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Identifying the behavioural phenotype in fetal alcohol spectrum disorder: sensitivity, specificity and screening potential

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Summary

Background: In most cases of Fetal Alcohol Spectrum Disorder (FASD), the pathognomonic facial features are absent making diagnosis challenging, if not impossible, particularly when no history of maternal drinking is available. Also because FASD is often comorbid with Attention Deficit Hyperactivity Disorder (ADHD), children with FASD are frequently improperly diagnosed and receive the wrong treatment. Since access to psychological testing is typically limited or non-existent in remote areas, other diagnostic methods are needed to provide necessary interventions.

Objectives: To determine if a characteristic behavioural phenotype distinguishes children with FASD from typically developing children and children with ADHD and use this information to create a screening tool for FASD diagnosis.

Methods: Parents and caregivers completed the Child Behavior Checklist (CBCL), a well-established standardized tool for evaluating children's behavioural problems. Results from 30 children with Fetal Alcohol Syndrome or Alcohol-Related Neurodevelopmental Disability, 30 children with ADHD, and 30 typically developing healthy children matched for age and socioeconomic status with FASD were analyzed. Based on our previous work, 12 CBCL items that significantly differentiated FASD and control groups were selected for further analyses. Stepwise discriminant function analysis identified behavioural characteristics most strongly differentiating groups and Receiver Operating Characteristics (ROC) curve analyses determined sensitivity and specificity of different item combinations.

Results: Seven items reflecting hyperactivity, inattention, lying and cheating, lack of guilt, and disobedience significantly differentiated children with FASD from controls. ROC analyses showed scores of 6 or higher on these items differentiated groups with a sensitivity of 86%, specificity of 82%. For FASD and ADHD, two combinations of items significantly differentiated groups with high sensitivity and specificity (i) no guilt, cruelty, and acts young (sensitivity = 70%; specificity = 80% (ii) acts young, cruelty, no guilt, lying or cheating, steals from home, and steals outside (sensitivity = 81%; specificity = 72%). These items were used to construct a potential FASD screening tool.

Conclusions: Our findings identifying the behavioural characteristics differentiating children with FASD from typically developing children or children with ADHD have the potential for development of an empirically derived tool for FASD tool to be used in remote areas where psychological services are not readily available. This technique may speed up diagnosis and intervention for children without ready access to formal assessments.

Keywords: FASD, ADHD, ■, ■.

Introduction

The damaging effects of prenatal alcohol exposure for human development are well recognized and lead to a condition known as Fetal Alcohol Spectrum Disorder (FASD). FASD involves several conditions resulting from gestational exposure to alcohol with the two most common being Fetal Alcohol Syndrome (FAS) and Alcohol-Related Neurodevelopmental Disability (ARND; Jones & Smith, 1973; Stratton et al, 1996). These conditions give rise to a number of challenges including mild to severe behavioural disturbance and significant developmental delay making FASD the single most prevalent preventable cause of congenital neurobehavioral dysfunction in the Western world (Carmichael et al, 1998; Mattson & Riley, 1998; Sampson et al, 1997). Because a large proportion of individuals with FASD require extensive mental health services through-

out their lifetime, the costs associated with FASD are staggering. Indeed, it is estimated that in Canada $344 million are spent annually on affected youth while in the United States, researchers estimate that a single child with FAS/FAE requires 1.4 million dollars of intervention in his or her lifetime (Stade et al, 2003). Since incarceration and difficult-to-measure costs such as lost productivity and poor quality of life are excluded from these estimates, the actual price of FASD is likely much higher. It is recognized that early intervention can help alleviate some of the debilitating consequences of FASD, proper diagnosis must be made (Streissguth, 1997), which is not always easy to do.

