PREMASCOL : étude de corrélation entre test de Brunet-Lezine à 24 mois et scolarité à 5 ans, étude monocentrique chez les prématurés ≤ 32SA+6J

Laure Jacquez, Lauriane Hatton

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PREMASCOL

CORRELATION BETWEEN BRUNET-LEZINE TEST AT AGE 2 AND SCHOOLING AT AGE 5 IN PRETERM CHILDREN < 33 WEEKS

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLÔME D'ÉTAT

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TABLE DES MATIERES

LISTE DES ABBREVIATIONS

BLR: “Brunet-Lézine Révisé”

DQ: Development Quotient

GA: Gestational Age

SGA: Small for Gestational Age

IVH: Intraventricular haemorrhage

EOS: Early onset sepsis

BPD: Bronchopulmonary Dysplasia

BMI: Body Mass Index

CA: Corrected Age

GMFCS: Gross Motor Function Classification Systems

ADHD: Attention Deficit Hyperactivity Disorder

ASD: Autism Spectre Disorder

IQ: Interquartile

NICU: Neonatal Intensive Care Unit

ASQ: Age and Stages Questionnaire

ERTL: “Epreuve de Repérage des Troubles du Langage”

ABSTRACT

Aim: To study the correlation between the Brunet-Lézine test at age 2 and schooling at age 5, in premature infants born ≤32+6 weeks. To study the neurological outcome of this population.

Methods: In 270 children born ≤32+6 weeks between 01.2010 and 01.2014 and included in the local health network "Naitre et Devenir" , the Brunet-Lézine Revise test (BLR) was performed at age 2 and evaluation of schooling assessed at age 5. BLR test covers 4 domains and results are expressed as a standardized coefficient according to the normal population. Unassisted age appropriate schooling was defined as being in the appropriate classroom without any assistance or health interventions, in or outside school.

Results: BLR test was interpretable in 251 children and median BLR score was 93.0. A total of 171/251 children (68%) had unassisted age-appropriate schooling. The correlation between a BLR score ≥100 and unassisted age appropriate schooling was highly significant ($p<0.0001$), with a positive predictive value of 88%. The association between BLR DQ and schooling remained significant after adjustment on maternal education, bronchopulmonary dysplasia, and BLR. In the study population, 156/270 (58%) had no neurological, sensory or neurodevelopmental disorders. The most common disorders were language impairment (28%), visual impairment (28%), and dysgraphia (17%).

Conclusion: The Brunet-Lézine test at 2 years is feasible and has good predictive property for child's schooling at 5 years. It seems therefore possible to lighten the follow-up of children presenting a BLR ≥100 for the benefit of other children.

RESUME

But : Etudier la corrélation entre le test de Brunet-Lézine à 2 ans avec la scolarité à 5 ans chez les prématurés nés ≤32+6 SA. Etudier le devenir neurologique de cette population.

Méthodes : Deux-cent soixante-dix enfants nés ≤32SA+6J entre 01.2010 et 01.2014, suivis dans le réseau « Naitre et Devenir » ; ont bénéficié d'un test de Brunet-Lézine Révisé (BLR) à l'âge de 2 ans et d'une évaluation de la scolarité à 5 ans. Deux-cent cinquante et un enfants présentaient un résultat interprétable au test du BLR. La scolarité à 5 ans était définie comme appropriée quand l'enfant était dans sa classe d'âge sans aucune aide à l'extérieure ni à l'école.

Résultats : Un total de 171/251 enfants (68%) avaient une scolarité appropriée pour l'âge. La corrélation entre un BLR ≥100 et une scolarité appropriée était très significative ($p<0.0001$), avec une valeur prédictive de 88%. En analyse multivariée, les facteurs influençant la scolarité étaient le niveau d'étude maternel, la dysplasie broncho-pulmonaire et le BLR. Le lien entre BLR et scolarité restait très significatif après ajustement sur les autres facteurs. Cent-cinquante-six enfants (58%) ne présentaient aucun trouble neurologique, sensoriel ou neurodéveloppemental. Les troubles les plus fréquents étaient les troubles du langage (28%), le déficit visuel (28%), et la dysgraphie (17%).

Conclusion : Le test de Brunet-Lézine est un bon marqueur prédictif de la scolarité de l'enfant. Il nous semble donc envisageable d'alléger le suivi des enfants présentant un BLR ≥100 au profit des autres enfants.

INTRODUCTION

Preterm birth affects about 15 million children a year worldwide [1]. In France, 12,000 infants (1.5% out of 800,000 births) were born before 32 weeks' gestation in year 2015 [1].

Nowadays, improved obstetric and neonatal care has led to better vital prognosis of preterm infants [2]. However, these children remain at risk of developmental disorders, such as motor disorders (40%), behavioral disorders (21%), cerebral palsy (9%), language disorders, specific learning disorders and lower cognitive test scores [2–7]. Lower academic performances are described, that justify the systematic follow-up recommended until school age [4,6,8–10]. In France, 30% of children born ≤ 32 weeks of gestation age (GA) have school difficulties [11]. Specific follow-up enables the detection of neuro-developmental difficulties in order to offer adapted care – e.g. speech therapy, physiotherapy, psychomotricity or school life support. Studies have shown that the earlier this help is provided, the more it enables the children to progress [12,13].

The follow-up of preterm infants living in the Grenoble agglomeration (around 140 neonates per year born < 32 GA) is ensured by the preterm follow-up health network "Naitre et Devenir". The objectives of the ambulatory-hospital network are to standardize the follow-up visits and evaluations. The Brunet-Lezine Revised Test (BLR) is a tool developed in France to assess neuro-development [14] and is systematically offered at the age of 24 months to the former preterm children followed in the network. As this test is only used in France, there is seldom data regarding its correlation with neurodevelopment and cognitive performances at school age in the international scientific literature. Only one French research, studying 244 children born in 1997 from the EPIPAGE 1 cohort, has showed a significant degree of correlation [11]. A second study on the subject, using a more recent population, could comfort the relationship between neuro-development assessed at 2 years of age and school

performances. This would help to target earlier children at risk of school difficulties, and thus provide them with early assistance.

