Holoprosencephaly in the west of Scotland 1975–1994

M L Whiteford, J L Tolmie

Abstract
Cases of holoprosencephaly which occurred in the west of Scotland over the past 20 years were ascertained from genetics, paediatric, and pathology department records. Fifty cases were identified of which 17 had an underlying cytogenetic abnormality. Of the remaining 33 cases, 26 were delivered after 28 weeks’ gestation giving a birth prevalence of 1 in 26 730. Twenty-one babies were liveborn and nine children are currently alive. All survivors are profoundly mentally retarded and most have seizures. Twenty-eight patients with non-chromosomal holoprosencephaly had a total of 23 sibs and three families were identified where there was either recurrence of holoprosencephaly (one family), a related cerebral malformation (one family), or mental handicap (one family) giving an overall recurrence risk for serious neurological disability of 12% (standard error 7%). We conclude that holoprosencephaly does not necessarily breed true and this observation should be taken into account when giving genetic counselling and attempting ultrasound prenatal diagnosis after the birth of an affected child (J Med Genet 1996;33:578–584)

Key words: holoprosencephaly; frequency; recurrence risk.

Holoprosencephaly is a congenital malformation which encompasses a spectrum of abnormalities affecting the forebrain and midface. Its mildest form comprises orbital hypotelorism, a single central incisor, and arhinencephaly (absence of the olfactory bulbs and tracts), whereas its most severe manifestation is the cyclops phenotype with complete failure of division of the embryonic forebrain into right and left cerebral hemispheres.1 Estimates of the birth incidence of holoprosencephaly lie between 1:16002 and 1:53 3943 and a study from south-west England found incidences of 1:14 520 and 1:5200 in two consecutive three year periods.5 Most cases of holoprosencephaly occur sporadically and published reviews have suggested that approximately 50% of cases are associated with chromosome abnormalities, trisomy 13 being the commonest chromosomal cause.7 Nevertheless, sparse data are available on the frequency of holoprosencephaly associated with cytogenetic abnormalities compared with the frequency of non-chromosomal holoprosencephaly and a detailed population based, clinical genetic study of this cerebral malformation has not previously been reported.8 Genetic counselling advice given to couples who have had one child affected by holoprosencephaly is complicated by the malformation’s heterogeneity. Both autosomal recessive and autosomal dominant gene defects are reported but X linked holoprosencephaly is especially rare.7–10 Dominantly inherited holoprosencephaly has variable expression and can be difficult to diagnose since only subtle signs, such as reduced head circumference or a single central incisor, may indicate the mildly affected parent of a severely affected child. Teratogenic factors or maternal illness, especially maternal insulin dependent diabetes mellitus, may also predispose to holoprosencephaly.11 Usually, genetic advice is empirical and often refers to an American study of 30 families with liveborn, cytogenetically normal children affected by holoprosencephaly, who were assessed at the Indiana University Medical Center between 1957 and 1970. In this study, Roach et al12 derived a recurrence risk for holoprosencephaly of 6%, the figure which is quoted today by many clinical geneticists.

The present study aimed to identify all cases of holoprosencephaly which have occurred in the west of Scotland over a 20 year period, to assess the circumstanes of the malformation’s diagnosis, its frequency, and its clinical associations. We also sought to discover whether close relatives of an affected person were affected by cerebral malformation or neurological disability to help clarify genetic counselling implications following the birth of an affected fetus or infant.

Setting and methods
The west of Scotland has an estimated population of just under 3 million. The area included in this study is that served by five regional health boards: Argyll and Clyde, Ayrshire and Arran, Forth Valley, Greater Glasgow, and Lanarkshire. Over 90% of paediatric deaths are referred to the Royal Hospital for Sick Children in Glasgow for necropsy; a small number of paediatric necropsies are also carried out in two of the other health board areas. The Glasgow pathology department currently obtains consent for necropsy for approximately 80% of all childhood deaths and fetal losses.

Patients (fetuses, infants, and children) were ascertained through examination of day books and records from local pathology departments and paediatric departments as well as the files of the regional paediatric neurology and genetic

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The patients selected for this study were those diagnosed as having holoprosencephaly or arhinencephaly on CT scan or at necropsy or both and who were born between years 1975 and 1994. The obstetric case notes of the mothers were studied to obtain details of the pregnancy and delivery, and probands’ paediatric case notes were reviewed. General practitioners of the mothers were contacted by letter in order to obtain information about the health of other members of the family and to confirm the number of sibs of each index case. Eleven surviving patients (two of whom subsequently died) were personally examined by the authors.

