Hypoplastic Left Heart Complex

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Lev (1952) wrote, 'a group of congenitally malformed hearts are conveniently placed in the category of hypoplasia of the aortic tract complexes'. He considered that their basic feature was a hypoplasia of the left side and a hypertrophy of the right side of the heart. Noonan and Nadas (1958) expanded this concept and included in their series cases with aortic and mitral valve obstruction and cases with interruption and hypoplasia of the aortic arch, though not with uncomplicated infantile coarctation.

Previous studies of congenital heart disease (Carlgen, 1959; Mehrizi, Hirsch, and Taussig, 1964; Lambert, Canent, and Hohn, 1966) have shown that lesions belonging to this complex are relatively common at birth though prolonged survival is unusual, so that the group ranks as the second or third most important category of congenital heart defects in stillbirths and neonatal deaths. Aetiological factors are unknown and information on parental age and gestational maturity is scanty. Fifty stillbirths and neonatal deaths in the British Perinatal Mortality Survey (Butler and Bonham, 1963) were found to have lesions that could be classified as part of the hypoplastic left heart complex. We give here an account of their birthweight, length of gestation, associated malformations, and parental age, and discuss the significance of our finding of high paternal ages in a substantial proportion.

Material and Methods

The Perinatal Mortality Survey has been described by Butler and Bonham (1963). Detailed questionnaires were completed for 98% of all births in England, Wales, and Scotland during one week in March 1958, and this population of 16,994 singletons and 412 twins is termed the 'main week population'. In order to obtain comparable data on a large number of deaths, questionnaires

were completed for 94% of stillbirths and neonatal deaths occurring in the same areas during March, April, and May 1958. A total of 7822 stillbirths and neonatal deaths were ascertained, of which 705 were twins. Deaths among the main week population were included in this total. An estimate of the total number of births occurring in these three months is obtained by multiplying the main week population by a factor of 12 (Butler, 1965).

A total of 5300 stillbirths and neonatal deaths came to necropsy, and the 50 cases of the left heart complex in the present account were derived from this group. The questionnaire completed by the pathologists taking part in the Survey specifically asked about malformations of the valves of the heart, the condition of the endocardium, and any abnormalities of the chambers of the heart and great vessels.

The classification of the complex cardiac malformations was a major problem. In Table I each case has been arbitrarily assigned to a category, according to the cardiac lesion the authors considered the most important, so that the groups are mutually exclusive. For example, a case with a hypoplastic left heart and a septal defect would appear only once in the category of hypoplastic left hearts, and not again in that of septal defects. Further detailed descriptions of all congenital malformations of the heart in the Survey are in preparation.

Findings

Incidence. Table I lists the different types of congenital heart defect found at necropsy. Details are shown of the malformations classified as hypoplastic left heart complex, a group that accounted for 17% of the total heart lesions. Two of the 50 babies with this complex were twin births, both one of a pair of girls, and in both instances the other twin survived the neonatal period.

Necropsy Findings. Cases included in the hypoplastic left heart complex had lesions that ranged from aortic and mitral valve atresia, together with left-sided endocardial fibroelastosis, to isolated hypoplasia of the aorta.

Table II shows associated malformations in the different types of this complex. Among the cases with aortic valve obstruction with or without mitral

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TABLE I
PERINATAL MORTALITY SURVEY
(STILLBIRTHS AND NEONATAL DEATHS
IN THREE MONTHS)
HYPOPLASTIC LEFT HEART COMPLEX AND
OTHER CARDIAC MALFORMATIONS
(CASES WITH NECROPSY ONLY)

Major Cardiac Malformation	No.		Total	%
	Singleton	Twin		
<i>Hypoplastic Left Heart Complex</i>				
Aortic valve stenosis/atresia				
(a) only	16	0	16	5.5
(b) with mitral valve stenosis/atresia as well	13	0	13	4.4
Mitral valve stenosis/atresia (no aortic valve lesion reported)	5	1	6	2.0
Left-sided hypoplasia (no aortic or mitral valve lesion reported)	10	1	11	3.8
Interruption of the aortic arch (no aortic or mitral valve lesion reported)	4	0	4	1.4
Subtotal	48	2	50	17.1
Coarctation of the aorta	29	0	29	9.9
Right-sided obstructive lesions	30	0	30	10.2
Transposition and truncus arteriosus	42	1	43	14.6
Septal defects	78	6	84	28.7
Miscellaneous	53	4	57	19.4
Total	280	13	293	100.0

valve lesion nearly one-half had endocardial fibro-elastosis. This association was only rarely noted in the other subgroups. Coarctation of the aorta was an additional defect in over 1 in 10 of all cases, most often in association with aortic valve lesions. Only 4 of 29 babies with aortic lesions had extracardiac malformations, in contrast to the remaining cases in which 12 out of 21 had extracardiac lesions.

