Genetic study of congenital heart defects in Northern Ireland (1974-1978)

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Abstract

Congenital heart defects are a major congenital abnormality and are assuming increasing importance. A study was undertaken to estimate the incidence of congenital heart defects in Northern Ireland over a five year period (1974-1978), to determine the age at diagnosis and to assess the risk of recurrence in sibs. An incidence rate of 7.3 per 1000 total births was found. This reduced to 3.1 per 1000 total births if only invasive methods of diagnosis (catheter studies, surgery, or necropsy) were considered. The overall risk of recurrence for sibs (excluding index patients with chromosomal abnormalities and syndromes) was 3.1%. In addition, excluding families with an affected parent and child gave a recurrence risk of 2.6%.

By 6 weeks of age 63% of index patients had been diagnosed and this figure had risen to 88% by 1 year. This has important implications for studies which include only congenital heart defects diagnosed in the first year of life.

Of 388 patients with a congenital heart defect confirmed by invasive criteria, 96 (24.7%) were found to have an extracardiac abnormality (ECA). Excluding those with epilepsy or mental handicap as the sole ECA left 91 (23.5%) with an ECA. This highlights the importance of looking for other abnormalities in a child with a congenital heart defect.

The 388 index patients had 952 sibs of whom 72 (7.6%) had an ECA. Excluding those with minor abnormalities (inguinal hernias, undescended testes) as the sole ECA left 62 (6.5%) with a major ECA. In addition, excluding those with epilepsy or mental handicap as the sole ECA left 51 (5.4%) with a major ECA. Since parents are often reassured after the birth of a child with a congenital heart defect that their risk of having a child with a non-cardiac abnormality is no greater than the general population this finding has important implications for genetic counselling.

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echocardiography, have been able to diagnose lesions more accurately by non-invasive means.

The aim of this study, which allowed a follow up period of 6 to 10 years (1979-1984), was to obtain an accurate estimate of the incidence of CHD in Northern Ireland. It included the total live- and stillbirth population over a five year period (1974-1978) but unfortunately echocardiography was not available for all patients during the period of study.

Previous studies^{3,4,6,11-14} have shown a recurrence risk in sibs varying from 1.4% to 3.4%. To ascertain the recurrence risk in Northern Ireland, selected families identified by the incidence study were examined in greater detail. In addition it was decided to look at the age at diagnosis of the congenital heart defect to see what proportion escaped detection in the first year of life.

Many studies^{1,6,15-20} have shown that the prevalence of extracardiac abnormalities (ECA) in patients with congenital heart defects is much higher than in the general population, varying from 9% to 30%. In addition, several investigators have examined the prevalence of ECA associated with specific congenital heart defects. Campbell¹⁶ found the prevalence varied from 5% in index patients with atrial septal defect (ASD) to 13% in patients with coarctation of the aorta (CoA) and pulmonary valve stenosis (PVS). Lamy *et al*¹⁷ reported a prevalence of 7.4% associated with CoA rising to 26.8% with ASD. Boon and Roberts²¹ found a prevalence of 7% in 100 cases of CoA whereas Boon *et al*²² found a 16% prevalence of ECA in 100 cases of tetralogy of Fallot (TF). Williamson²³ found a prevalence of 8.2% of ECA in 135 cases of ASD secundum.

Some studies included only "major" abnormalities, while others included "minor" abnormalities, for example, inguinal hernia, undescended testis. Some were restricted to congenital malformations while others also included epilepsy and mental handicap. Overall, it appeared that the majority of ECA were related to the musculoskeletal, genitourinary, or gastrointestinal systems. We were interested to ascertain if similar associations were found in our population.

Subjects and methods

Multiple independent sources of ascertainment of infants with congenital heart defects were available in Northern Ireland during the study period. These included hospital cardiology records, the Registrar General's Congenital Malformation Notification, the Child Health System, necropsy records, death certificates, records of the Department of Medical Genetics, and neonatal paediatric records.

