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Fetal Lateral Cerebral Ventriculomegaly: Associated Malformations and Chromosomal Defects

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Abstract. In 267 consecutive cases of fetal lateral cerebral ventriculomegaly, additional fetal malformations were detected by ultrasonography in 209 (78%) of the cases. On the basis of the ultrasound findings, the patients were subdivided into three groups: (i) isolated ventriculomegaly (n = 58), (ii) ventriculomegaly and open spina bifida only (n = 172), and (iii) ventriculomegaly and other malformations (n = 37) with or without spina bifida. Antenatal karyotyping was performed in 64 cases from groups (i) and (iii), and 11 (18%) of the fetuses had chromosomal abnormalities. The incidence of chromosomal abnormalities was strongly related to the presence of multisystem malformations. Thus, only 3% of fetuses with isolated ventriculomegaly as opposed to 36% of those with additional malformations had chromosomal defects. Furthermore, the degree of ventriculomegaly in the chromosomally abnormal fetuses was relatively mild. In the chromosomally normal fetuses, mild, static ventriculomegaly was associated with apparently normal subsequent mental development.

Introduction

Congenital hydrocephalus, with an incidence of 5–25 per 10,000 births, may result from genetic aberrations or congenital infection, although the majority of cases have no clear-cut etiology. Prenatal diagnosis by ultrasonography is based on the demonstration of dilated lateral cerebral ventricles. Previous reports on fetal hydrocephalus have established an association with chromosomal defects (table 1) [1–9]. However, in many of these studies there were no strict criteria for the diagnosis of hydrocephalus and they included other brain abnormalities, such as ho-

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Table 1. Summary of reports on antenatally diagnosed hydrocephalus providing data on the presence of other defects

Author	Reference	n	Other defects						Abnormal karyotype[a]		Alive %
			total		HOLO		NTD				
			n	%	n	%	n	%	n	%	
Chervenak et al., 1985	1	53	44	83			15	28	4/NR[a]		28
Cochrane et al., 1984	2	41	32	78	3	7	15	37	1/NR[a]		34
Pretorius et al., 1985	3	40	28	70	1	3	13	33	2/7[a]	29	15
Pilu et al., 1986	4	30	9	30					3/30[a]	10	NR
Serlo et al., 1986	5	38	32	84	1	3			4/NR[a]		26
Nyberg et al., 1987	6	61	51	84	13	21	23	38	2/21[a]	10	16
Vintzileos et al., 1987	7	20	16	70	1	5	6	30	2/19[a]	11	45
Hudgins et al., 1988	8	47	35	74	15	32			1/47[a]	2	40
Drugan et al., 1989	9	43	31	72	3	7	18	42	5/19	26	44
Present study		267	209	78			184	67	11/64[b]	18	9

HOLO = Holoprosencephaly; NTD = neural tube defects. Under 'Abnormal karyotype', data is provided, where possible, only for cases without holoprosencephaly.

[a] Trisomy 13, n = 2; trisomy 18, n = 7; ring 18, n = 1; trisomy 21, n = 4; 46 XY/48 XY +7+8, n = 1; duplication 4p, n = 1; deletion 7q, n = 1; triploidy, n = 1; Turner's syndrome, n = 1.

[b] Trisomy 13, n = 1; trisomy 18, n = 1; trisomy 21, n = 1; 48 XYY+21, n = 1; duplication 9p, n = 1; triploidy, n = 6.

loprosencephaly or porencephalic cysts. Furthermore, data on the number of fetuses karyotyped, the presence of other defects, and the selection criteria used for undertaking this investigation were not clearly defined; the incidence of chromosomal defects varied from 2 to 29%. This study reports the findings in 267 consecutive cases of fetal cerebral ventriculomegaly, including 64 in which antenatal karyotyping was performed.

