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Consanguinity and complex cardiac anomalies with situs ambiguus

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SUMMARY A survey of British born Asian and English populations of children with congenital cardiac anomalies showed an increased incidence in the Muslim Asian population of complex lesions with visceral heterotaxia. There is a very high incidence of parental consanguinity among Muslim Asian children with complex congenital cardiac anomalies that is even higher than in the general Muslim Asian population of the area studied. The evidence suggests an important recessive genetic component in complex cardiac lesions with visceral heterotaxia, but segregation analysis does not support pure recessive inheritance.

Cardiac malformations with asplenia or polysplenia are rare: one study put the incidence of asplenia as 1/40 000 births.[1] For some years one of us (GHW) had the clinical impression that there was a greater proportion of these lesions among British born Asian children undergoing cardiac catheterisation than children of Caucasian British parents. A retrospective study was therefore undertaken of 4690 infants and children who had undergone cardiac catheterisation.

Material and methods

We examined the records of all infants and children under 15 years of age with congenital heart anomalies who had undergone cardiac catheterisation for the first time at the Royal Manchester Children's Hospital or at Killingbeck Hospital, Leeds, during the years 1965–80 inclusive. The diagnoses were classified into complex congenital heart disease and 9 other subgroups (see Table 1) on the basis of the main cardiac anomaly and the presence or absence in the medical notes of evidence of asplenia, polysplenia, and situs ambiguus. To oversimplify, situs ambiguus can be regarded as two left sides of the body with polysplenia, or two right sides with asplenia, and complex cardiac anomalies are commonly present, especially in asplenia. In this paper, however, complex lesion (CL) is defined as a cyanotic cardiac anomaly with single ventricle (double inlet left or right ventricle with or without outlet chamber) and asplenia or polysplenia. Evidence of asplenia or polysplenia was sought at the time of catheterisation in all children with a single ventricle but not necessarily in all other patients.

Sixty two children (35 boys and 27 girls) with cyanotic cardiac anomaly and a single ventricle had asplenia or polysplenia. In 33 children this diagnosis was based on necropsy findings, and in 29 on at least two of the following criteria: the presence of Howell Jolly bodies, interruption of the inferior vena cava with azygos continuation, bronchial heterotaxy, splenic scans, and clinical and radiological evidence of abdominal visceral heterotaxia.

Large populations of Asians from the Indian subcontinent, some British born and some immigrant, live within the catchment areas of both hospitals. Most of the children investigated (and all those with CL) had been born in Britain. All the children were classified into Asian Muslim, Asian Hindu, or 'English' on the basis of first names and surnames, and the Asian parents' religion was confirmed from the case notes. The 'English' group consisted almost entirely of native born Caucasian British. Data on parental consanguinity and on siblings of those Asian patients with CL were collected from the notes, supplemented as far as possible by interview or by correspondence with the parents in the appropriate language.

Consanguineous marriage is often favoured among Asian Muslims (but not Hindus). Since we were unable to find any published data on the extent of inbreeding among our local Asian Muslim population, a crude control group of normal Asian Muslim couples was randomly ascertained by one of us (ARG) who asked the relevant questions in the

appropriate language of people passing by in the markets of four towns in which most of the Asian children in the study lived. There are inherent problems in establishing the degree of consanguinity in Muslim Asians, and therefore every attempt was made to explain the reason for the study.

Results

Data were obtained on 4690 infants and children: 4476 were 'English' and 214 Asian, of whom 183 were Muslim and 31 Hindu; 2270 patients were investigated in Manchester and 2420 in Leeds. There was no significant difference between the two centres in the distribution of the types of malformation, therefore data from both have been combined.