Using a cohort of children born ≤ 32+6 GA, the main objective of our study was to assess the relationships between the BLR test at 24 months and school performance evaluated at 5 years, and to define the positive predictive value of a score ≥ 100 for normal schooling. The secondary objectives were to investigate the relationship between maternal, prenatal, perinatal, and neonatal characteristics and schooling at age 5 and to describe the cognitive and neuro-motor development at age 5.

POPULATION AND METHODS

1) Study population

All preterm children born ≤ 32+6 GA, between 01.01.2010 and 01.01.2014, hospitalized in the NICU of the Grenoble-Alpes University Hospital, alive at discharge, and subsequently followed up in the "Naitre et Devenir" network were included. Only children with complete data for the BLR evaluation at 2 years and schooling at 5 years were included in the analysis. The consent of the families was obtained when the network charter was signed, specifying that the network's data could be used to evaluate care practices.

The study received regulatory approval from the hospital's Delegation for Clinical Research and Innovation on 25.10.2019 and from the committee for the protection of persons.

2) Data collection

Data were collected from hospital and network charts and included maternal demographics, birth characteristics, prenatal and postnatal complications and follow-up of children. Gestational age (GA) refers to completed weeks of amenorrhoea. Maternal education level was collected from medical records and classified into 2 groups: high (university degree) versus low (secondary school level or lower and/or professional degrees). Small for Gestational Age (SGA) was defined by a birthweight below the 10th percentile according to the French AUDIPOG curves [15]. Bronchopulmonary dysplasia was defined according to the classification by Jobe and Bancalari [16]. Severe cerebral abnormality was defined by the presence of either an intraventricular haemorrhage (IVH) of grade III or IV of the Papile classification, or periventricular leukomalacia (cystic or not) [17]. Early-onset sepsis (EOS) was defined as the isolation of bacteria or fungi from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring ≤ 72 hours of life. Underweight at 24

months was defined by a Body Mass Index (BMI) < 3rd percentile on the French growth charts used at the time.

The “Naitre et Devenir” network gives each patient a follow-up chart, used at each visit, with pre-filled consultation sheets in order to carry out semi-directed, complete and reproducible evaluations. The standardized follow-up is ensured by a pair of paediatricians, one with hospital and the other with outpatient practice.

Within the network, BLR test is a standardized test systematically offered to all patients at 24 months of corrected age (CA). It is performed by a psychologist specifically trained in the follow-up of preterm infants. The test evaluates the child's performance in four main domains of neurodevelopment: posture, language, sociability and coordination [14]. The total of each domain give a score that becomes a development quotient (DQ) when compared to the mean result of children of the same age. A DQ of 100 means that the developmental age is consistent with the corrected age. Children who could not be tested (for example uncooperative child on the day of the test) were classified as "not-scorable" DQ and excluded from BLR analyses. Data for DQ were categorized according to the literature in four categories (<70, 70-84, 85-99, ≥100) [11]. The main threshold was set at 100 because it means that the developmental age corresponds to the corrected age of the child and it is the cut-off already used [11] .

All medical conditions present at 24 months were recorded and coded, including neurological, sensory or learning disabilities. Coding was systematically reviewed by the paediatrician coordinating the network.

Prevalence of neurodevelopmental disorders at 5 years was calculated on the study population. Cerebral palsy and its consequences were defined according to the Gross Motor Function Classification System (GMFCS) [18]. Learning disabilities (dyspraxia, dysgraphia, and language disorders), Attention Deficit Hyperactivity Disorder (ADHD), and Autism Spectrum

Disorder (ASD) were retained if the diagnosis was confirmed by the child's referring paediatrician. Absence of disability was defined by an absence of cerebral palsy, visual impairment, hearing impairment, and an overall DQ ≥ 85 [1]. Absence of neurological disorder was defined by an absence of disability and absence of other neurodevelopment conditions (ADHD, isolated attention deficit disorder, ASD, behavioral disorders, dyspraxia, dyslexia...).

In France, at 5 years old, children are normally welcomed in kindergarten. Data concerning schooling at 5 years of age were collected in medical and network records and by standardised questionnaires sent to the teacher by the network [Appendix 1] and eventually to the paramedical nursing staff (speech therapist, physiotherapist, psychologist...) [Appendix 2]. Schooling was classified into four categories: unassisted age appropriate schooling, age appropriate schooling with assistance and health interventions outside school (speech therapy or physiotherapy or psychomotricity or psychology), age appropriate schooling with assistance within the school (life support), and other (grade repetition or specialized establishment). The 3 last categories were grouped into “not normal schooling”.

3) Statistical analysis

Descriptive analysis was performed using median an interquartile (IQ) for continuous variables, percentage and frequencies for categorical variables. Comparisons among subgroups resulting from BLR at 2 years and schooling at 5 years were performed on a selection of demographic and neonatal variables. Due to the standardized follow-up, missing data were not exceeding 5%, except for maternal education (6%).

For univariate analysis, Mann-Whitney tests were performed continuous or ordered categorical variables. Fisher tests were executed for categorical variables.

A multivariate logistic regression was performed to describe effect of BLR ≥ 100 on unassisted age appropriate schooling, adjusting on significant co-factors. Univariate logistic regression was performed before inclusion on the multivariate analysis. Variables included for selection in the multivariate models were chosen based on the p-value, literature, and decision from expert paediatricians, public health specialists, and the coordinator of Paediatric Clinical Investigation Centre. Variables with a significance or trend deemed clinically relevant were selected. Selection for the final multivariate model was performed using a backward stepwise selection.

A p-value < 0.05 was considered statistically significant.

No imputation was performed on missing data.

