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Fetal Facial Defects: Associated Malformations and Chromosomal Abnormalities

Abstract

During an 8-year period, facial defects were observed in 146 (7%) of the 2,086 fetuses that underwent karyotyping in our unit because of fetal malformations and/or growth retardation. Chromosomal abnormalities were detected in 37 of 56 (66%) fetuses with micrognathia, in 10 of 13 (77%) with macroglossia, in 31 of 64 (48%) with cleft lip and palate, in 5 of 11 (45%) with severe hypotelorism or cyclops, and in 6 of 19 (32%) with nasal hypoplasia, proboscis or single nostril. Macroglossia was mainly associated with trisomy 21, micrognathia with trisomy 18 and triploidy, facial cleft with trisomies 13 and 18, and ocular or nasal defects with trisomy 13. In all chromosomally abnormal fetuses with facial defects, there were additional multisystem defects, and the pattern of these malformations was compatible with the type of the underlying chromosomal abnormality. In the total series of 2,086 fetuses with malformations and/or growth retardation, there were 31 with trisomy 13, 83 with trisomy 18 and 69 with trisomy 21; facial defects were found in 71, 36 and 14% of these fetuses, respectively.

Key Words
Facial defects
Prenatal diagnosis
Ultrasonography
Cordocentesis
Fetal karyotyping

Introduction

Postnatal and post-mortem studies have established that facial defects are commonly found in association with many chromosomal abnormalities and genetic syndromes [1, 2]. Several reports on individual cases and small series of affected fetuses have now documented the feasibility of prenatal diagnosis of facial defects by ultrasonography.

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This study examines the incidence of facial defects in a high-risk population of 2,086 fetuses who were karyotyped because of ultrasonographically detected fetal malformations and/or growth retardation. The aim of the study is to determine the pattern of associated malformations and chromosomal abnormalities.

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 all cases, a systematic ultrasonographic examination was undertaken for the detection of additional malformations and/or growth retardation. Examination of the face included the midsagittal view for the profile and serial axial scans at the level of the forehead, eyes, nose, upper and lower lips. Severe hypotelorism or cyclops, single nostril, and facial cleft were best seen by axial scans at the level of the eyes, nose and upper lip, respectively. Macroglossia, micrognathia and nasal hypoplasia or proboscis were diagnosed in the midsagittal view of the face. In macroglossia, an enlarged tongue protruding through the open mouth could be demonstrated. Severe micrognathia was diagnosed by the presence of a prominent upper lip and small chin.

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 to occipitofrontal 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 to femur length 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 was < 5th centile. However, in those fetuses with malformations affecting the abdominal circumference, such as exomphalos or dilated bladder or ascites, growth retardation was diagnosed if both the head circumference and femur length were < 5th centiles of the respective reference ranges.

Parents were counselled as to the possible association with chromosomal defects and chose to have fetal karyotyping. Cordocentesis was performed as an outpatient procedure, and results from lymphocyte culture [3] were given to referring obstetricians who undertook the further management of the pregnancies and subsequently provided details on outcome.

Results

Facial abnormalities including micrognathia (n = 56), macroglossia (n = 13), cleft lip and palate (n = 64), severe hypotelorism or cyclops (n = 11), and nasal hypoplasia, proboscis or single nostril (n = 19) were detected in 146 (7%) of the 2,086 fetuses.

Chromosomal abnormalities were detected in 37 of 56 (66%) fetuses with micrognathia, in 10 of 13 (77%) with macroglossia, in 31 of 64 (48%) with cleft lip and palate, in 5 of 11 (45%) with severe hypotelorism or cyclops, and in 6 of 19 (32%) with nasal hypoplasia, proboscis or single nostril. Macroglossia was mainly associated with trisomy 21, micrognathia with trisomy 18 and triploidy, facial cleft with trisomies 13 and 18, and ocular or nasal defects with trisomy 13 (table 1). In the total series of 2,086 fetuses with malformations and/or growth retardation, there were 31 with trisomy 13, 83 with trisomy 18, and 69 with trisomy 21; facial defects were found in 71, 36 and 14%, respectively, of these fetuses.

