Original Paper

Fetal Diagn Ther 1992;7:132–137

Strawberry-Shaped Skull in Fetal Trisomy 18

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Key Words
Strawberry-shaped skull
Prenatal diagnosis
Ultrasonography
Cordocentesis
Fetal karyotyping

Abstract

During an 8-year period, a strawberry-shaped skull (flattening of the occiput with pointing of the frontal bones), was observed in 54 (3%) of the 2,086 fetuses that underwent karyotyping in our unit because of fetal malformations and/or growth retardation. In all 54 cases with a strawberry-shaped skull, there were other fetal malformations; in 43 (80%) fetuses, there was trisomy 18 and in 1 triploidy. Therefore, the ultrasonographic finding of a strawberry-shaped skull should initiate a diligent search for the presence of other markers of trisomy 18 and is a strong indication for fetal karyotyping. However, in the total series of 2,086 fetuses with malformations and/or growth retardation, there were another 40 fetuses with trisomy 18 and 41 with triploidy who did not have a strawberry-shaped skull.

Introduction

In 1960, Edwards et al. [1] described the association between trisomy for chromosome 18 and a syndromal pattern of defects involving virtually every organ system [1, 2]. although many of the associated malformations are potentially detectable by detailed antenatal ultrasonography, the defects are often difficult to visualize at routine examination. This study describes the association between trisomy 18 and an ultrasonographically detectable characteristic strawberry shape of the skull. Since this shape is seen in the standard views for examination of the fetal brain, it may improve the sensitivity of routine ultrasound examination in the detection of fetal trisomy 18.

Patients and Methods

During an 8-year period (1983–1991), fetal karyotyping was performed in our unit in 2,086 patients who were referred because of ultrasonographically detected fetal malformations and/or growth retardation. In 54 of the 2,086 fetuses, there was a characteristic straw-

Received:
January 4, 1992
Accepted:
April 2, 1992

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1015–3837/92/
0072–0132$2.75/0

berry-shaped skull, with flattening of the occiput and pointing of the frontal bones (fig. 1). This shape was best seen in the suboccipitobregmatic view of the head.

In all cases, detailed ultrasound examination revealed additional defects and/or growth retardation. The diagnosis of fetal malformations, such as exomphalos or spina bifida, was based on the ultrasonographic demonstration of well-described anatomical defects. The diagnosis of abnormal biometry was based on the finding of measurements above the 97.5th and below the 2.5th centiles of our reference ranges, derived from the cross-sectional study of 1,010 normal fetuses. Thus, in brachycephaly, the biparietal (BPD) to occipitofrontal (OFD) diameter ratio was > 97.5th centile for gestation; in ventriculomegaly, the anterior and/or posterior cerebral ventricle to hemisphere diameter ratio was > 97.5th centile. If the head circumference (HC) to femur length (FL) ratio was > 97.5th centile, the fetus was considered to have a short femur, and if the ratio was > 2.5th centile, microcephaly was diagnosed. Fetal growth retardation was considered to be present if the abdominal circumference (AC) was > 5th centile. However, in those fetuses with malformations affecting the AC, such as exomphalos or dilated bladder or ascites, growth retardation was diagnosed if both the HC and FL were < 5th centiles of the respective reference ranges.

Parents were counselled as to the possible association wiht chromosomal defects and chose to have fetal karyotyping. Cordocentesis was performed as an outpatient procedure, and results from lymphocyte culture were given to referring obstetricians who undertook the further management of the pregnancies and subsequently provided details on outcome.

Statistical Analysis

Measurements of BPD/OFD ratio were compared to our reference range with gestation. Student's t test was used to determine the significance of differences in measurements between various subgroups of fetuses.

Results

In all 54 fetuses with a strawberry-shaped skull, there were additional malformations; chromosomal abnormalities were present in 44 (81%) of the cases, including 47,XX + 18 (n = 15), 47,XY + 18 (n = 28) and 69,XXX (n = 1). The pattern and incidence of additional malformations in the chromosomally abnormal (table 1) and normal (table 2) fetuses were similar except for a higher incidence of abdominal wall and gastro-intestinal defects in the abnormal group.

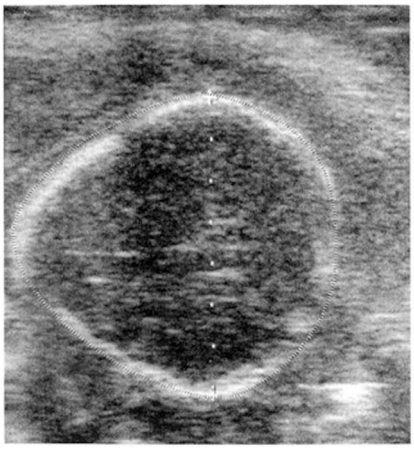

Fig. 1. Transverse section of the head demonstrating the characteristic strawberry-shaped skull in a 20-week fetus with trisomy 18.

