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Cognitive Functioning in Children Prenatally Exposed to Alcohol and Psychotropic Drugs

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Abstract

Cognitive functioning was compared in 29 children diagnosed with fetal alcohol syndrome (FAS), 35 children with fetal alcohol effects (FAE), and 66 psychotropic drugs-exposed (PDE) children using Wechsler tests and the neuropsychological test battery NEPSY. In the FAS group, verbal IQ (VIQ = 78), performance IQ (PIQ = 77), and full scale IQ (FSIQ = 75) were significantly lower as compared to the FAE and PDE groups. In the PDE group VIQ and FSIQ were significantly higher than in the FAE group. In the FAS group, processing speed (PS) was significantly lower than the other three factors. In the FAE group, perceptual organization (PO) was significantly higher, whereas PS was significantly lower than the other factors. In the PDE group, verbal comprehension (VC) was significantly higher than the other factors. Attention subscales on the NEPSY were significantly lower in all the three groups. Prenatal alcohol exposure affects IQ levels more than exposure to psychotropic drugs. Attentional problems were found in all children when tested with the NEPSY in all groups.

Introduction

In the present study we investigated different aspects of cognitive functioning in children diagnosed with fetal alcohol spectrum disorders (FASD), either fetal alcohol syndrome (FAS) or fetal alcohol effects (FAE), and psychotropic drugs-exposed (PDE) children.

It is well established that alcohol exposure in utero causes a reduced development of general cognitive level, resulting in different levels of mental retardation. For the entire FAS group, an average IQ of 65 has been reported [15]. According to Abel and Sokol [1] alcohol exposure in utero is ranked as the leading known cause of mental retardation.

A wide variety of FAS-related anomalies have been reported in the literature [2, 7, 13, 14, 24, 31]. A specific pattern of birth defects has been described in several studies [7]. Characteristic craniofacial malformations, like microcephaly, a poorly developed philtrum, a thin upper lip, and pre- and/or postnatal growth deficiency have been reported as clinical characteristics of FAS [31]. Although mental retardation is reported in many studies, the picture is more complicated. As summarized by Korkman, Kettunen, and Autti-Ramo [20], some studies have demonstrated that a general lowering of IQ scores does not fully explain all of the neurocognitive deficits observed. Subtle deficits like processing, attentional and organizational problems may also be present [32]. Consequently, other cognitive functions also need to be studied. In addition to children with a fully developed FAS, alcohol exposed children may also demonstrate some of the characteristics of this particular syndrome, described as FAE [6]. Neurocognitive impairment has been reported in the FAE children, including reduced general intelligence level, and more specific learning disabilities [20].

In addition to alcohol exposure in utero, substance abuse amongst pregnant women is a considerable risk factor for the developing fetus. In the 2002-2003 National Survey on Drug Abuse and Health in the U.S.A., 4.3% of pregnant women aged 15-44 reported having used illicit drugs during pregnancy [28]. One could assume these figures are relevant at least in the Western world. Different terms are used for the classification of this type of drug abuse. Terms like street drug exposure (SDE) [11] and psychotropic drugs exposure [35] have been used. The term psychotropic drugs includes substances like opioids, amphetamine...
mine, cocaine, cannabis, diazepam and selective serotonin reuptake inhibitors (SSRI).

To the best of our knowledge, most studies of psychotropic drugs exposure have focused on in utero cocaine exposure. In a review by Nordstrom-Klee [25], a substantial relationship between cocaine exposure in utero, and low birth weight was established. A relationship between intrauterine exposure to drugs like heroin, methadone, amphetamine, and combinations of different drugs, and low birth weight has been reported in various studies [10,25,28,30,36]. The neonatal abstinence syndrome (NAS) has been known for many years. Scoring systems for monitoring passively addicted infants have been developed for the assessment and treatment of the neonate born to the addicted mother [12]. For most of these drugs, long term effects of intrauterine exposure are sparsely described.

