Fetal alcohol syndrome: neuropsychiatric phenomics

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Abstract

Fetal alcohol syndrome (FAS) is a common developmental disorder with impairments in multiple neuropsychiatric spheres of varying severity. Few population-derived studies of the behavioral phenotype are available.

The purpose of this study was to estimate the prevalence of neuropsychiatric disorders in three groups: subjects who met criteria for FAS (n = 152); subjects who met criteria for partial FAS/ARND (n = 150); and referred subjects who did not meet criteria for either FAS or partial FAS/ARND (n = 86). Each subject had a standardized evaluation by a medical geneticist. All subjects were from North Dakota.

We found increases in the prevalence rates of neuropsychiatric disorders in subjects with FAS compared to subjects with partial FAS/ARND and the lowest rates in the group that did not meet criteria for either FAS or partial FAS/ARND. Comorbid attention deficit hyperactivity disorder occurred in 73% of cases with FAS, in 72% cases with partial FAS/ARND, and in 36% subjects who did not meet criteria for either. For other neuropsychiatric disorders, a similar distribution of comorbidity was found. This study supports the concept of a continuum of impairment resulting from prenatal alcohol exposure.

The presence of complex cognitive, behavioral, and physical symptomatology in the affected subjects with prenatal alcohol exposure would seem to fit well under the diagnostic rubric of fetal alcohol spectrum disorder (FASD). Diagnosis and long-term management will require increasing access to multidisciplinary child development teams including mental health professionals who treat children and adolescents. Adults will require care primarily from teams with expertise in mental health and developmental disabilities.

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1. Introduction

The clinical description of fetal alcohol syndrome (FAS) was first published in 1973 by Jones and Smith [16]. Since then, FAS has come to be accepted as the leading identifiable cause of mental retardation and neurologic deficit in the western world [2]. Increasing attention is also being paid to the role of prenatal alcohol exposure as an etiologic factor in a number of other developmental disorders and mental illnesses [7,23].

In the U.S., prevalence estimates of FAS and the partial manifestations of the syndrome range from 0.33 per 1000 live births to 1 to 2 cases per 1000 live births [1,4] to 9.1 per 1000 live births [19]. Prevalence rates vary even more widely in some minority populations [5].

In North Dakota, from a cohort of 7600 to 8000 live births per year, the prevalence rate of FAS ranges from 1.3 to 2.0 cases per 1000 live births or about 12–18 new cases each year (North Dakota Fetal Alcohol Syndrome Center, 1995 and 2002). This yields a population estimate for FAS in the state of North Dakota of between 180 and 320 children, birth through 18 years of age, and a total FAS population (children and adults) that could be as high as 1100.

Previous studies have produced prevalence rates of mental disorders or developmental disabilities in carefully selected populations of children, adolescents, and adults with...
FAS and related conditions. Streissguth et al. [23] found very high rates of mental disorders and other indicators of poor fit with societal expectations in over 90% of subjects in a cohort of over 400 affected people. In subsequent research, Steinhausen et al. [21] found high rates of mental health problems in a sample of subjects from Germany. In this sample, the prevalence of these problems seemed to increase with age. Famy et al. [14] reported very high rates of mental disorders in a sample of 78 patients with FAS/ fetal alcohol effect (FAE). Of the subjects in this study 92% received an Axis I diagnosis of drug or alcohol dependence. Forty-four percent had depression, 20% bipolar disorder, and 40% reported other psychiatric symptoms [14].

The diagnosis of FAS and the partial forms of the syndrome are most easily made between 4 and 14 years of age when the diagnostic signs are most evident. Attempts to identify FAS in the newborn period have been problematic [17]. It has been reported that many of the dysmorphic signs of FAS (small palpebral fissure, thin upper lip, absent indistinct philtrum) may become less distinct or disappear in late adolescence and adult life [20,23]. Thus, in adolescents or adults, the diagnosis of FAS can be difficult when based on a physical examination without supporting history, childhood pictures, or other developmental information. The lack of diagnostic precision makes efforts to screen for FAS in adolescents, developmentally disabled adults, or in institutional settings very difficult.

While the diagnosis of FAS or partial FAS/ARND (alcohol related neurodevelopmental disorder) requires a history of prenatal alcohol exposure, there is no widespread agreement on either the dose, the timing, or the duration of exposure necessary to cause FAS or partial FAS/ARND [1,13,18]. The outcome of exposure has been difficult to assess due in part to difficulty in assessing the exposure parameters of dose and timing, genetic factors influencing susceptibility, protective factors, and lack of agreement on diagnostic criteria.

