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Dysmorphic features in offspring of alcoholic mothers

I Autti-Rämö, E Gaily, M-L Granström

Abstract

The frequencies of 60 minor physical anomalies and various craniofacial measurements in 52 children with alcohol exposure of various durations in utero were determined and compared with 48 non-exposed healthy children at a mean age of 27 months. Compared with non-exposed children a significantly higher total minor physical anomaly count was observed in those children exposed prenatally to alcohol throughout pregnancy. Binge drinking was not associated with an increased minor physical anomaly count. During the first year of life facial features were judged according to subjective impression: 10 children had typical facial features of fetal alcohol syndrome (FAS) and 19 children were judged to have possible fetal alcohol effects on their face. Only six of them fulfilled the strict craniofacial criteria for diagnosis of FAS at the age of 27 months. Our results stress the importance of recognising also the subtle dysmorphic facial features associated with prenatal alcohol exposure: 22 of 29 (76%) of exposed children judged to have typical or possible features of FAS during the first year showed signs of central nervous system dysfunction at the age of 27 months.

When Jones and his colleagues reported the association between exposure to alcohol in utero and aberrant morphogenesis, the most frequent minor physical anomalies observed were short palpebral fissure, altered palmar crease patterns, maxillary hypoplasia, and epicanthus.[1 2] Since then a considerable variety of minor anomalies has been reported.[3–8] When the Fetal Alcohol Study Group of the Research Society on Alcoholism (RSA) set the minimum criteria for the diagnosis of fetal alcohol syndrome (FAS) only minor physical anomalies of the facial area were included.[9] In addition to growth retardation and dysfunction of the central nervous system, a diagnosis of FAS requires at least two of the following three craniofacial signs to be present: (i) microcephaly, (ii) microophthalmia and/or short palpebral fissure, and (iii) hypoplastic philtrum with thin upper lip and flattening of the maxillary area.

In addition to the widely used definition of the RSA, Majewski[10] and Vitez *et al*[11] have presented two different semiquantitative scoring systems for the probability and severity of FAS, both of which include the RSA criteria. Majewski included 23 minor and major anomalies in his 29 item scoring system and Vitez *et al* 45 malformations in their 51 item scoring system.

The first aim of the present study was to analyse the occurrence of minor physical anomalies in children exposed to alcohol in utero and to compare these with non-exposed children in order to see whether the duration of alcohol exposure was associated with the amount or type of minor physical anomaly. The second aim was to decide whether the subjective assessment of facial features during the first year of life suggestive of fetal alcohol exposure can be affirmed by an independent examination during the third year of life. The third aim was to study whether judgment based on a subjective impression can be of clinical value in diagnosing children with possible fetal alcohol effects.

Subjects

Eighty two children exposed to alcohol in utero were followed up prospectively at the Children's Castle Hospital, Helsinki. The mothers had entered the study in their second trimester and were followed up at two to four week intervals at a special outpatient clinic for pregnant women at the Helsinki University Central Hospital.[12] At each visit the mothers were informed of the harmful effects of fetal alcohol exposure and were encouraged to stop their drinking. The mothers' reports on their drinking, use of drugs, and smoking were recorded for each interval between visits. Alcohol consumption was assessed according to Rosett *et al* as heavy if it exceeded 140 g per week or 630 g per month.[13] Children were divided into three groups according to the recorded data. Group I consisted of children exposed to heavy alcohol consumption during the first trimester only (n=29). Group II consisted of children exposed to heavy alcohol consumption during the first and second trimesters (n=27). Group III consisted of children exposed to heavy alcohol consumption throughout pregnancy (n=26). Eight mothers reported mainly moderate (24–140 g per week) but regular alcohol consumption during their first trimester, and they were included in group I. The pattern of drinking was classified as either binge drinking (five or more drinks on one occasion) or not.

After birth the children were systematically followed up at the Children's Castle Hospital, the examiners being unaware of exposure status.[14 15] At the fifth assessment at a mean age of 27 months the developmental levels of 60 (73%) exposed children were assessed by a psychologist and a speech therapist.[16] Fifty two (63%) of these children underwent a thorough assessment of their dysmorphic features, which were recorded by one of the authors (EG); 51 of

Department of Child Neurology, University of Helsinki and Children's Castle Hospital, Helsinki, Finland
I Autti-Rämö
E Gaily
M-L Granström

Correspondence and reprint requests to:
Dr Ilona Autti-Rämö, Peuramäentie 1 H 18, 02700 Kauniainen, Finland.

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them were seen at least once during their first year of life.