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Many studies¹⁻¹⁰ have looked at the incidence of congenital heart defects (CHD) using different methods of ascertainment and differing follow up periods. Some studies^{6,8-10} have looked at the incidence of congenital heart defects in the first year of life and, with the advent of

Table 1 Congenital heart defects: source of ascertainment (total no of patients ascertained = 972)

1974–1978	Cardiologist records	Medical genetic records	Registrar General	Child health system	Necropsy records	Death certificates	Neonatal records
Total ascertained	545 (56.1%)	120 (12.3%)	303 (31.2%)	146 (15.0%)	187 (19.2%)	234 (24.1%)	261 (26.9%)
Solely ascertained	298 (30.7%)	12 (1.2%)	32 (3.3%)	1 (0.1%)	25 (2.6%)	37 (3.8%)	116 (11.9%)

At the time of the study there were two cardiologists in the province who dealt with the majority of paediatric referrals including all children who progressed to catheterisation or cardiac surgery. The Registrar General’s Congenital Malformation Notification is a voluntary system for the notification of congenital malformations in Northern Ireland and the Child Health System is a register of all births in Northern Ireland.²⁴ Each record, in addition to identification data, also includes information on a maximum of four congenital malformations. During the study period (1974–1978) records of necropsies, which were carried out mainly in the Belfast and Londonderry hospitals, were examined. Copies of all death certificates and stillbirth records were examined and details extracted on all children born between 1974–1978 inclusive who died with a congenital heart defect. The diagnostic index of the Department of Medical Genetics and neonatal records for all births in the three major maternity units in Belfast were also examined. Stillborn or premature babies with a patent ductus arteriosus or babies whose ductus closed spontaneously within two weeks of birth were not included in the study.

To estimate the recurrence risk in sibs, the family history of children with a congenital heart defect was documented. It was decided to investigate only the families of children in whom the diagnosis had been confirmed by catheter studies, surgery, or necropsy since echocardiography was not available for all patients during the period of study and was only becoming established during our follow up period (1979–1984).

During the period (1974–1978 inclusive), 972 children with a congenital heart defect were ascertained. Of these, 417 had the diagnosis confirmed by invasive criteria (catheter studies, surgery, or necropsy). In this group 388 families (93%) were traced, the parents were interviewed, and a detailed pedigree obtained.²⁵ Efforts were made to obtain all relevant hospital notes.

Results

INCIDENCE

During the five year study period (1974–1978), 972 patients with a congenital heart defect were

ascertained. Table 1 shows the distribution by source of ascertainment. The number of infants with congenital heart defects and the incidence for each year are shown in table 2. The incidence ranged from 6.0 per 1000 total births in 1975 to 8.6 per 1000 total births in 1977, with a mean for the study period of 7.3 per 1000 total births. If only those with a diagnosis confirmed by invasive methods (catheterisation, cardiac surgery, necropsy) are considered (417 patients) this gave an incidence rate of 3.15 per 1000 total births.

RECURRENCE RISK IN SIBS

Of the 417 index patients who had the diagnosis confirmed by catheter studies, surgery, or necropsy, 388 (93%) were traced. Only 29 families (7.0%) could not be contacted. Of these 24 could not be traced, four had moved from Northern Ireland, and the remaining child was in long term foster care and his natural mother was unavailable. The 388 index patients had a total of 952 sibs of whom 28 (2.9%) had a congenital heart defect. There were also 32 half sibs, of whom one (3.1%) had a congenital heart defect. A chromosomal abnormality was identified in 12 of the index patients. When these patients were excluded this left 376 index patients with a CHD confirmed by catheter studies, surgery, or necropsy who had been traced. When the sibs of the 12 index patients with a chromosomal abnormality were excluded, this left 921 sibs of whom 28 (3.0%) had a congenital heart defect.

Seven of the index patients had syndromes which were known to be associated with congenital heart defects (three with Noonan, one with Holt–Oram, one with Klippel–Feil, one with fetal hydantoin, and one with Goldenhar (oculoauriculovertebral) syndrome). When these patients were excluded this left 369 index patients who had 909 sibs of whom 28 (3.1%) had a congenital heart defect.

