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A Fetal Alcohol Syndrome Screening Tool

Susan J. Astley and Sterling K. Clarren

The purpose of this study was to derive a multivariate, quantitative case definition of the fetal alcohol syndrome (FAS) facial phenotype from a dysmorphologist-derived gold standard and use it to develop an effective screening tool for identification of children at risk for FAS. The facial and physical features of a racially mixed group of children (0.2–10.0 years of age), evaluated by a single dysmorphologist in the University of Washington FAS Clinic, were used to determine which feature or set of features best differentiated between children with and without a diagnosis of FAS. The study population was divided into two groups balanced on gender, age at examination, race, diagnosis, and date of examination. Group 1 was used to identify the most differentiating feature(s), and group 2 was used to validate the differentiating capability of the feature(s). Group 1 included 97 children (20 with FAS and 77 without FAS). Group 2 included 97 children (19 with FAS and 78 without FAS). Discriminant analysis identified smooth philtrum, thin upper lip, and short palpebral fissures as the cluster of features that best differentiated children with and without FAS based on the discriminant function [D = 1.7953086 + 0.8116083 (thin upper lip) + 2.6411562 (smooth philtrum) − 3.4073780 (% predicted right palpebral fissure length)]. Patients with a D-score ≥ 1.5 were classified as at-risk for FAS (screen positive). Using this cut-off value for the D-score, children in group 1 were classified with 100% sensitivity (20 of 20 true positives) and 90.0% specificity (70 of 77 true negatives). The children in group 2 were classified with 100% sensitivity (19 of 19 true positives) and 87.3% specificity (68 of 78 true negatives). Across all 194 patients, sensitivity was 100% [95% confidence interval (97–100)] and specificity was 89% [95% confidence interval (85 to 93)]. Seventy-one percent (n = 12) of the 17 false-positives had a true classification of possible fetal alcohol effects. Sensitivity and specificity were unaffected by race, gender, and age through 10 years. This screening tool is effective at differentiating children with and without FAS as diagnosed by a single dysmorphologist (S.K.C.) at the University of Washington FAS Clinic. Assessment of diagnostic interrater agreement between trained dysmorphologists and testing in other clinic populations will be needed to assess the tool's external validity.

Key Words: Fetal Alcohol Syndrome, Screening.

FETAL ALCOHOL syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FAS is characterized by cognitive/behavioral dysfunction, a unique cluster of minor facial anomalies, and is often accompanied by growth deficiency. FAS is the leading known cause of mental retardation in the Western World,[1] with an estimated incidence of 1–3 per 1000 live births.[2] Not all individuals exposed to alcohol during gestation have FAS. Individuals who have been exposed to alcohol in utero and present with cognitive/behavioral disabilities, but do not have the characteristic FAS facial appearance, are often classified as having possible fetal alcohol effects (PFAEs). Unlike FAS, PFAE is not a recognized medical diagnosis, for in the absence of the FAS facial phenotype, the cognitive/behavioral dysfunction cannot be definitively linked to the prenatal alcohol exposure in any one individual.[3] The cognitive/behavioral disabilities associated with PFAE are as severe as those associated with FAS. The incidence of PFAE is unknown, but is speculated to exceed that of FAS.

Individuals with FAS endure life-long disabilities. These disabilities are often compounded by secondary disabilities, such as low self-esteem, depression, aggression, school failure, and juvenile detention when the syndrome goes undiagnosed. These secondary disabilities come at a high cost to the individual, their family, and society, and can be reduced by early diagnosis and receipt of appropriate intervention.

Failure to diagnose FAS stems in large part from the difficulty inherent in making the diagnosis. Although confirmation of central nervous system dysfunction and growth deficiency are relatively straightforward clinical procedures, diagnosis of the FAS facial phenotype is less straightforward. An accurate diagnosis of the facial phenotype is best achieved by a trained dysmorphologist. Dysmorphologists typically use a "gestalt" approach to diagnosing FAS. The gestalt (or general clinical impression) approach focuses on the whole rather than the parts. It is qualitative rather than quantitative in nature. Use of a gestalt approach to pattern recognition is not unique to dysmorphologists. Anyone who has recognized an individual as having Down's syndrome is using a gestalt method. The phenotypic expression of Down's syndrome is sufficiently distinct that one need not measure the facial features to render an accurate phenotypic diagnosis. The gestalt method is a well-accepted standard of syndrome diagnosis that can be conducted with sufficient accuracy and reproducibility when performed by trained professionals.[4] The gestalt method becomes less accurate and reproducible when conducted by untrained individuals trying to diagnose a birth defect syndrome like FAS. Lack of diagnostic accuracy not only affects the individual patient, but also curtails public health screening and surveillance efforts aimed at tracking the incidence/prevalence of FAS; tracking that is paramount to service provision and primary prevention.[5]

From the Department of Epidemiology (S.J.A.), School of Public Health and Community Medicine; and the Department of Pediatrics (S.J.A., S.K.C.), School of Medicine, University of Washington, Seattle, Washington.