Birthweight and Gestation. Table II also shows further details of each case, including birthweight and length of gestation calculated from the first day of the last menstrual period. In contrast to most other congenitally malformed babies, the majority of these were born at 40 weeks or later. When extracardiac malformations were present the gestation period tended to be shorter and the birthweight low.

Sex. There were 30 boys and 20 girls in the series. The male preponderance was most striking in those cases with aortic valve involvement, of which 20 out of 29 were boys. All four cases with interruption of the aortic arch were girls.

Time of Death. Of the 50 babies, 7 were still-born, the remainder dying within four weeks.

Maternal and Paternal Age. The mean maternal and paternal ages of the cases in the complex (Groups A to E) were higher than in the main

week population (Table III) ($p < 0.01$). This age effect was found in all the groups in Table III, except in those cases with interruption of the aorta (Group E) in which parental ages were below the mean for the population. After exclusion of Group E, the mean maternal age was 31.0 and the mean paternal age was 35.9 years, both significantly higher than in the control population ($p < 0.01$). The difference between the means, 4.9 years, was also significantly raised ($p < 0.01$), showing that paternal age was raised relatively more than maternal. The most striking age effect was in those cases with aortic valve involvement but no lesions other than those forming a part of the complex, Group A. In this subgroup alone the mean paternal age and mean difference between this and mean maternal age were significantly ($p < 0.01$) raised compared with the population.

Because of possible difficulties in distinguishing between hypoplasia and coarctation of the aorta, parental age was studied in cases where 'coarctation' was the major cardiovascular lesion. In this condition only maternal age was raised (mean 29.5 years) and paternal age (mean 30.1 years) did not differ from that in the population.

The groups of cases with aortic valve obstruction and other malformations (Group B), with mitral valve obstruction (Group C), and with left-sided hypoplasia without valve lesions (Group D) in general showed similar features to the cases in Group A, a raised mean paternal age and a high male-female sex ratio, but to a slightly lesser extent.

Discussion

From previous accounts and the present study, it is clear that the hypoplastic left heart complex is neither pathologically clear cut nor aetiologically homogeneous. Indeed one weak point of the classification suggested by Noonan and Nadas (1958) is the difficulty of distinguishing between 'hypoplasia' and 'coarctation' of the aorta, a difficulty discussed by Evans long ago (1933).

The study of parental ages in this complex may be one way of identifying homogeneous groups. In the present series, both maternal and paternal age, in the complex as a whole, were significantly higher than in the control population, and the excessive mean difference between the two ages suggested that paternal age was the factor of more importance (Penrose, 1955).

To our knowledge the only cases previously described, falling into the hypoplastic heart complex, where parental age was given, are the ten with aortic or mitral valve atresia described by Friedman, Murphy, and Ash (1951, 1955). The paternal ages

