Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the North of England

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OBJECTIVE: This study was undertaken to provide epidemiologic data on the prevalence of holoprosencephaly and to assess the sensitivity of routine ultrasonographic screening in a low-risk population.
STUDY DESIGN: A population-based register of congenital abnormalities was used to identify reported cases of holoprosencephaly between 1985 and 1998. Sources included fetal losses, termination for fetal anomaly, stillbirths, and live births. Prenatal diagnoses and pregnancy outcomes were determined.
RESULTS: Sixty-eight cases of holoprosencephaly were found among 531,686 births. The total prevalence (including pregnancy terminations) was 1.2 cases/10,000 registered births, and the birth prevalence (affected live births and stillbirths at >24 weeks' gestation) was 0.49 cases/10,000 births. Prenatal diagnosis was achieved in 71% of cases, rising to 86% during the second half of the study period; the mean gestational age at diagnosis was 19.8 weeks' gestation. Chromosomal abnormalities (75% of which were trisomy 13) were present in 38% of cases in which a karyotype was established. All those with aneuploidy (80% diagnosed prenatally) had other nonfacial anomalies; additional anomalies were also common in the euploid group (61% diagnosed prenatally), with 90% having facial abnormalities and 70% having other abnormalities.
CONCLUSION: The prevalence of holoprosencephaly in second-trimester pregnancies was about 1 in 8000. Prenatal detection reached 86% with a routine anomaly scanning program. The etiology could usually be determined, which has important implications for recurrence risks. (Am J Obstet Gynecol 2001;184:1256-62.)

Key words: Fetus, holoprosencephaly, prenatal diagnosis, ultrasonography

Holoprosencephaly encompasses a range of abnormalities arising early in the embryonic development of the forebrain. Failure of septation, or cleavage, of the midline forebrain structures is the primary process by which these anomalies arise, and it is frequently accompanied by effects on development of the midfacial region. The forebrain pathologic characteristics of holoprosencephaly are subdivided into lobar, semilobar, and alobar types according to increasing degree of failed septation.[1] A good correlation is often observed between severity of brain pathologic development and the extent of the facial phenotype[2]; for example, cyclopia is almost exclusively associated with a single forebrain ventricle and fused thalami (alobar holoprosencephaly). The progressively less severe phenotypes of ethmocephaly (extreme hypotelorism, with proboscis between eyes), cebocephaly (hypotelorism and primitive, single-nostril nose), and median cleft (premaxillary agenesis) are also usually associated with alobar or semilobar holoprosencephaly. The holoprosencephaly spectrum includes less severe phenotypes, such as absence of the olfactory bulbs and tracts (arhinencephaly), some cases of agenesis of the corpus callosum, and facial-only phenotypes, such as unilateral or bilateral clefts, single central incisor, or hypotelorism.

The etiologic factors of holoprosencephaly, like the phenotypes, are diverse. Trisomy 13, the most commonly identified cause, and other chromosomal abnormalities (trisomy 18 and rearrangements or deletions) account for nearly 50% of holoprosencephaly cases. There are many syndromic associations, including Smith-Lemli-Opitz, Hall-Pallister, pseudotrisomy 13, and Meckel syndromes. Nonsyndromic holoprosencephaly cases recognized as familial or presumed to have a single-gene cause are themselves heterogeneous. The disease genes so far confirmed, *Sonic Hedgehog,*[3] *SIX3,*[4] and *ZIC2,*[5] represent only 3 of at least 12 candidate loci.[6] Numerous environmental factors have been shown to induce holoprosencephaly in other species, including alcohol[7] and retinoids,[8] but the only accepted link observed in human beings is with maternal diabetes.[9]

The epidemiology of holoprosencephaly is poorly described, because most studies have included only small numbers and have not been population based. Three recent population-based surveys from the United States[10-12]

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Table I. Holoprosencephaly prevalences during study period

Period	*All cases**	*Total live births, stillbirths, and terminations of pregnancy*	*Cases excluding spontaneous losses†*	*Total prevalence (cases/10,000 live births, stillbirths, and terminations of pregnancy)*	*Total live births and stillbirths*	*Cases among live births and stillbirths only*	*Birth prevalence (cases/10,000 live births and stillbirths)*
1985-1991	31	284,705	29	1.02	283,976	16	0.56
1992-1998	37	248,726	35	1.41	247,710	10	0.4
1985-1998	68	533,431	64	1.20	531,686	26	0.49