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Reprint requests: Susan J. Astley, Ph.D., Children's Hospital and Medical Center, 4800 Sand Point Way, N.E., Seattle, WA 98103.

The definition of a gold standard is "a method, procedure, or measurement that is widely accepted as being the best available. Often used to compare with new methods."[6] Although there is no officially recognized gold standard for the diagnosis of FAS, the gestalt method of diagnosis performed by a trained dysmorphologist was selected to serve as the gold standard for this study. The purpose of this study was to derive a case definition of the FAS facial phenotype from this gold standard and use it to develop an effective screening tool for identification of children at risk for FAS in the University of Washington FAS Clinic.

METHODS

Overview

This study was conducted at the Centers for Disease Control-sponsored FAS Clinic at the Center of Human Development and Disabilities at the University of Washington (Seattle, WA). The FAS Clinic serves a large, racially mixed patient population, all of whom are diagnosed by a single dysmorphologist (S.K.C.) with recognized expertise in FAS. The prevalence of FAS in the patient population is 20%. All patients from birth to 10.0 years of age, evaluated in the Clinic between January 1993 (the month the Clinic opened) and January 1995, were eligible for entry into the study (n = 194). The age range was restricted to maximize the accuracy of the FAS diagnosis, because the face often becomes less specifically anomolous after puberty. The 194 patients were randomly divided into two groups (n = 97 per group) balanced on age at examination, gender, race, diagnosis, and date of examination. A discriminant analysis was used to identify the facial/physical feature(s) that best differentiated the patients with and without FAS in group 1. The multivariate discriminant equation generated by the discriminant analysis served as both the FAS phenotypic case definition and the method (or screening tool) by which risk of FAS was assessed among patients in group 2. Application of the screening tool to group 2 served as an opportunity to test (or validate) the tool's performance among the University of Washington FAS Clinic patients.

Referral Population

The University of Washington FAS Clinic sees patients of all ages from all over the State of Washington. The geographic and racial distribution of the Clinic's patient population approximates the State's population. Referred patients typically have cognitive/behavioral dysfunction and a known or suspected history of in utero alcohol exposure. A small subset of the patients are referred solely on the basis of a history of in utero alcohol exposure. This subset tends to be infants awaiting foster/adoptive care.

Diagnosis

All patients were diagnosed by a trained dysmorphologist (S.K.C.) using a "gestalt" method of diagnosis (described herein). Patients were classified into 1 of 4 categories defined as follows:

FAS: Reported in utero alcohol exposure, CNS dysfunction, distinct presentation of the FAS facial phenotype, with or without documented growth deficiency.

AFAS (atypical fetal alcohol syndrome): Reported in utero alcohol exposure, CNS dysfunction, mild presentation of the FAS facial phenotype, with or without documented growth deficiency.

PFAE: Reported in utero alcohol exposure, CNS dysfunction, absence of the FAS facial phenotype, with or without documented growth deficiency.

Other: In utero alcohol exposure reported or suspected, but no diagnosis of FAS, AFAS, or PFAE was made because of the absence of both FAS-like facial anomalies and CNS dysfunction.

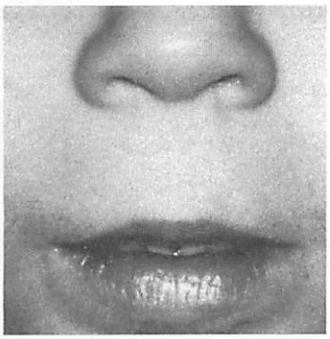
These classifications served as the "gold standard" (or true) classifications from which to compare the predicted classifications generated by the screening tool.

