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A family study of cases with unidentified multiple congenital abnormality

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A family study was conducted in 1384 index patients affected by unidentified MCAs, which represented a 50.6% sample of the population-based material of the Hungarian Congenital Malformation Registry, 1973—1980. 39 cases due to misdiagnosis, and 32 cases due to a recently achieved nosological diagnosis were excluded. Furthermore, for 109 index patients no new home address was available and 166 families refused to cooperate or they were not able to give a complex dataset. Finally, affected first degree relatives of 1038 index patients were evaluated on the basis of medical documentation. 5.1% of fathers and 4.2% of mothers were affected and more than half of them were affected by one component congenital anomaly of index patients. The sib-occurrence of congenital anomalies and of multiple congenital abnormalities was 11.0% and 3.5%, respectively. The specific sib-occurrence (i.e. fully of half-concordant congenital anomalies in sibs) was 5.5%. Furthermore, there is an increased risk for fetal death in previous and subsequent pregnancies of index patients' mothers. By the help of the family study multiple congenital abnormality entities were identified in 78% of sib-occurrence of unidentified multiple congenital abnormalities. Some previously delineated congenital anomaly syndromes were recognized and six probably new syndromes or associations were delineated.

The birth prevalence of recorded multiple congenital abnormalities (MCAs) was 4.0 per 1000 total births in Hungary, 1973—1982 [13]. The proportion of multimalformed cases represents 10% within all recorded index patients affected by congenital abnormalities (CAs) in the material of the Hungarian Congenital Malformation Registry (HCMR) [1]. Only 29% of multimalformed cases were notified with recognized MCA-entity, i.e., with CA-syndromes or CA-associations. Thus hundreds if not thousands of MCA-entities have remained unrecognized or undelineated [21, 23]. These facts prompted us to establish a population-based registry evaluation program for unidentified MCAs [13]. This program was completed by a family study in 1981 and some results of this approach will be summarised here.

The purpose of this family study was: 1) to attempt the identification of MCAs on the basis of family data; 2) to determine empiric risk figures of different CA sib-occurrences in unidentified MCAs.

Materials and Methods

Between 1973 and 1980, the HCMR registered 2733 index patients with specified but unidentified MCAs. However, our study sample included only 1384 unidentified MCAs (50.6%) because the families of the remaining 1394 index patients had been studied previously in other surveys of cases with hypospadias [3], undescended testis [5], exomphalos [6], oesophageal atresia [25], limb reduction deficiency [2], diaphragmatic defect [11] born in overlapping years of the study period including MCA cases too and of cases with congenital postural deformity association [24], schisis association [4], VACTERL-association [12]. Index patients born from 1980 were excluded because the Case-Control Surveillance System of Congenital Anomalies [9] has provided an opportunity for a continuous evaluation of CAs in the first degree relatives of index patients.

A specially designed post-paid questionnaire with an explanatory letter was mailed to index patients' parents in 1982 and 1983. Parents, mainly mothers, were asked to inform us on the number, date and outcome of all their pregnancies and the health condition or CAs of their children and their own. For the sake of higher validity of data we asked to send all medical documents connected with their pregnancies and their children's CAs and we returned these documents after two weeks. One hundred and nine letters (7.9 per cent) were sent back by the post as undeliverable. If there was no response, another questionnaire and letter were sent. Additionally, we asked the help of health visitors in order to obtain data of these families. We accepted only those questionnaires in which every question concerning the CAs of first-degree relatives, particularly CAs of sibs was correctly answered. One hundred and sixty-six parents (12.0 per cent) either failed or refused to respond or they were not able to give complete data concerning sibs. It appeared that some index patients had been given to foster homes or foster families and they could not reply to our questions. Thus, the total drop-out involved 275 cases, i.e., 19.9% of the study sample.

Siblings reported to be in good health were not examined by us personally, but the records of the HCMR were checked. Only two major CAs were detected in such a way: both of these sibs died on the first day of life. CAs and disorders of affected sibs were checked on the basis of medical documentation including autopsy records. A number of families were invited to our Department and we visited 19 families. Owing to the incompleteness and poor reliability of data concerning second and third degree relatives of index patients, they were excluded from the systematic evaluation.