The non-exposed group was composed of 48 children who were exposed only to vitamins, iron substitution, and non-teratogenic antibiotics. Sixteen children were born to abstinent mothers who had been checked regularly during pregnancy at the outpatient clinic for alcohol consuming pregnant women.[17] Thirty two children were born to abstinent low social class women collected from a large prospective population based study on alcohol consumption during pregnancy.[18]

Methods

During the first year of life the facial features of the child were subjectively assessed as normal, possible fetal alcohol effects (FAE face), typical FAS face, and abnormal not resembling FAS by one of us (IA-R).

At a mean age of 27 months (24–36 months), the minor physical anomalies of the children were systematically recorded according to a checklist of 60 minor physical anomalies (table 1) by one of us (EG). The checklist was based on the dysmorphology patterns presented by Smith[19] and modified according to the reports on dysmorphic features in children exposed to alcohol in utero.[1–4 11] Fingertip patterns were classified according to Penrose.[20] Three or more arches was regarded as abnormal, as in a previous Finnish study.[21]

The frequencies of all the features given in table 1 were computed for the exposed and non-exposed groups. According to Marden *et al*[22] and Leppig *et al*,[23] only those features found in less than 5% of the 48 non-exposed children were regarded as minor physical anomalies in this study (because of the small number of non-exposed children the limit was changed from the original 4% to 5%). Of those features omitted from further analysis dysmorphic ears (three of non-exposed and nine of exposed children, $p<0{\cdot}05$) and hypoplastic philtrum (three of non-exposed and nine of exposed children, $p<0{\cdot}05$) were seen significantly more often in the exposed children. For the analysis of data the number of minor physical anomalies in each child was used as the minor physical anomaly score.

*Table 1 Checklist of 60 minor anomalies. *Those observed in more than 4% of the non-exposed children*

Abnormal head shape	Hypoplastic fingernails (fingers or toes)	Thin upper lip
Prominent forehead*	Hypoplastic phalanges*	Thick upper lip*
Abnormal suturae	Digital thumb	Prominent upper lip
Midfacial hypoplasia	Syndactyly between fingers	Small mouth
Synophrys	Syndactyly between I and II toes	Wide mouth*
Upward slanting eyes	Wide gap between I and II toes	Maxillar hypoplasia
Downward slanting eyes	Toes overlapping	Mandibular hypoplasia
Epicanthus (deeply covered upper and lower lip joint)*	III toe as long as or longer that II toe*	Posteriorly rotated ears
Hypertelorism*	Hirsutism	Dysmorphic ears*
Strabismus	Haemangiomas*	Low set ears
Ptosis	Hypopigmentation	Adherent ears
Low nasal bridge	Hyperpigmentation	Outset ears
High nasal bridge	Pectus carinatum	Asymmetric ears
Short nose*	Joint contractures	High arch palate
Anteverted nostrils	Abnormal elasticity of skin	Lateral ridges
Long philtrum	Non-descended testes	Abnormally furrowed tongue
>3 Arches (dermatoglyphics of both hands)	Hypospadia	Abnormal teeth
Brachydactyly	Hypoplastic philtrum*	Low set hair
Clinodactyly		Abnormal hair
Arachnodactyly		Simian crease*
		Inguinal hernia
		Umbilical hernia

In addition to clinical inspection the following exact measurements were taken at the 27 month assessement: (a) the largest occipitofrontal circumference (metal band), (b) philtrum length (1 mm ruler), (c) interpupillary distance (1 mm ruler), (d) distance between inner canthi (1 mm ruler), (e) distance between outer canthi (1 mm ruler), and (f) distance from upper lip to inner canthus (1 mm ruler).

The head circumference was tranformed into SD scores of Finnish normative data. Mean palpebral length was calculated by subtracting the distance between the inner canthi from the distance between the outer canthi and dividing the result by two. Palpebral length below −2SD of our non-exposed children was regarded as short.

For the analysis of relationships between the facial measurements all ratios were calculated. The following ratios will be presented in this paper: (a) distance between inner canthi/distance between outer canthi, (b) philtrum length/distance from upper lip to inner canthi, (c) philtrum length/distance between outer canthi, and (d) distance from upper lip to inner canthi/distance between out canthi.

