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LONG TERM NEURODEVELOPMENTAL OUTCOME IN A COHORT OF PRETERM INFANTS BORN AT GESTATIONAL AGE <32 WEEKS

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Abstract. Advances in perinatal care have led to an increase in survival of preterm children but have also increased the risk of long-term sequelae, like neurodevelopmental impairment and behavioral or emotional disturbance. To investigate neurodevelopmental patterns of preterm infants born at S. Maria alle Scotte Hospital, Siena, Italy. 128 babies with gestational age (GA) ≤32 weeks were admitted in 2006-2008 to Siena Hospital; 105 infants survived and were followed until three years of age, corrected for prematurity. Neurodevelopmental follow up was performed using Bayley scale of Infant and Toddler Development IIIed that consisted of five scales: Cognitive (CS), Language (LS), Motor (MS), Social-Emotional (SES) and Adaptive Behavior Scale (ABS). Intraventricular haemorrhage (IVH) was associated with lower motor score (P<0,001). Babies with retinopathy of prematurity (ROP) showed a lower score in CS, LS, MS and SES Bayley's items (respectively p≤0,01; p≤0,05; p≤0,01; p≤0,05). Multiple regression analysis indicated as predictors of neurological outcome: gestational age (GA) for poor cognitive (p=0,016), language (p=0,004) and social-emotional development (p<0,0001), IVH for poor motor (p<0,0001) and adaptive behavior development (p<0,0001), twinship for better language (p=0,001) and social-emotional development (p=0,003). Bronchopulmoanry dyspasia (BPD) and patent ductus arteriosus (PDA) had a negative effect on respectively cognitive development (p=0,049) and social-emotional development (p=0,023). ROP, BPD, IVH, PDA, and GA significantly contributes to poor neurological outcome in preterm infants. BPD and IVH are the best predictors being associated with the lowest scores at Bayley scales. Surprisingly, twinship appeared to be a protective factor.

Key words: newborn infant, perinatal outcome, developmental, Bayley Scale.

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Abbreviations: GA, gestational age; BW, birth-weight; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; RDS, neonatal respiratory distress syndrome; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus, VLBW, very low birth weight.

INTRODUCTION

Advances in perinatal care have led to an increase in the survival rates of very low birth weight (VLBW) newborns but have also increased the risk of long-term sequelae, such as neurodevelopmental impairment and behavioral or emotional disturbance[1]. Of concern remains the relatively high proportion of VLBW infants surviving with significant problems in language, cognitive and motor skills that persist throughout childhood, needing special education placement [2,3,4]. The prevalence of disability in preterm mades important to assess neurodevelpmental at a later age, when the degree of disability can be more clearly defined and is more likely to be predictive of problems that will continue throughout childhood and into later life. Standardized developmental assessment is ideally suited to the identification, quantification, and monitoring of children with developmental difficulties [5]. The Bayley Scales of Infant Development-III^{ed} (BSID-III^{ed}) are the most frequently used for the determination and quantification of progress of high-risk infants [6,7]. The aim of the present study was to investigate neurodevelopmental outcomes at 3 years in a cohort of preterm infants born at gestational age (GA) ≤32 weeks by using the BSID-III^{ed}.

METHODS

This study included all premature infants with a ges-

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tational ages between 23 $^{0/7}$ and 31$^{6/7}$ weeks born in the Department of Paediatrics Obstetrics and Reproductive Medicine of the Hospital "S. Maria alle Scotte" of Siena, Italy, between April 1, 2006 and February 29, 2008, who were admitted to the NICU. Newborns with major congenital malformations, inborn errors of metabolism, incompatibility group, severe sensory impairment or with severe neuromotor deficiency, with blindness or deafness were excluded from the study. The final 3-year cohort comprised 128 children. Of these, 23 died soon after birth, 8 were lost to follow-up; 9 were excluded because severely impaired. Of the remaining 88 children, 3 could not be traced or had moved abroad, the parents of 5 children declined to participate, and there were no BSID-III^{ed} data available for 7 children due to follow-up elsewhere. The population studied had postmenstrual age 28^{+5} weeks mean (range 23^{+0} – 32^{+0}) birth-weight (BW) 1169 g mean (range 530-2310 g). Perinatal characteristics of children were recorded through patient's summary clinical chart with the objective to identify the presence of prematurity complication. We assessed the presence of IVH, BPD, PVL, ROP and PDA. After discharge, children were included in a follow-up program for an early identification of neurodevelopmental impairment.

