Diagnosing fetal alcohol spectrum disorder: History, challenges and future directions

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Fetal alcohol spectrum disorder (FASD) is one of the most common preventable causes of developmental disability, and is currently one of the most pressing public health concerns in Canada. FASD refers to the range of physical, mental, behavioural and learning disabilities that an individual may acquire as a result of maternal alcohol consumption. In the present paper, the history of the diagnostic approach to alcohol-related disorders over the past 35 years is reviewed. Research supporting the importance of early diagnosis for the long-term outcomes and management of individuals with FASD is presented, and challenges that have plagued efforts to efficiently diagnose individuals with FASD are discussed. Finally, the study reviews the future directions and implications regarding current diagnostic strategies.

Key Words: *Challenges; Diagnosis; Fetal alcohol spectrum disorder*

Le diagnostic de l'ensemble des troubles causés par l'alcoolisation fœtale : Historique, défis et futures orientations

L'ensemble des troubles causés par l'alcoolisation fœtale (ETCAF) est l'une des principales causes évitables de déficience développementale, et c'est actuellement l'une des préoccupations de santé publique les plus pressantes au Canada. L'ETCAF désigne le spectre de déficiences physiques, mentales, comportementales et d'apprentissage qu'une personne peut acquérir par suite de la consommation d'alcool de sa mère pendant la grossesse. Dans le présent article, les auteures analysent l'histoire de l'approche diagnostique des troubles liés à l'alcool depuis 35 ans. Elles présentent des recherches appuyant l'importance d'un diagnostic rapide pour l'issue à long terme et la prise en charge des personnes ayant l'ETCAF ainsi que des défis qui ont nui aux efforts visant à diagnostiquer avec efficacité les personnes ayant l'ETCAF. Enfin, elles analysent les futures orientations et les répercussions des stratégies diagnostiques courantes.

Fetal alcohol spectrum disorder (FASD) is the umbrella term currently used to denote the wide constellation of abnormalities that can result from prenatal alcohol exposure (PAE), but it is not considered to be a diagnostic term (1). FASD refers to individuals who have physical, mental, behavioural and/or learning disabilities as a result of PAE (1). FASD is one of the most common known causes of mental retardation (2), and the prevalence of FASD has been estimated to be at 9.1 per 1000 live births in the United States (1), although there are no national statistics for Canada. Within this spectrum disorder, there has been an increasing shift in emphasis to the cognitive and behavioural deficits experienced by these individuals because these impact on function and quality of life. Consequently, effective diagnosis has become essential but also problematic, because the wide spectrum of cognitive disabilities witnessed makes it difficult to pinpoint a profile specific to FASD. The present paper reviews the history, benefits and challenges of the diagnosis of alcohol-related disorders, as well as future directions regarding new techniques that may aid in the diagnosis.

THE HISTORY OF THE DIAGNOSTIC PROCESS

Since Jones and Smith (3) and Jones et al (4) first commented on the cardinal effects of fetal alcohol syndrome (FAS) after witnessing a unique pattern of altered development and function (stunted growth, neurobehavioural deficiencies and facial anomalies) in offspring with PAE, the nomenclature and diagnostic approach to FAS has been refined multiple times. Within a decade, the term 'fetal alcohol effects (FAE)' was proposed to describe children with substantial behavioural and cognitive effects, but without the full sentinel features and growth deficiencies classically associated with FAS (5). The term 'FAE' was applied indiscriminately by clinicians to a wide variety of problems, often solely on the premise of suspected PAE (6). Because it is the unique constellation of features that distinguishes FAS and attributes causation to PAE, the clinical use of the term 'FAE' has since been abandoned (6,7).

In 1996, the United States' Institute of Medicine (IOM) differentiated five separate classes of prenatal alcohol effects: FAS with and without confirmed alcohol exposure, partial FAS (pFAS), alcohol-related neurodevelopmental disabilities (ARND) and alcohol-related birth defects (ARBD) (8). pFAS refers to those individuals with confirmed PAE; evidence of some facial characteristics; and either growth, central nervous system (CNS) deficits, or a complex pattern of behavioural or cognitive abnormalities. ARND refers to those with CNS deficits or a complex pattern of behavioural or cognitive abnormalities, while ARBD includes individuals with congenital physical abnormalities. Both require a positive history of PAE for diagnosis.