There were 11 index patients who had a parent with a documented congenital heart defect (table 3). When these index patients were excluded this left 358 index patients who had 896 sibs of whom 23 (2.6%) had a congenital heart defect. Within the families with an affected parent and child, the recurrence risk was 38% (five recurrences out of 13 sibs).

Table 2 Congenital heart defects in Northern Ireland (1974–1978)

Year	No ascertained with CHD	Total no live and stillbirths	Incidence CHD /1000 total births
1974	194	27 536	7.05
1975	157	26 155	6.00
1976	214	26 350	8.12
1977	222	25 846	8.59
1978	185	26 559	6.97
1974–1978	972	132 446	7.34

AGE AT DIAGNOSIS

Table 4 shows the age at diagnosis. Under six weeks 62.9% of children with a congenital heart defect were detected, and by one year the figure had risen to 87.9%. Thus, 12.1% remained undetected at one year. Of those 47 cases which remained undiagnosed at one year, 17 had

Table 3 Congenital heart defects in parents of index patients

Sex	Parent CHD	Sex	Index patient CHD
F	VSD	F	CoA
F	VSD	M	VSD
F	VSD	M	VSD
F	PDA	F	PDA
F	PDA	F	PDA
F	PDA	F	PDA
F	TF	M	TF
F	AR	M	PS
M	HOCM	F	PS/VSD
M	ASD	F	ASD
M	SVAS	F	SVAS

VSD=ventricular septal defect; CoA=coarctation of aorta; PDA=patent ductus arteriosus; TF=tetralogy of Fallot; AR=aortic regurgitation; PS=pulmonary stenosis; HOCM=hypertrophic obstructive cardiomyopathy; ASD=atrial septal defect; SVAS=supravalvular aortic stenosis

Table 4 Age at diagnosis of congenital heart defect (total no of index patients = 388)

Age	No diagnosed	Percentage of total
Less than 1 wk	171	44.1
1-6 wk	73	18.8
6 wk-3 mth	40	10.3
3-6 mth	32	8.2
6-12 mth	25	6.4
1-2 y	15	3.9
2-3 y	15	3.9
3-4 y	6	1.5
4-5 y	6	1.5
5-6 y	4	1.0
6-7 y	1	0.3

Table 5 Extracardiac abnormalities in 368 index patients (excluding chromosomal abnormalities and syndromes)

System involved	No of index patients affected	Percentage of total index patients
Gastrointestinal	33	9.0
Musculoskeletal	22	6.0
Urinary	20	5.4
Eye and ear	14	3.8
CNS	11	3.0
CNS (excl epilepsy and mental handicap)	6	1.6
Immune-haematological	6	1.6
Endocrine	3	0.8
Reproductive	1	0.3
Other	3	0.8

Table 6 Extracardiac abnormalities in 388 index patients associated with specific congenital heart defects

Congenital heart defect	No of index patients	No of index patients with extracardiac abnormalities	Percentage
VSD	68	20	29.4
PDA	41	10	24.4
TGV	35	5	14.3
CoA	30	5	16.7
TF	26	4	15.4
ASD	24	4	16.7
Tr Art	18	5	27.8
PS	17	4	23.5
AVC	10	5	50.0
Multiple	91	30	33.0
Others	28	4	14.3

VSD=ventricular septal defect; PDA=patent ductus arteriosus; TGV=transposition great vessels; CoA=coarctation of aorta; TF=tetralogy of Fallot; ASD=atrial septal defect; Tr Art=truncus arteriosus; PS=pulmonary stenosis; AVC=atrioventricular canal defect

patent ductus arteriosus, six had ventricular septal defect, six had atrial septal defect, six had multiple congenital heart defects, five had coarctation of the aorta, and seven had other specific defects including one with truncus arteriosus type IV.

