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ARTICLE

Meckel–Gruber Syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features, and survival in Europe

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Meckel–Gruber Syndrome is a rare autosomal recessive lethal ciliopathy characterized by the triad of cystic renal dysplasia, occipital encephalocele and postaxial polydactyly. We present the largest population-based epidemiological study to date using data provided by the European Surveillance of Congenital Anomalies (EUROCAT) network. The study population consisted of 191 cases of MKS identified between January 1990 and December 2011 in 34 European registries. The mean prevalence was 2.6 per 100 000 births in a subset of registries with good ascertainment. The prevalence was stable over time, but regional differences were observed. There were 145 (75.9%) terminations of pregnancy after prenatal diagnosis, 13 (6.8%) fetal deaths, 33 (17.3%) live births. In addition to cystic kidneys (97.7%), encephalocele (83.8%) and polydactyly (87.3%), frequent features include other central nervous system anomalies (51.4%), fibrotic/cystic changes of the liver (65.5% of cases with post mortem examination) and orofacial clefts (31.8%). Various other anomalies were present in 64 (37%) patients. As nowadays most patients are detected very early in pregnancy when liver or kidney changes may not yet be developed or may be difficult to assess, none of the anomalies should be considered obligatory for the diagnosis. Most cases (90.2%) are diagnosed prenatally at 14.3 ± 2.6 (range 11–36) gestational weeks and pregnancies are mainly terminated, reducing the number of LB to one-fifth of the total prevalence rate. Early diagnosis is important for timely counseling of affected couples regarding the option of pregnancy termination and prenatal genetic testing in future pregnancies.
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INTRODUCTION

Meckel–Gruber Syndrome (MKS) (MKS1 MIM #249000, MKS2 MIM #603194, MKS3 MIM #607361, MKS4 MIM #611134, MKS5 MIM #611561, MKS6 MIM #612284, MKS7 MIM #267010, MKS8 MIM #613885, MKS9 MIM #614209, MKS10 MIM #614175, and MKS11 #615397) is a genetically heterogeneous severe lethal ciliopathy characterized by occipital meningoencephalocele and/or other central nervous system anomalies, polycystic kidneys, and postaxial polydactyly.[1–4]Additional malformations such as microphthalmia, facial clefting, heart defects, fibrotic changes in the portal area of the liver, incomplete/ambiguous development of external or internal genitalia are often present.[2,4–7]

The estimated prevalence of MKS worldwide ranges from 1 per 1304 in Gujarati Indians[8] to 1 per 140 000 in Great Britain.[9] There is evidence that the prevalence is higher in populations with higher consanguinity rates, as in India,[8,10] Pakistan,[11] Kuwait and other Arab countries.[12,13] In Europe, high rates were found in Belgium[14] and in Finland,[15] but there are currently no population-based epidemiologic data available for Europe or worldwide.

MKS is at the severe end of the ciliopathy phenotypic spectrum. So far, sequence variants affecting function in at least eleven genes are known to cause this autosomal recessive disorder: *MKS1*, *TMEM216 (MKS2)*, *TMEM67 (MKS3)*, *CEP290 (MKS4)*, *RPGRIP1L (MKS5)*, *CC2D2A (MKS6)*, *NPHP3 (MKS7)*, *TCTN2 (MKS8)*, *B9D1 (MKS9)*, *B9D2 (MKS10)*, *TMEM231 (MKS11)*, and more recently, a new one has been identified.[16] The encoded proteins are all implicated in the correct function of primary cilia, organelles found on the apical surface of most epithelial cell types which play an essential role in cellular function and organ development.[17–20]

The minimal diagnostic criteria are most often formulated as the presence of at least two of the three main manifestations, ie bilateral renal cystic dysplasia, occipital encephalocele or other anomalies of

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the central nervous system, and polydactyly.[2–4,21] However, after review of affected sibs of probands, it has been suggested to broaden the diagnostic criteria to include as obligatory cystic renal dysplasia plus at least two other more frequently seen anomalies.[5] Salonen[6] has suggested to include fibrotic changes of the liver/ductal proliferation among the major features of MKS, as they are a consistent finding at post mortem examination. Cystic renal dysplasia is also found in the vast majority of cases, but in spite of this, there is still general agreement that there are no mandatory features of MKS.[21,22]

