ORIGINAL ARTICLE

Cognitive development in low risk preterm infants at 3–4 years of life

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Arch Dis Child Fetal Neonatal Ed 2005;**90**:F474–F479. doi: 10.1136/adc.2004.070284

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Accepted 27 May 2005
Published online first 14 June 2005

Background: Major neurological handicaps and neuropsychological disturbances are more common in ex-preterm children than their counterparts born at term.
Objective: To establish in a prospective study whether a characteristic neuropsychological profile exists in ex-preterm children who do not exhibit neurodevelopmental deficits on routine clinical examination.
Methods: Thirty intellectually normal children born preterm (30–34 weeks gestation) without major neurological disabilities and a control group of term children matched for age, sex, and parental educational and occupational status were assessed at 3–4 years of age to obtain a complete neuropsychological profile. Intellectual ability, language comprehension and expression, perceptual and visual motor function, working memory, and attention and behavioural problems were investigated.
Results: Even in the absence of major neurological signs, children born preterm achieved lower mean scores than controls on the Stanford-Binet intelligence scale (110.8 *v* 121, $p<0.001$), visual perception test (33.8 *v* 42.7, $p<0.001$), visual motor integration test (42.6 *v* 47.4, $p = 0.049$), memory for location test (8.4 *v* 9.5, $p = 0.007$), sustained attention test (41.6 *v* 51.5, $p = 0.009$), and the picture vocabulary test (33.3 *v* 44.7, $p = 0.021$).
Conclusions: Neuropsychological abnormalities can be detected early in childhood in apparently normal ex-preterm children and are consistent with a growing body of evidence that prematurity may be associated with long term neuropsychological morbidity in childhood and adolescence.

Preterm children present more often than children born at term with neurological problems that include severe neurological handicaps, such as cerebral palsy or severe mental retardation, or more subtle cognitive impairments.[1 2]

Studies on medium and long term outcomes have shown that 50–70% of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants, even in the absence of major disabilities, have learning difficulties, attention-deficit/hyperactivity disorder, specific neuropsychological deficits, and behavioural problems.[3 4] It has been established that VLBW infants are more likely to develop visual perceptual and visual-motor impairments, delay in some language functions, working memory deficit,[5 6] and, at school age, they may have learning problems and attention deficit. These studies have included a wide range of gestational age, variable choice of cut off points for birthweight distributions, and variable clinical inclusions criteria (groups including children with neurosensory impairments and children with normal development), causing potential biases. Moreover, most investigations have focused on VLBW or ELBW children or high risk preterm groups (neonatal intensive care populations)[7–9] and often consist of data on motor development or cognitive level (or developmental quotient) in the first years of life, and few have focused on specific abilities of the cognitive spectrum from 5 years of age through the school years. In many studies it is not clear whether an unfavourable outcome for a preterm group as a whole is due to moderate to severe impairment in a few infants or to slight impairment in the majority. There has been some research, using neuroimaging, of brain abnormalities in children and adolescents born preterm, and their specific cognitive deficits (ventricular dilatation, atrophy of the corpus callosum, and reduced hippocampal volume) have been described.[2 10] It has also been shown that the size of the cerebellum is reduced in ex-preterm adolescents, and significant correlations have been found between cerebellar volume and intelligence quotient (IQ), digit span, and reading age.[11] However, the relation between the lesions and neurocognitive function remain unclear in many studies.[12 13] Neuropsychological difficulties have also been detected in preterm children at school age or adolescence, who do not show neurological deficit or cerebral abnormalities.[14 15] Despite the documented relation between prematurity and cognitive deficit and the absence of a clear relation to cerebral alterations, few studies have looked at which difficulties in cognitive measures are present in preterm children with low risk of neurological deficit, such as those with no history of perinatal complications, or high risk factors, or brain lesions. In fact, there are a few studies on cognitive outcome in low risk populations.[16–18] These reports, however, have suggested that, even in low risk infants, there may be specific cognitive deficits as a function of preterm birth (visual-motor integration, explicit and auditory memory in combination with integrative functions). In a previous study on part of the sample used in the present study, we found that children without evident brain damage, evaluated at 3–4 years of age, may have difficulties performing tasks requiring sustained attention, visuospatial processing, and spatial working memory functions.[19]

The possibility of detecting a specific cognitive deficit even in children with low risk of mental and neurological problems or in children with normal neuroimaging results may have both theoretical and practical importance. It may add information on the effect of the "prematurity" per se on the cognitive deficit and may indicate the need for a detailed neuropsychological long term follow up leading to specific rehabilitative strategies to prevent learning and/or behavioural problems.