No significant trends according to χ^2 test.
*Includes live births, stillbirths, terminations of pregnancy, and spontaneous losses at <24 weeks' gestation.
†Includes live births, stillbirths, and terminations of pregnancy.

derived from pediatric birth defect registers all used different prevalence parameters. Consequently, rates have varied from 0.48 cases/10,000 live births[12] to 1.2 cases/10,000 births including fetal losses and pregnancy terminations at >20 weeks' gestation.[10] A survey from the west of Scotland[13] indicated a total prevalence for holoprosencephaly of 0.72 cases/10,000 births and terminations. This survey did include second-trimester terminations and losses at <20 weeks' gestation, but it was not based on a single register and consequently probably had a lower case ascertainment rate.

Good-quality data relating to prenatal diagnosis of holoprosencephaly have been similarly lacking, comprising a few descriptive series from tertiary referral centers.[14-16] Among the larger epidemiologic series, only that of Whiteford and Tolmie[13] indicated the number of cases detected prenatally (8 of 33 euploid cases). Their study spanned the period of 1975 through 1994 and thus encompassed huge changes in the technology and practice of prenatal ultrasonographic screening.

Within the geographic area of England defined by the former Northern Region, the Northern Congenital Abnormality Survey has collected population-based data on all congenital malformations since 1984 and assigned appropriate *International Classification of Diseases, Ninth Revision,* codes, with proven high rates of ascertainment.[17] The population of about 3 million is relatively stable, with an average of almost 40,000 registered births per year during the period from 1985 through 1998. This study aimed to collect data on all cases of holoprosencephaly reported to the register to determine the prevalence, case outcomes, and the rate of prenatal diagnosis in a large low-risk population undergoing relatively uniform routine antenatal screening.

Methods

The Northern Congenital Abnormality Survey database receives notifications of congenital anomalies from a wide range of clinical practitioners and allied professionals through an established reporting system. This includes information about fetal losses, suspected and confirmed prenatal diagnoses, birth findings, early-childhood diagnoses, and autopsies.

Cases were identified by searching the Northern Congenital Abnormality Survey database for the *International Classification of Diseases, Ninth Revision,* codes for holoprosencephaly (742.26), cyclopia (759.80), and trisomy 13 (758.1). Lesser brain abnormalities in the holoprosencephaly spectrum, such as arhinencephaly or agenesis of the corpus callosum, were not included. In all cases the diagnosis of holoprosencephaly was verified by either an autopsy report, a definitive prenatal or postnatal radiology report, or a clinical geneticist's diagnosis (in conjunction with a compatible reported forebrain abnormality on prenatal or postnatal scan). Clinical details, including means and timing of diagnosis and outcome, were abstracted. Pathologic diagnosis was assigned to the standard alobar, semilobar, or lobar classification.

In the study population routine fetal anomaly screening by ultrasonography at 18 to 20 weeks' gestation was offered in all maternity units from 1992 onward. Before 1992, such screening was available in 15 of the region's 16 maternity units.

Statistical analysis included the χ^2 test to compare antenatal detection and prevalence of holoprosencephaly across time. The Student t test was used to compare maternal ages of subgroups. Statistical significance was accepted at the $P < .05$ level.

Results

Sixty-eight cases of holoprosencephaly were reported to the survey between 1985 and 1998, during which period there were 531,686 registered births and 1745 terminations for fetal abnormality. The total included 4 spontaneous losses at <24 weeks' gestation, 38 pregnancy terminations, 2 stillbirths (at >24 weeks' gestation), and 24 live births, representing a birth prevalence of 0.49 cases/10,000 births and a total prevalence of 1.2 cases/10,000 pregnancies. There were no statistically significant differences in total prevalence and birth prevalence between the two halves of the study period (Table I). The male/female ratio was 0.94, and more cases than

Table II. Identified cytogenetic, syndromic, familial, and environmental etiologies for holoprosencephaly

	No.	*Gestational age (wk)*	*Birth weight (g)*	*Prenatal diagnosis*
Chromosomal				
Trisomy 13	15	16-39		Yes, n = 12 No, n = 3
Trisomy 18	2	19	80	Indirect *
		23	410	Yes
46,XX, del(13)(q22)	1	35	1520	Yes (29 wk)
46,XY,t(2;4)del(2)(p13p21)	1	19		Yes
46,XY,del(13)(q?33)	1	16		Yes
Syndromic				
Smith-Lemli-Opitz type 2	1	26	685	Yes
Agnathia-holoprosencephaly	2†	19		Yes
		15		No
CHARGE (coloboma, heart disease, atresia choanae, restricted growth and development or central nervous system abnormalities, genital hypoplasia, and ear anomalies or deafness) syndrome	1	35	2760	Yes
Single-gene familial pattern (nonsyndromic)				
Probable autosomal dominant (3 of 3 children)	2†	19		Yes
		18		Yes
Possibly autosomal dominant or autosomal recessive	2†	36	2060	No
		38	2880	No
Autosomal dominant (mother and child)	1	39	2300	No
Environmental				
Maternal diabetes	1	19	216	Yes

*Amniocentesis for other noted anomalies.
†Sibling cases.

