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Fetal Alcohol Syndrome: An International Perspective

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This article represents the proceedings of a workshop at the 2000 ISBRA Meeting in Yokohama, Japan. The chairs were Kenneth R. Warren and Faye J. Calhoun. The presentations were (1) Epidemiological research on fetal alcohol syndrome (FAS) in the United States, by Philip A. May; (2) An overview of fetal alcohol syndrome in the Western Cape Province of South Africa, by Denis L. Viljoen and Ting-Kai Li; (3) Diagnostic perspectives of fetal alcohol and tobacco syndromes, by Harumi Tanaka; (4) FAS among pupils of special boarding schools and orphanages in Moscow, Russia, by Galina S. Marinicheva and Luther K. Robinson; and (5) Research on FAS and FAE in Germany: Update and perspectives, by Goetz Mundle.

Key Words: Fetal Alcohol Syndrome, Fetal Tobacco Syndrome, Epidemiology.

IT HAS BEEN more than 30 years since Lemoine et al. (1968) first reported, from France, on a common pattern of physical and neurodevelopmental problems observed among the children of mothers with alcohol problems. Independent observation in the United States shortly thereafter (Jones et al., 1973) led to the introduction of the term "fetal alcohol syndrome" (FAS) to describe the common features of these children (Jones and Smith, 1973). In Germany, Majewski et al. (1974) introduced the term "alcohol embryopathy" to describe children affected by prenatal alcohol consumption. In the United States, a committee of the Institute of Medicine (Stratton et al., 1996) proposed terminology to address the varying severity of alcohol-related fetal injury, including FAS and two expressions of fetal alcohol effects: alcohol-related birth defects and alcohol-related neurodevelopmental disorder.

The workshop entitled "Fetal Alcohol Syndrome: An International Perspective" brought together researchers from around the world involved in human epidemiological, dysmorphic, genetic, and clinical investigations on FAS and other consequences of alcohol use in pregnancy, with presentations from Africa, North America, Asia, and Europe. Cultural diversity in drinking behaviors and other environmental and potential genetic factors offer opportunities for international comparative investigations of alcohol and pregnancy outcome. Such studies will increase the understanding of risk factors that either heighten or lessen susceptibility to adverse alcohol-related fetal outcome. This report presents salient discussions from the workshop.

DISCUSSION

Epidemiological Research on FAS in the United States

Dr. May discussed various epidemiological approaches that have been used to measure the rates of FAS in the United States and around the world. Attempts to delineate the prevalence and other epidemiological characteristics of FAS in the United States have used three methods, alone or in combination: (1) passive systems of record collection and review, (2) clinic-based studies (generally prospective), and (3) active case ascertainment and diagnosis in specific populations. Passive systems use birth certificates and reviews of special registries for an inexpensive method of determining FAS characteristics. Clinic-based studies of pregnant women screen for alcohol use in the prenatal period and monitor the characteristics of their children at birth and/or shortly thereafter. Active case ascertainment studies seek referrals of all children who may have FAS within particular cohorts of specific populations. Each of these methods has advantages and disadvantages. The passive methods are the least expensive and time consuming. The active case ascertainment studies are the most expensive and logistically challenging but have been considered the least affected by selectivity in the samples. They are potentially the most accurate because of strict diagnostic criteria that are applied consistently to children whose ages are most relevant to accurate assessment (ages 3–12). The

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clinic-based studies are believed to be superior for assessing maternal alcohol consumption.

In the United States, these methods have produced various FAS prevalence estimates. Passive systems have found FAS to occur at a rate of 0.2 to 0.37 per 1000 births; prospective clinic-based studies have found prevalence to vary from 0.0 to 3.90 per 1000 children; and active case ascertainment has provided rates from 1.03 to 10.7 per 1000 in selected U.S. populations, many of them high-risk populations (May et al., 2001).

The most recent and generally accepted birth prevalence estimate for the general population of the United States is 0.97 per 1000 (Abel, 1995). This rate represents an average of the rates produced by a number of prospective studies in a variety of locales in the country. A recently completed active case ascertainment study of a large Western U.S. state found substantial variation in rate among various subpopulations, but the overall rate in this state does not depart substantially from the recent estimate of 1 per 1000.

FAS in the Western Cape Province of South Africa

Dr. Viljoen reported on a series of recent investigations undertaken in the Western Cape Province of South Africa. The studies were undertaken because of the clinical suspicion of a high incidence of FAS (Palmer, 1985) and observations in pediatric genetic clinics. It was considered likely that the heritage of the "Dop" system, in which agricultural workers received part of their remuneration in the form of wine, may have contributed to high levels of alcohol use in this population, including among pregnant women. The initial prospective study of alcohol consumption practices among agricultural workers in three areas of the Western Cape, conducted in 1995 and 1996, found 42.8% of pregnant women drinking, with 23.7% drinking greater than 50 ml of absolute alcohol per week or drinking in binges that exceeded 50 ml per occasion (Croxford and Viljoen, 1999). Most of the population drank alcohol in a binge manner on weekends, heightening the potential for an adverse pregnancy outcome. Combined alcohol and tobacco use occurred in 29.6% of this cohort of women, but the relative proportion of women smoking in this population was similar for drinking and nondrinking women.

