

Searching for the Fetal Alcohol Behavioral Phenotype

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Abstract

This narrative review presents the emerging published evidence on the existence of a phenotypic behavior in children with fetal alcohol spectrum behavior. Such a phenotype, exhibiting high sensitivity, specificity, and predictive values, may assist clinicians and families in identifying children who often miss some of the information needed for full diagnosis, but who may benefit from these screening tools in mobilizing help to these youngsters and their families.

Keywords

child behavioral checklist, alcohol, pregnancy, fetal alcohol spectrum disorder, behavioral phenotype

Introduction

The diagnosis of fetal alcohol spectrum disorder (FASD) is often very challenging, as it necessitates a history of maternal drinking, evidence of in utero and postnatal growth restriction, evidence of different domains of brain dysfunction, and pathognomonic facial changes (Figure 1). The presence of the typical triad of facial dysmorphism (flat upper lip, flat philtrum, and small palpebral fissures than the third percentile) can obviate the need for clear history of maternal drinking.^{1,2} However, there are numerous cases without clear evidence of maternal drinking and with no pathognomonic facial changes. These children will often not receive FASD diagnosis and will stay undiagnosed and hence not optimally managed.

Because FASD is characterized by a complex neurobehavioral deficit, a majority of FASD children exhibit disruptive behaviors, including aggression, impulsivity, rule breaking, and asocial behavior, to mention a few.³ Hence, since almost all the first diagnoses were presented in the early 1970s, efforts have commenced to define a behavioral phenotype to help in the diagnosis. The following statements have been made and are familiar to clinicians diagnosing and managing these children:

- “Children with FASD tend to lack conscience, guilt, and remorse after misbehaving.”
- “They tend to be cruel.” However, beyond the general statement of a “generalized deficit in

processing complex information,”⁴ there were no measures to quantify these impressions.

The objective of the present study was to review attempts at identifying a behavioral phenotype of FASD that may help clinicians screen children potentially afflicted by in utero alcohol exposure, with focus on predicting FASD in cases where maternal alcohol exposure cannot be substantiated, and/or when pathognomonic changes in facial morphology are not apparent.

Methods

We conducted a narrative review, focusing on studies that linked specific behavioral measures with the diagnosis of FASD. Searching PubMed, Mbase, Google Scholar, and Cochrane databases from inception to July 1, 2019, we identified articles in any language focusing on human studies that measured behavioral outcome and its correlation to in utero alcohol exposure and signs of FASD. Animal studies, reviews, letters to the editor, or meeting abstracts were not included.

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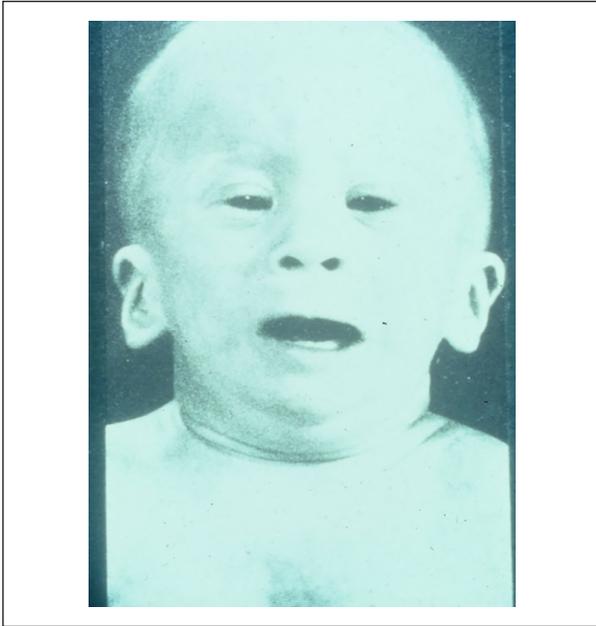


Figure 1. The typical pathognomonic triad facial dysmorphism: flat upper lip, flat philtrum, and small palpebral fissures below the third percentile.

Table 1. Behavioral Characteristics That Were Commonly Endorsed by Clinicians and Parents Managing Children With FAS or FAE.

Cannot take hints
Touching frequently
Thinking out of context
Sleep problems
Poor manners
Poor attention
Loosing things
Poor judgement
Cannot play team
Talkative
Center of attention
Loud voice
Raising unusual topics
Noise sensitive
Repeats often
Over-reacts
Chats with no content
Demands attention
Does not complete tasks
Unaware of consequences

Abbreviations: FAS, fetal alcohol syndrome; FAE, fetal alcohol effect.

Ethical Approval and Informed Consent

Ethics approval or informed consent was not needed, because this is merely a review of the published literature.

