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Fetal Alcohol Spectrum Disorders: Clinical Phenotype Among a High-Risk Group of Children and Adolescents in Korea

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Abstract

Little is known about the prevalence and phenotype of fetal alcohol syndrome (FAS) or spectrum disorders (FASD) in Korea. This study was performed to describe the distribution of alcohol-related physical features in a genetically homogeneous sample of children and adolescents in institutional settings in Korea. Children and adolescents receiving services in one of seven institutions in Seoul, Korea were screened for growth deficiency. Those who screened positive were assessed using a structured protocol for the key cardinal features of FAS, and for 11 additional alcohol-related dysmorphologic features. Based on these findings, children and adolescents were categorized as FAS, Deferred (some characteristic features of FAS), and No FAS. Groups were compared on the prevalence of specific additional features and number of additional features, stratified by gender and age. Of 307 children and adolescents screened, 87 received the dysmorphology evaluation. Thirteen were classified as FAS, 44 Deferred, and 30 No FAS. The frequency of 10 of the 11 additional alcohol-related features did not differ significantly by FAS category. Palmar crease abnormalities were more common in FAS (53.8%) than in the Deferred category (25.0%) or the No FAS category (6.7%) ($P = 0.003$). A high prevalence across all groups was found for midfacial hypoplasia and epicanthal folds, whereas only one child exhibited ptosis. This study suggests that an FASD phenotype variant related to ethnic differences in the range of defects specific to prenatal alcohol exposure may be present in the Korean population.

Keywords

fetal alcohol spectrum disorders; fetal alcohol syndrome; ethnic differences; alcohol-related physical features; FASD phenotype variant; Korea

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Conflict of interest: None.

INTRODUCTION

The effects of prenatal exposure to alcohol on the developing fetus include a range of defects termed fetal alcohol spectrum disorders (FASD) [Jones and Smith, 1973; Streissguth et al., 1991; Astley and Clarren, 2000; Chudley et al., 2005; Hoyme et al., 2005]. Though the phenotype (growth deficiency, microcephaly, and specific key alterations in facial development) of fetal alcohol syndrome (FAS), the most severe end of the spectrum, has been well established, a number of studies clarifying the broader phenotype of FASD and variability in different cultural and race/ethnic groups have been in progress [Jones et al., 2010; May et al., 2010]. Jones et al. [2010] reported in one study on eight specific additional structural defects seen more frequently in children with FASD (railroad track ears, ptosis, heart murmur, decreased elbow pronation/supination, incomplete extension of one or more digits, other joint contractures, hockey stick crease, and other palmar crease abnormalities).

Most studies that have estimated the prevalence of FASD and described the clinical phenotype have been conducted in non-Asian countries [Sampson et al., 1997; May et al., 2006; Urban et al., 2008]. We are not aware of any study that has documented either the prevalence or the phenotypic expression of FASD in an Asian population. As risky alcohol consumption has been increasing in recent years among young females in Korea [Lee et al., 2010], it is essential that the expression of FASD in the Korean population be determined.

This study was performed to investigate the prevalence of the physical features of FAS and the broader phenotype of FASD in a genetically homogenous population of Korean children and adolescents. Given the known associations between FASD and cognitive impairment as well as involvement with child welfare systems [Lange et al., 2013], the study was conducted among a sample of children receiving services in institutional settings.

MATERIALS AND METHODS

Study Population

Between the August 2nd and 6th, 2010, Korean children and adolescents from seven institutions (four institutions for children and adolescents with intellectual disability, two orphanages, and one school providing special education for the handicapped) in Seoul and Gyeonggi-do, South Korea were screened by the teachers at the institutions for growth deficiency (≤10th centile for age and sex on weight or height) using standard growth curves for Korean children [An, 2007]. Those children who met the criteria for growth deficiency were referred for a full dysmorphology evaluation for features of FASD. Children with disabilities or disorders of known etiology and not alcohol-related, such as Down Syndrome or cerebral palsy were identified by the investigators as ineligible for the study based on information obtained from medical records or medical history. The present study was approved by the Institutional Review Board of Uijeongbu St. Mary's Hospital, The Catholic University of Korea.

Dysmorphology Assessment

Dysmorphology evaluations were performed by a single examiner (KLJ). All subjects were assessed using a structured protocol for the key specific dysmorphologic features that

constitute FAS (short palpebral fissure length (PFL)), smooth philtrum, thin vermilion border, microcephaly, and growth deficiency) and selected additional alcohol-related features including 11 features that have been associated with the broader phenotype ("railroad track" ears, ptosis, heart murmur, decreased elbow pronation/supination, incomplete extension of one or more digits, other joint contractures, "hockey stick" palmar crease, other palmar crease abnormalities, strabismus, midfacial hypoplasia, and epicanthal folds) [Jones et al., 2010].

