Impact of preterm birth and low birth weight on the cognition, behavior and learning of school-age children

Impacto do nascimento pré-termo e com baixo peso na cognição, comportamento e aprendizagem de escolares

Impacto del nacimiento pretérmino y con bajo peso en la cognición, el comportamiento y el aprendizaje de escolares

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ABSTRACT

Objective: To assess the impact of preterm birth with low birth weight on neurodevelopment, cognition, and academic learning of school-age children.

Methods: This cross-sectional study enrolled 120 school-age children with ages between six and 15 years old, attending Elementary Schools, and socio-economically paired. All of them underwent neuropsychological, neurological and academic assessments. The Purpose Group (PG) was formed by 60 children born with gestational age <37 weeks and birthweight <2500g. The Control Group (CG) had 24 children who were siblings of the PG subjects, and 36 school-age children who were neighbors and colleagues of the PG subjects. The following tools were used for assessment: WISC III, Bender Gestalt Test, Trail Making, Rey Complex Figure, Luria Nebraska-C Neuropsychological Test, Rutter's Behavioral Scale A2, Child Behavior Checklist and Test of School Performance. Statistical comparison between groups used Fisher, Mann-Whitney and ANOVA tests.

Results: PG children presented impairments in the following areas: visual-motor coordination (87% of PG children), general psychomotor development (75%), visual-constructive skill (73%), mathematical thinking (66%), tactile-kinesthetic skill (65%) and visual memory (60%), all with a *p*-value=0.001. The Intellectual Quotient of the PG subjects was, in average, 10 points lower than CG children.

Conclusions: The school-age subjects born prematurely and with low birth weight displayed specific brain functional alterations associated to cognitive-behavioral and learning disorders.

Key-words: child development; premature birth; neuropsychology; cognition.

RESUMO

Objetivo: Avaliar o impacto do nascimento pré-termo e com baixo peso no neurodesenvolvimento, na cognição e, consequentemente, na aprendizagem de crianças e adolescentes em idade escolar.

Métodos: Estudo transversal caso-controle de 120 escolares com idades entre seis e 15 anos, regularmente matriculados no Ensino Fundamental e pareados socioeconomicamente. Todos foram submetidos ao protocolo de avaliação neuropsicológica, neurológica e escolar. O Grupo Propósito (GP) foi formado por 60 escolares nascidos com idade gestacional <37 semanas e peso <2500g. O Grupo Controle (GC) foi composto de 24 escolares irmãos dos sujeitos GP e 36 escolares vizinhos colegas dos sujeitos GP. Entre os instrumentos utilizados estão: WISC III, Teste Guestáltico

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Bender, *Trail Making Test*, Figura Complexa de Rey, Teste Neuropsicológico Luria Nebraska-C, Escala Comportamental A2 de Rutter, Lista de Verificação Comportamental para Crianças e Adolescentes e Teste de Desempenho Escolar. A comparação entre os grupos foi feita por teste de Fisher, Mann-Whitney e ANOVA.

Resultados: O GP mostrou resultados desfavoráveis em coordenação viso-motora (87% do GP), desenvolvimento psicomotor geral (75%), habilidade viso-construtiva (73%), raciocínio matemático (66%), habilidade tátil-cinestésica (65%) e memória visual (60%), todos com p=0,001. O QI dos sujeitos do GP mostrou-se, na média, 10 pontos abaixo do GC.

Conclusões: Os escolares nascidos pré-termo e com baixo peso apresentaram alterações funcionais cerebrais específicas, associadas aos transtornos cognitivo-comportamentais e de aprendizagem.

Palavras-chave: desenvolvimento infantil; nascimento prematuro; neuropsicologia; cognição.

RESUMEN

Objetivo: Evaluar el impacto del nacimiento pretérmino y con bajo peso en el neurodesarrollo, la cognición, y por consiguiente en el aprendizaje de niños y adolescentes en edad escolar.