As MKS is a rare disease and invariably lethal in early infancy, large clinical series of patients that address epidemiological and clinical findings are scarce.[4–6] It is possible to detect MKS in the first trimester of pregnancy and currently most cases are detected prenatally.[23,24] However, there is very limited data published on any type of birth outcomes—live births (LB), fetal deaths (FD), and terminations of pregnancy after prenatal diagnosis (TOPFA) in MKS patients.

The aim of this study is to investigate MKS, including the prevalence of the different types of birth outcomes, time of diagnosis, gender, gestational age (GA), birth weight, associated anomalies, family history, and consanguinity, using a large European database for the population-based surveillance of congenital anomalies (EUROCAT). To our knowledge, this is the largest series of MKS patients published so far.

MATERIALS AND METHODS

The EUROCAT congenital anomaly registries are population-based and collect data on all major structural congenital anomalies, chromosomal abnormalities and genetic syndromes among LB, FD with GA $\geq$ 20 weeks, and TOPFA using standardized definitions and coding. The definitions and coding instructions were described in previous publications.[25–27]

The data used in this study were routinely collected between 1990 and 2011 by 34 EUROCAT registries in 16 countries and extracted from the central database in June 2013. The central EUROCAT database was searched for International Classification of Diseases/British Paediatric Association version 9 (759.89) and 10 (Q61.90) codes assigned to cases of MKS. The minimal diagnostic criteria for inclusion in the study were the presence of at least two of three classic manifestations of MKS.[2–5] In EUROCAT registries, clinical geneticists are involved in the examination and diagnosing of almost all patients with multiple congenital anomalies and dysmorphic features.[28] A medical geneticist (IB) reviewed all records. Textual descriptions were evaluated to ensure that all relevant clinical information was included in the study. Local registries were contacted for any additional information required. For each case, the following data were evaluated: time of diagnosis, outcome of pregnancy, fetus/infant characteristics including gender, survival up to 1 week of age, GA (in completed weeks) and birth weight (in grams), associated anomalies, family history, consanguinity, maternal and paternal age at delivery, fertility treatment, multiple pregnancy (twin or triplet), post mortem examination, and karyotype. Data on genetic testing were not systematically collected. All phenotype and epidemiological data obtained in this study will be available to public phenotypic databases (eg, Online Mendelian Inheritance in Man or GeneReviews) upon publication.

Statistical analysis

Descriptive data are presented as numbers and percentages for categorical data. Mean and 95% confidence interval, based on Poisson distribution, was used for prevalence. Generalized linear/nonlinear model based on Poisson distribution was used for statistical testing of time trends in prevalence. A difference between two proportions test was used for statistical testing of prevalence differences between registries and total prevalence rate. χ^2 tests were performed to determine differences in maternal age distribution between MKS and other EUROCAT cases. When performing the statistical analyses, a *P*-value less than 0.05 was considered statistically significant.

RESULTS

Epidemiological data

To ensure a high rate of ascertainment of MKS patients, we have calculated the prevalence based on data from 16 registries that have the total non-chromosomal syndrome prevalence above the EUROCAT average (7.8 per 1000) following the Data Quality Indicators developed by EUROCAT (http://www.eurocat-network.eu/content/DQI-2010.pdf). Between January 1990 and December 2011, in these registries we monitored a total population of 5 483 380 births and identified 142 patients with MKS. This corresponds to a prevalence of 1 per 38 615 or 2.6 per 100 000 births. The prevalence rates for 1990–2000 and 2001–2011 periods were 2.4 and 2.8 per 100 000 births, respectively ($P = 0.06$) (Table 1). The number of MKS patients per registry is presented in Table 2.