After completion of the preliminary prospective study on drinking practices, an FAS epidemiological study was undertaken in a small, rural wine-producing community. By using an active case ascertainment approach, the entire school entry population of 12 of 13 schools from the community were assessed for FAS (May et al., 2000) by an international team of dysmorphologists, who achieved high interrater reliability. The researchers obtained height, weight, and head circumference measures; neurodevelopmental assessment, by using the Griffiths scales; and maternal interviews. All investigators were blind to school performance and maternal drinking status. Forty-six (46) of 992 first grade children were found to have FAS (48.2/1000), a FAS prevalence that was higher than that noted in any previous study. On analysis, investigators found that the specific risk factors included poor socioeconomic status (<$18[US]/week/family), poor maternal education (<4 years), a heavy alcohol-ingesting environment (particularly in the maternal partner and her father), and a binge-drinking pattern, among others. In all, a culture of heavy binge drinking that extended throughout pregnancy was found in rural communities of the Western Cape, with a consequent high prevalence of FAS in this population.

The large number of similar-age FAS children in South Africa permitted the undertaking of a research project to assess the neurocognitive development of these children. Statistically significant differences between FAS and control children were noted in intelligence, language ability, abstract thinking (Adnams et al., 2001), and social skills (C. M. Adnams et al., unpublished data, 2000).

A study of potential genetic factors that underlie risk for FAS also was undertaken in the Western Cape populations, collaboratively, with Dr. Li. Alcohol dehydrogenase (ADH) genotypes were determined for 41 FAS-affected children and their mothers and were compared with 178 controls from the same geographical area and ethnic group. The *ADH 2*2* allele was found to be significantly more common in the control group than in mothers of FAS-affected children ($p < 0.025$) and FAS children ($p < 0.01$). This suggested that the *ADH2*2* allele may have a protective effect against FAS. An investigation of alcohol pharmacokinetics also was conducted with women who had previously produced a FAS child and heavily drinking women who had not. The research design involved observation of the women, in the nonpregnant state, during free-choice drinking in their home environment. The study showed that the FAS mothers consumed significantly greater amounts of alcohol and achieved higher peak breath alcohol concentrations than did controls, with no significant difference in alcohol elimination kinetics.

Alcohol and Pregnancy in Moscow, Russia

Drs. Marinicheva and Robinson described a new FAS project undertaken in Moscow, Russia. Although alcoholism is an important social and medical problem in Russia, FAS research has only involved studies of newborn infants.

One of the goals was to determine the incidence of FAS in specific populations within Russia. An active case ascertainment approach was used in two special schools in Moscow: an orphanage and a boarding school. Parents of the children in the orphanage no longer had parental rights, and frequently these rights were terminated because of parents' severe alcohol problems. Parents of the children in the boarding schools maintained parental rights, but again many of the children attended these schools because of parental difficulties with alcohol. The expectation was that a greater percentage of children in the orphanage would have fetal alcohol-derived problems than those in the

boarding school. The Russian team has found that about half of all mentally retarded children of school age were placed in institutions of these two types.

A total of 184 children and adolescents from 8.5 to 17 years old were included in the study: 123 boys and 61 girls. Those children who displayed height, weight, or head circumference less than the 10th percentile or who were suspected of having FAS were referred for morphological examination by Dr. Kenneth L. Jones or Dr. Robinson. The diagnosis of FAS was made blind to any knowledge of alcohol-exposure history. In most cases, no reliable information was available on the degree of alcohol exposure. FAS was diagnosed in 14.1% of the subjects. The FAS incidence in the orphanage was almost three times higher than in the boarding school, consistent with the hypothesis.

All children and adolescents with FAS subsequently were tested with the Weschler Intelligence Scale for Children. A control group, selected from the same schools as the FAS children, was matched on age and sex. There were no indications of maternal alcohol abuse in the controls, and because of the population from which the children were selected, the controls had a mean IQ similar to those of the FAS children. Full scale IQ of the 26 FAS children tested was 68.3, compared with 70.4 for the controls. Verbal IQ was 72.1 and 85.3 for the FAS and control groups, respectively. The performance IQ was 81.4 and 75.3 for the FAS and control groups, respectively. However, the lower level of performance IQ in the controls was due to a small number of control children who did extremely poorly on this measure. For both groups, performance IQ tended to be higher than verbal IQ. These IQ data are similar to those reported by others (for a review, see Mattson and Riley, 1998).