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The IOM guidelines were comprised of vague categories that failed to define the diagnostic criteria used, resulting in an inconsistent approach across clinics (9). In 2005, Hoyme et al (10) revised the IOM guidelines in an effort to improve on this ambiguity. The diagnostic categories – ARBD and ARND – were defined, along with the degree of growth deficiency and the minor physical anomalies required for diagnosis. However, the Hoyme 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 (11).

1n 1997 and 1999 (and revised again in 2004 by Astley [12]), Astley and Clarren (13-15) responded to current limitations in diagnosis by introducing the 4-Digit Diagnostic Code, which provided standardized ordinal measurement scales that increased the objectivity of diagnosis and reflected the diverse continuum of disabilities found within FASD. Four key diagnostic features of FASD (growth deficiency, facial phenotype, brain damage/dysfunction and PAE) were independently assessed and ranked on a 4-point Likert scale, with 1 reflecting complete absence of the feature and 4 indicating a strong 'classic' presentation of the feature. Thus, the 4-Digit Diagnostic Code was capable of providing 256 possible codes, which were further subdivided into nine unique diagnostic outcome categories. The strengths of Astley and Clarren's (15) system resided in the objective measurement scales provided, which replaced the current gestalt approach. The growth component of the code relied on comparisons with age- and sex-adjusted height and weight percentiles. Ranking the facial characteristics required measuring the three classic phenotypes of small palpebral fissures, smooth philtrum and thin upper lip. Palpebral fissure lengths were computed as *z*-scores and adjusted for age and ethnicity when possible, whereas the philtrum and upper lip were assessed and coded independently using a 5-point pictorial Likert scale. These midfacial features correlate with the animal model of alcohol exposure on days 19 to 21 of gestation, leading to the blunting of fetal forebrain development (16). Other dysmorphic features may be present; however, they are not specific to FASD, and a thorough dysmorphology assessment to exclude other genetic syndromes is essential (1). When coding brain damage, structural and functional factors were evaluated for the presence of an organic cause for any brain dysfunction. The 4-Digit Diagnostic Code also provided guidelines for ranking the degree of PAE and the influence of prenatal (genetic conditions and poor prenatal care) and postnatal (multiple placements, adverse life experiences and premature birth) issues to consider all factors in a differential diagnosis and to identify comorbid conditions.

A weakness of the 4-Digit Diagnostic Code was that some trained paediatricians experienced difficulty reaching an agreement when assessing facial characteristics despite using categorical variables for measures (17). Difficulties may also arise in reaching a consensus on categorization and the labelling of codes (14), and the high number of diagnostic categories may be confusing and may diminish the practical utility of the guidelines (10). Furthermore, Hoyme et al (10) also contend that the system places too much emphasis on brain dysfunction – findings that are not highly specific to PAE. This, along with insufficient recognition of the familial and genetic backgrounds of the patient, could potentially result in overdiagnosis of FASD (10). In 2004, Astley (12) revised the 4-Digit Diagnostic Code to enhance accuracy and clarity. Higher resolution Caucasian and African American lip-philtrum guides were introduced, along with relaxation of the required growth criteria and a more comprehensive diagnostic form documenting 'domains of brain dysfunction'.

