CASE REPORT

DIFFERENTIAL CEREBRAL AND NEUROPSYCHOLOGICAL CONSEQUENCES IN DIZYGOTIC TWINS WITH PRENATAL ALCOHOL EXPOSURE

A. NARBERHAUS, D. SEGARRA, M. GIMÉNEZ, X. CALDÚ, C. JUNQUÉ, N. BARGALLO and F. BOTET

1 Department of Psychiatry and Clinical Psychobiology, University of Barcelona, 2 Neuroradiology Section, Radiology Department, Centre de Diagnòstic per la imatge (CDI), Hospital Clínic, Faculty of Medicine, University of Barcelona, and 3 Pediatrics Section, Department of Obstetrics and Gynecology, Pediatrics, Radiology and Physics Medicine, Hospital Clinic, Barcelona, Spain

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Abstract — Aim: To relate structural and functional findings in one adolescent dizygotic twin pair with prenatal alcohol exposure. Method: Neuropsychological and volumetric magnetic resonance studies were carried out on a 13-year-old preterm dizygotic twin pair with prenatal alcohol exposure. Results: Neuropsychological and brain structural findings differed between the twins. The child with the more affected phenotype had large-scale cognitive deficits and presented significant atrophy in several brain structures. Both subjects had white matter volume reductions relative to the whole cerebral volume. Conclusion: The neuropsychological and neuroimaging data reflect long-term consequences of prenatal alcohol exposure.

INTRODUCTION

The effects of prenatal alcohol exposure fall along a continuum, with perinatal death and fetal alcohol syndrome (FAS) at one end, and relative normalcy at the other (Mattson and Riley, 1998). Alcohol-exposed children who do not meet criteria for the full FAS syndrome are diagnosed as having PEA (prenatal exposure to alcohol). These children show few or no craniofacial malformations and little or no evidence of growth retardation, but clear evidence of neuropsychological deficits (Mattson et al., 1998). Prenatal alcohol exposure causes a variety of neuropsychological deficits, among them deficits in intelligence and attention (Mattson and Riley, 1998), verbal learning and memory (Mattson and Riley, 1999), visuospatial memory, language and motor speed (Mattson and Riley, 1998), visuospatial skills (Olson et al., 1998), and frontal lobe functions such as verbal fluency (Mattson and Riley, 1999), cognitive flexibility and planning (Mattson and Riley, 1998) and working memory (Mattson et al., 1996a).

Studies using magnetic resonance imaging have shown atrophy in basal ganglia and corpus callosum (CC) and an overall reduction of brain volume (Mattson et al., 1996b); white matter is more affected than gray matter (Archibald et al., 2001).

In dizygotic twins, some discrepancies have been described in the phenotypic abnormalities, and in the degree of mental retardation (Streissguth and Dehaene, 1993). Neuroimaging discrepancies have not been investigated to date.

The aim of this study was to perform neuropsychological and neuroimaging studies of an adolescent dizygotic twin pair with prenatal alcohol exposure, and to relate the structural and functional findings.

MATERIALS AND METHODS

Case report

A preterm pair of DZ twins (boy and girl) was delivered by Caesarean section at 34 weeks gestation. The mother was 41 years old and had drunk an average of 50 g alcohol per day until at least 1.5 years before pregnancy. She also reported alcohol misuse (120 g alcohol/day) during the first months of pregnancy. She suffered from gestational diabetes, which was controlled by diet, mild hypertension before pregnancy, also controlled to 130/80 mmHg, and presented chronic hepatopathy secondary to alcohol misuse. The placetas were normal. The twins were admitted to the Paediatric Unit of the Hospital Clinic in Barcelona.

Twin A was a boy, whose birthweight (1100 g), length (38.5 cm) and head circumference (29 cm) were in the third percentile for his gestational age. As for central nervous system findings, he presented Apgar scores of 6, 10 and 10 at 1, 5 and 10 min, and weak reflexes and muscle tone. Arterial blood taken from the umbilical cord showed a pH 7.16. He had some craniofacial malformations such as prominent forehead, carp-shaped mouth, and thin lips. He presented a periventricular haemorrhage with dilation of left frontal horn and was discharged after 2 months. Postnatal growth curve until the age of 12 was below the third percentile for length, weight and head circumference. His mother reported no difficulties in walking, but he had problems learning to talk and also with reading and writing. His academic performance is currently poor and he visits a child education specialist once a week for help in developing learning strategies.

Twin B was a girl, whose birthweight (1940 g), length (42 cm) and head circumference (31 cm) were in the normal range. She presented Apgar scores of 8, 10 and 10 at 1, 5 and 10 min, good colour, no distress, and weak reflexes and muscle tone. Arterial blood taken from the umbilical cord showed a pH 7.21. Thin lips were the only noticeable facial feature. Transfontanell ultrasound was normal. She was discharged at 1 month. At the age of 5 years her length was normal (106 cm) but her weight...
was in the third percentile (15 kg) and she had a slight microcephalia. No difficulties were reported with regard to the acquisition of motor abilities, language, reading and writing. Although her academic level is normal for her age, she currently receives private classes.

At the time of neuropsychological and neuroimaging studies the twins were 13 years old.

**Neuropsychological testing**

Both subjects underwent a set of neuropsychological tests in a session lasting two and a half hours, carried out over two days. We evaluated several cognitive abilities previously reported as sensitive to alcohol effects (see Table 1). Detailed information on the tests used is described in Spreen and Strauss (1998).

