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A genetic study of children with congenital heart defect

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Family history, anamnestic data concerning pregnancy and the incidence of minor and major malformations were examined in 213 children affected by congenital heart defect; a scoring system was elaborated for selecting patients for chromosomal study. The incidence of minor anomalies was not higher than among unselected healthy newborns; among children scoring 2 or more points there were two patients with chromosomal aberration and one with Noonan's syndrome. In 8% of the 213 children major concomitant non-cardiac malformations were present.

The incidence of congenital heart malformations among first-degree relatives amounted to 4.1%. Detection of familial cases is of utmost importance in genetic counselling.

Examination of genetic factors playing a part in the pathogenesis of congenital heart defects is of growing importance. An increasing number of patients with surgically corrected heart malformation reach fertile age in good health, seeking genetic counselling about the risk in their progeny. Progress in cardiac surgery has not only multiplied the number of persons needing genetic guidance but has also expanded knowledge about empirical risk figures. In addition, progress in diagnostic procedures has greatly helped in detecting and specifying congenital heart malformations in the index patients and their close relatives alike; as a result, the number of familial cases is in steady increase.

In more than 90% of congenital heart defects (chd) the pathogenesis is multifactorial including polygenic inheritance; in 5% chromosomal aberrations can be demonstrated and monogenic factors are present in 3% of cases. Differentiation of these groups is indispensible for a sound judgment in the individual case [4, 7].

In isolated chd, multifactorial pathogenesis and the polygenic nature of the heritable component have been demonstrated [2, 8]. The role of environmental factors is a matter of debate, a statistically significant relationship between birth order and incidence of ventricular septum defect found by one group could not be affirmed by others [2, 9]. There may be an association between the A_2 antigen and familial chd [1]. The genetic determination of the various defect groups is quite variable; it is most pronounced in ventricular septum defect, Fallot's tetralogy and pulmonary valvular stenosis [3]. Monogenic inheritance may occur, the dominant mode has been found in certain families affected by atrial

septum defect, supra- and subvalvular stenosis of the aorta, cardiomyopathy and primary pulmonary hypertension; recessive transmission has been observed in left heart hypoplasia.

There is an increased risk, variable according to the type of defect, of chd in the offspring if one parent or sibling is affected by sporadic chd; it amounts to 2—5% as compared with the incidence of 0.7—1.0% found in the general population [4, 7]. For defects with Mendelian inheritance or associated with chromosomal aberrations the recurrence risk is much higher; on the other hand, in defects of known dominant inheritance, the risk of recurrence in subsequent children after cases caused by fresh mutation may not be higher than for the unselected population.

This study has been aimed at detection of cases with high genetic risk. In our practice, great attention is paid to correct genetic counselling offered to families afflicted by chd, in addition to cardiological and surgical treatment. A prerequisite for this is detection of chromosomal aberrations and familiarity.

In a large series of unselected newborn babies a score system has been elaborated, based on familial and reproductive history and the presence of minor anomalies, for selection of patients needing deeper genetic analysis or a search for latent major anomalies; they aimed at high efficacy of chromosome studies without loss of positive cases [6, 7].

Chromosomal aberrations and inherited syndromes frequently comprise congenital heart defects. The opposite is not true: the incidence of chromosomal abnormalities is so low among children with chd that chd itself is no indication for cytogenetic study. It has been our general impression that chd is frequently accompanied by minor anomalies, apart from the typical old-looking face.

In this study we sought answers to the questions, whether minor anomalies have an increased incidence in children with congenital heart defect; is there a relationship between the type of minor anomaly respectively the congenital heart defect; is a scoring system based on family and birth history and presence of minor anomalies useful in screening patients for further chromosomal or genetic analysis.

Method

A questionnaire concerning the family and birth history and the presence or absence of minor and non-cardiac major anomalies was filled for all chd patients admitted between 1 January and 31 December, 1981. The data were scored according to the point system shown in Table I.