Results

The number of evaluated index patients within the study sample was 1109. However, data of this family study were considered only in 1038 cases with unidentified MCAs. The difference between the two figures can be explained by three factors. First, misdiagnoses of MCAs were detected in 33 cases (3.0%) on the basis of personal check-up or available medical documentation. These cases had mainly notified heart defects (some ventricular defects may be closed spontaneously) or CAs of the respiratory system (later on respiratory distress syndrome was confirmed) or undescended testis (due to subsequent descent); however, the diagnosis was not confirmed later. Second, data obtained at further clinical or pathological examination indicated special types of *isolated* CAs

instead of real MCAs in further 6 cases (0.5%). This misclassification was accepted in three cases of aortic arch sequence (with secondary tracheal stenosis), in two cases of spina bifida cystica sequence (where previously urinary CA was also notified but, as it appeared later, this was no CA but only secondary functional obstructive anomalies of the urinary system) and in one case caudal regression defect. Third, a nosological diagnosis was achieved by detailed clinical examination in further 32 cases (2.9%) after notification (Table I). The above-mentioned 71 cases demonstrate the improvement of diagnosis parallel with advancing age of index patients. These cases with recognized MCA-entities or isolated CAs were also excluded from the evaluation of the family study, therefore data of *1038* index patients will be published here.

TABLE I

Nosological diagnosis based on detailed clinical examinations

Mendelian phenotypes (McKusick catalogs' number)	CA-entity	Number of cases
Monogenic syndromes		
11960	Cleidocranial dysplasia	1
14290	Holt-Oram syndrome	1
16120	Nail-patella syndrome	1
18530	Sturge—Weber syndrome	1
18840	DiGeorge syndrome	1
20061	Achondrogenesis, type 1	1
20890	Ivemark syndrome	1
21191	Congenital adrenal hyperplasia	3
22260	Diastrophic dwarfism	1
22550	Ellis-van Creveld syndrome	1
22765	Fanconi pancytopenia	1
23410	Hallerman—Streiff syndrome	1
24900	Meckel syndrome	1
25250	Mucolipidosis, type II: I-cell disease	1
25290	Mucopolysaccharidosis, type III: Sanfilippo syndrome	1
26860	Rubinstein syndrome	1
31125	Oro-facial-digital syndrome, type I	1
Chromosome-syndromes	Patau syndrome	1
	Edwards syndrome	2
	Down syndrome	1
	Turner syndrome	1
	45X/46XY with inherited polymorphism of chromosomes 1 and 16	1
Others	Fetal hydantoin syndrome	3
	VACTERL-association	1

Some epidemiological features of index patients

The *sex ratio* of the evaluated 1038 index patients with unidentified MCAs was 0.569, i.e., a male preponderance was obvious. *Birth weight* distribution of the index patients showed a predominance of the lower birth weight groups, thus, a considerable part of index patients (40%) had a low birth weight. The study sample involved 38 *twins* with unidentified MCAs (3.7%) and this rate significantly exceeds the Hungarian figure which was 1 per cent in the study period.

The *stillbirth* rate was 5.68% which exceeds 7.6-times the Hungarian stillbirth rate in the period studied (0.75). The *infant death* rate is extremely high: 44.94 per cent, i.e., 440 of the 979 liveborn index patients died. The majority of cases died in the early neonatal period. However, in several cases the cause of death was not MCA but respiratory distress syndrome, immaturity, brain damage, perinatal cerebral hypoxia, sepsis, etc.

The distribution of the *sib-number* is shown in Table II. Parents of 225 index patients had no other children. The remaining 795 index patients had 1440 sibs, still- or liveborns. Female index patients have a considerably lower number of sibs. The average number of births in these families studied (1.39 + 1 = 2.39) exceeds the Hungarian average (ca. 1.80). The explanation of this high proportion may be the "substitution attitude" of parents in order to retrieve the child loss caused by higher stillbirth and postnatal death rate.