In a comparison of the subtest on the Weschler Intelligence Scale for Children, the FAS group did worse than did controls on comprehension, a verbal subtest that assesses general knowledge of social norms and convention. They also did more poorly than controls on picture arrangement, a performance subtest that measures sequencing ability and attention to detail.

As for other neurobehavioral domains, hyperactivity with attentional deficit was noted in a large number of both FAS and control children: 61.5% in the FAS group compared with 40% in the controls. Also, a high incidence (20%) of the children in both groups had some tendency for affective irritability.

Given the high incidence of attentional problems in both groups, the groups were tested by using a letter cancellation test (the Burdon test). Sixteen cases of FAS (mean IQ = 70.4) were compared with 16 matched controls (mean IQ = 73.0). In this test, the subject had to cross out a designated letter, looking line by line through a form filled with letters. All of the children selected for this test had a history of attentional deficits, and the purpose was to determine if the two groups of children with attentional problems, presumably of different etiologies, could be distinguished. On the Burdon test, the measures of attentional concentration and stability did not differ between the groups. However, on the switching component of attention, the FAS group had a mean score of 7.57, compared with a mean of 4.54 in the controls, which was statistically significant ($p < 0.05$). This deficit in the shifting component of attention has been reported previously (Coles et al., 1997; Mattson et al., 1999).

These data appear to indicate that children with FAS have a higher incidence of attentional problems than do children with the same level of IQ but without a history of prenatal alcohol exposure. Furthermore, within the domain of attention, switching or shifting sets was the aspect of attention with which the FAS children had the greatest difficulty.

In specialized Russian schools for children with mental deficiency, the incidence of FAS is very high, especially among children in an orphanage. Although only a relatively small number of subjects were sampled, these investigations are continuing. In conjunction with several American colleagues, a larger study has been initiated to ascertain the incidence of FAS in these two settings and to make a more complete behavioral assessment. This study should provide ample data on the incidence of FAS in these two settings. Furthermore, if the percentage of children with FAS is maintained at the level determined in this initial study, a large enough sample should be available to assess the clinical characteristics of FAS as a function of age. The investigators expect this should result in improved knowledge on which to develop appropriate intervention strategies for children with FAS.

Diagnostic Perspective of Fetal Alcohol and Tobacco Syndromes in Japan

Dr. Tanaka presented the first report on FAS from an Asian country. Dr. Tanaka assessed Japanese data on maldevelopment of the brain in offspring whose mothers drank and/or smoked during pregnancy. Similar to findings from other continents, the effects of alcohol on the central nervous system were more frequent and of greater severity than those observed from tobacco use, and central nervous system involvement was shown to increase with increasing consumption of alcohol and tobacco.

Research on FAS and Fetal Alcohol Effects (FAE) in Germany

Dr. Mundle presented a historical perspective on FAS research in Germany. One of the first German FAS researchers was Frank Majewski, who, in 1976, investigated 68 children with FAS, which he referred to as "alcohol embryopathy" (AE) (Majewski et al., 1976). Based on an investigation of 230 children with AE, he later graded the severity of AE from mild to severe (AE I–III) according to dysmorphological appearance (Majewski, 2000).

The mild form (AE I) was characterized by pre- and

postnatal growth retardation, underweight, and microcephaly. Mental development was normal or slightly subnormal. The typical dysmorphic facial features were absent, so diagnosis was only possible by verification of severe maternal alcoholism during pregnancy. The severe form (AE III) was characterized by marked pre- and postnatal growth retardation, microcephaly, and mental retardation. The face in AE III showed typical FAS features, which included short palpebral fissures. Also, many of these children had other organ malformations.

A positive correlation was found between the degree of AE and the frequency of mental retardation, congenital heart defects (10% in AE I, 19% in AE II, and 63% in AE III), or other internal malformations. Also, a positive correlation was found between the degree of AE and the stage of maternal alcohol illness according to Jellinek; however, no correlation was found between the amount of alcohol consumed and the degree of AE.

The second German FAS researcher, H. Löser, diagnosed 312 newborn children with FAS and 119 with FAE, at the University Children's Hospital in Münster, between 1973 and 1999. He found that the number of severe cases of FAS (AE III) decreased in the last 10 years, but the number of mild cases of FAS (AE I and II) and FAE increased (Löser, 1999). In a long-term outcome study, he investigated 51 children and young adults (26 male, 25 female) ages 14 to 24 years (mean 18.5; Löser, 1995). Eighteen of these subjects were AE I, 16 were AE II, 14 were AE III, and 3 had alcohol effects. Twenty-nine percent showed normal physical development and 71% showed insufficient physical development. The characteristic craniofacial changes of the chin and nose decreased over the years, whereas the typical changes of eyes, lips, ears, and hair remained. The intellectual development was insufficient in most cases.