Table III. Antenatal detection of holoprosencephaly through study period

		Prenatal diagnoses		
Period	*Cases reported (No.)*	*No.*	*%*	*Gestational age at diagnosis (wk, mean)*
1985-1991	31	16	52*	21.7
1992-1998	37	32	86*	19.0
1985-1998	68	48	71	19.8

*$P < .01$, versus 1985-1991.

expected (4/68; 5.9%) occurred in twin gestations. Mean (±SD) maternal age was 28.5 ± 6.2 years (range, 15-41 years) in the whole group; there was no significant difference between the aneuploid (30.3 years) and euploid (27.3 years) groups.

An autopsy was performed in 72% of deaths, and a karyotype was successfully obtained in 78% of all cases. Chromosomal anomalies were present in 20 (38%) of the 53 affected infants with a known karyotype. These included 15 cases of trisomy 13, 2 cases of trisomy 18, 2 cases of deletions, and 1 case of an unbalanced de novo translocation (Table II). The 15 cases of trisomy 13 associated with confirmed holoprosencephaly represented 15.6% of the 96 cases reported during the study period. In 4 other cases genetic or syndromic diagnoses were made, and there were 5 individuals from 3 families in whom a nonsyndromic, single-gene mode of inheritance was considered likely (Table II). Maternal insulin-dependant diabetes was recorded in 1 case, in which the euploid fetus had semilobar holoprosencephaly, normal facies, and an occipital encephalocele.

Overall, 48 of the 68 cases of holoprosencephaly (71%) were detected prenatally, with 1 case (an intrauterine death at 17 weeks' gestation) never having been screened by ultrasonography. Table III shows the significant improvement in prenatal diagnosis during the second half of the study period compared with the first half ($\chi^2 = 8.27$; $P < .01$). Overall, detection included 16 of 20 cases with abnormal fetal karyotype (80%), 20 of 33 cases in which chromosomes were proved to be normal (61%), and 12 of 15 cases in which the karyotype was not determined. The mean (±SD) gestational age at prenatal diagnosis of holoprosencephaly was 19.8 ± 4.4 weeks, with no statistically significant difference between the abnormal and normal karyotype groups (19.3 weeks and 20.2 weeks, respectively). Brain pathologic classifications are shown in Table IV, together with rates

Brain pathologic classification	*Other features*	*Outcome*
Alobar, n = 12 Semilobar, n = 1 Lobar, n = 1 Unknown, n = 1	All cases had other anomalies, typical of Patau syndrome	Termination of pregnancy, n = 10 Live birth, n = 3 Stillbirth, n = 1 Miscarriage, n = 1
Semilobar	Cystic hygroma, exomphalos, cleft	Termination of pregnancy
Alobar	Horseshoe kidney	Termination of pregnancy
Alobar	Cloacal anomalies, abnormal thumbs	Died (d 9)
Alobar	Cyclopia, ventricular septal defect, arch hypoplasia, talipes, malrotation of gut, absent lung lobation	Termination of pregnancy
Alobar	Micrognathia, malrotation of gut	Termination of pregnancy
Semilobar	Cebocephaly, renal agenesis, oligohydramnios sequence, polydactyly, vaginal agenesis	Termination of pregnancy
Alobar	Agnathia, distal arthrogryposis	Termination of pregnancy, n = 1 Miscarriage, n = 1
Semilobar	Posterior urethral valves, coloboma, choanal atresia, hemivertebrae	Died (d 2)
Alobar	Third sibling had cleft and agenesis of the corpus callosum with holoprosencephaly spectrum	Termination of pregnancy
Alobar	Third sibling had cleft and agenesis of the corpus callosum with holoprosencephaly spectrum	Termination of pregnancy
Semilobar	Hypotelorism, flat nose, microcephaly	Died (10 mo)
Semilobar	Midline cleft, microcephaly	Died (27 mo)
Semilobar	Unilateral cleft (mother had bilateral clefts repaired)	Severe delay at age 4 y
Semilobar	Encephalocele	Termination of pregnancy

of prenatal diagnosis and karyotype abnormality associated with each type.

