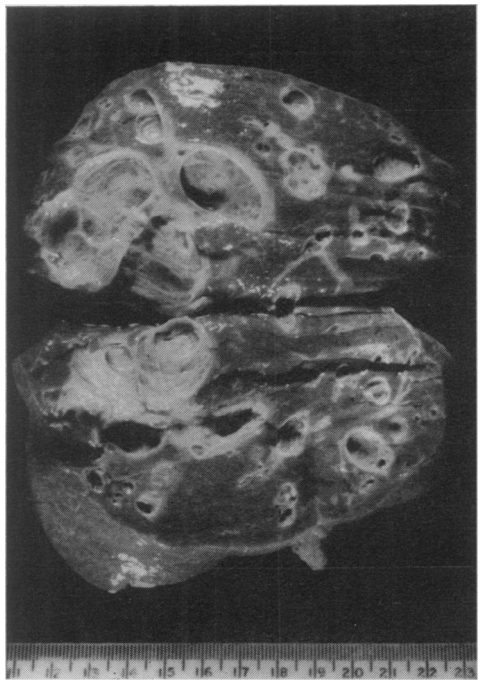

FIG. 4. Polycystic liver with focal fibrosis of case II.5, family B (scale in centimetres).

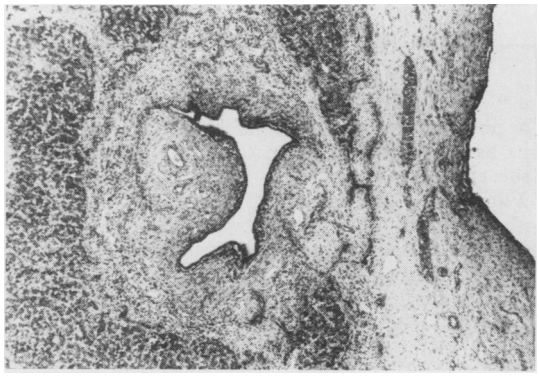

FIG. 5. Microscopic photograph of liver, case II.5, family B. In the centre there is an enlarged fibrosed portal space with an irregularly dilated bile duct, and on the right the fibrosed wall of a large cyst. Haematoxylin and eosin, × 25.

and II.7). In only one malformed infant (II.8) in this family were necropsy data available. She died immediately after birth. The last child (II.9) is a healthy boy.

Discussion

In 1822, Meckel described necropsy findings in a brother and sister with polycystic kidneys associated with malformations of the brain, polydactyly, and

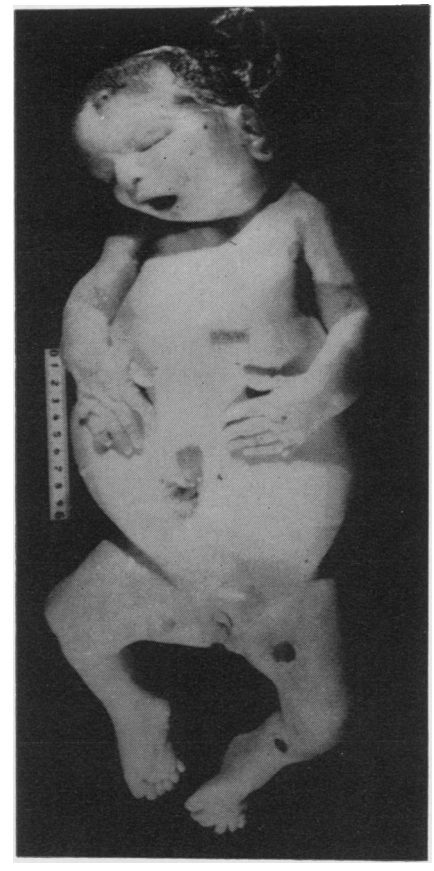

FIG. 6. Case II.9, family B (male stillborn infant). Note the occipital meningocoele, micrognathia, large abdomen, polydactyly of hands and feet, and hypoplastic genitalia.

other birth defects. Cryptorchidism, was noted in the brother. A century later, Stockard (1921) briefly reported male twins with this syndrome; their brain malformation being posterior occipital meningocoeles. Lelièvre and Walther (1927) recorded three sibs with meningocoeles and polycystic kidneys. Cornelia DeLange (1930) reported three affected sibs the products of a nonconsanguineous marriage. Gruber wrote a good review of this syndrome in 1934, and named it 'Dysencephalia splanchnocystica'.

Simopoulos *et al* (1967) described a family with three prematurely born male sibs who were found to have polycystic kidneys, internal hydrocephalus, polydactyly, and other developmental anomalies. Two brothers with hydrocephalus, polydactyly, and polycystic dysplasia of the kidneys were also described by Walbaum *et al* (1967). The parents were first cousins. The first affected son was

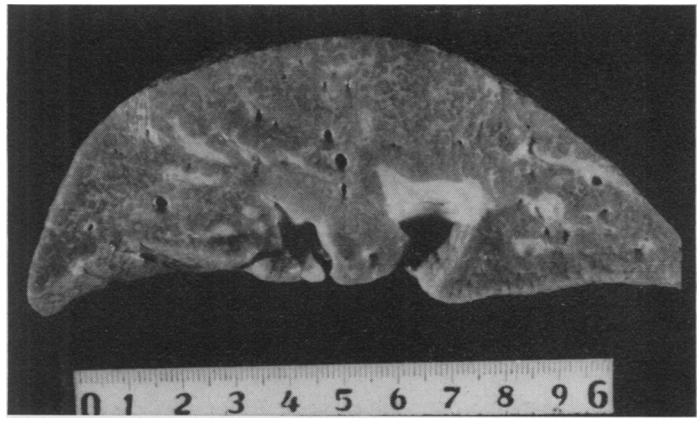

FIG. 7. Congenital fibrosis of liver, case II.9, family B (scale in centimetres). Cysts were seen on microscopic examination.

stillborn whereas the propositus was born by Caesarean section at term and survived for 34 days. A case of multiple malformations in Japan briefly reported in an abstract of Ohashi *et al* (1969) may be a case of this syndrome, although the status of the kidneys is not mentioned. Recently Opitz and Howe (1969) put the literature together, reported another case, and gave it the eponymic designation of Meckel syndrome.

