Review Article

Diagnosing Fetal Alcohol Spectrum Disorder: Historical to Present Day Challenges

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Abstract

This paper will give a brief review of historical and currently proposed diagnostic systems of fetal alcohol spectrum disorder (FASD), a neurocognitive and developmental disability which can be created when a woman consumes alcohol in pregnancy. Although FASD is totally preventable, pregnant women worldwide still continue to consume alcohol, making it is a major public health and social issue. FASD has been described as a clinical term rather than a diagnosis. It was introduced over 40 years ago by two Americans – Jones and Smith.

In 2005, the first Canadian guidelines for the diagnosis of FAS and its related disabilities was authored by Hoyme et al., and developed based on widespread consultation of Canadian and American expert practitioners and partners in the field being organized into seven categories: screening and referral; physical examination and differential diagnosis; the neurobehavioral assessment; treatment and follow-up; maternal alcohol history in pregnancy; diagnostic criteria for fetal alcohol syndrome (FAS), partial FAS (pFAS) and alcohol-related neurodevelopment disorder (ARND); and harmonization of Institute of Medicine (IoM) and 4-Digit Diagnostic Code approaches.

The diagnosis requires a comprehensive history and physical and neurobehavioral assessments; a multidisciplinary approach is necessary. This is made more difficult because a biomarker has not yet been established. Challenges that have thwarted diagnostic efforts in individuals is discussed followed by current diagnostic strategies and their implications.

ABBREVIATIONS

FASD: Fetal Alcohol Spectrum Disorder; pFAS: Partial Fetal Alcohol Syndrome; FAS: Fetal Alcohol Syndrome; ARND: Alcohol Related Neurodevelopment Disorder; PAE: Prenatal Alcohol Exposure; ARBD: Alcohol Related Birth Defects; ND-PAE: Neurobehavioral Disorder with Prenatal Alcohol Exposure; IoM: Institute of Medicine; SFF: Sentinel facial features; CNS: Central Nervous System

INTRODUCTION

The effects that can occur in an individual whose mother consumed alcohol in pregnancy have implications for the affected person, the mother, the family and the community. For the individual these effects represent a spectrum of structural anomalies and neurocognitive and behavioural disabilities termed FASD. The disability is complex and multifaceted, originating with organic brain damage caused by alcohol, but interacting with genetic and other influences. Over the lifespan of the affected person, these features may be exacerbated or mitigated by environmental experiences. Of note, is that new research from Denmark states that pregnant women who abuse alcohol are more than five times likely to have a child with schizophrenia than healthy mothers [1].

Cook [2], stated that Canadian estimates put the number of individuals with FASD at 1 in 100, translating to more than 330,000 people. Children at the most severe end of this spectrum and displaying the complete phenotype of characteristic facial anomalies, growth retardation and developmental abnormalities of the central nervous system (CNS) have been defined as having FAS.

May et al. [3], recently recorded combined rates of FAS and pFAS of 10.9 to 25.2 per 1000 (1.1%-2.5%) in a Rocky Mountain community, whereas the complete continuum of FASD (including ARND) was observed to be 24 to 48 per 1000 (2.4%-4.8%) in a community in the Northern Plains [4]. In the mixed race population of the Western Cape Province in South Africa, the highest prevalence rates of FASD in the world have been documented, 135.1 to 207.5 per 1000 (13.5% - 20.8%) [5].

Whilst FAS is the most readily clinically recognized form of FASD, other categories within the continuum of adverse effects due to prenatal alcohol exposure (PAE) are alcohol-related birth defects (ARBD) and alcohol-related neurodevelopment disorder (ARND); the latter having replaced the term FAE (fetal alcohol effects) (see later). As more was learned regarding the exact manifestations of alcohol on brain development, these classifications were expanded and/or refined as discussed later.

Because FASD represents a major public health concern early recognition of at-risk children is important for initiating interventional strategies [6]. A common misconception is that FASD is associated with ethno-cultural background. However, the data suggest that risk factors for PAE include higher maternal age and lower education level, prenatal exposure to cocaine and smoking, custody changes, lower socioeconomic status, paternal drinking and drug use at the time of pregnancy [7], reduced access to prenatal/postnatal care and services, inadequate nutrition and a poor developmental environment (e.g., stress, abuse, neglect) [8].

It became apparent that the disability is complex; affected people exhibiting a wide range of expression, from severe growth restriction, intellectual disability, birth defects and characteristic dysmorphic facial features to normal growth, facial features and intellectual abilities, but with life-long deficits in several domains of brain function.