In 2005, the Canadian diagnostic guidelines were published in an attempt to harmonize the IOM's guidelines with Astley's 4-Digit Diagnostic Code (2004), all while further stressing a comprehensive and multidisciplinary approach (1). The Canadian guidelines advocated for six key areas to be addressed during the diagnostic process: screening and referral; physical examination and differential diagnosis; neurobehavioural assessment; treatment and follow-up; maternal alcohol history during pregnancy; and diagnostic criteria for FAS, pFAS and ARND. Emphasis was placed on making FASD a diagnosis of exclusion with full exploration of all other possible etiologies, such as genetic causes or multifactorial disorders (1). The 4-Digit Diagnostic Code was used to objectively measure the four key diagnostic features of FASD, while borrowing the nomenclature established by the IOM (FAS, pPAS and ARND). ARBD was abandoned due to indeterminate causation of nonspecific congenital anomalies from PAE. The Canadian guidelines recommended assessment of pre- or postnatal growth against appropriate norms, while taking into consideration confounding variables such as parental size and the facts that growth parameters can be normal if there was no alcohol exposure in the third trimester and that deficiencies may not persist with age (1). Facial features and PAE were measured and ranked using similar criteria as the 4-Digit Diagnostic Code. Neurobehavioural assessment was recommended across nine independent domains (hard and soft neurological signs including sensory-motor signs, brain structure, cognition, communication, academic achievement, memory, executive functioning, attention and adaptive behaviour) that nevertheless exhibit some overlap, necessitating a need for clinical judgement when determining how many domains are impaired (1). A domain is considered to be impaired when standardized scores are either two or more SDs below the mean or there is a discrepancy of at least one SD between subdomains. Unlike the 4-Digit Diagnostic Code in which a diagnosis within FASD could be assigned with only one structural or neurological indicator, the Canadian guidelines required impairment in three different domains before a diagnosis could be considered (1). This constraint acknowledged the myriad of etiologies, which could result in organic brain damage and help prevent the overdiagnosis of FASD. Despite improving on the weaknesses of its two diagnostic predecessors, the recommendations laid

out in the Canadian guidelines have not yet been tested for sensitivity or specificity (18), nor has research evaluated the diagnostic process using the Canadian guidelines. Currently, there is ongoing work under the lead of the Canada Northwest FASD Research Network to define the relevant psychometric tools that will lead to proper identification of brain damage due to PAE. Information on brain dysfunction is essential to determine what type of intervention to put in place to support the individual with FASD.

WHY EARLY DIAGNOSIS IS IMPORTANT

Individuals with FASD display numerous secondary disabilities that stem from primary disabilities and are potentially preventable, including disrupted school experiences, mental health problems, inappropriate sexual behaviours, alcohol and drug abuse, and incarceration and retention in the justice system (19). There is a very high prevalence of persistent psychiatric problems among individuals with PAE and/or FASD (20-24), which can persist into adulthood (25). Streissguth (19) and Streissguth et al (26) found that early diagnosis, ideally before six years of age, is one of the strongest correlates with a reduced risk of adverse outcomes. Delayed diagnosis of individuals lacking the sentinel physical features of FAS may be responsible for increased secondary disabilities (27) and special education services (28) seen within this subset of FASD.

An early diagnosis not only better prepares the child and their family for difficulties in transitioning to young adulthood, but it also helps them qualify for appropriate supports and benefits (26,29). This translates into increased independence and fewer employment problems as an adult (19). Early diagnosis can help build self-esteem within the child by increasing accessibility to appropriate school programs, counselling services and specialized community programs aimed at dealing with the challenges of living with FASD (29). Early developmental interventions and preventive measures to limit future health problems are also benefits derived (30). Furthermore, the early diagnosis of FASD can serve as a potential marker for maternal mental health, and effective treatment of the mother may reduce mother-child separation rates, prevent future offspring from being affected, and allow for recognition and interventions for any affected siblings (30).

Traditionally, there have been very limited research and scientific evidence on appropriate interventions for children with FASD, making it difficult to formulate treatment recommendations for these individuals (31). More recently, however, research has begun to document the benefits derived from focused interventions aimed at those with FASD. O'Connor et al (32) found improvements in social skills and reductions in problem behaviours following social skills training in children with FASD, and they noted that these changes were maintained three months later. In addition, classroom interventions for children with FASD produced specific cognitive improvements in language and literacy in South Africa (33). Sociocognitive rehabilitation programs aimed at children with FASD have also generated improvements in behaviour and math performance (34). A recent study (35) found that teaching young children with FASD how to rehearse information improved their performance on a memory task. The benefits derived from interventions extend to older FASD populations as well, with one study (36) showing multiple life improvements among 19-year-old women with FASD following a 12-month community intervention program. This current research documents the immense importance of early detection and diagnosis of FASD, and provides hope to the individual and their family that diagnosis will facilitate effective treatment.