Statistical comparisons were performed in Statview, version 1992-1998 (SAS institute inc, North Carolina, USA), R4web 1.2 (UGA & CHUGA with EIT Health support, Grenoble, France), and Stata 15.1 (StataCorp, College Station, Texas, USA) for the multivariate analysis.

RESULTS

Among 456 children born ≤ 32+6 GA between 2010 and 2014, hospitalized in Grenoble NICU and living in Grenoble area, 13 died and 16 refused the follow-up. 427 patients were included in the study. BLR test was available at 24 months of age for 322 patients. Data on BLR and schooling were known for 270 patients, but were interpretable for only 251 patients, because 19 children had a not scorable BLR. They were subsequently excluded from every analysis including BLR but maintained in the analysis studying the neurological outcomes.

The flow chart of 270 patients selected for analysis is shown in Figure 1.

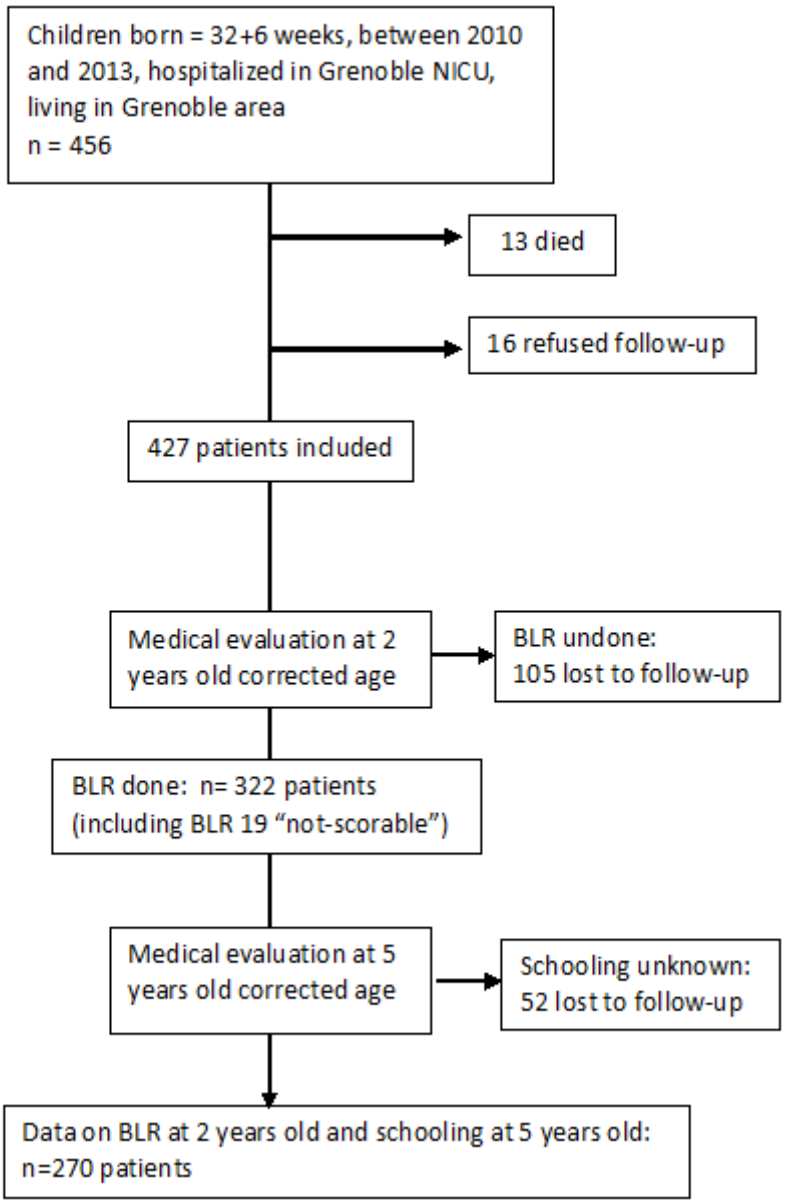


Figure 1: Study population

NICU: neonatal intensive care unit. BLR: Brunet-Lezine Revised test.

The comparison of perinatal and socio-demographic data between the study and the lost to follow-up populations is presented in Table 1. The median GA of the followed-up children was 30 weeks GA (IQ25-75: [28-32], min 24, max 32), median birth weight was 1360 grams (IQ25-75: [1011-1650], min 464, max 2520), and median birth cerebral perimeter 28.0 cm (IQ25-75: [25-29], min 20, max 33). The followed-up children had significantly lower GA, lower birth weight, more bronchopulmonary dysplasia and longer hospital length of stay that lost to follow-up children. They had a higher proportion of breastfeeding and a higher level of maternal education.

Table 1. Comparison between the study population and the lost to follow-up population

	Study population n = 270	Lost to follow-up population n = 157	p
Maternal characteristics			
Maternal age (years), median [IQ25;IQ75]	30 [27 ; 24]	29 [27 ; 33]	0.118
High maternal education level [a], n (%)	126 (49.6 %)	37 (30.1%)	< 0.001
Multiple pregnancy, n (%)	102 (37.8%)	55 (35.0%)	0.604
Chorioamniotitis, n (%)	27 (10.0%)	15 (9.6%)	0.488
Vascularobstetrical pathology [b], n (%)	108 (41.4%)	46 (31.9%)	0.083
Newborn characteristics			
Gestational age (weeks), median [IQ25;IQ75]	30 [28 ; 32]	31 [30 ; 32]	0.001
Birthweight (g), median [IQ25;IQ75]	1360 [1011 ; 1650]	1500 [1210 ; 1750]	0.001
Boy, n (%)	157 (58.1%)	73 (46.5%)	0.071
Apgar test (5 min), median [IQ25;IQ75]	9 [8 ; 10]	9 [8 ; 10]	0.914
Antenatal corticosteroids, n (%)	219 (81.1%)	122 (77.7%)	0.160
Small for gestational age [c], n (%)	39 (14.6%)	18 (11.5%)	0.461
Bronchopulmonarydysplasia, n (%)	93 (35.6%)	30 (20.3%)	0.001
Postnatal corticosteroids, n (%)	9 (3.4%)	4 (2.7%)	0.778
Severe cerebral abnormality [d], n (%)	5 (1.9%)	6 (3.8%)	0.153
Early onset sepsis [e], n (%)	20 (7.5%)	10 (6.4%)	0.699
Breastfeeding, n (%)	157 (60.9%)	84 (60.4%)	0,020
Length of hospital stay (days), median [IQ25;IQ75]	48 [38 ; 70]	42 [33 ; 61]	0,020
24-months underweight [f], n (%)	32 (11.9%)	10 (8.3%)	0,406

Abbreviations: IQ = interquartile. Mann Whitney or student test when appropriate.