EXTRACARDIAC ABNORMALITIES IN INDEX PATIENTS

Of the 388 index patients with a congenital heart defect confirmed by invasive criteria who

were traced, 96 (24.7%) had extracardiac abnormalities (ECA). Three of them had epilepsy and two had mental handicap as the sole abnormality. Excluding these patients, 91 (23.5%) had ECA. A chromosomal abnormality was found in 12 patients (3.1%). This figure is low owing to fewer patients with a chromosomal abnormality (in particular Down syndrome) having invasive cardiac investigations which was the criteria for inclusion in this part of the study. Eight patients (2.1%) were known to have a syndrome. Three had Noonan syndrome, one had Holt-Oram syndrome, one had Klippel-Feil syndrome, one had testicular feminisation syndrome, one had fetal hydantoin syndrome, and one had Goldenhar (oculoauriculovertebral) syndrome. Also excluding index patients with chromosomal abnormalities and syndromes left 71 (18.3%) who had ECA.

Several index patients had more than one ECA and table 5 shows the percentage accounted for by each system after patients with chromosomal abnormalities and "syndromes" have been excluded leaving 368 index patients. The commonest system affected was the gastrointestinal followed by the musculoskeletal and urinary systems. Of the 33 patients with a gastrointestinal ECA, nine had oesophageal atresia ± tracheo-oesophageal fistula, five had situs inversus, five had cleft palate ± cleft lip, five had inguinal hernia, three had imperforate anus, and six had other abnormalities.

Table 6 shows the extracardiac abnormalities in association with specific congenital heart defects in the 388 index patients (patients with chromosomal abnormalities and known syndromes included). Half the patients with A-V (AVC) canal defect had an ECA (Down syndrome in four of the five cases with an ECA), and more than a quarter of index patients with multiple heart defects, ventricular septal defect (VSD), or truncus arteriosus (Tr Art) had ECA. Between 20 and 25% of patients with patent ductus arteriosus (PDA) or pulmonary stenosis (PS) had ECA, and between 10 and 20% of patients with atrial septal defect (ASD), coarctation of the aorta (CoA), tetralogy of Fallot (TF), or transposition of great vessels (TV) had ECA.

Of the five index patients with Tr Art who had an ECA, one had four toes on the right foot and three on the left foot, one had a bifid big toe, and a third had absence of the left thumb and radius. Two of the five patients had bilateral iris colobomata. No other association was noted between specific heart defects and specific types of ECA.

EXTRACARDIAC ABNORMALITIES IN SIBS

Of the 952 sibs, 72 (7.6%) had one or more ECA. When minor abnormalities such as inguinal hernia or undescended testes were excluded, this left 62 (6.5%) with a major ECA. Of these, eight had mental handicap and three others had epilepsy as the sole ECA. When these were excluded, 51 (5.4%) had a major ECA.

Table 7 shows the distribution of ECA

Table 7 Extracardiac abnormalities in 952 sibs of index patients by system involved

System	No of affected sibs	Percentage total
Central nervous	28	2.9
Gastrointestinal	17	1.8
Musculoskeletal	11	1.2
Urinary	6	0.6
Eye	5	0.5
Immune-haematological	4	0.4
Reproductive	4	0.4
Chromosomal	3	0.3
Other	4	0.4

between the various systems in the 952 sibs. Abnormalities in the CNS included 12 patients with mental handicap (1.3% of total sibs) and three with epilepsy. There were also 10 cases of neural tube defect or hydrocephalus or both, thus affecting 1.1% of all sibs.

Table 8 shows the percentage of ECA found in sibs of patients with specific congenital heart defects. This varies from 4.3% to 11.4%. Truncus arteriosus had the highest rate (11.4%) but the majority of these ECA were minor. PDA had the highest overall rate for major ECA in sibs.

There were five sibs of index patients with pulmonary stenosis who had ECA. It is interesting that in two cases the abnormality was a large cavernous haemangioma affecting the forehead and shoulder in one, and the right knee in the other. No other associations were noted between specific types of congenital heart defect in the index patients and specific types of ECA in their sibs.

The 28 CHD recurrences in sibs occurred in the families of 27 index cases. Three of these index cases had ECA and six of the 28 recurrences also had ECA. Of their remaining sibs, nine had an ECA without a CHD and 53 were apparently normal although five died in infancy from undocumented causes.

Discussion

The incidence rate of 7.3 per 1000 total births for the five year study period is comparable to surveys from other countries²⁻⁵ and is in good agreement with the rate of 7.6 per 1000 births obtained by Stoll *et al*⁶ from France and the rate of 7.2 per 1000 births obtained by Bower and Ramsay⁷ from data from the Western Australian Birth Defects Registry.