Results

CASES AND CYTOGENETIC ANALYSIS

Throughout the 20 year period, 50 cases of holoprosencephaly occurred giving an overall frequency of 1:14,000. Eighteen patients were ascertained from the genetic department database, 16 from pathology department records, and 12 from the paediatric neurology department database. One patient’s name was found from all three sources and 15 patients’ names were found in two of the three sources. Cytogenetic results were available for 43 patients (see 1).

The first of two cases with 13q deletions was detected after amniocentesis was performed because of increased Down syndrome risk (1 in 34) from maternal serum screening; the pregnancy was subsequently terminated. The other patient was a liveborn child who survived for 14 days. Two patients had 7q deletions which included band 7q36, the location of the designated HPE3 gene. These cases were also diagnosed by amniocentesis following abnormal maternal serum screening results and the observation of abnormalities on ultrasound scanning. Both pregnancies were subsequently terminated at 22 weeks’ gestation. One fetus had a cyclopia phenotype while the other had lobar holoprosencephaly.

Patients known to have chromosomal abnormalities were excluded from further analysis of the results and the following refers to the remaining 33 patients, 26 of whom had proven normal karyotypes and seven in whom cultures failed or cytogenetic analysis was not attempted.

FREQUENCY

Table 2 shows the frequency of non-chromosomal holoprosencephaly for each health department. The patients selected for this study were those diagnosed as having holoprosencephaly or arhinencephaly on CT scan or at necropsy or both and who were born between years 1975 and 1994. The obstetric case notes of the mothers were studied to obtain details of the pregnancy and delivery, and probands’ paediatric case notes were reviewed. General practitioners of the mothers were contacted by letter in order to obtain information about the health of other members of the family and to confirm the number of sibs of each index case. Eleven surviving patients (two of whom subsequently died) were personally examined by the authors.

<table>
<thead>
<tr>
<th>Health board</th>
<th>No of births*</th>
<th>Cases of HPE</th>
<th>Frequency of HPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrghyll and Clyde</td>
<td>117 891</td>
<td>8</td>
<td>1 : 14 736</td>
</tr>
<tr>
<td>Ayrshire and Arran</td>
<td>97 090</td>
<td>5</td>
<td>1 : 19 415</td>
</tr>
<tr>
<td>Forth Valley</td>
<td>68 545</td>
<td>1</td>
<td>1 : 68 545</td>
</tr>
<tr>
<td>Greater Glasgow</td>
<td>256 554</td>
<td>12</td>
<td>1 : 21 380</td>
</tr>
<tr>
<td>Lanarkshire</td>
<td>154 870</td>
<td>7</td>
<td>1 : 22 124</td>
</tr>
<tr>
<td>Total west of Scotland</td>
<td>694 950</td>
<td>33</td>
<td>1 : 21 059</td>
</tr>
</tbody>
</table>

* Total births (livebirths and stillbirths) supplied by Vital Statistics Branch, General Register Office for Scotland, Edinburgh.
board area and for the whole region. Twenty-six infants were delivered after 28 weeks' gestation giving a birth prevalence of 1 in 26 730.

PREGNANCY OUTCOME
Obstetric case notes for 30 of the 32 mothers were examined. One mother was identified as having two children with holoprosencephaly and in two cases there was insufficient information available from necropsy reports for the obstetric case notes to be traced. Information regarding the parents, pregnancies, and birth details is summarised in table 3.