Métodos: Estudio transversal caso-control en 120 escolares con edades entre 06 y 15 años, regularmente matriculados en la Primaria y pareados socioeconómicamente. Todos fueron sometidos al protocolo de Evaluación Neuropsicológica, Neurológica y Escolar. El Grupo Propósito fue formado por 60 escolares nacidos con edad gestacional <37 semanas y peso <2500g. El Grupo Control fue compuesto por 24 escolares hermanos de los sujetos GP y 36 escolares vecinos compañeros de los sujetos GP. Entre los instrumentos utilizados, están: WISC III, Test Gestáltico Bender, *Trail Making Test*, Figura Compleja de Rey, Test Neuropsicológico Luria Nebraska-C, Escala Comportamental A2 de Rutter, Lista de Verificación Comportamental para Niños y Adolescentes y Test de Desempeño Escolar. La comparación entre los grupos se hizo mediante test de Fisher, Mann-Whitney y ANOVA.

Resultados: El GP mostró resultados desfavorables en Coordinación Visomotora, Desarrollo Psicomotor General, Capacidad Visoconstructiva, Razonamiento Matemático, Habilidad Tátil-Cinestésica y Memoria Visual, todos con p=0,001. El CI de los sujetos del GP se mostró, en promedio, 10 puntos inferior al del GC.

Conclusiones: Los escolares nacidos pretérmino y con bajo peso presentaron alteraciones funcionales cerebrales específicas, asociadas a los trastornos cognitivo-comportamentales y de aprendizaje.

Palabras clave: desarrollo infantil; nacimiento prematuro; neuropsicología; cognición.

Introduction

Dramatic improvements in prenatal, perinatal and neonatal care have resulted in premature children being born and growing up who in the recent past would have had very little chance of survival[1]. This increase in the survival rate of children born preterm and underweight has brought with it an increase in cognitive and behavioral disorders, observed from the earliest phases of childhood right up to adulthood. Scientific research has turned its attention to the possible consequences of premature birth on overall development, with special focus on precise assessment of the effects of premature birth on cognitive-behavioral abilities and, consequently, on quality of life, since these issues are the most common subjects in questions asked by parents and carers and also by professionals working in the areas of health and education[2]. Concerns over long-term development are even greater in underdeveloped countries and those still in development, since poverty is a sociopolitical and economic aggravating factor that potentiates the underlying biological vulnerability[3,4].

Evidence of nervous system damage is very often to be found in minor signs. This type of neurological signs can be observed during the process of academic learning[5] and their subtlety of presentation means that they are often only observable at later stages. This being so, Learning Disorders can be considered to be indicators of neurofunctional problems that are observable in schoolchildren[6]. Within this context, this study was conducted in order to investigate associations between premature birth and low birth weight and the neuropsychological development of children and adolescents in order to identify differences in cognitive-behavioral function and to determine the prevalence of Learning Disorders in schoolchildren born preterm and underweight.

Method

This was a case-control study of schoolchildren who had been born premature and with low birth weight (PT-LBW). The Study Group (SG) contained 60 children of both sexes

aged from 6 years to 15 years, 11 months, who had been born at, or admitted to, the Center for Integral Women's Healthcare (*Centro de Atenção Integral à Saúde da Mulher*) at the *Universidade Estadual de Campinas*. Patients were recruited according to the following inclusion criteria: children born preterm and with birth weights of less than 2500 grams, with neonatal appropriateness of weight for age classifications of Small for Gestational Age (SGA) Appropriate for Gestational Age (AGA) or Large for Gestational Age (LGA); who had studied or were studying in primary education in a grade for 8 and 9 year-year-olds at a public or private school in or around the city of Campinas; who had a sibling or neighbor born at full term and with birth weight ≥2500 grams; and whose parents or guardians signed a free and informed consent form. Children were excluded from the sample if they had been born with congenital malformations and/or genetic syndromes, were twins or had Severe Hypoxic-Ischemic Encephalopathy (Grades III and IV), Intraventricular or Periventricular Hemorrhages (Grades III and IV), acute neuroinfections with repercussions, had suffered a head trauma, had tetraplegia or tetraparesis, sensory disorders that were severe or which were not being treated or were not clinically controlled, or if the peer or neighbor was not from the same socioeconomic strata as the SG child.

