Congenital malformations associated with anencephaly in the Fylde peninsula of Lancashire

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SUMMARY The necropsy reports of 174 cases of anencephaly, born in the Fylde peninsula of Lancashire between 1957 and 1980, have been analysed for the presence of other malformations. The results were compared with a similar previous series from Bristol, though the Bristol study differed both in time (1948 to 1975) and in the fact that it was hospital based and, unlike the present study, did not achieve near complete ascertainment. Of the Lancashire anencephalics, 24% had other malformations, a significantly lower rate than in the Bristol series. There was a much higher rate of renal and urinary tract defects in the Bristol series, and a higher rate of cardiovascular defects in the Lancashire series. The distribution of associated malformations differed in the two areas, possibly representing different patterns of aetiological heterogeneity. The iniencephaly rate was so much lower in Lancashire as to suggest an artefact, perhaps owing to the lack of a precise definition of the condition.

It is becoming increasingly apparent that within a group of apparently similar congenital malformations, there exists considerable aetiological heterogeneity. Even for such apparently discrete defects as oesophageal atresia or diaphragmatic hernia, population based studies clearly demonstrate considerable heterogeneity.^{1,2} Future progress will depend on our ability to recognise different aetiological categories at present concealed within a group of similar defects.

Aetiological heterogeneity applies no less to neural tube defects,³ and a plea has been made for detailed anatomical studies of affected infants.⁴ Furthermore, it has recently been postulated that cases of neural tube defects without other malformations might be aetiologicaly different from those with other non-neural malformations.⁵ Further impetus for the study of other malformations in cases of neural tube defects stems from the suggestion of an increased frequency of neural tube defects in the sibs of children with oesophageal atresia, diaphragmatic hernia, cleft lip and palate, bladder exstrophy, or renal agenesis.⁶

A systematic review of congenital malformations in patients with anencephaly born in Bristol between

1948 and 1975⁷ showed that 98 of the 294 cases (33.3%) had other major congenital malformations. The most frequent single malformations were hydronephrosis, cleft palate, diaphragmatic hernia, exomphalos, cleft lip, and horseshoe kidney. Further studies were suggested to see if the pattern of associated malformations in anencephaly varied according to the geographical area. This has prompted the present study, which is an analysis of the congenital malformations found in patients with anencephaly born in the Fylde peninsula of Lancashire. The Lancashire data have the advantage of coming from a complete area study, whereas the Bristol study was more likely to include babies born in hospital than home deliveries and did not cover a defined population.

Subjects and methods

The cases of anencephaly were those used for two previous epidemiological studies of anencephaly in the Fylde peninsula of Lancashire,^{8,9} and they were born between 1 January 1957 and 31 December 1980. These cases were previously ascertained by a study of all case histories of babies dying in the perinatal period in this area,^{8,9} and it is thought that complete ascertainment has been achieved for cases of anencephaly. Of all babies dying in the perinatal period, 93% had been examined at necropsy,⁹ and of

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the 180 anencephalics a necropsy had been performed in 174 cases (96.7%). Whole body radiographs were not a routine part of the necropsy, as was the case for the Bristol series.

There were six cases that were not necropsied and accordingly these have been excluded from the present study. The details of these cases were (1) female, twin two (other twin normal), anencephaly, born 13.9.58; (2) female, anencephaly plus craniorachischisis, born 2.6.66; (3) male, anencephaly, born 21.11.67; (4) male, anencephaly, twin one (other twin normal), born 2.8.67; (5) female, anencephaly, born 8.5.68; (6) male, anencephaly, born 16.10.75.

There were only three cases of iniencephaly and these cases have not been included in this study either because of their extreme rarity. The details are (1) female, born 30.8.61, iniencephaly with enormous meningoencephalocele; (2) male, born 14.1.64, iniencephaly with cyclopia, complete rachischisis, gross distortion of the thoracic cage, a large left diaphragmatic hernia; (3) female, born 13.9.67, iniencephaly with meningoencephalocele lying over thoracic vertebrae, left diaphragmatic hernia, bilocular heart with truncus arteriosus.

Results

There were 130 females and 44 males, a sex ratio of 0.34. Of the 174 cases, 41 had from one to five other congenital malformations (23.6%). The distribution of associated malformations is given in table 1, with the cases subdivided as in the previous paper by sex and by the presence or absence of spina bifida. The following were not included as malformations: unusual dimensions of the adrenals, the thymus, the thyroid, or the pituitary; club foot; hypoplasia of the lungs; high arched palate.

