Empirical recurrence risk after unidentified multiple congenital abnormalities

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SUMMARY Thirty-five fetal deaths (30.4%) and 12 cases of congenital abnormality (15.0%) occurred in 117 subsequent pregnancies and 80 sibs of 112 consultands who had babies with unidentified multiple congenital abnormalities after genetic counselling. The specific recurrence risk of unidentified multiple congenital abnormalities was 5%.

The identification of multiple congenital abnormalities (MCA), that is, two or more different major congenital abnormalities in the same person,¹ is important from several points of view. For example, the estimation of prognosis and recurrence risk are much more accurate in recognised syndromes than in unidentified MCA. In genetic counselling clinics MCA have caused many difficulties. The identification of several recognisable but rare or not uniformly expressed MCA is not an easy task, and a considerable number of MCA are not delineated as entities. Probands with unidentified MCA represented 2.2% of the material in our genetic counselling clinic from 1975 to 1980. According to Roberts,² "Any medical advice is better than no advice" and this prompted us to determine the empirical recurrence risk of unidentified MCA. The so-called empirical risk figures deserve study until adequate theoretical models provide the necessary information.³

Materials and methods

There is a continuous follow-up study of consultands in our genetic counselling clinic.⁴ A reply-paid purpose designed postal questionnaire is sent to the address of consultands after 1 to 5 years of counselling. In this paper, the outcome of pregnancies of 112 consultands who have had a previous child with unidentified MCA is evaluated from the material of 1975 to 1980. Data from all probands and their affected first degree relatives are based on medical documentation including necropsy reports.

Results

The outcome of 117 pregnancies of 112 consultands

who had previously had babies with unidentified MCA was ascertained after counselling. Two induced abortions were reported and 35 spontaneous abortions (30.4%) occurred in the remaining 115 pregnancies. This figure is higher than the recorded national value (13%) in the period studied. Among 80 sibs, 12 (15%) had congenital abnormalities (table); this is higher than both the registered Hungarian value (about 4%) and the theoretical expectation (about 6%). However, it is necessary to separate this figure into two categories. One category is affected sibs showing the specific recurrence. Four subsequent sibs had MCA resembling those in the proband.

CASE 365/78

This stillborn male proband had spina bifida cystica within the MCA. Amniotic fluid AFP examination was done in the next pregnancy and it gave a normal value (19.4 µg/ml), but the child, a boy, again had a lethal MCA. The congenital abnormalities in these two MCA showed considerable similarity: bilateral split hands and feet as well as uni- or bilateral obstructive urological anomalies. The differences were a neural tube defect in the proband and a diaphragmatic hernia, Bochdalek type, in his brother. However, these abnormalities may have an aetiological relationship.^{5,6} An important point was that the mother also had MCA involving hydronephrosis, spina bifida occulta, and syndactyly of the fingers and toes. The familial cluster of these unidentified MCA suggests autosomal dominant inheritance. It is unlikely that these were cases of any of the recognised syndromes exhibiting digital and renal abnormalities, for example, acrorenal, trisomy 18, Weyers, SCE, Poland, LARD, Duane, or VACTERL.

TABLE Data of probands with unidentified MCA and their affected sibs.

Case No															Comments	
Affected sibs																
of	consultant	Sex	Birth date	Birth weight (g)	Gesta- tion (wk)	Birth order	Parents	Description of MCA	Date of death (cause)	Sex	Birth date	Birth weight (g)	Gesta- tion (wk)	Description of MCA	Date of death (cause)	
411/75	F	F	29.4.73	2300	35	1	—	Atrial septal defect type I, stricture of urethra	29.4.73	F	10.12.75	4000	40	Dislocation of hip	—	—
502/75	?	?	27.3.74	2680	34	1	Father 46,XY, mother 46,XX	Hermaphroditism, partial agenesis of ribs and vertebrae, agenesis of suprarenal gland ls, intestinal anomalies	27.3.74	F	15.6.77	4100	41	Pes equinovarus	—	—
68/76	F	F	22.2.72	2300	?	5	—	Microcephaly, adactyly of hand lu, mental retardation	—	F	22.11.78	?	?	Hermaphroditism	11.7.79	—
932/77	M	M	27.8.77	2500	33	1	Father 46,XY, mother 46,XX	Diaphragmatic hernia ls (Bochdalek), coarctation of aorta (juvenile), ectasia of ductus Botalli, low set ears lu, deformities of hand and foot lu (flexion contractures), hydrocephalus	27.8.77 (RDS)	M	18.5.78	2300	35	Deformities of digits 2-5	18.5.78 (RDS)	Male paternal cousin has a limb reduction abnormality
365/78	M	M	30.9.77 (Still- birth)	2750	34	1	Mother 46,XX. Dysmorphic face with minor anomalies, hydronephrosis ld (nephrectomy), spina bifida occulta, scoliosis, syndactyly (total) of digits 4-5, (partial) of digits 3-4 in hands, (partial) of digits 4-5 in feet	Spina bifida cystica (lumbosacral) with hydrocephalus, ureteric atresia ld with hydronephrosis ld, adactyly of digits 3-4 in hands and digits 2-4 in feet, syndactyly of digits 1-2 in hands, 46,XX	—	M	10.4.79	2200	34	Diaphragmatic hernia ld (Bochdalek), megaloureter and hydronephrosis lu, split hand and foot lu, hydrocephalus	11.4.79 (abnormalities)	—

