Congenital malformations associated with anencephaly and iniencephaly

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Summary. The necropsy reports of 294 cases of anencephaly and 50 cases of iniencephaly have been examined, and a tabulated list of associated malformations produced. Cases were divided by sex and the presence or absence of spina bifida. Forty-one per cent of the series had other malformations, and other malformations were more common in those cases with spina bifida than in those without. The most frequent single malformations were: hydrenephrosis (8%), cleft palate (8%), diaphragmatic hernia (5%), exomphalos (5%), hare lip (4%), and horseshoe kidney (4%). It is suggested that the presence of other malformations in anencephaly or iniencephaly may imply some aetiological heterogeneity.

Since anencephaly is a lethal malformation, the presence in some cases of other malformations does not seem to have attracted much interest. Indeed, with the exception of the Second Report of the British Perinatal Mortality Survey of 1958 (Butler and Alberman, 1969), it has not been possible to trace a fully tabulated list of associated malformations in a large necropsy series of anencephalics. Standard teratological texts such as Ballantyne (1904) and Warkany (1971) only briefly mention without giving any idea of their frequency the associated malformations. The explanation for these associated malformations may be so simple and obvious that it is hardly ever mentioned—abnormal fetal growth at an early stage leading to other malformations. Ballantyne (1904) stated (referring to the pathogenesis of associated malformations in iniencephaly): ‘Further ontogeny is hindered and cramped, and so the associated malformations (e.g. diaphragmatic hernia) arise’. Liggins (1974) went a little further than this when he wrote: ‘The diversity of associated anomalies raises the possibility that the teratogenic influence responsible for the failure of the anterior extremity of the neural tube to develop has widespread effects, including reduction in cell number and consequent growth retardation. Determinations of cell number in anencephaly have not been reported.’

A study of diaphragmatic hernia (David and Illingworth, 1976) showed a strong association between diaphragmatic hernia and both anencephaly and iniencephaly. An interest in the reverse association prompted the present study, a simple systematic review of malformations in patients with anencephaly or iniencephaly.

Subjects and methods

The cases were all born in the Bristol region, and were ascertained through the necropsy diagnostic index compiled by Dr N. J. Brown, consultant pathologist, at Southmead Hospital. The necropsy records of all cases listed under the headings of anencephaly and iniencephaly from 1948 to 1975 were studied. Four cases of anencephaly were excluded because a full necropsy had not in fact been performed, leaving 294 cases of anencephaly and 50 cases of iniencephaly.

Results

The associated malformations are given in the Table, with the cases subdivided by sex and by the presence or absence of spina bifida. The following were not included as malformations: changes in the size of the adrenals, the thymus, the thyroid or the pituitary; club foot; hypoplasia of the lungs; high arched palate.

The seven ‘genital’ defects were: hypospadias with penile hypoplasia (1); hypoplastic penis (2); very hypoplastic testes (1); absent left Fallopian

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### Table

**ASSOCIATED MALFORMATIONS IN 294 CASES OF ANENCEPHALY AND 50**

<table>
<thead>
<tr>
<th></th>
<th>Male AC + SB</th>
<th>Male AC only</th>
<th>Female AC + SB</th>
<th>Female AC only</th>
<th>Male IC + SB</th>
<th>Male IC only</th>
<th>Female IC + SB</th>
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<tbody>
<tr>
<td>Horseshoe kidney</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>11</td>
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<td>Hydronephrosis</td>
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<td>Polycystic kidney</td>
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<td>4</td>
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<td>Absent kidney (unilateral)</td>
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<td>Hypoplastic kidney</td>
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<td>Urethral atresia</td>
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<td>Oesophageal atresia</td>
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<td>Meckel’s diverticulum</td>
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<tr>
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<td>Other gastrointestinal malformations</td>
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<td>Diaphragmatic hernia</td>
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<td>5</td>
<td>3</td>
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<td>Lung-defects</td>
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<td>0</td>
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<tr>
<td>Hare lip</td>
<td>2</td>
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<td>2</td>
<td>3</td>
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<td>0</td>
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<tr>
<td>Cleft palate</td>
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<td>6</td>
<td>5</td>
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<td>0</td>
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<td>Cardiovascular malformations (excluding single umbilical artery)</td>
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<td>3</td>
<td>5</td>
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<td>Skeletal defects</td>
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<td>Absent pinna</td>
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<td>Twin*</td>
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<td>1</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>Cases with no other defects</td>
<td>19</td>
<td>25</td>
<td>61</td>
<td>91</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Totals</td>
<td>33</td>
<td>40</td>
<td>103</td>
<td>118</td>
<td>9</td>
<td>4</td>
<td>27</td>
</tr>
</tbody>
</table>

AC: Anencephaly  SB: Spina bifida  IC: Iniencephaly

* Twinning was not counted as a malformation but is included in this table for interest.

tube (1); absent right Fallopian tube and ovary (1); bicornuate uterus (1).