The 19 cardiovascular system defects were: atrial septal defect (7); single ventricle (2); cor biloculare (2); truncus arteriosus (2); ventricular septal defect (in one case with a large aorticopulmonary fenestration) (2); pulmonary atresia + VSD (1); hypoplastic left heart (2); coarctation of the aorta (1).

The six gastrointestinal malformations were: duodenal atresia (2); imperforate anus (1); absent spleen (1); absent liver and spleen (1); oesophageal cyst (1).

The eight skeletal defects were: sacral agenesis (2); thoracic scoliosis (1); hips acutely flexed with genu recurvatum (1); bilateral congenital dislocation of

TABLE 1 Associated malformations in 174 cases of anencephaly.

Malformation	Male AC + SB	Male AC only	Female AC + SB	Female AC only	All female(%)	All male(%)	Total (%)
Horseshoe kidney	0	0	0	0	0	0	0
Hydronephrosis	0	1	2	3	5 (3.8)	1 (2.3)	6 (3.4)
Polycystic kidney	0	0	1	0	1 (0.8)	0	1 (0.6)
Absent kidney (unilateral)	0	1	0	0	0	1 (2.3)	1 (0.6)
Absent kidney (bilateral)	0	0	0	0	0	0	0
Hypoplastic kidneys*	0	0	0	1	1 (0.8)	0	1 (0.6)
Urethral atresia	0	0	0	0	0	0	0
Oesophageal atresia	1	0	0	0	0	1 (2.3)	1 (0.6)
Meckel's diverticulum	0	0	0	0	0	0	0
Multiple spleens	0	0	0	0	0	0	0
Situs inversus	0	1	0	0	0	1 (2.3)	1 (0.6)
Malrotation	1	0	1	0	1 (0.8)	1 (2.3)	2 (1.1)
Other gastrointestinal malformations	0	2	4	0	4 (3.0)	2 (4.5)	6 (3.4)
Exomphalos	1	1	3	1	4 (3.0)	2 (4.5)	6 (3.4)
Diaphragmatic hernia	3	1	6	1	7 (5.3)	4 (9.0)	11 (6.3)
Lung defects	0	1	0	0	0	1 (2.3)	1 (0.6)
Cleft lip	0	0	0	1	1 (0.8)	0	1 (0.6)
Cleft palate	0	0	3	1	4 (3.0)	0	4 (2.3)
Cardiovascular malformations (excluding single umbilical artery)	2	2	5	8	13 (10.0)	4 (9.0)	17 (9.8)
Single umbilical artery	0	0	1	1	2 (1.5)	0	2 (1.1)
Cyclopia	0	0	0	0	0	0	0
Skeletal defects	1	0	4	3	7 (5.3)	1 (2.3)	8 (4.6)
Genital defects	1	0	0	0	0	1 (2.3)	1 (0.6)
Absent pinna	0	0	0	0	0	0	0
Inguinal hernia	0	0	0	0	0	0	0
Microphthalmia	0	1	0	0	0	1 (2.3)	1 (0.6)
Twin†	0	1	2	2	4 (3.1)	1 (2.3)	5 (2.9)
Cases with no other defects	12	22	40	54	94 (72.3)	34 (77.2)	128 (73.6)
Totals	17	27	59	71	130	44	174

AC, anencephaly; SB, spina bifida; *there were no unilateral cases; †twinning was not counted as a malformation, but is included in this table for interest. Details of zygosity are not available, but all the twins were discordant.

the hip (1); "greatly shortened spinal cord" (1); "neck very short with fusion of the vertebrae" (1); absent cervical vertebrae (1).

The single genital defect was hypospadias.

Of the 11 diaphragmatic hernias, eight were left-sided, two were right-sided, and in one the side was not mentioned.

Discussion

Before comparing the Lancashire and Bristol findings it is important to point out that whereas the Lancashire study was based on near total ascertainment, the Bristol study was hospital based. Furthermore, the two series were collected at different times. It is not possible to compare the incidence of anencephaly in the two series, for although this has been carefully analysed for the Lancashire series^{8,9} it is not available for the Bristol series.