There were 32 (16.8%) confirmed familial cases, of these there were 27 affected sibs and in five cases, one of the parental relatives had an anomaly from the MKS spectrum. The consanguinity was recorded in 23 cases according to the EUROCAT definition.[26] Almost all consanguineous cases came from the registries with a statistically significantly higher prevalence rates of MKS compared with the total average prevalence for selected registries ($P < 0.05$) (nine from NW Thames, eight from Paris, four from Vaud, and two families from Hainaut) (Table 2).

The mean maternal age was 29.3 ± 6.8 years and the mean paternal age 33.5 ± 7.1 years. Maternal age distribution did not differ significantly from that for the total EUROCAT population ($P = 0.06$).

Data on karyotyping were available for 94 cases and all results were normal. Results of post mortem examination were available for 113 (59%) cases six in neonatal deaths and 107 in TOPFA. Multiple pregnancies of undetermined zygosity were recorded in 6 (3.14%) cases (only one twin affected). Nine out of 102 (8.8%) patients from registries that provide the information on assisted reproductive technology (ART) were conceived by induced ovulation. There were no cases of *in vitro* fertilization or intracytoplasmic sperm injection.

Clinical data

Between January 1990 and December 2011, we identified 191 cases of MKS in the population of 34 European congenital anomaly registries. Among the patients for which the time of diagnosis was known ($n = 183$), 90.2% were diagnosed prenatally, 4.9% at birth and 4.9% in the first week of life. The mean GA at prenatal diagnosis by obstetric ultrasound was 14.3 ± 2.6 (range 11–36) gestational weeks. The pregnancies with prenatally diagnosed severe anomalies were terminated at 18.1 ± 2.53 (range 12–39) gestational weeks. At least two anomalies (sometimes three or more) were detected by prenatal ultrasound in all but three cases of renal cystic dysplasia in which at post mortem additional malformations supporting MKS diagnosis were found.

The prenatal detection rate was 93.8% (165/176), with no significant trend over 1990–2000 and 2001–2011 periods ($P = 0.07$).

Table 1 Prevalence of MKS in 16 selected EUROCAT registries, 1990–2011

Monitored period	*Total births*	*Total no. of patients*	*Birth prevalence per 100 000 (95% CI)*
1990–2000	2 448 022	58	2.4 (1.9–2.8)
2001–2011	3 035 358	84	2.8 (2.4–3.1)
1990–2011	5 483 380	142	2.6 (2.1–3.0)

Abbreviations: 95% CI, 95% confidence interval; MKS, Meckel–Gruber Syndrome.

Table 2 The number of cases and prevalence of MKS patients in 16 selected EUROCAT registries in 1990–2011

Registry	No. of MKS patients in 1990–2011	Population	Prevalence per 100 000
Styria (Austria)	1	229 506	0.4
Antwerp (Belgium)	8	341 573	2.3
Hainaut (Belgium)	8	277 204	2.9[a]
Dublin (Ireland)	1	489 614	0.2
Odense (Denmark)	0	121 532	0
Paris (France)	35	703 650	5[a]
Strasbourg (France)	4	230 664	1.7
Mainz (Germany)	1	75 496	1.3
Cork And Kerry (Ireland)	1	131 119	0.8
N Netherlands (NI)	10	421 026	2.4
Vaud (Switzerland)	11	166 950	6.6[a]
Northern England (UK)	9	382 900	2.3
N W Thames (UK)	22	661 527	3.3[a]
Thames Valley (UK)	11	291 759	3.8[a]
Wales (UK)	10	466 301	2.1
Wessex (UK)	10	492 559	2
Total	142	5 483 380	2.6

Abbreviations: EUROCAT, European Surveillance of Congenital Anomalies; MKS, Meckel–Gruber Syndrome.
[a]Registries with statistically significant higher prevalence rates compared to the total average prevalence rate of selected registries ($P<0.05$).