1150/78	F	29.12.77	2500	34	1	Father 46,XY, mother 46,XX	Omphalocele (mild), cleft palate, bicornate uterus, 46,XX	2.1.78 (pneumonia)	F	15.12.81	3000	40	Omphalocele (mild), cleft palate, 46,XX	20.12.81 (pneumonia)	
	F	12.5.79	2800	35	2	Father 46,XY, mother 46,XX	Omphalocele (mild), duplex uvula, hydro- cephalus int, 46,XX	16.5.79 (pneumonia)							
111/79	F	15.10.76	1600	32	1	Mother scoliosis	Cleft palate, syndactyly of hands	17.10.76	M	4.3.80	1800	?	Hydrocephalus	Stillborn	—
234/79	M	16.9.76	2450	39	2	Father 46,XY, coronal hypospadias, mother 46,XX	Omphalocele (severe), congenital heart defect, hypospadias, undescended testes	9.10.76 (ileus)	M	27.11.79	2000	34	Hypospadias, undescended testes	09.10.80 (invagination of intestine)	Spontaneous abortion in first (1974) and last (1981) pregnancies
1917/79	F	21.2.76	1650	30	2	Mother used contraceptive pills at the time of conception	Microcephaly, microtia lu, atresia of external meatus lu, cleft palate	21.2.76	F	27.8.79	3550	40	Microcephaly, atresia of external meatus lu, dysplasia of auricles, 46,XX	—	Spontaneous abortion in first preg- nancy (1974). Third preg- nancy: healthy girl (1978)
1253/80	F	21.7.79	3350	39	5	Mother diabetes mellitus	Atrial septal defect, hydrocephalus int	22.7.79	F	11.3.71	3700	40	Aortic stenosis	—	—
1615/80	M	16.8.77	1750	32	1	Mother had a hearing loss probably owing to her otitis media	Dysmorphic face, hypertelorism, epicanthus, dis- location of hips and knee, general joint laxity, 46,XY	—	M	28.12.80	2600	40	Dislocation of hip, asymmetrical teeth, spastic tetraparesis with left sided domin- ance, 46,XY	—	—

CASE 1150/78

Both probands had similar MCA involving omphalocele and cleft palate (uvula duplex is considered to be its minor manifestation). The possibility of schisis association with a recurrence risk of 4%⁵ or an unknown autosomal recessive syndrome with 25% recurrence was considered. Amniotic fluid AFP examination showed a normal value (17.5 µg/ml). The third sib, a girl, had the same syndrome. The lethal outcome of all cases is inexplicable.

CASE 1917/79

After the birth of a healthy female, an affected sister with MCA was born from the mother's fourth pregnancy. The paediatric consultant suggested Goldenhar syndrome on the basis of her and the proband's MCA, though vertebral and ocular anomalies were absent. Marked variability in the clinical picture of this syndrome is described. As far as we know only two other families have been reported with two affected sibs, suggesting autosomal recessive inheritance.^{6a, 7} Proto and Scullica⁸ and Summitt⁹ reported two families with dominant inheritance of varying degrees of anomalies. However, in general, the aetiology of Goldenhar syndrome is not known and it usually has a sporadic manifestation.¹⁰

CASE 1615/80

The second boy born after the counselling had similar but not identical MCA. On the basis of their phenotypes, in spite of the absence of a flat face with depressed nasal bridge, hand anomalies, and cleft lip or palate, Larsen syndrome was suggested by our consultants. According to Smith¹⁰ the aetiology of Larsen syndrome is unknown, but McKusick's catalogue lists Larsen syndrome as showing both autosomal dominant and autosomal recessive inheritance. One of the original cases of Larsen *et al*¹¹ had an affected child, but this syndrome is usually recessive as in our family.

Discussion

The study of the recurrence of unidentified MCA in sibs of probands often helps to clarify the diagnosis¹² because the various abnormalities are more accurately represented in the affected sibs than in the atypical probands. Our series appears to delineate two unknown syndromes: a vertebral-hydro-nephrosis-limb (central axis) syndrome with autosomal dominant inheritance, and a cleft palate-omphalocele syndrome with autosomal recessive inheritance. Furthermore, on the basis of this follow-up study, our consultants identified two

atypical examples of recognised syndromes, Goldenhar and Larsen. An important conclusion is that all MCA in subsequently affected sibs seem to have an aetiological relationship with the unidentified MCA of probands.

The other category of congenital abnormalities in sibs are those which are probably unrelated to the unidentified MCA of the proband and have probably occurred by chance. Thus, the seven isolated congenital abnormalities in sibs all appear to be coincidental. However, the validity of the diagnosis of hydrocephalus in a stillborn baby (case 111/79) is not high. An aetiological relationship of the congenital heart defects in case 1253/80 and her sister, and the hand deformities in the proband 932/77 and his affected brother, cannot be excluded. The 12th case (234/79) is exceptional. The brother of the proband may have inherited hypospadias from the father and so it may not be coincidental. However, this abnormality is independent of the proband's MCA.

In summary, the specific recurrence risk of unidentified MCA in this series was 5.0%, while the risk of probably unrelated congenital abnormalities was 8.8%. The latter proportion is slightly, though not significantly, higher than the theoretical expectation and so a causal relationship in some instances could not be excluded.

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