In our total group of 2,086 fetuses who were karyotyped because of malformations and/or growth retardation, there were 40 fetuses with trisomy 18 where no strawberry-shaped skull was observed, in addition to the 43 fetuses where trisomy 18 was associated with a strawberry-shaped skull. Comparison of these two subgroups of trisomic fetuses demonstrated no difference in the incidence of growth retardation (58 versus 57%), male karyotype (65 versus 63%), or mean gestation at diagnosis (24 weeks in both). However, the incidence of certain abnormalities of the brain and face as well as normal/increased rather than decreased amniotic fluid volume

was higher in the group with strawberry-shaped skull (table 3).

In the 43 fetuses with trisomy 18 and strawberry-shaped skull, the mean BPD/OFD ratio was significantly higher than the normal mean for gestation (fig. 2; mean difference = 0.05, SE = 0.009, t = 6.2, n = 43, $p < 0.0001$), and higher than that in the group of fetuses where trisomy 18 was not associated with a strawberry-shaped skull (mean difference = 0.04, SE = 0.01, t = 2.85, n = 83, $p < 0.01$). The mean BPD/OFD ratio in the 10 chromosomally normal fetuses with strawberry-shaped skull was not significantly different from the normal mean for gestation (fig. 2; mean difference = 1.1 SD, SE = 0.5 t = 2.2).

Table 1. Findings in 10 chromosomally normal fetuses with a strawberry-shaped skull including gestational age (GA in weeks), ultrasonographic findings, karyotype and outcome

Case	GA	AF	Additional defects						Karyotype	Outcome
			brain	face	chest	abdomen	extremities	other		
1	24	I				H2	syndactyly		46,XX	TOP
2	35	I			DH		OF, RB	NE	46,XX	IUD
3	18	N					OF, talipes	ascites	46,XX	TOP
4	24	N			CD	H2		IUGR	46,XX	TOP
5	32	N	V						46,XY	IUD
6	25	N	PFC, V			MK		IUGR	46,XX	TOP
7	26	N	V	FC			polydactyly		46,XY	TOP
8	16	N	CPC	MG		H1		IUGR	46,XY	alive
9	22	I	V	MG	CD	H2	OF	IUGR	46,XY	TOP
10	27	I		HN		H2	SF		46,XX	alive

TOP = Termination of pregnancy, IUD = intrauterine death, NND = neonatal death. Amniotic fluid volume (AF) was normal (N) or increased (I); brain defects included ventriculomegaly (V), posterior fossa cyst (PFC) and choroid plexus cysts (CPC); facial defects included micrognathia (MG), hypoplastic nose (HN) and facial cleft (FC); abnormalities in the chest included cardiac defects (CD) and diaphragmatic hernia (DH); abnormalities in the abdomen included mild (H1) or moderate (H2) hydronephrosis and multicystic kidneys (MK); abnormalities of the extremities included syndactyly, polydactyly, overlapping fingers (OF), rocker-bottom feet (RB), short femur (SF) and talipes; other abnormalities included nuchal oedema (NE), growth retardation (IUGR) and ascites.

(Footnote to table 2)

TOP = Termination of pregnancy, IUD = intrauterine death, NND = neonatal death. Amniotic fluid volume (AF) was reduced (R), normal (N) or increased (I); brain defects included ventriculomegaly (V), holoprosencephaly (HOLOP), posterior fossa cyst (PFC) and choroid plexus cysts (CPC); facial defects included micrognathia (MG) and facial cleft (FC); abnormalities in the chest included cardiac defects (CD) and diaphragmatic hernia (DH); abnormalities in the abdomen included exomphalos (Exom), absent stomach bubble (AS), mild (H1) or moderate (H2) hydronephrosis, multicystic kidneys (MK) or renal agenesis; abnormalities of the extremities included syndactyly, clinodactyly, polydactyly, overlapping fingers (OF), rocker-bottom feet (RB), short femur (SF) and talipes; other abnormalities included nuchal oedema (NE) and growth retardation (IUGR).