The aim of this prospective study was to provide a comprehensive neuropsychological profile at 3–4 years of

Abbreviations: ELBW, extremely low birthweight; IQ, intelligence quotient; LBW, low birthweight; VLBW, very low birthweight age in children born between 30 and 34 weeks gestation with a low risk of developmental deficits. Children with major disabilities or developmental delay, detected during the two year follow up by a child neurologist, were excluded from the study. A control group of term children matched for age, sex, and social class were compared.

METHODS

Subjects

The cohort was selected from all preterm infants discharged from the Department of Gynecology, Perinatology and Child Health, Policlinico Umberto I, Rome, Italy, between 1 January and 31 December 1998, who were enrolled in the paediatric and neurological follow up. The inclusion criteria were: (*a*) gestational age 30–34 weeks and 6 days; (*b*) no congenital abnormalities; (*c*) enrolment in the programme of paediatric and neurological follow up for at least two years; (*d*) no major neurological signs. Forty six children fulfilled these criteria. Nine children were not enrolled in the study as their parents declined to participate, and seven were no longer traceable. All 30 children of the final cohort had normal hearing and vision assessed in the first two years of life. Cranial ultrasound scans were performed serially with an ATL Ultramark scanner using a 5 or 7.5 MHz transducer. At least two examinations were made on 19 preterm infants, one within the first 48 hours and one at the end of the first week of life. No abnormal cerebral ultrasound findings, including minimal changes during the neonatal period, were found in this group, as described in a previous study.[19]

The control group comprised 30 children born at term with no history of perinatal problems matched for age, sex, parental education level, and occupational status from four schools in Rome. Information on the socioeconomic and educational status of the parents was gained from a short questionnaire containing questions on educational qualifications and occupation of both mother and father, health problems and hospital admissions of the child, child care in the first two years of life (divided into the first 6 months and thereafter), and child's age when they started school. The same observers examined the study and control groups.

Neuropsychological evaluation

The following test battery was performed on the study and control groups. Intellectual development was assessed by the Italian version of the L-M form of the Stanford-Binet intelligence scale.[20]

Perceptual and motor abilities

Visual-motor integration test[21]

This is a paper and pencil test in which the child has to copy a series of geometric shapes of increasing complexity one by one until he or she produces three consecutive wrong figures. The score indicates the accuracy of the copies and ranges from 0 to 24. The lower the score, the less competent the performance. It is possible to convert the raw score into a mental age equivalent.

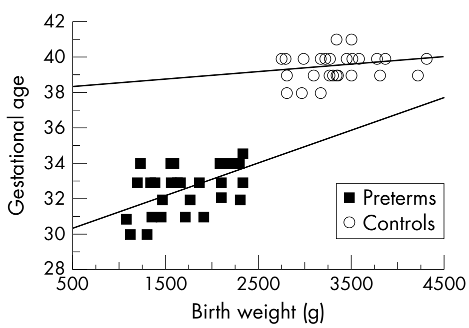

Figure 1 Distribution of gestational age by weight of the preterm and control infants.

Block construction[22]

Each child is presented with a set of eight wooden parallel piped blocks measuring 7.5 × 5 × 2 cm. Using an identical set of bocks, the examiner constructs a model behind a screen, out of the sight of the child. After lifting the screen, the examiner asks the subject to make a similar construction. The child is asked to make six different block models, and he or she can achieve a score of 0, 1, or 2 for each construction. As described by Stiles *et al*,[22] the scoring system is divided into two sections: three models are designed as ''simple'' constructions and three as ''complex''.

Visual-perceptual tasks[23]

This is a perceptual test with four sections where the child is asked to observe a geometric shape and to recognise the same one or a similar one from a group of others. In the first section the child has to match the same figure within a group of figures that differ with respect to spatial orientation; in the second he/she has to find the right shape in the context of overlapping images; in the third section the child has to recognise the figure between partially raised images; in the fourth he/she must match the target with other figures that have the same shape but differ in dimension, colour, and/or spatial disposition. The standard score is obtained by the sum of the four sections and ranges from zero to 70.

Language abilities

The language battery comprised two tests of language production and two of language comprehension.

Boston naming test[24]

This test measures lexical production elicited through pictures. The children is asked to name the objects shown in the pictures, which gradually become less familiar. The score is from zero to 60.