Females outnumbered males, the sex ratio being 0.34 in the Lancashire series compared with 0.35 in the Bristol⁷ series. As for the associated malformations, cleft palate was commoner in females, whereas in the Bristol series it was commoner in males. Another reversed trend is that in this series females were more likely to have an associated malformation, whereas in the Bristol series the reverse was true. In the present series, as can be seen from table 2, 23.6% of cases of anencephaly had associated congenital malformations, a significantly lower rate than in the Bristol series (33.3%). This difference was evident both in anencephalics and in anencephalics who had spina bifida as well. The cardiovascular system was the most frequently affected system, with defects occurring in 11% of cases, a higher rate than in the Bristol series (6%, see table 3). Gastrointestinal defects were the next most frequent, followed by renal and urinary tract malformations.

The striking differences between the Lancashire and Bristol series are the much higher rate of renal

TABLE 3 *Anencephaly: associated malformations by system.*

	Lancashire(%)	Bristol(%)	χ^2	p
Renal and urinary tract defects	9 (5.2)	48 (16.3)	12.71	<0.001
Cardiovascular defects	19* (10.9)	17† (5.8)	4.06	<0.05
Gastrointestinal defects	10 (5.7)	17 (5.8)		
Skeletal defects	8 (4.6)	5 (1.7)		

*Including two single umbilical artery.

†Including six single umbilical artery.

TABLE 4 *Anencephaly: common associated single malformations.*

	Lancashire(%)	Bristol(%)
Diaphragmatic hernia	11 (6.3)	8 (2.7)
Exomphalos	6 (3.5)	10 (3.4)
Hydronephrosis	6 (3.5)	25 (8.5)
Cleft palate	4 (2.3)	21 (7.1)
Cleft lip	1 (0.6)	9 (3.1)
Horseshoe kidney	0	7 (2.4)

and urinary tract defects in Bristol and the higher rate of cardiovascular system defects in Lancashire. In looking at the differing rates for other malformations (see tables 3 and 4) one needs to bear in mind both the relatively small numbers and the large number of comparisons that can be made.

It is difficult to know what the biological significance is of the different rates for different malformations in the two areas. A possible explanation for the different rates is aetiological heterogeneity, but our numbers are perhaps too small to invoke this explanation with any confidence. While in theory different pathologists could have different thresholds for noting certain disorders, it is very difficult to see how this could apply to malformations such as the ones listed in tables 3 and 4. The overall rate of associated malformations was lower in the Lancashire series, yet cardiovascular defects, which might escape detection in a necropsy quickly performed, were in fact more common in the Lancashire series, and we believe that the differences in overall rates for these malformations are real. Using a χ^2 test, the overall differences between the malformation rate in anencephaly between Lancashire and Bristol, and the differences in these rates specifically for hydronephrosis and for cleft palate, reached statistical significance at the 1 in 20 level.

The Bristol series comprised 294 cases of anencephaly, and collected over the same period, 50 cases of iniencephaly. The Lancashire series

TABLE 2 *Malformations in anencephaly with and without spina bifida.*

	Other malformations present(%)	No other malformations present(%)	
Anencephaly only			$\chi^2_{(1)} = 1.72$
Lancashire	19 (19.4)	79 (80.6)	
Bristol	42 (26.6)	116 (73.4)	NS
Anencephaly + spina bifida			$\chi^2_{(1)} = 3.14$
Lancashire	22 (28.9)	54 (71.1)	
Bristol	56 (41.2)	80 (58.8)	NS
All cases of anencephaly			$\chi^2_{(1)} = 5.00$
Lancashire	41 (23.6)	133 (76.4)	
Bristol	98 (33.3)	196 (66.7)	p<0.05

comprised 174 cases of anencephaly, but only three cases of iniencephaly. The differing incidence for iniencephaly between the two areas is so enormous as to suggest an artefact and perhaps the lack of any clear agreement between pathologists as to what constitutes iniencephaly.

Indeed, one might speculate that the case with "neck very short with fusion of the vertebrae" and the case with "absent cervical vertebrae" both had iniencephaly, though even then there is a remarkable lack of iniencephalics in the Lancashire series. There is some disagreement as to the relation between iniencephaly and other neural tube defects. Some geneticists treat iniencephaly as a neural tube defect for the purposes of genetic counselling, but other authorities state that iniencephaly should be considered separately as it may not have the same aetiology as anencephaly.⁴ In view of the fact that in iniencephaly there is a particularly high rate of other malformations, underdiagnosis of iniencephaly would produce a spuriously high rate of other malformations in the remaining cases of anencephaly, and vice versa.

The reasons for the differences for the associated malformations between the Lancashire and Bristol series, if real, are unknown. As was concluded in the first paper, it would be useful to know whether the different associated malformations in anencephaly manifest different epidemiological or genetic patterns. We hope that others who have access to similar data will report them in a comparable way.

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