TABLE II
HYPOPLASTIC LEFT HEART COMPLEX:
MALFORMATION, SEX, PARENTAL AGE, PARITY, BIRTHWEIGHT, AND LENGTH OF GESTATION

Serial No.	Sex	Malformations						Maternal Age (yr.)	Paternal Age (yr.)	Parity	Birthweight (g.)	Gestation (days)
		AV	MV	EFE	Aorta	Other Cardiac	Extra-cardiac					
Group A—Aortic valve obstruction with no lesion other than mitral valve obstruction and endocardial fibroelastosis												
X32186	M	++						38	48	3	3707	283
383056	M	+		++				29	37	1	3849	282
720144	M	+			H			27	28	2	3736	X
986299	M	++		++	H			34	34	1	3509	282
540020	M	++			H			21	33	0	2802	308
565124	M	+		++				37	41	3	3170	282
986514	F	++		++	H			30	32	4	3481	283
784061	M	+						23	30	1	3170	291
*950311	F	+	+	+				44	53	9	2604	279
X69034	F	++	++					37	37	4	3170	268
X55026	M	+		+				22	34	1	2604	308
782205	F	++			H			37	49	6	3792	263
433053	M	+	+					28	35	5	4415	300
534003	M	+	+	++	H			34	39	1	2830	282
Group B—Aortic valve obstruction with additional cardiac or extracardiac lesions												
514201	M	+			C	VSD		28	28	0	2519	269
550147	M	++			C	VSD		23	38	0	2943	283
986346	M	B+	+	++				35	42	1	3566	290
092527	M	++	++		H	+		39	40	1	2094	237
520083	M	B+			I	VSD		33	44	1	3170	265
092274	M	B+		+	H			19	22	0	X	289
550293	F	++	++	++	H	VSD		21	27	1	X	247
510269	M	B+	+	++	H			23	25	1	3368	X
986548	M	B+			H	VSD		33	32	1	3849	274
514165	F	++	++		H	VSD		28	33	2	3962	294
436040	M	+	+				+	34	33	0	2094	275
511232	F	++	++		HI		+	41	49	1	1613	X
092204	F	B+			C	VSD	+	30	33	2	3255	265
X80277	M	B+				VSD	+	36	35	3	2717	258
432043	F	B+			C	VSD		24	25	2	3170	300
Group C—Mitral valve obstruction without aortic valve lesions												
T950205	F		++	++	C	VSD +	+	35	41	1	1075	X
X32143	F		++			VSD +	+	29	30	1	2660	285
730112	M		++			VSD	+	29	41	1	2490	281
515086	M		++			VSD +	+	30	29	2	1189	284
423017	M		++	++	I	VSD +	+	28	33	1	3679	281
289263	M		++		H	VSD	+	26	30	2	X	261
Group D—Hypoplasia of left-sided chambers or aorta without valve lesions												
091053	F				H			24	34	1	3028	X
823035	F				H			43	44	4	3170	283
300186	F				H			25	25	1	4188	280
X82445	F				H	VSD		20	X	0	2519	281
681080	M				H	VSD		35	48	9	3396	283
289148	M				H	VSD		41	33	2	2433	282
X80245	M				H		Mongol	25	25	1	2717	292
939044	M				H	VSD +	+	X	X	2	2830	290
517202	M					VSD +	+	34	34	5	2519	259
X25096	M					VSD +	+	41	41	2	708	227
TX78128	F				H			36	51	11	1981	X
Group E—Interruption of the aorta												
935042	F				I			23	28	0	2887	296
083098	F				CHI	VSD		24	27	0	2830	252
986403	F				I		+	18	21	0	X	X
099065	F				I		+	23	27	0	1443	209

* Mother has congenital aortic stenosis.

Valve lesion: AV = aortic valve; MV = mitral valve; B = bicuspid valve. + = stenosis; ++ = atresia.

EFE: ++ = fibroelastosis; + = opaque.

Aorta: H = hypoplasia; I = interruption; C = coarctation.

Other cardiac: + = other.

T = preceding serial number denotes twin.

X = Not known.

where known were 35, 32, 38, 26, 38, 35, 29. Four out of the seven fathers were aged 35 or more. Moreover, Zoethout, Bonham Carter, and Carter (1964) gave details of parental ages in children pre-

senting with aortic stenosis at The Hospital for Sick Children in London, a proportion of which almost certainly represents survivors of our Groups A and B in their mildest form. The mean maternal age in

TABLE III
GROUPS OF HYPOPLASTIC LEFT HEART
COMPLEX: MEAN MATERNAL AND PATERNAL
AGE AND MEAN DIFFERENCE

Group	Malformations	Number (with known parental ages)	Mean Maternal Age (yr.)	Mean Paternal Age (yr.)	Mean Differ- ence (yr.)
A	Aortic valve ob- struction with no lesions other than mitral valve obstruction and endocardial fi- broelastosis	14	31.5	37.9	6.4
B	Aortic valve ob- struction with additional car- diac or extra- cardiac lesions	15	29.8	33.7	3.9
C	Mitral valve ob- struction with- out aortic valve lesions	6	29.5	34.0	4.5
D	Left-sided hypo- plasia without valve obstruc- tion	8*	32.9	37.7	4.8
E	Interruption of aortic arch	4	22.0	25.7	3.7
A-E	All	47	30.4	35.0	4.6
Con- trol	Main week popu- lation	16520	27.5	30.5	3.0

* Mongol excluded.