Measures

All patients evaluated in the FAS Clinic receive a comprehensive evaluation by a team of professionals, including a pediatrician/dysmorphologist (S.K.C.), a developmental pediatrician, a geneticist, a clinical psychologist, an educational psychologist, an educational liaison, a communication specialist, an occupational therapist, a social worker, and a public health nurse. Each patient receives a complete physical and dysmorphic examination. The physical and facial measures recorded and entered into this analysis are listed and defined in Table 1. The phenotypic

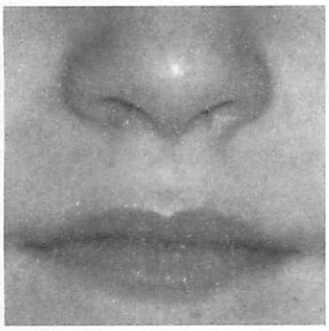
Table 1. Physical and Facial Measures Collected at the Time of Clinical Evaluation

Measure	Description
Eyes and eyebrows	
Palpebral fissure length	Distance between outer and inner canthi for right and left eyes (cm)
Inner canthal distance	Distance between right and left inner canthi (cm)
Clown eyebrows	High-arched eyebrows; (definitely, somewhat, or not present)
Ptosis	Drooping of the eyelid(s); (definitely, somewhat, or not present)
Epicanthal folds	Lateral extension of the skin of the nasal bridge down over the inner canthus; (definitely, somewhat, or not present)
Midface	
Nose length	Distance from inner canthus to the subnasion (cm)
Midface height	Distance from inner canthus to the lower border of the upper lip (cm)
Flat nasal bridge	(Definitely, somewhat, or not present)
Hypoplastic midface	Flat midface; (definitely, somewhat, or not present) (Fig. 2)
Mouth	
Smooth philtrum	Vertical ridges between the upper lip and the subnasion; (definitely, somewhat, or not present) (Fig. 1)
Thin upper lip	(Definitely, somewhat, or not present) (Fig. 1)
Abnormal palate	(Definitely, somewhat, or not present)
Palmar creases	
Hockey stick creases	(Present, absent)
Body measures	
Height	Height percentile for age and gender
Weight	Weight percentile for age and gender
OFC	% predicted occipital frontal circumference (OFC) for age and gender



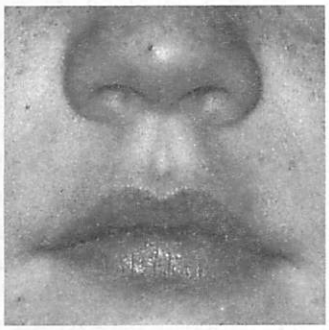
Definitely smooth philtrum and definitely thin upper lip

Likert scale 2



Somewhat smooth philtrum and somewhat thin upper lip

Likert scale 1



Well defined philtrum and full upper lip

Likert scale 0

Fig. 1. Illustration of the 3-point Likert scale used to rank smooth philtrum and thin upper lip.

expression of several facial features are ranked on a 3-point Likert scale (definitely present, somewhat present, and not present). Pictorial examples of each of these rankings for thin upper lip, smooth philtrum, and hypoplastic midface are presented in Figs. 1 and 2. Right and left palpebral fissure lengths were measured for all patients and were found to be identical in 85% of the patients and within 0.1 cm of one another in 97% of the patients. Therefore, the right palpebral fissure length was arbitrarily selected for entry into the analysis. Several of the measures were transformed to age and/or sex-standardized measures as follows. Right palpebral fissure length, inner canthal distance, and occipital frontal circumference were converted to percent predicted measures for age and/or gender using formulas derived from plots of normal values published in Hall et al.[7] The formuli used to compute percent predicted palpebral fissure length for age were:

Predicted mean palpebral fissure length (mm)

$$= 19.154 + 3.2385\,(\text{age}) - 0.6242\,(\text{age}^2) + 0.0689\,(\text{age}^3) - 0.0037\,(\text{age}^4) + 0.000076\,(\text{age}^5)$$

where age is measured in years and is between 0 and 16 years.

Percent predicted right palpebral fissure length (PFL)

$$= \text{observed right PFL/predicted mean PFL}.$$

Height (cm) and weight (kg) were converted to height and weight centiles adjusted for age and gender using EPI-INFO, public-domain software distributed by the Centers for Disease Control and Prevention.[8] Norms for nose length and midface height were not available; therefore, the nose/midface ratio was used rather than the absolute measure of each feature.

