Objective: The aim of this study was to compare the cognitive development, at the age of seven, of Brazilian children, without global developmental deficits, born preterm at the Hospital das Clínicas/Federal University of Minas Gerais, with gestational age ≤34 weeks and birthweight <1500g, but adequate to the gestational age, with children of the same age who were born full term.

Method: Forty-four children underwent neuropsychological tests to assess their intelligence, episodic memory and executive functions. The preterm group was comprised of 22 children with normal neurological exams, and the control group of 22 children born full term.

Results: Children born preterm had lower scores than those born full term on measurements of intelligence and planning, which are related to executive function.

Conclusions: The results point to the importance of ample investigation of the cognitive capabilities of preterm, even if the children present normal intelligence levels and neurological examination.

Key words: preterm, low birth weight, intelligence, episodic memory, executive functions

Declaration of interest: none

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As a result of major technological advances, preterm neonates with increasingly lower birth weight have improved survival rates; this has in turn raised issues regarding the possible consequences on these children’s development and education (Sebastiani and Ceriani 2008). They might present learning disabilities, heterogeneous neurological deficiencies, and specific cognitive and perceptual-motor disorders (Aarnoudse-Moens et al. 2009, Anderson and Doyle 2008, Campos et al. 2011, Chyi et al. 2008, Magalhães et al. 2003).

Among the methods used in the cognitive assessment of preterm infants, prominence is given to tests and scales focused on intelligence. A meta-analysis indicates that among preterm and controls, all over the age of five years, preterm infants had lower scores on intelligence tests, greater incidence of Attention-Deficit Hyperactivity Disorder (ADHD) and behavioral disorders, as well as a greater need for specialized schooling (Bhatta et al. 2002). Several studies concur with these findings and show that these children’s global cognitive level is lower than those born full term (Chyi et al. 2008, Esbjorn et al. 2006, Espirito Santo et al. 2009).

According to Mikkola et al. (2005), performance on intelligence tests is directly related to gestational age (GA) and mainly with birth weight, which is influenced by the family’s socioeconomic level (Aylward 2005). However, it is important to point out that the intelligence assessment is insufficient to verify the existence of more specific cognitive deficiencies. Several studies have shown that preterm infants present disorders related to executive function and behavior (Baron et al. 2009, Bayless and Stevenson 2007, Ford 2011, Mikkola et al. 2005, Mulder 2010). The episodic memory, that involves the ability to learn, store, and retrieve information about unique personal experiences that occur in daily life, can also be affected (Briscoe et al. 2001, Rose et al. 2005). Some authors have compared the performance of preterm children (<1750g birth weight) to children born full term on memory tests.
at the age of 12, 24 and 36 months. Already at the age of 12 months, the preterm infants' memory is shown to be impaired, with worse results in sequence of events and temporal order (Rose et al. 2005). It is still unknown whether these problems are truly specific or caused by a global cognitive decline (Esbjorn et al. 2006).

Vulnerability to neurologic and neuropsychological deficiencies caused by preterm birth may be associated with impaired intellectual capacity and can persist into adulthood (Ailln et al. 2006). Therefore, it is necessary to thoroughly investigate cognitive abilities in order to better characterize the difficulties associated with prematurity (Aylward 2005).

In Brazil, there have been few longitudinal follow-ups of preterm children over the age of three. Also reduces the publications focus on school performance and behavior of preterm children with weight adequate to gestational age (AGA), probably because they have better clinical prognosis and are considered with less risk for future disorders than those who are small for the gestational age (SGA). However, the risks in AGA preterm can be being overlooked (Bayless and Stevenson 2007). The present study aimed to compare the cognitive development of seven year old children born preterm with weight adequate to gestational age and without global developmental deficits, with children of the same age who were born full term and also AGA.

Methods

This transversal study was carried out between April/2007 and June/2008 with seven-year-old children who were born prematurely at the Hospital das Clínicas, Federal University of Minas Gerais (HC/UFMG), in Belo Horizonte, and who were followed by an interdisciplinary team at the High-Risk Children’s Outpatient Clinic (ACRIAR), which assists preterm infants born in HC/UFMG with GA ≤ 34 weeks and/or birth weight ≤ 1500g.

