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Fetal Holoprosencephaly: Associated Malformations and Chromosomal Defects

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Abstract. In 38 fetuses with holoprosencephaly, cordocentesis and blood karyotyping was performed. The karyotype was normal in all 12 cases with isolated holoprosencephaly, and in all 5 with holoprosencephaly and facial defects only. In contrast, 11 of the 21 (52%) fetuses with extrafacial malformations were chromosomally abnormal [47xx+13, n = 6; 47xy+13, n = 2; 47xx+18, n = 1; 46xx–18+i(18q), n = 1; 46xy 21q$^-$, n = 1]. In the chromosomally normal group, there was parental consanguinity in 2 cases and recurrence of holoprosencephaly in 3.

Introduction

Holoprosencephaly, with an incidence of 0.6–1.9 per 10,000 births [1, 2], encompasses a heterogeneous group of cerebral malformations resulting from either failure or incomplete cleavage of the forebrain. Prenatal diagnosis by ultrasonography is based on the demonstration of a single dilated midline ventricle replacing the two lateral ventricles. Although confident diagnosis may require the additional demonstration of facial abnormalities, such as hypotelorism, these are not always present [3].

Data on antenatally diagnosed holoprosencephaly is mainly derived from reports of single cases, with the three largest series reporting on 5–14 cases [3–5]. Nevertheless, these reports have established an association with facial and other malformations as well as chromosomal defects (table 1). This study extends knowledge on antenatally diagnosed

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holoprosencephaly and reports the findings of associated malformations and chromosomal defects in 38 cases.

Patients and Methods

During a 4-year period (1986–1990), fetal blood karyotyping was performed in 38 patients referred to our centre at 16–36 (mean = 24) weeks' gestation for further assessment, because of the detection of fetal brain malformation by ultrasound examination at the referring hospital.

The diagnosis of holoprosencephaly was made by ultrasonographic demonstration of either a monoventricular cavity or partial segmentation of the ventricles, in the standard transverse view of the fetal head for measurement of the biparietal diameter. In addition a systematic search was made for the detection of any associated facial and other malformations (Aloka SSD-650 or Hitachi EUB 340, 3.5 or 5-MHz curvilinear transducer). Subsequently, the parents gave informed consent for rapid fetal karyotyping, which was performed by cytogenetic analysis of fetal blood obtained by cordocentesis.

The results of the ultrasound examinations and fetal karyotype were given to the referring obstetricians, who undertook the further management of the patients. Details on the outcomes of pregnancies were obtained from the referring hospitals.

Results

The prenatal findings and outcome of the 38 fetuses with holoprosencephaly are shown in tables 1 and 2. Facial defects were detected in 19 (50%) of the cases. These included facial cleft (n = 14), absent nose, single nostril or proboscis (n = 11), and cyclopia or severe hypotelorism (n = 5). The most common extrafacial abnormalities were defects of the extremities (n = 13), kidneys (n = 10), and heart (n = 6).

Post-mortem examination revealed 5 fetuses in which one of multiple malformations was not detected antenatally. The latter

Table 1. Summary of major series on antenatally diagnosed holoprosencephaly providing data on the presence of associated malformations and chromosomal defects

		Filly et al. [4]	Chervenak et al. [3]	Nyberg et al. [5]	Present series
Number of cases		5	7	14	38
Facial cleft		0	0	3	14
Extrafacial defects		0	1	4	21
Abnormal karyotype[a]		1/?	4/?	6/11	11/38
Outcome	TOP	1	0	5	29
	IUD	3	3	2	3
	PND	1	4	5	4
	Alive	0	0	2	2

In parentheses are the findings from post-mortem examination. TOP = Termination of pregnancy; IUD = intra-uterine death; PND = postnatal death.

[a] Trisomy 13, n = 7; triploidy, n = 1; deletion 13q, n = 2; duplication 5p, n = 1.

[b] Trisomy 13, n = 8; trisomy 18, n = 1; 46 XX – 18 + i (18q), n = 1; deletion 21q, n = 1.

Table 2. Gestation at diagnosis (GA), ultrasound findings, karyotype and outcome (TOP = termination of pregnancy, NND = neonatal death) of fetuses with holoprosencephaly