Patients and Methods

During a 5-year period (1985–1989), fetal lateral cerebral ventriculomegaly was diagnosed in 267 patients referred to our centre at 15–38 (mean = 23) weeks' gestation for further assessment, because of raised maternal serum alpha fetoprotein or the detection of fetal malformations by ultrasound examination at the referring hospital. The mean maternal age was 27 (range 17–41) years.

The diagnosis of ventriculomegaly was made if the ratios of the width of the anterior and/or posterior horn of the lateral cerebral ventricle to that of the cerebral hemipshere were above the 95th centile of our reference ranges for gestation [10]. The ventricles were examined in the section of the fetal head that is used routinely in our centre for measuring the biparital diameter. This is a transverse plane of the brain that shows a central midline echo broken in the anterior third by the cavum septi pellucidi and in which both the anterior and posterior horns of the lateral ventricles can be visulaized. In 217 cases both the anterior and posterior ventricles were dilated, while in 9 cases there was anterior and in 41 posterior ventriculomegaly only (fig. 1).

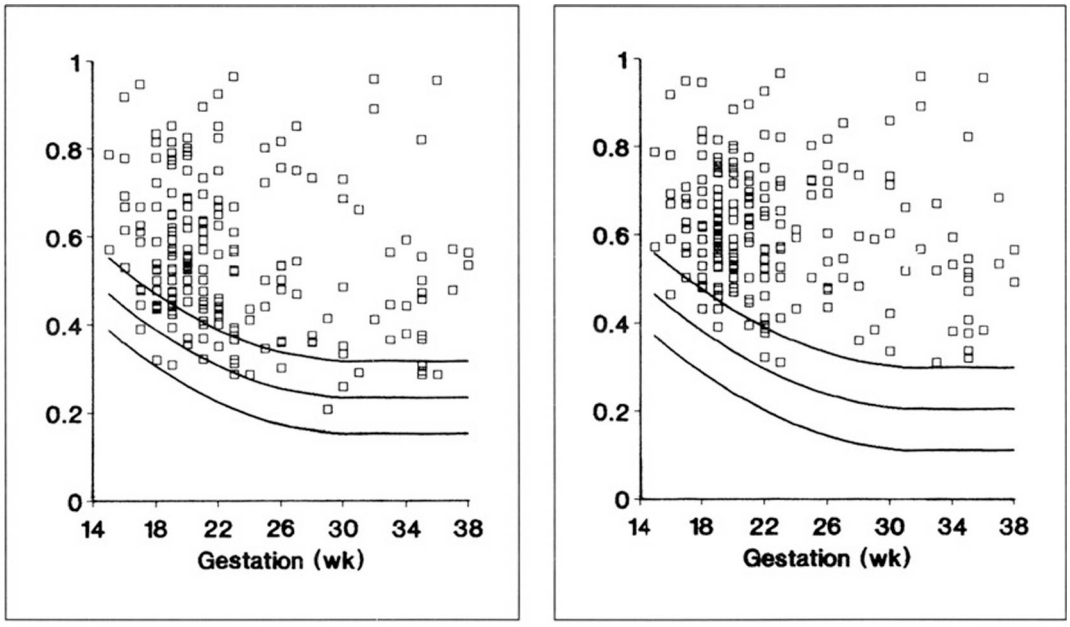

Fig. 1. Anterior (**a**) and posterior (**b**) lateral cerebral ventricle-to-hemisphere ratio in 267 fetuses with ventriculomegaly, plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation. In 217 cases both the anterior and posterior ventricles were dilated, while in 9 cases there was anterior and in 41 posterior ventriculomegaly only.

Subsequently, a systematic ultrasound examination was performed (Aloka SSD-650 or Hitachi EUB 360, 3.5- or 5-MHz curvilinear transducer) for the detection of any associated malformations. On the basis of our ultrasound findings, the patients were subdivided into three groups: (i) isolated ventriculomegaly (n = 58), but including 1 fetus with micrognathia that was postnatally diagnosed as having Pierre Robin syndrome and another that was thought to have isolated ventriculomegaly but was postnatally found to have Goldenhar's syndrome; (ii) ventriculomegaly and open spina bifida only (n = 172), and (iii) ventriculomegaly and other malformations (n = 37) with or without spina bifida.