[a] High maternal education level = university studies. [b] vascularo obstetrical pathology: vascular intrauterine growth restriction, maternal high blood pressure, or preeclampsia. [c] small for gestational age = birthweight <10^{e} percentile on AUDIPOG curves. [d] severe cerebral abnormalities = presence of either an IVH of grade III and IV of the Papile classification, or periventricular leukomalacia (cystic or not). [e] early onset sepsis = isolation of bacteria or fungi from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring ≤ 72 hours of life. [f] 24-months underweight = BMI < 3^{e} percentile.

The proportions of neurological disorders present at the age of 5 are presented in table 2. One hundred and fifty-six children (57.8%) had no disability at age 5 and 143 children (52.9%) had no disorder at all at age 5.

Thirty-five children (13.0%) had a motor disorder. Nine children (3.3%) had cerebral palsy: six with possible running (GMCSF I) and three more severe but none with GMCSF V. The 26 remaining children had motor abnormalities with possible running that were related to delayed acquisition or fine motor disorders.

Table 2. Prevalence of neurological disorders in study population at 5 years of age.

	Prevalence n = 270
No disabilities	156 (57.8%)
No disorders	143 (52.9%)
Motor disorder	
Possible running	32 (11.9%)
Possible walking	1 (0.4%)
Possible standing	1 (0.4%)
Possible sitting	1 (0.4%)
Visual impairment	72 [a] (28.3%)
Hearing impairment	4 [a] (1.6%)
Dyspraxia	8 (3.0%)
Dysgraphia	46 (17.0%)
Language disorders	75 (27.8%)
ADHD confirmed or suspected	15 (5.5%)
Isolated attention deficit	7 (2.6%)
Behavioral disorder	21 (7.8%)
Autism spectrum disorder	3 (1.1%)

Abbreviations: ADHD attention deficit/ hyperactivity disorder.

[a] data known for 254 patients.

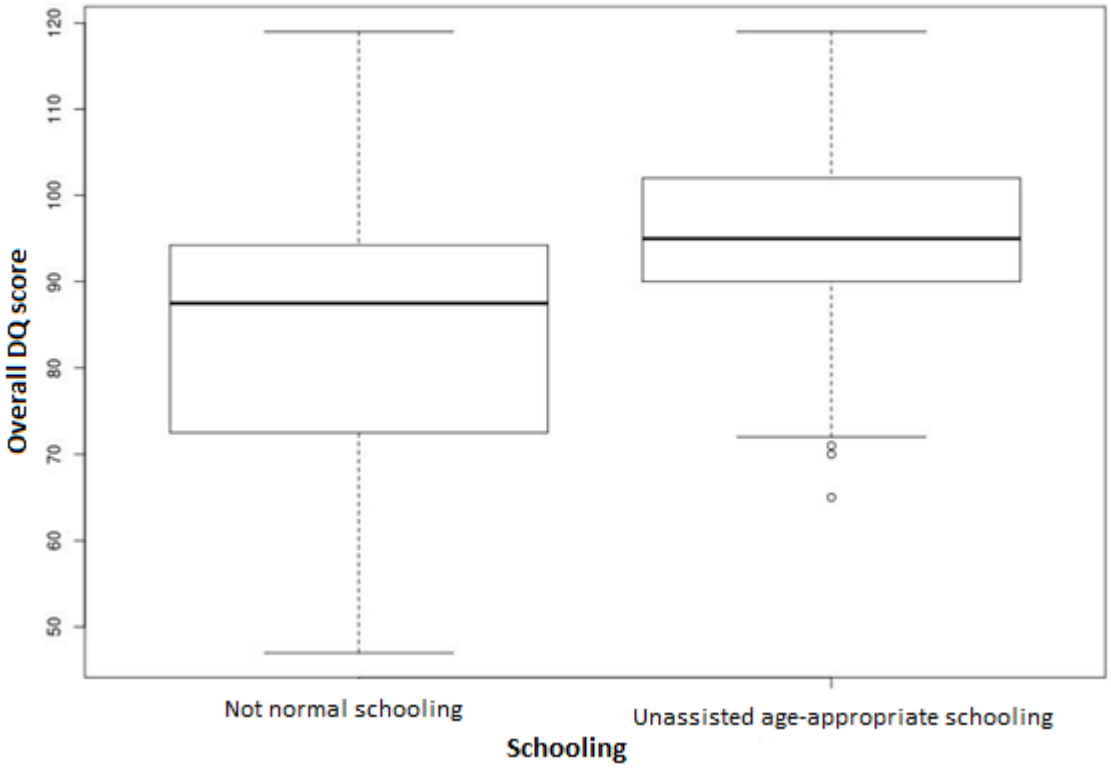
Of the 270 children studied, 20 (7.4%) had an overall DQ below 70, 32 (11.9%) had a DQ between 70 and 84, 131 (48.5%) had a DQ between 85 and 99, and 68 children (25.2%) had a DQ ≥100.

The BLR was not-scorable for 19 children (7.0%) which were excluded from the further analysis. One hundred and seventy-one children (68.1%) had age-appropriate schooling without assistance, 51 children (20.3%) had external assistance, 19 children (7.6%) had school life support, and 10 children (4.0%) had a grade retard or were attending a specific institution. There were no unschooled children.