Case No.	GA	Facial abnormalities				Extrafacial abnormalities			Karyotype	Outcome
		FC	nose	eyes	skeletal	renal	CHD	other		
1	31								46 XX	IUD
2	32								46 XX	TOP
3	32								46 XX	alive
4	36								46 XX	IUD
5	36								46 XY	TOP
6	18								46 XY	TOP
7	20								46 XY	TOP
8	20								46 XY	TOP
9	22								46 XY	TOP
10	26								46 XY	TOP
11	26								46 XY	TOP
12	27								46 XY	alive
13	17	Y	A (1N)	H					46 XX	TOP
14	18	Y	A						46 XX	TOP
15	19		P	H					46 XX	TOP
16	32	Y	A						46 XX	NND
17	32	Y	A						46 XX	NND
18	22			H	talipes	H_1-H_1		scalp oedema	46 XX	TOP
19	23				rocker-bottom feet		(CHD)	CHD	46 XX	TOP
20	35				talipes	H_1-H_1			46 XX	NND
21	19	Y				(RA)	CHD		46 XY	TOP
22	22			H		H_1-H_1			46 XY	TOP
23	23	Y				H_1-H_1			46 XY	TOP
24	23				sandal gap	H_1-H_1			46 XY	TOP
25	24	Y	A		talipes				46 XY	TOP
26	24		1N	H					46 XY	TOP
27	27				(polydactyly)				46 XY	NND
28	16	Y	A	cyclops				EXOM-B	47 XX + 13	TOP
29	19	Y	A	H	polydactyly	H3	CHD		47 XX + 13	TOP
30	20	Y			polydactyly	H3			47 XX + 13	TOP
31	21		A (1N)		polydactyly				47 XX + 13	TOP
32	21					RA-RA	CHD		47 XX + 13	TOP
33	21	Y	A				CHD		47 XX + 13	TOP
34	18	Y			polydactyly	H_1-H_1			47 XY + 13	TOP
35	20	Y			talipes		CHD	EXOM-B	47 XY + 13	TOP
36	27	Y			overlapping fingers	RA	CHD	CDH, cord 2V	47 XY + 18	TOP
37	19				rocker-bottom feet				46 XX– 18 + i(18q)	TOP
38	20	Y					CHD	(cord 2V)	46 XY,21q–	TOP

Facial defects included facial cleft (FC), absent nose (A), single nostril (1N) or proboscis (P) and hypotelorism (H) or cyclops. Extrafacial abnormalities included mild (H_1) and severe hydronephrosis (H_3), renal agenesis (RA), congenital diaphragmatic hernia (CDH), congenital heart disease (CHD), exomphalos containing bowel (EXOM-B) and umbilical cord with two vessels (2V). The additional defects detected at post-mortem examination are given in parentheses.

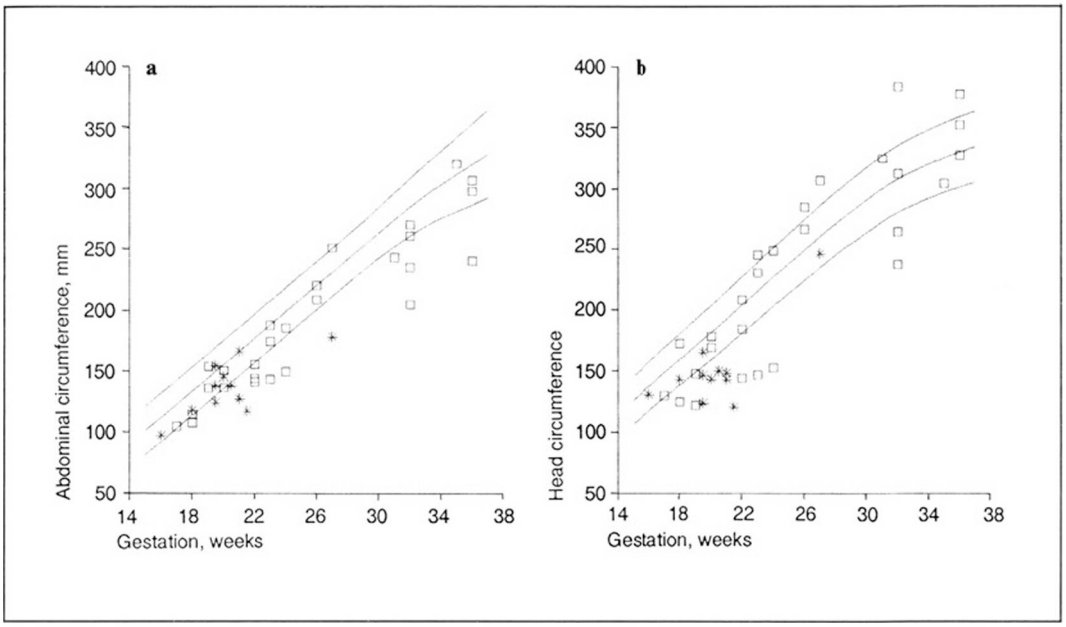

Fig. 1. Head circumference (**a**) and abdominal circumference (**b**) in 38 fetuses with holoprosencephaly that were karyotyped antenatally, plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation.

included 1 case each of ventricular septal defect, cleft palate, polydactyly, unilateral renal agenesis and umbilical cord with two vessels. Some fetuses also had abnormalities that are not amenable to prenatal diagnosis by ultrasonography, such as ambiguous genitalia, displaced anus, malrotation of the gut or bicornuate uterus. There was 1 false-positive finding of a sandal gap.

