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Collaborative Initiative on Fetal Alcohol Spectrum Disorders: Methodology of Clinical Projects

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Abstract

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) was created in 2003 to further understanding of fetal alcohol spectrum disorders. Clinical and basic science projects collect data across multiple sites using standardized methodology. This paper describes the methodology being used by the clinical projects that pertain to assessment of children and adolescents. Domains being addressed are dysmorphology, neurobehavior, 3D facial imaging, and brain imaging.

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*The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) (E. Riley, San Diego State University, Principal Investigator) includes 16 different centers where data collection and analysis take place. The data collection sites and associated investigators described in this paper are: San Diego State University (S.N. Mattson), Folkhälsan Research Center-Helsinki (I. Autti-Rämö, Å. Fagerlund, M. Korkman), University of New Mexico and Northern Plains (P.A. May, W. Kalberg, A. Aragon), University of Cape Town (C. Adnams), Moscow Institute of Psychiatry (V. Konovalova, G. Marintcheva), University of California, Los Angeles (E.R. Sowell), Emory University (C.D. Coles).

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Keywords

CIFASD; Fetal Alcohol Spectrum Disorders; Fetal Alcohol Syndrome; International Collaboration; Neurobehavioral Phenotype; Dysmorphology; 3-D Facial Imaging; Brain Imaging; DNA

Introduction

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) was created in 2003 and is a consortium of clinical and basic scientists whose collective goal is to further understanding of fetal alcohol spectrum disorders (FASD). The clinical collaboration involves researchers from multiple sites, using samples with ethnic, cultural, social, and language differences to find common features of FASD. Crossover between basic and clinical science encourages a broader perspective on the disorder (Riley et al., 2003; Strömmland et al., 2005). This paper describes the basic methodology of the CIFASD clinical projects that include assessment of children and adolescents.

The aims of the CIFASD are to establish standardized diagnostic criteria and methods of assessing FASD, enhance understanding of the neurobehavioral phenotype of the disorder, dissect the relationship between face and brain dysmorphology through 2D and 3D image analyses, characterize and correlate structural and functional brain abnormalities with neurobehavioral deficits, improve early case identification, develop *in utero* therapeutics and other interventions to reverse or ameliorate neurobiological deficits, and identify genetic factors that may increase the risk of FASD. In particular, the clinical projects are relevant to the following aims: enhancing understanding of both dysmorphology and the neurobehavioral phenotype and characterizing the structural and functional deficits in FASD.

As part of the CIFASD, subjects are between the ages of 7 and 21 years of age and are recruited from multiple sites. All races or ethnicities and both sexes are eligible. Other inclusion and exclusion criteria apply, and are detailed below. All participants are recruited for several aspects of the CIFASD project, including dysmorphology, neurobehavioral assessment, 3-D facial imaging, brain imaging, and DNA collection. Standardized measures are used across sites and data are collected in a central repository for cross-study data analysis and future dissemination. Descriptions of each component follow.

Recruitment Sites

Eight sites are used for subject recruitment. Phase I took place between 2003- and 2007 and included five sites: (1) Center for Behavioral Teratology, San Diego State University, San Diego, CA; (2) Seven Northern Plains communities, including six Indian reservations; (3) University of Cape Town, South Africa, and a town in the Western Cape Province; (4) Institute of Psychiatry, Moscow, Russia; and (5) Folkhälsan Research Center, Helsinki, Finland. Phase II, which began in 2007 and runs until 2012, includes six sites: (1) Center for Behavioral Teratology, San Diego State University, San Diego, CA; (2) Emory University, Atlanta, GA; (3) University of New Mexico, Albuquerque, NM; (4) Seven Northern Plains communities, including six Indian reservations; (5) University of Cape Town, South Africa, and a town in the Western Cape Province; and (6) the University of California, Los Angeles, Los Angeles, CA. The combination of these sites allows for a study population that is both large in number and heterogeneous in nature. Such a sample ensures our results are unbiased by specific site characteristics. A description of each site follows.