The distribution of the *pregnancy outcomes* of index patients' mothers (Table III) shows a high spontaneous abortion and stillbirth, i.e., fetal death rate. The rate of spontaneous abortions was 13.1 per cent in the period between 1971—1980, but declined over the decade [10]. Spontaneous abortion rate in the study sample (17.5 per cent) significantly

Table II

Distribution of sib-number (including stillbirths) in study sample

Index patients	No of index patients without sibs[a]	No. of index patients with 1...6 or more sibs						Total No. of index patients with one or more sibs	Total of sibs	$\bar{x}$
		1	2	3	4	5	6 or more			
Male (N = 591)	151	247	163	38	15	13	13	489	893[b]	1.51
Female (N = 447)	74	151	103	30	12	8	2	306	547[c]	1.22
Together (N = 1038)	225	398	266	68	27	21	15	795	1440	1.39

[a] Excluded from further study
[b] Including two half-sibs
[c] Including three half-sibs

TABLE III

Previous and subsequent pregnancy outcomes of index patients' mothers

Index patients	Induced abortion		Ectopic pregnancy		Spontaneous abortion		Stillbirth		Live birth		Together	
	No.	%	No.	%	No.	%*	No.	%**	No.	$\bar{x}$°	No.	$\bar{x}$°
Male (N = 591)	278	20.5	4	0.30	178	16.6	37	4.13	856	1.45	1353	2.29
Female (N = 447)	113	14.3	1	0.13	129	19.1	17	3.11	530	1.19	790	1.77
Total (N = 1038)	391	18.2	5	0.23	307	17.5	54	3.75	1386	1.34	2143	2.06

* Spontaneous abortion rate = spontaneous abortions/total births + spontaneous abortions

** Stillbirth rate = stillbirths/total births

° Average per person

exceeds the national level. Some families with extremely large number of spontaneous abortions were detected. A higher prenatal selection in pregnancies of index patients' mothers seems to be obvious.

Parental data

The observed CA rate in *fathers* was 5.06 per cent and this fits well the expected one of about 4—6 per cent. (No adequate information concerning 30 fathers was available owing to extramarital birth or divorce.) The sex ratio of these fathers' children shows an obvious male preponderance (33:18 = 0.647). Two fathers had MCA (GAM-complex and congenital dislocation of hip with unilateral undescended testis), both were concordant for MCA of their sons. Of further 49 fathers, 27 (55.1%) had a CA which was "half-concordant" with a component CA of MCA in their children. It seems to be noteworthy that 56.9% of the fathers (29/51) had a concordant MCA or a half-concordant isolated CA. The other CAs of fathers may indicate mere coincidence with MCAs of index patients.

All affected *mothers* had isolated CAs. The affected rate is 4.24%. There is again a male preponderance in their children (28 : 16 = 0.636). Half-concordance occurred in 22 of 44 affected mothers (50.0%). Congenital cardiovascular malformations show a surprisingly high half-concordant manifestation, they occurred in six mother-child pairs. The CA-distribution of affected parents has been published elsewhere [13].

Three main conclusions can be drawn from the study on *affected parents* of index patients with MCA:

1. The total affected rate of CAs in parents does not exceed the usual population prevalence of CAs. This underlines the importance of social limitations and biological (mainly

prenatal) selection in the transmission of severe CAs from parents to offspring.

2. Affected parents have mainly mild CAs. This point proves again the importance of selection, which is relaxed in the reproduction of mildly affected persons.

3. In more than half of the cases (51.5%), one of the parents and their children were affected by half-concordant CAs, i.e., there may be a causal connection of their phenotypic manifestations. In further two father-son cases a full-concordance was detected. One of them was diagnosed as GAM-complex. Finally a certain concordance of CAs in parents and their children was found in 50 cases. Thus, our study has revealed the occurrence of a special *additive CA-association* where one or two CAs of index patients is explained by their independent parental origin. These additive CA-associations may represent about 5% of unidentified MCAs in our study sample, but explain more than 50% parent-child pairs.

Sib-occurrence

The birth prevalence of CAs in sibs was calculated for 1000 total births. Altogether 159 CAs were ascertained in 1440 sibs of 1038 index patients. Thus, sib-occurrence of CAs is 110.42 per 1000 total births. This sib-occurrence is 2.75 times higher than the recorded Hungarian figure (4%) in the study period. However, this must be a *minimum*, i.e., an underestimated figure. In Hungary the parents are not often informed about the presence of CAs in most severe cases, generally lethal within the perinatal period. The explanation is probably the physician's false clemency towards parents: they do not want to frighten them with this really shocking information. On the other hand parents prefer to forget the mild CAs or they do not consider these defects as CAs. The results of a similar study [8], in which nearly all sibs of index patients were personally or medically checked up, confirm our suspicion because sib-occurrence of 15.0 per cent was found. Thus, it is probable that the ascertainment of this family study is not complete and the sib-occurrence of index patients with unidentified MCAs may be near to 150.0 per 1000.