For FAS, the diagnostic criteria include a characteristic facial dysmorphology, pre- and postnatal growth retardation, a complex and pervasive pattern of neurobehavioral anomalies, and a history of maternal drinking during pregnancy (Chudley et al, 2005; Astely, 2004). In ARND, by contrast, which affects as many as 90% of cases, the distinctive facial features and growth abnormalities are typically absent necessitating reliance on confirmed drinking history and pathognomonic neurobehavioral features (Greenbaum et al, 2002; Greenbaum, 2004). However, because many children with ARND are adopted or fostered, information about their biological mothers' drinking patterns during pregnancy is often not available. Furthermore, since proper neurobehavioral diagnosis requires a specialized team of professionals including psychometrists, psychologists, and pediatricians, diagnosis is costly, involves long wait lists, and does not adequately serve children living in remote areas where access to full diagnostic services and mental health professionals is limited. Because FAS/ARND is also comorbid with other psychiatric disorders, such as Attention Deficit Hyperactivity Disorder (ADHD), occurring in as many as 70% of FASD children, children with ARND are typically misdiagnosed and given psychostimulant medications, which may not be sufficient to ameliorate all aspects of FASD (Nanson & Hiscock, 1990; Coles et al, 1997; Greenbaum, 2004). Thus, there is an urgent need to develop better methods for identifying children with FASD, one that is both effective in discriminating children with FASD from ADHD and that can be used in remote areas.

Since its inception in 1996, the Motherisk FAS clinic has conducted comprehensive evaluations on over 200 children in order to diagnose FAS or ARND according to both Institute of Medicine criteria and our own empirically derived standards (Greenbaum et al, 2001; Astley, 2004) for ruling out non-cases from cases. During this evaluation, parents or caregivers completed the Child Behaviour Checklist (CBCL), a well-established standardized questionnaire for assessing behaviour problems in children (Achenbach, 1991). This instrument serves to identify problematic areas of behaviour (e.g., attention problems) as well as resemblance to clinical psychiatric syndromes (e.g., ADHD). Recent studies have applied advanced statistical techniques to CBCL results in order to identify the characteristic behavioural phenotypes in selective pathological conditions. However, this research was based on the measure's global scales and not the specific behaviors (Hudziak et al, 2004; Biederman et al, 2005). We have previously shown that individual CBCL items can be effectively used to distinguish children with FASD from normal controls and significant characteristics unique to FASD, thereby constituting a distinct phenotype (Greenbaum, 2000). Also, because the particular items can be studied apart from the test as a whole, they have potential to be used as a screening tool in diagnosing FAS or ARND, especially in remote areas where access to testing is limited.

Thus the purpose of the present study was to replicate our earlier findings using a newer version of the CBCL and determine the particular item combinations best discriminating FASD and ADHD groups. A supplementary goal was to use this information to develop an empirically derived FASD screening tool.

Methods

Participants

The FASD group consisted of 54 children with FAS ($n = 11$) or ARND ($n = 43$) diagnosed in the Motherisk FAS clinic between 2001 and 2004. They were drawn from a sample of 75 cases aged 6 to 16 years who had received a diagnosis of FAS or ARND after 2001 and whose parent or caregivers had completed the CBCL. All children were brought to the clinic by a (a) foster or adoptive parent regarding concerns about suspected alcohol exposure or (b) biological relative concerned whether child's current problems reflected his or her prenatal alcohol exposure (Greenbaum et al, 2002). In all cases, exposure history was confirmed by one of three criteria: (i) verbal report of the biological parent or relative, (ii) the child suffered alcohol withdrawal at birth, or (iii) the child was placed in care because of maternal alcohol abuse. All children were evaluated by both a physician who measured their height and used a validated system for evaluating facial dysmorphology and by a team of psychologists and psychometrists who administered a battery of neuropsychological tests to each child. All parents or guardians provided signed informed consent allowing us to use clinical information for research purposes.

Controls were typically developing 6 to16 year old children recruited from local schools in the Toronto area, postings within

the hospital and who had participated in previous studies (Greenbaum, 2004; Hepworth, 2004). Controls were screened for learning disabilities, for ADHD and maternal history of alcohol consumption in pregnancy using parent-completed questionnaires.