Word and phrase retrieval test[25]

This is a word and phrase repetition test designed to ascertain the child's ability to imitate verbal stimuli, particularly their morphological and syntactic aspects. The number of correctly pronounced sentences is scored. The score varies from zero to 56.

Peabody picture vocabulary test revised[26]

This is a widely used test, selected to provide a reliable measure of receptive vocabulary. IQ levels can be obtained from the raw scores and chronological age.

Test of grammar comprehension [27]

This measures syntax comprehension. The child is asked to choose the correct picture (from four) after listening to a sentence. The number of correct answers is scored and ranges from zero to 31.

Working memory ability

Memory for location[28]

This is a test of spatial short term memory. The testing apparatus consists of six identical plastic cups and two small toys. The child has to remember under which cup one or two toys are hidden after the cups are covered with a screen for one second. In detail, the test consists of two trials for each spatial arrangement of the cups (one toy under one of four and six cups arranged in straight lines, one toy under one of six cups arranged diagonally, one toy under one of six cups in an L shape, two toys under two of six cups in a straight line).

Table 1 Comparison of the performances obtained by the two groups on the cognitive level assessment

Test	Preterm (n = 30)		Control (n = 30)		p Value
	Mean (SD)	Range	Mean (SD)	Range	
Stanford-Binet full scale IQ	110.8 (10.41)	94–131	121 (10.63)	100–138	<0.001

p Value by analysis of variance.

In each session the number of correct responses is scored (range 0–10).

Attention sustained test (Leiter international performance scale revised)[29]

This test measures sustained attention for stimuli arranged in different spatial positions. It is a barrage task with a time limit (30 seconds). Each of the four sections of growing difficulty is composed of a sheet of paper on which are represented the target picture (a puppet) on the top and a series of two different pictures (puppets and balls) below. The child is requested to select, by crossing them off, all the pictures identical with the target. The total number of correctly crossed out images is scored. The score ranges from zero to 64.

Each evaluation consists of two or three sections of 25–50 minutes according to the availability of the child and his/her family and is followed by a neurological examination focusing on fine motor skills and coordination ability.

Statistical analysis

Data were analysed with the Statistical Package for Windows, version 5.0 (StatSoft, Inc, Tulsa, Oklahoma, USA).[30] Single analysis of variance and analysis of covariance were performed to compare the results of each neuropsychological test between the groups.

Ethics

The families of the study and control groups provided written informed consent in accord with hospital institutional review board regulations for studies on human subjects.

RESULTS

We tested 30 low birthweight (LBW) children born preterm at the Policlinico Umberto I, University of Rome, Italy, between 1 January and 31 December 1998. The children selected were born at 30–34 weeks gestation (mean 32) with a birth weight of 910–2400 g (mean 1755). Twenty five were appropriate size for gestational age, and five were small for gestational age. Figure 1 shows the distribution of gestational age and birth weight of the two groups.

Cognitive level

The IQ scores of the preterms and controls obtained with the Stanford-Binet intelligence scale were in the normal range (94–130 and 100–143). However, the mean (SD) IQ of the preterm group was significantly lower than that of the control group: 110.8 (10.4) *v* 121 (10.6); $F_{(1,11)} = 15$; $p<0.001$ (table 1).

To control for the effect of general intelligence on all the other performances, we covaried results obtained on the visual-perceptual and motor, language, attention, and memory tests with IQ scoring.

Perceptual and motor abilities

In the visual-motor integration test, the preterm group performed less well than the term children (mean 42.6 *v* 45.8). The significance was confirmed even when data where covaried with IQ levels $F_{(1,34)} = 4$; $p = 0.5$.

On block construction tests, the two groups differed significantly only in the simplified models task; the results were nevertheless reasonable for the IQ levels (table 2).

In the visual-perceptual test the mean full scale standard scores of the preterm children were significantly lower than those of the controls even when data were covaried with the IQ levels of the two groups (means 33.8 *v* 42.7; $F_{(1,47)} = 24$; $p<0.001$; table 2).

Attention

Preterm children achieved a lower score in the sustained attention task (mean 41.6 *v* 51.5), and the differences between the groups were significant even when IQ levels were taken into account ($F_{(1,56)} = 7.3$; $p = 0.009$; table 2).

Memory

In the spatial working memory test, the study group reached lower a mean score than the control group (8.4 *v* 9.5). The difference was significant on the analysis of covariance also ($p = 0.0073$; table 2).