In groups (i) and (iii) fetal karyotyping was offered to the parents and 36 of 58 and 28 of 37, respectively, gave their consent; Gosden et al. [11] had previously demonstrated the lack of association between fetal spina bifida (group ii) and chromosomal abnormalities. Rapid prenatal karyotyping was performed by cytogenetic analysis of fetal blood obtained by cordocentesis [12].

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

Karyotype

In the group of fetuses with isolated ventriculomegaly who underwent cordocentesis, the karyotype was abnormal in one (3%; 47 XX + 21) and normal in 34 (46 XY, n = 16; 46 XX, n = 18). The prenatal find-

Table 2. Gestation age at diagnosis (GA, weeks), ultrasound findings, karyotype and outcome (TOP = termination of pregnancy, IUD = intra-uterine death, NND = neonatal death) of fetuses with ventriculomegaly and other abnormalities including mild (H_1), moderate (H_2) and severe (H_3) hydronephrosis, multicystic kidneys (P_2) and renal agenesis (RA), hydrops (Hyd), spina bifida (SB), congenital diaphragmatic hernia (CDH), congenital heart disease (CHD), exomphalos (Exo)

Case No.	GA	Abnormalities								Karyotype	Outcome
		SGA	Hyd	SB	CDH	CHD	Exo	renal	other		
1	19	Y			Y				syndactyly, micrognathia	69 XXX	TOP
2	20	Y		Y					syndactyly	69 XXY	TOP
3	20	Y				Y			syndactyly, molar placenta	69 XXX	TOP
4	22	Y							syndactyly	69 XXX	TOP
5	22	Y							syndactyly	69 XXX	TOP
6	22	Y		Y					syndactyly, talipes, micrognathia	69 XXX	TOP
7	18							H_2-H_2		47 XY + 13	TOP
8	23					Y			overlapping fingers	47 XY + 18	TOP
9	18	Y		Y					talipes, facial cleft	46 XX, 9q+	TOP
10	22					Y			talipes	48 XYY + 21	TOP
11	16	Y						P_2-P_2		46 XY	TOP
12	17							P_2-P_2		46 XY	TOP
13	19				Y	Y		H_1-H_1	overlapping fingers	46 XY	TOP
14	19	Y							overlapping fingers, facial cleft	46 XY	TOP
15	20				Y	Y	Y	H_1-H_1		46 XY	TOP
16	20							N-RA		46 XY	TOP
17	20		Y							46 XY	IUD
18	21			Y		Y		RA-RA	kyphoscoliosis, nuchal oedema	46 XY	TOP
19	22		Y							46 XY	TOP
20	24								asphyxiating thoracic dystrophy	46 XY	TOP
21	25		Y							46 XY	TOP
22	29							N-H_2		46 XY	TOP
23	33		Y							46 XY	NND
24	18			Y	Y					46 XY	IUD
25	19			Y			Y		talipes	46 XX	TOP
26	21	Y								46 XX	TOP
27	22					Y	Y	H_2–H_3	talipes	46 XX	TOP
28	27	Y						P_2–P_2	prominent forehead	46 XX	TOP
29	35	Y		Y					small bowel obstruction		IUD
30	35		Y								IUD
31	29			Y			Y				IUD
32	25	Y		Y				H_1–H_2	talipes		TOP
33	21	Y						RA-RA	kyphoscoliosis		TOP
34	20			Y				H_1–H_1			NND
35	20			Y				RA-RA			TOP
36	20			Y			Y				TOP
37	18		Y								TOP

SGA = Small for gestational age.