Table 1 compares the incidence of different types of heart disease in the three groups. There is a highly significant excess of patients with CL in the Asian Muslim group compared with the English children; the Hindu group is too small for significant results but does not suggest a similar excess. The 20 Asian Muslim children with CL included 12 with asplenia (7 boys and 5 girls) and 8 with polysplenia (5 boys and 3 girls); of the 41 English children with CL 24 had asplenia (14 boys and 10 girls) and 17 polysplenia (9 boys and 8 girls); the single Asian Hindu with CL was a boy with asplenia. There was also a significant excess (P=0·05) of patent ductus among the Asian Muslims, even after correcting for the number of comparisons made. None of the other differences was significant.

There were five pairs of siblings among the 183 Muslim children, including two pairs with CL. Among the 41 English children with CL there were no sibling pairs. Although we did not study the incidence of pairs of catheterised siblings among the other English groups, a previous survey (GHW, unpublished) suggested that it is about 1%.

Table 2 shows the prevalence of consanguineous marriage (defined as second cousin or closer) among Asian Muslim groups. Counting only those where the case notes or subsequent contacts provided adequate information about parental consanguinity, 14 of 16 (87·5%) parental marriages in the CL group and 61 of 110 (55·5%) in all other groups were consanguineous. Among the randomly ascertained control series, 121 of 300 (40·3%) marriages were consanguineous. Compared with this control series, consanguinity was significantly increased (P=0·005) among parents of CL children but barely so (P=0·04) among parents of children with all other heart defects.

Table 2 *Consanguinity among Asian Muslim parents*

	Parents of affected children		
	Complex lesions	*Others*	*Control series*
No of couples	18	160	300
No with adequate information	16	110	300
No (%) consanguineous	14 (87·5)	61 (55·5)	121 (40·3)

Segregation analysis. The 18 Asian Muslim parental couples in the CL group had 20 children with CL and 40 known not to have CL. A further five children had been born in the Indian subcontinent and had died in infancy and although it is possible that some of these died of CL, there is no adequate information to support such an assumption. The segregation ratio (that is, the probability that a child of those parents would have CL) was estimated using standard genetic techniques. The appropriate model is complete truncate ascertainment[2] because most of the cases occurring in the catchment areas of the two hospitals are likely to have been ascertained. The maximum likelihood method of Finney[3] gives a segregation ratio of 0·089 ± 0·058, and the method of Li and Mantel[4] gives 0·091 ±

Table 1 *Distribution of subtypes of congenital heart disease in the three groups*

Type of congenital heart disease	*English*		*Asian Muslim*		*Hindu*		*Comparison of English and Asian Muslim*
	No	*%*	*No*	*%*	*No*	*%*	
Complex lesion	41	0·9	20	10·9	1	3·2	χ^2=134·6, P<0·001
Patent ductus arteriosus	143	3·2	13	7·1	2	6·5	χ^2=8·0, P=0·05
Ventricular septal defect	794	17·7	33	18·0	7	22·6	NS
Tetralogy of Fallot	571	12·8	32	17·5	4	12·9	χ^2=3·0, NS
Atrial septal defect	458	10·2	13	7·1	2	6·5	NS
Pulmonary stenosis	455	10·2	14	7·7	2	6·5	NS
Transposition of the great vessels	411	9·2	14	7·7	3	9·7	NS
Aortic stenosis	252	5·6	6	3·3	—		NS
Coarctation of the aorta	244	5·5	10	5·5	1	3·2	NS
Other	1107	24·7	28	15·3	9	29·0	χ^2=6·4, NS
Total	4407	100	183	100	31	100	

Probabilities have been corrected for the number of tests done, ie, multiplied by 10.

0·061. If CL were an autosomal recessive condition this ratio would be 0·25.

Discussion

Incidence of CL. The data show a significant excess of CL in the Asian Muslim children compared with children of English origin. Two possible sources of spurious effect can be discounted:

(1) If the Asian population had increased disproportionately as the study progressed, and if CL were more likely to be diagnosed in the later part of the study, there might have been a false correlation between the Asian population and CL. In fact the ratio of Asian to English patients investigated remained the same throughout the study, as did the distribution of patients with CL.