The largest long-term outcome study carried out in Germany on children with FAS was performed within an interdisciplinary research project (Spohr et al., 1993; Steinhausen and Spohr, 1998). In this longitudinal project, 158 children were assessed during preschool age, early school age (6–12 years), and late school age (<13 years). Lifetime assessments of their environment revealed that most children were living in disorganized families. Only 26% were living with their biological parents, 24% lived with foster or adoptive parents, and 25% lived in institutions. Twenty-four percent were subjected to various changes of domestic environment over time. The assessments of psychopathology, behavior, and intelligence included psychiatric interviews, behavior checklists for parents and teachers, and intelligence tests. The results of that study showed excessive psychopathological symptoms, which were not confined to the core symptoms of hyperactivity and attention deficits.

The authors concluded that maternal alcoholism not only results in a specific dysmorphic syndrome but, even more importantly, also may result in behavioral and psychiatric symptoms as well as in cognitive impairment that limits successful adaptation to life. Because most children were living in disorganized family environments, the authors pointed out that it was difficult to disentangle the teratogenic effects of alcohol and the environmental risk factors on the child's development.

New studies in Germany will focus on identification and intervention in risk drinking as early as possible during pregnancy.

SIGNIFICANCE

Thirty years after the recognition of alcohol's teratogenicity, many questions important to reducing the occurrence of FAS and its health consequences remain. Some issues in FAS may best be addressed through research undertaken beyond the confines of any single country. These include questions about epidemiology, concurrent risk factors, neurodevelopmental profile, and potential environmental and genetic risk factors.

The subtle nature of many of the hallmarks of FAS in neonates and infants makes diagnosis of FAS difficult during these periods (Stratton et al., 1996). Consequently, passive ascertainment that focuses on this early period through birth defect registries may significantly underestimate the true prevalence of this disorder. To facilitate case recognition, the methodology of active case ascertainment has been developed and applied to FAS case recognition. This methodology can be used for case finding in the age range of 3 to 12 years, when the dysmorphic features of FAS are believed to be most prominent and the neurodevelopment impairments recognizable. When active case ascertainment was used in a Western state of the United States, suspected variations in prevalence among distinct subpopulations were confirmed with an overall average occurrence of 1 case per 1000 individuals.

Active case methodology also is being used in the research projects from South Africa and Russia addressed in this conference report. In the Western Cape Province of South Africa, the heritage of the now-outlawed Dop system, which provided partial wages in the form of wine to mixed-ancestry agricultural workers, has resulted in creation of a heavily drinking culture. The high prevalence of heavy drinking by women from this population extends into pregnancy (Croxford and Viljoen, 1999).

Active case ascertainment undertaken in a school entry population of a farming community revealed the highest incidence of FAS thus far reported in the literature, at 46.4 per 1000 (May et al., 2000). This knowledge has helped this community create a significant FAS prevention campaign, with prevention activities targeted at three levels suggested by the Institute of Medicine (Stratton et al., 1996): "universal" interventions for the broad community, "selected" interventions for women in the high-risk agricultural sector, and "indicated" interventions for women drinking in a risky manner and women who have already given birth to a child with FAS.

The presence of a large, similar-age population of FAS children is affording the opportunity to better characterize neurodevelopmental deficits among individuals with FAS. In turn, this provides the potential to improve the diagnostic recognition of individuals with FAS, as well as better-guided educational assistance.

A research project that investigated allelic variants of ADH has provided evidence that an *ADH 2*2* allele in the mother may be protective with respect to FAS development in the fetus. Another study that involved nonpregnant women who previously had used alcohol during pregnancy, and who either had or had not produced a child with FAS, showed differences principally in the amount of alcohol consumed and peak breath alcohol level, rather than in alcohol elimination kinetics.

Research in Tokyo, Japan, is providing the first reports on FAS in an Asian population. In Moscow, Russia, a high prevalence of FAS among a population of children in an orphanage and boarding school is leading to a better understanding of neurocognitive deficits in these children, with implications for interventions to aid them. The prevalence of FAS in the orphanage, where parental rights had been waived, exceeded that of the boarding school, where parental rights were still retained. This difference likely reflects the prevalence of severe alcohol problems in the mothers among these two school populations.

Although many of the research projects from Germany have used a nomenclature different from that in the United States and elsewhere, many important findings on the clinical and psychiatric attributes of children exposed prenatally to alcohol have arisen from research in Germany.

The research conducted within the studies presented in this report was approved by Institutional Review and Ethics Boards. Women who on interview reported drinking in pregnancy were counseled on the risks of alcohol use during pregnancy and were assisted to the extent they were willing in seeking treatment for alcohol problems.

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