Possible effects of cocaine exposure on cognitive functions have been described by Accornero and collaborators [3]. In their studies, test results of cocaine exposed children have been compared to non-exposed control subjects. When comparing results obtained on continuous performance tests [9], findings supporting cocaine-associated deficits in attention processing are reported [3]. Attentional problems are also reported in other studies using different approaches to study attention [27], and behaviour problems [5] in cocaine exposed children are also reported in other studies. Interestingly, cocaine exposure has been found to have no direct effect on the child’s general cognitive level (full-scale IQ) but on the child’s behavioural characteristics [8,29]. In our study, however, none of the children have been exposed to cocaine, as this drug was scarcely available and therefore expensive in Norway.

There are different approaches to the study of attention. One approach uses specialized tests, or a restricted battery of tests. When using specialized tests, more specific conclusions concerning the type of attentional problems can be drawn. In a study by Accornero and collaborators, the continuous performance Test (CPT) was used for the study of attentional problems in cocaine exposed children [3]. As discussed by the authors, the CPT is just one measure of attention. Test results should be considered in the context of other clinical data. When reporting results from the study of prenatally exposed children, it is common to report results obtained from a restricted range of tests. When the results demonstrate impairments on these tests they may create the impression that they represent specific weaknesses characteristic for this diagnostic group. While this may be true, only a comprehensive assessment can demonstrate whether such impairments are specific weaknesses or whether they are part of more generalized impairments [20].

Another approach to the study of attention is to compare different subtests included in a test battery, or in intelligence tests like the WISC-R or the WISC-III. In our study, for all the children tested with the WISC-III the four underlying factors were analyzed [16]. These factors are verbal comprehension (VC), perceptual organization (PO), freedom from distractibility (FFD), and processing speed (PS). When analyzing the four factors, more specific functions are taken into account, as compared to more global scores like verbal IQ (VlQ), performance IQ (PILQ), and full scale IQ (FSIQ). Attention can also be studied when analyzing the results of neuropsychological tests used in our study. When using a test battery like the NEPSY [19,21], the subtests are organized into five domains: attention and executive functions, language, sensorimotor functions, visuospatial functions, and memory and learning [20]. When using this approach, the results of these tests are compared to the level of the other test results for the same subjects. When choosing amongst these approaches to the study of attention we decided to use the broader approach, deriving data on attentional functions from a wide battery of tests.

The main aim of this study is to test whether the neuropsychological profiles were different between the three groups, with an emphasis on differences between attention and other measures. Both the Wechsler tests and the NEPSY will be used, to base the conclusions on a comprehensive set of tests. We hypothesized that alcohol and drug exposure affect IQ levels and neuropsychological profiles differently.

Materials and Methods

Subjects

In 1997 the Pediatric Department, Haukeland University Hospital, started a project for identifying children with a confirmed exposure to alcohol and/or psychotropic drugs during pregnancy. The aim of the project was to identify neuroimpairments in these children to provide an as adequate follow-up as possible at school and in other areas of the children’s lives. The project, therefore, was initiated for remedial rather than for research purposes. The Pediatric Department contacted primary community health units for children, social welfare authorities for children, and child psychiatric units in the county of Hordaland. The units were encouraged to refer suspected cases. Only cases with confirmed exposure to drugs and/or alcohol were included in the study. There was no documented overlap in use of drugs and alcohol in the groups. Information was obtained from the social authorities, the obstetric records, and in a few cases from the biological mother. For the children adopted from abroad, this information was provided by social and health authorities in the country where the child was born. A total of 130 consecutively admitted patients, age 4-14 years, met the criteria for neuroimpairment, after evaluation by a child neuropsychologist and a child neuropsychologist in the period 1997–2007. Of the 64 children prenatally exposed to alcohol, 29 (F = 12, M = 17, mean age = 7.62 years) met the criteria for FAS, whereas 35 (F = 13, M = 22, mean age = 9.07 years) met the criteria for FAE. Thirty-six children (M = 44, F = 22, mean age = 7.8 years) had prenatally been exposed to substances like opioids, amphetamine, cannabis, diazepam and SSR, and met the criteria for PDE. For a more detailed description of the subjects, see Table 1.