The development level of the children was assessed by a psychologist using the manual for the Bayley scales of infant development[24] and by a speech therapist using the manual for the Reynell developmental language scales (verbal comprehension A).[16 25]

STATISTICS

The non-parametric Kruskal Wallis one way analysis of variance (3S) was used to compare the differences in the minor physical anomaly scores between the various groups; between two groups the Mann-Whitney U test was used. The difference in occurrence of two or more minor physical anomalies between the groups was tested using the χ^2 analysis and linear trend test. One way analysis of variance (ANOVA) was used to compare the morphological measurements between the groups; in pairwise analysis the Bonferroni correction was used. These measurements were also adjusted for the head circumference (ANCOVA). Differences in the occurrences of single minor physical anomalies between non-exposed and exposed children were tested for significance using Fisher's exact test for fourfold tables. A p value below 0·05 was considered significant. The computations were made using the Biomedical Data Package (BMDP).[26]

This study was accepted by the ethical committee of our hospital.

Results

The facial features of the 51 children during the first year of life are shown in table 2. All non-

Table 2 Facial features of 51 children seen during first year of life

	Normal (n=19)	*Possible FAE (n=19)*	*Typical FAS (n=10)*	*Abnormal not resembling FAS (n=3)*
Group I	9	3	1	3
Group II	8	9	1	—
Group III	2	7	8	—

exposed children were judged to have a normal looking face.

At the 27 month dysmorphic assessment we saw a significant difference between the groups in minor physical anomaly scores (table 3). Those children exposed to heavy alcohol concentrations throughout pregnancy had significantly higher minor physical anomaly scores than the children belonging to any other group (group III/any other group, $p<0.01$). There was a significant linear trend in those with two or more minor physical anomalies towards longer exposure time. Binge drinking was not connected with an increased minor physical anomaly count. No typical patterns of minor physical anomalies were formed.

Head growth was significantly affected by the duration of fetal alcohol exposure (table 4) but no differences in facial measurements were found between the groups. All horizontal distances in the eye region were significantly dependent on head circumference ($p<0.001$ for distance between outer canthi, interpupillary distance, and palpebral size; $p=0.002$ for distance between inner canthi). Vertical distances measured on the face were not dependent on the head circumference. The various relationships between the facial measurements showed no significant differences between the groups.

The single facial features mandatory for diagnosis of FAS[9] were observed more often in the exposed children; short palpebral fissure only in exposed children (table 5). No limit based on the relationships between horizontal measurements could be set to identify short palpebral fissure. The criteria of Vitez *et al* for short palpebral fissure—distance between inner canthi over one third of the distance between outer canthi—defined all the non-exposed children to have short palpebral fissure.[11] Hypoplastic philtrum and thin upper lip were observed together only in exposed children. The craniofacial criterias set by the RSA were fulfilled in two (10%) group II children and four (24%) group III children.

The six children meeting either two or three craniofacial criteria set by the RSA[9] had significantly smaller head size, interpupillary distance, distance between the outer canthi, and palpebral size (table 6). After adjustment for head circumference the mean values were smaller in the FAS group, but a significant difference was observed only in palpebral fissure length. The actual philtrum length was not significantly higher in FAS children but the ratio between philtrum length and distance from upper lip to inner canthi and the ratio between philtrum length and distance between the outer canthi were significantly higher in children who met the craniofacial criteria for FAS. However, contrary to Vitez *et al* no limit for the ratios of vertical distances could be given to define long philtrum.[11] When those features included in the craniofacial criteria for FAS were excluded from the minor physical anomaly score, these six children still had a significantly higher score (range 1–5) than non-exposed children (range 0–3) ($p<0.01$).

In order to evaluate the relationship between a subjective assessment during the first year of life and an assessment at 27 months based on strict criteria, the results of the 51 exposed children seen at both assessments were compared (table 7). All those six children who met at least two craniofacial criteria for diagnosis of FAS were judged to have a possible FAE or typical FAS face during their first year of life. However, four of the 10 children considered to have typical FAS face during their first year of life met no craniofacial criteria for FAS diagnosis at the 27 month assessment. At the 27 month assessment the 10 children assessed to have a typical FAS face during their first year of life had significantly smaller head circumference and horizontal measurements (table 6). The differences in horizontal measurements did not remain significant after adjustment for head

Table 3 Minor physical anomalies recorded per child

Group	No of children	No of minor physical anomalies							No (%) with ≥2 minor physical anomalies†
		0	1	2	3	4	5	6	
Non-exposed	48	26	13	5	4				9 (19)
Group I	16	7	5	3	1				4 (25)
Group II	19	4	8	3	3	1			7 (37)
Group III	16*		1	6	2	2	3	2	15 (94)

*One child excluded because of insufficient data.
Kruskal-Wallis between groups: $F=31.25$, $p<0.0001$.
†χ^2: $F=30.43$, $p<0.001$; linear trend: $F=24.26$, $p<0.001$.