Discriminant Analysis and Computation of Sensitivity and Specificity

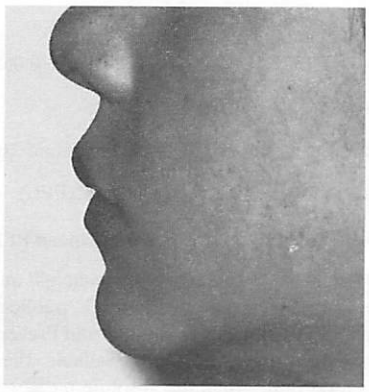
Discriminant analysis with step-wise variable selection (Wilk's lambda; F to enter = 3.84, F to remove = 2.71) was used to identify the physical features that best differentiated patients with and without FAS/AFAS. Prior probability of FAS/AFAS was computed from the prevalence in the study sample. The unstandardized canonical discriminant function coefficients were computed to derive the formula for calculation of each patient's discriminant score (or D-score). The D-score was used to classify whether or not a patient was at risk for FAS/AFAS. The D-score distributions for the patients with and without FAS/AFAS in group 1 were plotted to identify the D-score cut-off value that resulted in the highest sensitivity and specificity with priority given to maximizing the sensitivity. Sensitivity is the proportion of patients with FAS/AFAS who are correctly screened positive for FAS/AFAS. Specificity is the proportion of patients without FAS/AFAS who are correctly screened negative for FAS/AFAS.

D-scores for patients in group 2 were computed using the discriminant equation derived from group 1. Patients with D-scores ≥ 1.5 were classified as at-risk for FAS/AFAS (screen positive). Patients with D-scores < 1.5 were classified as not at risk for FAS/AFAS (screen negative). The sensitivity and specificity of the discriminant function (or screening tool's) performance were computed for group 2 as previously described.

RESULTS

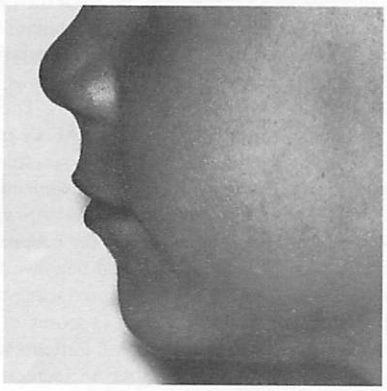
The total population of 194 patients, 0.2–10.0 years of age, was divided into two groups ($n = 97$ per group) and successfully balanced on age at examination, gender, race, diagnosis, and date of examination (Table 2). Selected physical and facial characteristics of all patients are presented by diagnostic category (FAS, AFAS, PFAE, and Other) in Table 3. As would be expected, the presence of many of the individual physical and facial characteristics decrease as one progresses from the diagnostic classification of FAS, AFAS, PFAE, to Other. No two children with FAS had an identical pattern of facial features. The variation of phenotypic expression across the 27 children with FAS is displayed in Fig. 3.

In group 1, step-wise discriminant analysis selected hypoplastic midface, smooth philtrum, and thin upper lip as the three characteristics that best differentiated the patients with and without FAS/AFAS (sensitivity = 100%, specificity = 89.4%). Palpebral fissure length and hypoplastic midface were observed to be correlated (Spearman rank correlation coefficient = -0.37, $p < 0.000$) (Fig. 4). In an effort to identify features that could be most accurately recorded and were least influenced by race, palpebral fissure length was substituted for hypoplastic midface in the model without any loss of discrim-



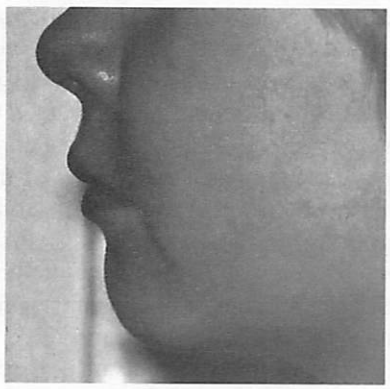
Definitely Hypoplastic Midface

Likert Scale = 2



Somewhat Hypoplastic Midface

Likert Scale = 1



Well Developed Midface

Likert Scale = 0

Fig. 2. Illustration of the 3-point Likert scale used to rank hypoplastic midface.

inating power. Because a flattened midfacial profile is a "normal" characteristic in some races (including Asian and American Indian), inclusion of this feature would limit the positive predictive value of the tool. Discrimination was best when smooth philtrum and thin upper lip were dichotomized as 0 = not present, 1 = somewhat/definitely present. The discriminant equation for computation of the D-score was:

$$D = 1.7953086 + 0.8116083\ (\text{thin upper lip}) + 2.6411562\ (\text{smooth philtrum}) - 3.4073780\ (\%\ \text{predicted right palpebral fissure length}).$$

This discriminant equation served as the quantitative, multivariate, phenotypic case definition for FAS/AFAS. A D-score cut-off value of ≥1.5 = at-risk for FAS/AFAS resulted in the maximum sensitivity (100%; 20 of 20 correctly classified as having FAS/AFAS) and specificity (90.9%; 70 of 77 correctly classified as not having FAS/AFAS) for patients in group 1. The discriminant equation classified the FAS/AFAS risk of group 2 patients with 100% sensitivity (19 of 19 correctly classified as FAS/AFAS) and 87.2% specificity (68 of 78 patients correctly classified as not having FAS/AFAS).