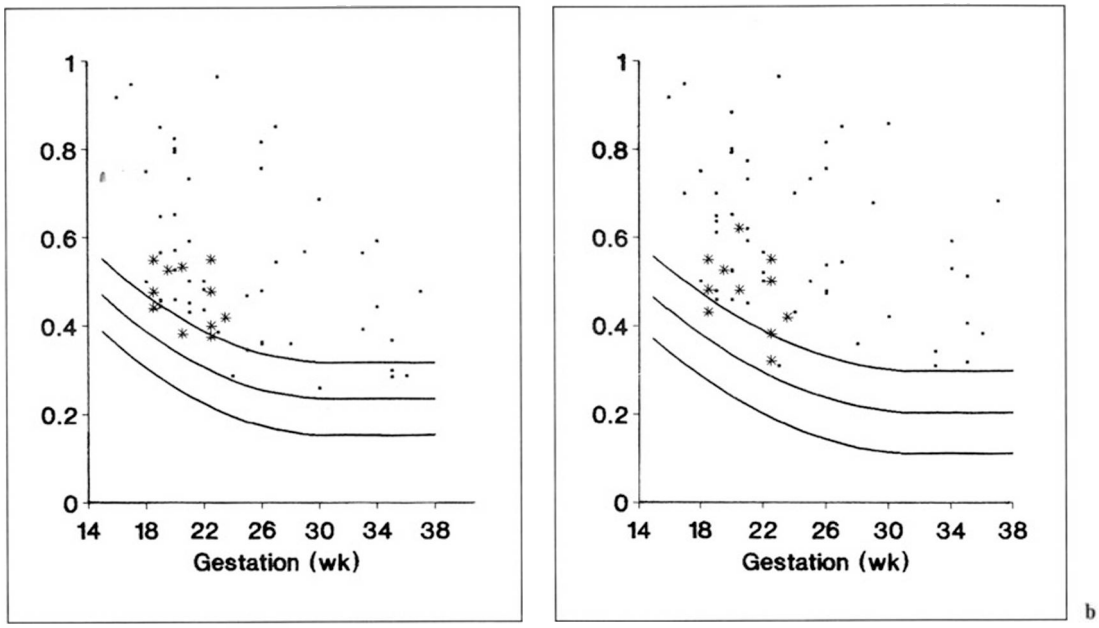

Fig. 2. Anterior (**a**) and posterior (**b**) lateral cerebral ventricle-to-hemisphere ratio in 64 fetuses with ventriculomegaly that were karyotyped antenatally, plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation. The chromosomally abnormal fetuses (*) tended to have mild ventriculomegaly.

ings in the 37 pregnancies with fetal ventriculomegaly and multiple malformations are shown in table 2. In the subgroup who underwent cordocentesis (n = 28), the karyotype was abnormal in 10 (36%) and normal in 18. In one of the latter (case 13), fibroblast culture from samples of skin taken at post-mortem examination demonstrated Pallister-Killian syndrome [46, XY/47 XY + i(12p)].

In general, the chromosomally abnormal fetuses had mild ventriculomegaly (fig. 2). The mean maternal age of the chromosomally abnormal fetuses (31.5, range 20–40 years) was significantly higher ($t = 2.29$, $p < 0.05$) than that of the chromosomally normal fetuses (27.5, range 18–38 years).

Survival

The outcome of pregnancies in the three groups of fetuses with ventriculomegaly is summarized in table 3. There were no survivors among the fetuses with multiple abnormalities. In the group with isolated ventriculomegaly, there were 19 live births and all infants are presently alive (mean age = 2 years; range 3 months to 4 years). This group includes 1 infant with Pierre Robin syndrome, 1 with Goldenhar's syndrome and 1 with deletion of the short arm of chromosome 6. In 7 of the cases the diagnosis of ventriculomegaly was made before 28 weeks' gestation and the parents decided to continue with the pregnancy because serial ultrasound examinations demonstrated mild and static