Neuropsychiatric phenomics is analogous to genomics and is a useful conceptual model to utilize in developing a comprehensive phenotype from prenatal alcohol exposure. Therefore, large databases will be required to identify and quantify both risk and protective factors. The prenatal alcohol exposure data will need to be linked to multiple environmental and genetic factors, only a few of which can currently be reliably measured.

In FAS and ARND, one of the most problematic areas of research has been in the determination of the behavioral phenotype. An important area of current emphasis is to determine if prenatal alcohol exposure results in a unique or clearly definable behavioral or cognitive phenotype. Most research in this area is unidirectional and has focused on the study of impairments. In this paper, the term phenomics is used to describe the development of a field of study of behavioral phenotypes [15], which encompasses both the possibility of a distinctive phenotype of impairments from prenatal alcohol exposure, and second may include an enhanced susceptibility to common neuropsychiatric disorders as a typical outcome from prenatal alcohol exposure. In the second scenario, the results of prenatal alcohol exposure would result in more mild rather than severe outcomes. These outcomes would include a range of sensory impairments, cognitive impairments, increased rates of mental illness, and developmental disorders.

The purpose of this study was to estimate the prevalence of mental disorders in a population of subjects from North Dakota. The subjects were diagnosed with FAS, partial FAS/ARND, or were subjects referred for possible FAS or partial FAS who did not meet diagnostic criteria for those disorders. We examined the prevalence of mental disorders at the time of the evaluation (point prevalence) for FAS, partial FAS/ARND, or non-FAS/ARND.

2. Methodology

We utilized subjects from the North Dakota FAS registry. All subjects who had been referred and seen...
for evaluation of a possible diagnosis of FAS \((n=397)\) were included. Most subjects were referred for assessment to determine if they had FAS. In this paper, we present data on the neuropsychiatric outcomes at the time of diagnosis for a population of people with FAS/FAE/ARND in North Dakota. Each person has an individualized and standardized evaluation, which was organized around a diagnostic tool, the FAS Diagnostic Checklist (FASDC) \([4]\). The tool serves both as a database of prenatal alcohol exposure data and signs and symptoms of FAS/FAE/ARND. The tool was developed from a theoretical model of FAS where outcome is determined by multiple additive elements in a lifelong causal chain. A frequent example is prenatal alcohol exposure, prenatal nicotine exposure, poor diet, and infrequent prenatal care \([3]\). The accretion of those elements produces the impairments, disabilities, and resulting handicaps that can occur as a result of prenatal alcohol exposure \([6,8]\).

### 2.1. Diagnostic criteria

In the present study, we utilized three diagnostic categories. The first was FAS with confirmed maternal alcohol exposure defined by scores on the FASDC of 68 or above \([22]\). The second category consisted of subjects meeting criteria for ARND, partial FAS that has also been described as FAE. This group had scores on the FASDC ranged from 59 to 67. The third group were referred subjects who did not meet criteria for either of the two previous categories and thus did not have any diagnosis we attributed to prenatal alcohol exposure. Subjects in this group had scores on the FASDC below 58. The sensitivity of the FASDC is 84.9% and the specificity estimates are 82.4% \([12]\).

### 2.2. Statistical analysis

Association between the presence of a specific comorbid illness and diagnostic cohort was measured using two

### Table 2

Prevalence, risk ratios, and significance testing of multiple comorbid risk factors in FAS, partial FAS, and children without FAS