Results

Out of 124 titles suggesting linkage of measures of neurobehavior and fetal alcohol behaviors, the vast majority did not present data that could be used to predict statistically a link between child behavior and fetal alcohol exposure.

Altogether, 2 research groups focused on such links.

Streissguth, Seattle, WA

The pioneering scientist in exploring and defining a phenotypic behavior for FAS was Seattle's Ann Streissguth in her work on the Personal Behavioral Checklist. Her aim was to develop a scale that describes the essence of fetal alcohol syndrome (FAS) and fetal alcohol effects (FAEs).⁵ In 1998, her team presented a list consisting of 68 items that were endorsed by clinicians and parents managing children with FAS or FAE. The most frequently endorsed items were impulsivity (>85%) and stubbornness (>85%). Some of the other highly endorsed items are listed in Table 1.

Streissguth's study sample included 472 patients diagnosed with FAS or FAE between the ages of 2 and 51 years. The Fetal Alcohol Behavioral Scale (FABS) exhibited high item-to-scale reliability (Cronbach α of 0.91) and good test-retest reliability ($r = 0.69$). The FABS was able to correctly identify many of the children in detection studies from both prison and general populations. While the FABS predicted dependent living, as hoped by the researchers it did not correlate with IQ, sex, age, or race. While the authors outline areas of further work needed "to define the specificity and utility of this FABS," we cannot find published evidence in the ensuing 20 years, and there have not been published studies utilizing the FABS to identify FASD children based on their behavioral scores.

Rovet, Toronto, Canada: The Neurobehavioral Screening Test (NST)

In Toronto, Canada, child psychologist Joanne Rovet and her colleagues have tried to address the effort to describe an FASD phenotype by utilizing Achenbach's Child Behavior Checklist (CBCL). This validated scale has been used in the diagnosis of FASD in a large cohort of children. Hence, it has provided the researchers an opportunity to examine the predictive value of items from the CBCL.⁶

Achenbach's Child Behavior Checklist⁷

This battery of tests aims at children 6 to 18 years of age.⁷ It consists of 113 questions, scored on a 3-point

Table 2. The Child's Behavior Checklist Syndrome Scales.

Anxious or depressed
Somatic complaints
Social problems
Thought problems
Attention problems
Rule-breaking behavior
Aggressive behavior

Table 3. Original Items Differentiating Fetal Alcohol Spectrum Disorder From Controls.

Acts young for age
Argues a lot
Cannot concentrate or poor attention
Cannot sit still, restless and hyperactive
Cruelty, bullying, or meanness to others
Disobedient at home
Does not show guilt after misbehaving
Impulsive or acts without thinking
Lying or cheating
Showing off or clowning
Steals from home
Steals outside

Likert-type scale (0 = absent, 1 = occurs sometimes, 2 = occurs often).

Using the 2001 version of the revised CBCL, the scoring system identifies several syndrome scales (Table 2).

Rovet's original work compared the achievements on the CBCL in 3 groups of children: 30 children diagnosed with FASD; 30 children with attention deficit hyperactivity disorder (ADHD), but no FASD; and 30 healthy children matched for age and socioeconomic status.⁶ Originally, 12 CBCL items significantly differentiated children with confirmed FASD from controls (Table 3).

In analyzing these data, 6 items significantly separated children with FASD from those exhibiting ADHD (Table 4).

Discriminant function analysis identified predicting differences among groups. The following set of 7 items separated FASD from controls: "no guilt," "lying or cheating," "cannot concentrate," "restless," "impulsive," "disobedient," and "acts young." Scores of 6 on these items differentiated the groups with a sensitivity of 86% and specificity of 82%.⁶

FASD Versus ADHD

Because 70% of children with FASD exhibit symptoms of ADHD, it was critical to try to distinguish between

Table 4. Items That Significantly Separated Children With FASD From Those Exhibiting ADHD.

Acts young
Cruelty
No guilt
Lying and cheating
Stealing from home
Stealing outside

Abbreviations: FASD, fetal alcohol spectrum disorder; ADHD, attention-deficit hyperactivity disorder.

Table 5. Differentiating FASD From ADHD: Option 1.

No guilt, cruelty, and acts young (sensitivity = 70%; specificity = 80%)
Acts young, cruelty, no guilt, lying or cheating, steals from home, and steals outside home (sensitivity = 81%; specificity = 72%)
Child behavior suggestive of FASD (at least 6 positives):
Does the child act young for age?
Difficulty concentrating and cannot pay attention for long?
Disobedient at home?
Lies or cheats?
Lacks guilt after misbehaving?
Impulsive?
Hyperactive?

Abbreviations: FASD, fetal alcohol spectrum disorder; ADHD, attention-deficit hyperactivity disorder.

the 2 conditions. Two combinations of items significantly differentiated these groups with high sensitivity and specificity (Table 5).