Ocular and Nasal Defects

Severe ocular and nasal defects were observed only in association with holoprosencephaly. In the total series of 2,086 fetuses with malformations and/or growth retardation, there were 58 fetuses with holoprosencephaly, and 15 (26%) of these had chromosomal abnormalities. All chromosomally ab-

Table 1. Incidence of chromosomal abnormalities in 149 fetuses with facial defects

Facial defect	Total		Trisomy				Triploidy	Deletion or translocation
	n	%	13 n = 31	18 n = 83	21 n = 69	other n = 9	n = 42	n = 24
Micrognathia	37/56	66	3 (10)	21 (25)	–	1 (11)	9 (21)	3 (13)
Facial cleft	31/64	48	15 (48)	10 (12)	1 (1)	2 (22)	1 (2)	2 (8)
Ocular defects	5/11	45	4 (13)	1 (1)	–	–	–	–
Nasal defects	6/19	32	5 (16)	–	–	–	–	1 (4)
Macroglossia	10/13	77	–	–	9 (13)	1 (11)	–	–
Total	80/146	55	22 (71)	30 (36)	10 (14)	3 (33)	10 (24)	5 (21)

The values in brackets are percentages indicating the incidence of facial defects in the group of 258 fetuses with abnormalities involving autosomal chromosomes; in 42 fetuses with sex chromosome abnormalities, no facial defects were detected.

Table 2. Incidence of chromosomal abnormalities in 58 fetuses with holoprosencephaly in the presence or absence of extrafacial and facial defects

Karyotype	Extrafacial defects		No extrafacial defects	
	+ facial	– facial	+ facial	– facial
Normal	6	19	8	10
Abnormal	13	2	–	–
Trisomy 13	10	1	–	–
Trisomy 18	2	1	–	–
Deletion 21p	1	–	–	–

normal fetuses had extrafacial defects, but 13 of the 15 had the triad of holoprosencephaly, extrafacial and facial defects (table 2).

Macroglossia

The group of 13 fetuses with macroglossia included 9 with trisomy 21 and 2 with the Beckwith-Wiedemann syndrome (table 3). In the latter 2 fetuses, in addition to macroglossia, there was hepatosplenomegaly, multiple adrenal cysts and hyperechogenic pancreas. In 1 of the chromosomally normal fetuses, the macroglossia was associated with a constantly open mouth, prominent forehead, thoracolumbar kyphoscoliosis and cavum excavatum, and the diagnosis of Coffin-Lowry syndrome was suspected. In another case with normal fetal karyotype and antenatal findings of macroglossia, nuchal oedema and clinodactyly, no abnormalities were detected at birth. Although the incidence of macroglossia in fetuses with trisomy 21 who were diagnosed at <28 weeks gestation was 10% (5 of 49), compared to 20% (4 of 20) for those diag-

Table 3. Findings in 13 fetuses with macroglossia including gestational age (GA), ultrasonographic findings, karyotype, outcome and gestation at delivery (Ge)

Case No.	GA weeks	Additional defects	Karyotype	Out-come	Ge weeks
1	30	cardiac, talipes, growth retardation	47,XY+21	IUD	31
2	20	nuchal oedema, choroid plexus cysts, brachycephaly	47,XX+21q	TOP	25
3	23	cardiac, duodenal atresia, clinodactyly	47,XX+21	TOP	24
4	24	nuchal oedema, mild hydronephrosis, sandal gap	47,XX+21	TOP	25
5	37	nuchal oedema, mild hydronephrosis, clinodactyly, (cardiac)	47,XX+21	alive	38
6	23	nuchal oedema, mild hydronephrosis, sandal gap	47,XX+21	alive	38
7	33	nuchal oedema, duodenal atresia	47,XX+21	alive	38
8	35	nuchal oedema, (cardiac)	47,XX+21	alive	40
9	23	mild hydronephrosis, growth retardation	47,XX+21	TOP	24
10	23	short femur, adrenal cysts, hepatosplenomegaly	46,XX,dup(11p)	TOP	24[1]
11	30	adrenal cysts, hepatosplenomegaly	46,XX	NND	30[1]
12	25	kyphoscoliosis, cavum excavatum, prominent forehead	46,XY	TOP	25[2]
13	33	nuchal, oedema, clinodactyly	46,XX	alive	38

In 2 cases, cardiac defects were diagnosed only postnatally (cardiac). IUD = Intra-uterine death; TOP = termination of pregnancy; NND = neonatal death.

[1] Beckwith-Wiedemann syndrome.

[2] Coffin-Lowry syndrome.

nosed at ≥ 28 weeks, this difference was not statistically significant ($\chi^2 = 1.2$, 1 d.f.). Similarly, in our total series of 2,086 fetuses with malformations and/or growth retardation, there were 4 with the Beckwith-Wiedemann syndrome diagnosed at 16, 22, 23 and 30 weeks gestation; macroglossia was observed in the cases diagnosed at 23 and 30 weeks.