Across groups 1 and 2 combined, the discriminant formula classified the patients' FAS/AFAS risk status with 100% sensitivity (39 of 39 true positives) and 89% specificity (138 of 155 true negatives). The 95% confidence intervals for the estimate of sensitivity was 97–100%. The 95% confidence interval for the estimate of specificity was 85–93%. The distribution of D-scores for all 194 patients with and without FAS/AFAS is illustrated in Fig. 5. Seventeen of the 197 patients (9%) were classified as false-positives. Twelve of the 17 false-positive classifications (71%) had a true classification of PFAE. Selected characteristics of these 17 patients are presented in Table 4. Misclassification was not associated with race, gender, or age. Race, gender, and age had little influence on the sensitivity and specificity, as illustrated in Table 5. Three of the 194 patients had other syndrome diagnoses: Marfan syndrome, William's syndrome, and Schprintzen's syndrome. None of these patients received a diagnosis of FAS/AFAS in the FAS Clinic, and all three were correctly screened as not having FAS/AFAS.

Table 2. Illustration of the Balance Achieved on Selected Characteristics between Groups 1 and 2

Characteristic	Group 1 (n = 97)	Group 2 (n = 97)
Age at time of exam [mean (SD)]	5.3 (2.6)	5.2 (2.6)
Females [n (%)]	43 (44)	43 (44)
Race [n (%)]		
Caucasian	46 (47)	47 (48)
African American	11 (11)	7 (7)
American Indian	20 (21)	19 (20)
Alaskan Native	4 (4)	3 (3)
Asian	0 (0)	1 (1)
Other	16 (17)	20 (21)
Diagnosis [n (%)]		
FAS	14 (14)	13 (13)
AFAS	6 (6)	6 (6)
PFAE	57 (59)	56 (58)
Other	20 (21)	22 (23)

Table 3. Physical and Facial Characteristics among the Different Diagnostic Groups

Characteristic	1 FAS (n = 27)	2 AFAS (n = 12)	3 PFAE (n = 113)	4 Other (n = 42)	Total (n = 194)	Statistic	p value and group contrasts
Age at exam [mean (SD)]	5.1 (2.5)	5.2 (2.8)	5.4 (2.6)	4.9 (2.6)	5.2 (2.6)	F, 0.4	0.74
Female [n (%)]	10 (37)	7 (58)	48 (43)	21 (50)	86 (44)	χ^2, 2	0.52
Race [n (%)]							
Caucasian	13 (48)	5 (42)	56 (50)	19 (45)	93 (48)	χ^2, 9	0.89
African American	4 (15)	1 (8)	8 (7)	5 (13)	18 (9)		
American Indian	4 (15)	4 (33)	23 (20)	8 (19)	39 (20)		
Alaskan Native	1 (4)	1 (8)	4 (4)	1 (2)	7 (4)		
Asian	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)		
Other	5 (18)	1 (8)	22 (19)	8 (19)	36 (18)		
Parity of index child							
Mean (SD)	3.5 (2.1)	3.6 (1.9)	2.7 (1.6)	2.3 (1.4)	2.7 (1.7)	FL, 8	0.006
n*	22	9	103	37	171	SNK	1 ≠ 4
Birth weight [kg, mean (SD)]	2.7 (0.8)	2.8 (0.5)	3.1 (0.7)	2.9 (0.5)	3.0 (0.7)	F, 3	0.03
n	17	9	89	34	149	SNK	1 ≠ 3
Gestational age [(wks), mean (SD)]	36.2 (4.0)	37.9 (3.0)	38.2 (2.7)	37.9 (2.3)	37.9 (2.8)	FL, 3	0.07
n	15	8	65	29	117		
Weight for age centile [mean (SD)]	24 (24)	54 (34)	52 (31)	46 (30)	47 (32)	FL, 8	0.002
						SNK	1 ≠ 2, 3, 4
Height for age centile [mean (SD)]	26 (28)	39 (32)	43 (32)	39 (28)	40 (31)	FL, 3	0.09
% predicted OFC	0.97 (0.04)	1.00 (0.03)	0.99 (0.07)	0.99 (0.03)	0.99 (0.03)	FL, 3	0.08
% Predicted right palpebral fissure length [mean (SD)]	0.81 (0.05)	0.87 (0.09)	0.89 (0.08)	0.89 (0.09)	0.88 (0.09)	FL, 16	0.0001
						SNK	1 ≠ 2, 3, 4
Ptosis [n (%)]	7 (26)	5 (42)	8 (7)	2 (5)	22 (11)	MH, 12	0.0005
Clown eyebrows [n (%)]	7 (26)	0 (0)	7 (6)	0 (0)	14 (7)	MH, 12	0.0005
Epicanthal folds [n (%)]	14 (52)	7 (58)	37 (33)	19 (45)	76 (39)	MH,	0.72
						0.1	
Hypoplastic midface [n (%)]	24 (89)	10 (91)	26 (23)	8 (19)	68 (35)	MH, 48	<0.0000
Abnormal palate [n (%)]	11 (41)	2 (17)	21 (19)	9 (21)	41 (21)	MH, 8	0.005
Nose length/midface height [mean (SD)]	0.64 (0.08)	0.61 (0.03)	0.65 (0.06)	0.64 (0.05)	0.64 (0.06)	F, 2	0.12
Smooth philtrum [n (%)]	27 (100)	12 (100)	16 (14)	6 (14)	61 (31)	MH, 80	<0.0000
Thin upper lip [n (%)]	25 (93)	11 (92)	35 (31)	11 (26)	82 (42)	MH, 41	<0.0000
Hockey stick palmar creases [n (%)]	7 (27)	5 (42)	26 (25)	6 (14)	44 (23)	MH, 3	0.09