Center for Behavioral Teratology, San Diego State University

The CBT is a university-wide research center focused on the study of brain and behavioral changes associated with prenatal exposure to drugs and alcohol. Alcohol-exposed children are referred by Dr. Kenneth Lyons Jones (Principal Investigator of the CIFASD Dysmorphology Core), other local professionals, and self-referrals. Alcohol exposure histories are obtained from maternal report and review of medical, legal, and social service records. In Phase I, the San Diego site also included a small contrast group of subjects with attention-deficit/hyperactivity disorder (ADHD). In Phase II, two contrast groups are included: ADHD and a group of children with below average IQ scores (the IQ group). Contrast groups are described in more detail below.

Emory University

The Fetal Alcohol and Drug Exposure Clinic at Emory University in Atlanta, GA evaluates and provides clinical services to large numbers of individuals with FASD. Alcohol exposure histories are obtained from maternal report and review of medical, legal, and social service records. In Phase II, the Emory site includes ADHD and IQ contrast groups.

University of New Mexico

Children at this site are recruited from the University of New Mexico (UNM) Center on Alcoholism, Substance Abuse and Addictions and special remedial and diagnostic programs that draw from the entire state. Alcohol exposure histories are obtained through maternal interviews and questionnaires. In Phase II, the UNM site includes ADHD and IQ contrast groups.

Northern Plains - Seven communities including Indian reservation communities

For these sites, American Indian and White alcohol-exposed children are recruited through active case ascertainment methods at one urban site and six reservations throughout North Dakota, South Dakota, and Montana. Controls are recruited through advertisements and announcements in tribal and community health centers providing health, education, and social services. Alcohol exposure histories are obtained through maternal interviews and questionnaires. In Phase I, the Plains site included FASD and control subjects while in Phase II, both ADHD and IQ contrast groups are included.

University of Cape Town, South Africa

Children are recruited from the community in this region that has one of the highest documented rates of FAS in the world (May et al., 2007). Children of various ages have been identified in the community and screened through previous epidemiologic research. Alcohol exposure histories are obtained through maternal interviews and questionnaires. In Phase I, the South Africa site included FASD and control subjects while in Phase II, an IQ contrast groups is included.

University of California, Los Angeles

Children are recruited through the UCLA Fetal Alcohol and Related Disorders Clinic and Dr. John Graham, Director of Clinical Genetics and Dysmorphology in the UCLA Department of Pediatrics. Alcohol exposure histories are obtained from maternal report and review of medical, legal, and social service records. In Phase II, the UCLA site includes ADHD and IQ contrast groups.

Folkhälsan Research Center, Finland

Alcohol-exposed children at this site were recruited in one of two ways: from a clinical patient pool at the Hospital for Children and Adolescents, University of Helsinki, or from a prospective follow-up study. Alcohol exposure histories were obtained either from the prenatal period, in the case of the prospective study, or from medical records. Controls were recruited from a national population register using a computerized randomization method and contacted by telephone. In Phase I, the Finnish site included an IQ contrast group.

Moscow Institute of Psychiatry, Russia

This institute is responsible for psychological services for children living in boarding schools and special orphanages in Moscow. Children in the special orphanages typically have below average intellectual functioning and either are orphans or have parents who have lost parental rights. Children in the boarding schools may still be in the legal custody of their parents, but are felt to be better cared for in the special boarding schools and have below average intelligence or special needs. Thus, the special orphanages and boarding schools house children with below average intellectual function, including a large number of children with FASD. Alcohol exposure histories were obtained from review of records pertaining to medical and social histories. The comparison subjects had similar IQ scores and living environments and had no evidence of heavy prenatal alcohol exposure. Although children in both groups were orphans, children in the FASD group were born to mothers who either died of alcohol-related causes or who lost parental rights due to alcoholism. Mothers of the controls typically died of causes other than those related to alcohol (e.g., heart disease, accident). In Phase I, the Moscow site included FASD and an IQ contrast group. Because all children in the orphanages and boarding schools had below average IQ scores, traditional control subjects (with average IQ scores) were not recruited.