Procedures

Tests

Psychometric intelligence was assessed in the subjects below the age of 7.3 years (≤87 months, N = 63, F = 21, M = 42), with the Wechsler Preschool and Primary Scale of Intelligence – Revised [33] and with the Wechsler Intelligence Scale for Children (WISC-R) [17] for children above the age of 7.3 years (≥88 months; N = 9, F = 5, M = 4), or the WISC-III [N = 58, F = 21, M = 37 (one of these was actually only 85 months old)]. The Norwegian versions of the tests were used, and complete versions of the tests were used for all children.

Two Norwegian versions of the neuropsychological test battery NEPSY were used. They are both organized into the same five domains: attention and executive functions, language, sensorimotor functions, visuospatial functions, and memory and learning. The NEPSY has been standardized on a single sample of...
children and was designed for the clinical neuropsychologist [21]. For children between 4 and 7 years of age, the NEPSY 1990 [19] version was used, whereas the 1998 version [21] was used for children between the ages 8 through 14 years. For the 1990 version, a standard sample of 37 out of 46 subtests was used. For the 1998 version, 13 out of 27 subtests were used. The reason for the selection of subtests was two-fold. In the Norwegian version of NEPSY, some of the verbal subtests are not translated. The testing took place in a clinical setting, and there was no limitation in time available for testing. However, the children were prone to loss of concentration and attention, and some selection had to be done. As Korkman and collaborators have stated [20] tests can be selected from different domains. The NEPSY can be used for general diagnostics, selective or full assessments, ranging from a basic overview of a child’s neurological status to a full comprehensive neuropsychological evaluation. As Norwegian norms are not available, Swedish norms were used for both versions of the NEPSY. In both versions sum scores for the following domains are computed: Attention (6 items for NEPSY 1990, and 4 for NEPSY 1998), language (9 items for NEPSY 1990 and 2 for NEPSY 1998), sensory motor (9 items for NEPSY 1990 and 1 for NEPSY 1998), visuospatial (7 items for NEPSY 1990 and 2 for NEPSY 1998), and memory (6 items for NEPSY 1990 and 4 for NEPSY 1998). Subscale scores were computed as means of item scores when at least half the items within each scale were valid, with higher scores indicating better functioning.

Statistics
To judge whether the use of scale scores for NEPSY was appropriate, Chronbach’s alpha for the five scales were computed, separately for the NEPSY 1990 and 1998 (except for sensory motor for NEPSY 1998, one item). FSIQ, VIQ, and PIQ were compared between the three groups of children by ANOVA with Scheffé post hoc tests. For the four indexes (VC, PO, FFD, and PS) based on the WISC-III, we first compared each index with the means of the others, by separate paired sample t-tests within each group of children. In addition we compared the ability profiles by a linear mixed effects model [26]. Mixed effects models are appropriate for data structures with multiple measurements for each individual, taking correlations between measurements within individuals into account by including random variations between individuals. In the present case, the four Wechsler indexes were measured for each child, and the hypothesis of different profiles in the three groups of children was represented as an interaction between index (VC, PO, FFD, and PS) and group (FAS, FAE and PDE). A similar model was used for the 5 NEPSY scale scores, separately for the 1990 and the 1998 versions. In the mixed effects models, Benjamini-Hochberg correction for multiple testing was used for contrasts involving FFD scores in the Wechsler tests, and attention in the NEPSY tests.