Prenatal detection was achieved by second-trimester anomaly scan in 39 cases, by ultrasonography during the third trimester in 6 cases, and incidentally after amniocentesis performed because of maternal age in 3 cases of fetal trisomy. The principal ultrasonographic diagnoses pertained to the brain in 43 of the 45 scan-detected cases; the diagnosis was specified as holoprosencephaly in 30 cases (70%) and in a further 13 as ventriculomegaly (n = 5), brain cyst (n = 4), microcephaly (n = 2), or encephalocele (n = 2). In 2 other cases lethal anomalies were diagnosed (trisomy 18 with cystic hygromas and bilateral renal agenesis), and holoprosencephaly was diagnosed only at postmortem examination.

In the group with a confirmed normal karyotype, 90% had an abnormal facial phenotype, with abnormalities of the lip and palate (33%) occurring less frequently than those of the eyes or nose (both 60%). Nonfacial congenital anomalies were also found in 70% (23/33) of this euploid group, with most having a skeletal anomaly (Fig 1). All the fetuses with chromosomal abnormalities had other anomalies in addition to those of the face and brain.

Twenty-four (35%) infants were born alive, and 2 (3%) were stillborn at ≥24 weeks' gestation. Of these, 9 had the condition diagnosed prenatally (5 detected only in the third trimester), and 3 were twins with an apparently normal co-twin. All but 1 of the 26 had antenatal ultrasonographic scans performed, with 1 affected infant not being detected despite 5 scans. Of the 24 live-born infants, 8 died within the first 24 hours and a further 6 (including all 4 with an abnormal karyotype) died within the neonatal period. Thus 10 (42% of live-born infants) survived the first month (Table V), and 7 (29% of live-born infants and 35% of euploid live-born infants) were alive at 1 year. All 5 of the affected children currently alive (aged 2-6 years) have global developmental delay.

Comment

This study represents the first population-based survey of holoprosencephaly prevalence that includes all cases in which pregnancy was terminated after prenatal diagnosis. The total prevalence of holoprosencephaly (live births, stillbirths at >24 weeks' gestation, and terminations) was 1.20 cases/10,000 births and terminations, the same figure as in a population-based study from California[10] with only slightly differing inclusion criteria (terminations and fetal losses at >20 weeks' gestation). A recent prevalence figure from another racially diverse population in Hawaii was also similar at 1.09 cases/10,000 births

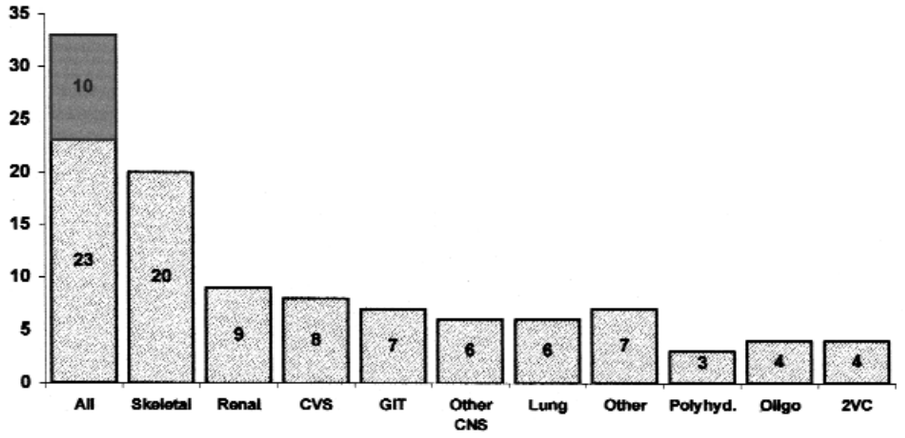

Fig 1. Distribution of nonfacial anomalies in cases of holoprosencephaly without chromosomal abnormality (n = 33), including prenatal diagnosis, autopsy, and neonatal data. *Dark gray bar,* No nonfacial anomalies; *light gray bars,* other anomalies. *CVS,* Cardiovascular system; *GIT,* gastrointestinal tract; *CNS,* central nervous system; *polyhyd.,* polyhydramnios; *oligo,* oligohydramnios; *2VC,* two-vessel cord.