Brain ultrasonography was performed in all intensive care units within 48 h after birth with real-time ultrasound machine with transducer frequency emission of 7.5 mHz in all preterm newborns. The scans were repeated serially at 5 or 6 day intervals until a mean postmenstrual age of 40 weeks to check for IVH. The occurrence of IVH was diagnosed according to Volpe's classification [8]. PLV was diagnosed by persistent diffuse periventricular hyperechogenicity for more than 7 days, or by periventricular cysts. BPD was defined, as an oxygen requirement and the presence of radiographic abnormalities at 36 weeks postmenstrual age [9]. All children were screened for ROP. Ophthalmologists were skilled in the identification of ROP including location and staging as described in the International Classification of Retinopathy of Prematurity revisited [10]. PDA was diagnosed echocardiographically: a left atrium–to–aortic root diameter ratio of 1.4 in the parasternal long-axis view, a DA diameter of 1.4 mm/kg body weight, left ventricular enlargement, and holodiastolic flow reversal in the descending aorta indicated a significant PDA shunt [11].

After discharge, neurodevelopmental examination was routinely performed by experienced developmental pediatricians at 36 months' corrected age at the neonatal follow-up center. Age was corrected for preterm birth to be consistent with assessments of earlier cohorts and to avoid bias in the cognitive test scores [12]. Children with severe sensory impairment or with severe neuromotor deficiency were excluded because they were unable to complete the test. Neurodevelopment was assessed using the The Bayley Scale of Infant and Toddler Development-Third Edition (BSID-III^{ed}).

BSID-III^{ed} is an individually administered examination assessing the developmental function of infants from 1 month to 4 year of age. It was developed by Bayley in 1969, revised in 1993 (BSID-II^{ed}) and in the 2006 (BSID-III^{ed}). The BSID-III^{ed} consists of five scales: the Language Scale (LS), the Cognitive Scale (CS), the Motor Scale (MS), the Social-Emotional Scale (SES) and the Adaptive Behavior Scale (ABS). The LS is formed by two subtest: Receptive and Expressive Communication, because these two language's aspects require different abilities and can develop independently. Similarly, the MS includes the subtest: Gross Motor and Fine Motor [6,7]. The five scales have a standardization mean of 100 and standard deviation of 15 points. Development was considered severely impaired if the scores were less than 55, moderately impaired if they were 55 to 69, and mildly impaired if they were 70 to 84. Scores over 100 indicated advanced development for age. We used the U.S standardization norms (bayley), with a mean of 100 and standard deviation of 15.

The data were analyzed with the SPSS software for Windows. The results obtained from 5 Bayley Scales were compared in relation to the risk factors, using the the non-parametric test of Kruskall-Wallis, with Bonferroni correction for the multiple comparisons. All statistical tests were two tailed with significance level α=0,05. Multiple regression (method: Stepwise) was used to compare the results of Bayley Scales and to highlight possible and best predictors of neurodevelopmental impairment.

RESULTS

The characteristics of study population are described in Table 1. Table 2 reports frequency and differences of mean Bayley Scales score in relation to characteristics of preterm babies.

Cognitive scale

The cognitive score average over the whole sample was 95,7 (SD=7,3). Statistically significant differences were found between children of GA ≤ or >28 weeks; the latter reported a score of 4,8 points higher than the first (p ≤0,01); also the birth weight and the type of pregnancy can determine different outcomes: children whose birth weight was ≤1000g had a score of 5,2 points lower than those whose birth weight was >1500 g (p ≤0,05) and babies born from multiple pregnancies had a score of 5,1 points higher than that of children born from single pregnancy (p ≤0,05). Children with 3rd-4th grade IVH obtained a score of 10,9 points lower than those without IVH (p ≤0,01); children with BPD reported a score of 8 points lower than children without BPD (p ≤0,01) and children with ROP obtained a score of 5,5 points lower than those without ROP (p ≤0,01).

In relation to the variables presence/absence of PDA,

PVL and IUGR statistically significant difference was not observed (Figure 1).

Males scores were higher than females (points=1,3 but the difference between the two groups was not statistically significant.

Lauguage scale

The language score average over the whole sample was 97 (SD=9). Statistically significant differences were observed in relation to GA and type of pregnancy: children of GA ≤28 weeks reported a score of 4,5 points lower than children of GA >28 weeks (p ≤0,01) and babies born from multiple pregnancies had a score of 8,7 points higher than that of children born from single pregnancy (p ≤0,01).

Even for language scale IVH, BPD and ROP resulted associated with a worse outcome: children with IVH grade 3 or 4 obtained a score of 9,7 points lower than those without IVH (p ≤0,01). children with BPD reported a score of 8 points lower than children without BPD (p ≤0,01); and children with ROP obtained a score of 4,4 points lower than those without ROP (p ≤0,05).