Children with not-scorable BLR appeared to have slightly worse schooling at 5 years than children with scorable BLR : 11 (58 %) children had unassisted age appropriate schooling vs 68% and 7 (37 %) had age appropriate schooling with external assistance versus 20 %.

Among the 251 children with available DQ value, the median was 93.0 (IQ25-95 [87.0-100.0], min 47, max 119) with a mean of 91.8. The median DQ for children with unassisted normal schooling was 95.0 (IQ25-75 [90.0-102.0], min 65, max 119) with a mean of 95.6. The median DQ for other children was 87.5 (IQ25-75[72.8-94.1], min 47, max 119) with a mean of 83.7 (figure 2). The difference was statistically significant (Mann-Whitney, $p < 0.001$)

Figure 2: Comparison of BLR distributions by schooling



There was a strong correlation between schooling and overall DQ categories (p-value for trend < 0001) (table 3). Children with DQ ≥100 were significantly more likely to have unassisted normal schooling (p<0.001).

Table 3. Distribution of schooling by overall BLR groups

	DQ < 70	DQ 70-84	DQ 85-99	DQ > 100
	n = 20	n = 32	n = 132	n = 67
Unassisted age-appropriate schooling	**2 (10.0%)**	**16 (50.0%)**	**94 (71.2%)**	**59 (88.1%)**
Others	**18 (90.0%)**	**16 (50.0%)**	**38 (28.8%)**	**8 (11.9%)**
Age-appropriate schooling with external assistance	3 (15.0%)	9 (28.1%)	31 (23.5%)	8 (11.9%)
Age-appropriate schooling with help within the school (life support)	10 (50.0%)	4 (12.5%)	5 (3.8%)	0
Other (grade repetition or special establishment)	5 (25.0%)	3 (9.4%)	2 (1.5%)	0

The sub scores DQ ≥100 of the different domains were also statistically associated with unassisted age-appropriate schooling (Table 4).

Table 4. Distribution of schooling by BLR Sub-Scores > 100

	Language DQ ≥ 100	Coordination DQ ≥ 100	Posture DQ ≥ 100	Sociability DQ ≥ 100
	n = 50	n = 80	n = 104	n = 153
Unassisted age-appropriate schooling	45 (90.0%)	65 (81.3%)	83 (79.8%)	117 (76.5%)
Not normal schooling	5 (10.0%)	15 (18.8%)	21 (20.2%)	36 (23.5%)
p	0.0002	0.0017	0.0007	0.0004

The positive predictive value of a DQ ≥100 for unassisted age-appropriate schooling was 88.0%, with a sensitivity of 34.5% and a specificity of 90.0%. The language score had the best positive predictive value of 90.0%, a sensitivity of 26.3% and a specificity of 93.8%.

In univariate analysis, DQ ≥100 was statistically related to higher GA, less bronchopulmonary dysplasia, higher rate of breastfeeding, and shorter hospital stay (Table 5). There was a non-significant trend for Intra Ventricular Hemorrhage (IVH), and twin pregnancy.

In univariate analysis, unassisted appropriate-age schooling was significantly associated with higher maternal education level, higher GA, shorter length of hospital stay (Table 5). They had significantly less severe cerebral abnormalities, less IVH and less bronchopulmonary dysplasia.

Table 5. Univariate analysis of neonatal factors associated with BLR and schooling

	Overall DQ > 100			Unassisted age-appropriate schooling		
	No	Yes	p-value	No	Yes	p-value
	n = 184	n = 67		n = 80	n = 171	
Maternal age (years), median [IQ25; IQ75]	30 [27 ; 34]	30 [25 ; 33]	0.463	30 [26 ; 34]	30 [27 ; 34]	0.389
High maternal education level [a], n (%)	81 (47.4%)	36 (55.4%)	0.309	27 (37.5%)	90 (54.9%)	0.016
Multiple pregnancy, n (%)	74 (40.2%)	18 (26.8%)	0.056	23 (28.8%)	69 (40.3%)	0.092
Antenatal corticosteroids, n (%)	149 (81.0%)	57 (85.1%)	0.432	65 (83.3%)	141 (84.4%)	0.852
Gestational age (weeks), median [IQ25; IQ75]	30 [28 ; 31]	31 [30 ; 32]	0.001	30 [27 ; 31]	30 [29 ; 32]	0.013
Boy, n (%)	111 (60.3%)	32 (47.7%)	0.085	51 (63.8%)	92 (53.8%)	0.171
Small for Gestational Age [b], n (%)	26 (14.1%)	8 (11.9%)	0.835	12 (15.0%)	22 (13.0%)	0.695
Bronchopulmonary dysplasia, n (%)	73 (39.7%)	13 (19.4%)	0.002	39 (51.3%)	50 (30.0%)	0.002
Postnatal corticosteroid, n (%)	9 (4.9%)	0 (0.0%)	0.117	4 (5.3%)	5 (3.0%)	0.465
Intraventricular hemorrhage (IVH), n (%)	11 (6.0%)	0 (0.0%)	0.039	7 (8.8%)	4 (2.3%)	0.041
Severe cerebral abnormality [c], n (%)	6 (3.3%)	0 (0.0%)	0.195	4 (5.1%)	1 (0.6%)	0.037
Early Onset sepsis [d], n (%)	12 (6.4%)	8 (11.9%)	0.189	5 (6.3%)	15 (9.0%)	0.620
Breastfeeding, n (%)	116 (63.0%)	56 (83.6%)	<0.001	49 (65.3%)	123 (75.0%)	0.162
Length of hospital stay (days), median [IQ25; IQ75]	53 [30; 80]	42 [34; 52]	<0.001	59 [41; 84]	46 [37; 65]	0.006
24 months head circumference <3th percentile (cm), n (%)	5 (2.7%)	1 (1.5%)	0.999	3 (3.8%)	3 (1.8%)	0.387

Abbreviations: sd = standard deviation. Mann Whitney or Student test when appropriate.