The pathological findings in the 10 cases described are very similar to those reported in the literature but some additional features can be noted. All infants were either stillborn or died very shortly after birth, this was probably due to the polycystic kidneys, which at this age is incompatible with life. In most of the cases the diagnosis could be made clinically by the observation of the markedly enlarged abdomen and by palpatation of the renal masses. In this series in all cases except in one, in which the liver was not examined microscopically, congenital fibrosis with bile duct proliferation or polycystic liver was found. In 5 cases the cysts were large and macroscopically visible, in the others there was fibrosis with bile duct proliferation and often mild dilation of the proliferated bile ducts.

In 2 cases there was anencephaly and in 8 occipital meningocoele or meningoencephalocoele, which was associated in some of the cases with agenesis or hypoplasia of the cerebellum, microcephaly, absence of corpus callosum, and fusion of cerebral hemispheres. In this series there were no cases of internal hydrocephalus.

Polydactyly is a malformation that can be easily diagnosed both by the clinician and the pathologist. However in cases of multiple congenital malformations it may be unrecorded and this probably happened in one case (case II.2, family B). On the other hand it may be that due to the variability in the expressivity of this syndrome, not all cases will show this manifestation. Polydactyly is a well known benign hereditary anomaly, or it may be part of some rare genetic disease, but we are not aware of polydactyly being part of any recessive syndrome that is incompatible with life.

The genitalia of the males were strikingly abnormal; the penis being either aplastic or hypoplastic and the testes were undescended. The palate was noted to be cleft in half the cases and in one case it was accompanied by cleft lip. Microphthalmus or anophthalmus was noted in some cases. Other malformations recorded were: hypoplasia of the urinary bladder, malformations of the larynx and tongue, contracture of joints, and malrotation of the intestines. It is of interest that all 9 children born in family B (Fig. 1) were males. This may be due to chance alone as there was no peculiarity of the sex ratio among the relatives of the parents, or in the other families. Of the 14 cases recorded in the pedigrees (Fig. 1) 7 were males and 7 were females (5 out of 10 necropsied cases were males). The sexes were equally affected and the findings of consanguinity between the parents in two out of the four sibships strongly suggests an autosomal recessive mode of inheritance. The high proportion of affected sibs is easily explained by the biased incomplete ascertainment. Three of the families (families B, C, and D) were of Yemenite Jewish origin. No common ancestors could be traced to the three families. In spite of this, they may be distantly related or the gene may be relatively common among Yemenite Jews.

The syndrome may have escaped attention until recently because the children were either stillborn or died soon after delivery. Such children would be

simply classified as cases of multiple congenital malformations. In view of our experience, it seems worthwhile, to search necropsy records of hospitals for necropsies of stillborn infants and in-infants who died in their first days of life for cases with the combination of polycystic kidneys, central nervous system malformations, and polydactyly. Such data may serve as a basis for the estimation of the gene frequency in different populations.

Summary

A lethal syndrome caused by an autosomal recessive gene is described in 10 necropsied cases belonging to four separate families. The main features of the syndrome are polycystic kidneys, malformation of the central nervous system, and polydactyly. Additional common congenital defects are polycystic or fibrotic liver with bile duct proliferation, microphthalmus or anophthalmus, and cleft palate. In the males hypoplasia or absence of penis and undescended testes are the rule. The infants were either stillborn or died soon after birth.

References

DeLange, C. (1930). Zum Studium der Encephalocele posterior. *Jahrbuch für Kinderheilkunde*, **126**, 253–288.

Gruber, G. B. (1934). Beiträge zur Frage "gekoppelter" Missbildungen (Akrocephalo-syndactylie und Dysencephalia Splanchnocystica). *Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie*, **93**, 459–476.

Lelièvre, A. and Walther, P. (1924). Cinq cas de reins polykystiques à l'appui de la théorie dysembryoplastique. *Bulletins et Mémoires de la Société anatomique de Paris*, **94**, 34–40.

Meckel, J. F. (1822). Beschreibung zweier durch sehr ähnliche Bildungsabweichungen entstellter Geschwister. *Deutsches Archiv für Physiologie*, **7**, 99–172.

Ohashi, T., Hajima, M., Wakitani, T., and Nakayama, H. (1969). A case of multiple malformations. *Proceedings of the Congenital Anomalies Research Association of Japan*, **9**, 62–63.

Opitz, J. M. and Howe, J. J. (1969). The Meckel Syndrome (Dysencephalia Splanchnocystica, the Gruber Syndrome). In *Birth Defects: Original Article Series* 5, 2, pp. 167–179. The National Foundation—March of Dimes, New York.

Simopoulos, A. P., Brennan, G. G., Alwan, A., and Fidis, N. (1967). Polycystic kidneys, internal hydrocephalus and polydactylism in newborn siblings. *Pediatrics*, **39**, 931–934.

Stockard, C. R. (1921). Developmental rate and structural expression: an experimental study of twins, 'double monsters' and single deformities, and the interaction among embryonic organs during their origin and development. *American Journal of Anatomy*, **28**, 115–277.

Walbaum, R., Dehaene, Ph., and Duthoit, F. (1967). Polydactylie familiale avec dysplasie neuro-crânienne. *Annales de Génétique*, **10**, 39–41.