Six of 7 endorsed items are positive for FASD with 86% sensitivity and 82% specificity.

For children not showing ADHD symptoms the following 3 different combinations of items appear to distinguish FASD from non-FASD (Tables 6-8).

Testing Children at 4 to 6 Years of Age

A potential challenge is the fact that the CBCL uses an age cutoff of 6 years, whereas in many cases families and clinicians may wish to apply this scoring system for children 4 to 6 years of age.

The authors compared the scores of children 4 to 6 years diagnosed with FASD to those referred but not receiving a diagnosis, as well as healthy children of the same age.⁸

Out of the 10 CBCL items used at age 6 to 13 years, 3 are not scored in children between 4 and 6 years (lies and cheats, steals at home, steals outside home). Using the 7 remaining items, children with FASD endorsed significantly more items (6.7 ± 1.3) than healthy

Table 6. With 3/4 Positives Identify FASD.

-
1. Lacks guilt after misbehaving?
 2. Lies or cheats?
 3. Disobedient at home?
 4. Act too young for age?
-

Abbreviation: FASD, fetal alcohol spectrum disorder.

Table 7. With 2/3 Positives Identify FASD.

-
1. Lack of guilt after misbehaving?
 2. Acts of cruelty, bullying, or meanness?
 3. Acts young for age?
-

Abbreviation: FASD, fetal alcohol spectrum disorder.

controls (2.3 ± 1.2), or alcohol-exposed children who were not given an FASD diagnosis (4.7 ± 1.9).

Using a cutoff of 5 out of 7 items, the NST had a 94% sensitivity and 96% specificity in identifying children aged 4 to 6 years with FASD.

Differentiating Children With FASD From Psychopathology Without Alcohol

The previous steps of development of the behavioral phenotype tool for FASD have shown that the items distinguishing children with FASD from non-FASD (eg, ADHD) are all signs of conduct disorder, which can very well be genetic-familial. There is a strong correlation between parental alcoholism and psychopathy or other forms of conduct disorder, and hence, the test results till now do not rule out psychopathy versus fetal alcohol disorder. The next task in developing the CBCL-based phenotype analysis included trying to separate maternal alcohol use from maternal psychopathology.

For that end the authors recruited 4 nonexclusive groups of children (8–15 years).⁹

1. Children exposed to alcohol in utero ($n = 25$)
2. Children not exposed to alcohol in utero ($n = 46$)
3. Children exposed to parental psychopathology ($n = 37$)
4. Children not exposed to parental psychopathology ($n = 34$)

To distinguish between the effects of alcohol and parental psychopathology, the children were further subdivided into groups with alcohol exposure in utero and parental psychopathology ($n = 23$), and psychopathology without alcohol exposure ($n = 14$).

Children exposed to alcohol scored significantly lower than unexposed children on school competency,

Table 8. With 3/6 Positives Identify FASD.

-
1. Acts young
 2. Cruelty
 3. Lack of guilt
 4. Lies or cheats?
 5. Steals outside home?
 6. Steals from home?
-

Abbreviation: FASD, fetal alcohol spectrum disorder.

special classes, repeating a grade, more disobedience, and vandalism.

Children with parental psychopathology differed from children without parental psychopathology in the anxious/depressed, social problems, and attention problems subscales. The subscale items that were significantly different between the groups were nervousness, self-consciousness, feelings of worthlessness, loneliness, and difficulty in concentration.

No significant differences were found when the groups with alcohol and parental psychopathology, and psychopathology without alcohol were compared.

Parental psychopathology was a significant predictor of a child's internalizing behaviors, as well as social problems, whereas alcohol exposure was more predictive of externalizing behaviors.

Differentiating Children With FASD From Those With Prenatal Alcohol Exposure but No FASD

A study from Edmonton, Alberta, compared the NST achievement among children 6 to 17 years of age, among 48 FASD children, 22 with prenatal alcohol exposure but no FASD diagnosis and 32 typically developing children.¹⁰ The NST yielded 62.5% sensitivity among participants with FASD and 50% among those exposed to alcohol but not diagnosed with FASD. Specificity was 100% and no normative child scored positive. The fact that alcohol-exposed, but not FASD diagnosed scored often as positive highly suggests that many of them may have FASD. Within the FASD cases, the sensitivity among adolescents (70.8%) tended to be higher than among children aged 6 to 11 years (54.2%), suggesting that with age more items become positive as FASD symptoms may be clearer.