[a] High maternal education level = university studies. [b] small for gestational age = birthweight <10[e] percentile on AUDIPOG curves. [c] severe cerebral abnormalities = presence of either an IVH of grade III and IV of the Papile classification, or periventricular leukomalacia (cystic or not). [d] early onset sepsis = isolation of bacteria or fungi from a blood or placenta culture associated with clinical and/or ongoing laboratory anomalies, occurring ≤ 72 hours of life.

Multivariate analysis was adjusted on gestational age, length of hospitalization, bronchopulmonary dysplasia, maternal education, breastfeeding, using a backward stepwise selection. Variables included were chosen has described, based on the p-value, clinical relevance and previous literature.

The association between BLR > 100 with unassisted age appropriate schooling remained significant after adjustment, as well as the presence of BPD and level maternal education (Table 6).

Table 6. Odds Ratios of univariate and multivariate analysis for schooling

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	Unassited age-appropriate schooling	p-value	**Unassited age-appropriate schooling**	p-value
Overall DQ ≥ 100				
No	1		1	
Yes	4.74 [2.14-10.50]	<0.001	3.93 [1.65-9.37]	0.002
Length of hospital stay (days), mean +/- sd	0.987 [0.978-0.996]	0.006		
Bronchopulmonary dysplasie, n (%)				
No	1		1	
Yes	0.41 [0.23-0.71]	0.002	0.46 [0.25-0.86]	0.014
Gestational age (weeks), mean +/- sd	1.20 [1.06-1.35]	0.003		
Maternal education level				
Low [a]	1		1	
High [b]	2.03 [1.15-3.58]	0.015	2.21 [1.20-4.07]	0.011
Breastfeeding				
No	1			
Yes	1.59 [0.88-2.88]	0.12		

Odd ratios.

[a] Low maternal education level = secondary school level or lower and/or professional degrees.

[b] High maternal education level = university studies.

DISCUSSION

This study confirmed the association between BLR test at age 2 and schooling at age 5, with a higher predictive value than in previous study [11]. In our population, median DQ was 91.8, which was lower than described previously [11]. This difference could be partly explained by the inclusion of all children, even those with DQ < 70.

There is few studies about BLR and schooling in literature because this test is used in France only. To our knowledge, the direct relationship between the BLR score and schooling has not been established in other studies. However, the relationship between the BLR scale and other neurodevelopmental scales used elsewhere has been studied. A previous study has found a strong correlation for language between the BLR and the Bayley III at 18-24 months ($r=0.890$; $p<0.001$) [19]. Previous study has shown a strong correlation between Bayley III score and schooling [20].

Language DQ was the sub-score with the highest positive predictive value. A previous study described the correlation of BLR at 24 months, and "Age and Stages Questionnaire" (ASQ) at 18 and 24 months, and the French test "Epreuve de repérage des troubles du langage" (ERTL) at four years old [21]. These four scales were correlated with each other regarding language development, which is an important element for good schooling [5].

In univariate analysis, perinatal factors significantly associated with normal schooling were gestational age, level of maternal education, bronchopulmonary dysplasia, presence of IVH or periventricular leukomalacia, and finally the duration of hospitalization.

Those factors are commonly found in the literature as influencing DQ, neurodevelopment and schooling [8,22–24]. Contrary to a previous study, we did not find any impact of head circumference < 3rd percentile at 2 years [11]. In univariate analysis, breastfeeding had a significant impact on DQ, as described by a previous study, but it did not have a significant influence on schooling [22].

The association between BLR and schooling remains significant, after adjustment on BPD and maternal education by logistic regression as described in previous study [11].

A total of 88.0% of the children had an age-appropriate schooling, of which 68.1% unassisted and 20.0% with an external assistance. This result is better compared to other French studies following preterm children having the same schooling practices. Larroque and Charkaluk, found 41.0% and 70.0% of children with age-appropriate schooling respectively [4,11]. This could probably be explained by the fact the analysis was done at 5 years and not 8 years old and difficulties can increase later [6]. Moreover, the study population is more recent and much progress has been made in prenatal and perinatal care in the last few decades. The average GA was 29.7SA, which was comparable with the last French study about the same subject [11]. International comparisons are more difficult because of different schooling rules. Two pieces of research confirm the overall educational difficulties, reading disorders, mathematics, attention and behavioral disorders registered in preterm children [8,10].

Diagnosed or suspected ADHD was identified in 5.5% of the study population, and 2.6% of children presented an isolated concentration deficit. These results are coherent with those announced by the French National Health Autority in 2019 (4.6-8.8% among children born under 33SA)[25]. These numbers are lower than those found in previous studies [26,27]. However, the assessment was carried out at 5 years of age in our study versus 6 to 9 years in previous studies, and some of the children with ADHD are not diagnosed until primary school (6 years old).

Regarding language development, premature infants presented poorer performance than full-term newborns [5,21,28]. Among the study population, the rate of language delay was of 27.8% at age 5, higher than the literature, ranging from 4.0% to 12.0% [21,29,30]. Evaluations were performed at different ages, with different methods, which may partially explain these differences.

Of 251 children, 57.8% did not present any disability defined by the absence of cerebral palsy, visual or auditory impairment and with a DQ > 85 on the overall BLR score. This number is close to the 59% described in the population of 29-30 weeks GA of cohort Epipage 1 [1]. A total of 53.0% of the children did not have any neurological disorder whatsoever (isolated attention deficit disorder, behavioral disorders, dyspraxia...), which underlines the fact that difficulties persist in almost half of the former preterm infants ≤ 32+6 weeks GA.