TABLE IV
SYNDROMES WITH RAISED PATERNAL AGE
(ADAPTED FROM BLANK, 1960)

Syndrome	No. of Cases	Mean Pater- nal Age (yr.)	Mean Mat- ernal Age (yr.)	Mean Differ- ence	Source
Achondroplasia	97 16	38.7 37.7	32.1 34.3	6.6 3.4	Mørch } (quoted by Krooth } Penrose, 1955)
Marfan's syn- drome	37	40.2	33.3	7.2	Stevenson (1957)
(sporadic cases)	7	36.5	28.5	8.0	Lynas (1958)
Apert's syndrome	37	36.9	31.8	5.1	Blank (1960)
Group A	14	37.9	31.5	6.4	Present series

their series was 28.4 years, compared with 28.3 years in a control population. The mean paternal age (for which there was no control) was 32.3 years, and the average difference between this and maternal age was 3.9 years.

There are some grounds for believing this to be excessive. First this is a larger mean difference than 3.0 years found among the control births in the Perinatal Mortality Survey. Secondly, though there are no population data on paternal age at this time, data published on ages of all bridegrooms and brides (Registrar General, 1966) show that in the 12 years preceding 1964 the biggest mean difference between age of husband and wife in any one year

was 3.1 years. Thirdly, 15% of fathers in the aortic stenosis series of Zoethout *et al.* (1964) had been aged 40 years or more, compared with 9.5% in the Survey control population, a difference which seems unduly large even allowing for the fact that the Survey mothers were slightly younger than the controls used by Zoethout *et al.* (27.5 years compared with 28.3 years). While these findings clearly cannot be interpreted as confirming a paternal age effect in neonatal deaths with aortic valve obstruction they would be compatible with such a thesis.

Within the group of hypoplastic left hearts described in the present account it was clear that the paternal age effect was maximal in the cases with aortic valve involvement and without malformations other than those forming part of the complex, our Group A. In contrast, there seemed to be no age effect in the group where interruption of the aorta was the major defect. Since Gasul, Arcilla, and Lev (1966) consider that interruption of the aorta is the most severe form of preductal coarctation, it is interesting that in the present series no undue rise in mean paternal age was found in the cases where 'coarctation' of the aorta was the major cardiovascular defect. This finding is supported by Campbell's (1965) report, that while the mean paternal age was raised in all the groups with malformations of the heart, he did not think the increase was significant for the group with coarctation. Gasul and his colleagues also stated that it was possible to distinguish between 'hypoplasia' of the aorta, in which the ascending aorta is narrower than the aortic arch, and 'coarctation' in which the reverse relation occurs.

The distinction between interruption of the aorta and the remaining groups in the complex was also supported by the sex distribution. When our cases with aortic interruption were added to those described by Noonan and Nadas (1958), 9 out of the 10 were female. This was in contrast to all the other groups in the complex where there was a male preponderance, as in the series collected by Noonan and Nadas, and in other reported groups of aortic and mitral stenosis.

Raised paternal age has been described in some cases of Down's syndrome with a G/21 structural anomaly (Penrose, 1962) and in some patients with XO/X isochromosome for the long arm of the X (Polani, 1965). It has also been demonstrated in three non-chromosomal syndromes: achondroplasia, Marfan's syndrome, and acrocephaly-syndactyly (Apert's syndrome). Table IV shows that the increase in father's age in our Group A is of the same order as that described for these last conditions. The relevance of this finding lies in the

consideration that an increase in the age of fathers of sporadic cases of genetically determined conditions favours an error of gene replication during spermatogenesis rather than other causes of mutation such as natural irradiation (Penrose, 1955).

If all cases in our Groups A to D were part of the same condition, the incidence would be about 1 in 4000 births, too high to suggest that all cases were due to dominant gene mutation. It is, however, possible that a proportion, perhaps only those uncomplicated by extracardiac malformations, were due to a gene mutation. Confirmation of a high parental age from other studies of this condition would support such a suggestion.

Summary

There were 50 cases falling into the category of hypoplastic left heart complex, either stillborn or dying during the neonatal period, which were included in the British Perinatal Mortality Survey.

It is considered that this complex is a heterogeneous group with one subgroup, interruption of the aorta, contrasting sharply with the others in sex and parental age distribution. In this sample, a feature of the remaining cases, particularly those with aortic valve obstruction uncomplicated by other types of cardiac or extracardiac malformation, was a high mean parental age. The relevance of such a finding is briefly discussed.

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