Table 1. General characteristics of the study subjects

Male	52,3%	(n=34)
Female	47,7%	(n=31)
Multiple pregnancy	26,2%	(n=17 twins)
Single pregnancy	73,8%	(n=48)
GA ≤26 weeks	21%	(n=14)
27 weeks ≤GA ≤29 weeks	35,4%	(n=23)
30 weeks ≤GA ≤32 weeks	43,1%	(n=28)
Birth-weight ≤1000 g	43,1%	(n=28)
1000 g <Birth-weight ≤1500 g	33,8%	(n=22)
Birth-weight >1500 g	23,1%	(n=15)
IUGR	14%	(n=9)
PVL	9%	(n=6)
ROP	22%	(n=14)
BPD	17%	(n=11)
PDA	62%	(n=40)
IVH	28%	(n=18)
- 1st grade	3,1%	(n=2)
- 2nd grade	13,9%	(n=9)
- 3rd grade	1,5%	(n=1)
- 4th grade	9,2%	(n=6)

Motor scale

The motor score average over the whole sample was 97 (SD=9).

Children of GA ≤28 weeks reported a score of 4,6 points lower than children of GA >28 weeks p ≤0,01). Babies from multiple pregnancies showed score of 5,1 points higher than children from single pregnancy p ≤0,05). Children with IVH grade 3 or 4 obtained a score of 13,4 points lower than those without IVH p ≤0,001). Children with BPD reported a score of 7,9 points lower than children without BPD p ≤0,01). Children with ROP have obtained a score of 6,4 points lower than those without ROP, p ≤0,01).

Social-emotional scale

The social-emotional score average over the whole sample was 96 (SD=10). Significant differences were found in relation to GA: (GA ≤28 weeks *vs* GA >28 weeks, score of 6,2 points lower in the first, p ≤0,001); BW (BW ≤1000g *vs* BW >1500 g (score 4,4 points lower in the first, p ≤0,05); type of pregnancy (multiple pregnancies *vs* single pregnancy, score of 7,1 points higher in the first, p ≤0,01); IVH (IVH 3-4 *vs* no IVH, score of 13,2 points lower in the first, p ≤0,001); BPD (BPD *vs* no BPD, score of 11,2 points lower in the first, p ≤0,001); ROP (ROP *vs* no ROP: score of 5,2 points lower in the first p ≤0,05).

Adaptive behavior scale

The adaptative behavior score average over the whole sample was 96 (SD=9). Significant differences were found in relation to: GA (GA ≤28 weeks *vs* GA >28 weeks, score of 5,4 points lower in the first, p ≤0,01); BW: (BW≤1000g *vs* BW >1500 g, score of 7,1 points lower in the first, p ≤0,05); type of pregnancy (multiple pregnancies *vs* single pregnancy, score of 5,3 points higher in the first, p ≤0,01); IVH (IVH 3-4 *vs* no IVH, score of 11

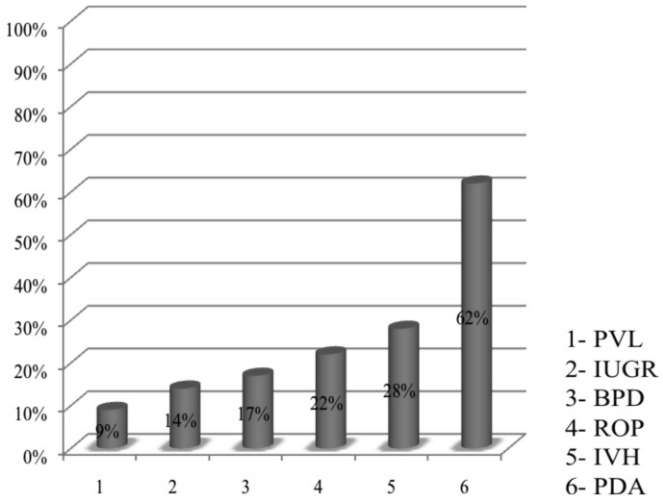

Figure 1. Neonatal morbidity

points lower in the first, p ≤0,001); BPD (BPD *vs* no BPD, score of 8,9 points lower in the first, p ≤0,001).

Language outcome, motor outcome, social-emotional outcome, and adaptive behavior outcome, males scores resulted higher than females but the difference between the two groups was not statistically significant.