THE CHALLENGES OF DIAGNOSIS

Numerous fundamental challenges exist in providing accurate and reliable diagnosis of FASD. For one, obtaining an accurate and reliable history of alcohol use during the pregnancy can be very problematic. Birth mothers may no longer be in their children's life at the time of assessment, precipitating a reliance on indirect reports of maternal alcohol use during pregnancy (11). Even when alcohol exposure can be obtained, maternal self-report is often fraught with unreliability and under-reporting. This can be due to simple forgetfulness (11) or from societal stigmas related to drinking during pregnancy, which may create maternal denial arising from awareness of the potential harm caused (37). Research has concentrated on evaluating the effectiveness of different questionnaires (AUDIT, CAGE, TWEAK, T-ACE, MAST, TLFB) aimed at differentiating at-risk from nonrisk drinkers (38-41). Moderate evidence exists supporting the T-ACE and TWEAK questionnaires as effective tools for distinguishing pregnant women who would benefit from assistance for their drinking; the Canadian guidelines recommend that all pregnant and postpartum women receive screening with these instruments (1). Moreover, Gupman et al (42) have shown that assessment instruments yield higher prevalence estimates of alcohol use in women than simple physician documentation alone. However, physicians need to be prepared to support pregnant women who are identified as drinking alcohol by addressing the contributing psychosocial and mental health factors, by providing counselling and by connecting the individual to resources in the community.

There is much interest in developing a screening tool for FASD and, recently, the Public Health Agency of Canada requested the Canadian Association of Paediatric Health Centres to assess this using a literature review and workshops involving expert panels and stakeholders. From this, it was determined that there is not a single effective screening tool for all age groups or communities, and further work will need to be performed to pilot effective screening tools with thorough evaluation (43). Also, barriers to screening implementations include accessibility, cost, expertise, ease of use and cultural appropriateness, and these must all be addressed when assessing screening tools (43). Currently, the criteria for entry to an FASD

diagnostic clinic are a confirmed history of PAE and a history of maladaptations or dysfunction. A recent survey (44) of FASD diagnostic clinics in western and northern Canada suggested that this current screening technique may be simple, yet effective. Of those assessed at these clinics, 67% were diagnosed with an FASD, suggesting that the correct at-risk population is being targeted with the current screening guidelines (44). However, questions still arise over individuals being missed for assessment under the current screening parameters, and additional research is needed to establish more effective tools.

Other challenges to diagnosis include the fact that many of the key diagnostic features of FASD change with age and with environmental influences. The individual's age will dictate the relevant cognitive measures requiring assessment (45), and consideration must always be given to cumulative environmental influences, which may distort brain function and cannot be attributed to PAE (1). In addition, the classic facial phenotype of FAS can diminish with age (46); however, others (47,48) contend that those facial features that change with age are usually neither specific nor sensitive to PAE, and therefore, facial analysis should remain an integral part of assessment even in adulthood.

Moreover, differentiation of FASD from other similar disorders (1), and recognition of the nonspecific abnormalities found in certain manifestations of the spectrum disorder also provides challenges. Although facial phenotype serves as an important marker for alcohol exposure (11) and has been shown to correlate with brain dysfunction (47), Greenbaum et al (49) have demonstrated that an increase in physical FAS signs within children with ARND did not translate into increased behavioural problems. Other studies (50,51) have also discovered similar neurobehavioural deficits across all FASD subtypes. As stated previously, alcohol affects facial development only during a short gestational period (16), but the developing brain may be susceptible to alcohol throughout the entire pregnancy (48,52). In a Canadian study (53) on FASD, it was found that none of the children scored a 4 for facial features, and only a handful (18%) had a facial score of 3, with the majority showing no FAS facial features. Therefore, reliance on facial dysmorphology during the diagnostic process could potentially result in many false negatives (51), which is a cause for concern considering that it is not the FAS face, but rather the functional deficits that require treatment (52). Consequently, it is becoming increasingly evident that assessment should focus more on the functional neurobehavioural deficits than on the facial and growth characteristics; attempts have been made to delineate the unique behavioural profile common to the full spectrum of FASD (53-55).