Table IV. Brain pathologic classifications of holoprosencephaly and their relation to prenatal diagnosis and karyotype abnormality

	Total		*Prenatal diagnosis*		*Karyotype*		
	No.	*%*	*No.*	*%*	*Normal*	*Abnormal*	*Unknown*
Alobar	45	66	37	82	19	16	10
Semilobar	12	18	7	58	10	1	1
Lobar	3	4	1	33	2	1	
Unknown	8	12	3	38	2	2	4

and terminations.[18] Other total prevalence figures for holoprosencephaly have been lower: The reported prevalence in Scotland was 0.72 cases/10,000 births and terminations,[13] and that in Italy was 0.77 cases/10,000 births and terminations,[19] but neither survey was both from a single register source and population based. A previously published lower prevalence figure from the Northern Congenital Abnormality Survey register (1985-1990) of 0.8 cases/10,000 fetuses[17] (compared with 1.05 for 1985-1991 in this study) was the result of searching the database only for holoprosencephaly, which missed some cases of trisomy 13 that were picked up in this survey.

Although it was not statistically significant, the apparent change in total prevalence between the two halves of the study period (Table I) may well be a reflection of the increase in prenatal diagnosis during the latter half, as well as of corresponding improvements in postnatal imaging techniques. The fall in birth prevalence was not significant despite a substantial increase in the number of therapeutic terminations of pregnancy for holoprosencephaly, from 12 in the first half of the study to 26 in the second half.

The birth prevalence in our study of 0.49 cases/10,000 births differs significantly ($P < .01$) from that of Croen et al[10] (0.88 cases/10,000 births), which suggests either a marked difference in the rate of prenatal diagnosis or a lower uptake of termination of pregnancy after prenatal diagnosis at >20 weeks' gestation in California. Other recent birth prevalence figures derived from population-based birth-defect registers have ranged from 0.48 (live births only[12]) to 0.72 cases/10,000 births,[11] with little or no reference to the presence or influence of prenatal screening and diagnosis of holoprosencephaly.

Matsunaga and Shiota[20] recorded a prevalence of holoprosencephaly of 41 cases/10,000 gestations (150 cases) among embryos (<10 weeks' gestation) and early fetuses. The specimens in the Kyoto University collection were collected from low-risk women undergoing "social" termination of pregnancy and were not karyotyped. The reported birth prevalence of 0.97 cases/10,000 births in Japan at the time[21] is comparable to prevalences in other populations discussed. This suggests a marked natural loss of fetuses with holoprosencephaly, presumably mostly during the first trimester. There are a number of case reports of first-trimester ultrasonographic diagnosis of holoprosencephaly and from the growing literature on early ultrasonographic screening a suggestion of a

Table V. Infants with holoprosencephaly surviving beyond neonatal period

Birth year	*Brain pathologic classification*	*Initial diagnosis*	*Other features*	*Development*	*Outcome*
1992	Alobar	Ultrasonographic scan, seizures at <2 h old	Bilateral cleft lip and palate	Seizures never controlled; diabetes insipidus	Died on d 56; apneic episodes
1985	Not specified	Possible hydrocephalus on d 3			Died on d 95
1990	Semilobar	Abnormal facies*	Hypotelorism; flat nasal bridge	Possible aspiration; apneic episodes	Died at 10 mo; pneumonia
1996	Semilobar	Face, history,* ultrasonographic and computed tomographic scans on d 1	Midline cleft, head circumference <1st percentile	—	Died at 27 mo
1989	Semilobar	By plastic surgeons at 3 mo	Nasal "dermoid" with tract; mild hypotelorism		Died at 25 mo; holoprosencephaly cited
1997	Semilobar	Incidental scan related to prematurity on d 11	Head circumference tailing, now <3rd percentile	Global delay (not crawling); no seizures	Alive at 24 mo
1995	Semilobar		Unilateral cleft	Severe delay (cognitive and motor)	Alive at 4 y
1991	Lobar	Ultrasonographic scan related to prematurity and apnea	Plagiocephalic	Moderate global delay (walked at 2 y)	Alive at 4.5 y (moved from area)
1990	Lobar	Seizures from 4 d	Hypotelorism; single central incisor; small left nostril	Delay (walks with aids at 5 y; using sentences)	Alive at 5 y (not seen for examination since)
1993	Alobar	Referred by general practitioner for possible cerebral palsy at 5 mo	Nil	Severe learning difficulties; diabetes insipidus	Alive at 6 y

All had normal karyotypes; all were postnatal diagnoses.
*Siblings.

slightly higher prevalence of holoprosencephaly (2 cases from 6443 screened fetuses) at 10 to 14 weeks' gestation.[22] In our study 4 cases (a further 6%) were not included in the total prevalence figure because spontaneous loss occurred at <24 weeks' gestation; this finding supports the indication of a marginally higher prevalence at the end of the first trimester, although more data are undoubtedly required.