Table 3 Outcome of pregnancies and prenatal detection rate in MKS in the EUROCAT registries, 1990–2011

Monitored period	Total no. of patients	LB	FD	TOPFA	Prenatally detected/ number of patients with available data	Prenatal detection rate % (95% CI)
1990–2000	72	13	4	55	60/66	91 (86.5–95.7)
2001–2011	119	20	9	90	105/110	95.5 (89.1–98.0)
1990–2011	191	33	13	145	165/176	93.8 (89.1–98.4)

Abbreviations: 95% CI, 95% confidence interval; EUROCAT, European Surveillance of Congenital Anomalies; FD, fetal deaths; LB, live born; MKS, Meckel–Gruber Syndrome; TOPFA, terminations of pregnancy for fetal anomaly.

There were 145 (75.9%) TOPFA, 13 (6.8%) FDs, 33 (17.3%) LBs (Table 3).

The male-to-female ratio was 1.2:1. The mean GA in live born was 34.2 ± 3.4 (range 21–41) gestational weeks for males and 33.9 ± 4.1 (range 28–41) gestational weeks for females. The mean birth weight was 2540 ± 964 g for males and 2620 ± 246 g for females. Data on survival were known for 175 patients. Of 33 live born, only six survived the first week of life.

Detailed description of congenital anomalies was available for 173 patients. The type and frequency of major congenital anomalies in the present study and in the larger series of MKS patients published so far are shown in Table 4. In addition to cystic kidneys (97.7%), encephalocele (83.8%) and polydactyly (87.3%), frequent features include other central nervous system anomalies (51.4%), fibrotic/cystic changes of the liver (65.5% of cases with post mortem examination) and orofacial clefts (31.8%).There were 64 (37%) patients with anomalies other than the classical triad. Among these 64 patients, one additional associated major anomaly was present in 29 (16.8% of the total population), two anomalies in 21 (12.1%), and three or more associated anomalies in 14 (8.1%) patients.

DISCUSSION

Prevalence

Although MKS has been reported worldwide, more extensive data on the true prevalence in different populations are rare. In Europe, hospital-based prevalence has been reported for Belgium (1 per 3 408)[14] and Great Britain (1 per 140 000)[9] and population-based for Finland (1 per 9000).[15] In our population-based study, the prevalence of MKS in 16 selected EUROCAT registries is 2.6 per 100 000 or 1 per 38 615 births and that prevalence has been stable since 1990. MKS includes severe and distinctive anomalies that are easily detected prenatally or at birth. Therefore, it is unlikely that a significant number of cases were missed. It is, however, possible that some of the fetuses with atypical presentation were terminated or resulted in stillbirth without syndrome diagnosis, particularly when there was no post mortem examination. Therefore, the established prevalence represents a minimal estimate.

There is heterogeneity in the prevalence rates, with significantly higher rates in Hainaut (Belgium), Paris (France), Vaud (Switzerland), NW Thames (UK) and Thames Valley (UK), Presumably, in the regions with a higher prevalence rate, there are families residing with the mutated genes as most of the consanguineous cases come from there. The highest prevalence rate was observed in Vaud (Switzerland) (1 per 15 177 births).

As expected, no correlation with maternal or paternal age was found. The number of multiple pregnancies was within the normal range for EUROCAT registries.[29] MKS was previously described following ART[30,31] and epidemiologic surveillance of rare autosomal recessive syndromes, such as MKS, in ART pregnancies was proposed.[31] In our study, no association of MKS and ART was observed when compared with the data for general European population.[32]

Clinical presentation

MKS is a lethal disorder. Most infants are stillborn or die within a few hours or days after birth. The majority of prenatally detected cases in our series were subsequently terminated due to the presence of severe anomalies (88%). Therefore, we did not observe a high rate of FD. Only 17.3% of patients were live born. About two-thirds of live born of both sexes had GA at birth ≤ 37 gestational weeks and birth weight $< 2\,500$ g. The male-to-female ratio was equal.This is in accordance with an autosomal recessive inheritance and previous observations.[4]

The longest known survival recorded in the literature is 28 months.[33,34] The major causes of early death include impaired kidney function with subsequent oligohydramnios, pulmonary hypoplasia, and liver disease. In our study from 17 LB with recorded survival, only six (35.2%) survived the first week of life.