Approximately 3,000 children were registered at the Center for Integral Women's Healthcare between January of 1995 and February of 2000. In view of the difficulties involved in identifying and contacting participants for a retrospective study, a total of 540 subjects were invited to take part. However, the low number of parents and guardians who gave permission, together with the strict inclusion criteria, meant that the Study Group (SG) contained 60 children. The Control Group (CG) comprised 60 siblings, or neighbors who were schoolmates with the SG member, born at full term and with birth weights ≥ 2,500g, aged from 6 years to 15 years and 11 months, all of whom were brought for clinical assessment at the same time as the child in the SG.

After free and informed consent forms had been signed by parents or guardians, each participant was assessed using the following instruments: Neonatal Medical Chart, the Wechsler Intelligence Scale for Children[7], Socioeconomic Questionnaire[8], the Luria-Nebraska Neuropsychological Battery for Children LNNB-C[9], a School Performance Assessment[10], the Rey Complex Figure Test[11], the Bender Visual Motor Gestalt Test[12], the Trail Making Test[11], the Rutter A2 Behavioral Scale[13], the Child Behavior Checklist[14], a Traditional Neurological Examination and the Evolutionary Neurological Examination (ENE)[15]. The instruments that make up the Neuropsychological Assessment protocol were all administered and scored by the same researcher.

Once collected, the data were transcribed and input into SPSS/PC type database files (Statistical Package for Social Sciences for Personal Computer, Version 11).

The chi-square test or Fisher's exact test were used to test for associations between categorical variables and membership of the study group. The Mann-Whitney nonparametric

Table 1 - Distribution of Mean IQs according to the WISC- III Intelligence Test

IQ	Group	Mean	SD	Minimum	Median	Maximum	p*
IQ-T	SG	93.53	17.05	53	92.00	135	0.001
	CG	106.10	14.72	75	108.00	144	
IQ-V	SG	96.97	17.00	57	97.00	140	0.001
	CG	109.08	15.38	73	107.50	150	
IQ-E	SG	91.48	16.84	57	89.00	131	0.001
	CG	101.62	13.42	79	102.50	132	
IQ -VU	SG	98.93	15.38	62	98.50	146	0.001
	CG	110.03	16.23	71	110.00	148	
IQ-PO	SG	89.30	15.47	58	85.00	129	0.001
	CG	100.47	13.59	78	101.00	132	
IQ -RD	SG	94.57	22.30	51	93.00	139	0.001
	CG	107.95	16.46	75	107.00	144	
IQ-PS	SG	94.58	21.31	5	99.00	130	0.210
	CG	100.70	13.17	68	101.00	136	

SG: Study Group; CG: Control Group; IQ: Mean for Quotient; IQ-T: Total IQ; IQ-V: Verbal IQ; IQ-E: Executive IQ; IQ-VU: Verbal Understanding IQ; IQ-PO: Perceptual Organization IQ; IQ-RD: Resistance to Distraction IQ; IQ-PS: Processing Speed IQ; *Mann-Whitney test.

test was used for continuous variables. Descriptive statistics for continuous variables by group and appropriateness of weight for gestational age were produced using Analysis of Variance (ANOVA) with rank transformation. When differences were significant, the Tukey test was used to identify the differences. The significance level was set at 5%.