Ethical considerations
As the data were initially collected in consecutively admitted patients for treatment or remedial purposes, informed consent for using the data for research purposes had not been obtained from the children’s caretakers. When realizing the value of the collected data for research purposes, we found it too complicated to ask for informed consent. The majority of the children were in foster homes (see Fig. 1), some of them had moved several times, and the process of identifying the persons with custody would have been very difficult. Consequently, we decided for complete anonymization of the data, according to

Table 1 Description of the fetal alcohol syndrome (FAS), fetal alcohol effects (FAE), and psychotropic drugs-exposed (PDE) children.

<table>
<thead>
<tr>
<th>Domain</th>
<th>FAS (n=29)</th>
<th>FAE (n=35)</th>
<th>PDE (n=66)</th>
<th>Total (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>verified NAS</td>
<td>1</td>
<td>6</td>
<td>25</td>
<td>32 (24.6%)</td>
</tr>
<tr>
<td>suspected RAD</td>
<td>7</td>
<td>17</td>
<td>31</td>
<td>55 (42.3%)</td>
</tr>
<tr>
<td>central stimulants</td>
<td>25</td>
<td>31</td>
<td>47</td>
<td>103 (79.2%)</td>
</tr>
<tr>
<td>foster home</td>
<td>22</td>
<td>28</td>
<td>59</td>
<td>109 (83.8%)</td>
</tr>
<tr>
<td>adopted</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>14 (10.8%)</td>
</tr>
<tr>
<td>(from abroad)</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>7 (5.4%)</td>
</tr>
</tbody>
</table>

NAS: (neonatal abstinence syndrome) is a constellation of behavioural and physiological signs and symptoms due to maternal use of substances that result in withdrawal symptoms in the newborn child. The children in our study all had verified NAS and were hospitalized and treated medically for 4–8 weeks [11].

RAD: (reactive attachment disorder [23]) is a complex psychiatric disturbance characterized by serious problems in attachment to others, due to multiple or traumatic losses or changes in their primary caregiver. 55 of the children in our study were characterized by serious problems in attachment to others, due to multiple or traumatic losses or changes in their primary caregiver. 55 of the children in our study were suspected of RAD, based on information from foster parents, primary community health units for children, social welfare authorities for children, and child psychiatric units. The children affected had all moved to different caregivers and environments 4–7 times during the first 5 years of their lives.

Central stimulants: 109 of the children in our study, from 6–14 years, were successfully administered central stimulants due to suspected hyperkinetic disorder.

Fig. 1 WISC-III factors verbal comprehension (VC), perceptual organization (PO), freedom from distractibility (FFD), and processing speed (PS) for the fetal alcohol syndrome (FAS), fetal alcohol effects (FAE), and psychotropic drugs-exposed (PDE) children. Normative mean = 100, SD = 15.
Results

There were significant differences between the three groups on VIQ, PIQ (p < 0.001). In the FAS group the IQ levels were as follows: VIQ = 78, PIQ = 77, and FSIQ = 75. The IQ levels in the FAE group were as follows: VIQ = 91, PIQ = 94, and FSIQ = 91. In the PDE group VIQ and FSIQ were significantly higher than in the FAE group (p < 0.01) whereas PIQ was not significantly higher. For more details, see Table 2.

Mean scores for the four Wechsler indexes are shown in Table 3.

Table 2 Full scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ) for the fetal alcohol syndrome (FAS), fetal alcohol effects (FAE), and psychotropic drugs-exposed (PDE) children. Comparison between the groups by ANOVA and Scheffé post hoc tests.

<table>
<thead>
<tr>
<th></th>
<th>FAS (n=7, mean (SD))</th>
<th>FAE (n=19, mean (SD))</th>
<th>PDE (n=29, mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>75 (16)</td>
<td>91 (19)</td>
<td>103 (16)</td>
</tr>
<tr>
<td>VIQ</td>
<td>78 (16)</td>
<td>91 (18)</td>
<td>103 (15)</td>
</tr>
<tr>
<td>PIQ</td>
<td>77 (16)</td>
<td>94 (19)</td>
<td>101 (16)</td>
</tr>
</tbody>
</table>

* Mean (SD)

Table 3 WISC-III indexes in the fetal alcohol syndrome (FAS), fetal alcohol effects (FAE), and psychotropic drugs-exposed (PDE) children.