Our study was complementary to the only study that specifically investigated the correlation between BLR and schooling [11]. Our cohort was more recent by an average of 15 years, which may have an impact given the evolutions in neonatology over this period. We also chose to

include all children in the cohort, without excluding those with a DQ <70, nor children with cerebral palsy or neurosensory impairment. Finally, we compared the neonatal population followed and the lost-to-follow-up which were almost comparable.

The originality of our study was to focus on the need for external assistance such as physiotherapy, speech therapy, psychomotricity and psychologist. This type of care seemed important to be considered because it concerns 20.3% of patients and early intervention has demonstrated to improve their cognitive and school performances [31,32]. A study showed a benefit of early preventive care program at 8 years of age in mathematics [31], and another one found a benefit in motor performance [32]. It was also previously shown that these interventions also improves quality of life and decreases anxiety and depression (5% vs. 27% with standard follow-up) [31].

Our study showed some weaknesses. It was a monocentric and a retrospective study. BLR was defective (i.e not-scorable) for 19 children (7.0%), which had not been described yet. Of these 19 children, 11 had unassisted age appropriate schooling. This can be explained by unfavorable test conditions (i.e uncooperative child on the day of the test).

Moreover, 36.8% of our population was lost to follow-up at age 5. This could be explained by moving and interruptions in the follow-up. Nevertheless, our numbers and results remain comparable with the Charkaluk study [11]. The children lost to follow-up in our study had a higher weight and GA, less bronchopulmonary dysplasia and shorter hospital stays. Since these factors are usually associated with better neurodevelopment, we hope that discontinuation of follow-up for these children had fewer negative effects. However, the lost in follow-up had mothers with lower education which is associated with poorer academic

performance. This might result in less statistical power, and potential underestimation of the link between BLR and schooling.

Another limitation was that the evaluation of schooling was carried out at 5 years of age while some difficulties may appear later, for example in reading and writing [6]. We hoped that the remaining undetected children with later difficulties were limited by taking into account external aid, which is put prior to schooling disorder. Furthermore, we did not study performance in fine motor skills nor executive functions, factors that can influence schooling. Finally, schooling is different between countries, which limit possible international comparisons.

The strong correlation between an overall BLR score (DQ) ≥100 and unassisted age appropriate schooling might lead to reducing the number of consultations in the DQ ≥100 population, in favor of intensified follow-up for children with a lower BLR. This would lead to a better screening, earlier management and in long term a reduction in school difficulties among this at-risk population.

CONCLUSION

Preterm infants are at increased risk for neurodevelopmental disorders and difficulties in schooling. In the study population born ≤32+6 weeks, the overall BLR score ≥100 was well correlated with normal schooling at 5 years of age.

These results could improve the follow-up of former preterm infants by alerting the practitioner at the age of 2 years old (CA). Intensifying medical, paramedical and school follow-up for children who require it or reducing the follow-up for others, could be easier to identify. This earlier care improves cognitive development and schooling.

In addition, neonatal factors already known to be associated with lower educational achievement will remain warning signs for the doctor in charge of the child's follow-up, such as low GA, bronchopulmonary dysplasia, neurological abnormalities.

It could be interesting to confirm the link between the BLR and schooling at a later age. The language score seems to be the most predictive of schooling. It would be interesting to do a new study to confirm these results.

THÈSE SOUTENUE PAR : Laure JACQUEZ et Lauriane HATTON

TITRE :
PREMASCOL : Etude de corrélation entre test de Brunet-Lezine à 24 mois et scolarité à 5 ans, étude monocentrique chez les prématurés ≤ 32SA+6J.

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These results could improve the follow-up of former preterm infants by alerting the practitioner at the age of 2 years old (CA). Intensifying medical, paramedical and school follow-up for children who require it or reducing the follow-up for others, could be easier to identify. This earlier care improves cognitive development and schooling.
In addition, neonatal factors already known to be associated with lower educational achievement will remain warning signs for the doctor in charge of the child's follow-up, such as low GA, bronchopulmonary dysplasia, neurological abnormalities.
It could be interesting to confirm the link between the BLR and schooling at a later age. The language score seems to be the most predictive of schooling. It would be interesting to do a new study to confirm these results.

VU ET PERMIS D'IMPRIMER
Grenoble, le : 17/08/2020

LE DOYEN

Pour le Président
et par délégation
—
Le Doyen de Médecine
P. Patrice MORAND

Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE

Pr. Thierry DEBILLON

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APPENDIX

APPENDIX 1: The standardised questionnaire sent by the network to the teacher

FICHE DE RENSEIGNEMENTS A REMPLIR PAR L'ENSEIGNANT

Les renseignements fournis sont confidentiels, en accord avec les parents de l'élève. Ils ont pour but de mieux comprendre les difficultés de l'enfant. Nous vous en remercions.
NOM et prénom de l'enfant:_____Classe :
Date de naissance : _ _ / _ _ / _ _ _ _ Age : _____
NOM et prénom de l'enseignant(e) : _____
Ecole (adresse complète et coordonnées téléphoniques) : _____
Questionnaire rempli le : _ _ / _ _ / _ _ _ _
□ Port de lunettes en classe

_____

Appréciation du niveau de l'enfant par rapport à la classe :

Scolarité actuelle :
Rencontre-t-il des problèmes ? _____
Fréquente-t-il régulièrement l'école ? oui ☐ non ☐ en cas de non, pourquoi ?

Général :

- Graphisme :
- Coordination gestuelle / utilisation des outils (ciseaux …) :
- Attention :
- Mémorisation :
- Motricité :
- Comportement (opposition, agité, agressivité, anxiété …) :
  - En classe :
  - Avec les autres enfants :
  - Avec les adultes de l'école :

Langage oral :

- Qualité de l'expression, richesse du vocabulaire, syntaxe :
- Déformation des mots (donner des exemples) :
- Compréhension des consignes :

Langage écrit :

Mathématiques :

Remarques, commentaires :
Pensez-vous nécessaire que cet enfant bénéficie de bilan complémentaire pour cerner ses troubles ou difficultés ?