Height, weight, and occipital frontal circumference (OFC) were measured and their age-specific centiles were determined using standard growth curves for Korean children [An, 2007]. PFL was measured, and its age-specific centile was determined using a previously published chart [Thomas et al., 1987]. The morphologic characteristics of the upper lip and philtrum were assessed and scored with the lip/philtrum guide described by Astley and Clarren [Astley and Clarren, 2000]. Likert scale scores between one and five were assigned for the thinness of the vermilion border of the upper lip and the flatness/smoothness of the philtral ridges, with higher scores indicating greater thinness or flatness/smoothness. Scores of four or five for each scale were considered to be consistent with FASD.

All the subjects were categorized into one of three groups based solely on physical features and growth: FAS, Deferred, and No FAS. Subjects were classified as "FAS" on the basis of the presence of the following key features: PFL ≤10th centile, a smooth philtrum (score of 4 or 5), a thin vermilion border (score of 4 or 5), microcephaly (OFC ≤10th centile), and growth deficiency (height and/or weight ≤10th centile). Subjects were classified as "Deferred" if they had some features suggestive of FAS, but insufficient to meet the specific diagnostic criteria for FAS (e.g., only one key facial feature, only growth deficiency and microcephaly, or growth deficiency or microcephaly, and one of the additional alcohol-related features evaluated). Subjects who did not meet the criteria for either the FAS or Deferred group were classified into a "No FAS" group.

In this classification scheme, information was not available on prenatal alcohol exposure, nor was any study-related comprehensive neurobehavioral testing performed. For these reasons, the classifications were based on physical features and growth alone. The criteria used for the FAS category were consistent with the criteria for FAS as defined by Hoyme et al. [2005]. The Deferred category was less restrictive than the partial FAS diagnosis as defined by Hoyme et al. [2005] in that fewer key facial features or growth deficiencies were required. Without documented alcohol exposure or comprehensive neurobehavioral testing, it was not possible to classify children as having or not having Alcohol Related Neurodevelopmental Disorder (ARND) in this study setting.

Statistical Analysis

Characteristics of the study children were compared across the three diagnostic classification groups of FAS, Deferred and No FAS using Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. We compared the prevalence of the specific additional features and the number of features (0, 1, 2, or more) across diagnostic classification groups using Fisher's exact test. We further examined, the number of any additional features within FAS diagnostic category by age group (< 12 years and 12 or

older) and child sex using Fisher's exact test. Statistical analysis was performed using SPSS (Release 15.0.1.1, version 17.0; SPSS, Inc. (Chicago, IL), 1989–2006. *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 307 children and adolescents were initially screened for growth across the seven participating institutions. Of these, 113 children screened positive for growth and were referred for the full dysmorphological evaluation. At the time of the dysmorphological evaluation, 15 children were not available, and 11 children were excluded (two with Down Syndrome, four with cerebral palsy, and five who refused to cooperate with the evaluation). The final sample consisted of 87 children who received the dysmorphological evaluation. Of the 87 subjects evaluated, 13 were classified as FAS, 44 as Deferred, and 30 as No FAS. There were no significant differences among the three groups with respect to age at the time of examination, sex ratio, height, and weight (Table I). However, there were differences in the proportion classified as intellectually disabled (defined as a full-scale IQ score under 70), differences in the proportion classified as microcephalic, and a significant difference in head circumference across groups, with impairment in FAS>Deferred>No FAS (Table I). Intellectual disability was significantly correlated with microcephaly ($P = 0.001$).

As shown in Table II, among the 11 specific additional features evaluated, only other palmar crease abnormalities demonstrated a statistically significant difference between groups, with FAS>Deferred>No FAS. Although not statistically significant, the direction of the associations for railroad track ears, decreased elbow pronation/supination, incomplete extension of one or more digits, and hockey stick crease was also suggestive of the expected pattern of FAS>Deferred>No FAS. Ptosis, heart murmur, and other joint contractures were infrequently observed or not observed at all across groups. There were no significant differences across groups for strabismus, midfacial hypoplasia or epicanthal folds. Although there was evidence of increased frequency of strabismus in FAS compared to Deferred or No FAS, the prevalence of midfacial hypoplasia and epicanthal folds was high in all groups.

We also examined, the association between mental deficiency and the one additional feature that significantly differed across groups, other palmar crease abnormalities, and found no association ($P = 0.293$).

Comparisons on the number of the additional features (0, 1, 2, or more) by FAS classification resulted in statistically significant differences in the expected direction (Table III). However, number of additional features did not differ by child sex or age category (Tables IV and V).