Children with ADHD were recruited from the practices of local behavioral pediatricians or psychiatrists and by advertising at a local ADHD parent support group. To be included, all children had to have received a DSM-IV diagnosis of ADHD. Any child with a report of maternal drinking during pregnancy was excluded.

From the 54 potential cases, 30 (5 FAS & 25 FAE) were suitable for age matching with children with ADHD. This research was approved by the Research Ethics Board at The Hospital for Sick Children.

Test and analytic methods

The Child Behaviour Checklist (CBCL; Achenbach, 1991) is a parent/caregiver questionnaire, which assesses social competencies and behaviour problems in children aged 6 to 18 years. The CBCL is comprised of both a series of open-ended questions and a rating scale of 113 behavioural descriptors scored on a 3-point scale from 0 = not true, 1 = sometimes true, and 2 = often true. Computer scoring of the CBCL yields a Total Behavior Problems score, two broad-band scores assessing Internalizing and Externalizing behavior problems, and eight narrow-band scales assessing Withdrawn/Depressed, Somatic Complaints, Anxious/Depressed, Social, Thought, Attention, Rule-Breaking Behaviour, and Aggressive problems.

Our previous work comparing 35 children with ARND and 35 controls (Greenbaum, 2000) matched for age, gender and SES on all 113 CBCL items showed significant differences on 62 items with 12 differing beyond the $p < 0.001$ level. These 12 items were: 'acts too young for age', 'argues', 'can't concentrate/poor attention', 'can't sit still/restless/hyperactive', 'cruelty, bullying or meanness to others', 'disobedient at home', 'no guilt after misbehaving', 'impulsive/acts without thinking', 'lying or cheating', 'showing off/clowning', 'steals from home', and 'steals outside'. In the present study, we selected these 12 items for comparing the three groups of children. Items were currently scored 1 or 0 depending on whether they were endorsed (with a 1- or 2-point score) or not respectively.

Statistics and data analyses

Item frequencies were compared among groups using chi-square analyses. Discriminant function analyses (DFA) conducted separately between the FAS/ARND group and controls and between FAS/ARND and ADHD groups served to identify items most strongly differentiating the groups. Finally, Receiver Operating Characteristic (ROC) curve analyses were performed on different combinations of frequently endorsed items to determine sensitivity, specificity, and cut-off scores. Area-under-the-curve (AUC) values were used to classify cases as being FAS/ARND or not based on the number of endorsed items and critical cutoff values.

Results

Table 1 shows the endorsement rates for each group on all 12 items. Children with FAS/ARND had significantly higher endorsement rates than controls on every item with all but two differing at the $p < 0.001$ level. Children with FAS/ARND had higher endorsement rates than ADHD on 6 of the 12 items, particularly "acts young", "cruelty", "no guilt", "lying or cheating", "stealing from home", and "stealing from outside". Children with ADHD had higher endorsement rates than controls on all items except "cruelty". Although not significant, ADHD were slightly more restless than FASD.

Discriminant function analysis was used to identify the items and their order of predicting differences between groups. A comparison between children with FAS/ARND and controls revealed the following set of 7 items

Table 1. Endorsement rates for FASD, ADHD, and control groups on the 12 discriminating CBCL items

Item number	Item description	Percent endorsements			p-value		
		FASD	ADHD	Control	FASD vs Control	FASD vs ADHD	ADHD vs Control
1	Acts young for age	90	60	23	0.001	0.02	0.01
3	Argues a lot	93	87	57	0.01	ns	0.05
8	Can't concentrate or poor attention	97	97	11	0.001	ns	0.001
10	Can't sit still, restless, hyperactive	93	97	31	0.001	ns	0.001
16	Cruelty, bullying or meanness to others	48	3	3	0.001	0.001	ns
22	Disobedient at home	93	80	27	0.001	ns	0.001
26	Doesn't show guilt after misbehaving	97	50	17	0.001	0.001	0.01
41	Impulsive or acts without thinking	97	87	35	0.001	ns	0.001
43	Lying or cheating	90	67	18	0.001	0.05	0.001
74	Showing off or clowning	70	70	30	0.01	ns	0.01
81	Steals from home	59	30	0	0.001	0.05	0.01
82	Steals outside	45	17	0	0.001	0.05	0.05