Subjects

Four groups of children are included: children with prenatal alcohol exposure with or without a diagnosis of FAS (the FASD group); non-exposed typically developing controls (the CON group); and two contrast groups of non-exposed children with other developmental conditions, including low IQ scores (the IQ group), and attention-deficit/hyperactivity disorder (the ADHD group). Inclusion of contrast groups differs by site, as indicated above. See below for details of contrast groups. The age ranges for Phase I and Phase II were 7-21 years and 8-16 years, respectively. Additional inclusion criteria are that the subjects speak the language of assessment at each site and meet the specific requirements for one of the subject groups. Exclusion criteria include: significant head injury with loss of consciousness (>30m) and significant physical (e.g. uncorrected visual impairment, hemiparesis) or psychiatric (e.g. psychosis) disability that would preclude participation. Children are excluded from the FASD group based on other *known* causes of mental deficiency (e.g. congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities) and from the control and contrast groups if greater than minimal prenatal alcohol exposure is known or suspected or if exposure information is unavailable. Comparison group participants are matched, by site, to the FASD group on the basis of age (+/- 6 months), race/ethnicity, sex, and socioeconomic status or geographic region. In addition, the IQ group, as described below, is matched on IQ to the FASD group. Maternal variables, including prenatal alcohol use, are assessed using questionnaires and/or in person interviews. Specific methods varied by site, given the wide variety of ages, cultures and socioeconomic status across the sites.

FASD Group

Two subgroups of children with prenatal alcohol exposure are recruited for participation: Children with FAS, as defined by the Dysmorphology Core, have two of three key facial features typical of FAS (short palpebral fissures, smooth philtrum, thin vermilion) and either microcephaly or growth deficiency or both (see Table 1). The second subgroup is children identified as alcohol-exposed but who do not meet the physical criteria for FAS, based on examination by a dysmorphologist (see below for discussion of dysmorphology methodology). Our previous research demonstrates qualitative similarities between alcohol-exposed children with and without FAS, thus both groups are included in the project. The majority of subjects in this study are recruited retrospectively, although the Finnish site includes some prospectively-ascertained subjects. Overall, the sample is heavily exposed (>4 drinks/occasion at least once/week or > 13 drinks/week). In all cases, positive exposure histories are confirmed via review of records or maternal report, if available. FASD subjects are recruited at every site.

Control Group

Non-exposed controls are recruited from ongoing studies at each site or specifically for this study. Recruitment strategies include advertisements, word of mouth, use of national registers, or through in-school studies. Controls are screened for prenatal alcohol exposure and excluded for evidence of greater than minimal alcohol exposure, defined as greater than one drink per week on average and never more than 2 drinks on any one occasion during pregnancy. Control subjects are recruited at every site.

Contrast Groups

The goal of including contrast groups is to compare the FASD group to children with other conditions or exposures that might be clinically confused with children with FASD. Since one of the overarching goals of the CIFASD project is to develop definitive diagnostic characteristics for FASD, and thus to improve differential diagnosis, including contrast groups with important similarities is critical. Therefore, subjects in the FASD group are drawn from the same general population as the contrast groups: children with various developmental conditions of pre- or postnatal origin. The two contrast groups (ADHD and IQ) are described below. These two groups were chosen because they share two important features with children with FASD: attention problems and low IQ scores. All children in the contrast groups are screened for prenatal alcohol exposure, as described above, and excluded if evidence of such is known or suspected.

ADHD Contrast Group—Children in the ADHD group meet the criteria for ADHD, as defined by the DSM-IV (American Psychiatric Association, 2000), using the procedure described by Nigg et al. (Nigg et al., 2002), as follows. Children are considered as possible ADHD participants based on parent and teacher versions of the Child Behavior Checklist or Teacher Report Form, a DSM-IV symptom checklist, or a previous diagnosis of ADHD by a physician or psychologist in the community.

Diagnosis of ADHD is confirmed with parents by means of a structured diagnostic parent interview using the Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al., 2000), supplemented by teacher-reported symptoms on the DSM-IV symptom checklist. These procedures are consistent with the DSM-IV field trials validity data (Lahey et al., 1994).

IQ Contrast Group—In Phase II, children with low IQ scores are recruited from the community using the same procedures as for the typically developing controls, emphasizing interest in lower functioning individuals. Based on data from Phase I, in which the IQ scores

for the FASD group ranged from 50-143 (Mn=88.5, SD=17.2), the target IQ range for the proposed IQ group is 54-88 (Mn-2SD). The upper range of IQ scores in the FASD group overlaps with the CON group, which has IQ scores within the average range. In Phase I, the Finnish site included an IQ-matched contrast group that was recruited from the medical records of the same University hospital as the subjects with FASD and matched on IQ, sex, and geographic region.