MKS is characterized by central nervous system malformation (usually occipital encephalocele), bilateral large multicystic kidneys, fibrotic changes of the liver, and polydactyly.[1–6,35] In addition to the characteristic anomalies, other congenital anomalies are frequently found, leading to a wide phenotypic variation. The differential diagnosis of fetuses and infants with these multiple anomalies would include trisomy 13, Smith-Lemli-Opitz, hydrolethalus (Salonen-Herva-Norio), Joubert and Bardet Biedel syndromes.[6,7] The diagnosis is clear in most instances because of the distinctive combination of the key features. Additional conditions that could present a diagnostic challenge include Joubert syndrome and related disorders (probably allelic ciliopathies), acromelic frontonasal dysplasia, oral–facial–digital syndromes type 1 and 2, cerebro–reno–digital syndrome, Mullerian duct/Renal aplasia–cervicothoracic

Table 4 Type and frequency of major anomalies in MKS in present study and in previously published reviews/series of patients

Type of anomaly	*Patients* N = *173(%)*	*Salonen*[6] N = *67(%)*	*Fraser and Lytwyn*[5] N = *65(%)*	*Hsia et al*[4] N = *51(%)*
Nervous system				
Encephalocele	145 (83.8)	57/64 (89)		
Encephalocele—occipital	99 (57.2)		48 (74)	41 (80.4)
Encephalocele—nasophrontal	1 (0.6)			
Encephalocele—orbital	1 (0.6)			
Encephalocele—NOS	44 (25.4)			
Cervical rachishisis	4 (2.3)	4 (6)		
Microcephaly	4 (2.3.)	41/65 (63)[a]		25 (49)
Anencephaly	6 (3.5)		8 (12.3)	
Holoprosencephaly	5 (2.9)			
Agenesis/hypoplasia of corpus callosum	3 (1.7)			
Dandy Walker anomaly	23 (13.3)			
Arnold Chiari anomaly	2 (1.2)			
Agenesis/hypoplasia of cerebellum	11 (6.4)	7 (10.4)		
Atretsia of foramina Magendi and Luschka	3 (1.7)			
Congenital cerebral cyst	2 (1.2)			
Congenital hydrocephalus	14 (8.1)	11/64 (17)	10 (15.4)	
Other	12 (6.9)	4 (6)	20 (30.8)	30 (58.9)
Head and neck				
Eye			18 (27.7)	
Lid anomalies	2 (1.2)			
Microphthalmia/anophthalmia	35 (20.2)	16/61 (26)		13 (25.4)
Retinal dysplasia	3 (1.7)[b]			
Coloboma	1 (0.6)			
Anomalies of tongue	13 (7.5)	9/61 (15)		
Orofacial clefting	44 (25.4)		20 (30.8)	29 (56.9)
Cleft palate	34 (19.7)	27/42 (64)		
Cleft lip	10 (5.8)	12/62 (19)		
Cleft lip and palate	11 (6.4)			
Respiratory				
Lung/thorax hypoplasia	12 (6.9)	19 (28)		
Heart	28 (16.2)	11/56 (20)	21 (32.3)	10 (19.6)
Ventricular septal defect	9 (5.2)	2 (3)		
Atrial septal defect	4 (2.3)	6 (9)		
Stenosis of pulmonar artery	2 (1.2)			
Persistent left superior vena cava	2 (1.2)			
Double outlet right ventricle	1 (0.6)			
Dextrocardia	1 (0.6)			
Coarctation of aorta	2 (1.2)			
Common ventricle	1 (0.6)			
Congenital heart disease, NOS	6 (3.5)			
Digestive				11 (21.6)
Anomalies of intestinal fixation	3 (1.7)			
Fibrotic and/or cystic liver/ductal plate malformation	74 (65.5)[c]	47/47 (100)	25 (38.5)	
Anal stenosis/atresia	7 (4)			
Omphalocoele	3 (1.7)			
Persistent cloaca	1 (0.6)			
Spleen anomaly	6 (3.5)	6 (9)	12 (18.4)	6 (11.8)
Adrenal	2 (1.2)	8 (11.9)	6 (9.2)	8 (15.7)
Kidney				
Cistic kidney disease	169 (97.7)	55/55 (100)	65 (100)	41 (80.4)
Renal agenesis	6 (3.5)			
Renal hypoplasia/dysplasia	24 (13.9)			
Accessory kidney	2 (1.2)			
Ren arcuatus	2 (1.2)			
Other anomalies, NOS	8 (4.6)			