Table 2. Canonical correlation coefficients for items shown to discriminate FASD and control groups on the discriminant function analysis

Order	Item	Canonical correlation coefficient
1	no guilt	0.694
2	lying or cheating	0.546
3	can't concentrate	0.521
4	restless, hyperactive	0.506
5	impulsive	0.479
6	disobedient	0.463
7	acts young	0.454

Table 3. Canonical correlation coefficients for items shown to discriminate FASD and ADHD groups on the discriminant function analysis

Order	Item	Canonical correlation coefficient
1	no guilt	0.580
2	cruelty	0.569
3	acts young	0.413
4	steals from home	0.322
5	steals outside	0.303
6	lying or cheating	0.272

most strongly differentiated these groups (χ^2 (7) = 72.2, $p < 0.001$): "no guilt", "lying or cheating", "can't concentrate", "restless", "impulsive", "disobedient", "acts young". Table 2 shows the canonical correlations for these 7 items. A similar comparison between FAS/ARND and ADHD groups revealed a different combination of discriminating items (χ^2 (6) = 38.4, $p < 0.001$): "no guilt", "cruelty", "acts young", "steals from home", "steals outside", and "lying or cheating".

Next, we submitted different combinations of the most discriminating items to ROC curve analyses. Comparison between FAE/ARND children and controls revealed the largest AUC was achieved with the full set of 7 items as shown in Table 2 (AUC = 0.965, $p < 0.001$). With a cutoff of 6 (i.e., selecting 6 of the 7 items for a child), a sensitivity of 86% and specificity of 82% could be achieved. The next strongest combination of items were the following five, which produced an AUC of 0.901 ($p < 0.001$) with a cutoff of 3 yielding maximum sensitivity and specificity of 70% and 80% respectively: "no guilt", "lying/cheating", "disobedient at home", and "acts young".

Similarly ROC curve analyses comparing FAS/ARND and ADHD groups yielded an AUC of 0.863 ($p < 0.001$) with the full set of 6 items differentiating these groups (see Table 3). A cutoff of 3 items yielded sensitivity of 81% and specificity of 72% (see Fig. 2). Surprisingly, the next largest combination of items consisting of "no guilt", "cruelty", and "acts young" yielded almost as large an AUC as with 6 items (0.849, $p < 0.001$) with endorsements of 2 items yielding a sensitivity of 70% and specificity of 80%.

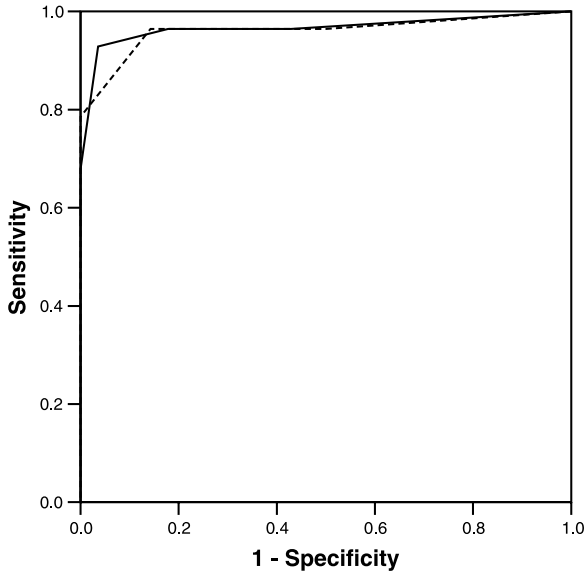

Fig. 1. ROC curves showing items most significantly discriminating children with FASD from Controls. —— All 7. ----- No guilt, lying, cheating, disobedient at home, acts young