It is noteworthy that 54 stillborn sibs had 12 CAs. It means a CA-prevalence of 222.22 per 1000 stillbirths in sibs. Three MCAs were detected in stillborn sibs, all of them were concordant for the MCA of index patient. Also the 55.56/1000 stillbirth rate of sibs considerably exceeds the recorded one in the general population.

Out of 1389 liveborn sibs, 147 had CA (10.61%), 48 among them MCAs. These occurred in siblings of 121 index patients. The rate of CA-affected brothers is 11.10% while this figure is 10.12% in sisters. The birth prevalence of CAs is 106.06 per 1000 live-births.

Fifty-one MCAs occurred among sibs. The rate of 35.42 per 1000 total births is extremely high taking into

consideration the birth prevalence of MCAs, which is about 4. It is 8.35 times higher than the usual occurrence of MCAs in newborns, i.e., the MCAs have on obvious familial cluster in sibs, 32.1% of affected sibs had MCA.

Fifty postnatal deaths were ascertained among liveborn sibs. This rate of 36.08 per 1000 somewhat higher than that of infant mortality (27/1000) in the study period. 26 of these 50 lethal cases (52%) had CAs.

This family study offered an opportunity to identify hitherto unidentified MCAs in some index patients on the basis of parallel evaluation of affected sibs. In twenty-five specific MCA sib-occurrences, the pattern of CAs in sibs helped to identify the recognizable and previously delineated MCA-entities of index patients (Table IV). The delineation of the polycystic kidney-congenital cardiovascular malformation association was based on our previous biomathematical analysis [16]. These 25 cases represent 49.0% of MCA sib-occurrences, 15.7% of all CA sib-occurrences and 2.4% of all unrecognized MCAs. Finally, the analysis of component CAs of MCAs in index patients and of MCAs or CAs of their sibs indicated recognizable probably new, previously undelineated MCA entities in 15 cases (Table V). This subgroup explains the 29.4% of MCA sib-occurrences, 9.4% of all CA sib-occurrences and 1.4% of all unrecognized MCAs.

The point is that 40 MCA-entities were identified among 51 sib-occurrences of MCAs. This group represents 78.4% of all MCA sib-occurrences in the study sample. The remaining group of 11 MCA sib-occurrences (21.6%) involves probably independent familial cluster of different MCAs. Although the causal connection cannot be excluded in some cases, e.g., in a sib-occurrence of the so-called

TABLE IV

Identified recognizable MCA-entities on the basis of sib-occurrence

Mendelian phenotypes (McKusick catalogs' number)	CA-entity	Number of family	Number of index patients (cases)
11845	Alagille syndrome	2	3
18070	Robinow syndrome	1	2
18550	Williams syndrome	1	3
20850	Jeune syndrome	1	2
20853	Ivemark syndrome	1	2
22560	Wiedemann—Beckwith syndrome	1	1
24560	Larsen syndrome	2	2
30010	X-linked Addison syndrome (Figure 1)	1	3
31360	Opitz hypertelorism-hypospadias syndrome	1	1
—	Polycystic kidney-congenital cardiovascular malformation association	1	2
—	Fetal alcohol syndrome	2	4

TABLE V

Probably new, previously undelineated MCA-entities*

CA-syndromes	Number of families	Number of index patients (cases)	Origin	Reference
Extrahepatic biliary atresia-ventricular septal defect syndrome	2	2 (4)	AR	[17]
MCM (*m*acrocephaly and congenital cardiovascular malformation = aortic stenosis or ventricular septal defect and *m*ental retardation)	1	4	AR	(Figure 2)
Lethal omphalocele — cleft palate syndrome	1	3	AR	[7]
Postaxial polydactyly — progressive myopia syndrome	2	2 (7)	AD	[15]
SPOUSE (*s*plit hands, *o*bstructive anomaly of *u*rinary system and *s*pinal *e*rror)	1	2 (3)	AD	[18]
Congenital adrenal hyperplasia — cleft lip syndrome	1	1 (1)	AR	(Figure 3)

AR = autosomal recessive
AD = autosomal dominant

* (Numbers of all sibs including both index and non-index sibs are shown in brackets)