It is, however, higher than that found when only cases diagnosed in the first year of life by

echocardiography, catheterisation, surgery, or necropsy are included. Grabitz *et al*⁸ found an incidence of 5.54 per 1000 livebirths in the first year of life using these diagnostic criteria and Ferencz *et al*⁹ reported an incidence of 3.7 per 1000 livebirths in the first year of life. However, using clinical criteria, Grabitz *et al*⁸ obtained an incidence of 6.58 per 1000 livebirths.

If only those cases confirmed by invasive means are considered, that is, catheterisation, surgery, or necropsy, our rate of 3.15 per 1000 total births is higher than that found in other studies using similar invasive criteria (2.4 per 1000 livebirths by Ferencz *et al*⁹ and 2.20 per 1000 livebirths by Fyler¹⁰). These studies only considered livebirths and diagnosis made in the first year of life, so it is not surprising that the incidence rates found were lower. However, Grabitz *et al*⁸, who also studied livebirths with follow up in the first year of life, found an incidence of 3.36 per 1000 livebirths using invasive criteria.

Our figure of 7.3 per 1000 total births is still likely to be an underestimate for several reasons. Firstly, there will be some children whose congenital heart defect remained undetected. For example, one of the authors (EJH) diagnosed an unsuspected ASD secundum requiring cardiac surgery in a 5 year old boy during the course of this study. Secondly, there will be children attending their general practitioner or paediatrician because of a cardiac murmur who have not been notified to any data recording system. Children with patent ductus arteriosus or ventricular septal defect which close spontaneously are likely to fall into this category. Thirdly, the majority of stillborn infants delivered in major teaching centres had a necropsy, but this service was not so readily available in other areas of Northern Ireland.

The paediatric cardiologist was the most important source of ascertainment. Of the total 972 cases, 545 (56.1%) were ascertained from the records of the cardiologists, 298 (30.7%) being ascertained solely from this source. Interestingly 116 cases (11.9%) were ascertained solely by the neonatal recording system and 25 cases (2.6%) were diagnosed only at necropsy. Most cases ascertained by examination of neonatal records had also been assessed by a paediatric cardiologist but were not always entered in the cardiologist's records.

The overall recurrence rate among sibs of 3.1% (excluding index patients with chromoso-

Table 8 Extracardiac abnormalities in 952 sibs of index patients: variation with specific heart defects in the index patient

Congenital heart defect in index patient	No of sibs	Percentage of sibs with ECA	Percentage sibs with major ECA	Percentage sibs with major ECA excl mental handicap and epilepsy
VSD	141	7.1	5.7	4.3
PDA	89	10.1	10.1	9.0
ASD	72	8.3	8.3	2.8
TF	60	8.3	8.3	6.7
TGV	106	9.4	6.6	6.6
CoA	75	6.7	6.7	5.3
PS	57	8.8	8.8	5.3
Tr Art	35	11.4	5.7	2.9
Others	93	4.3	3.2	3.2
Multiple	224	6.7	6.3	5.8
Total	952	7.6	6.5	5.4

VSD=ventricular septal defect; PDA=patent ductus arteriosus; ASD=atrial septal defect; TF=tetralogy of Fallot; TGV=transposition great vessels; CoA=coarctation of aorta; PS=pulmonary stenosis; Tr art=truncus arteriosus

mal abnormalities and syndromes) is comparable with that of other studies.^{3,4,6,11-14}

While the numbers in this study were too small to estimate accurately recurrence risks in sibs for specific congenital heart defects, a number of interesting families were ascertained (table 3). For many years it has been suggested that isolated ASD may rarely exhibit autosomal dominant inheritance.²⁶ In our study a family was identified in which a father in his early thirties had two daughters with ASD secundum. After the diagnosis was made in both girls the father was found to have a similar lesion but unfortunately died undergoing corrective cardiac surgery.