Furthermore, ethnic and familial influences must always be considered while assessing for FASD. The Canadian guidelines are largely based on normative data for Caucasian populations, and Chudley et al (1) conceded that standardized values for growth and facial data are needed for different populations. Some studies (56) have failed to find ethnic differences in facial assessment, whereas others (57) have reported disparities; however, there is no research on the validity of facial measurement tools for Aboriginal children in Canada. The assessment of cognitive traits, such as intelligence, must also take into account genetic potential by considering the performance of parents (45).

The assessment of FASD also faces many social and medical barriers that impede early and accurate diagnosis. Surveys (58,59) have shown alarmingly low rates of education among physicians regarding identification of the essential diagnostic features of FASD, and many physicians identified their training as inadequate in this area. In a Canadian survey (60), only 60% of health care providers could specify the three cardinal diagnostic features of FASD. Furthermore, Tough et al (61) found that at least 30% of physicians did not discuss the risks to women who were pregnant and drinking, and only 54% felt prepared to care for pregnant women who were abusing alcohol. Stoler and Holmes (62) found that even with the knowledge of significant PAE, a majority of infants were not assessed for specific FAE. Even more worrisome is the admission by many physicians that they have suspected but not diagnosed FASD due to concerns of stigmatization and worries that the parents would resist referral for assessment and treatment (58). Societal stigmas must be addressed and improvements must be made in educational guidelines before primary care physicians can effectively assess and refer patients for the diagnosis of FASD (58,62).

Finally, the lack of international consensus on diagnostic protocol creates undue confusion among health care professionals and complicates comparisons of research (63). Intervention-oriented diagnostic strategies for children with disabilities are important (64), and the Canadian guidelines advocate for services based on the profile of brain function/dysfunction, rather than on the diagnostic term itself (1).

FUTURE DIRECTIONS

Although still very experimental, novel techniques have been developed and researched for use in the diagnosis of FASD. Biomarkers for PAE, which can be screened for in both neonatal hair and meconium, have been investigated as an alternative to the unreliability of maternal reports of drinking (65,66). In particular, the use of free fatty acid ethyl esters in meconium has demonstrated a fivefold increase in sensitivity over self-report-based screening in Ontario (67), and has been associated with developmental problems in early childhood (68). However, meconium is not produced until after the first trimester (69) and would, therefore, not identify alcohol exposure before this time. Biomarkers are not diagnostic of FASD, but may prove valuable in risk identification and screening. Nevertheless, there may be issues surrounding the ethical ramifications of collecting such information, and more research is needed to determine how these biomarkers correlate with neurobehavioural outcomes in children with PAE.

Neuroimaging could also prove valuable in establishing brain-behaviour relationships inherent to FASD (70). Microcephaly is a key indicator of CNS deficit in the Canadian guidelines (1), and neuroimaging studies (70) have documented specific brain size and shape abnormalities stemming from PAE, particularly in the corpus callosum and cerebellum. Diffusion tensor magnetic resonance imaging is a new magnetic resonance imaging technique that measures the white matter and structural integrity in the brain, and has been used to detect subtle brain abnormalities in individuals with FASD (71-74). In particular, Lebel et al (71) have demonstrated widespread abnormalities across a variety of white matter tracts including the corpus callosum and temporal and commissural connections among children with FASD. Although preliminary, another novel tool that may be useful in the assessment of FASD is the measurement of saccadic eye movement deficits (75). A pilot study conducted by Green et al (75) revealed that children with FASD have longer reaction times and make more direction errors on saccadic eye movement tasks than control children, which is indicative of deficits in executive functions and motor control. Thus, the authors concluded that the measurement of saccadic eye movements may be a powerful tool to assess executive dysfunction in individuals with FASD.