Dysmorphology

All children at all sites are examined by a member of the Dysmorphology Core (K. Jones, PI) using standardized methodology (Jones et al., 2006). As a result of the exam, each child is assigned a diagnosis of FAS, not FAS or Deferred (see Table 1). The Deferred category is a temporary label to be updated with additional information at the end of the study. One of the primary goals of the CIFASD is to delineate the full range of structural anomalies in children prenatally exposed to alcohol in order to determine the boundaries that encompass FASD. A further goal is to determine a profile of neurobehavioral features that are useful diagnostically and this information will be used to further clarify diagnoses of alcohol-exposed children categorized as Deferred. Procedures remain constant between Phase I and Phase II.

Neuropsychology

All children eligible for neurobehavioral testing are given a standardized test battery, as prescribed by the neurobehavioral project (E. Riley, S. Mattson, PI). Although measures differed from Phase I to Phase II (see Table 2), in both cases, the test battery was administered in one day by a trained examiner. Data were scored by the examiner and rechecked by a second person. When possible, testing and scoring were conducted by examiners blind to subject group membership.

3-D Facial Imaging

At most sites, subjects are assessed using 3-D facial imaging (Moore et al., 2007) as part of the facial imaging project (T. Foroud, PI). Data were collected previously with the Minolta Vivid910fw (Phase I) and currently with the 3dMD system (Phase II). These images are used to examine facial dysmorphology across ethnic groups and to understand how dysmorphic features change with age in order to better differentiate the broader spectrum of FASD. Facial shapes obtained from the images will also be used to determine the relationship between facial dysmorphology and known quantities and frequencies of prenatal alcohol exposure as well as between facial dysmorphology and brain function, including neuropsychological and structural MRI data.

Brain Imaging

In Phase II, FASD and control subjects at several sites are participating in the brain imaging project (E. Sowell, PI). Quantitative brain mapping techniques with high-resolution structural and functional MRI are collected both cross-sectionally and longitudinally. These data allow assessment of relationships between brain dysmorphology, brain functional abnormalities, facial dysmorphology, and neurobehavioral deficits. Functional MRI paradigms tap cognitive functions known to differentiate alcohol exposed from control subjects, namely working memory and verbal learning.

DNA Collection

In Phase II, saliva samples are collected at several sites for the extraction of DNA (T. Foroud, PI). These samples may be used in future studies that may include the evaluation of candidate genes and/or a genomewide association study. The primary hypothesis will compare the frequency of SNP allele and genotypic frequencies between subjects with FASD and alcohol-exposed individuals without evidence of FASD.

Informatics

The CIFASD includes an Informatics Core (W. Barnett, PI) that supports the mission of the CIFASD through the development and maintenance of tools for standardized data collection, management, analysis, and dissemination and by developing resources critical for advancing the collaborative nature of the CIFASD (Arenson et al., 2010). Input tools have been developed, are in development, or are planned for dysmorphology, neurobehavior, alcohol exposure, and demographics data. Repositories have been developed, are in development, or are planned for each of the aforementioned plus 3-D facial imaging, brain imaging, and DNA samples. The Informatics Core ensures data protection, including encryption, security, backups and archiving, particularly pertaining to electronic protected health information.

To support the collaborative nature of the CIFASD, a cross-project query environment has been developed that facilitates combined data analysis of multiple studies, allowing researchers to compare results across populations and diagnostic criteria. Data standardization was integral to the success of these cross queries. Data dictionaries that clearly define a standard, controlled vocabulary were developed for each modality (dysmorphology, neurobehavior, etc.) for which data is being collected. Software tools developed by the consortium use the data dictionaries to help assure that only high quality data are stored in the central repository. These efforts to develop a 'data infrastructure' are enabling FASD researchers to bring together the data from multiple populations and modalities, which are collectively necessary to meet the consortium goals.