A characteristic craniofacial profile associated with FAS was first described by Jones and Smith in 1975 and later refined by Astley, Clarren and others [9-11]. Individuals with FAS have short palpebral fissures, a thin upper lip and an indistinct philtrum. Adults with FASD have a higher incidence of impairments in social adaptive and executive function and a higher degree of psychopathology when compared to the general population [12]. The sub-sets of individuals with attenuated phenotype subsumed under the umbrella term of FASD provide clinicians with a challenge in that the diagnosis is complex and guidelines are warranted [10].

Since then, the field has evolved and additional evidence, expertise and experience have emerged to suggest that a revision was required to improve both diagnoses and outcomes. The literature has also shown that impairments in behaviour and function associated with FASD have been detected from exposure to binge drinking [14,15], even infrequently or early in pregnancy, which underscores the importance of pre-pregnancy counselling. Specific research involving infants, young children and adults with FASD as well as further insight into the neurodevelopment dysfunction and nomenclature, prompted the update and revision process. A literature review and broad consultation process was undertaken to revise the 2005 guideline for diagnosing FASD.

HISTORICAL PERSPECTIVES

FAS, the most severe manifestation of the adverse effects of alcohol on fetal development was first described in the French medical literature by Lemoine et al., in 1968. In this paper Lemoine et al. [16], documented some commonly occurring problems in over 100 offspring of women who drank heavily during pregnancy. While the authors documented many physical and behavioural patterns in the children, their conclusions had little impact. This article neither presented definitive diagnostic criteria nor did their observations lead to recognition of FAS in France or elsewhere in Europe [17].

The diagnosis of FAS by Jones and Smith in 1973

Five years later, Jones and Smith [18], were the first to delineate systematically the association between maternal alcohol abuse and a specific pattern of birth defects and to provide diagnostic criteria for this condition (a novel diagnosis of FAS). This term was first introduced in Jones and Smith's second paper which described three additional cases of alcohol-related birth defects (ARBD). In their third article the authors provided further evidence for the teratogenicity of alcohol using data from the Collaborative Perinatal Project of the National Institute of Neurological Disease and Stroke. The data were retrospective and based on chart reviews. They were able to identify 23 women with a history of chronic alcoholism and six cases of suspected FAS among these 23 women drawn from a total sample of 55,000 cases [17]. Clinicians soon recognised that physical and a neurobehavioral outcome of prenatal alcohol exposure was variable, ranging from the classic form to a few minor anomalies.

The term FAE introduced by Clarren and Smith in 1978

Clarren and Smith [12], then introduced the term suspected fetal alcohol effects (FAE) to denote the partial expression of the syndrome. Because health care professionals subsequently misapplied the term FAE, using it to label any child with behavioural problems coming from families with suspected alcohol abuse, it was abandoned.

Alcohol and pregnancy is not a new phenomenon

Several reports later pointed out that the deleterious effects of alcohol on the developing fetus had been known for centuries [20,12]. One of the earliest reference to this association is found in an ancient Greek and Roman belief that alcohol intoxication at the time of procreation results in the birth of a damaged [18,19]. Surprisingly, similar epidemiological reports linking maternal drinking to birth defects did not appear in the literature until the 1980s [17].

A new classification of FASD in 1996

In 1996, the Institute of Medicine (IoM) recommended adopting a new classification of FASD which included FAS with and without a confirmed history of alcohol exposure, partial FAS (pFAS), ARBD and ARND.

The late 1990s – the 4-Digit Diagnostic Code introduced

In the late 1990s another diagnostic system was developed by Astley and Clarren – the 4-Digit Diagnostic Code – to increase diagnostic reliability. However, it was felt that these two diagnostic categories (the IoM report to replace the term FAE) were ambiguous and the question of the utility of multiple categories created by the 4-Digit Code has been questioned [21].

The Canadian Diagnostic 2005 Guidelines

The Canadian diagnostic guidelines of 2005 were developed

by harmonizing the IoM criteria and the 4-Digit Code. The authors have described the diagnostic process in detail (see above) and underscore the necessity of a multidisciplinary team for accurate and comprehensive diagnosis. ARBD was abandoned owing to indeterminate causation of non-specific congenital anomalies from PAE [22].

Revised IoM Diagnostic Classification System by Hoyme 2005

The Revised IoM Diagnostic Classification System [21] is very similar to the Canadian diagnostic guidelines but have been field tested in a large multi-racial international cohort of children prenatally exposed to alcohol and have been found to accurately define the range of FASD [17]. Hoyme et al. [21], described specific clinical guidelines that allowed for assigning diagnoses within the 1996 IoM classification. However, Hoyme et al., diagnostic criteria disregarded the cognitive and behavioural impairments central to FASD and relaxed the facial dysmorphology and structural CNS impairments required, resulting in potential misdiagnosis of FASD [23].