Table 4  Clinical features, classification, survival, and sibs

<table>
<thead>
<tr>
<th>Case</th>
<th>Karyotype</th>
<th>Sex</th>
<th>Clinical features</th>
<th>Severity of HPE</th>
<th>Age at death</th>
<th>Age now (y)</th>
<th>Position in family</th>
<th>Later sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, epicanthic folds, oblique palpebral fissures, malformed ears, micrognathia, midface hypoplasia, high arched palate, talipes, pectus excavatum, hypoplastic genitalia, seizures</td>
<td>Semilobar</td>
<td>3 y</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, arhinencephaly, cerebellar hypoplasia, absent nose, bilateral cleft lip and palate, bilateral simian creases, absent digit 1 foot</td>
<td>Alobar</td>
<td>13 h</td>
<td>2nd</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46, XY</td>
<td>M</td>
<td>Encephalocele, absent pituitary gland, single orbit, NTD, complex congenital heart defect, absent ribs, adrenal hypoplasia, absent kidney and ureter, 2 cord vessels</td>
<td>Alobar/cyclops</td>
<td>TOP</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unknown</td>
<td>M</td>
<td>Arhinencephaly, single orbit, NTD, exomphalos</td>
<td>Alobar/cyclops</td>
<td>TOP</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Failed culture</td>
<td>F</td>
<td>Microcephaly, midline cleft lip and palate</td>
<td>Alobar</td>
<td>Stillborn</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Unknown</td>
<td>F</td>
<td>Single orbit with fused globes, proboscis, arhinencephaly, NTD, adrenal hypoplasia</td>
<td>Alobar/cyclops</td>
<td>TOP</td>
<td>3rd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>46, XX</td>
<td>F</td>
<td>Hydrocephalus, midline cleft lip and palate, hypotelorism, absent nose, low set ears, neck webbing, posterior fossa cyst, 2 accessory gilds</td>
<td>Alobar</td>
<td>1 h</td>
<td>1st</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46, XX</td>
<td>F</td>
<td>Cyclops, proboscis, anencephaly, unilateral absent adrenal gland and kidney</td>
<td>Alobar/cyclops</td>
<td>TOP</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, sloping forehead, mental retardation, spastic diplegia</td>
<td>Semilobar</td>
<td>9-5</td>
<td>2nd</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>46, XX</td>
<td>F</td>
<td>Non-dysmorphic, colpocephaly, mental retardation, seizures</td>
<td>Semilobar</td>
<td>8-0</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>11*</td>
<td>46, XY</td>
<td>M</td>
<td>Median cleft lip and palate, arhinencephaly, abnormal cerebellar vermis, diabetes insipidus, adrenal hypoplasia</td>
<td>Semilobar</td>
<td>3 d</td>
<td>1st</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Unknown</td>
<td>M</td>
<td>Median cleft lip, absent nasal septomaxillary, arhinencephaly</td>
<td>Alobar</td>
<td>6 d</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Failed culture</td>
<td>M</td>
<td>Median cleft lip and palate, absence of crista galli and olivoid plates</td>
<td>Alobar</td>
<td>Stillborn</td>
<td>2nd</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>14†</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, cebocephaly, hypotelorism, single nostril, choanal atresia, microstomia, 2 cord vessels, single hypogastric artery</td>
<td>Alobar</td>
<td>Stillborn</td>
<td>3rd</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>46, XX</td>
<td>F</td>
<td>Central cleft lip and palate, single nostril, seizures, diabetes insipidus, abnormal temperature control</td>
<td>Alobar</td>
<td>Stillborn</td>
<td>3-6 y</td>
<td>2nd</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, iris coloboma, mental retardation, spastic quadriplegia</td>
<td>Semilobar</td>
<td>4-5</td>
<td>3rd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, cerebellar hypoplasia, sloping forehead, low set ears, bilateral cleft lip and palate, complex congenital heart disease</td>