Facial Cleft

In all chromosomally abnormal fetuses with facial cleft, there were additional multisystem defects, and the pattern of these malformations was compatible with the type of the underlying chromosomal abnormality. Thus, in the fetuses with trisomy 13, compared to the chromosomally normal fetuses with facial cleft, there was a higher incidence of cardiac, digital and renal defects, exomphalos and diaphragmatic hernia (table 4). Similarly, in trisomy 13 there was a higher incidence of strawberry-shaped skull, cardiac and digital defects and diaphragmatic hernia. Isolated facial cleft was found in only 8 (13% of the 64) fetuses (table 5); 6 were live-born and underwent corrective surgery, but in 2 cases, the parents elected to have termination of the pregnancy. In both of the latter 2 cases, 1 of the parents also had a facial cleft.

Micrognathia

Micrognathia was diagnosed in 56 fetuses, and in all cases there were additional malformations and/or growth retardation. Chromosomal abnormalities, mainly trisomy 18 or triploidy, were found in 37 (66%) of the cases; the pattern of fetal defects was compatible with the type of the underlying chromosomal abnormality. The individual features of the 19 chromosomally normal fetuses with mi-

Table 4. Incidence of additional defects in relation to karyotype in 64 fetuses with facial cleft

Additional anomalies	Karyotype							
	normal		abnormal					
			trisomy 18		trisomy 13		other	
	n	%	n	%	n	%	n	%
Brain defects	18	55	7	70	13	81	2	40
Facial defects	6	18	2	20	6	38	1	20
Strawberry-shaped skull	1	3	6	60[1]	–		–	
Brachycephaly	2	6	2	20[1]	4	25	1	20
Diaphragmatic hernia	–		3	30[1]	2	13	–	
Cardiac defects	1	3	5	50[1]	7	44[1]	2	40[1]
Exomphalos	3	9	3	30	6	38[1]	–	
Renal defects	6	18	2	20	9	56[1]	–	
Abnormal extremeties	8	24	9	90[1]	12	75[1]	2	40
Short femur	4	12	2	20			1	20
Growth retardation	9	27	6	60	8	50	1	20
Total	33		10		16		5	
Number of defects:								
Mean	3		7		6		4	
Range	1–7		5–9		3–9		4–4	

[1] Defects where χ^2-test demonstrated significant differences between those with normal and abnormal karyotypes.

crognathia are shown in table 6; there was only 1 survivor in this group. Comparison of the pattern and incidence of additonal malformations in the chromosomally abnormal and normal fetuses is shown in table 7.

Discussion

The findings of this study indicate that in a substantial proportion of fetuses with antenatally diagnosed facial abnormalities, there are other malformations and chromosomal abnormalities. This is not surprising, because the primary indication for ultrasound scanning in our population was the detection of extrafacial defects and/or growth retardation in the referring hospital. In this respect, no conclusions can be drawn regarding the prevalence of fetal facial defects in unselected populations.

The incidence of facial defects in our group (7%) is similar to the 8% reported by Pilu et al. [4] in their ultrasonographic study of 223 fetuses with extrafacial defects or chromosomal abnormalities, family history of craniofacial malformations, or maternal exposure to teratogens. In contrast, Hegge et al. [5], who examined a mixed low- and high-risk population of 7,100 fetuses, detected facial defects in only 11 (0.15%); in all cases there were additional malformations or polyhydramnios or a history of maternal exposure to teratogens.

Table 5. Findings in 33 chromosomally normal fetuses with a facial cleft including gestational age (GA), ultrasonographic findings, karyotype, outcome, gestation at delivery (Ge) and sex.