The Effect of Maternal Depression on the NST Score

Maternal depression is not uncommon among families with FASD, and it may affect the maternal reporting of symptoms of the child. Heynes and colleagues compared

the NST scores among 134 children previously diagnosed with FASD, 112 typically developing children, and prospectively collected results of children born to and reared by mothers suffering from clinical depression ($n = 49$) and additional typically developing children. In this study, none of the children born to depressed mothers screened positive on the NST; however, substantial numbers scored positive on the hyperactivity item. The mother's level of depression as measured by her score on the Center for Epidemiologic Studies Depression Scale correlated with the child's conduct, specifically on the item of lying/cheating and disobedience at home. This study indicated that the sensitivity and specificity of the NST are not affected by maternal depression.¹¹

Clinical Application of the NST for FASD Behavioral Phenotype

Over the last 5 years, Rovet et al's NST tool has been utilized in several FASD diagnostic clinics in Israel as an adjunct tool¹² to the international criteria for diagnosing FASD.^{1,2} Its role was especially directed to cases where maternal drinking history was not directly apparent or when the pathognomonic facial dysmorphic features have not been evident. It has been included in clinical reports and presented to the court system in cases dealing with youngsters potentially afflicted by fetal alcohol exposure.

The appendix presents the guidelines for the NST, through 2 exemplary cases.

Conclusions

Because of the overwhelming range of brain insult caused by fetal exposure to alcohol, studies continue to describe different aspects of this "generalized deficit in processing complex information,"⁴ but such information has not been used to date to identify a neurobehavioral phenotype that can assist in the diagnosis of the most common cause of congenital mental morbidity.¹³ The NST system described above may help numerous afflicted children in whom some of the needed criteria for FASD diagnosis may be missing, whereby the behavioral phenotype may help them get the support they urgently need. More work is needed to further validate this tool.

Appendix

The Neurobehavioral Screening Test (NST) for FASD Behavioral Phenotype

Step 1: Identifying Behavior Suggestive of FASD. The following questions should be asked of the child's parent/guardian to determine whether the child's behavior is suggestive of FASD.

1. Does your child act too young for his/her age?
2. Does your child have difficulty concentrating, and cannot pay attention for long?
3. Is your child disobedient at home?
4. Does your child lie or cheat?
5. Does your child lack guilt after misbehaving?
6. Does your child act impulsively and without thinking?
7. Does the child have difficulty sitting still/is restless/hyperactive?

If the parent/guardian answers "yes" to at least 6 out of 7 items, this is suggestive of FASD with 86% sensitivity and 82% specificity.

If the child does not exhibit behavior consistent with ADHD (attention deficit hyperactivity disorder; ie, the answer is negative for questions 2, 6, and 7) then a score of 3 out of the 4 following questions needs to be positive:

1. Does your child lack guilt after misbehaving?
2. Does your child lie or cheat?
3. Is your child disobedient at home?
4. Does your child act too young for his/her age?

Step 2: Differentiating FASD From ADHD

- (a) The child needs to exhibit 2 of the 3 following:
 1. Does your child experience a lack of guilt after misbehaving?
 2. Does your child display acts of cruelty, bullying, or meanness to others?
 3. Does your child act young for his/her age?
- (b) OR the child needs to exhibit 3 of the following 6:
 1. Does your child experience lack of guilt after misbehaving?
 2. Does your child display acts of cruelty, bullying, or meanness to other?
 3. Does your child act young for his/her age?
 4. Does your child steal from home?
 5. Does your child steal outside of home?
 6. Does the child lie and cheat?

Examples of How to Score the NST (Adapted From Koren et al¹²):

Case 1. A 7-year-old boy with severe learning and behavioral issues. He behaves like a 4-year-old boy. His mother says he commonly does not listen to her; he was caught several times telling that he lost the money mom gave him, although he used it to buy candies; after hitting his young sibling, he never expresses remorse; he cannot concentrate on a task for more than 7 minutes; he is very impulsive and explodes easily; he is all over the place nonstop; he is often torturing his cat; he takes money from his mom's purse without her knowing; and he took a friend's toy when he visited with him.

Scoring: This child achieves maximum 7 positive scores and is screened positive for FASD.

Case 2. A 9-year-old girl who reads at Grade 1 level and cannot do any math. She prefers to play with Grade 2 kids; she often does not follow her mom's instructions; no previous cases of cheating or lying; she was not remorseful when her little brother fell after she pushed him; she cannot concentrate for more than a few minute on a task, but she is not all over the place and is not impulsive; on several occasions, she savagely hit a toddler; her mom was advised several times that she took and hid in her bag things belonging to other kids, and she does the same at home.

Scoring: In Step 1, this girl endorsed only 5 positive answers. Because she is not a typical ADHD, you continue to Step 2. Here she endorses 3 positive scores, which is a positive screen for FASD.

Author Contributions

GK conceived this project and wrote the first draft. AO critically reviewed the manuscript and added additional elements.

Declaration of Conflicting Interests

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