Si oui, de quel type ?

APPENDIX 2: The standardised questionnaire sent to the paramedical nursing staff (speech therapy/physiotherapy/psychologist...)

FICHE DE RENSEIGNEMENTS

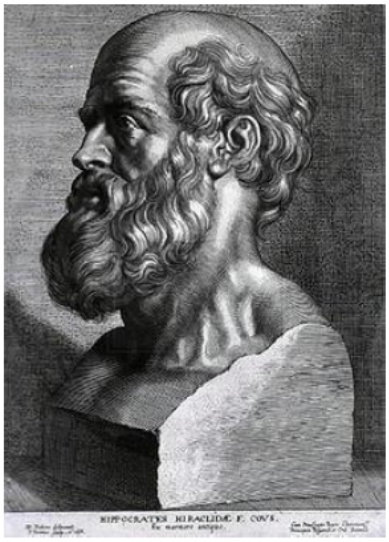
A REMPLIR PAR L'ERGOTHERAPEUTE, LA NEURO-PSYCHOLOGUE, L'ORTHOPHONISTE OU LA PSYCHOMOTRICIENNE

Les renseignements fournis sont confidentiels. Ils ont pour but de mieux comprendre les difficultés de l'enfant. Nous vous en remercions.

NOM et prénom du professionnel qui suit l'enfant : _____
Fonction exercée :
Téléphone : E-mail :
Adresse : _____
NOM et prénom de l'enfant : _____ Date de naissance : _ _ / _ _ / _ _ _ _
Questionnaire rempli le : _ _ / _ _ / _ _ _ _
Diagnostic : …….....
……...
Depuis quand suivez-vous cet enfant ? …….....
……...
Combien de fois par semaine ? ……
……...
Rencontrez-vous des difficultés dans la rééducation ? …….....
……...
Quels sont les domaines abordés en rééducation ? …….....
……...
Quels sont les matériels et techniques utilisés ? …….....
……...
Quelle appréciation donneriez-vous sur l'évolution de l'enfant ? ……...
……...

Remarques, commentaires :

SERMENT D'HIPPOCRATE



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

PREMASCOL : CORRELATION BETWEEN BRUNET-LEZINE TEST AT AGE 2 AND SCHOOLING AT AGE 5 IN PRETERM CHILDREN < 33 WEEKS

Laure JACQUEZ [Données à caractère personnel]
Lauriane HATTON [Données à caractère personnel]

Thèse soutenue à la faculté de Grenoble le 15/09/2020

Jury :
Monsieur le Professeur Thierry DEBILLON (Président)
Madame le Docteur Maya GEBUS
Monsieur le Docteur Guillaume MORTAMET
Monsieur le Professeur Dominique PLANTAZ

ASTRACT

Aim: To study the correlation between the Brunet-Lezine test at age 2 and schooling at age 5, in premature infants born ≤32+6 weeks. To study the neurological outcome of this population.

Methods: In 270 children born ≤32+6 weeks between 01.2010 and 01.2014 and included in the local health network "Naitre et Devenir" , the Brunet-Lezine Revise test (BLR) was performed at age 2 and evaluation of schooling assessed at age 5. BLR test covers 4 domains and results are expressed as a standardized coefficient according to the normal population. Unassisted age appropriate schooling was defined as being in the appropriate classroom without any assistance or health interventions, in or outside school.

Results: BLR test was interpretable in 251 children and median BLR score was 93.0. A total of 171/251 children (68%) had unassisted age-appropriate schooling. The correlation between a BLR score ≥100 and unassisted age appropriate schooling was highly significant (p<0.0001), with a positive predictive value of 88%. The association between BLR DQ and schooling remained significant after adjustment on maternal education, bronchopulmonary dysplasia, and BLR. In the study population, 156/270 (58%) had no neurological, sensory or neurodevelopmental disorders. The most common disorders were language impairment (28%), visual impairment (28%), and dysgraphia (17%).

Conclusion: The Brunet-Lezine test at 2 years is feasible and has good predictive property for child's schooling at 5 years. It seems therefore possible to lighten the follow-up of children presenting a BLR ≥100 for the benefit of other children.

RESUME

But : Etudier la corrélation entre le test de Brunet-Lézine à 2 ans avec la scolarité à 5 ans chez les prématurés nés ≤32+6 SA. Etudier le devenir neurologique de cette population.

Méthodes : Deux-cent soixante-dix enfants nés ≤32SA+6J entre 01.2010 et 01.2014, suivis dans le réseau « Naitre et Devenir » ; ont bénéficié d'un test de Brunet-Lézine Révisé (BLR) à l'âge de 2 ans et d'une évaluation de la scolarité à 5 ans. Deux-cent cinquante et un enfants présentaient un résultat interprétable au test du BLR. La scolarité à 5 ans était définie comme appropriée quand l'enfant était dans sa classe d'âge sans aucune aide à l'extérieure ni à l'école.

Résultats : Un total de 171/251 enfants (68%) avaient une scolarité appropriée pour l'âge. La corrélation entre un BLR ≥100 et une scolarité appropriée était très significative (p<0.0001), avec une valeur prédictive de 88%. En analyse multivariée, les facteurs influençant la scolarité étaient le niveau d'étude maternel, la dysplasie broncho-pulmonaire et le BLR. Le lien entre BLR et scolarité restait très significatif après ajustement sur les autres facteurs. Cent-cinquante-six enfants (58%) ne présentaient aucun trouble neurologique, sensoriel ou neurodéveloppemental. Les troubles les plus fréquents étaient les troubles du langage (28%), le déficit visuel (28%), et la dysgraphie (17%).

Conclusion : Le test de Brunet-Lézine est un bon marqueur prédictif de la scolarité de l'enfant. Il nous semble donc envisageable d'alléger le suivi des enfants présentant un BLR ≥100 au profit des autres enfants.

MOTS CLES : prématurité, Neuro-développement, Brunet-Lézine, scolarité