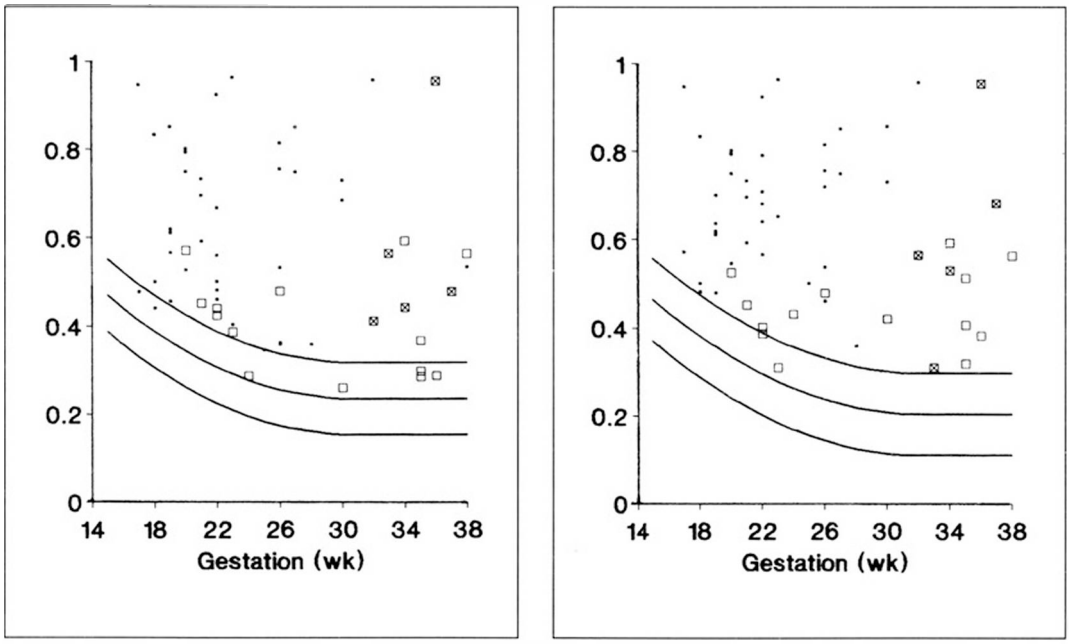

Fig. 3. Anterior (**a**) and posterior (**b**) lateral cerebral ventricle-to-hemisphere ratio in the 58 fetuses with isolated ventriculomegaly, plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation. There were 19 survivors (□) and 5 of the infants required shunting (×). In 7 of the cases, mild, static ventriculomegaly was diagnosed before 28 weeks' gestation.

disease; postnatally, the diagnosis was confirmed but none of the infants required shunting (fig. 3). In the 12 cases diagnosed after 28 weeks, the degree of ventriculomegaly was not predictive of either the need for postnatal shunting or mental development.

In the 172 cases with ventriculomegaly and open spina bifida but no other abnormalities, there were 13 live births. Of the latter, 3 babies died in the neonatal period, and 3 died at the age of 1, 6 and 18 months, respectively. The mean age of the surviving children is 3 years (range 1–5 years). The main determinant of survival was gestation at diagnosis, because the vast majority of pregnancies diagnosed at <28 weeks were terminated. There was no obvious difference in the degree of ventriculomegaly of infants that survived compared to that in postnatal deaths (fig. 4).

Development

Developmental follow-up was available in 18 of the 19 surviving infants in group (i). Mental development was apparently normal in 12 (67%), although 2 of these infants suffer from seizures (table 4). In the 6 surviving infants with ventriculomegaly and open spina bifida but no other abnormalities, mental development was apparently normal, although in all cases there was motor impairment in the lower limbs.