<table>
<thead>
<tr>
<th></th>
<th>FAS (n=7)</th>
<th>FAE (n=19)</th>
<th>SDE (n=29)</th>
<th>Total (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>72 (13.7)</td>
<td>85 (16.9)</td>
<td>97 (12.9)</td>
<td>90 (16.7)</td>
</tr>
<tr>
<td>PO</td>
<td>71 (17.6)</td>
<td>93 (23.0)</td>
<td>94 (17.2)</td>
<td>91 (20.6)</td>
</tr>
<tr>
<td>FFD</td>
<td>67 (13.9)</td>
<td>81 (20.6)</td>
<td>89 (13.2)</td>
<td>84 (17.5)</td>
</tr>
<tr>
<td>PS</td>
<td>62 (12.1)</td>
<td>74 (13.9)</td>
<td>90 (16.0)</td>
<td>81 (18.1)</td>
</tr>
</tbody>
</table>

Discussion

One of the more striking findings is the difference in IQ levels between the groups. As reported in previous studies, alcohol exposure results in a significant reduction in IQ. This finding is replicated in our study. Although not as dramatic as the reduction in the FAS group, a significant reduction is also demonstrated in the FAE group, as compared to the PDE group. The difference between these two groups is significant for VIQ and PIQ.
Central stimulants (see other studies [18]. In our study, 79.2% of all children were on stimulants as an indicator of ADHD, the prevalence of ADHD in the three groups studied is at the same level as found in other studies.

Interestingly, language was also lowered in the FAS group as compared to the FAE and PDE groups when measured with the NEPSY 1990. In several studies an association of attentional problems and language problems has been reported. Language problems are a frequent comorbid condition with ADHD. Different approaches have been used for the study of language problems, such as children's narratives [22], speed of language comprehension [34], and different language problems like speech sound disorders [23] have been in focus. Cognitive functioning when measured with the NEPSY 1990 demonstrated attentional problems in all groups. In addition, language problems, a condition often associated with attentional problems was also found in the FAS group.

For the older children tested with the NEPSY 1998, slightly different patterns emerged, as compared to the younger children. The NEPSY profiles were not significantly different in the three groups. In the FAE and the PDE group, attention was significantly lower than the other scales on the NEPSY 1998. Again, attention seems to be vulnerable for alcohol or PDE in utero.

As mentioned previously, different approaches can be used in the study of cognitive assets and deficits. When using a comprehensive test battery, as in our study, the relative impact of alcohol or drug exposure on different cognitive functions can be studied. Widespread impairment has also been reported in earlier studies on FAS/FAE that have employed relatively comprehensive assessments [20].

When discussing the relevance of our findings, some of the methodological strengths including prospective enrolment of all diagnosed FAS, FAE and PDE children in the Hordaland County have to be taken into account. The enrolment procedure reduces the likelihood of a biased sample of exposed children, at least among children with verified diagnoses. This is in contrast to studies where only some of the children participate.

There are also some limitations of our study that need to be mentioned. As the data were anonymized, we are unable to collect supplementary data from biological parents. Consequently, genetic predispositions cannot be controlled for. To some degree, a limitation of our study is that the influence of non-optimal social background has not been controlled for. However, the impact of this factor is significantly reduced, as almost all children were adopted or in foster homes. Another limitation is the lack of a control group consisting of individually matched subjects.

Although quite large groups of exposed children are included in the study, the age range is quite wide. A more homogeneous age range would have made it possible to present the same tests to all participants. In future studies, a multicenter approach is recommended, making it possible to establish larger, more homogeneous groups, including matched control subjects.
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