Children were divided into two groups in order to assess their neuropsychological development. Socioeconomic levels were measured using the Criteria for Economic Classification Brazil/2008 (Associação Brasileira de Empresas de Pesquisa 2008). The participants of this study are in class B1, C1 and C2, in which 58% of the Brazilian population are included.

The study was approved by UFMG’s Committee on Ethics in Research. In addition, all parents of participants had given written consent.

Participants

Preterm group

From July/1999 to August/2000, 114 preterm infants were born in HC/UFMG with birth weight ≤ 1500g. Among these infants, 89 (78%) were sent to ACRIAR. Unfortunately, being referred to the clinic for follow-up after neonatal discharge does not guarantee that the children will remain assiduous or even linked to ACRIAR until school age, whether by death or leaving the program. In addition, children with severe sequelae or diagnoses were not referred for neuropsychological assessment because of the inclusion criteria of this study. Forty were referred to the neuropsychology department at the age of seven and all were assessed. Only 22 (15 girls, seven boys) fulfilled the inclusion criteria: GA of up to 34 weeks; birth weight < 1500g and AGA; seven years of age; normal neurologic exam and cephalic perimeter; intelligence quotient (IQ) within the normal range; no use of medications that affect the central nervous system (CNS) and enrolled in first grade at a public school. Out of the 40 assessed children, 18 did not participate in this study for the following reasons: three were excluded for presenting IQ lower than the average for their age and slight alterations in the neurologic exam; four were small for the gestational age; six had birth weight > 1500g; one had GA > 34 weeks; and the remaining four were not submitted to the neurological exam. These exclusions were necessary in virtue of the focus of the research concentrating only on preterm children without global developmental deficits. Even including children with intelligence within the average range, the present study contemplated an ample extension of IQ considering that the normal IQ range corresponds to a variation of two standard deviations in relation to the mean score of 100 points (SD=15, range=70-130). The intelligence test was used only to exclude children with mental retardation (IQ ≤ 69).

Control group

In order to match for age, sex and schooling level with the preterm group, the control group was comprised of 22 children (15 girls, seven boys) born full term and AGA. Parents attested that their children were born without clinical or neonatal surgical complications. The children of the control group were born in the same period of time as the preterm infants. Children in the control group came from a public school, where they were assessed. They were between seven years and seven years and nine months and did not use CNS-affecting medications. They were selected for the control group because their socioeconomic level was similar to the preterm group and their development was typical for their age. They were all within the normal IQ range. There were no losses in the control group.

Measures

The neuropsychological tests were performed in Portuguese with all children in three one-hour sessions with a seven-day interval.

General intelligence

Wechsler Intelligence Scale for Children-III (Figueiredo 2002): Cognitive functions are expressed by IQ and correspond to Verbal IQ, Performance IQ, Verbal Comprehension, Perceptual Organization, Freedom from Distractibility and Processing Speed. A score below 70 suggests a deficit (mental retardation), 70-79 means boundary, 80-89 means a low average intelligence quotient (IQ), 90-109 average, 110-119 average – superior and 120-129 superior. The third version of test is standardized for the Brazilian population and was used a confidence interval of 95%.

Episodic memory

Rey’s Auditory-Verbal Learning Test (RAVLT) (Malloy-Diniz et al. 2000): A list of 15 nouns (A list) is read out loud to the child five successive times, trials A1-A5, followed by a spontaneous evocation test. After the fifth try, an interference list, also with 15 words (B
is presented and followed by a memory test. The child is then asked to recall the words from the A list, without looking at it (A6). There is a 20-minute interval and the child is then asked to recall the words from the A list (A7) from memory. Then, the examiner reads to the child a list of 50 words that include all from the A and B lists and 20 intrusions. The child must then point out which words are from the A list. The score of the recognition memory test is calculated by subtracting the words wrongly identified (not belonging to the A list) from those identified correctly. Among the items on the test, only recognition memory and learning trial (A1-A5) were used.

Rey’s Complex Figure Test-Osterreith (Spreen and Strauss 1988): The child must copy a complex figure as best he/she can, then repeat it three minutes later without seeing the figure again.

Executive function

Verbal Fluency Test (Malloy-Diniz et al. 2007): In the phonemic category, the child must say many words he/she can, beginning with the letters F, A and S (one trial of one minute for each letter); and in the semantic category the child must name animals, body parts and food. In the present study, only the phonemic and the subcategory “animals” were considered.

