IDENTIFYING THE NEUROBEHAVIORAL PHENOTYPE OF FETAL ALCOHOL SPECTRUM DISORDER IN YOUNG CHILDREN

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ABSTRACT

Background
Most children with Fetal Alcohol Spectrum Disorder (FASD) do not display the typical facial changes, making the diagnosis much more challenging due to poor specificity of the brain dysfunction exhibited by these children. We have recently described and validated a behavioral phenotype of FASD using items from the Child Behavior Checklist (The Neurobehavioral Screening Test, NST). This tool has high sensitivity and specificity in separating children aged 6-13 yrs with FASD from those with ADHD and from healthy controls.

Objectives
To test the validity of the NST for children aged 4-6 years in order to help facilitate diagnosis of FASD in young children.

Methods
Children referred to Motherisk for FASD diagnosis are all tested using the Child Behavior Checklist. We compared the scores of children 4-6 yrs diagnosed with FASD to those referred but not receiving a diagnosis, as well as to normal healthy control children of the same age range.

Results
Out of the 10 items of NST used at age 6-13 years, 3 are not scored in children 4-6 years of age. Using the 7 remaining items, children with FASD endorsed significantly more items (6.7+/-1.3) than healthy controls (2.3+/-1.2), or alcohol- exposed children who were not given an FASD diagnosis (4.7+/- 1.9). Using a cut-off of 5 out of7 items, the NST had a 94% sensitivity and 96% specificity in identifying children with FASD. Nine of 19 children exposed to alcohol with whom an FASD diagnosis could not be confirmed, scored 5 or more on the NST.

Conclusions
In this pilot study, the NST has shown very high sensitivity and specificity and can be used to identify children who are very likely to be diagnosed with FASD.

Key Words: *Fetal alcohol spectrum disorder, FASD, neurobehavioral phenotype, Neurodevelopmental Screening Test, NST*

FASD is characterized by a wide range of disabilities, including reduced IQ[1,2], learning disabilities and severe behavior problems.[3,4] Attention problems are exhibited in 70% of children with FASD, three to nine times higher than in the general population.[5–8] Importantly, children with FASD exhibit oppositional defiant/conduct disorder (ODD/CD).[8–10] The greatest challenge in developing a method to identify the behavioral characteristics of FASD is the wide and non-specific range of deficits exhibited by these children. In 2006 we developed and validated a 10-item screening tool based on items from a standardized behavior problems

questionnaire, the Child Behavior Checklist (CBCL) developed by Achenbach and colleagues.[11] The full CBCL tool includes 113 items filled by caretakers or teachers who know the child. Out of these items, factor analysis revealed a combination of 10 items that accurately separated children 6-13 years of age with FASD from the two comparison groups[12], children with ADHD and typically developing children.[12] This neurobehavioral screening test (NST) has shown 86% sensitivity and 82% specificity for FASD. The NST, validated for children aged 6-13 years old, can be completed by health or social workers interviewing the primary caretaker of the child. This test has been endorsed by the Public Health Agency of Canada as a screening tool for FASD as part of the agency-sponsored FASD Screening Toolkit.[13] The NST was further validated in two different cohorts in Toronto[14] and Edmonton.[15] Studies have repeatedly shown that early diagnosis of FASD and, hence, early interventions, confer more favorable neurobehavioral outcome.[1] The present pilot study aimed at examining whether the NST can be extended to younger children, aged 4-6 years of age.

PATIENTS AND METHODS

The study sample included 17 children aged 4 to 6 years of age, diagnosed with FASD according to the Canadian Guidelines; 18 in whom FASD diagnosis could not be confirmed or was deferred; and 25 typically developing normal control (NC) children who participated as controls in neurodevelopmental follow up studies at Motherisk.

The NST

As part of our diagnostic process, all caretakers complete the CBCL. At age 4-6 years, 3 of the 10 Achenbach items used in the NST are not included due to the inability to verify these items in most young children. These included:

- Does your child lie or cheat?
- Does your child steel at home?
- Does your child steel outside home?

Hence we used in the present study the scores achieved on the remaining 7 existing items, as shown in Table 1. Differences in scores among the 3 groups were compared by ANOVA. Sensitivity and specificity of the NST in predicting FASD diagnosis were calculated.

TABLE 1 Screening checklist for FASD behavioral phenotype in children 4-6 years of age

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 can't pay attention for long?
3. Is your child disobedient at home?
4. Does your child lack guilt after misbehaving?
5. Does your child act impulsively and without thinking?
6. Does your child have difficulty sitting still/is restless/hyperactive?
7. Does your child display acts of cruelty, bullying or meanness to others?

TABLE 2 Endorsement of the 7 NST items by children 4-6yr with FASD, those tested but not diagnosed with FASD, and healthy controls.

