

Distinguishing between attention-deficit hyperactivity and fetal alcohol spectrum disorders in children: clinical guidelines

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Abstract: Fetal alcohol spectrum disorders (FASD) are the physical and neurodevelopmental outcomes of fetal alcohol exposure. The behavioral phenotype of children with FASD includes difficulties with executive function, memory, planning, processing speed, and attention. Although attention deficit hyperactivity disorder (ADHD) is diagnosed in up to 94% of individuals with heavy prenatal alcohol exposure, the exact relationship between FASD and ADHD is unclear. There is some evidence that ADHD in FASD may be a specific clinical subtype and thus may require a different treatment approach. Although traditional behavioral observation scales may not distinguish between the two groups, there is evidence that children with FASD have a different profile on the four-factor model of attention than children with ADHD who do not have FASD. There is a paucity of good scientific evidence on effective interventions for individuals with ADHD and FASD. There is weak evidence that children with FASD and ADHD may have a better response to dexamphetamine than methylphenidate. There is a strong need for larger, high quality studies to examine the relationship between ADHD and FASD and identify effective treatments because management of inattention and hyperactivity may improve learning and ameliorate the common secondary disabilities associated with FASD.

Keywords: fetal alcohol spectrum disorders, attention deficit hyperactivity disorder

Introduction

Disruptive, hyperactive, and impulsive behaviors are highly prevalent in individuals with fetal alcohol spectrum disorders (FASD).¹ In this paper we discuss the relationship between attention deficit hyperactivity disorder (ADHD) and FASD. Firstly, we define ADHD and FASD and review the epidemiology of these conditions. Then we discuss the rationale for distinguishing between ADHD with and without FASD and review the evidence regarding the relationship between ADHD and FASD. Finally, we discuss the approach to diagnosis and management of ADHD in individuals with FASD.

Attention deficit hyperactivity disorder

ADHD may be thought of as a group of conditions with similar behavioral symptoms consequent to different etiologies.² ADHD is defined as a persistent pattern of behavior including hyperactivity and impulsivity, and/or inattention that is more severe and frequent than is usually seen in an individual at the same stage of development. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) defines three subtypes, ie, a combined type which includes symptoms of inattention and hyperactivity or impulsivity, a predominantly inattentive type, in which hyperactive

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and impulsive symptoms are minor, and a predominantly hyperactive-impulsive type, in which inattentive symptoms are minor.³ The subtypes may be discontinued in DSM-5.⁴ The mean intelligence quotient (IQ) score and IQ distribution in the ADHD population are similar to that in the general population.^{2,5} ADHD is a neurobiologic disorder with genetic and environmental origins. Family, adoption, and twin studies demonstrate a strong genetic contribution to ADHD, which involves polymorphisms in a number of genes, such as those which code for dopamine transporters. Environmental risk factors for ADHD include antenatal exposure to toxins, such as alcohol and tobacco, prematurity, adverse childhood experiences, childhood illness, head trauma, and exposure to environmental toxins.³ The heterogeneity of ADHD may be explained partially by the varying contribution of genes and environmental factors for individual children. ADHD is reported in all ethnic groups and social classes. The prevalence of ADHD in children in the general population ranges from 5% to 11%.^{3,6}