Supravalvular aortic stenosis (SVAS) is well recognised as segregating in an autosomal dominant manner in some families.²⁷ We ascertained a family in which a number of persons had SVAS but many of their offspring had peripheral pulmonary artery stenosis (PPAS) in addition to SVAS while other offspring had SVAS or PPAS but not both. Male to male transmission was present in this family in which 17 subjects were affected in four generations.

Similarly, families have been described in which PDA appears to be inherited in an autosomal dominant manner.²⁸ We ascertained two families in which the mother and each of her two children (two daughters in one family and a daughter and son in the other) had a PDA. In a further family a mother and her son both had tetralogy of Fallot and in two other families a mother, son, and daughter in one and a mother and son in the other all had ventricular septal defects. Further families with a parent with a documented congenital heart defect included a mother with aortic regurgitation who had a son with pulmonary stenosis, a mother with a VSD who had a daughter with coarctation of the aorta, and a father with hypertrophic obstructive cardiomyopathy who had a daughter with pulmonary stenosis and a VSD.

It is of interest that the majority of affected parents (eight out of 11) were female (table 3). Nora and Nora²⁹ postulated that an important subset of cases, particularly in high risk families, may be better explained by cytoplasmic rather than by multifactorial or mendelian inheritance. However, our study is too small for us to be certain whether the excess of females found in affected parents is of significance or not.

A previous study⁵ in Blackpool (1957-1971) examined the age at diagnosis of patients with a congenital heart defect and found that 74% were diagnosed before 3 months of age, 82% before 1 year, and 90% before 3 years. In our study, 73% were diagnosed before 3 months of age, 88% before 1 year, and 96% before 3 years (table 4). It would thus appear that there has been little improvement in early diagnosis during the time interval between these two studies and even major defects may remain undetected during the first year. This is an important point when considering studies⁸⁻¹⁰ which record only congenital heart defects diagnosed in the first year of life.

Selection of index patients will obviously be an important factor in the estimate of ECA in

children with congenital heart defects. In this study only families where the defect had been confirmed by invasive criteria (catheter studies, surgery, or necropsy) were included. This selection criteria meant that less severe defects and chromosomal abnormalities were under-represented, as these were less likely to have further invasive investigations. Ascertainment of children with multiple abnormalities will also be affected since fewer will have further cardiac investigations but more may have necropsy.

These selection biases makes it difficult to be sure if the figure of 24.7% of index patients with an ECA is an over- or underestimate. However, it is comparable with that found in most other studies^{1,15,17-20} and is in good agreement with the figure of 25.7% found by Stoll *et al.*,⁶ who also found that the most frequent ECA were in the gastrointestinal, musculoskeletal, and urinary systems. The 9% found by Campbell¹⁶ is probably an underestimate as he included only patients suitable for cardiac surgery. Several studies^{1,15,19,20} also included a higher proportion of index patients with Down syndrome, and these accounted for 23 to 29% of their index patients with ECA. Heinonen¹⁸ and Scott¹⁹ also found a significant number of index patients with other syndromes (11.9% and 4.9% respectively).

Our finding of 24.7% of index patients with ECA which is approximately 10 times the incidence of major congenital abnormalities in our population³⁰ highlights the importance of looking for other abnormalities in a child with a congenital heart defect. However, the numbers in our study were too small to comment meaningfully on the prevalence of ECA associated with specific congenital heart defects.

The incidence of neural tube defects in Northern Ireland for the period 1974-1976 was estimated to be 8.6 per 1000 births²⁴ so our finding of 1.1% of sibs with a neural tube defect or hydrocephalus or both may not be significant. Interestingly, Heinonen¹⁸ found that malformation of the head or spine or both in an older sib was associated with a doubling of the risk of cardiovascular malformation.

After the birth of a child with a congenital heart defect genetic counselling is important. The parents are appraised of the risk of having a further affected child. In addition, they are usually reassured that their risk of having a child with a non-cardiac abnormality is no greater than the general population. For the period 1974-1979 the population incidence of major non-cardiac congenital abnormalities in Northern Ireland extrapolated from data published by Nevin³⁰ was estimated to be 1.9% of total births. Our finding of 6.5% of sibs with a major ECA has obvious important implications for genetic counselling.

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