Language skills

The language test results indicate a general difference between the preterm and control group. In the lexical

Table 2 Neuropsychological test scores obtained by the two groups on the non-linguistic abilities

Test	Preterm (n = 30)		Control (n = 30)		p Value*	p Value†
	Mean (SD)	Range	Mean (SD)	Range		
VMI	42.56 (6.13)	35–57	47.36 (5.76)	38–64	0.0027	0.049
Block construction						
Simple	4.76 (1.54)	0–6	5.6 (0.54)	4–6	0.0039	0.18
Complex	2.33 (2.03)	0–6	3.03 (1.92)	0–6	0.17	0.51
TPV	33.82 (8.39)	14–44	42.66 (4.74)	31–52	<0.001	<0.001
LIPS (attention)	41.62 (11.57)	13–60	51.5 (5.78)	42–63	<0.001	0.009
Memory location	8.37 (1.32)	6–10	9.53 (0.68)	8–10	<0.001	0.0073

VMI, Visual-motor integration test; TPV, perceptual tasks of visual perception test; LIPS, attention sustained task of Leiter international performance scale.
*Analysis of variance.
†Covaried with IQ levels.

Table 3 Neuropsychological test scores obtained by the two groups on linguistic abilities

	Preterm (n = 30)		Control (n = 30)			
Test	Mean (SD)	Range	Mean (SD)	Range	p Value*	p Value†
BNT	14.86 (4.2)	6–22	18.13 (4.51)	8–29	0.0052	0.11
TRF	40.63 (7.17)	22–49	45.3 (4.83)	32–51	0.0045	0.084
PPVT-R	33.27 (13.35)	11–68	44.73 (11.6)	14–72	<0.001	0.021
TCG	8.72 (5.38)	4–26	13.2 (7.43)	6–27	0.01	0.054

BNT, Boston naming test; TRF, word and phrase retrieval test; PPTV-R, Peabody picture vocabulary test revised; TCG, test of grammar comprehension.
*Analysis of variance.
† Covaried with IQ levels.

comprehension test (Peabody Picture Vocabulary Test Revised), the difference between the two groups was significant even when analysis of covariance was applied ($F_{(1,56)}$ = 5.3; p = 0.021), whereas in the grammar comprehension test (test of grammar comprehension) the difference approached significance ($F_{(1,57)}$ = 7.3; p = 0.054). The data from the lexical and morphological production test (Boston naming test and word and phase retrieval test) did not reach significance when covaried with the IQ levels (table 3).

DISCUSSION

This prospective, follow up study with a matched control group showed that even preterm infants with a low risk of neurodevelopmental deficit may have difficulties in specific cognitive areas at 3–4 years of age. In contrast with many earlier studies which included entire populations of preterm children and made no differentiation according to neurological status,[5 6 31] we selected our study group using strict inclusion criteria to create a more homogeneous group without measurable neurological damage. Very few studies that have performed a comprehensive analysis of the neuropsychological outcome in premature children are available. It can be argued that the ultrasound technique is not 100% sensitive for accurately selecting subjects according to absence of brain lesion and that magnetic resonance imaging may give more exhaustive information on subtle brain lesions in these children.[2] This is certainly true, but the preterm children included in our study were very young and such an examination could only have been performed under general anaesthesia. The absence of signs of neurological impairment did not justify the use of such an intrusive examination, and for ethical reasons it could not be performed for research purposes only.

The criteria used to match the preterms with controls took into account parental educational level and occupational status obtained using a short questionnaire that also considered postnatal care arrangements in terms of hours a day the mother spent with the child in the first 6 months of life. Other factors may influence cognitive outcome in children, but from the literature we considered those to be the most important.[32]

The results strongly agree with earlier studies on cognitive outcome of LBW or VLBW children which reported mean IQ levels 6–7 points or 0.5 SD less than for control groups.[12 33] IQ levels appear to remain stable in VLBW subjects (high risk preterm), and their mean IQ scores can still be significantly lower than those of controls even at 20 years of age.[34] However, in a long term prospective study of moderately immature, low risk preterm children, the differences in cognitive outcome from their counterparts born at term appeared to gradually attenuate.[18]

There are few studies that account for general IQ level in the analysis of data on neuropsychological tests.[35] More often in studies that consider a big sample of children, researchers calculate the difference between preterms and term controls in the statistical analysis, first including all the group and then excluding children with cognitive or major neurological deficit.[36] We performed a covariation analysis on all the neuropsychological measures, accounting for the differences in IQ levels even if the preterm cognitive levels were in the normal range, in order to obtain a more specific picture of the real deficit.