The fetal karyotype was normal in 71% (n = 27) of the fetuses, 13 male and 14 female, and abnormal in 29% (n = 11). The abnormalities were: 47 XX + 13, n = 6; 47 XY + 13, n = 2; 47 XX + 18, n = 1; 46 XX – 18 + i(18q), n = 1; 46 XY, 21q–, n = 1. None of the 12 fetuses with isolated holoprosencephaly had chromosomal abnormalities. Similarly, no abnormal karyotypes were found in the 5 cases in which holoprosencephaly was accompanied by facial defects only. In contrast, 11 (52%) of the 21 fetuses with extrafacial defects were found to be chromosomally abnormal.

The abdominal circumference was below the mean for gestation in 84% (32 of 38) of the fetuses; in 24% it was below the 2.5th centile (fig. 1). There was no obvious difference in the degree of growth retardation between the chromosomally abnormal and normal fetuses with holoprosencephaly. There was a significant trend for change from microcephaly to macrocephaly with advancing gestation (fig. 1; $r = 0.41$, $n = 38$, $p < 0.05$). Thus, in the 25 fetuses diagnosed before 26 weeks, the head circumference was below the 2.5th centile in 13 (52%) and

above the 97.5th in 1. In contrast, in the 13 fetuses diagnosed at ≥ 26 weeks, the head circumference was above the 97.5th centile in 5 (38%) and below the 2.5th in 2 (15%).

The mean maternal age in the group with chromosomally abnormal fetuses (28, range 21–40 years) was not significantly different ($t = -0.31$) from that of pregnancies with chromosomally normal fetuses (29, range 21–42 years). All but 1 of the chromosomally abnormal fetuses were referred at <22 weeks' gestation and risk factors for chromosomal abnormalities had been identified in only 2 cases: in 1 the mother was >35 years and in another there was threatened abortion in early pregnancy.

The chromosomally normal fetuses with holoprosencephaly were referred at 17–36 (mean = 26) weeks' gestation. Risk factors for fetal abnormalities were identified in 12 (44%) of the 27 pregnancies. These included parental consanguinity (n = 2), previous pregnancy complicated by fetal holoprosencephaly (n = 3), maternal thyrotoxicosis treated with carbimazole (n = 1), previous spontaneous abortions (n = 7) and threatened abortion in the present pregnancy (n = 10) [6].

In the 38 cases with holoprosencephaly, there were 29 elective terminations of pregnancy, 3 intra-uterine and 4 neonatal deaths. Two infants with semilobar holoprosencephaly, treated with postnatal shunting, are alive at 1 and 2 years of age, respectively; both are severely mentally retarded.

Discussion

Fetal holoprosencephaly is associated with a high incidence of other morphological (68%) and chromosomal defects (29%). Furthermore, the incidence of chromosomal abnormalities is strongly related to the presence of multisystem malformations. Thus, none of the fetuses with isolated holoprosencephaly, as opposed to 52% of those with extrafacial malformations, had chromosomal defects. This is not surprising, because the most commonly found chromosomal defect was trisomy 13, which is usually associated with multisystem malformations that are easily recognizable by diligent ultrasonographic examination.

There was a high (40%) overall incidence of threatened abortions in this group of pregnancies with fetal holoprosencephaly. Furthermore, the incidence of threatened abortions was higher in the group with chromosomally normal (33%) than abnormal (18%) fetuses. It is possible that morphologically and chromosomally abnormal fetuses indeed abort during episodes of 'threatened abortion', whereas morphologically abnormal but chromosomally normal fetuses tend to survive. This may also explain the observation that the incidence of chromosomal abnormalities was much higher in cases referred <22 weeks (59%) than those seen after this gestation (5%).

Although growth retardation is a common feature of chromosomally abnormal fetuses, measurement of the fetal abdominal circumference was not a useful predictor of trisomy, because many of the chromosomally normal fetuses were also growth-retarded. The present study has demonstrated that abnormal brain development leads to microcephaly in early pregnancy, but with advancing gestation progressive macrocephaly develops, presumably due to the disturbed cerebrospinal fluid dynamics. This finding is compatible with the progressive cerebral ventriculo-