<td>Alobar</td>
<td>3 h</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Failed culture</td>
<td>F</td>
<td>Hydrocephalus, arhinencephaly, cebocephaly, single orbit, central prolapse, supernumerary digit on 1 hand (so did older sib)</td>
<td>Alobar/cyclops</td>
<td>1 h</td>
<td>2nd</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, plagiocephaly, mental retardation, spastic quadriplegia</td>
<td>Semilobar</td>
<td>5-8</td>
<td>3rd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, hypotelorism, central cleft lip and palate, flat nose, VSD, seizures</td>
<td>Alobar</td>
<td>5 m</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>46, XX</td>
<td>F</td>
<td>Hypotelorism, partly occluded nostril, unilateral cleft lip, microcephaly, cerebellal hypoplasia</td>
<td>Semilobar</td>
<td>9 m</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Failed culture</td>
<td>F</td>
<td>Hydrocephalus, posterior fossa cyst, microphthalmia, absent optic bulbs, absent nose, bilateral cleft lip and palate, malformed low set ears, complex congenital heart defect, abnormal liverlobation</td>
<td>Alobar</td>
<td>Stillborn</td>
<td>2nd</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, frontal encephalocele</td>
<td>Semilobar</td>
<td>3-0</td>
<td>3rd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, frontal encephalocele</td>
<td>Alobar</td>
<td>3-5</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>46, XY</td>
<td>M</td>
<td>Microcephaly, iris coloboma, single nostril, bilateral cleft lip and palate, hypoplastic cerebellum, seizures, talipes</td>
<td>Semilobar</td>
<td>1-3 y</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>26‡</td>
<td>46, XX</td>
<td>F</td>
<td>Hydrocephalus, 11 pairs of ribs, 2 cord vessels</td>
<td>Alobar</td>
<td>TOP</td>
<td>3rd</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>46, XX</td>
<td>F</td>
<td>Posterior encephalocele, cleft palate</td>
<td>Semilobar</td>
<td>5 d</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, sloping forehead, optic nerve hypoplasia, lisencephaly, seizures</td>
<td>Semilobar</td>
<td>1-8</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>46, XY</td>
<td>M</td>
<td>Hydrocephalus, flat forehead, hypotelorism</td>
<td>Alobar</td>
<td>TOP</td>
<td>1st</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>46, XY</td>
<td>M</td>
<td>Hydrocephalus, arhinencephaly, midline cleft lip and palate, extremely low set, malformed ears, micrognathia, 2 cord vessels</td>
<td>Alobar</td>
<td>TOP</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>31‡</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, hypotelorism, seizures, diabetes insipidus, hypoplastic nails</td>
<td>Semilobar</td>
<td>1-8</td>
<td>4th</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>46, XY</td>
<td>M</td>
<td>Extreme hypotelorism, central proboscis, accessory auricles, facial skin tag</td>
<td>Alobar</td>
<td>TOP</td>
<td>1st</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>46, XX</td>
<td>F</td>
<td>Microcephaly, arhinencephaly</td>
<td>Alobar</td>
<td>TOP</td>
<td>2nd</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Sib had cerebral malformation. † Sib has single central incisor and mental retardation. ‡ Sib pair.
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Table also shows the severity of the lesion, the position of the affected child in the family, and the number of sibs born after the proband. Note that cases 2, 3, 7, 14, 17, 20, and 24, had abnormalities which would have been in keeping with a diagnosis of trisomy 13 but had normal karyotypes; for this reason we did not exclude patients with multiple abnormalities from the non-chromosomal group if karyotype data were not available.