<table>
<thead>
<tr>
<th>Number of comorbid conditions</th>
<th>FAS</th>
<th>Partial FAS</th>
<th>No FAS</th>
<th>FAS to partial FAS</th>
<th>FAS to no FAS</th>
<th>Partial FAS to no FAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) (%)</td>
<td>(n) (%)</td>
<td>(n) (%)</td>
<td>RR</td>
<td>(P)</td>
<td>RR</td>
</tr>
<tr>
<td>1 or more</td>
<td>137 (90.1)</td>
<td>133 (88.1)</td>
<td>49 (56.3)</td>
<td>1.12</td>
<td>0.697</td>
<td>2.60</td>
</tr>
<tr>
<td>Males</td>
<td>80 (93.0)</td>
<td>84 (90.3)</td>
<td>31 (59.6)</td>
<td>1.22</td>
<td>0.703</td>
<td>3.24</td>
</tr>
<tr>
<td>Females</td>
<td>57 (86.4)</td>
<td>48 (84.2)</td>
<td>17 (50.0)</td>
<td>1.09</td>
<td>0.835</td>
<td>2.23</td>
</tr>
<tr>
<td>Infant to 4 years old</td>
<td>48 (81.4)</td>
<td>28 (68.3)</td>
<td>11 (37.9)</td>
<td>1.38</td>
<td>0.205</td>
<td>2.14</td>
</tr>
<tr>
<td>5 to 9 years old</td>
<td>51 (96.2)</td>
<td>49 (92.5)</td>
<td>23 (56.1)</td>
<td>1.53</td>
<td>0.339</td>
<td>6.89</td>
</tr>
<tr>
<td>10 and older</td>
<td>38 (95.0)</td>
<td>56 (98.2)</td>
<td>15 (34.2)</td>
<td>0.61</td>
<td>0.933</td>
<td>1.43</td>
</tr>
<tr>
<td>2 or more</td>
<td>108 (71.1)</td>
<td>100 (66.2)</td>
<td>30 (34.5)</td>
<td>1.12</td>
<td>0.434</td>
<td>1.80</td>
</tr>
<tr>
<td>Males</td>
<td>64 (74.4)</td>
<td>67 (72.0)</td>
<td>16 (30.8)</td>
<td>1.07</td>
<td>0.850</td>
<td>2.11</td>
</tr>
<tr>
<td>Females</td>
<td>44 (66.7)</td>
<td>32 (56.1)</td>
<td>13 (38.2)</td>
<td>1.24</td>
<td>0.312</td>
<td>1.51</td>
</tr>
<tr>
<td>Infant to 4 years old</td>
<td>32 (54.2)</td>
<td>16 (39.0)</td>
<td>6 (20.7)</td>
<td>1.28</td>
<td>0.200</td>
<td>1.56</td>
</tr>
<tr>
<td>5 to 9 years old</td>
<td>45 (84.9)</td>
<td>38 (71.7)</td>
<td>14 (34.2)</td>
<td>1.56</td>
<td>0.157</td>
<td>3.34</td>
</tr>
<tr>
<td>10 and older</td>
<td>31 (77.5)</td>
<td>46 (80.7)</td>
<td>10 (58.8)</td>
<td>0.89</td>
<td>0.897</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Fig. 1. Percent of subjects with comorbidities by category.
by two prevalence rates and Yates corrected chi-square tests. The relative risk of FAS subjects compared to partial FAS and no FAS subjects and partial FAS subjects compared to non-FAS subjects were estimated.

3. Results

Of the 397 subjects in this study, 152 (38.29%) were diagnosed with FAS, 151 (38.04%) were diagnosed with partial FAS, 87 (21.91%) were found not to have FAS, and 7 (1.76%) had no diagnosis. Fifty-nine percent were male and 41% were female. The majority (73%) were American Indian, 25% were White, and 2% other or unknown. The average age of the sample was 8.2 years, ranging from 1 month to 56 years.

Table 1 shows the prevalence of specific comorbid mental disorder by cohort. FAS and partial FAS subjects had similar prevalence rates of mental disorders with the exception of anger problems, where FAS subjects had half the risk of partial FAS subjects (RR = 0.58). FAS and partial FAS subjects had significantly increased risks of ADHD, learning disability, developmental disability, and social skills problems compared to subjects without FAS. Risks for these disorders were increased by 37% to 82%. The risks of other medical problems and anger problems were increased 46% and 38%, respectively, in FAS subjects compared to those without FAS.

Fig. 2. Percent of comorbidities in males by category.

Fig. 3. Percent of comorbidities in females by category.
Fig. 1 shows the proportion of subjects having none to nine comorbid mental disorders by cohort. There was no significant difference between FAS and partial FAS subjects. However, these two groups had significantly higher likelihood of one or more and two or more comorbid mental disorders (Table 2). The risks of having one or more mental disorders were more than doubled for subjects with FAS (RR = 2.60) and partial FAS (RR = 2.27). The risks for multiple comorbid disorders (more than 1) also increased by 80% and 63% for FAS and partial FAS subjects, respectively.

The number of comorbid mental disorders was then broken down by gender and age group. Figs. 2 and 3 show the proportion of mental disorders for males and females, respectively. Males with FAS had triple the risk of those without FAS for one or more comorbid mental disorders and double the risk for two or more. Males with partial FAS also had double the risk for single or multiple comorbid disorders (Table 2). Females also had an increased risk, though not as high as males. Females with partial FAS had no significant increase in risk of multiple comorbid mental disorders compared to those without FAS.