Tower of London Test (Malloy-Diniz et al. 2008): It consists of a wooden structure with three vertical stems of different lengths in which the child must transpose, one by one, three spheres colored blue, green and red, from a fixed position in order to achieve a target configuration. The test uses 12 cards with target configurations that are increasingly more difficult. To reach each card’s target configuration, the child must manipulate the spheres in a minimum number of movements, being allowed only three attempts for each configuration. If the child is correct on the first attempt, he or she is given three points, on the second, two points, and on the third, one point. The maximum score is 36 points. The child is expected to plan before executing the actions.

Wisconsin Card Sorting Test (Heaton et al. 2005): Four stimulus cards (reference models) are given to the child with two 64-card decks. The child must pick up the card on top of the deck and match it to one of the model cards. The possible matching criteria are color, shape and number. The examiner does not tell the child how to group the cards, but the child is told whether a match is right or wrong. If wrong, the child is supposed to put the next card in the correct manner. For each 10 successive correct matches, the matching criteria are changed without the child’s knowledge. He or she must perceive the change and adapt accordingly. Only three measures were considered: perseverative errors (total number of errors occurred in persisting on the error); categories achieved (number of sequences of 10 successive correct matches) and failure to maintain a set (number of sequences of five or more successive correct matches followed by an error that occurs before completing the set). Perseverant errors and failure to maintain a set evaluates cognitive flexibility, while categories achieved verifies ability to categorize.

Statistical analysis

A descriptive analysis of perinatal variables, mother’s educational level and age was performed, followed by a descriptive analysis of the measures and SD of each assessment method.

Mann-Whitney’s non-parametric test was adopted for the comparative analysis between the two groups, with significance level set at <0.05. Since the sample size was small, and according to the Kolmogorov-Smirnov test, most results showed abnormal distribution.

Data were analyzed using the statistical software program Statistics Package for Social Science (SPSS, version 15.0).

Results

The 22 children in the preterm group had GA between 27 weeks and 34 weeks (mean=30, SD=2). Their mean birth weight was 1172.5g (SD=222.5), with a range from 770 to 1475g and APGAR score taken at five minutes ranged from three to 10. The distribution of preterm infants in relation to gestational age and birth weight is shown in Table 1. The five most frequent complications reported in the neonatal period were jaundice (82%), respiratory difficulty (73%), sepsis (50%), anemia (41%) and hyaline membrane disease (41%). Peri intraventricular hemorrhage degree I, was detected in four neonates and 12 had normal cranial ultrasound, which was not performed on the remaining six. The mothers’ mean age during gestation was 28 years (SD=5) and educational level was eight years (SD=3). The average age at evaluation was seven years and four months (SD=3 months).

Gestational age and APGAR score at five minutes

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>Birth weight</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 1.000g</td>
<td>&gt; 1.000g e&lt; 1.200g</td>
</tr>
<tr>
<td>27</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Note. GA= Gestational age.
in the control group could not be determined. However, parents attested that their children were born full term and without complications, and the reported birth weight matches GA for the gestational time (mean=3120; SD=299). The mothers’ age ranged from 17 to 39 years (mean=26, SD=7) and educational level from 11 years (SD=3) of formal education.

Concerning the family’s socioeconomic level, there was no statistically significant difference between the groups (p=0.154), but mothers’ educational level was higher in the control group (p=0.002).

General intelligence

Data related to intelligence of the two groups are presented in table 2. Except for Perceptual Organization and Freedom from Distractibility, the preterm children performed worse on all subtests of intelligence at statistically significant levels.

Table 2. General intelligence of preterm and full term children

<table>
<thead>
<tr>
<th>Intelligence (WISC-III)</th>
<th>Preterm (n= 22)</th>
<th>Control (n= 22)</th>
<th>Mann-Whitney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>96.32</td>
<td>12.10</td>
<td>109.86</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>94.32</td>
<td>10.17</td>
<td>102.40</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>99.32</td>
<td>12.60</td>
<td>115.32</td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td>98.64</td>
<td>12.08</td>
<td>115.00</td>
</tr>
<tr>
<td>Perceptual Organization</td>
<td>91.54</td>
<td>9.55</td>
<td>97.77</td>
</tr>
<tr>
<td>Freedom from Distractibility</td>
<td>100.32</td>
<td>16.06</td>
<td>107.18</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>104.18</td>
<td>8.60</td>
<td>111.32</td>
</tr>
</tbody>
</table>

Note. WISC-III = Wechsler Intelligence Scale for Children-III.