Intrauterine growth retardation (a birthweight lower than the 10th percentile value corrected for gestational age and gender) was given one point. The minor anomalies of distinct importance [6] i.e. antimongoloid palpebral fissure, hypertelorism, preauricular fistula, four-finger crease and abnormal hallux, were rated by one point, while the remaining minor signs, e.g. epicanthus, syndactyly, mongoloid palpebral fissure, gothic palate, auricular anomalies, were given 0.5 point. Major extracardiac malformations and somatomental retardation of a degree exceeding that expected in chronically ill patients were rated by one point. Patients in whom retardation could be attributed to hypoxia secondary to the heart defect were evaluated with utmost caution.

TABLE I

The scoring system

1. Intrauterine growth retardation		1 point
2. Family history:		
First- or second-degree relative with congenital heart defect or Stillbirth or infant death of unknown cause within the family		1 point
3. Minor anomalies		
a) important according to Méhes [5]	each	1 point
b) other	each	0.5 point
4. Major non-cardiac anomalies	each	1 point

Chromosomal studies were carried out in all patients who scored two points or more and in patients scored at least one point in whom familial occurrence was suspected or demonstrated.

RESULTS

Table II shows the distribution of patients by their score values; also, the individual factors are specified. Seven patients received two points or more, this was 3.4% of the total. The highest score (5 points) was found in a patient with Turner syndrome (Figure 1); no chromosomal anomaly was found in the patients with the next highest score (3.5 points). Similarly, no abnormal caryotype was observed in the patient with 3 points who exhibited symptoms of Noonan syndrome (Figure 2). The three patients with 2.5 points had no chromosomal anomaly, one patient with two points had Down syndrome caused by central fusion of the supernumerary chromosome 21 and one of the chromosomes 14 (Figure 3). Chromosome analysis was carried out in nine patients with a score lower than two points: the finding was normal in seven in one the cell culture failed to grow and the test could not be repeated because of the patient's death; and in one case pericentric inversion

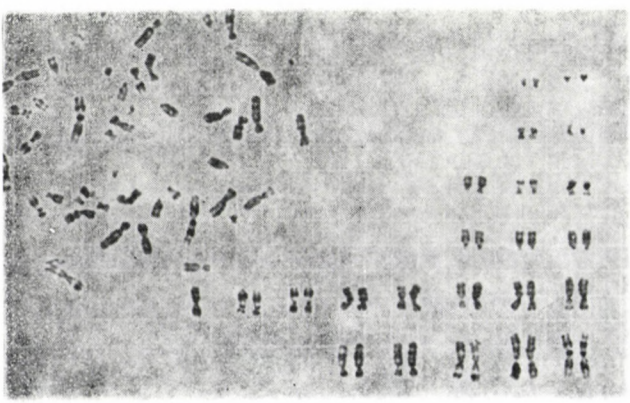

FIG. 1. Karyotype of patient with Turner syndrome: 46,XO

Table II

Distribution of patients by score

Number of points	Patient		Intrauterine growth retardation	Family History		Minor anomalies									Major anomalies				Karyotype	
						Each 1 point			Each 0.5 point											
	n	per cent		Stillbirth	Relative with cld	Four-finger crease	Abnormal hallux	Hypertelorism	Epicanthus	Malformed ears	Mongoloid palpebr. fiss.	Craniofacial dysmorphism	Syndactyly	Gothic palate	Gastrointestinal	Bones or joints	Nervous system	Kidneys	Abnormal	Normal
0	137	64.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
0.5	18	8.4	0	0	0	0	0	0	8	5	1	2	2	0	0	0	0	0	0	0
1	42	19.7	12	5	10	1	1	0	1	2	0	1	1	1	2	2	4	2	1*	2
1.5	9	4.2	0	0	2	1	1	0	4	5	0	3	0	1	0	1	1	1	0	3
2	1	0.5	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	1**	0
2.5	3	1.4	1	0	2	1	0	0	0	1	0	2	0	0	0	2	0	0	0	3
3	1	0.5	0	0	0	0	0	0	1	0	0	0	1	0	0	1	1	0	0	1+
3.5	1	0.5	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0	0	0	1
5	1	0.5	0	0	0	1	0	1	1	1	0	0	0	0	0	1	0	1	1++	0
	213	100.0	13	5	14	6	3	1	17	15	1	9	5	2	2	7	6	4	3	12
	per cent		6.1	2.3	6.6	2.8	1.4	0.5	8.0	7.0	0.5	4.2	2.3	1.0	1.0	3.3	2.8	1.9		