Table 2. Findings in 43 fetuses where trisomy 18 was associated with a strawberry-shaped skull including gestational age (GA in weeks), ultrasonographic findings, karyotype and outcome

Case	GA	AF	Brain	Face	Chest	Abdomen	Extremities	Other	Karyotype	Outcome
1	37	R						IUGR	47,XX,+18	NND
2	30	I				OA	OF		47,XY,+18	IUD
3	23	I			CD	OA	OF, RB	IUGR	47,XX,+18	TOP
4	20	I			CAM	OA	OF, talipes		47,XY,+18	TOP
5	36	I				Exom	OF, talipes		47,XX,+18	NND
6	39	N			CD	Exom, H1	OF, RB	IUGR	47,XY,+18	NND
7	19	N			CD, DH	Exom	OF, SF	IUGR	47,XY,+18	TOP
8	33	I			CD	Exom, OA, H1	OF, SF, talipes		47,XY,+18	IUD
9	20	N				Exom	OF, SF, talipes		47,XX,+18	TOP
10	23	N			CD	Exom	SF, talipes		47,XY,+18	TOP
11	23	N			DH	Exom, OA	OF, SF, talipes	IUGR	47,XY,+18	TOP
12	29	I		MG	CD		OF, talipes		47,XX,+18	IUD
13	24	I		MG	CD	OA	OF	IUGR	47,XY,+18	TOP
14	21	I		MG		Exom	OF		47,XY,+18	TOP
15	17	N		MG		Exom	OF, SF	NE	47,XY,+18	TOP
16	31	I		MG	CD	Exom, OA	OF, SF, talipes	IUGR	47,XY,+18	IUD
17	21	I		MG	CD	Exom	RB		47,XY,+18	TOP
18	21	N		MG	CD	Exom	OF, RB		47,XY,+18	TOP
19	26	I		FC	CD	Exom	OF		47,XY,+18	TOP
20	32	I		FC		OA	OF	IUGR	47,XY,+18	IUD
21	30	I		FC	CD, DH		OF	IUGR	47,XX,+18	NND
22	24	I	CPC					IUGR	47,XX,+18	TOP
23	24	I	CPC	MG	DH		OF	IUGR	47,XX,+18	TOP
24	21	N	CPC	MG	DH		OF	IUGR	47,XX,+18	TOP
25	25	N	CPC	MG			OF	IUGR	47,XX,+18	TOP
26	21	N	CPC	MG		H1	OF, talipes	IUGR	48,XXX,+18	TOP
27	26	I	CPC	MG		OA	OF	IUGR	47,XX,+18	TOP
28	18	N	CPC	MG	CD	Exom	OF, talipes		47,XY,+18	TOP
29	22	N	CPC			Exom	OF	IUGR	47,XY,+18	TOP
30	20	N	CPC	FC	CD	Exom	OF, SF, salipes	IUGR	47,XY,+18	TOP
31	18	N	CPC			Exom			47,XY,+18	TOP
32	21	N	CPC			Exom, MK	OF		47,XY,+18	TOP
33	27	I	CPC		CD, DH	Exom, OA, MK	OF, talipes	IUGR	47,XX,+18	TOP
34	24	N	CPC, V		CD		OF, talipes	IUGR	47,XY,+18ill	TOP
35	24	N	CPC, V		CD	Exom	OF, RB		47,XY,+18	TOP
36	20	N	CPC, V	MG	CD	Exom, H1	RB	NE	47,XY,+18	TOP
37	20	N	CPC, V	MG		Exom, H1	OF, SF, RB	IUGR	47,XY,+18	TOP
38	23	N	CPC, PFC		CD	H1	OF, RB	IUGR	47,XX,+18	TOP
39	22	N	V			Exom	OF	IUGR	47,XY,+18	TOP
40	37	I	PFC	MG	CD	OA	OF	IUGR	47,XY,+18	IUD
41	20	N	HOLOP	FC			polydactyly, RB	IUGR	47,XY,+18	TOP
42	27	I	HOLOP	FC	CD, DH	renal agenesis	OF		47,XX,+18	TOP
43	24	I	ACC		CD	OA	OF, talipes	IUGR	47,XY,+18	TOP