FL, F statistic—one-way analysis of variance test for weighted linear trend; F, F statistic—one-way analysis of variance; SNK, Student-Newman-Keuls multiple comparison test used to identify which group pairs differed at $p < 0.05$; MH, Mantel-Haenszel test for linear association across the diagnostic categories; χ^2, Pearson χ^2 test; OFC, occipital frontal circumference.

* Sample size is reported when they differ from the total sample size in each diagnostic group.

DISCUSSION

This study has demonstrated that children with and without FAS, as diagnosed by a single dysmorphologist (S.K.C.) at the University of Washington FAS Clinic, can be consistently differentiated based on the combined level of expression of three facial features: palpebral fissure length, philtrum smoothness, and upper lip thinness. The clinical population included males and females, 0.2 and 10 years of age, from several racial backgrounds, including Caucasian, African, American, American Indian, Alaskan Native, Asian, Hispanic, and Mexican American. The screening tool performed with a high level of accuracy, with minimal influence by gender, race, and age up to 10 years. The patient population was purposely restricted to individuals ≤10.0 years of age, because it is well documented that the FAS facial features often change with the onset of adolescence.[9–12]

The development of this FAS screening tool represents a potential turning point in our ability to reliably and effectively screen children at risk for FAS. Emphasis was placed on identifying discriminating facial features for several reasons. First, they can be readily measured by individuals other than fully trained dysmorphologists/clinical geneticists. Second, unlike CNS dysfunction and growth deficiency, the facial phenotype is the only aspect of the syndrome that is specific to FAS, thereby serving as an ideal screening factor. Third, the facial features captured in this screening tool can be readily assessed from facial photographs, opening up the possibility of conducting population-based screening and/or surveillance with relative ease and efficiency. A recently completed pilot study (n = 20) assessing the feasibility of developing an FAS screening tool using facial features captured from photographs resulted in 100% sensitivity and specificity (Astley and Clarren, unpublished data).

This study represents the first step in the development of this tool. The next step is to test its performance in other clinical and population-based samples. Application in a variety of populations will serve to further validate its sensitivity and specificity, as well as document it's predictive value positive (PV+) and negative (PV−) in the field. The PV+ is the probability that a person with a positive FAS screening result does indeed have FAS. The PV− is the probability that a person with a negative FAS screening result does not have FAS. PV+ and PV− are dependent on the sensitivity and specificity of the screening tool, as well as the prevalence of FAS in the population being screened.