* = peric. inv. (9)
** = tris. transl. 21/13
\+ = Noonan syndrome
++ = Turner syndrome

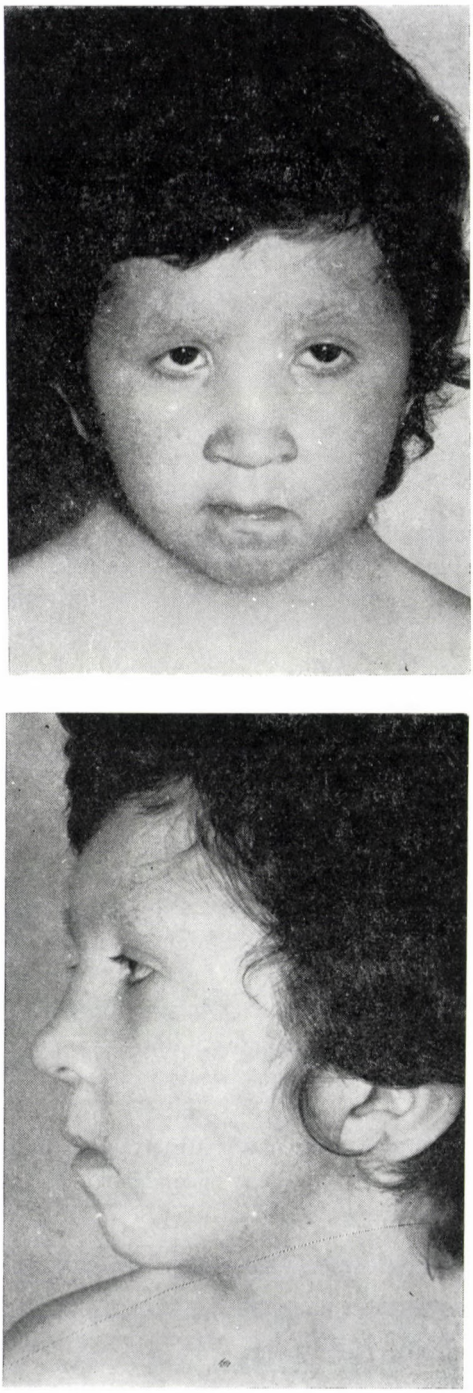

FIG. 2. Patient with Noonan syndrome

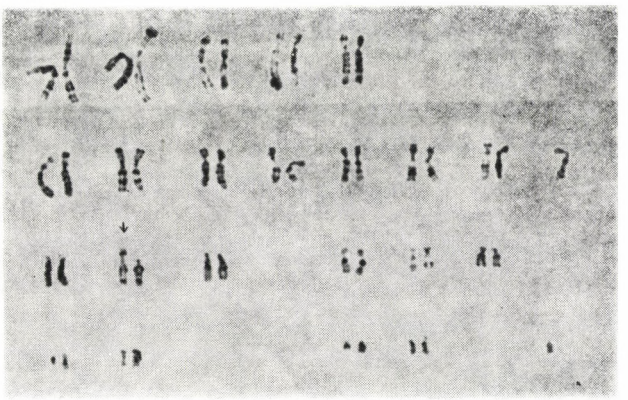

FIG. 3. Karyotype of patient with Down syndrome: 46,XY, —14, + t (21; 14) (14qter → cen → 21qter)

of chromosome 9 was detected. The incidence of minor anomalies was compared with the data obtained by Méhes in unselected newborn babies; this is shown in Table III. Table IV presents the major anomalies.