Other guidelines

Similar diagnostic approaches have been adopted internationally, but they differ in the specificity of recommendations, criteria and clinical cut-offs [24-27]. For example, an at risk designation includes situations where a full neurodevelopment assessment is not conclusive because of age or situational factors; therefore, FASD may not be the diagnosis. Clinical judgment is recommended [2].

CHALLENGES

The fundamental challenges that exist in obtaining an accurate and reliable diagnosis of FASD are numerous, including obtaining an accurate and reliable history of alcohol use by a pregnant woman. If the biological mother is not caring for the affected individual at assessment time, there will be reliance on significant others and medical history for maternal alcohol use during pregnancy [14,15,28]. Many biological, social and medical barriers are inherent to FASD and have created significant challenges for identifying those at risk. Benz et al [22], discuss other relevant challenges e.g. delayed diagnosis of individuals lacking the sentinel physical features of FAS may be responsible for increased secondary disabilities [29], and special education services seen within the subset of FASD. Moreover, differentiation of FASD from other similar disorders [13], and recognition of the nonspecific abnormalities found in certain manifestations of the spectrum disorder also provides challenges.

Unanswered questions on the diagnosis of FAS

Calhoun and Warren [17] state that the last three decades have witnessed notable advances in the development and validation of diagnostic criteria for FAS and related disorders, but there are a number of unanswered questions. One question concerns the validity of diagnostic criteria. Second, ethnic variations in the expression of ARBD need to be carefully examined. Third, little is known about minor physical anomalies in children with PAE who do not exhibit the full syndrome of FAS.

These questions may be answered by Chudley et al. [13], who

purport that the term "partial" as in partial FAS does not imply that these individuals are less severely impaired in day-to-day functioning than those with a diagnosis of FAS, as the deficits in brain function may be similar. There should be harmonization of the IoM and 4-Digit Diagnostic Code approaches. The approach identified in the 4-Digit Diagnostic Code should be used to describe, assess and measure objectively alcohol exposure, growth, facial features and brain damage. The 4-Digit Diagnostic Code should be recorded for each assessment and may be useful for surveillance and research purposes. The terminology in the IoM criteria should be used to describe the diagnosis.

The ARBD category has limited utility in the diagnosis, but it is recognized that alcohol is teratogenic and may be responsible for birth defects if exposure occurs during critical periods of development. However, in the absence of other features of FAS or brain deficits, it is difficult to attribute causation.

Biomarkers

Several diagnostic systems have since been developed with a view to capturing the wide spectrum of physical and behavioural anomalies resulting from PAE. Compounding this, although evidence suggests that FASD is common and worldwide, it is different from most genetic syndromes in that there are no reliable means to confirm maternal drinking using biochemical markers in pregnancy. High levels of whole blood-associated acetaldehyde, carbohydrate-deficient transferrin, gamma-glutamyl transpeptidase and mean red blood cell volume may be useful markers in pregnant women [30]. Studies have been undertaken to determine the utility of fatty acid ethyl esters in meconium as markers for PAE [31].

This marker would only be useful if it can be established that fatty acid ethyl ester levels in meconium are predictive of developmental outcome. Meconium testing could alert caregivers to infants who might be at risk for alcohol effects and lead to appropriate monitoring, intervention and prevention. Ethical issues regarding informed consent surround the use of biological markers in the baby that may indicate maternal drinking [32]. Other innovations have led to the development of laser surface scanning, a non-invasive method for acquiring 3-dimensional images [33].

Importantly, it has recently been reported that Canadian researchers are one step closer to uncovering a biomarker associated with FASD after identifying distinct patterns associated with the DNA of children who were exposed in the womb. The investigation, led by the University of British Columbia, analysed DNA samples from 110 children with FASD across the country. The study relied on data collected through the Kids Brian Health Network: a national collaboration that aims to improve the understanding and treatment of neurodevelopment disorders, such as FASD and autism [34].

SUMMARY OF SPECIFIC CHANGES IN THE UPDATED 2016 CLINICAL GUIDELINES

The new Canadian guideline incorporates updated evidence for detecting and diagnosing FASD across the lifespan. It is aimed at health care providers with specialized training and experience in FASD who are part of multidisciplinary diagnostic teams.

Family physicians may find the guideline useful, but the diagnosis must be made with input from other experienced health care professionals [2].

The new terminology – as authored by Cook et al (2015)

Previously the cluster of birth defects (including restricted growth, craniofacial abnormalities and intellectual disabilities) caused by PAE was known as FAS. The new terminology includes a wider spectrum of disabilities and presentations. FASD is now a diagnostic term.