**Survival and Prognosis**

Nine of the 21 liveborn babies are still alive (table 4). The oldest survivor is currently aged 9-5 years. Three surviving children have alobar holoprosencephaly and all the survivors are profoundly mentally retarded. Twelve children died and approximately 60% of these deaths occurred within the first week of life (table 4).

**Sex Ratio**

The overall sex ratio for non-chromosomal holoprosencephaly was 18 females:15 males and within the alobar subtype of holoprosencephaly the ratio was 11 females:10 males. For cyclopia, the ratio was three females: two males.

**Parents**

The mean maternal age of 26-7 years (range 19–39 years) and mean paternal age of 27-4 years (range 20–36 years) were not significantly different from expected. Two sets of parents were Pakistani and first cousins, but no other parents were known to be consanguineous. One mother was a poorly controlled, insulin dependent diabetic and another took an oral contraceptive pill during the first 12 weeks of pregnancy. No other possible teratogens were identified.

**Pregnancy Outcome and Prenatal Diagnosis**

Twenty-one babies (64%) with non-chromosomal holoprosencephaly were liveborn at an average gestation of 37 weeks, one pregnancy was diagnosed as a missed abortion at 16 weeks' gestation, and a further three babies were stillborn at an average gestation of 32 weeks.

A total of eight pregnancies were prenatally diagnosed by ultrasound examination and none represented a sib recurrence. All eight pregnancies were terminated. Four of these cases had an associated neural tube defect and it was the latter malformation rather than holoprosencephaly which was detected by ultrasound scanning. Two cases were terminated because of the antenatal detection of hydrocephalus and in these cases holoprosencephaly was only diagnosed at necropsy. In the remaining two cases, holoprosencephaly was diagnosed prenatally at the Regional Fetal Medicine Centre, one case having been referred from another obstetric unit at 25 weeks' gestation on account of ultrasonographically diagnosed growth retardation, the second case being diagnosed at 32 weeks' gestation when the mother presented with abdominal pain. One liveborn male infant, who had an unaffected female co-twin, was also diagnosed at 28 weeks' gestation and this pregnancy continued to term. A further liveborn child was noted to have a posterior fossa malformation.

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Figure 1  Case 11. (All photographs of children reproduced with parental consent.)

Figure 2  Sib of case 11.
tachypnoea without other clinical features of Joubert syndrome. Neuroimaging studies indicated that he had cerebellar hypoplasia and a neuronal migration disorder. On clinical examination there was an impression of mild hypotelorism (not confirmed by measurement) and midface hypoplasia (fig 2). He died at the age of 10 months and necropsy confirmed disturbed neuronal migration and cerebellar hypoplasia with underdevelopment of the cerebellar vermis. There was no abnormality of the forebrain. The proband with holoprosencephaly also had a structurally abnormal cerebellum and these male sibs were presumed to have genetically related cerebral malformations.

Case 14 (fig 3), identified through pathology department records, was the stillborn son of a Pakistani couple who were also first cousins. When the mother’s obstetric case notes were examined, we realised that his older sister had previously been referred to the genetic clinic because of her dysmorphic appearance and mild-moderate mental retardation. No diagnosis was made and cranial CT scan was normal. Clinical review of the older sister revealed hypotelorism, midface hypoplasia, a broad nose, and a single central incisor with an intact sense of smell (fig 4). Both parents have normal teeth, head circumferences, and normal facial appearances. Although we cannot be certain, the facial appearance of the handicapped sib suggests she has microscopic cerebral dysgenesis that is genetically related to holoprosencephaly which affected her stillborn brother.

Case 31 (fig 5) is the child of Scottish, non-consanguineous parents. At the age of 3 months she was referred to our clinic with microcephaly and holoprosencephaly. Her mother told us that her previous pregnancy had been terminated at 25 weeks’ gestation after diagnosis of hydrocephalus by ultrasound scanning. We obtained a copy of the necropsy report for this fetus (case 26, fig 6) which stated clearly that the pathological diagnosis was alobar holoprosencephaly in addition to hydrocephalus.

In summary, 23 children were born after the affected fetus or child and recurrence of holoprosencephaly was identified in one family. In two families another cerebral malformation was present in one sib. This gives an overall recurrence risk of 12% (standard error 7%) for holoprosencephaly or mental handicap or both.

**Discussion**

**FREQUENCY OF HOLOPROSENCEPHALY**

Previous studies which noted the frequency of holoprosencephaly did not identify proportions of chromosomal and non-chromosomal cases, or considered only non-chromosomal holoprosencephaly. In this study, we discovered that 34% of all cases of holoprosencephaly had a cytogenetic abnormality. Thirteen patients, or three quarters of all cytogenetically abnormal patients, had trisomy 13. We identified a further seven cases of trisomy 13 from necropsy records and since these cases did not have holoprosencephaly, during our study some 65% of

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**Figure 3 Case 14.**

**Figure 4 Sib of case 14 showing single central incisor on right.**

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**AFFECTED SIB PAIRS AND RECURRENCE RISK**

Information regarding sibs was available for 28 families. In one family two sibs had holoprosencephaly and in two families one sib had holoprosencephaly while a second sib had another cerebral malformation. These three families are discussed in more detail.

The parents of case 11 (fig 1) are both Scottish and non-consanguineous. The first born affected child died at the age of 3 days and necropsy showed an abnormality of the cerebellar vermis in addition to holoprosencephaly. His parents subsequently had a healthy daughter but their third child, also a male, was noted from birth to have episodic
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agreement with 70% quoted by Taylor, the
total frequency of holoprosencephaly in fetuses
and infants who were born within the west of
Scotland is 1:8000, and the frequency of non-
chromosomal holoprosencephaly is 1:21 000.
Considering cases born after 28 weeks' gesta-
tion and using total births as the denominator,
the birth prevalence estimate is 1 in 26 730.
Certainly, this is a minimum estimate because
of incomplete ascertainment of cases, for ex-
ample, cases of semilobar and lobar holo-
prosencephaly may have been missed because
facial signs were lacking and neuroimaging in-
vestigations were not routinely performed on
children with mental retardation. Nevertheless,
we regard our local population frequency and
prevalence estimates as being good approxi-
mations to the true figures.