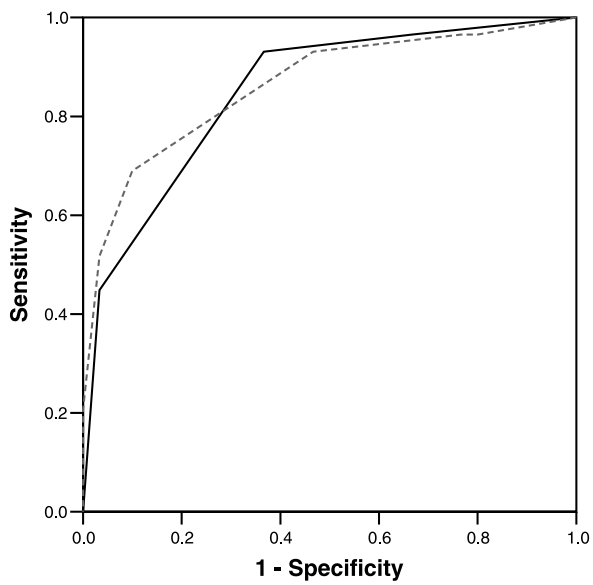

Fig. 2. ROC curves showing items most significantly discriminating children with FASD from ADHD. —— All 6. ----- No guilt, cruelty, acts young

Discussion

Present findings based on analysis of the 12 CBCL items we previously found to most highly discriminate children with ARND from controls showed that these behaviours continue to differentiate strongly children with FASD and typically developing children as well as children with ADHD. These findings are of paramount

importance because the particular items can lay the groundwork for developing a screening tool, which can accurately and consistently distinguish FAS/ARND from ADHD and lead to earlier interventions for children with FASD, particularly those who live in remote areas where access to diagnostic services are not often available. We found that while children with FASD exhibited attention deficits and hyperactivity, as do children with ADHD, the FASD group unlike ADHD additionally consistently displayed a lack of guilt after misbehaving, cruelty, and a tendency to act young for their age. Furthermore, children with FASD were also more likely to lie and steal than children with ADHD.

The prevalence of FASD estimated to be about 0.91 percent in the general population is as high as 10 to 20 percent in some First Nations communities (Sampson et al, 1997; Sokol et al, 2003). Since many of these communities are isolated, these children with FASD may not have access to a psychologist. This is especially problematic because the majority of children with prenatal alcohol exposure does not present with the characteristic facial features and therefore need extensive testing with specialized professionals to determine whether they meet formal diagnostic criteria for ARND and so are eligible for special services. Moreover, even if diagnostic clinics are available, wait lists are typically lengthy and distances to attend such clinics are often very long. Therefore, there is an urgent need to develop an FASD screening tool that can expedite a diagnosis. The findings from the present study offer an empirical approach for developing such a tool, which can be used by teachers, social workers, guidance counselors and other frontline professionals to diagnose and treat children at highest risk.

We presently propose the following FASD screening tool to be completed by parents or caregivers and used in such circumstances. This involves a 2-step approach with the first step identifying behaviors suggestive of FASD and the second step discriminating children with FASD from ADHD. This is based on parents'/caregivers' responses to the 10 questions shown in Table 4. If the parent/caregiver answers ''yes'' to at least 6 of items 1 to 7, this is suggestive of FASD with 86% sensitivity and 82% specificity. However, if the child does not exhibit behaviour consistent with ADHD (i.e., the answer is negative for items 2, 6, and 7 or inattention, impulsivity, hyperactivity), then the child must receive a score of 3 or more on items 1, 3, 4, and 5 (acts young, disobedient, lie or cheat, lacks guilt). To rule out ADHD alone when items 2, 6, or 7 are affirmed, the child needs to receive a score of 2 or more for items 1, 5, 8, (acts young, lacks guilt, cruelty) or 3 or more for items 1, 4, 5, 8, 9, 10 (acts young, lies or cheats, lacks guilt, misbehaves, cruelty, steals at home, steals outside).