Case No.	GA weeks	Additional abnormalities brain and skull	Face	Other	Out-come	Ge weeks	Sex
1	21				alive	38	M
2	23				alive	40	M
3	20				alive	37	M
4	22				alive	39	F
5	23				alive	36	F
6	31				alive	33	M
7	20				TOP	20	M
8	22				TOP	22	M
9	23				alive	39	F
10	21			H2,	TOP	23	M
11	33			growth retardation, SF (duodenal atresia)	NND	39	F
12	18			gastroschisis, kyphoscoliosis, OF	TOP	18	M
13	33			gastroschisis	alive	36	F
14	22			exomphalos, pleural effusion	TOP	22	M
15	19	ventriculomegaly		H1	TOP	20	F[1]
16	22	ventriculomegaly		nuchal oedema	TOP	23	M
17	37	ventriculomegaly		MK, right anophthalmia	alive	37	M
18	24	ventriculomegaly		growth retardation, H2, bowel obstruction, SF	TOP	24	M
19	30	ventriculomegaly		growth retardation, ascites, OF, SF	IUD	31	M
20	23	holoprosencephaly		H1	TOP	23	M
21	21	holoprosencephaly		cardiac, kyphoscoliosis, nuchal oedema	TOP	20	F
22	17	holoprosencephaly	absent nose		TOP	17	F
23	18	holoprosencephaly, microcephaly	absent nose		TOP	18	F
24	24	holoprosencephaly, microcephaly	absent nose	growth retardation, nuchal oedema, OF	TOP	24	M
25	32	holoprosencephaly	absent nose		NND	37	F
26	19	ventriculomegaly	absent nose	growth retardation, OF, SF	TOP	19	M[2]
27	18	anencephaly		exomphalos, talipes	TOP	18	M[1]
28	22	anencephaly		exomphalos	TOP	24	F
29	30	anencephaly		growth retardation, clinodactyly	NND	30	F
30	27	encephalocele, microcephaly		growth retardation	TOP	27	F
31	26	ventriculomegaly, strawberry		growth retardation, polydactyly	TOP	27	M[2]
32	32	holoprosencephaly, brachycephaly	absent nose	growth retardation	NND	32	F
33	20	brachycephaly		ascites, oedema, arthrogryposis	IUD	23	M

Table 6. Findings in 19 chromosomally normal fetuses with micrognathia gestational age (GA), amniotic fluid volume (AF), ultrasonographic findings, karyotype, outcome, sex and gestation at delivery (Ge)

Case No.	GA weeks	AF IUGR	Additional defects head and neck	Chest and abdomen	Extremities	Out-come	Ge weeks	Sex
1	23	R +	NO			NND	39	M
2	23	N +			OF, talipes	TOP	23	F
3	21	N	NO	hydronephrosis		TOP	22	F
4	20	I		cardiac, hydronephrosis	RB, clinodactyly	TOP	21	M
5	30	R		cardiac, hydronephrosis	SF, talipes	IUD	37	F
6	33	I		diaphragmatic hernia	caudal regression	IUD	35	F[1]
7	36	I	encephalocele	cardiac, diaphragmatic hernia		IUD	38	M
8	18	N	brachycephaly, NO	pleural effusion, hydronephrosis		NND	32	F[2]
9	22	N +	ventriculomegaly, microcephaly, NO	hydronephrosis		TOP	22	F
10	30	N +	ventriculomegaly	cardiac, exomphalos	OF, talipes	IUD	32	M
11	27	R +	ventriculomegaly, brachycephaly	multicystic kidneys	SF	TOP	27	F
12	19	N +	ventriculomegaly		SF, clinodactyly	TOP	19	M
13	35	I +	ventriculomegaly		FlW	IUD	36	F
14	33	R +	ventriculomegaly	hydronephrosis	SF, talipes	NND	38	M
15	23	N +	ventriculomegaly	hydronephrosis	arthrogryposis	TOP	24	M
16	17	N	choroid plexus cysts, strawberry	hydronephrosis		alive	41	M
17	22	I	ventriculomegaly, strawberry	cardiac, hydronephrosis	OF	TOP	23	M
18	35	R +	single nostril		phocomelia	NND	36	M
19	21	I	hypoplastic nose	absent stomach bubble	OF	TOP	21	M

In 1 case, a cleft palate was diagnosed postnatally. R = Reduced; N = normal; I = increased; IUGR = intra-uterine growth retardation; NO = nuchal oedema; OF = overlapping fingers; RB = rocker-bottom feet; SF = short femur; FlW = flexed wrists; NND = neonatal death; TOP = termination of pregnancy; IUD = intra-uterine death.

[1] Amniotic band syndrome.

[2] Cardiomyopathy.

Footnote to table 5

Additional abnormalities that were missed antenatally included duodenal atresia and unilateral anophthalmia. SF = Short femur; OF = overlapping fingers; H1 and H2 = mild and moderate hydronephrosis; MK = multicystic kidneys; TOP = termination of pregnancy; NN = neonatal death; IUD = intra-uterine death.

[1] Amniotic band syndrome.