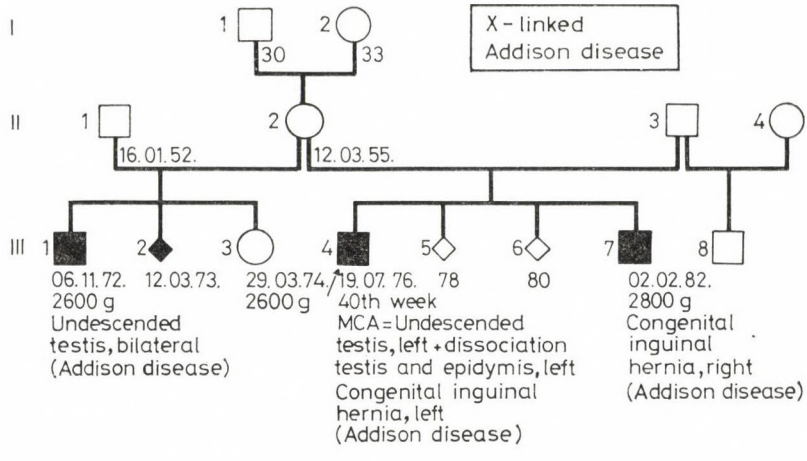

FIG. 1. Sib-occurrence of X-linked Addison disease

mesenchyma weakness (congenital dislocation of hip, undescended testis, congenital inguinal hernia) „syndrome" (Figure 4) and of an entity of unusual skull with hydrocephaly, cerebral hypoplasia and mental retardation as well as congenital dislocation of hip with some other different