Figs. 4–6 show the distribution of number of comorbid mental disorders by age group and FAS cohort. Children 4 years old and younger with FAS had double the risk of a comorbid mental disorder and a 56% increase in risk of multiple mental disorders (Table 2). Children in that age group with partial FAS had negligible increase in risk compared to those without FAS. Children 5–9 years old with FAS had a nearly sevenfold increase in risk of one or more comorbid mental disorders compared to those without FAS, and those with partial FAS had a nearly fourfold...
The risk of multiple comorbidities was increased two to three times for the partial FAS and FAS children, respectively. There was no significant increase in risk for subjects 10 years old or older.

4. Discussion

The prevalence of comorbid mental disorders in the FAS and partial FAS groups were very similar. The between-group differences were found primarily between subjects with FAS and partial FAS/ARND compared to the group of subjects who did not meet criteria for any FAS-related diagnosis. Subjects with partial FAS were more likely to have an anger disorder, and FAS subjects were more likely to have other medical problems. While the comparison groups (no FAS or partial FAS/ARND) in this paper trial did not meet our criteria for FAS, this group should not be considered as a comparison group of normal controls. They had very high rates of neuropsychiatric comorbidities. For example, ADHD affects 4.3% of North Dakota children [9,10]. The FAS group had a 16.9-fold increase in the prevalence rates of ADHD compared to the base population rate of ADHD in North Dakota Children of 4.3% [9,10]. The partial FAS group had ADHD at 16.6 times the base rate in the state, and the non-FAS group had ADHD at 8.6 times the base rate in North Dakota. The rates for learning disabilities, mood disorders, oppositional defiant disorder, and self-injurious behavior in both the FAS and partial FAS groups were also increased more than five times the rate in North Dakota children in the general population [9,10]. The finding of multiple comorbid mental disorders confirms the presence of a very complex phenotype for FAS and partial FAS. Estimating phenotype severity is important and a preliminary tool is presented in Fig. 7. The tool may also be helpful for assessing change over time as development progress and as the features of the phenotype change. The severity score may also be useful to examine response to interventions.

FAS appears to be an important marker for an increased risk of multiple neuropsychiatric comorbidities. The prevalence of comorbidity in subjects with FAS and partial FAS was increased 5 to 16 times over the base rates for most of these disorders. This increase in prevalence was several times the rates in the high-risk non-FAS subjects with identical evaluations, which did not have FAS or partial FAS.

Increased rates of comorbid mental disorders in the non-FAS group as compared to the general population could reflect a number of factors. One might be an ascertainment bias on the part of those referring for a FAS evaluation. Presumably, to consider such an evaluation, two factors would come into play, either individually or in concert. One would be in referred subjects with a degree of impairment sufficient to warrant concern with even just a suspicion of a history of prenatal alcohol exposure. The other would be in referred subjects with a range of impairment in whom there was a conviction of the likelihood of prenatal alcohol exposure. Subjects with prenatal alcohol exposure with little or no impairment would likely not be referred. Thus, the pool of referred subjects would be preselected for a greater burden of neuropsychiatric comorbidity across all three groups studied.

The rates of multiple comorbidities in subjects with FAS and partial FAS compared to the non-FAS group were also greatly increased. Females were more likely to have fewer mental disorders than males, particularly multiple disorders. In the 5- to 9-year-old age group, comorbid disorders appeared to be strongly related to the type of FAS diagnosis, with FAS children having more mental illness than children with partial FAS.
Prenatal alcohol exposure presents a useful environmental teratogen for the study of etiology of several neuropsychiatric disorders. The interplay between timing of exposure, dose, duration, susceptibility, and the effects of other elements in the causal chain such as smoking provides a useful model for study of this teratogen in vivo in humans. Multiple causal mechanisms can also be examined using prenatal alcohol exposure as a model behavioral teratogen. Exposure late in pregnancy seems likely to be particularly harmful to the developing brain [18]. Prenatal alcohol exposure represents a huge naturalistic experiment involving over a million pregnancies each year in the United States alone. This tragic state of affairs provides a useful opportunity for the study of several common disorders of childhood, including ADHD, learning disabilities, and disorders of behavior regulation. Since as little as 2 h of increased blood alcohol levels can produce massive apoptic-induced cell loss in the brain, prenatal alcohol exposure may be a very common cause of mental illness in both childhood and adult life. A model of neuropsychiatric impairment from prenatal alcohol exposure is presented in Fig. 8. This model is a companion model with the theoretical model defining a causal chain for outcome from prenatal alcohol exposure [8].