In reality, some LBW children with apparently normal overall measures of motor and cognitive ability have specific deficits in certain areas of performance such as attention, memory, language, visual-motor integration, and visual-spatial skills.[1 17 31] On the neuropsychological tests, there was a significant difference between the preterm and full term groups with respect to scores on the visual-perceptual and visual-motor integration tests in our study. No differences between groups were found in the block construction test. As far as we know, this is the first time that these abilities have been investigated at 3 years of age. Poor performance of LBW children in visual-motor abilities are well documented and have been described in several studies of children 5–11 years of age.[31 37] Previous studies have found

What is already known on this topic

- Studies on medium and long term outcome of preterm birth show that learning difficulties, attention-deficit/hyperactivity disorder, specific neuropsychological deficits, and behavioural problems result in more than 50% of cases
- Most investigations have focused on VLBW or ELBW children or high risk preterm groups, looking at motor development or cognitive quotient in the first years of life, with little attention focused on specific abilities of the cognitive spectrum in school age children

What this study adds

- Neuropsychological abnormalities can be detected early in childhood in apparently normal preterm children, and appropriate evaluations should be performed routinely to prevent problems at school age
- The finding of specific difficulties in sustained attention, visuospatial processing, spatial working memory, and some language aspects in LBW preterm children should be considered in the development of early educational and rehabilitative interventions to improve cognitive and behavioural outcome

that preterm children may have visual and perceptual motor disorders at school age compared with children born at term or in a population based study.[38 39] These characteristics have been reported even in the absence of neurological impairments.[14] Other studies have, in contrast, reported a small prevalence of visual-perceptual dysfunction or the absence of any difference in visual processing in VLBW or ELBW children.[40]

Vocabulary delays were evident in our study group, consistent with previous reports of language difficulties after premature birth.[6 41] In our study, differences in grammatical comprehension abilities between preterm and term approached significance. These data confirm a risk of language difficulties even in low risk preterm infants. Previous studies on language development have found that premature children are comparatively delayed in expressive and receptive language.[7 42] Some studies that compared preterm and full term children suggested that the early difference may disappear in the first years of life especially in some aspects. For example, Ment *et al*[42] described a group of VLBW infants in a prospective long term follow up study from 3 to 8 years old and showed that preterm children may have difficulties in receptive verbal abilities but that this function can improve over time. However, other more complex verbal processes, such as understanding of syntax, abstract verbal skills, verbal production, and word fluency have been found to be deficient.[43]

Our results show that in the spatial working memory test, the preterm group achieved a lower performance than the controls. Selective memory deficit has been described in LBW children, and preterm children, relative to controls, showed lower scores on spatial working memory and planning tasks.[44] We reported in a previous study a working memory deficit in a group of 19 preterm children who are part of the group we are describing here. Participants were selected if they had at least two cranial ultrasound and normal findings. We found specific spatial working memory difficulties characterised by a progressive worsening considering the interval delay and the complexity of spatial configuration.[19]

Our data showed a significant difference between the study group and the controls on the sustained attention abilities. This task involves attention in terms of duration and direction and has been reported to correlate with problem solving abilities and school performances. Similar findings to ours have been found previously in VLBW infants without evident brain disorders.[14] In most papers, attention difficulties in preterms are described in the context of the increased risk of attention deficit and hyperactivity disorder.[45 46]

Our findings on neuropsychological outcome in children at low risk of developmental disorder should clarify the necessity for specific cognitive assessments early in childhood even in populations of children usually followed up for a short time.

Continued assessment is necessary to observe behaviour modifications over time and to determine whether the findings on neuropsychological outcome indicate a developmental lag in brain maturation that will change over time or whether other problems will become evident in these children as the demands become increasingly challenging (such as at school).

ACKNOWLEDGEMENTS

The financial support of the Italian Ministry of Health Project 0AN/F ''Hypoxic-ischemic brain damage in the newborn: epidemiological and experimental studies on diagnosis, therapy and rehabilitation'' is gratefully acknowledged. We thank Arianna Terrinoni and Cristina Vagnoni for their assistance in collecting data. We especially thank the children who participated in the study and their families.

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Competing interests: none declared

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