It is recommended that infants and young children with all three sentinel facial features (SFF) and small head circumference be diagnosed with "FASD with sentinel facial features." These children are at high risk for neurodevelopment disorder. The three facial features are: palpebral fissure length of at least two standard deviations below the mean (below the third percentile), philtrum rated 4 or 5 on the 5-point scale of the University of Washington Lip-Philtrum Guide and thin upper lip rated 4 or 5 on that scale. Growth is no longer a diagnostic criterion. Infants and young children who do not meet the criteria for FASD, but have confirmed PAE, should be designated as "At risk for neurodevelopment disorder and FASD associated with PAE".

The revision and refinement of brain domains

As evaluated in the neurodevelopment assessment; specific changes and additions include:

- "Hard and soft neurological signs including sensory motor" is renamed "motor skills" and redefined

- "Brain structure" is renamed "neuroanatomy/ neurophysiology" and redefined

- "Communication" is renamed "language"

- "Attention deficit/hyperactivity" is renamed "Attention" and redefined

- "Affect regulation" is added

- "Executive function" is expanded and clarified

The guideline includes an algorithm –

a decision-making tool – to help multidisciplinary teams diagnose the disorder based on the recommendations [2]. These authors also comment that the guideline will be re-evaluated when substantial new evidence emerges.

It is important to note that the updated guidelines for diagnosing FASDs by Hoyme et al. [28], do not necessarily represent the policy of the American Academy of Pediatrics. They also differ in some respects from those outlined above by Cook et al. [2], Hoyme et al. [28], updated criteria continue to include ARND as a necessary diagnostic category as well as ARBD. With the introduction of Neurobehavioral Disorder with Prenatal Alcohol Exposure (ND-PAE) into the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition as a "condition in need of further study," there has been significant confusion about the necessity of retaining both ARND and ND-PAE as diagnostic entities. Nonetheless, Hoyme et al. [28], retain both diagnoses in their guidelines.

DISCUSSION

Despite 40 years of research, there are still gaps in knowledge and evidence related to the diagnosis of FASD. For obvious ethical reasons, it is impossible to perform titrated dose–response studies of prenatal alcohol exposure and subsequent teratogenicity that would undoubtedly provide more definitive answers [2]. Despite this apparent limitation, researchers and clinicians continue to study the effects of PAE using different models and methodologies, and evidence continues to emerge that improves the understanding and knowledge base of FASD. For example, diagnostic biomarkers and eye-tracking movements are under investigation, as are additional tools to assess sensory processing and integration dysfunction and sleep disorders in those with FASD [35].

In general, diagnostic guidelines differ on the number of sentinel facial features required to make a diagnosis; the inclusion of growth deficits as a diagnostic criterion; the neurodevelopment assessment process and criteria; and the approaches and measures used to confirm PAE. However, with the introduction of the new nomenclature, it is difficult to compare them directly. The diagnosis first needs to be suspected and confirmation requires a diagnostic assessment that is best carried out in the context of a multi-disciplinary team approach, but services to diagnose and treat these individuals are limited [13,2]. There is a need for improved access to diagnosis and further research is required to determine the association between PAE and other mental health problems including autism spectrum disorder and perhaps schizophrenia.

CONCLUSION

It has been well documented that technology and health care costs are rapidly increasing and that health care systems are re-evaluating existing programs to develop more cost-efficient and effective practices and models. It is anticipated that the updated evidence-based recommendations for best practices in the diagnosis of FASD will improve the current process and will lead to more efficient and effective care for affected individuals across their lifespan [2].

Although the assessment is meant to provide information about individuals' strengths as well as their challenges and aims to inform interventions, it is not solely for the purpose of diagnosis. The assessment for PAE is a diagnosis for the affected person, the birth mother and possibly affected siblings. Rather than labelling, a diagnosis provides a blueprint for early intervention. It also confirms the suspicion of the biological mother that her child may have FASD [14]. Treatment planning and implementation, specifically targeted toward the unique needs of the individual and the family, form a large part of the diagnosis.

Databases containing diagnostic data need to be analyzed for correlations between sentinel facial features and patterns of neurodevelopment deficits. Research is ongoing, and their findings may reveal novel approaches that can improve available

technologies, screening, diagnosis and management [13]. The 2005 guidelines and recommendations were developed in parallel and in consultation with a United States committee charged with the same task [36].

The challenges for prevention and diagnosis of FASD and intervention (including ethics) to assist those affected by this disorder are evolving and dynamic. Research is ongoing to determine whether tools, such as novel brain imaging techniques, biomarkers and DNA micro-array techniques [35], might enhance accurate and reliable alcohol-related diagnoses and treatment.

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