Results

The total sample studied included 120 subjects. There were 60 schoolchildren who had been born premature at the Center for Integral Women's Healthcare with a mean birth weight of 1272g, gestational age of 30 weeks and maternal age when the child was born of 27 years (SG). The CG contained 60 schoolchildren born at full term and with weight ≥ 2500g. Twenty-four (40.0%) of them were siblings of an SG member, and 36 (60.0%) were neighbors and schoolmates of an SG member. Their mean birth weight was 3183g, mean gestational age was 39 weeks and maternal age when the child was born was 29 years. The mean age of SG members was 8 years, 7 months (standard deviation [SD]: 1 year, 1 month) and mean age of CG members was 10 years, 10 months (SD: 2 years). The children in the SG and CG were paired for family socioeconomic strata, with the following distribution: socioeconomic level B, n=10 (16.7%); level C, n=39 (65.0%) and level D, n=11 (18.3%) children.

The results of the WISC III intelligence test are shown in Table 1. It will be observed that there were statistically significant differences between CG and SG members in all categories except processing speed.

Forty-four of the SG (73%) children scored below the 50th percentile on the Rey Complex Figure Test, which tests visuoconstructive abilities, indicating that these abilities were compromised, and in contrast with the CG, 12 of whom scored below the 50th percentile (21%).

On the Bender Visual Motor Gestalt Test, 52 SG members (87%) had a total score below expected for their chronological age, indicating compromised visuomotor coordination, in contrast with the CG members, 13 of whom had performance below expected for their chronological age (22%, p=0.001).

There were also differences between the SG and CG children in general performance on the Luria-Nebraska Neuropsychological Test. Twenty-six SG members (43%) were classified with "Neuropsychological Deficit", 16 (27%) had "Intermediate" performance and 18 (30%) scored "Very Good". In the CG, the distribution was as follows: 4 (6.7%) members were classified as having "Neuropsychological Deficit", 14 (23%) had "Intermediate" performance and 42 (70%) had "Very Good" general performance, indicating that the SG members had worse neuropsychological performance (chi-square, p=0.001).

With regard to Laterality, 74 (95%) CG children (94.9%) had consistent right-side preference and 4 (5%) had consistent left-side preference, whereas 28 SG children had cross-laterality (47%) and 31 (52%) had consistent laterality, with a significant difference between the groups (p=0.003).

The majority of children exhibited average performance on the Trail Making Test, indicating that there were no differences in terms of concentrated attention or impulsivity (p=0.147).

No difference was observed between the groups in terms of the frequency of Behavior Disorder during the neurological assessment. The statistical treatment suggested a tendency towards a greater degree of hypertonia among the PT-LBW schoolchildren (p=0.057). The remaining conditions investigated during the neurodiagnosis, such as Speech Disorders, Hypotonia, Signs of Dysmorphism, Psychomotor Agitation, Inattention and Anxiety, were all more common in the SG (p<0.05). There was a significant difference (p=0.001) between the children in the SG and the CG in terms of their Neurological Development Profiles: 34 (63%) children in the SG were classified as below-expected for their chronological age, in contrast with 8 (15%) in the CG, which indicates greater neurological immaturity in the SG children.

The results of the Rutter A2 Behavioral Scale indicated that 44 of the control children (75%) did not require psychological and/or psychiatric care, whereas 37 (62%) of the schoolchildren born PT-LBW had symptoms of irritability, anxiety and impatience, suggestive of behavioral disorders needing psychological and/or psychiatric care (p=0.001).

There were no significant differences between SG and CG in terms of behavioral symptoms according to the Child Behavior Checklist (p=0.095) but the SG had a tendency for a greater proportion of children to have internalizing behavior. The School Questionnaire traced a constant median profile of the CG children, who were classified as "Good" in all categories. In contrast, the SG members were divided between Good and Poor: 27 (45%) were classified as "Poor" for Reading and 27 (45%) as "Good"; 30 (50%) were classified as "Poor" for Writing and 24 (40%) as "Good"; and 28 (47%) SG children were in the "Poor" category and 26 (43%) in the "Good" category for Mathematical Calculations.