17 Diagnosed with FASD

- Acts too young: Yes 15/17 - 88%
- Disobedient Yes: 15/17 – 88%

- Lacks guilt: 15/17 – 88%
- Can't concentrate: 17/17 – 100%
- Impulsive 16/17 – 94%
- Hyperactive 16/17 – 94%
- Cruelty to others 13/17 – 76%

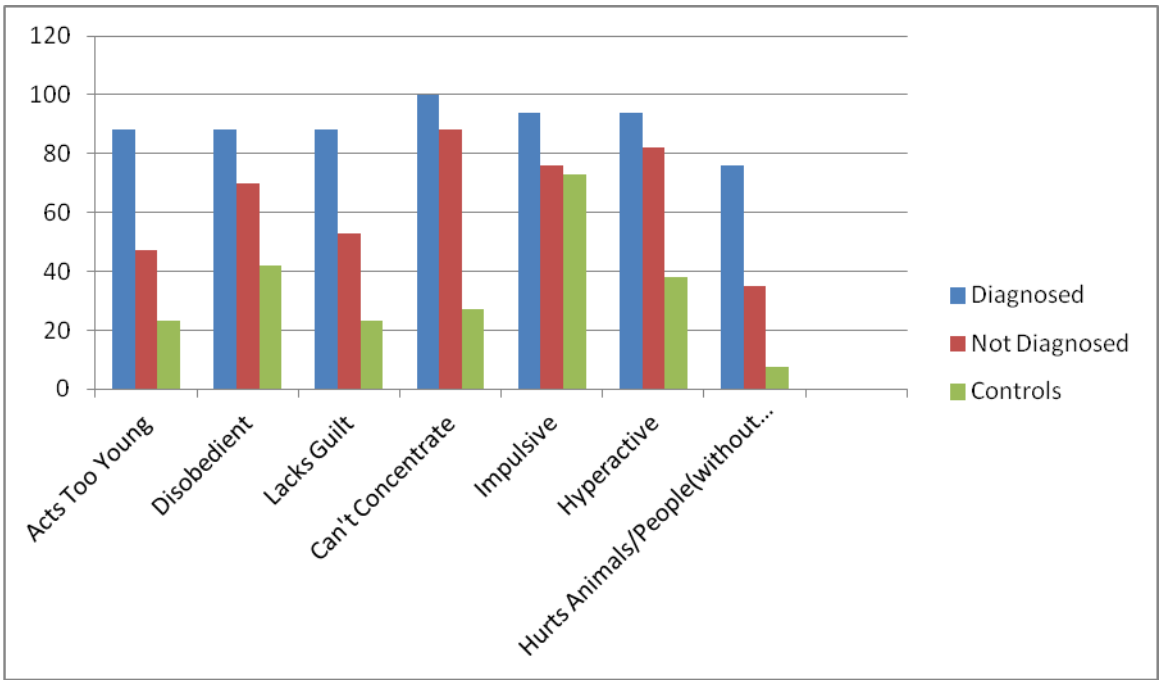
18 Not diagnosed

- Acts too young: Yes 8/17 - 47%
- Disobedient Yes: 12/17 – 70%
-
- Lacks guilt: 9/17 - 53%
- Can't concentrate: 15/17 – 88%
- Impulsive: 13 /17 – 76%
- Hyperactive 14/17 – 82%
- Cruelty to others 6/17 – 35%

Controls – 26 total

- Acts too young: 6 - 23%
- Disobedient Yes: 11 - 42%
- Lacks guilt: 6 - 23%
- Can't concentrate: 7 - 27%
- Impulsive: 19 - 73%
- Hyperactive: 10 - 38%
- Cruelty to others: 2 - 7.7%

FIG. 1 Endorsement of the 7 NST items by children 4-6 year old with FASD, those tested but not diagnosed with FASD, and healthy controls.



RESULTS

The children diagnosed with FASD included 12 cases of ARND, 4 partial FAS and one with full FAS. The endorsement of the 7 NST items by the 3 study groups is presented in Table 2 and Figure 1. Children with FASD endorsed significantly more items than the healthy controls (6.7+/-1.3 vs. 2.3+/-1.2; p=0.0001) and the alcohol exposed-non diagnosed children (6.7+/-1.3 vs. 4.7+/-1.9; p=0.002). Using a cut-off of 5 out of 7 items, the NST had 94% sensitivity and 96% specificity in identifying children with FASD. Nine of 19 children exposed to alcohol with whom an FASD diagnosis could not be confirmed scored 5 or more on the NST.