**Magnetic resonance imaging acquisition**

Magnetic resonance imaging (MRI) scans were conducted using a 1.5 T Sigma GE (Milwaukee, WI) by a 3D FSPGR-IR sequence (TR = 12 ms; TE = 5.2 ms; TI = 300; NEX = 1), FOV = 24 × 24 cm and 256 × 192 acquisition matrix. Slice thickness was 1.5 mm. A control group of four male and four female subjects, mean age 14.25 years, was recruited from amongst families of friends and colleagues. There was no statistical difference between the controls and the twins regarding the variable age. The non-parametric Mann–Whitney U-test was used for the analysis.

Magnetic resonance imaging volumetric measures were performed manually by Analyze 5.0 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN).

![Fig. 1. High-resolution T1-weighted images. (1) Hippocampus atrophy (surrounding by a white line); (2) ventricular enlargement; (3) thinning of corpus callosum (see white arrow).](image-url)
We analysed the caudate nucleus, hippocampus and CC. The procedure used to measure caudate volumes is described elsewhere (Bartrés-Faz et al., 2002). For the quantification of hippocampal volumes we followed the indications from Pruessner et al. (2000). The CC area was quantified by selecting a midsagittal slice and the ‘distinction between intensities’ process was used to define it.

Segmentation measures of the white and grey cerebral matter and of the CSF were performed to obtain individual global brain volume. We used this global volume to correct the caudate nucleus and hippocampus. The automatic segmentation processing was done with SPM99 (Wellcome Department of Cognitive Neurology, London, UK). For the correction of CC area we estimated the total intracranial area of the same midsagittal slice used for the quantification of CC.

**RESULTS**

**Neuropsychological examination**

Twin A showed a low, full-scale intelligence quotient (FSIQ) (81), with a verbal IQ (VIQ) of 82 and a performance IQ (PIQ) of 84. He showed impaired performance in verbal learning, immediate recall, everyday memory, working memory and letter fluency. The other cognitive functions were normal.

Twin B showed deficits in verbal learning, immediate recall and working memory. Visuospatial skills were impaired in Block Design and in Object Assembly. The remaining cognitive functions assessed were not impaired.

**Volumetric analysis**

Twin A presented a total intracranial volume increase of 12% compared to the controls (twin A: 1198594 mm$^3$; controls: 1065834 ± 57640.33 mm$^3$), with a lower percentage of white matter than the controls (22.04 vs 36.75%), a higher percentage of CSF (18.94 vs 12.98%) and a higher percentage of grey matter (59.01 vs 50.28%). We also observed an atrophy of 43% in right hippocampus (twin A: 1673.51 mm$^3$; controls: 2906.51 ± 602.45 mm$^3$) and of 55% in left hippocampus (twin A: 1243.99 mm$^3$; controls: 2743.53 ± 400.32 mm$^3$), CC was reduced by 25% (twin A: 34124.98 mm$^3$; controls: 45112.88 ± 6519.32 mm$^3$); right caudate nucleus by 23% (twin A: 2788.49 mm$^3$; controls: 3591.46 ± 478.23 mm$^3$) and left caudate nucleus by 24% (twin A: 2708.79 mm$^3$; controls: 3554.08 ± 478.23 mm$^3$).

Twin B showed a total intracranial volume increase of 1% (twin B: 1080761 mm$^3$; controls: 1065834 ± 57640.33 mm$^3$) with a lower percentage of white matter (23.15%), higher percentage of CSF (15.69%) and higher percentage of gray matter (61.15%). None of the other structures appeared to be different from the controls.

**DISCUSSION**

Though the twins described here shared the same intrauterine and extraterine environment, their phenotypes and their neurocognitive and neurobehavioural development indicate that prenatal alcohol exposure affected the two fetuses to different degrees. Twin A had more craniofacial malformations, more impaired brain structures and altered neuropsychological functions. In addition, the mother reported more behavioural problems in this twin.

In the verbal memory section, both twins performed normally on recognition and showed impairment on immediate recall, as in Mattson and Riley’s study (1999). Moreover twin A showed a level of performance clearly within the abnormal range in the Rivermead Behavioural Memory Test. This greater memory impairment in twin A may be related to the extreme reduction of the hippocampal volume in each hemisphere. In frontal functions, twin A performed slightly worse than his sister, a finding perhaps associated with the reduced volume of the caudate nucleus. Twin A also had a low IQ, possibly related to his CC atrophy. Visuospatial skills were slightly affected in twin B, due possibly to right hemisphere learning disabilities described in white matter lesions (Rourke, 1995).
Both twins showed a higher CSF proportion than their controls. This may be due to an *ex-vaquo* ventricular dilation compensating white matter loss, usually found in PEA children, as alcohol leads to damage in the glial cells (Archibald et al., 2001; Guerri et al., 2001). In twin A this higher amount of CSF may partially explain the larger total intracranial volume, causing a disproportion between his relatively big head and his low length and weight values, even though the head circumference was always below normal for his age.

The mother’s gestational diabetes, hypertension and chronic hepatopathy cannot explain the dysmorphic facial features, the prenatal growth retardation or the neurodevelopmental outcome of our subjects. The premature birth can only partially explain our data; the twins’ gestational age was 34 weeks and so the prematurity was not extreme. We therefore think that neuropsychological and neuroimaging results reflect long-term consequences of prenatal alcohol exposure.

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### REFERENCES


### Table 2. Detailed performance in the WISC-R subtests

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The digits in bold indicate deficit.