Episodic memory

There was no significant difference between groups in episodic memory, both visual and verbal, as shown in table 3.

Table 3. Episodic memory of preterm and full term children

<table>
<thead>
<tr>
<th></th>
<th>Preterm (n= 22)</th>
<th>Control (n= 22)</th>
<th>Mann-Whitney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Trial learning (RAVLT)</td>
<td>15.77</td>
<td>6.69</td>
<td>16.05</td>
</tr>
<tr>
<td>Recognition memory (RAVLT)</td>
<td>12.32</td>
<td>3.01</td>
<td>13.45</td>
</tr>
<tr>
<td>Recall (Rey’s Complex Figure)</td>
<td>3.16</td>
<td>2.87</td>
<td>4.45</td>
</tr>
</tbody>
</table>

Note. RAVLT= Rey’s Auditory-Verbal Learning Test.

Executive function

Regarding executive function, the preterm children’s performance was inferior on the planning. There were no significant differences between groups in other aspects of this cognitive ability, as shown in table 4.

Discussion

Knowledge of the preterm infant’s perinatal history is very important because it helps to identify risk factors for future health, growth and developmental problems. In the present study, all preterm children were born AGA, which is a favorable prognosis. Besides, at the age of seven, all were studying in a regular school, did not present developmental disorders and had normal neurologic exams. Nevertheless, statistically significant differences were found in the measures of intelligence, and within the components of executive function, in the measures of planning. Children born preterm had worse performances.

Concerning the intelligence scale, the data obtained here are similar to those reported by other authors in that the means for Verbal IQ, Performance IQ and Full Scale IQ of the preterm group were well within the normal range but lower than the results of the full term children (Esbjorn et al. 2006, Espírito Santo et al. 2009). The control group attained an average score 13.54 points higher than the preterm group. In this study, the interpretation of the tests was performed by the third author, who was appointed to this task in order to avoid bias resulting from prior knowledge of the IQ by the psychologist who performed the whole evaluation of both groups. The most pronounced difficulties on the intelligence test in the present study were verbal skills and processing speed. At the age of seven, two children in the preterm group were undergoing speech-language therapy and psychological treatment at ACRIAR.

Even though IQ is not effective in detecting brain dysfunction, it provides fundamental data on the child’s global level of ability and orients the search for possible
deficiencies in specific functions. Therefore, a detailed investigation of cognitive skills is needed in order to better characterize the difficulties associated with prematurity. There is evidence of alterations related to episodic memory in preterm children, but there are few reports and disagreement over the results. For example, Briscoe et al. (2001) used the Rivermead Behavioural Test for Children to compare the episodic memory of 20 children born at or before 32 weeks gestation with a control group of 20 born full term children. Deficiencies were detected in only three children of the preterm group, ascribed to lower performance in receptive language. The authors suggest that the deficiencies were not characteristic of prematurity, but the children did present greater risk of having certain difficulties with episodic memory, which might reflect in learning disabilities at school age. Deficits in this area will limit learning and the accrual of knowledge. In the present study, there were no statistically significant differences between the groups in verbal and visual memory specific abilities, in reproducing Rey’s Complex Figure (Spreen and Strauss 1988) and RAVLT (Malloy-Diniz et al. 2000) values. Perhaps the fact that the children in the preterm group were born AGA influenced the results.

Despite evidence of dysfunctional components of executive function in preterm children (Aarnoudse-Moens et al. 2009, Baron et al. 2009, Bayless and Stevenson 2007, Böhm et al. 2004, Ford et al. 2011), in the present study only deficiencies in planning abilities were detected, as measured by the Tower of London Test, in which preterm children performed significantly worse than those born full term. Baron et al. (2009) found significant differences between infants who were born premature and full term, in relation to verbal fluency, one of the components of executive functions. Although the results of Baron et al. (2009) differ from the results found in this research, it is important to mention that the group of premature infants of this study was evaluated at three-years-old and had more impairment in verbal fluency tasks compared to the control group, even if they were born with GA between 34-36 weeks. However, the follow-up of these children until school age is necessary in order to verify the possible permanence of the verbal fluency difficulty.