Figure 5 Case 31.

Figure 6 Case 26 (sib of case 31).

patients with trisomy 13 had holo-
prosencephaly. However, not all cases of tri-
 somy 13 will have been ascertained from
 necropsy records. Therefore, we also examined
the regional cytogenetic register and discovered
a total of 78 cases of trisomy 13 during the
study period, giving a frequency of trisomy 13
of 1:9000. Assuming that 65% of all cases of
trisomy 13 have holoprosencephaly, a figure in

CLINICAL FEATURES AND SEVERITY OF LESION

The clinical features of the children and fetuses
with holoprosencephaly were extremely vari-
able with all manifestations of the cerebral
lesion being represented. We found that 21
patients had alobar holoprosencephaly, 11 had
semilobar holoprosencephaly, and one had
lobar holoprosencephaly (table 3). Five of the
patients with alobar holoprosencephaly had a
cyclops phenotype. The majority of patients
had multiple abnormalities, with cleft lip/palate
and neural tube defects being present most
frequently. One important practical point
which emerged is that even severely affected
children with premaxillary agenesis may have
prolonged survival for several years and this
was not always appreciated at the time of their
birth. Only three children had normal facial
features (cases 2, 9, and 17). These three chil-
dren are still alive and in each case holo-
prosencephaly was diagnosed by neuro-
imaging when investigating mental retarda-
tion and seizures. Therefore, as in previous
studies, we found the “face predicts the brain” in most
but not all children with holoprosencephaly
and the majority of patients with the facial
features of holoprosencephaly have alobar holo-
prosencephaly.

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We found that 28 cases had a total of 23
subsequent sibs and three sib pairs were iden-
tified. In two families the proband was the
second affected child because the first child/
fetus was not diagnosed as affected by holo-
prosencephaly. Only one sib had holoprosencephaly but, on clinical grounds, there
was evidence that the affected sibs had a related
cerebral malformation. Thus, in this small
study the “recurrence risk” for non-chro-
mosomal holoprosencephaly and related ce-
rebral malformations is 12% (standard error
7%). Although this is greater than the 6% re-
currence risk figure calculated by Roach et al.,
in our study, the recurrence risk will decrease
if more unaffected sibs are born, and as only
10 mothers had their last pregnancy more than
five years ago, there is a possibility that some families are not yet complete.

In 1985 Chervenak et al. reported ultrasound prenatal diagnosis of alobar holoprosencephaly and in our series, which extended from 1975 to 1994, there were three cases with alobar holoprosencephaly were diagnosed by prenatal scans at Regional Fetal Medicine Centres. Unfortunately we could not establish the number of times an affected fetus was subject to detailed ultrasound examination and holoprosencephaly was missed. Certainly, in the three families where there was recurrence of holoprosencephaly or a related cerebral malformation, each fetus underwent detailed ultrasound examination at the local hospital. However, there were reasons for missing the recurrence in each case: in the first the affected sib had cerebellar vermis aplasia, which is probably more difficult to detect; in the second family, although the ultrasonographer was aware that there was a sib with mental handicap and malar hypoplasia, it was not recognised that this could be related to holoprosencephaly; in the third family, recurrence of holoprosencephaly was missed, but perhaps the contributory factor was missed diagnosis of hydrocephalus in the proband. Finally, in respect of prenatal diagnosis, it is notable that six cases (20%) with non-chromosomal holoprosencephaly had a posterior fossa abnormality, and also that cerebellar vermis aplasia was the major intracranial sign of recurrence in one family. We therefore suggest that when detailed ultrasonographic evaluation of the fetus is indicated on account of a previous family history of holoprosencephaly, special attention is paid to the fetal posterior fossa and the significance of any abnormality therein is carefully considered, even in the presence of normal hemispheric division. We would also suggest that the ultrasonographic evaluation is carried out at the most experienced centre available.

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