DISCUSSION

In this study, we identified 13 children who met criteria based on physical features alone for full FAS. Within these special institutional settings, this number represents 14.9% of those who screened positive (13/87) and 4.2% of all children in the sample (13/307). Our findings are comparable to those of Strömland et al. [2015] who evaluated 94 children in a Brazilian orphanage setting, and found 3.2% with full FAS and 17% with the broader classification of

FASD. Our findings are also consistent with the prevalence estimate developed in the recent meta-analysis conducted by Lange et al. [2013], in which published studies that used active case ascertainment were analyzed to derive a pooled prevalence estimate of 6% for FAS and 16.9% for FASD.

With respect to the additional features of FASD that were evaluated, we can compare to the larger international sample of 831 children reported by Jones et al. [2010], of whom 245 had FAS, 244 were Deferred and 342 No FAS. It should be noted in that sample, although there was race/ethnic diversity, only nine children were classified as Asian and only eight additional features were evaluated. In both studies, the number of additional features was clearly related to the FAS category. In both studies, there was no evidence of differences in the number of additional features by sex. In both studies, there was some evidence of a greater number of additional features detected in those children who were 12 years or older.

However, the distribution of some specific features differed in our study. The frequency distribution of decreased elbow pronation/supination, incomplete extension of one or more digits, other joint contractures and hockey stick palmar crease were similar to the larger international sample, despite the smaller numbers of children in each category in the Korean sample. However, children in the Korean sample more commonly had railroad track ears (38.5% of those with FAS, 29.5% of Deferred) compared to the larger international sample (11.8% of those with FAS, and 4.1% of Deferred). Similarly, children in the Korean sample were more likely to have other palmar crease abnormalities (53.8% of FAS, 25.0% of Deferred) compared to the international sample (15.5%ofFAS,7.3%ofDeferred). In addition, in the Korean sample, other palmar crease abnormalities was the only additional feature that varied significantly by FAS classification.

Although not statistically significantly different in the Korean sample, 15.4% of children in the FAS category exhibited strabismus compared to 9.1% in the Deferred and 3.4% in the No FAS groups. These figures can be compared to general population prevalence estimates. In a sample of 3009 Chinese children 6–72 months of age, 0.8% had strabismus [Chia et al., 2010]. In contrast, in a U.S. sample of children in the same age range, 3.6% of 1522 Asian and 3.2% of 1514 non-Hispanic white children had strabismus [McKean-Cowdin et al., 2013].

However, perhaps more relevant to the present study are data from a sample of children in a Brazilian orphanage who were evaluated by Strömland et al. [2015]. Children in that study received a comprehensive ophthalmologic evaluation in addition to an assessment for FASD. Among all children evaluated, the overall prevalence of any ophthalmologic abnormality was 16%; the prevalence of strabismus was 7%. Of the 16 children in the sample who received an FASD diagnosis, only the three who were classified with full-blown FAS had any ophthalmologic abnormalities, one of whom had strabismus. Although numbers were small in both studies, the finding of a higher risk of strabismus in Korean children with FAS is consistent with the orphanage study in Brazil.

Although the study subjects in Korea were selected from high-risk settings, the near absence of ptosis (1 of 87 children or 1.1%), the high prevalence of midfacial hypoplasia across all

groups (57 of 87 children or 65.5%), and epicanthal folds (79 of 87 children or 90.8%) was notable. Each of these three features are regarded as clinical findings characteristic of FASD in the dysmorphology scoring system [Hoyme et al., 2005]. In contrast, our findings likely reflect underlying ethnic differences in the Korean population, suggesting that these features may be unrelated to prenatal alcohol exposure in this ethnic group. Midfacial hypoplasia and epicanthal folds are thought to be a normal inherent variant, and ptosis may have a different diagnostic value for FASD among Koreans.

There is some evidence in the literature for ethnic variation in the FAS or FASD phenotype. For example, Jones et al. [2010] reported that FAS children classified as “white” race exhibited more additional alcohol-related features than those of Cape Colored ethnicity in South Africa. Similarly, May et al. [2010] reported variations in dysmorphic features believed to be specific for FASD diagnosis across three populations (Northern Plains American Indian, South African, and Italian). In each of these three populations, there were specific dysmorphologic features that were more or less relevant to the FASD phenotype in that group, that is, considered either a normal genetic variant for that population, or represented a different FASD diagnostic value. Our study had limitations that require consideration. The sample size was small which limited statistical power for detecting differences across groups. The specific high-risk settings in which children were identified cautions against generalizing the results. And finally, information regarding history of prenatal exposure to alcohol was not obtained and was not integrated with the results.

In summary, this study suggests that an FASD phenotype variant may be present in Korean population, which should be considered in the diagnosis. To confirm and clarify these findings regarding FASD phenotypes among Asian ethnicities, further studies in a larger population with alcohol exposure histories, and in other Asian groups will be required.