Finally, PT-LBW schoolchildren had lower academic performance than would be expected for their grade and

chronological age according to the Academic Performance Test, which was statistically different to the CG children ($p<0.005$). Academic performance was worst in Arithmetic.

Discussion

According to the World Health Organization[3], it is estimated that more than 20 million children are born with low birth weight every year, which is equivalent to 15 5% of births. The rate is higher in undeveloped countries (16.5%) when compared with which is observed in developed regions (7.0%). In Brazil, the prevalence of infants born with birth weights <2500g is 10.0%. Countries that have the greatest amount of data on the impact of PT-LBW also have the lowest rates of preterm birth and the best socioeconomic, educational and cultural conditions.

There is no denying that poverty exacerbates the risk factors conferred by preterm birth[16]. This is why care was taken with the study design and the control group were selected from siblings of the PT-LBW children. The wide-ranging effects of socioeconomic, cultural and educational influences can be minimized when children from the same environmental background are compared. However, it remains important to survey participants' socioeconomic condition not only at the time of assessment but also when they were born[17].

In general, children in the SG group performed worse on the neuropsychological tests than children in the CG group[18]. The PT-LBW schoolchildren had average overall intelligence quotient scores, which means that they had normal intelligence. However, when compared with the CG group members their weighted scores were lower. This is in line with what other Brazilian studies of PT-LBW schoolchildren have found[16,19]. The IQ scores in the SG were lower than the CG's IQ scores, but, in contrast with results in the literature[20-21], no significant differences were detected between SG subsets when they were subdivided into Extremely Low Weight, Very Low Weight and Low Weight groups.

These results indicate the importance of the method used to subdivide subsets of PT-LBW samples. It is suggested that preterm SGA be differentiated from preterm AGA, in order to investigate possible correlations between intrauterine growth pattern and the development of cognitive functions[22].

As was expected, PT-LBW children had greatest cognitive difficulties with nonverbal tasks. Although some authors suggest that PT-LBW children have generalized cognitive function compromise[23,24], the results of this study indicate that the cognitive difficulties identified were specific. Affected cognitive functions most often cited in the literature include: attention, memory, visuomotor ability, specific difficulties with numbers, processing speed and executive function deficits[2,25]. With the exception of processing speed, abnormalities were detected in all of these cognitive functions.

With regard to laterality, the majority of subjects (94.9%), both in the SG and in the CG, had consistent right-side laterality. However, there was an interesting observation with regard to cross-laterality. Forty-six percent of the schoolchildren born PT-LBW exhibited cross-laterality, while just 21.7% of the control group children exhibited the same characteristic, which is a statistically significant difference. The most common form of cross-laterality among SG members was a preference for the right arm, the right leg and the left eye. This failure of interhemispheric crossover may be explained as the brain adapting to acquired damage caused by premature interruption of the gestation or by perinatal and postnatal intercurrent conditions. Linhares, Carvalho, Bordin and Jorge[26] also observed abnormal laterality in this population in a longitudinal study of children aged 8 to 10 years, born preterm and at extremely low weights in the Brazilian city of Ribeirão Preto, SP. However, in contrast with what was observed in the present study, those authors observed a greater prevalence of left-handedness among PT-LBW children. Other studies have also described specific neuropsychological compromise and structural abnormalities of the corpus callosum in PT-LBW children[27-29].

With regard to the Neurological Development Profiles, the SG schoolchildren were below-expected for their chronological age, indicating that PT-LBW children are neurologically immature. In support of these findings, Samson *et al*[30] have stated that the motor and behavioral impairment observed in PT-LBW children are minor neurological signs caused by interruption of gestation and sequential interference with synaptogenesis, leading to cerebral dysfunctions and, consequently, having repercussions for cognition[31].

With regard to behavioral assessment, Allin *et al*[32] used the Rutter Behavioral Scale to assess 18-to-19-year-olds who had been born with gestational ages of less than 33 weeks and found differences in personality styles. These authors observed a tendency towards a more introverted behavioral style, indicating a risk of psychiatric conditions in young adults who had been born premature.