Multiple regression analysis

The multiple regression analysis was constructed with stepwise method to find, among the risk factors, the best predictors to describe each outcome of Bayley Scales (Table 3). It showed that: cognitive development is influenced by GA (for each additional week the score increases by 0,91 points) and significance BPD (BPD decreases the score of 4,91 points) with statistically significative difference (p=0,016 and p=0,049 respectively). Language development is influenced by GA (for each additional week the score increases of 1.13 points) and multiple pregnancy (twinship increases the score of 7.7 points) with statistically significative difference (p=0,004 and p=0,001 respectively). The presence of IVH of any grade decreases the score of 10,43 points (p <0,0001). GA for each additional week increases the motor development score of 1,56 points (p <0,0001); twinship increases the score of 6,56 points (p=0,003); PDA decreases the score of 4,63 points (p=0,023). The presence of IVH of any grade decreases the Adaptative Behavior score of 9,06 points (p <0,0001).

Table 2. Frequency and differences of mean Bayley Scales score in relation to characteristics of preterm babies.

Charateristics of preterm (SD)	N° of preterm in means	CS Mean (SD)	CS Difference in means	LS Mean (SD)	LS Difference in means	MS Mean (SD)	MS Difference in means	SES Mean (SD)	SES Difference in means	ABS Mean (SD)	ABS Difference in means
Sex											
-male	34	96,3 (6,4)	1,3	97,0 (7,4)	0,70	97,0 (8,9)	1,00	95,9 (9,1)	-0,70	96,5 (9,3)	2,00
-female▽	31	95,0 (8,2)	–	96,3 (10,7)	–	96,0 (8,7)	–	96,6 (10,1)	–	94,5 (8,9)	–
GA (weeks)											
- <28	30	93,1 (8,0)#	-4,8	94,2 (8,7)#	-4,50	94,1 (10,0)#	-4,60	92,9 (11,4)♦	-6,20	92,7 (9,2)#	-5,40
- >28▽	35	97,9 (6,1)	–	98,7 (9,0)	–	98,6 (7,1)	–	99,1 (6,2)	–	98,1 (8,6)	–
Birth-weight (g)											
- <1000	28	93,8 (8,1)δ	-5,2	95,1 (8,8)	-4,60	95,1 (9,7)	-4,10	93,6 (11,1)δ	-4,40	92,3 (8,6)δ	-7,10
-1000<g>1500	22	96,0 (7,0)	-3	96,4 (11,0)	-3,30	96,3 (7,8)	-2,90	96,6 (8,3)	-4,10	97,0 (8,0)	-2,40
- >1500▽	15	99,0 (5,0)	–	99,7 (5,5)	–	99,2 (8,0)	–	100,7 (5,7)	–	99,4 (10,1)	–
Pregnancy											
- multiple	17	99,4 (5,9)δ	5,1	103,0 (10,7)#	8,70	100,2 (8,7)δ	5,10	101,4 (8,2)#	7,10	99,4 (5,7)#	5,30
- single▽	48	94,3 (7,4)	–	94,3 (7,3)	–	95,1 (8,5)	–	94,3 (9,2)	–	94,1 (9,9)	–
IVH											
- grade 3-4	7	86,4 (8,0)#	-10,9	88,6 (8,1)δ	-9,70	85,9 (6,2)♦	-13,40	85,7 (6,1)♦	-13,20	87,1 (7,3)♦	-11,00
- grade 1-2	11	94,6 (4,7)	-2,7	94,7 (3,6)	-3,60	91,0 (7,7)	-8,30	91,9 (7,8)	-7,00	89,8 (6,3)	-8,30
- no▽	47	97,3 (6,7)	–	98,3 (9,4)	–	99,3 (7,5)	–	98,9 (8,9)	–	98,1 (8,8)	–
BPD											
- yes	11	89,0 (7,4)#	-8	90,0 (6,4)#	-8,00	90,0 (8,7)#	-7,90	86,9 (10,8)♦	-11,2	88,1 (10,4)♦	-8,90
- no▽	54	97,0 (6,6)	–	98,0 (9,0)	–	97,9 (8,2)	–	98,1 (8,0)	–	97,0 (8,3)	–
PDA											
- yes	40	94,8 (7,8)	-2,4	95,8 (9,7)	-2,20	95,1 (8,3)	-3,60	94,2 (9,6)	-5,20	93,8 (8,0)	-4,80
- no▽	25	97,2 (6,3)	–	98,0 (8,0)	–	98,7 (9,2)	–	99,4 (8,5)	–	98,6 (10,4)	–
IUGR											
- yes	9	96,1 (6,0)	0,4	95,2 (6,8)	-1,70	95,3 (7,6)	-1,40	96,0 (5,9)	-0,20	94,2 (4,9)	-1,60
- no▽	56	95,7 (7,6)	–	96,9 (9,4)	–	96,7 (8,9)	–	96,2 (10,0)	–	95,8 (9,8)	–
PVL											
- yes	6	94,2 (4,9)	-1,7	94,1 (4,0)	-2,90	91,0 (6,9)	-6,00	91,7 (7,5)	-5,00	92,7 (5,7)	-3,20
- no▽	59	95,9 (7,6)	–	97,0 (9,4)	–	97,0 (8,8)	–	96,7 (9,6)	–	95,9 (9,5)	–
ROP											
- yes	14	91,4 (9,7)#	-5,5	93,2 (9,7)δ	-4,40	91,5 (10,4)#	-6,40	92,1 (11,8)δ	-5,20	91,1 (10,1)	-5,70
- no▽	51	96,9 (6,2)	–	97,6 (8,7)	–	97,9 (7,8)	–	97,3 (8,6)	–	96,8 (8,7)	–