Table 4. Proposed FASD screening tool

Questionnaire

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 lie or cheat?
5. Does your child lack guilt after misbehaving?
6. Does your child act impulsively and without thinking?
7. Does your child have difficulty sitting still/is restless/hyperactive?
8. Does your child display acts of cruelty, bullying or meanness to others?
9. Does your child steal from home?
10. Does your child steal outside of home?

Step 1: Identifying behaviour suggestive of FASD

Answering 'yes' to at least 6 of items 1–7 is suggestive of FASD with 86% sensitivity and 82% specificity.

If child does not exhibit behavior consistent with ADHD (i.e., parent/caregiver answers 'no' to items 2, 6, 7), child must receive a score of 3 for items 1, 3, 4, and 5.

Step 2: Differentiating FASD from ADHD

Child needs to receive a score of 2 for items 1, 5, 8 or a score of 3 for items 1, 5, 8, 9, 10.

To the best of our knowledge, this is the first study to identify the specific features that characterize the behavioural phenotype in FAS/ARND. In 1998, Streissguth and colleagues used parent questionnaires to develop a tool that was able, with high sensitivity, to distinguish children with FASD from healthy controls (Streissguth et al, 1998). However, these researchers did not address the issue of specificity by distinguishing between their patients and those with other psychopathology, most notably ADHD. Thus our findings and the proposed novel tool for screening FASD are applicable in identifying children at highest risk.

Nevertheless, this study is not without limitations. First, our sample sizes were small and our approach needs validating in larger groups. Second, our sample was not young. This is a critical issue when according to Streissguth and colleagues. A major predictor of fewer secondary disabilities is the receipt of services before age 6, because early intervention acts as a buffering factor (Streissguth et al, 2004). Thus, our approach must also be replicated on samples of young children with FASD. A third factor concerns that we lacked information on reported dose and timing of prenatal alcohol exposure since most cases were not living with a biological parent. Similarly, because this information was not available, our original diagnosis was based soley on how well the child's neuropsychological results fit our diagnostic criteria, which were developed through findings in

the literature, experience, and empirical testing. Thus, the present approach needs to be validated in other diagnostic clinics that use different approaches for diagnosing ARND or on samples followed from pregnancy into later childhood on whom extensive prenatal exposure data were collected. Fourth, because we did not have information regarding psychopathology in both biological parents, we still do not know whether children's behavioural characteristics reflect a genetic predisposition or are due to prenatal alcohol exposure. Fifth, while we were successful in differentiating FASD from ADHD, we do not know whether the features we identified are unique to FASD or might also be seen in other pathologic conditions such as conduct disorder and oppositional defiant disorder. Finally, because our sample represents clinic-referred children, who are at the most severe end of the behavioural spectrum, it is important that our approach also be tried in centers that deal with less severe cases in order to distinguish those items that reflect exposure generally from those that reflect only severe FASD. Further studies stratifying children by FASD severity may help in identifying those who need services immediately from those who should be evaluated further where there is doubt if FASD services are really needed. An approach that allows for triaging patients may help reduce wait-times for assessment as well as costs in assessing every child versus only those where there is doubt.

Regardless, we are convinced that the present findings will have important implications for providing appropriate interventions early to children with limited access to broad comprehensive diagnostic services and highlighting the importance of developing alternate screening assessment strategies for this population. By facilitating earlier diagnosis and treatment of the most severe cases, this proposed screening tool should alleviate some of the burden and high cost of FASD on society. Since replication of our approach with very young children is likely to improve the behavioural disturbances and social cognition deficits that are most amendable to early intervention and reduce the risk of later disturbance, it is important that our approach be tried in younger populations of affected children.

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