Fetal alcohol spectrum disorders

Fetal alcohol syndrome (FAS) was first described in 1973,⁷ but descriptions of the effects of alcohol exposure during pregnancy date back to ancient history.⁸ FASD is a nondiagnostic umbrella term for the possible childhood outcomes of prenatal alcohol exposure. FASD includes FAS, partial FAS, alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects. Individuals with FAS have specific facial features (including short palpebral fissures, flat philtrum, and thin upper lip), impaired prenatal and/or postnatal growth, and structural or functional problems of the central nervous system. If all of these features are present and differential diagnoses are excluded, the diagnosis of FAS can be made even if alcohol exposure during pregnancy is not confirmed. Individuals with partial FAS have most, but not all, the features of FAS. Individuals with ARND have a complex pattern of behavioral and/or neurologic impairment without the physical features of FAS. Fetal alcohol effects (FAE) is an obsolete term previously used to describe individuals with incomplete features of FAS. The facial features of FAS occur with fetal alcohol exposure early in the first trimester, but neuropsychologic deficits may occur independent of the physical features of FAS.⁹ In FAS, IQ scores are reported to range from 20 to 120 with an average IQ score between 68 and 72. Individuals with ARND have a slightly higher IQ than individuals with FAS.² Internationally, several diagnostic approaches to FASD have been proposed. Although the diagnostic criteria and terminology used differ

only slightly, the use of different approaches is confusing and makes comparison of study results difficult.^{10–13} The estimated prevalence of FAS is 0.5–2.0 per 1000 births, although a prevalence of up to 68 per 1000 has been reported in some high-risk communities.^{14,15} The prevalence of the other FASD diagnoses is not well defined, but it is estimated that FASD affects 1% of all births in the US.¹⁴

Many studies have focused on defining the behavioral phenotype of FASD to assist diagnosis and intervention. Individuals with FASD frequently display deficits in executive functioning, memory, attention, visual-spatial abilities, planning, cognitive flexibility, processing speed, inhibition and inhibition/switching, deductive reasoning and verbal abstract thinking, problem solving, verbal and spatial concept formation, phonemic switching and phonologic working memory, and motor skills.^{16,17} Executive function deficits are present in individuals with FASD whether or not they have FAS.^{18,19} Older children with FASD are more impaired than younger children on verbal processing tasks.¹⁷ These deficits may contribute to lower IQ scores, poor academic achievement, and learning problems.¹⁷ Long-term studies show that adolescents and young adults with FASD have high rates of secondary disabilities including mental health problems (90%), inappropriate sexual behavior (49%), disrupted school education (60%), and trouble with the law (60%). More than one third experience drug and alcohol problems.²⁰ These secondary disabilities may arise from the neurobehavioral deficits caused by prenatal alcohol exposure, with exacerbation or amelioration by environmental factors.⁹

Attention and hyperactivity problems in FASD

Children with FASD are often described as hyperactive, distractible, and impulsive, with short attention spans.²¹ ADHD is the most commonly reported mental health diagnosis in individuals with prenatal alcohol exposure.^{1,22} The prevalence of ADHD (diagnosed according to DSM-IV criteria) in children with heavy prenatal alcohol exposure is between 49.4% and 94%.^{1,22} Unfortunately, prevalence studies have included children with heavy prenatal alcohol exposure (variously defined), with and without a diagnosis of FASD, hence the wide prevalence range. However, the prevalence of ADHD in cohorts with FASD is consistently much higher than that in the general population. The proportion of children with a diagnosis of ADHD who also have FASD is not known and will be influenced by underdiagnosis of FASD. Underdiagnosis occurs due to a variety of factors, including health professionals' reluctance to ask about alcohol exposure in pregnancy or to make

a diagnosis due to lack of knowledge or fear of stigmatizing the child.^{23–25} The proportion of children with FAS diagnosed with ADHD increases with the level of alcohol exposure.¹ Attention deficit in individuals with FASD is independent of IQ and persists into adolescence and adulthood.^{22,26,27} Inattention symptoms are more commonly reported in children with FASD who meet DSM-IV criteria for ADHD, than in children with ADHD who do not have FASD.²⁸

Rationale for distinguishing between ADHD and FASD

The prognosis and treatment responses for children with ADHD and FASD differ to those of children with ADHD alone. Children with FASD often present with early onset ADHD with predominant inattentive symptoms.⁶ They are at high risk of secondary disabilities, which can be ameliorated by early diagnosis of FASD and management of its symptoms, especially if diagnosis is before the age of six years. The reason for the improved prognosis is unclear because there are few specific interventions for children with FASD, but it may relate to improved understanding and appropriate expectations of the children by their caregivers and teachers.²⁰