[2] Robert's syndrome.

Table 7. Incidence of additional defects in relation to karyotype in 56 fetuses with micrognathia

Additional anomalies	Karyotype							
	normal		abnormal					
			trisomy 18		triploidy		other	
	n	%	n	%	n	%	n	%
Brain defects	10	50	12	57	4	44	3	43
Facial defects	2	10	1	5	–		2	29
Strawberry-shaped skull	2	10	17	81[1]	–		2	29
Brachycephaly	2	10	6	29	–		–	
Diaphragmatic hernia	2	10	3	14	1	11	1	14
Cardiac defect	5	25	11	52	2	22	4	57
Exomphalos	1	5	8	38	–		1	14
Renal defects	10	50	5	24	–		–	
Abnormal extremities	10		21	100[1]	8	89	5	71
Short femur	4	20	3	14	7	78[1]	1	14
Growth retardation	10	50	14	67	8	89[1]	4	57
Total	20		21		9		7	
Number of defects								
Mean	5		7		5		6	
Range	3–8		5–10		2–7		2–9	

[1] Defects where χ^2-test demonstrated significant differences between those with normal and abnormal karyotypes.

Cleft lip and palate are among the commonest congenital abnormalities, found in approximately 1:700 live births, and both genetic and environmental factors are implicated in their causation [1, 2]. Although postnatal studies have reported chromosomal abnormalities in less than 1% of babies with facial clefts [6], in our series of 64 cases of antenatally diagnosed facial cleft, 56 (88%) of the fetuses had additional malformations and 31 (48%) had chromosomal abnormalities. Similarly, Saltzman et al: [7] reported on 10 fetuses with facial cleft, all of which had additional defects, and 4 were chromosomally abnormal.

The association between holoprosencephaly and severe ocular and nasal abnormalities as well as facial cleft is well documented [8]. When holoprosencephaly is diagnosed antenatally, it is important to specifically search for facial defects because their presence helps confirm the primary diagnosis and increases the likelihood of finding extracraniofacial abnormalities. Furthermore, fetuses with facial defects have a poorer prognosis, presumably because they are more likely to have alobar or semilobar rather than lobar holoprosencephaly [9]. The findings of the present study indicate that although all chromosomally abnormal fetuses with holoprosencephaly have extrafacial defects, the risk for chromosomal abnormalities increases if facial defects are also present.

Postnatally, a protuberant tongue is a common finding in infants with trisomy 21 and macroglossia is present in more than 95% of those with the Beckwith-Wiedemann syndrome [1, 2, 10]. Antenatally, an enlarged tongue protruding through the open mouth can be demonstrated in the midsagital view of the face. In our study, a specific search for this feature was undertaken especially in those cases with extrafacial defects suggestive of trisomy 21 and the Beckwith-Wiedemann syndrome; macroglossia was diagnosed in 13 and 50% of the cases, respectively. It is possible that in these conditions there is progressive enlargement of the tongue with advancing gestation to account for the higher incidence of macroglossia at birth.

In all 56 cases with sufficiently severe micrognathia to be diagnosed antenatally by ultrasonography, there were additional malformations and/or growth retardation, and the condition was associated with very poor perinatal outcome. Chromosomal abnormalities, mainly trisomy 18 or triploidy, were found in 37 (66%) of the cases. Although pathological studies have demonstrated micrognathia to be present in $>80\%$ of fetuses with trisomy 18 or triploidy [1, 2], in our series of 83 fetuses with trisomy 18 and 42 with triploidy, micrognathia was detected by ultrasonography in only 21 (25%) and 9 (21%) of the cases, respectively. These findings suggest that at present only the most severe degrees of this defect are amenable to prenatal diagnosis.

In this study, the diagnosis of severe hypotelorism, macroglossia and micrognathia was based on subjective assessment, and these defects were considered to be 'gestalt' markers, rather than measurable features, of chromosomal abnormalities or genetic syndromes. It is possible that more sensitive prediction of the abnormalities will be provided by measurements of internal orbital diameter and length of the tongue and mandible, or by the introduction of techniques such as pattern recognition analysis.

The sensitivity of ultrasound screening for facial defects in unselected populations remains to be determined. Nevertheless, present evidence suggests that many of these defects are amenable to prenatal diagnosis by ultrasonography, and their detection provides useful prediction of the likelihood of an underlying chromosomal abnormality or genetic syndrome, and in some cases helps confirm the primary diagnosis.

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