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TABLE 1

Characteristics of 87 Children and Adolescents Who Screened Positive on Growth Deficiency and Received the Dysmorphology Examination, Korea, 2010

	FAS	Deferred	No FAS	*P*-value
N	13	44	30	
Age in years at the time of examination—mean±standard deviation (range)	12.5±3.0	107±3.6	11.2±2.9	0.252[b]
	(72–17.2)	(4.0–12.8)	(4.3–15.3)	
Male—n (%)	11 (84.6)	27 (28.8)	19 (63.3)	0.339[a]
Height in cm— mean±standard deviation	130.0±17.8	129.3±18.9	137.4±15.1	0.141[b]
Weight in kg—mean±standard deviation	26.3±9.9	27.0±9.4	31.8±8.8	0.063[b]
Occipital frontal circumference in cm —mean±standard deviation	50.2±1.8	51.4±2.3	53.9±3.5	<0.001[b]
Microcephaly OFC ≤10th centile—n (%)	13 (100)	20 (45.5)	3 (10)	<0.001[a]
Intellectual Disability IQ <70—n (%)	11 (84.6)	31 (20.5)	13 (43.3)	0.015[a]

[a] Fisher's exact test.

[b] ANOVA.

TABLE II

Prevalence of Additional Features by Fas Diagnostic Category in 87 Children and Adolescents, Korea, 2010

Feature	N (%)	*P*-value[a]
Railroad track ears		
FAS	5 (38.5)	0.140
Deferred	13 (29.5)	
No FAS	4 (13.3)	
Ptosis		
FAS	0 (0.0)	1.000
Deferred	1 (2.3)	
No FAS	0 (0.0)	
Heart murmur		
FAS	0 (0.0)	0.395
Deferred	3 (6.8)	
No FAS	0 (0.0)	
Decreased elbow pronation/supination		
FAS	2 (15.4)	0.058
Deferred	1 (2.3)	
No FAS	0 (0.0)	
Incomplete extension of one or more digits		
FAS	3 (23.1)	0.741
Deferred	8 (18.2)	
No FAS	4 (13.3)	
Other joint contractures		
FAS	0 (0.0)	—
Deferred	0 (0.0)	
No FAS	0 (0.0)	
Hockey stick crease		
FAS	2 (15.4)	0.589
Deferred	6 (13.6)	
No FAS	2 (6.7)	
Other palmar crease abnormalities		
FAS	*7* (53.8)	0.003
Deferred	11 (25.0)	
No FAS	2 (6.7)	
Strabismus		
FAS	2 (15.4)	0.362
Deferred	4 (9.1)	
No FAS	1 (3.4)	
Midfacial hypoplasia		
FAS	12 (92.3)	0.100
Deferred	*27* (61.4)	

Feature	N (%)	*P*-value[a]
No FAS	18 (62.1)	
Epicanthal fold		
FAS	10 (76.9)	0.142
Deferred	42 (95.5)	
No FAS	27 (93.1)	

[a]Fisher's exact test.

TABLE III

Number of Additional Features by Fas Diagnostic Category in 87 Children and Adolescents, Korea, 2010

	Number of additional features			
	0	**1**	**≥2**	***P*-value**[a]
FAS	1 (7.7)	8 (61.5)	4 (30.8)	<0.001
Deferred	11 (25.0)	25 (56.8)	8 (18.2)	
No FAS	20 (66.7)	9 (30.0)	1 (3.3)	

[a] Fisher's exact test.

TABLE IV

Number of Additional Features by Gender and Fas Diagnostic Category in 87 Children and Adolescents, Korea, 2010

	Number of additional features			
	0	**1**	**≥2**	***P*-value[a]**
FAS				
Male	0 (0.0)	*7* (63.6)	4 (36.4)	0.231
Female	1 (50.0)	1 (50.0)	0	
Deferred				
Male	7 (25.9)	14 (51.9)	6 (22.2)	0.705
Female	4 (23.5)	11 (40.7)	2 (11.8)	
No FAS				
Male	12 (63.2)	6 (31.6)	1 (5.3)	1.000
Female	8 (72.7)	3 (27.3)	0 (0.0)	

[a]Fisher's exact test.

TABLE V

Number of Additional Features by Age and Fas Diagnostic Category in 87 Children and Adolescents, Korea, 2010

	Number of additional features			
	0	**1**	**≥2**	***P*-value[a]**
FAS				
<12 years	1 (7.7)	5 (38.5)	0	0.070
≥12 years	0	3 (23.1)	4 (30.8)	
Deferred				
<12 years	6 (13.6)	15 (34.1)	3 (6.8)	0.593
≥12 years	5 (11.4)	10 (227)	5 (11.4)	
No FAS				
<12 years	12 (40.0)	3 (10.0)	1 (3.3)	0.236
≥12 years	8 (26.7)	6 (20.0)	0 (0.0)	

[a]Fisher's exact test.