Individuals with FASD may respond differently to stimulant medication than other children with ADHD. Specifically, children with FASD appear to have a differential response to methylphenidate and dexamphetamine. In a case series of 30 children with FASD and ADHD, 22% (of 23 children) responded to methylphenidate, while 79% (of 19 children) responded to dexamphetamine. Of the children given both medications, eight did not respond to methylphenidate but later responded to dexamphetamine, one child did not respond to dexamphetamine but later responded to methylphenidate, and three children did not respond to either medication.²⁹ The apparently increased response rate to dexamphetamine may be explained by animal work showing that rats who were prenatally exposed to alcohol and had physical hyperactivity showed “hyperresponsiveness” to methylphenidate and that alcohol exposure acts on the D₁ dopamine receptors of the mesolimbic system, which is the site of action of dexamphetamine.^{6,30,31} Decreased effectiveness of methylphenidate in animal and human studies suggests that the front nigrostriatal pathway may not be the mechanism in patients with FASD and comorbid ADHD.⁶

ADHD and FASD

There may be multiple pathways to the coexistence of ADHD symptoms and FASD, so there may be different

subsets of ADHD and FASD.^{6,32} The relationship between ADHD and FASD may be coincidental because ADHD is a common disorder affecting up to 11% of children in the general population. Adults with ADHD are more likely to drink alcohol, thus pregnant women with ADHD who drink alcohol during pregnancy may genetically transmit ADHD to their offspring.⁶

There may be common etiological pathways to ADHD and the behavioral phenotype of FASD. Alternatively, acquired ADHD secondary to prenatal alcohol exposure may be due to the effect of alcohol on the developing dopamine transmitter system. These two hypotheses are supported by changes in the neurochemistry seen in animal studies of fetal alcohol exposure in which deficits have been found in most neurotransmitter systems, including the dopaminergic, noradrenergic, serotonergic, cholinergic, glutaminergic, gamma aminobutyric acid (GABA)-ergic, and histaminergic systems. Deficits in noradrenergic and dopaminergic systems are the most likely ones to be related to the ADHD symptoms seen in animals with prenatal alcohol exposure. The D₁ receptors of the mesolimbic dopamine system tend to be affected by alcohol exposure more than other dopamine systems.⁶

Some studies support the idea that ADHD in FASD is a particular clinical subtype with earlier onset, a different clinical and neuropsychologic profile, and a different response to psychostimulant medications. The Seattle Longitudinal Prospective Study suggests that infants with a history of prenatal alcohol exposure have an infant regulatory disorder and temperament disturbance which precede the diagnosis of ADHD. Research has shown that animals with prenatal alcohol exposure have an exaggerated response to psychostimulants, which is mediated by age, gender, and drug dosage. There is evidence suggesting that individuals with FASD and ADHD have a better response to dexamphetamine than methylphenidate. Patients, such as those with FASD, who have neurochemical or structural changes in the central nervous system are often hypersensitive to the effects and side effects of medication, and psychostimulant response in these patients may improve with age.⁶

Adaptive behavior

Adaptive function is the ability to meet developmentally appropriate expectations of personal independence and social responsibility, including performance of everyday tasks, and adapt to changes in the environment.³³ Adaptive behavior is affected in both FASD and ADHD. Using the Vinelands Adaptive Behavior Scale, three groups were compared, ie, children with heavy prenatal alcohol exposure, children with