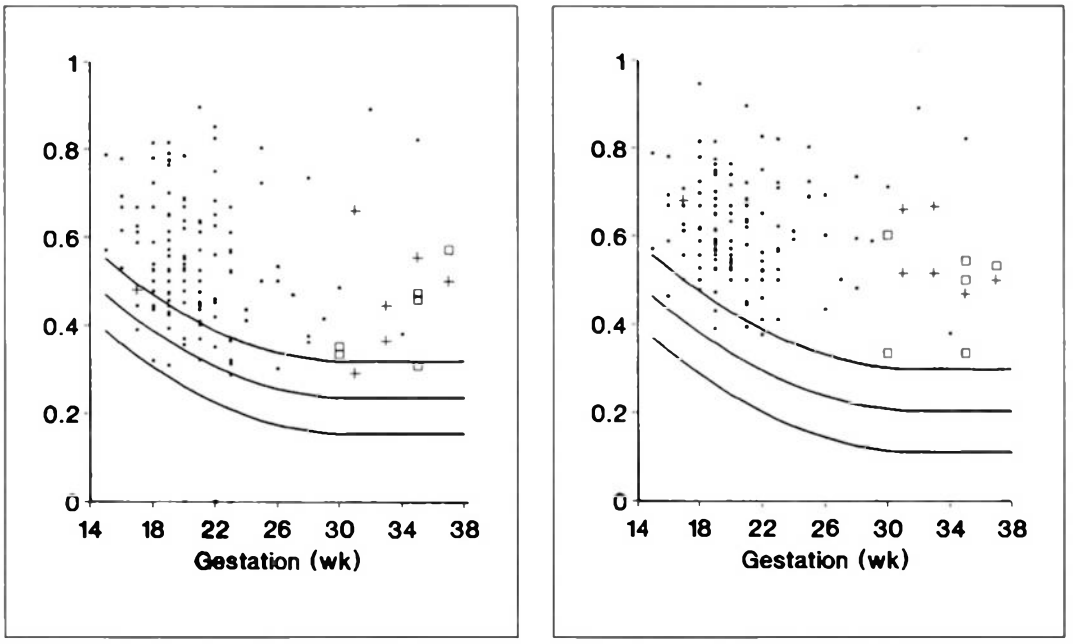

Fig. 4. Anterior (a) and posterior (b) lateral cerebral ventricle-to-hemisphere ratio in 172 fetuses with ventriculomegaly and open spina bifida but no other abnormalities, plotted on the appropriate reference range (mean, 5th and 95th centiles) for gestation. There were 159 terminations of pregnancy or intra-uterine deaths (·). There was no obvious difference in the degree of ventriculomegaly of infants that survived (□), compared to that in postnatal detahs (+).

Table 3. Lateral cerebral ventriculomegaly

Ventriculomegaly	n	TOP	IUD	DEAD	Alive	
					n	%
Isolated	58	28	10	0	19	33
Karyotyping	36	15	6	0	15	
No karyotyping	22	14	4	0	4	
With spina bifida	172	153	6	4 + 3*	6	3
With multiple defects	37	30	5	2	0	0
Karyotyping	28	25	2	1	0	
No karyotyping	9	5	3	1*	0	

There were 212 elective terminations of pregnancy (TOP), 21 intra-uterine deaths (IUD), and 34 live births. In the latter, there were 5 neonatal and 4 postneonatal (*) deaths (DEAD).

Table 4. Developmental follow-up in 18 of the 19 surviving infants with antenatally diagnosed lateral cerebral ventriculomegaly

Case No.	Gestation		Shunt		Mental development	
	scan	birth	age			age, months
1	20[a]	38	no		normal	12
2	21[a] (PR)	37	no		normal	6
3	22[a]	39	no		normal	30
4	22[a] (G)	37	no		normal	6
5	23[a]	39	no		normal	12
6	24[a]	36	no		normal	12[b]
7	26[a]	40	no		normal	12
8	30	36	no		moderate delay	18
9	35	39	no		normal	18[b]
10	35	40	no		normal	3
11	35	38	no		normal	12
12	36	39	no		severe delay	3[c]
13	38	39	no		moderate delay	12
14	32	38	yes	6 months	normal	24
15	33	34	yes	9 weeks	moderate delay	36[b]
16	34	38	yes	1 month	mild delay	24[b]
17	36	38	yes	3 years	severe delay	48
18	37	40	yes	2 weeks	normal	9

This group includes 1 infant with Pierre Robin syndrome (PR), and 1 with Goldenhar's syndrome (G).