The 17 cardiovascular system defects were: transposition of the great vessels (3); Fallot’s tetralogy (3); coarctation of the aorta (2); hypoplastic left heart (2); ostium primum atrial septal defect plus ventricular septal defect (1); secundum atrial septal defect (1); cor biloculare and absent pulmonary artery (1); right-sided aortic arch (1); truncus arteriosus, atrial septal defect, ventricular septal defect, atresia of left pulmonary artery (1); single ventricle (2).

The five other gastrointestinal defects were: absent gall bladder (1); reduplication of the ileum (1); extra-hepatic biliary atresia with absent gall-bladder (1); ectopic anus (1); rectal atresia (1).

The seven skeletal defects were: radial club hands (1); absent left big toe (1); polysyndactyly (1); extra right thumb (1); bowed tibiae (1); absent right thumb (1); right radial club hand (1).

## Discussion

Females outnumbered males by exactly three to one in this series, a sex ratio of 0.33. As for the associated malformations, the principal sex differences were for cleft palate and genital anomalies (commoner in males), and single umbilical artery and malrotation (commoner in females). Females were less likely to have an associated malformation.

Forty-one per cent of the series had other malformations (i.e. outside the nervous system). Associated malformations were more common in those cases with spina bifida (50%) than in those without spina bifida (31%). Exactly half the cases had spina bifida in addition to either anencephaly or iniencephaly. Eighty-four per cent of iniencephalics had other malformations.

The urinary tract was the most frequently affected system, urinary defects occurring in 19% of cases. This is followed by the cardiovascular and gastrointestinal systems each being affected in 8% of cases. The most frequent single malformations were, in order, hydronephrosis (8%), cleft palate (8%), diaphragmatic hernia (5%), exomphalos (5%), hare lip (4%), and horseshoe kidney (4%).

Certain defects tended to affect the same side. All the diaphragmatic hernias were left-sided except for one bilateral case. All but one of the unilaterally absent kidneys were left-sided, and all but two of the unilaterally hypoplastic kidneys were left-sided. Of the six lung defects, five were a bi-lobed right lung and the sixth was an absent right lung.

Of what significance are associated malformations?
in anencephaly and iniencephaly? It is not dif-
cult to understand that the presence of a major de-
fect such as anencephaly could impair embryonic
growth and development, though the way certain
structures are selectively affected suggests that this
is not merely a non-specific effect of poor growth.
It seems at least conceivable that a genetic pre-
disposition which lays the fetus bare to various
teratogens causing anencephaly could also predis-
pose the fetus to the action of other teratogens.
Certainly the limited range and characteristic pat-
tern of malformations excludes a random associa-
tion. However, it is difficult to envisage that these
associated malformations stem from a single local-
ized anomaly resulting in a ‘cascade’ of defects, as
for example, in the Pierre Robin syndrome (Hanson
and Smith, 1975; Smith, 1975). The exception
would perhaps be the association of cleft palate; this
probably is a simple developmental sequence that
stems from the high position of the palatine raphe
relative to the lateral palatine processes (Potter,
1961). It should be noted that anencephaly, with
or without other malformations, can occasionally be
associated with chromosome abnormalities, though
exactly how frequent this is has not been established
with the new banding techniques (Wright, Clark,
and Breg, 1974; Schmid et al., 1975).

The literature on iniencephaly is cautious on the
relation between it and anencephaly. However, it
shares a female preponderance with anencephaly,
it is apparently commoner in areas where anen-
cephaly is common (Warkany, 1971), and it is often
accompanied by spina bifida. Gardner (1973) re-
garded iniencephaly as ‘ruptured anencephaly’, this
being part of his theory that rupture of the neural
tube is the pathogenic mechanism in neural tube
defects (rather than failure of the tube to close).
For the purposes of genetic counselling inience-
phaly seems to be treated as a neural tube defect.

It is concluded that in the same way that there are
epidemiological and aetiological differences between
spina bifida and anencephaly, so it is possible that
anencephaly itself may consist of more than one
aetiological distinct entity. Further investigation
will be needed to see if the different associated mal-
formations in anencephaly correspond with different
epidemiological variables or different genetic pat-
terns.

This study would not have been possible without the
detailed records made by Dr N. J. Brown, and we are
debted to him for his help. We are very grateful to
Professor N. R. Butler for his help and encouragement.

REFERENCES

Ballantyne, J. W. (1904). Manual of Antenatal Pathology and Hy-
Green and Sons, Edinburgh.


in the south-west of England. Journal of Medical Genetics, 13,
253–262.


Hanson, J. W. and Smith, D. W. (1975). U-shaped palatal defect in

pituitary on growth. In Size at Birth, Ciba Foundation Sym-


Ring chromosome 13 in a polymalformed anencephalic. Human-
genetic, 27, 63–66.

Smith, D. W. (1975). Classification, nomenclature, and naming of

ments, pp. 189–200; 234–236. Year Book Medical Publishers,
Chicago.

rachischisis in a partially trisomic 11 fetus in a family with repro-
ductive failure and a reciprocal translocation, t(6p +; 11q –).
Journal of Medical Genetics, 11, 69–75.
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