ADHD, and normally developing children. Children with prenatal alcohol exposure and children with ADHD had significantly lower scores on the communication domain than controls and, in the prenatal alcohol exposure group, age was negatively associated with score. Children in the prenatal alcohol exposure and ADHD groups had significantly lower scores on daily living skills, but the prenatal alcohol exposure group had significantly lower scores than the ADHD group. Children in the prenatal alcohol exposure and ADHD groups had significantly lower scores on socialization, but did not differ from each other. Again, age was negatively associated with the scores in the prenatal alcohol exposure group. Within the FASD group, children scored best in daily living skills and scored worst on socialization and communication domains. They demonstrated increasing adaptive behavior deficits with age. The children with ADHD had difficulty with socialization skills and their adaptive behavior skills improved with age. Overall, children in the prenatal alcohol exposure group were more likely than children in the ADHD and control groups to be rated as having inadequate adaptive skills. When analyzed with matched IQs, the prenatal alcohol exposure and ADHD groups did not differ from each other. For adaptive behavior skills, the differences between children with prenatal alcohol exposure and children with ADHD may be accounted for by IQ.³³

Executive function

Executive function is the higher order process involved in thought and action under conscious control, usually to achieve a goal. It involves planning, inhibition, working memory, organized speech, set-shifting, strategy employment, flexible thinking, and fluency.¹⁷ Executive function is probably mediated by the frontal cortex, and prenatal alcohol exposure may affect frontal cortex development.¹⁷ Neuropsychologic measures of executive function assess organization, planning, working memory, inhibition of inappropriate responses, and set-shifting.²

The common symptoms of behavioral disinhibition and attention deficit in FASD and ADHD may be related to problems with executive function.² There is evidence that executive function is a core deficit in FASD and ADHD, and neuroimaging shows that children with FASD and ADHD may have structural and functional abnormalities in the frontal-subcortical circuits, which are areas associated with executive function. Behavioral data also confirm that both populations have deficits in global adaptive abilities. There is conflicting evidence regarding executive function deficits in ADHD.²

Nanson et al²¹ conducted a prospective cohort study comparing children with FAS or FAE with normal developing (control) children and children with attention deficit disorder (ADD) without FAS or FAE. Behavioral characteristics were similar between the FAS/FAE and ADD groups. There were no differences on parental rating for the two groups, suggesting it is difficult to distinguish between the two groups using traditional observational scales. The FAS/FAE group tended to have slower performance and was more likely to improve with practice than the ADD group. Unlike the ADD group, the FAS/FAE group was not able to trade off accuracy in favor of increased speed.²¹

Coles et al³⁴ compared children with prenatal alcohol exposure, children with ADHD without prenatal alcohol exposure, and control children with neither prenatal alcohol exposure nor ADHD. They used traditional behavioral and psychiatric measures of ADHD and externalizing behavior and neurocognitive measures of a four-factor model of attention. Children with FAS or FAE had similar global intellectual deficits to children with ADHD. Both groups had difficulty with sequential functioning, but the FAS/FAE group had greater difficulties on visual-spatial reasoning. The FAS/FAE group struggled on arithmetic, while ADHD group were poorer on reading/decoding. The FAS/FAE group had nonsignificant decreases in scores on reading/decoding. Both the FAS/FAE and ADHD groups had trouble with coding in the revised edition of the Wechsler Intelligence Scale for Children. The FAS/FAE children had problems with encoding on the second list of the paired-associate task and the number of categories completed on the Wisconsin Card Sorting Test (WCST). On behavioral measures, the ADHD group scored highest on the Child Behavior Checklist, the SNAP and the DISC (diagnostic interview schedule for children) interview items but the FAS/FAE group only differed from the control group on the attention score on the Child Behavior Checklist. On the Computer Performance Task, the ADHD group had poor speed and accuracy, slower reaction times, and more false alarms (associated with impulsivity). They also had fewer hits and more misses. However, there was a large dropout of children from the Computer Performance Task (60% of the ADHD group, 52% of the FAS/FAE group, and 43% of controls). Using the four-factor model of attention, the FAS/FAE group had problems with encoding and shift, while the ADHD group had difficulties with focus and sustain. The results of this study suggested that children with ADHD and FAS/FAE have unique attentional profiles, and thus the neurocognitive deficits may not be the same. The authors recommend that children with ADHD are best identified using

behavior checklists and measures of the ability to focus and sustain attention, while children with FAS/FAE have deficits in visual-spatial skills, encoding of information, and flexibility in problem solving.³⁴