Table 4 Results of the growth and morphological measurements. Results are mean (SEM); the numbers of children excluded because of unreliable data are in parentheses

	Non-exposed (n=48)	Group I (n=16)	Group II (n=19)	Group III (n=17)
Head circumference (SD)	0·1 (0·15)	−0·005 (0·24)	−0·58 (0·39)	−1·494 (0·34)***
Height (SD)	−0·37 (0·12)	−0·4 (0·27)	−0·63 (0·27)	−1·45 (0·25)***
Relative weight (%)	4·26 (1·49)	1·49 (2·29)	−0·08 (2·66)	−10·46 (1·40)***
Distance between inner canthi (mm)	(2) 26·02 (0·32)	26·06 (0·78)	26 (0·5)	(1) 25·5 (0·46)
Adjusted for head circumference	25·75 (0·33)	25·94 (0·55)	25·75 (0·54)	26·09 (0·58)
Distance between outer canthi (mm)	(2) 69·48 (0·42)	69·75 (0·93)	69·3 (0·68)	(1) 67·56 (0·95)
Adjusted for head circumference	68·9 (0·71)	69·5 (0·71)	69·6 (0·7)	68·8 (0·74)
Interpupillary distance (mm)	(1) 45·87 (0·32)	45·94 (0·62)	45·23 (0·5)	(1) 44·31 (0·63)
Adjusted for head circumference	45·44 (0·32)	45·79 (0·53)	45·6 (0·52)	45·04 (0·56)
Palpebral fissure (mm)	(2) 21·73 (0·14)	21·84 (0·26)	21·68 (0·25)	(1) 21·03 (0·4)
Adjusted for head circumference	21·58 (0·16)	21·78 (0·27)	21·78 (0·26)	21·35 (0·3)
Philtrum length (mm)	14·12 (0·37)	14·87 (0·54)	14·84 (0·52)	(1) 14·62 (0·364)
Upper lip to inner canthus (mm)	(3) 42·33 (0·32)	41·99 (0·95)	41·89 (0·78)	(1) 42·2 (0·55)
Inner canthi/outer canthi	0·374 (0·003)	0·373 (0·008)	0·375 (0·005)	0·378 (0·006)
Philtrum/upper lip to inner canthus	0·336 (0·007)	0·354 (0·009)	0·354 (0·011)	0·347 (0·009)
Philtrum/outer canthi	0·204 (0·005)	0·2213 (0·008)	0·214 (0·007)	0·217 (0·007)
Upper lip to inner canthus/distance between outer canthi	0·609 (0·005)	0·602 (0·013)	0·605 (0·02)	0·626 (0·011)

***$p<0.001$ compared with non-exposed children.

Table 5 Single facial features mandatory for diagnosis of FAS

	Non-exposed (n=48)	*All exposed (n=52)*	*Group I (n=16)*	*Group II (n=19)*	*Group III (n=17)*
Palpebral fissure <−2SD	0	6*	1	1	4
Hypoplastic philtrum	3	9	1	1	7
Thin upper lip	1	10*	1	2	7

*p<0·05 all exposed *v* non-exposed.

Table 6 Facial measurements of exposed children meeting two or three craniofacial criteria at the 27 month assessment in the first column and of exposed children subjectively assessed to have a FAS face during their first year of life in the second column. Results are mean (SEM) and are compared with those for non-exposed children (see table 4)

	27 month assessment: FAS face (n=6)	*First year assessment: FAS face (n=10)*
Head circumference (SD)	−2·58 (0·35)***	−2·03 (0·43)***
Distance between outer canthus (mm)	65·0 (1·05)**	65·4 (0·7)***
Adjusted for head circumference	67·3 (1·38)	66·47 (0·96)
Interpupillary distance (mm)	43·00 (0·73)*	42·9 (0·5)***
Adjusted for head circumference	44·6 (0·95)	43·56 (0·65)
Palpebral fissure (mm)	19·92 (0·69)***	20·4 (0·51)***
Adjusted for head circumference	20·45 (0·52)*	20·68 (0·38)
Philtrum length (mm)	16 (0·58)	14·9 (0·64)
Upper lip to inner canthus (mm)	41·27 (1·08)	42·9 (0·43)
Inner canthi/outer canthi	0·39 (0·009)	0·38 (0·43)
Philtrum/upper lip to inner canthus	0·39 (0·016)*	0·35 (0·012)
Philtrum/outer canthi	0·25 (0·009)**	0·23 (0·011)
Upper lip to inner canthus/distance between outer canthi	0·64 (0·027)	0·66 (0·012)***

*p<0·05; **p<0·01, ***p<0·001.