In case of familial occurrence a detailed family tree was set up, at least for three generations. These cases are shown in Table V.

DISCUSSION

The majority of chd cases (64.3%) scored zero; 96.6% had a value lower than 2 points. In this group the points mostly derived from intrauterine growth retardation or a positive family history. Among the minor anomalies those shown by Méhes [5] to be of equivocal importance prevailed.

Among patients with two points or more the minor anomalies thought by Méhes to be of increased importance occurred at a high frequency. The score seemed to be effective in selecting the appropriate patients for chromosomal examination. Among the seven patients with two points or more, two had chromosomal aberration, one turned out to have Noonan syndrome. Both chromosomal syndromes (X-monosomy and translocational 21-trisomy) could be suspected on inspection). The pericentric inversion of chromosome 9, however, could not be recognized by phenotype.

No significant difference against Méhes's data was encountered in respect of family and birth history or the incidence of the more important minor anomalies; in other words, our previous impression that minor anomalies are more frequent in patients affected by chd has not been confirmed. The score system, however, is useful in systematic and objective judgment of the phenotype: by statistical analysis of dysmorphic features the paediatrician is forced to omit loose descriptions like funny face, chromosomal looking head or extraordinary facial expression.

TABLE III

Percentual incidence of scored anomalies

	Intrauterine growth retardation	Positive family history	Four-finger crease	Abnormal hallux	Hypertelorism
Present study n = 213	6.1	8.9	2.8	1.4	0.5
Méhes [5] n = 1000	8.9	10.7	3.6	0.2	3.1
p	NS	NS	NS	NS	NS

TABLE IV

Associated major anomalies in 213 children affected by congenital heart defect (17 children with 19 anomalies)

Gastrointestinal tract	
Duodenal atresia	1
Oesophagus atresia	1
Bones or joints	
Pes equinovarus	2
Pterygium colli	2
Vertebral anomaly	1
Costal anomaly	1
Cleft palate	1
Kidneys	
Aberrant blood vessel	3
Horseshoe kidney	1
Nervous system	
Microcephaly + somatomental retardation	5
Meningocele	1

TABLE V

Congenital heart defect in relatives of 213 children affected by congenital heart defect, excluding chd in 4 second-degree relatives

Diagnosis in index patient	Diagnosis in 10 first degree relatives	Relationship to index patient
1. Coarctation of aorta	Coarctation of aorta	Parent
2—3. Atrial septal defect	Fallot tetralogy	Sibling
4—5. Atrial septal defect	Cardiomyopathy	Sibling
6—7. Atrial septal defect	Atrial septal defect	Twin
8. Fallot tetralogy	"heart defect"	Parent (dead)
9. Cardiomyopathy	Cardiomyopathy	Sibling (dead)
10. Left heart hypoplasia	Aortic stenosis	Parent

In this study the incidence of minor dysmorphic features showed Poisson's distribution. The incidence of individual minor anomalies among normal, deaf, chd, or otherwise pathological newborns varies within wide limits and is subject to observational error (e.g. the shape of the palate can only be unequivocally classified in case of normality or pronounced deformity, the intermediary conditions cannot be quantified).

A striking finding was the comparatively high incidence of other major malformations among children with chd: they were present in 13 cases (8%). Among these malformations microcephaly and somatomental retardation had an outstanding part (2.5%). The frequent association is a further stimulus for genetic studies in children affected by chd. In paediatric practice, only Down syndrome can be excluded on clinical grounds, all other chromosomal aberrations need laboratory confirmation. The increased association of major extracardiac malformations with chd is a well-known fact.

The importance of detailed and exact family data in correct genetic counselling is emphasized. There was a congenital heart defect in first-degree relatives of 10 patients (4.1%). In two cases the mode of inheritance proved to be dominant, in four patients polygenic inheritance and in the remaining four cases autosomal recessive inheritance could be anticipated on the basis of published data. HLA-typing may prove to be a helpful tool in precising the risk. In familial chd, calculation of the individual risk figure is based on theoretical and empirical figures extracted from large scale studies.

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