Table 4 (Continued)

Type of anomaly	*Patients* N = *173(%)*	*Salonen*[6] N = *67(%)*	*Fraser and Lytwyn*[5] N = *65(%)*	*Hsia et al*[4] N = *51(%)*
Urinary	18 (10.4)	29/54 (54)	9 (13.8)	
Congenital hydronephrosis	4 (2.3)			
Double ureter	2 (1.2)			
Anomalies of bladder	4 (2.3)			
Other anomalies, NOS	8 (4.6)			
Genital	40 (23.1)		18 (27.7)	
Uterus duplex	3 (1.7)			
Unicornuate uterus	4 (2.3)			
Uterus bifidum	6 (3.5)			
Hypoplastic scrotum	9 (5.2)			
Ambiguous genitalia	18 (10.4)	9 (13.4)		22 (43)
Skeletal				
Pes equinovarus	15 (8.7)	32/62 (52)		
Polydactyly legs	122 (70.5)	58/64 (91)		
Polydactyly hands	133 (76.9)	61/64 (95)		
Polydactyly unspecified	18 (10.4)			
Polydactyly total cases	151 (87.3)		44 (67.7)	42 (82)
Syndactyly	6 (3.5)	5 (7.5)		7 (13.7)
Limb reduction	1 (0.6)			
Short limbs	33 (19)	18 (26.9)		14 (27.5)

Abbreviations: MKS, Meckel–Gruber Syndrome; NOS, not otherwise specified.
Please note that in all studies the rate of each congenital anomaly is calculated using as denominator the total number of cases and not the number of performed appropriate diagnostic procedures.
NOS, individuals with more than one anomaly within a category were counted only once.
[a]Microcephaly + anencephaly.
[b]Two recorded in SB and one in LB.
[c]Recorded in 74/113 post mortem reports.

somite dysplasia syndrome, and renal–hepatic–pancreatic dysplasia—Dandy Walker cyst syndrome. Additional investigations, in particular histopathologic studies, molecular testing, and karyotype are of help in clarifying atypical cases, but in the absence of the simple and reliable genetic test, there is always a possibility of the wrong diagnosis. Genetic mapping is probably still incomplete, although mutations in about dozen genes are reported to be pathogenic. The genotype–phenotype correlations and identification of founder mutations in specific ethnic groups are in progress.[17,36,37] In EUROCAT, systematic data collection has only started recently for the results of genetic testing and thus, this study is not able to contribute to this effort.

The cystic kidneys are reported in 95–100%, occipital encephalocele in 60–80%, and postaxial polydactyly in 55–75% of patients.[2–6] Our results are in line with these findings. Cystic kidney dysplasia was the most constant feature in our study, although it was not present in all patients. This is in contrast with the assumption of some authors that cystic kidneys are an obligatory finding in MKS.[5] Similarly, we recorded liver fibrosis and proliferation of bile ducts in 65.5% of cases in which pathological examination was performed. This is considerably less in comparison with a series of patients reported by Salonen,[6] in which all patients had liver lesions on post mortem examination. Both findings could be explained by the fact that our series of patients differed significantly from those reported in the literature so far. Whereas all patients investigated by Salonen[6] died immediately before, during, or after birth, most of the patients in our series were ascertained in the first trimester of pregnancy. It is possible that some of the pathological changes were not clearly visible or fully developed and thus were difficult to diagnose in TOPFA, which accounted for 75.9% of cases. For the same reason, some anomalies appearing later in pregnancy (eg, hydrocephalus) were observed less frequently.