Vaurio et al² examined executive function in children with heavy prenatal alcohol exposure, children with ADHD who were not exposed to prenatal alcohol, and children with neither ADHD nor prenatal alcohol exposure. The children with prenatal alcohol exposure performed worse than the ADHD group on letter fluency and category fluency. On Trail making Test-B, the prenatal alcohol exposure group differed significantly from the control group. The ADHD group did not differ significantly from the control group on this test. The prenatal alcohol exposure and ADHD groups had similar deficits on the WCST and both performed more poorly on letter fluency than category fluency. However, letter fluency was significantly poorer in the prenatal alcohol exposure group. In this study the prenatal alcohol exposure group performed better on the WCST than predicted by IQ but the ADHD group performed more poorly than predicted by IQ. This finding for the prenatal alcohol exposure group was in conflict with previous studies in which executive function deficits remained or worsened when IQ was controlled.²

Summary

In summary, there is some evidence for distinguishing between children with FASD and children with ADHD. Using the four-factor model of attention it has been shown that children with FASD have difficulties with encoding and shift, while the children with ADHD have problems with focus and sustain. Other findings have not been consistently reproduced across studies and the usefulness of traditional behavioral observation scales for distinguishing between the two groups has not been proven. The main obstacles to comparison of study findings are the use of different inclusion criteria, definitions and outcome measures. In particular, published studies frequently include children with heavy prenatal alcohol exposure (variously defined) with or without confirmed FASD in one group.

Diagnosis of the impulsive, hyperactive, or inattentive child

The diagnosis of ADHD should only be made after a comprehensive assessment including a medical, developmental and psychosocial history, and examination. The DSM-IV criteria are the minimum requirement for a diagnosis of ADHD.³ ADHD is not an etiologic diagnosis, and assessment of the impulsive, hyperactive, or inattentive child should always

include a thorough history and examination for potential causes, including alcohol exposure in pregnancy. Although enquiry regarding alcohol exposure in pregnancy should be routine, many health professionals do not ask.^{24,25}

Behavioral rating scales can provide useful information, in a standardized format, from multiple informants, and can be used to monitor response to treatment. Many measures are available, such as the Child Behavior Checklist, the Strength and Difficulties Questionnaires, and specific ADHD scales, eg, the Conners' rating scales. The Behavior Rating Inventory of Executive Function (BRIEF) is a useful tool for evaluating behavioral, social, and emotional aspects of executive functioning in children with FASD.³⁵

Standard criteria should be used for the diagnosis of FASD.¹⁰⁻¹³ The choice of diagnostic criteria will be determined by local guidelines and clinician preference. Assessment and diagnosis of FASD usually requires input from medical and allied health professionals due to the range of physical and neurologic structural and functional issues which can occur in FASD and are required to fulfill diagnostic criteria.

Treatment of ADHD in FASD

There is a paucity of high quality evidence assessing interventions for children with both FASD and ADHD.³⁶ There are two very small, randomized, controlled trials which examine the use of stimulant medication. The first study compared methylphenidate with placebo (n = 4). Compared with placebo, methylphenidate improved hyperactivity and impulsivity symptoms but not attention.³⁷ Adverse effects from the methylphenidate were reported for three of the four children, and one child had to discontinue methylphenidate 12 weeks into the trial due to excessive weight loss. In the second study, usual stimulant medication was compared with placebo (n = 12). Compared with placebo, stimulants improved hyperactivity symptoms but not attention.³⁸ Psychopharmacologic agents have also been examined in retrospective and uncontrolled studies.^{29,39,40} In one study, stimulant medication improved hyperactivity and impulsivity scores, but inattention was less responsive to medication.⁴⁰ In a retrospective study, there was a suggestion that children with ADHD and FASD had a preferential response to dexamphetamine.²⁹ The role of atomoxetine is being assessed in two studies including one randomized controlled trial.³⁶

There is one study of behavioral or psychological intervention for children with FASD and ADHD symptoms, in which 23 children were randomized to receive attention process training or contact control sessions.³⁶ The group

receiving attention process training had significantly more improvement on measures of sustained attention and non-verbal reasoning ability than controls, but not on measures of executive function.