Data Analysis

This collaboration will generate a large amount of data, which will be combined across projects for analysis, as described above. These data will include information on dysmorphology, neuropsychology, 3-D facial imaging, brain imaging, and DNA. Data will be analyzed separately by project or core as well as across projects. Data analysis will include a variety of techniques including standard analysis of variance techniques, regression analyses, latent profile analyses, morphometric analyses, and other methods designed to classify subjects or test for main effects and interactions. Groups (exposed, control, contrast) will be included in analyses based on the questions of interest and the relation of outcome variables to other factors, like IQ or environmental or genetic factors will be considered. Potential interactions between prenatal alcohol exposure and cultural or environmental factors will be examined, as well as gene by environment interactions. Analyses based on data from more than one site will covary for site or will be analyzed separately by site, depending on the type of analysis performed.

Conclusion

The CIFASD is committed to furthering understanding of the spectrum of effects of heavy prenatal alcohol exposure. Using the methodology described herein, CIFASD researchers seek to address important questions in the field using state-of-the-art tools and analyses. Correlation of measures within and between projects will allow for a unique and

comprehensive analysis of the spectrum of effects of this disorder, which will result in a better definition of FASD.

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Table 1

Diagnostic Criteria used by the CIFASD Dysmorphology Core

Criterion	Definition
Growth Deficiency	Weight and/or Height $\leq 10^{\text{th}}$ percentile
Microcephaly	Head circumference $\leq 10^{\text{th}}$ percentile
Structural Abnormality ¹	At least two of the following <u>KEY</u> facial features: Palpebral fissure length $\leq 10^{\text{th}}$ percentile Smooth Philtrum (score of 4 or 5 on Lipometer ²) Thin Vermillion Border (score of 4 or 5 on Lipometer)

Category	Required Criteria
FAS	Structural Abnormality and Growth Deficiency OR Structural Abnormality and Microcephaly OR Structural Abnormality and Microcephaly and Growth Deficiency
Deferred	At least one <u>KEY</u> facial feature (listed above) OR Microcephaly and Growth Deficiency OR Microcephaly or Growth Deficiency AND at least one of the following additional features: Railroad track configuration ears ² Ptosis Heart murmur Decreased pronation/supination at elbows Camptodactyly Other joint contractures Hockey stick upper palmar crease ¹
Not FAS	Does not meet criteria for either FAS or Deferred category

¹ See (Hoyme et al., 2005)² See (Astley, 2004)

Table 2

Neuropsychological measures and questionnaires used in the CIFASD projects

Functional Domain	Measure	Subtests	Phase
General Intellectual Ability	Leiter International Performance Scale-Revised (Leiter-R)	Figure Ground, Form Completion, Sequential Order, Repeated Patterns, Attention Sustained	Phase I
	Wechsler Intelligence Scale for Children — fourth edition (WISC-IV) Integrated		Phase II
Attention	NES3 - Continuous Performance Test	Animals	Phase I
Executive Function	Delis-Kaplan Executive Function System	Verbal Fluency, Trail Making	Phase I & Phase II
		Color-Word Interference, Tower, 20 Questions, Design Fluency	Phase II
	Progressive Planning Test		Phase I
	Visual Discrimination Reversal Learning		Phase I
	CANTAB	Intra/Extradimensional Shift	Phase II
	BRIEF	Parent and Child versions	Phase II
Working Memory/Memory	CANTAB	Spatial Working Memory	Phase I & Phase II
		Spatial Span, Pattern Recognition Memory, Spatial Recognition Memory	Phase I
		Delayed Matching to Sample	Phase II
	Virtual Water Maze		Phase I
Visual-Motor	Visual-Motor Integration Test		Phase I
Motor/Reaction Time	CANTAB	Motor Screening, Big/Little Circle,	Phase I & Phase II
		Simple Reaction Time, Choice Reaction Time	Phase II
	Grooved Pegboard Test		Phase I
Interhemispheric Transfer	Finger Localization Test		Phase I
Psychological Symptomatology	ASEBA	Child Behavior Checklist, Teacher Report Form, Youth Self Report	Phase I & Phase II

Functional Domain	Measure	Subtests	Phase
	Disruptive Behavior Rating Scale		Phase I & Phase II
	Sluggish Cognitive Tempo Scale		Phase I & Phase II
	Vineland Adaptive Behavior Scales, Second Edition	Parent/Caregiver Rating Form, Teacher Rating Form	Phase II
	Pictorial Depression Scale		Phase I
	C-DISC Psychiatric Interview	Demographics, GAD, MDD, ADHD, ODD, CD modules	Phase II