▽Reference category; δKruskall Wallis Test, p<0,05; #Kruskall Wallis Test, p≤0,01; ♦Kruskall Wallis Test, p≤0,001.
In BOLD differences statistically significant (Bonferroni correction for multiple comparisons) for birth-weight and IVH variables.

Table 3. Summary of Multiple Regression* Analyses for predictors of Bayley Scales Score.

	OUTCOME variables				
PREDICTORS	**CS**	**LS**	**MS**	**SES**	**ABS**
	R^2=0,27	**R^2=0,24**	**R^2=0,28**	**R^2=0,34**	**R^2=0,30**
	b (CI 95%)	**b (CI 95%)**	**b (CI 95%)**	**b (CI 95%)**	**b (CI 95%)**
GA (weeks)	1,31 (0,68;1,94) p value <0,0001	1,10 (0,27;1,86) p value 0,009		1,53 (0,73;2,33) p value<0,0001	
BIRTH-WEIGHT (g)					
SEX (male/female)					
PREGNANCY (multiple/single)	3,82 (0,23;7,41) p value 0,037	7,64 (3,12;12,16) p value 0,001		6,58 (2,10;11,10) p value 0,005	
IVH**			-10,39 (-14,51;-6,26) p value<0,0001		-9,47 (-14,10;-4,90) p value<0,0001
BPD**	p value=0,049				
PDA**				-4,33(-8,49;-0,18) p value 0,041	

*Method:stepwise; **dicothomous (yes/no) variables.

DISCUSSION

In this study we intended to ascertain the long-term effects of prematurity by means of a follow-up program from discharge to the end of developmental age with the aim not to miss subject with "minimal brain damage". The results showed very encouraging results compared to those presented in literature [13-17].

The majority of children reported, for each scale, a score between 85 and 114, indicating a performance within normal limits. Scores slightly below normal (between 70 and 84, as -1 SD) were achieved in 4 children for cognitive scale, 6 children for language scale, 5 children for motor scale, 7 children for social-emotional scale and 6 children for adaptive behavior scale. No child reported a moderate or severe delay in the acquisition of developmental milestones. This suggests that institutional protocols, such as a strict control of oxygen in delivery room, if applied correctly, can significantly reduce neonatal diseases.

The lack of difference of language, motor, social-emotional and adaptive behavior outcome between males and females is in contrast with literature's data [18,19]. The differences observed in all 5 scales between children of GA<28 weeks and GA>28 weeks, confirm that the first are at increased risk of long-term sequelae and therefore require more attention, not only during hospitalization period but also during childhood [14,15,20]. Besides, the differences between the three BW categories analyzed are slighter evident, demonstrating that GA is the variable that best describes the degree of maturity [21-23]. Interestingly, twins and triplets of our population obtained higher scores in all scales, especially in language and social-emotional scales. This could be completely random or reflect greater attention from the parents of the twins in the care of their children and, perhaps, a higher social-economic level. The data reported in the literature about twins outcome are discordant [24,25]. BPD and IVH were associated with low score in all the scales. Especially IVH (3rd and 4th grade) determined a significant decrease in the motor scale score (–13,4 points). ROP decreased equally all outcomes examined but less than the diseases mentioned above. Multiple regression models confirmed that the best predictors of neurological outcome are GA for poor cognitive, language and social-emotional development, IVH for poor motor and adaptive behavior development, and twinship for better language and social-emotional development. Moreover, BPD and PDA had a negative effect on cognitive and social-emotional development.

In conclusions, the data analysis allowed identification of a set of predictors useful to identify children at high risk of worst neurological outcome. The results underlines the importance of follow-up programs to monitor children at risk of neurological damage and to early identify those who need special attention. An appropriate follow-up is important to plan interventions improving long-term cognitive and behavioral outcome [26].

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