CONCLUSIONS

The approach to the diagnosis of FASD has evolved continuously since its conception in the research literature in 1973. Many biological, social and medical barriers are inherent to FASD and have created significant challenges for identifying those at risk. While attempts are continually being made to improve on the diagnostic strategies currently in place, experimental diagnostic techniques are also being evaluated in the research. The Canadian guidelines advocate for an assessment of multiple brain domains by a trained multidisciplinary team consisting of a psychologist, occupational therapist, speech and language pathologist, social worker and physician, yet provide little recommendation on how clinics should implement this in practice (44). Evaluation of cognitive performance, along with prenatal and postnatal factors, is required to make an FASD diagnosis.

A recent survey (44) of 15 FASD diagnostic clinics across western and northern Canada (representing 85% of all evaluations in this region) highlighted several areas of concern regarding the diagnostic process in this region. For one, the cost of an individual assessment is high, averaging anywhere from $2000 to $5500 for private clinics. The assessment process is also very demanding on the multidisciplinary team. Each team member can spend hours on both direct and indirect care for each case, with psychologists alone averaging up to 10 h of work load for each individual assessed. This is to be expected when diagnosis requires evaluation across multiple domains; however, it poses definite challenges to building clinical capacity (44). Furthermore, the adult FASD population is vastly under-represented in diagnostic clinics, with only three clinics reporting regular assessment of individuals older than 18 years of age as part of their mandate (44). Overall, the survey found the diagnostic capacity of this region of Canada to be insufficient, especially based on the proposed rates of FASD within the general population, and identified many areas that would be challenging with regard to increasing the clinical capacity (44).

Therefore, there is obviously a great need to improve access to multidisciplinary teams for diagnosis and assessment. This requires training and mentoring by an established team, sustainable funding and recruitment of professional disciplines. This, in turn, relies on retaining committed staff, providing sufficient time and having adequate long-term funding (44). Attempts have been made in Manitoba to establish telemedicine diagnosis in adjunct with the multidisciplinary approach endorsed in the Canadian guidelines (76). Telemedicine negates the challenges of travel, and does not require the child to leave the supports of his or her home environment (76). This approach also maximizes the efficiency of the small number of FASD experts, and with experience, delegates the assessment of less complex cases to the onsite team, thus increasing assessment capacity (76). Innovative approaches such as this can help to alleviate the challenges of FASD diagnosis and increase clinical capacity, while serving populations that might otherwise have not been assessed.

After the diagnosis, appropriate supports need to be put in place for both the individual with FASD and his or her caregivers, with an established plan to re-evaluate the individual's functional deficits over time, because expectations will change into the patient's adolescent and adult years. While it is known that early diagnosis and intervention is beneficial for the individual with FASD, it is only now that research is starting to elucidate exact techniques and programs that will provide known benefits and treatment. These supports include educational programs, sensory approaches, respite programs, supportive employment and housing, diversion within the justice system, psychopharmacology for targeted behaviours and mental health support (44). The recent survey (44) by the Canada Northwest FASD Research Network identified multiple projects and pilots; however, many lacked formal evaluations of outcomes that can be used to inform policy and funding based on best practices. This needs to be the focus of research as the cost to society and stress to caregivers from FASD is substantial and needs to be properly addressed (77). As these interventions are shown to improve the lives of those living with FASD, primary care physicians will hopefully no longer view FASD as a futile diagnosis and will become more willing to refer suspected patients for assessment and diagnosis. Caregivers also need to be supported in meeting the challenges of raising a child with FASD because they will be required to be the decision maker, advocate and life planner into the patient's adult years. Education about the syndrome itself, along with knowledge of successful strategies to deal with the affected individual, will benefit everyone involved and ease the challenges of living with FASD.

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