Only Whiteford and Tolmie[13] have previously quoted a figure for antenatal detection of holoprosencephaly in a population-based survey. However, their figure of 24% (euploid cases only) emanated from a period that largely predated routine ultrasonography. Our figure for prenatal diagnosis of 71% (mean gestational age at diagnosis of 19.8 weeks' gestation) for the entire study period resulted from a policy of second-trimester ultrasonographic screening. There was a significant improvement in detection from 52% to 86% in the second half of the study, by which time implementation of this policy had been extended to all women in the region. Developments in ultrasonographic equipment, improved training of sonographers, and accumulated experience also undoubtedly contributed to the increase in detection. The earliest in utero diagnosis, at 14 weeks' gestation, was made because of threatened miscarriage, whereas in contrast 6 cases were not suspected until the third trimester. Among the 48 fetuses with holoprosencephaly in which major abnormalities were detected prenatally, it is interesting that only 30 (62.5%) were specifically noted at that time as having holoprosencephaly. Only half of these cases were seen in a tertiary referral center, but presumably in other cases more precise antenatal diagnosis of the brain pathologic condition would not have altered decision making by parents.

We found 38% of karyotyped fetuses with holoprosencephaly to have a cytogenetically proven chromosomal abnormality, a figure comparable with other large surveys (39% in northern France[23] and 47% in California[10]). In common with the latter survey, in other cases holoprosencephaly was clinically designated as trisomy 13 but with no successful karyotype result, and these cases are not included in the previously cited figures. Autopsy is also often omitted or declined by parents in prenatally diagnosed cases of trisomy 13, and thus holoprosencephaly may still be underreported in this group. The chromosomal rearrangements described in our study are comparable with known rearrangements and gene mutations causing holoprosencephaly. Two cases (Table II) describe loss of material from 13q, with the case described as del(13)(q?33), probably deleting or affecting the holoprosencephaly

gene *ZIC2* located at 13q32.[5] In the de novo translocation case material was deleted from the 2p21 region, the location of holoprosencephaly disease gene *SIX3*.[4]

The high frequencies of chromosomal, syndromic, and familial cases of holoprosencephaly contrast with most major malformations, including other major central nervous system anomalies. This is of great importance for establishing recurrence risk. Our survey was purely observational, with no specific collection of clinical details about family members or active review of cases to determine retrospective syndromic diagnoses. Even so, significant numbers of cases of holoprosencephaly without chromosomal abnormalities were obviously familial (7%) or syndromic (6%), similar to the combined figure of 15% reported by Croen et al.[10] Not surprisingly, clinical geneticists have described higher percentages, with rates of 20% syndromic cases and 9% familial cases among 158 nonchromosomal cases collected by two regional genetic centers in France.[23] In clinical practice the exclusion of familial cases requires an appropriate history to be taken; relatives with mental retardation or a facial cleft may have manifestations of holoprosencephaly spectrum. It is also important that subtle physical signs, such as hypotelorism, a single central incisor tooth,[24] ocular coloboma,[24] or absent superior labial frenulum,[25] be excluded in both parents and siblings.

Even when a case of holoprosencephaly appears to be sporadic, the recurrence risk remains higher than with other major malformations. A figure of 6% was widely quoted for many years on the basis of relatively small numbers, but this estimate has since been superseded by the study of Odent et al.[23] From 79 sibships of nonchromosomal, nonsyndromic holoprosencephaly, Odent et al[23] predicted a recurrence risk of 13% to 14% after an isolated case.

In summary, holoprosencephaly is present in 1 in 8000 second-trimester pregnancies and is an important malformation that is eminently detectable by routine population screening. The common severe forms are associated with poor outcomes. Diagnosis and counseling regarding outcomes are well within the scope of interested obstetricians. However, the high incidence of syndromic and subtle familial cases and the high recurrence rates associated with apparently sporadic cases make full investigation by a perinatal pathologist, cytogeneticist, and clinical geneticist, together with appropriate counseling, absolutely essential.

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