Executive function deficits in preterm children are compatible with structural alterations frequently reported in this group. Aylward (2005) cites the hippocampus and the frontal-striatal circuit as particularly vulnerable to stressors related to prematurity, such as the excess of bilirubin and perinatal hypoxia. These structures are related, respectively, to memory and executive function. In the present study, correlation between the most common perinatal complications and test results was not tested due to small sample size and multiple perinatal variables. It is known, however, that hypoxia, severe hyperbilirubinemia, peri-intraventricular hemorrhage degree III and IV, prolonged period under mechanic ventilation and sepsisemia, among others, are factors that increase neurological, behavioral, and developmental problems in preterm infants with very low birthweight (Ford et al. 2011, Luu et al. 2009).

As reported by Esbjörn et al. (2006), after statistical control of the effect of intelligence variations in preterm children, there were no significant deficiencies in specific functions such as memory and executive function, which suggests that the preterm children’s difficulties are more general than specific. Still, Böhm et al. (2004) have verified that even when variation in intelligence was controlled, there were deficiencies in executive function, suggesting that this cognitive variation is stable. However, Taylor (2006) argues about the possibility of both deficits, overall and in specific skills, in children born prematurely or with very low birthweight. Normally, these changes occur in association with low IQ, commonly found in this population. Thus, it is difficult to isolate them, mainly due to the high correlation found between the different instruments that assess the different cognitive functions (Friedman et al. 2006). In the present study, the inclusion of children with IQ within the normal range, which for premature infants was between 71 and 117, might have influenced the results.

One of the limitations of the present study was the impossibility to assess most children with the same characteristics as the sample, born at the same period and enrolled at ACRIAR. This kind of program for at-risk neonates is still uncommon in Brazil. Loss to follow-up is expected, especially in long-term studies, and was one of the reasons for this difficulty. Another reason for the small sample was the rigorous inclusion criteria, allowing for only children born AGA, without neurological alterations at the age of seven, and intelligence levels within the normal range to be included. The specificity of the sample makes it difficult to generalize the results, especially when considering the heterogeneity of the preterm population in Brazil, most of which do not even have access to follow up programs.

Socioeconomic status has effects on cognition, academic achievement and mental health (Hackman et al. 2010). The two groups of infants had a similar socioeconomic level, however, the mothers’ educational

<table>
<thead>
<tr>
<th>TABLE 4. Executive function of preterm and full term children</th>
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<tr>
<td></td>
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<tr>
<td><strong>Preterm (n = 22)</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Phonemic verbal fluency*</td>
</tr>
<tr>
<td>Semantic verbal fluency (animals)*</td>
</tr>
<tr>
<td>Planning (Tower of London)*</td>
</tr>
<tr>
<td>Perseverative errors (WCST)</td>
</tr>
<tr>
<td>Categories achieved (WCST)</td>
</tr>
<tr>
<td>Failure to maintain set (WCST)</td>
</tr>
</tbody>
</table>

Note. *Raw score; WCST = Wisconsin Card Sorting Test.
level in the control group was higher, which may be related to greater cognitive stimulation of the child at home. Research has implicated prenatal factors, parent-child interactions and cognitive stimulation in the home environment in the effects of socioeconomic status on neural development (Hackman et al. 2010). Due to the complexity of the involved variables, it is extremely difficult to identify each factor’s role in the complications manifested by the preterm child at various developmental stages. If the preterm children had not benefited from interdisciplinary follow-up, during which parents were oriented as to their child’s special care and development, there might have been more pronounced differences between the two groups.

The main focus of this study was to show that preterm and AGA children, who are considered normal for school age, may present difficulties that remain clinically undetected, and without adequate assessment. Even in cases with the probability of favorable outcomes, monitoring is indicated in order to make sure that the children have no signs, though subtle, that may affect their cognitive potential. These results point to the need for long-term follow-up of preterm neonates. Even though there are several studies on the development of preterm children, the high frequency of specific alterations in the cognitive and behavioral areas requires further research. Longitudinal studies are needed to evaluate the impact of these deficits on academic performance and to identify those children who continue with difficulties even though they may not show global developmental deficits.

References


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