Because there is little evidence specific to the management of ADHD in FASD, the approach to intervention is mostly extrapolated from the ADHD literature. Multimodal therapy is the recommended treatment for ADHD in all age groups. This could include pharmacologic and behavioral interventions. The Multi-modal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder demonstrated that pharmacologic management was superior to an intensive behavioral intervention at a 14-months follow-up. Compared with pharmacologic management alone, combined pharmacologic and intensive behavioral interventions did not significantly improve core ADHD symptoms, but treatment outcomes were achieved with a significantly lower dose of medication in the combined treatment group than in the pharmacologic management group.⁴¹ The management plan should also take into consideration the comorbidities of ADHD and FASD.^{3,6}

Medication will not be needed for all individuals with ADHD and should only be used when the symptoms are pervasive across settings and are causing significant impairment in academic, social, or behavioral domains. Individuals receiving medication require regular review, at least six monthly. Medications for ADHD include stimulant (methylphenidate and dexamphetamine) and nonstimulant medications (eg, atomoxetine). Stimulant medications are thought to act by altering the availability of dopamine and noradrenaline, which influences behavior inhibition, impulse control, and attention.³ Clinicians should consider trialing dexamphetamine first, because there is some evidence suggesting that children with FASD have a preferential response to dexamphetamine over methylphenidate. Methylphenidate is available in immediate-release and extended-release formulations, but there is no evidence regarding the use of extended-release methylphenidate preparations in children with FASD. Atomoxetine is a nonstimulant medication which is classified as a noradrenaline reuptake inhibitor.³ The evidence regarding atomoxetine use in FASD is pending. There is no evidence available regarding the use of other nonstimulant medications in FASD.

Conclusion

ADHD is the most frequent comorbidity of FASD but the exact relationship between the two entities is not well defined. There is some evidence that a specific clinical subtype of

ADHD occurs in FASD, with earlier onset and a different response to medication. However, the relationship between ADHD and FASD may be coincidental, may reflect a common etiologic pathway, or may reflect the frequent genetic origin of ADHD and its prevalence in the general population. It is likely that a range of these etiologic factors account for ADHD in FASD, resulting in a heterogeneous population, which makes it difficult to replicate or generalize findings across studies.

Impairment of executive function may be a common underlying factor in ADHD and FASD but, using the four-factor model of attention, there is evidence of difference between these two groups. Children with FASD have difficulties with encoding and shift, and children with ADHD without FASD have problems with focus and sustain. If this difference is reproducible in large cohorts, then it may be useful for diagnosis in the clinical population.

There are clinical benefits to clarifying whether an individual has FASD because early diagnosis of FASD can ameliorate the secondary disabilities. There may be a differential medication response in individuals with ADHD who also have FASD, in particular a possible preferential response to dexamphetamine. However, the evidence to support treatments for ADHD in FASD is scarce.

There is a need for large, high quality studies examining the etiology, diagnosis, and interventions for ADHD in FASD because there is the potential to modify significantly the poor adult outcomes associated with the secondary disabilities. Agreement on the most appropriate diagnostic criteria and terminology for FASD and standardization of outcome measures would improve the translation of research findings into clinical practice. The development of effective interventions will be guided by improved understanding of the etiology of ADHD in FASD and the ability to diagnose FASD more accurately.

Disclosure

The authors report no conflict of interest in this work.

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