DISCUSSION

This study, using for the first time the NST on children 4-6 years of age, shows that by age 4-6 years, children affected by FASD already exhibit the strong traits captured in older children. These include deficits in moral development, lack of social judgment and failure to learn from experience. Although at young age it is more challenging to identify hyperactivity and inattention, these characteristics were also more common in young children with FASD (Figure 1). The CBCL for children 4-6yo does not include 3 items used by us for children 6-13 years of age , namely lying, and steeling at home and outside home, as Achenbach and coworkers believed that the validity of these items is questionable at young age. Evaluation of the seven remaining individual NST items has revealed that children with FASD

differed from healthy controls in behaviors reflecting immaturity, cruelty, inattention, and general disobedience. These findings suggest that the NST is highly discriminative between the FASD and healthy controls groups at age 4-6 years. Children brought to testing but who did not receive an FASD diagnosis scored significantly lower on the NST, although the predictive value was not as high. This is not surprising, as in some of them the diagnosis of FASD was deferred, meaning that the diagnostic team could not rule it out. In such cases, an NST score of 5 or more may indicate a high probability of a later diagnosis of FASD. These findings support previous and current research indicating poor social and moral development in children with FASD.[10,16-18]

It is important to stress that the NST is intended for screening purposes only, and is not at the present time a diagnostic tool. A number of challenges in this study need to be acknowledged. We could not adequately control for maternal smoking and drug use, depression and other mental illnesses common among alcohol-dependent women, as well as maternal history of abuse and neglect. Since data were collected retrospectively, certain background information was not available, and further studies are needed to fill these gaps.

In summary, extension of the NST to children as young as 4 years of age has allowed to identify a set of behavioral characteristics that distinguish children with FASD from healthy controls as well as from children with severe behavioral issues who do not receive an FASD diagnosis. After the NST 4-6 year old age is further validated on larger and more diverse samples, it may allow clinicians to use this behavioral phenotype to diagnose FASD in cases with unclear maternal drinking history and lack of the pathognomonic facial features of FASD.

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REFERENCES

1. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004;25:228-238.
2. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res 2004;28(11):1732–1745.
3. Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. Alcohol Clin Exp Res 2005;29:1359-1367.
4. Mattson SN, Riley EP. Parent Ratings of Behavior in Children with Heavy Prenatal Alcohol Exposure and IQ-Matched Controls. Alcohol Clin Exp Res 2000;24(2):226–231.
5. Niccols A. Fetal alcohol syndrome and the developing socio-emotional brain. Brain Cogn 2007;65(1):135–142.
6. O'Malley KD, Nanson J. Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. Can J Psychiatry Rev Can Psychiatr 2002;47(4):349–354.
7. Oesterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H. Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and attention deficit/hyperactivity disorder: a controlled pilot study. J Child Adolesc Psychopharmacol 1998;8(1):39-48.
8. Steinhausen HC, Willms J, Spohr HL. Long-term psychopathological and cognitive outcome of children with fetal alcohol syndrome. J Am Acad Child Adolesc Psychiatry 1993;32:990-994.
9. O'Connor MJ, Shah B, Whaley S, Cronin P, Gunderson B, Graham J. Psychiatric illness in a clinical sample of children with prenatal alcohol exposure. Am J Drug Alcohol Abuse 2002;28:743-754.
10. Famy C, Streissguth AP, Unis AS. Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. Am J Psychiatry 1998;155:552-554.
11. Achenbach T, Rescolora A. Child Behavior Checklist for 6-18 Years. 2001. Available at: http://www.aseba.org/forms/schoolagecbcl.pdf.

12. Nash K, Rovet J, Greenbaum R, Fantus E, Nulman I, Koren G. Identifying the behavioural phenotype in fetal alcohol spectrum disorder: sensitivity, specificity and screening potential. Arch Womens Ment Health 2006;9(4):181–186.
13. Goh YI, Chudley AE, Clarren SK, et al. Development of Canadian screening tools for fetal alcohol spectrum disorder. Can J Clin Pharmacol 2008;15(2):e344–e366.
14. Nash K, Koren G, Rovet J. A differential approach for examining the behavioural phenotype of fetal alcohol spectrum disorders. J Popul Ther Clin Pharmacol 2012;18(3):e440–453.
15. Rasmussen C. Screening and early assessment for FASD: Links to prevention and intervention. FASD Prevention Conference. Institute of Health Economics, Edmonton, Alberta. September 2013.
16. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 2007;119:e733-e741.
17. Greenbaum RL, Stevens SA, Nash K, Koren G, Rovet J. Social cognitive and emotion processing abilities of children with fetal alcohol spectrum disorders: a comparison with attention deficit hyperactivity disorder. Alcohol Clin Exp Res 2009;33(10):1656-1670.
18. Rasmussen C, Talwar V, Loomes C, Andrew G. Brief report: lie-telling in children with fetal alcohol spectrum disorder. J Pediatr Psychol 2008;33(2):220-225.