The performance of this screening tool is dependent on the accuracy and precision with which morphometric data is collected and to that end, standardized methods of data collec-

tion must be established[13] and intra- and interrater reliability will need to be documented. The gold standard selected for use in this study was the clinical judgment of a single dysmorphologist (S.K.C.). Because a formal assessment of diagnostic agreement between trained dysmorphologists has never been conducted, the results of this study reflect the clinical judgment of this dysmorphologist.[14]

One of the purposes of this study was to derive a case definition of the FAS facial phenotype using the gestalt method of diagnosis as the gold standard. The FAS facial phenotype is characterized by a cluster of minor facial anomalies that include small palpebral fissures, a flat midface, a smooth philtrum, and a thin upper lip.[15] But how small do the palpebral fissures have to be? How thin must the upper lip be? How is thinness measured? What combination of features must be present to establish a phenotypic diagnosis? Must all features be present? Are four of five sufficient? These are questions continually being asked by clinicians and researchers faced with diagnosing or classifying individual patients. Because the gestalt method of diagnosis does not rely on direct measurement of these features, answers to these questions have never been available. Without answers to these questions, establishment of an FAS phenotypic case definition has remained elusive. By quantitatively recording the phenotypic expression of facial features in our patient population, discriminant analysis was able to derive a multivariate, quantitative case definition that, for the first time, provides answers to these questions. Establishment of a case definition will provide a consistency of diagnosis across clinical and research

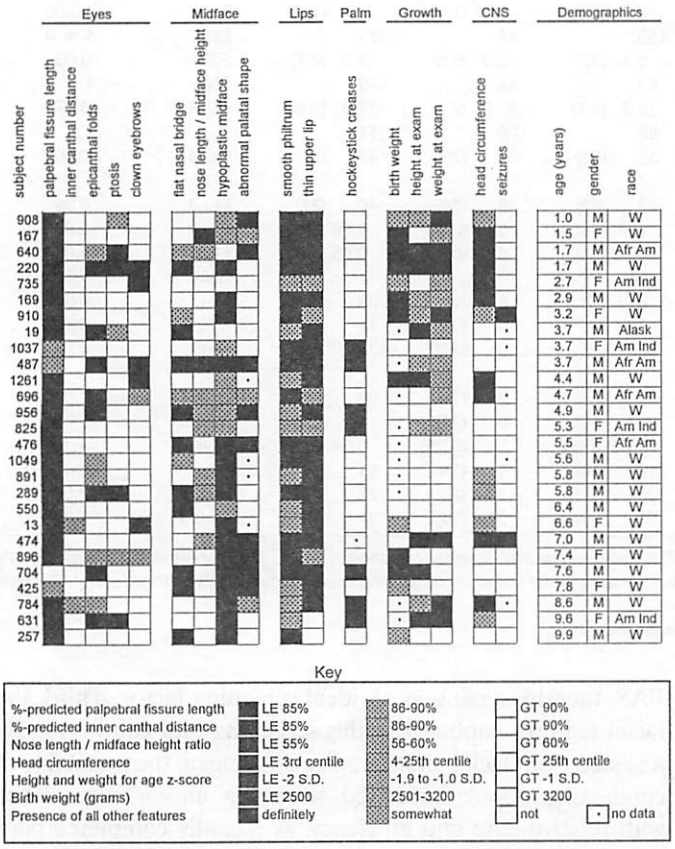


Fig. 3. Variability of selected facial and physical features among the 27 children with FAS. LE, less than or equal to; GT, greater than; W, White; Afr Am, African American; Am Ind, American Indian; Alask, Alaskan Native.

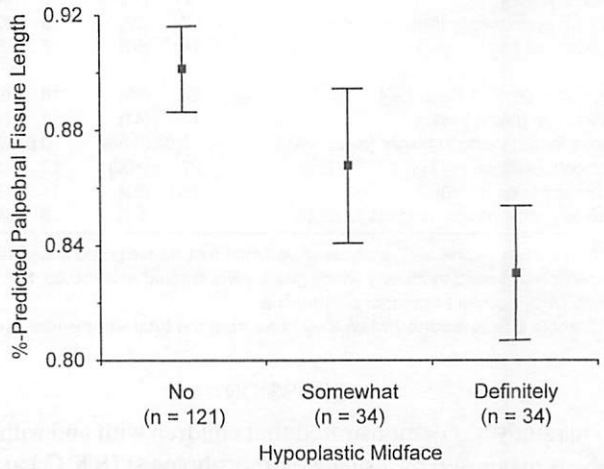


Fig. 4. Correlation between percent predicted right palpebral fissure length for age and midface hypoplasia among the 194 children (0.2–10.0 years of age). The mean and 95% confidence intervals are displayed. Mean percent predicted right palpebral fissure length ± 1 SD for each midface group are as follows: no (0.90 ± 0.08); somewhat (0.87 ± 0.08), and definitely (0.83 ± 0.07). One-way analysis of variance, linear trend, $F = 22.9$, $p < 0.0000$.