Table 7 Comparison of a subjective assessment of facial features during the first year of life and an objective assessment at 27 months of age

At 27 months of age	*Assessment of facial features during the first year of life*			
	Normal (n=19)	*FAE (n=19)*	*FAS (n=10)*	*Atypical (n=3)*
Microcephalia	1	3	4	0
Short palpebral fissure	1	1	4	0
Hypoplastic philtrum	2	5	2	0
Thin upper lip	3	3	4	0
Two or three craniofacial criteria	0	3	3	0

circumference. The restricted growth of the head meant that these 10 children had a long midface in relation to horizontal measurements. The number of minor physical anomalies was significantly higher in children judged to have FAE features (p<0·05) and FAS features (p<0·01) compared with the non-exposed children.

Thirty two (62%) of the 52 exposed children who had undergone a thorough dysmorphic study showed poor performance in the developmental tests used at the 27 month assessment. All those six children that met the craniofacial criteria for FAS in the dysmorphic study performed under the −2SD level in the development tests. All 10 children judged to have typical FAS face during their first year of life, 12/19 judged to have possible FAS face, 1/3 judged to have abnormal face not resembling FAS, and only 8/29 judged to have normal looking face performed poorly in the used developmental tests (p<0·05).

Discussion

There is no consensus regarding the specific number and types of minor physical anomalies that should be included in a dysmorphological assessment. Studies on dysmorphology in children with alcohol exposure in utero have used varying, self constructed minor dysmorphology scales.[27 28] The 18 item weighted minor physical anomaly scale of Waldrop and Halverson[29] has been used in several studies on children with behavioural problems.[30–32] It was not accepted for this study as none of the facial features mandatory for FAS diagnosis[9] are included and several of its items are observed in over 4% of Finnish children.[21] For this study we tried to form a clinically applicable and representative minor physical anomaly scale that would include those minor physical anomalies reported in children exposed to alcohol in utero.

A significantly higher total minor physical anomaly count was observed only in those children exposed to alcohol throughout pregnancy, which is in conflict with the results of Day *et al*[27] but supports the results of Tennes and Blackard.[28] Contrary to earlier studies[10 11] we were not able to form a scoring system for various minor physical anomalies or set limits for facial relationships to identify fetal alcohol effects.

Features regarded as minor physical anomalies may be formed by several mechanisms: they can represent true malformations, disruptions, deformations, or dysplasia.[33 34] True malformations arise in the first trimester during the period of organogenesis, while other types of minor physical anomaly may be formed later during gestation. As a teratogen alcohol could interfere with an originally normal developmental process causing disruption at any stage of gestation. Frias *et al* has postulated that some observed features regarded as malformations are secondary to restricted growth of the brain.[35] Fetal hypomobility during periods of alcohol exposure in utero may also cause various deformations. Our results suggest that alcohol should be regarded as a teratogen that leads to dysmorphic features, especially during the time of rapid intrauterine growth. The inconsistent drinking patterns, one to 20 drinks per day, may explain why binge drinking was not associated with a higher minor physical anomaly count in this study.

Short palpebral fissure was a constant feature in the first children with FAS reported.[4] Jones *et al* have claimed that the short palpebral fissure in children with FAS is secondary to decreased growth of the eye.[36] This has been contradicted by Bierich *et al*[37] and Fuchs *et al*.[38] Stengel-Rutkowski *et al* have shown that normally the outer canthi lateralise more than the inner canthi with increasing age.[39] In our children the distance between the outer canthi was more dependent on head circumference than the distance between the inner canthi. Our results suggest that the short palpebral fissure seen in children exposed to alcohol in utero is mainly secondary to impaired head growth, although the possible additive influence of restricted growth of the eye could not be excluded.

The subjective assessment of facial features typical of FAS during the first year of life could not be confirmed in all cases when strict criteria were used over one year later. However, those 10 children judged to have a typical FAS face

during their first year of life had significantly more minor physical anomalies than our non-exposed children, impaired head growth, and relatively long midface at the 27 month assessment as also observed by Clarren *et al.*[40] Subjective assessment of FAE or FAS features in early infancy recognised also most of those children that had been exposed prenatally to alcohol in amounts that had affected their central nervous system.

The craniofacial criteria of the RSA[9] for FAS were too strict to identify those children with clear central nervous system dysfunction but no typical FAS face.[16] It is important to learn to recognise various minor physical anomalies and subtle changes in facial relations when children with disorders of central nervous system or growth retardation of unknown aetiology are examined.

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I Autti-Rämö, E Gaily and M L Granström

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Notes