A significant difference was detected between the groups in terms of the number of school years repeated (due to not passing the end of year exams), with more children repeating in the SG (25%) than in the CG (5%). These data are in agreement with results reported by Linhares, Carvalho, Bordin and Jorge[26]. The children in the CG had good performance at writing, but their academic performance was below what is appropriate for their current grade at school, both overall and in terms of reading and arithmetic. The schoolchildren in the SG were below-expected for learning in general, for reading, arithmetic and writing and had worse performance than the CG children. Litt, Taylor, Klein and Hack[21] analyzed 72 PT-LBW schoolchildren and 52 control schoolchildren of both sexes, with mean ages of 11 years and found a prevalence of reading and mathematical disorders of 15% and 11% respectively in their population of PT-LBW schoolchildren while in their control group the figures were 6% and 2%.

Seventy-five percent of the children born full term and with normal weight did not suffer from learning difficulties, 20% exhibit some type of academic difficulties and Learning Disorders are observed in 5%. The data on the SG children were significantly different: 33% had Learning Disorders, 35% had academic difficulties of some type and just 32% were free from difficulties. The SG children therefore had a six times greater frequency of Learning Disorders than the CG group children. It is possible that interactions between socioeconomic, cultural, familial and educational variables explain why the SG had such poor neuropsychological assessment results when compared with what is observed in the international literature from developed countries. Another Brazilian study, conducted by Meio *et al*[4], undertook a cognitive assessment of 79 PT-VLBW children aged 4 years to 5 years and 11 months. The conclusions of that study indicated that cognitive development compromise was also at higher levels than described in the international literature[33].

One possibility that should be considered is that the SG was made up of children born SGA who had suffered Intrauterine Growth Restriction. According to Schaap *et al*[34] and Sommerfelt *et al*[35] children born after Intrauterine Growth Restriction suffer a series of disadvantages with regard to academic performance and behavioral problems, when compared with PT-LBW who are not exposed to intrauterine malnutrition. This possibility is not only true of the present study, but also of other longitudinal studies of PT-LBW children and it is very important that the conditions of prenatal growth be recognized and taken into account[36] Maranha[37] studied 170 mothers and their LBW children born in the city of Campinas, SP, and compared the children's growth velocity and the mothers' sociodemographic and cultural variables in addition to factors related to health, family, social support networks and childcare. One of their conclusions was that the growth velocity of LBW children is strongly associated with the environmental conditions in which they live. A lack of basic sanitation was the situation that conferred greatest risk.

When the data recorded in this study were compared for the two groups of schoolchildren studied, it was found that PT-LBW children had worse results: in particular there were differences in specific cognitive-behavioral variables and in academic learning and IQ scores were lower by 10 points. The greatest intellectual deficit observed was in nonverbal perceptual organization ability. The PT-LBW children also had worse neuropsychological performance, with specific problems in tactile-kinesthetic, mathematical reasoning, visuoconstructive, visual memory and visuomotor coordination abilities. There was a high frequency of cross-laterality, with a predominance of the combination right arm, right leg and left eye preference. Furthermore, schoolchildren who were born premature had immature neurological development with worse academic performance and problems in the academic activities of arithmetic and reading. The frequency of Learning Disorders was six times greater in the group of low birth weight preterms. It can, therefore, be concluded that while these PT-LBW schoolchildren were intelligent children, they exhibited neuropsychological peculiarities which predisposed them to suffer from poor academic performance and Learning Disorders, Attention Disorders and a need for psychological and/or psychiatric support with greater frequency than those born at full term and with normal weight. These children tended to be more irritable, anxious, and impatient and there was a predominance of symptoms of internalization. As a final consideration, the results of this study underscore the need for public policies on health and education that promote primary, secondary and tertiary care and prevention that is focused on minimizing the negative adulthood cognitive-behavioral effects of prematurity and low birth weight.

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