These data also have implications for promoting the conceptual label of fetal alcohol spectrum disorder (FASD) [23]. This term has the benefit of stressing the concepts of a spectrum of signs, symptoms, and variable impairments in FAS. An additional conceptual or diagnostic concept may be required in the future to enhance the conceptual understanding of the causal role of prenatal alcohol exposure as a very common cause of developmental disorders, such as ADHD or learning disabilities. The term FASD may be helpful in the conceptual understanding of diagnosis by reducing the current emphasis on facial features and growth impairment as the essential features of diagnosis of adverse outcomes from prenatal alcohol exposure. The primary cause of impairment in people with FASD or FAS results not from facial features (thin upper lip, indistinct philtrum) but from brain damage or dysfunction. The very high rates of comorbidity of mental disorders in this population have higher prevalence and produce more impairment than the few cases of birth defects. Most subjects seem to manage with the modest impairment in height and weight that largely disappears by adult life but they may remain unemployed or be socially impaired to a striking degree from brain damage or dysfunction. While a small proportion of affected people have birth defects affecting other organ

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**Fig. 7.** Severity score for FAS and related disorders.

**Fig. 8.** Continuum of brain damage dysfunction from prenatal alcohol exposure.
systems or severe facial birth defects, cleft lip and/or palate, most do not.

We seem to have a lasting distraction in FAS and partial FAS with the need to avoid diagnostic error from over diagnosis of subjects without the classic phenotype. While accuracy is important and producing very restrictive diagnostic criteria may increase the reliability of the diagnosis, this strategy also may miss most affected people who have less severe forms of the disorder. Thus, we may routinely misdiagnose the majority of affected patients as not FAS or ARND. These results present compelling evidence that prenatal alcohol exposure causes brain damage or dysfunction and results in extraordinarily high rates of neuropsychiatric disorders, which often produce substantial impairment for people affected by prenatal alcohol exposure. The behavioral abnormalities contrast with growth impairments in this population, which are increasingly less detectable as they enter adult life [11,13]. We find a vanishing small number of subjects with impairment from facial abnormalities.

Clinicians may wish to reflect on why we continue with repetitive efforts at keeping dysmorphia (short palpebral fissure or absent philtrum) as the essential diagnostic features for the spectrum of FAS and partial FAS when the primary problem from prenatal alcohol exposure is brain damage or dysfunction manifesting as common disorders of development and as mental illness. If 40–50% of all pregnancies in the United States are exposed, would we not expect high rates of impairment?

Alternatively, when we portion out neuropsychiatric comorbidities, we find that the defining characteristics of the severity of impairment as defined by the prevalence of neuropsychiatric comorbidity is the presence of dysmorphia. Thus, we may need to consider dysmorphia as markers that correlate with neuropsychiatric abnormalities and influence severity rather than a finding that defines them etiologically.

Clearly we need further research to examine the possibility that the phenomics of the phenotype from prenatal alcohol exposure is primarily neurodevelopmental and not dysmorphia (facial features and growth impairment). Future research could address the possibility that in FAS or FASD, most affected people likely have brain damage without easily detectable growth impairment or abnormal facial features. We have reservations about the concept of spectrum disorders. This conceptual schema has caused much mischief in disorders such as autism and pervasive developmental disorders, obsessive compulsive disorder, or in bipolar disorder. Spectrum has been used to conflate the concept of dimensionality with the concept of categories leading to an intermediate netherworld of sloppy thinking especially where diagnosis is concerned. Clarification of these issues will likely result in improved estimates of prevalence rates and an enhanced reliability and validity of diagnosis. This would improve studies of management and interventions with affected people. This would also be an important step to promote the prevention of the adverse consequences of drinking during pregnancy.

Lastly, it seems that the time has come to consider a move of FAS, partial FAS, FAE, ARND, or FASD out of the genetics and dysmorphology settings and into neurobehavioral clinics. These settings may improve the diagnosis and management of the most common manifestations of FAS and partial FAS. Children with dysmorphic features who do not fit diagnostic criteria could then be referred to the genetic specialty clinics for evaluation. The move of this population into developmental disability and mental health clinics would enhance access to systems of care with expertise in the areas of impairment most commonly experienced by people affected from prenatal alcohol exposure. This study should encourage policy planners and public health effects to examine the effects of these proposals over time.

References