The encephalocele was mostly occipital. Other central nervous system anomalies ranging from mild to severe were also frequently recorded. In particular, we observed a higher rate of different degrees of cerebellar hypoplasia and dysgenesis of posterior fossa structures including Dandy Walker anomaly. These anomalies are presumably due to the impairment of Sonic hedgehog-dependent proliferation of granule cell progenitors in MKS and Joubert syndrome patients.[17]

Postaxial polydactyly, the most variable of the three major presentations, typically affects all four limbs but in our sample only hands or feet were affected in 31 and 20 cases, respectively.

Other more frequently observed anomalies included cleft lip/palate, microphthalmia, congenital heart defects, genital anomalies, and skeletal defects. All types of recorded anomalies were previously described in MKS patients, with the exception of omphalocele that we recorded in three patients, a case of persistent cloaca and a case of limb reduction defect (agenesis of humerus and femur).

The lower rate of microcephaly, club foot, and lung hypoplasia in our series of patients is explained by the fact that these anomalies are considered to be a sequence of encephalocele and oligohydramnios, respectively, and as such not regarded as anomalies of their own according to the EUROCAT coding rules.

Prenatal diagnosis

Prenatal ultrasound diagnosis of MKS is possible from 11–14 weeks of gestation, based on the observation of two out of the three major anomalies in the fetus.[24] The early demonstration of an unusual

corticomedullary differentiation and appearance of small pyramidal cysts during the first trimester and early second trimester are considered to be significant distinguishing features.[23] Later in pregnancy, the diagnosis may be more difficult because of the oligohydramnios. The presence of oligohydramnios, invisible bladder, and discrepancy in the biparietal and abdominal diameter, however, can lead to the diagnosis.[6,7,23,38] Fetal magnetic resonance imaging can be used as a complementary method when findings are inconclusive or equivocal.[39] This is the first study to provide population-based data on prenatal diagnosis and termination of pregnancy for MKS. Prenatal detection rate of major anomalies characteristic of MKS by prenatal ultrasound examination was 93.4%. The mean GA at diagnosis was 14.3 gestational weeks. The prenatal detection rate did not substantially change during the study period. Prenatal diagnosis resulted in termination of pregnancy in approximately two-thirds of all cases, which shows the important impact of prenatal diagnosis on the outcome of MKS pregnancies in Europe.

Study strengths and limitations

This is the only epidemiological population-based study and the largest series of MKS patients published to date. The main strengths of this study are the large population that includes all types of pregnancy outcomes, standardized data collection and the use of genetic expertise in patient evaluation and coding. However, when combining epidemiological data from many different registries, certain variation due to coding practices, completeness and accuracy of case description must be taken into consideration. Post mortem results were unavailable for some patients, which could be the reason for underreporting of some anomalies not detected by prenatal ultrasound. Certain anomalies are difficult to diagnose in a post mortem following a TOPFA, which accounted for about two-thirds of cases in our series. Finally, some of the cases registered in EUROCAT database as isolated encephalocele or isolated bilateral renal cystic dysplasia for which the post mortem examination was not performed or was negative for other key defects because of the early termination of pregnancy, could be unrecognized MKS cases.

In conclusion, MKS is a rare genetic disorder with the minimal total prevalence of 2.6 per 100 000 births in Europe. The prevalence is stable, but regional differences due to characteristics of resident populations are observed. Cystic kidneys and fibrous dysplasia of the liver are probably present in all cases at birth, but as nowadays most patients are detected very early in pregnancy, these changes may not yet be developed or may be difficult to assess. Consequently, at present, they should not be considered obligatory for the diagnosis of MKS. Most of the cases are suspected prenatally due to the presence of characteristic severe anomalies, and pregnancies are mainly terminated, reducing the number of LB to one-fifth of the total prevalence rate. Parents should be counseled about the high mortality and morbidity and poor prognosis for survival. Early diagnosis is important for the timely counseling of affected couples regarding their decision on pregnancy termination. In view of the high recurrence risk, detailed investigation by first trimester ultrasound scans and the possibility of prenatal genetic testing from chorionic villi sampling in subsequent pregnancies should also be discussed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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