Table 3. Estimated risk of recurrence in 38 cases of holoprosencephaly

Case No.	History				Ultrasound findings	Fetal karyotype	Recurrence risk, %
	age	CONS	PrH	POH			
1	40			2 (1)	isolated	normal	> 6
2	36			0	isolated	normal	< 6
3	27			7 (1)	isolated	normal	> 6
4	27			1	isolated	normal	< 6
5	23	+		1 (1)	isolated	normal	~ 25
6	33			0	isolated	normal	< 6
7	30			3	isolated	normal	< 6
8	27			0	isolated	normal	< 6
9	31			0	isolated	normal	< 6
10	32			0	isolated	normal	< 6
11	24			0	isolated	normal	< 6
12	23			2 (2)	isolated	normal	> 6
13	30			2	+ facial	normal	< 6
14	31		+	2 (1)	+ facial	normal	~ 25
15	24			1	+ facial	normal	< 6
16	26			1	+ facial	normal	< 6
17	21			0	+ facial	normal	< 6
18	27			0	+ other	normal	> 6
19	31			2	+ other	normal	> 6
20	29			4 (1)	+ other	normal	> 6
21	34		+	3 (1)	+ other	normal	~ 25
22	21			0	+ other	normal	> 6
23	42			0	+ other	normal	> 6
24	32		+	8 (2)	+ other	normal	~ 25
25	26	+		0	+ other	normal	~ 25
26	21			1	+ other	normal	> 6
27	32			5 (2)	+ other	normal	> 6
28	24			0	+ other	abnormal	~ 1
29	23			0	+ other	abnormal	~ 1
30	30			1 (1)	+ other	abnormal	~ 1
31	25			0	+ other	abnormal	~ 1
32	27			0	+ other	abnormal	~ 1
33	24			0	+ other	abnormal	~ 1
34	33			1	+ other	abnormal	~ 1
35	33			2	+ other	abnormal	~ 1
36	40			2	+ other	abnormal	~ 2
37	31			1	+ other	abnormal	? 1
38	21			0	+ other	abnormal	~ 1

In cases of primary trisomy the risk is approximately 1%, and in those with parental consanguinity (CONS) and previous fetus with holoprosencephaly (PrH) the risk may be 25% or more. For sporadic, non-chromosomal holoprosencephaly, the empirical recurrence risk is 6% [2]. However, within this group, in the 7 cases with fetal extrafacial defects and in the 3 with previous spontaneous abortions and/or intra-uterine deaths (in parentheses under previous obstetric history; POH) the parents should be cautioned that the risk may be higher.

megaly observed in fetuses with open spina bifida [7].

Previous studies have established criteria for the prenatal sonographic differential diagnosis between alobar and semilobar holoprosencephaly [3–5]. However, both types of holoprosencephaly are uniformly fatal or associated with severe mental retardation. Therefore, the main aim of further investigations is to determine risk of recurrence and plan for management of any subsequent pregnancies.

The risk of recurrence in cases of primary trisomy is less than 1%, while in the presence of a parental balanced translocation the risk is 12–30%, depending on the breakpoints of the translocation and the chromosomes involved (table 3). In the group without chromosomal defects, the presence of associated malformations may lead to the diagnosis of a syndrome with a known mode of inheritance. In others, parental consanguinity or a history of affected siblings would suggest a genetic, probably autosomal recessive inheritance and the risk of recurrence might be as high as 25%. For sporadic, non-chromosomal holoprosencephaly, an empirical recurrence risk of 6% has been derived [2, 8].

Therefore, in our group of 38 cases, the risk of recurrence would be (i) approximately 1% in the 11 (29%) with mutant fetal chromosomal defects, although 1 case of recurrence of isochromosome 18q has been reported in normal parents [9], (ii) up to 25% in the 5 (13%) with parental consanguinity or previous pregnancies with fetal holoprosencephaly, and (iii) 6% in the remaining 22 (58%) cases. However, within the latter group, there were 7 with extrafacial defects but normal karyotype and in these cases the parents could be cautioned that the risk may be higher because of a possible genetic syndrome, including recessive, dominant, or X-linked condition [8]. Nevertheless, the exact risk of recurrence may not be clear until the molecular genetic basis for holoprosencephaly has been elucidated. Management of subsequent pregnancies would include fetal karyotyping for those at high risk of chromosomal defects and ultrasound examinations, from the first trimester, expecially for those at high risk of recurrence of holoprosencephaly.

This study has confirmed the need for both detailed sonographic examination and karyotyping of malformed fetuses [10]. Furthermore it demonstrates that chromosomal abnormalities are usually associated with multisystem malformations, whether the primary sonographic defect is small, such as choroid plexus cyst, or large, such as holoprosencephaly [11].

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Note Added in Proofs

At the end of January 1991 49 fetuses with holoprosencephaly were karyotyped. Chromosomal defects were found in 12 of the 26 (46%) with extrafacial malformations but in none of the 23 with either isolated holoprosencephaly or with facial defects only.

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