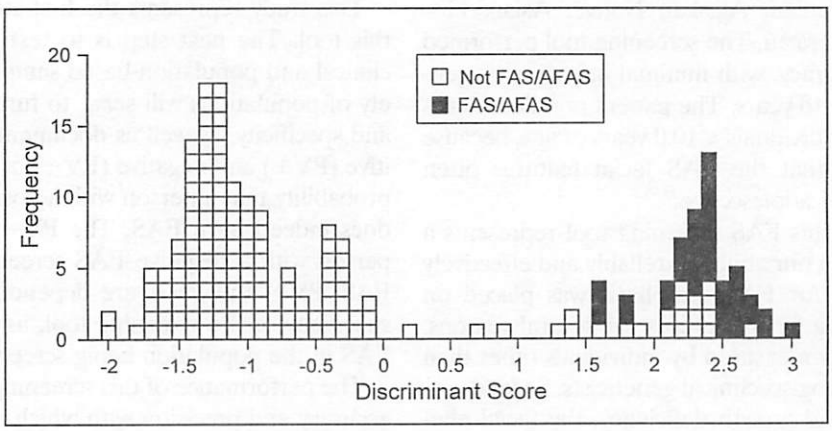


Fig. 5. Distribution of discriminant scores among the patients with (■) and without (□) FAS/AFAS across study groups 1 and 2 combined ($n = 194$).

Table 4. Selected Characteristics of the 17 Patients without FAS/AFAS Who Were Screened Positive for FAS/AFAS by the FAS Screening Tool

Diagnosis	Gender	Race	Age (yr)	Thin lip	Smooth philtrum	% Predicted palpebral fissure length for age	Discriminant score
PFAE	M	Am Ind	6.8	No	Somewhat	85	1.55
PFAE	F	Wh	6.6	No	Somewhat	77	1.80
PFAE	F	Wh	1.7	No	Somewhat	73	1.94
PFAE	F	Wh	6.0	Yes	Yes	93	2.07
PFAE	M	Wh	7.0	Yes	Somewhat	92	2.12
Other	M	Am Ind	9.9	Yes	Somewhat	91	2.15
PFAE	F	Wh	8.8	Somewhat	Somewhat	89	2.21
PFAE	F	Wh	2.9	Yes	Somewhat	89	2.22
Other	F	Wh	6.4	Yes	Yes	89	2.22
Other	M	Afr Am	4.7	Somewhat	Yes	88	2.25
PFAE	F	Wh	7.5	Yes	Somewhat	87	2.27
PFAE	M	Wh	7.4	No	Somewhat	62	2.33
PFAE	M	Wh	4.3	Somewhat	Somewhat	85	2.35
PFAE	M	Wh	7.1	Somewhat	Somewhat	84	2.38
Other	M	Wh	5.3	Yes	Somewhat	83	2.41
PFAE	M	Wh	8.3	Somewhat	Somewhat	83	2.43
Other	M	Wh	9.2	Yes	Somewhat	74	2.72

Subjects are listed in order of increasing discriminant score. Other, not FAS, AFAS, or PFAE; Am Ind, American Indian; Wh, White; Afr Am, African American; discriminant score, computed using the formula presented in the text.

Table 5. Sensitivity and Specificity of the FAS Screening Tool Stratified by Gender, Age, and Race, among Groups 1 and 2 Combined

Characteristic	*n*	Sensitivity (%)	95% CI	(*n*/*n*)	Specificity (%)	95% CI	(*n*/*n*)
Males	108	100	(96–100)	(22/22)	87	(80–94)	(75/86)
Females	86	100	(95–100)	(17/17)	90	(83–97)	(62/69)
Young (0–5.0 yr)	92	100	(96–100)	(20/20)	93	(87–99)	(67/72)
Old (5.1–10.0 yr)	102	100	(96–100)	(19/19)	84	(76–92)	(70/83)
Caucasian	93	100	(95–100)	(18/18)	84	(76–92)	(63/75)
African American	18	100	(91–100)	(5/5)	92	(77–100)	(12/13)
American Indian	39	100	(93–100)	(8/8)	94	(86–100)	(29/31)
Alaskan Native	7	100	(86–100)	(2/2)	100	(91–100)	(5/5)
All other races	36	100	(92–100)	(6/6)	90	(79–100)	(27/30)

CI, confidence interval.

arenas that currently does not exist. This study does not proclaim to have established *the* FAS phenotypic case definition. The case definition must be reached by consensus across clinical and research teams. This study simply presents a methodologic approach that could be used to derive a phenotypic case definition.

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