(2) Catheterisation might have been performed more often when the patient was Asian, perhaps because of greater clinical doubt in relation to possible cyanosis. We think that this may well explain the modest excess of cases of patent ductus that we observed among the Asians. Most children with patent ductus were not catheterised. Most children, English or Asian, with diagnoses of CL, tetralogy, atrial septal defects, or transposition of the great arteries would, however, have been catheterised.

The greater prevalence of CL among catheterised Asian Muslim children almost certainly reflects a higher population incidence. Among the cases reported here, 9 Asian Muslim and 16 English children with CL were diagnosed at the Royal Manchester Children's Hospital. According to the 1981 Census, the approximate catchment area of this hospital contained 23 996 children aged 0 to 15 years whose fathers were born in 'the new Commonwealth, including Pakistan' (who, in these areas, are largely Asian Muslims), and 386 858 whose fathers were born in Britain. If these can be taken as rough guides to the numbers of 'English' and Asian children at risk during the study period 1965–80, then the incidence among the English population is about 1/24 000 and among the Asians about 1/2700. The English figure, which refers to asplenia and polysplenia, is comparable with the figure of 1/40 000 found by Rose *et al* in Canada for asplenia alone.[1]

Affected siblings. Most cases of CL are sporadic, but there have been at least 12 reports of sibling pairs with asplenia/polysplenia[5–9] (see reference 5 for a review of the earlier literature on familial asplenia). In 8 pairs both had asplenia, in two pairs both had polysplenia, and in two pairs one sibling had asplenia and the other polysplenia. The present report adds two more pairs, one where both had asplenia, and one where one sibling had asplenia and the other had polysplenia.

Parental consanguinity. Consanguineous marriages are very common among Asian Muslims, but they are even more common among those with CL children: at least 14 of the 18 marriages in the CL group were consanguineous. Parental consanguinity was noted in only one of the previously reported families with affected siblings[9] but was present in both our families. Case notes are an imperfect source of information on consanguinity, perhaps especially so with Pakistani patients; therefore 16 of the CL families and as far as possible the other Asian Muslim families without adequate information in the notes were followed up by correspondence or interview. Since consanguinity is more likely to be noted in the case notes than non-consanguinity, it is likely that most of the patients without adequate data were not children of consanguineous marriages. Thus among the Asian Muslims, the true consanguinity rate in the CL group probably lies between 14 of 16 (87·5%) and 14 of 18 (77·8%), whereas for the other groups it probably lies between 61 of 110 (55·5%) and 61 of 160 (38·1%) (Table 2). It is unlikely that the latter group differs significantly from the admittedly imperfect control series (40·3%), but there is unquestionably increased consanguinity among parents of CL children.

Among Asian Hindus consanguineous marriage is rare, and our small sample shows no evidence of a high incidence of CL. For the English children, data on parental consanguinity were not collected in the present study, but a previous survey of children attending the cardiac clinics at the Royal Manchester Children's Hospital had established a very low parental consanguinity rate of about 1/600–800 in the general population and no significant increase in those with CL (GHW, unpublished data).

Taken together with previous reports, these findings provide convincing evidence for genetic factors in at least a proportion of cases, and Ivemark syndrome is listed as a probable autosomal recessive condition (catalogue no 20853) in McKusick's catalogue of Mendelian conditions.[10] Nevertheless, segregation analysis shows a recurrence risk of only 9·0 ± 6·0%, far below the 25% figure for autosomal recessive conditions. Interestingly, Rose, Izukawa, and Moes[1] found precisely the same segregation ratio among 60 Canadian children, although one might have expected a lower ratio from their series because there was no known parental consanguinity. It seems likely that the condition as observed is heterogeneous, with a mixture of autosomal reces-

sive and sporadic (environmental or new dominant mutations) cases. In principle, these can be separated by more refined segregation analysis,[2] but a much larger series would be needed. The relevance of environmental factors is supported by the case of Wilkinson *et al*[11] in which an infant with asplenia syndrome had a normal identical twin.

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