[a] Ultrasound examinations at 2- to 3-weekly intervals demonstrated mild, static ventriculomegaly.

[b] Seizures.

[c] Cerebral palsy.

Discussion

Fetal lateral cerebral ventriculomegaly is associated with a high incidence of morphological and chromosomal defects. In this series, 78% of the 267 fetuses with ventriculomegaly had additional malformations, and 18% of the 64 fetuses that were karyotyped had chromosomal abnormalities. These data are in general agreement with those of previous series on antenatally diagnosed ventriculomegaly [1–9]. However, the incidence of chromosomal abnormalities was strongly related to the presence of multisystem malformations. Thus, only 3% of fetuses with isolated ventriculomegaly as opposed to 36% of those with additional malformations had chromosomal defects. Indeed, this finding may offer an explanation for the conflicting data of previous studies in which the incidence of chromosomal abnormalities varied from 2 to 29%.

In the chromosomally abnormal fetuses, there was a tendency for the degree of ventriculomegaly to be mild (fig. 2), and the most consistent associated malformations were subtle defects, such as syndactyly and overlapping fingers (9 of 11 cases). This is be-

cause the most common chromosomal defect in this series was triploidy; although in 1 of the 6 cases the diagnosis was suspected from the presence of a molar placenta, in the others the placenta was normal, and the most striking features were severe asymmetrical growth retardation and apparent fixed flexion deformity of the wrists with no splaying of the fingers.

There is an intimate relation between spina bifida and hydrocephalus. Thus, in this series the incidence of spina bifida in fetuses with ventriculomegaly was 67% (184 of 267), while Van den Hof et al. [10] reported the presence of cerebral ventriculomegaly in approximately 75% of fetuses with open spina bifida. Gosden and Brock [personal commun.] did not find any chromosomal abnromalities in 226 consecutive fetuses with isolated neural tube defects that were karyotyped at 16–18 weeks' gestation. However, the data of the present study suggest that in those fetuses with ventriculomegaly, spina bifida and additional malformations, chromosomal defects could be common (3 of 6).

Some of the previous reports on antenatally diagnosed ventriculomegaly attempted to define the natural history of the condition. In the present series the survival rate was only 9%. However, neither this nor previous studies could be considered appropriate for defining the natural history of the condition, because in the vast majority of cases the cause of fetal death was iatrogenic. Nevertheless, fetal or perinatal death was strongly related to the presence of other malformations and chromosomal defects. Thus, survival in the cases with isolated ventriculomegaly was 33%, in contrast to 3% in those with additional malformations. Furthermore, among live births the survival rate for infants with isolated ventriculomegaly (n = 19) was 100%, for those with spina bifida (n = 13) survival was 46%, while both infants with multiple defects died in the neonatal period.

Apparently normal mental development was found in 75% of the suriving infants. However, as with survival, this is not representative of the natural history of antenatal ventriculomegaly. Certainly in those cases diagnosed before 28 weeks' gestation, the decision to continue with the pregnancy was based on the demonstration that the ventriculomegaly was isolated, mild, and static; these infants did not require postnatal shunting and are developing normally.

Fetal ventriculomegaly is associated with a high incidence of other malformations and chromosomal defects. Although the natural history of the disease cannot be defined accurately, isolated mild, static ventriculomegaly is associated with normal postnatal development.

Note Added in Proof

To the end of January 1991 a total of 105 fetuses with ventriculomegaly were karyotyped. Abnormal karyotypes were found in 1 of 51 (2%) fetuses with isolated ventriculomegaly and in 14 of 54 (26%) of those with additional malformations.

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