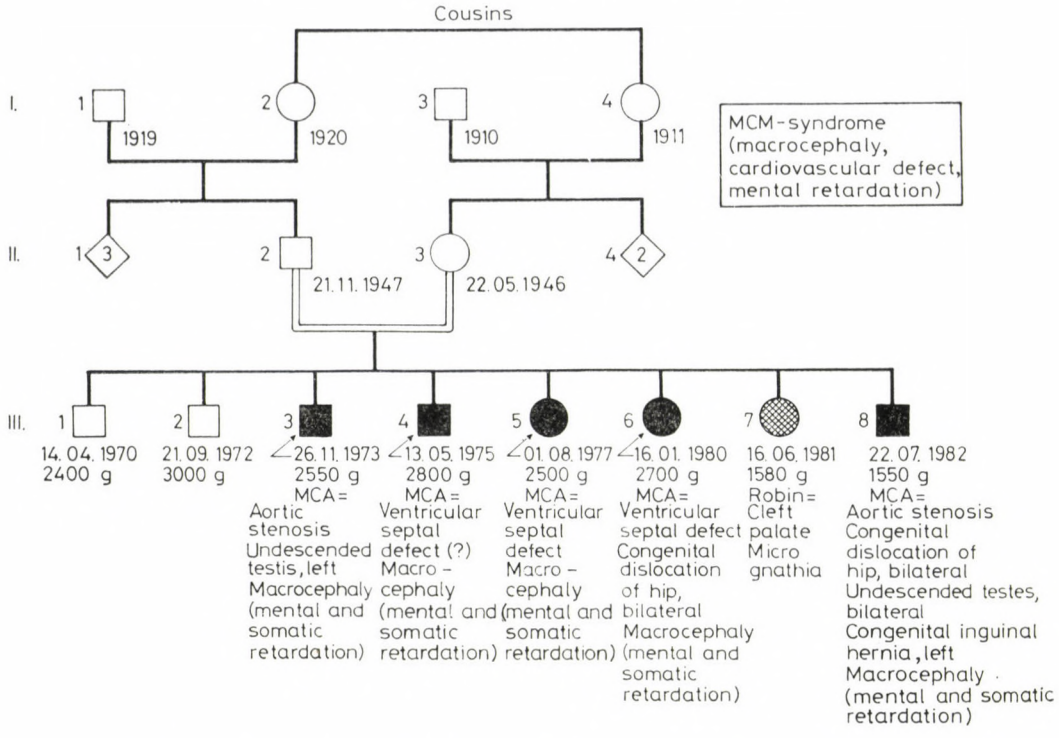

FIG. 2. Sib-occurrence of MCM syndrome of autosomal recessive origin

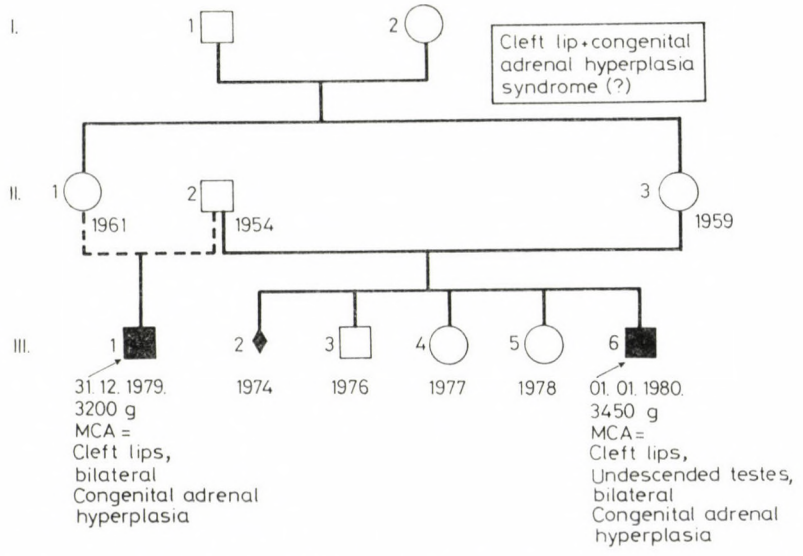

FIG. 3. Cleft lip-congenital adrenal hyperplasia syndrome (?) of autosomal recessive origin

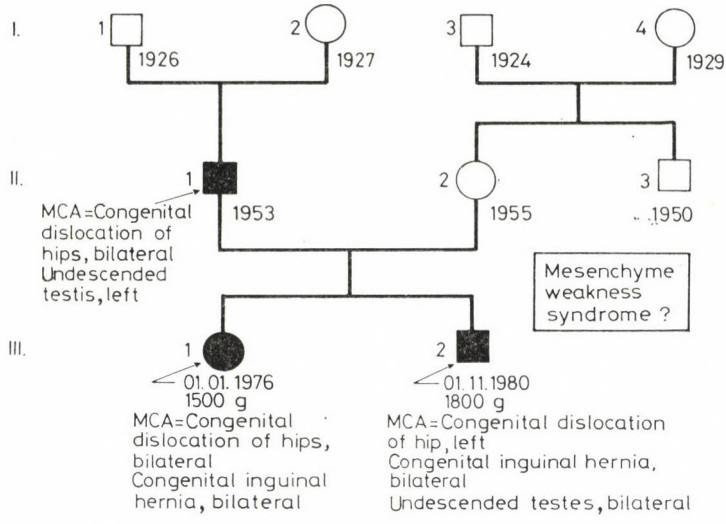

FIG. 4. Familial clustering of the so-called mesenchyme weakness syndrome (?)

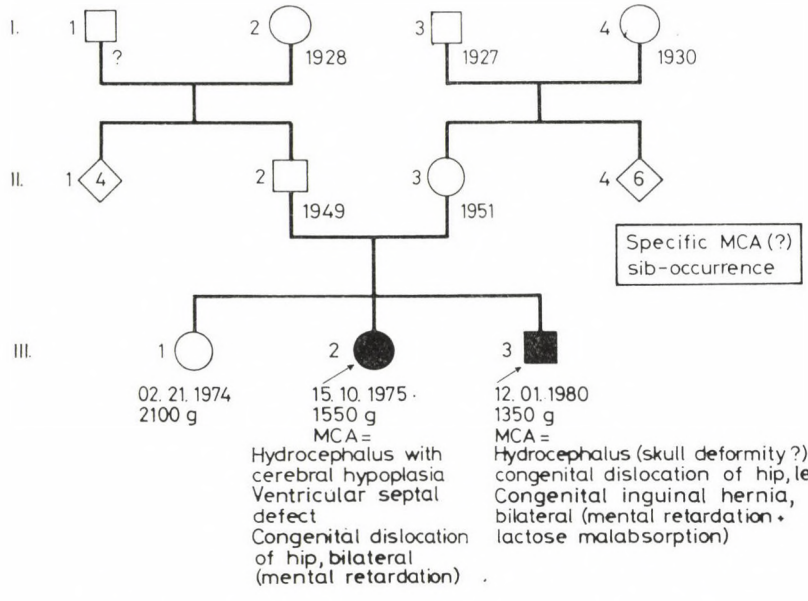

FIG. 5. Specific sib-occurrence of an unidentified syndrome

CAs in sibs (Figure 5). Obviously the parallel examination of affected sibs is a great help in the identification of unidentified MCA cases.