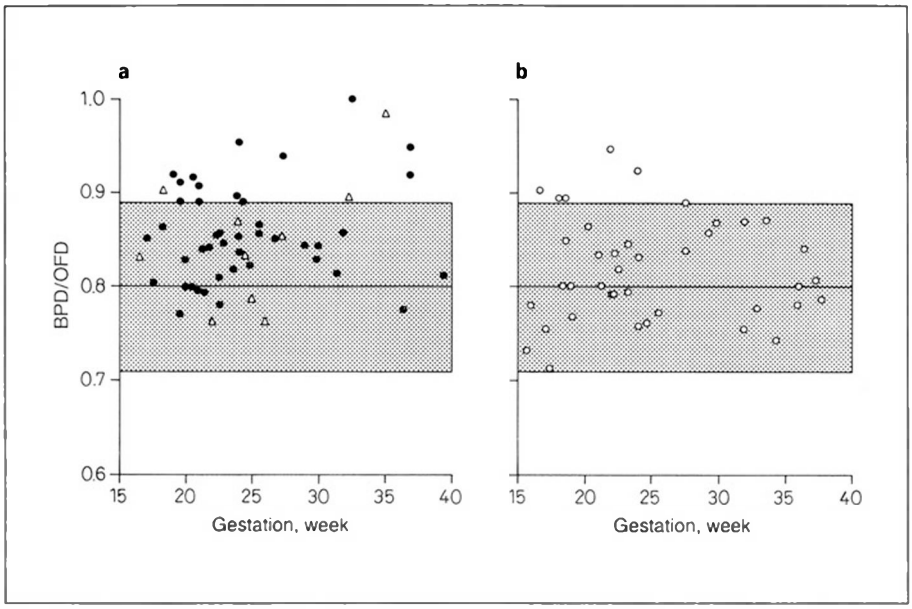

Fig. 2. BPD/OFD ratio in 10 chromosomally normal (△) and 44 abnormal (●) fetuses with a strawberry-shaped skull (**a**), and in 40 trisomic fetuses without a strawberry-shaped skull (○; **b**) plotted on the reference range (mean, 2.5th and 97.5th centiles) with gestation.

Table 3. Incidence of brain and facial abnormalities and reduced amniotic fluid volume in the 43 fetuses where trisomy 18 was associated with a strawberry-shaped skull (+S) compared to incidence in the 40 trisomic fetuses without a strawberry-shaped skull (–S)

Feature	+S	–S	χ^2	p
Brain defect				
Ventriculomegaly	5 (12%)	7 (18%)	0.49	
Holoprosencephaly	2 (5%)	1 (3%)	0.27	
Choroid plexus cyst	17 (40%)	13 (33%)	0.10	
Absent corpus callosum	1 (2%)	–	0.97	
Posterior fossa cyst	2 (5%)	6 (15%)	2.37	0.25
Facial defect				
Micrognathia	16 (37%)	4 (10%)	3.86	0.05
Facial cleft	6 (14%)	4 (10%)	0.23	
Reduced amniotic fluid	1 (2%)	7 (18%)	5.88	0.02

Discussion

Strawberry-shaped skull is a 'gestalt' marker, rather than a measurable feature, of trisomy 18; although the BPD/OFD ratio is increased, this ratio does not reliably reflect presence or absence of the marker. The extent to which the introduction of techniques such as pattern recognition analysis will provide more objective description of the marker remains to be determined.

The characteristic pointing of the frontal bones with flattening of the occiput, in trisomy 18, should be distinguished from the scalloping of the frontal bones, or lemon sign and cerebellar abnormalities, banana-shaped or absent, observed in association with open spina bifida [3].

The most likely explanation for the pointing of the frontal bones in trisomy 18 is the

narrow bifrontal region due to hypoplasia of the face and frontal cerebral lobes. Similarly, flattening of the occiput may be due to hypoplasia of the hindbrain. Thus, postnatal and post-mortem studies have documented hypoplasia of the frontal lobes and poor development of the facial artery, several of the facial muscles, of the maxilla, mandible, frontal as well as the temporal bones, together with microphthalmia, narrow nasal bridge and palate, and absent or rudimentary parotid and submandibular salivary glands [4–6]. These features may be the consequence of abnormal development of the first and second branchial arches, due to vascular defects [7]. Hindbrain abnormalities include hypoplasia of the occipital lobes, cerebellum and brain stem, and the alteration in the shape of the occipital bones may be due to abnormalities of induction of the skull by the developing brain [4, 8, 9].

In the trisomic fetuses without a strawberry-shaped skull, the higher incidence of posterior fossa cysts may have prevented the flattening of the occipital bones, and the lower incidence of micrognathia may be indicative of lesser degrees of facial hypoplasia and therefore lesser pointing of the frontal bones. Furthermore, the higher incidence of reduced amniotic fluid volume or oligohydramnios may have caused lateral compression of the head and resulted in dolichocephaly rather than strawberry shape of the skull.

In the chromosomally normal fetuses with a strawberry-shaped skull, the high incidence of other organ malformations and the poor prognosis suggest the presence of an underlying genetic syndrome, such as Robert's syndrome, which is also characterised by abnormal development of the first and second branchial arches. In this respect, the parents should be counselled that the risk of recurrence may be as high as 25%.

The findings of this study indicate that in a substantial proportion of fetuses with trisomy 18, there is an ultrasonographically detectable strawberry shape of the skull, which is best seen in the standard view for examination of the fetal brain. Therefore, the finding of a strawberry-shaped skull should prompt the ultrasonographer to undertake a diligent search for the presence of other major and minor defects associated with trisomy 18, such as choroid plexus cysts, facial cleft, cardiac defects, exomphalos, diaphragmatic hernia and abnormalities of the extremities.

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