Further forty-six index patients had sib(s) who exhibited one component CA of MCA which was found in the index patient, i.e., they were

"half-concordant". This group represents 28.9% of all affected sibs. The distribution of these half-concordant CAs is as follows: congenital cardiovascular malformations: 15 (32.6%), congenital inguinal hernia: 9 (19.6%), congenital dislocation of hip or Ortolani click: 4 (8.7%), microcephaly: 4 (8.7%), hypospadias: 3 (6.5%), congenital hydrocephaly: 3 (6.5%) and anencephaly, exomphalos, cystic kidney, face-skull CA, clubfoot, congenital goitre, undescended testis, teratoma: 1 (each 2.2%). Seventy-three affected sibs (45.9%) had no concordant CAs.

Conclusions

The *first* purpose of the family study was to set up the nosological diagnosis of unidentified MCAs on the basis of sib-occurrence. It was successful in 161 cases of the study sample involving 1109 evaluated index patients. It means a 14.5 per cent of the study sample and the proportion of specified MCA-entities had thus increased considerably. On the one hand, the longer time interval helped to identify the nosological diagnosis in 71 cases due to recent medical examinations independent of this study. In addition the family study is a useful approach for the identification of MCA-entities because the parallel evaluation of component CAs in index patients and affected first degree relatives revealed a nosological diagnosis of known MCA entities in further 25 cases. This approach has a number of further advantages, e.g., the determination of the phenotypic spectrum of a given MCA-entity [19]. Finally, data of this family study helped to delineate some new (or re-discovered?) CA-syndromes and further provisional CA-associations in 15 index patients.

The higher proportion of specified MCA-entities, and further exclusion of some non-MCA cases have significantly improved the quality of the study sample. By help of extrapolation of data in this 50% sample, the total figure of identified MCAs is estimated as 55.4% instead of the figure of 48.9%, which was achieved by the nationwide registry-evaluation of MCA cases [13].

The *second* purpose was to establish the empiric risk figure of different CA sib-occurrences of index patients with unidentified MCAs. At least three different figures must be distinguished. First of all, sibs of index patients had a high, 11.0 per cent, rate of total CAs. It 2.75 times exceeds the expected figure. The 3.54 per cent rate of MCA occurrences in sibs is nearly 9 times higher than the figure for the population at large. There were 40 specific MCA sib-occurrences, it represents a 3.9 per cent of all MCA cases, and 25.1%of all sib-occurrences. However, further 46 sibs had a half-concordant CA. It means that 54.1 per cent of MCAs was fully or half concordant in sibs and the sib-occurrence of specific CAs is 5.5%. Obviously, these rates can be considered as being minimal since they were only based on parents' information. (The reported CAs were checked and

only confirmed ones were evaluated.) The ascertainment bias may be higher in early lethal cases and in mild CAs. A comparison between the data of this and our previous [8] family studies of index patients with unidentified MCAs confirms the suspicion of under-ascertained sib-occurrences in the material of this Registry. The sib-occurrence of CAs was 15% in the previous study. However, the specific sib-occurrence (about 5%) was nearly the same in two studies.

At the evaluation of isolated CAs in sibs of index patients with unidentified MCAs, two groups of CAs have to be separated: half-concordant and discordant CAs in sibs. Nearly one third of CAs (29%) were half-concordant in sibs. However, taking into consideration both the full concordance and half-concordance sibs the specific sib-occurrence represents 54% of all affected sibs and it indicates causal relation with the MCAs of index patients.

The remaining, discordant portion of CAs in sibs may represent a random familial cluster. However, this rate of 5.1 per cent seems to be somewhat higher than the expected percentage based on the recorded Hungarian figure (4%) in the study period. Thus, some further causal relations below the phenotypic level cannot be excluded [20]. The specific sib-occurrence fits well our knowledge. However, the somewhat increased rate of discordant CAs in sibs of index patients with unidentified MCA requires further studies and meditation because this phenomenon offers an opportunity to better understanding of the relations between CAs.

It can be concluded that unidentified MCAs indicate a considerable risk for their sibs. First, there is an elevated risk for fetal death owing to increased prenatal selection. In addition, there is a specific sib-occurrence risk for MCA of the index patient and it may lie between 2.7% (fully concordant MCAs) and 5.5% (fully half-concordant CAs). The figure is nearly equal to the previously published 5% specific sib-occurrence rate of MCAs [8].

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