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RESEARCH ARTICLE

Neurodevelopmental Outcome at 3 Years of Age in Very Low Birth Weight Infants According to Brain Development and Lesions

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Abstract: ***Background*:** During the last decades, severe brain lesions affecting very low birth weight (<1500 gr, VLBW) infants were gradually substituted by milder lesions with debatable prognoses.

***Objective*:** The objective of this study is to define type, frequency and 3 years of neurodevelopmental outcome of prematurity-related brain lesions in a modern cohort of VLBW infants.

***Methods*:** VLBW infants admitted to our NICU in 5 years period with brain MRI at term-equivalent age were included. MRI scans were reviewed to identify and grade white matter lesions (WML), intraventricular hemorrhage (IVH), and cerebellar hemorrhage (CBH). Linear measurements of brain size, biparietal width (BPW) and trans-cerebellar diameter (TCD) were carried out. Total maturation score (TMS) was calculated. Developmental Coefficients (DQ) on Griffiths Scale at 3 years of age were compared between patients with different types and grades of lesions and patients without lesions; possible correlations between linear brain measurements, brain maturation and outcome were explored.

***Results*:** Study included 407 patients. Of them, 187 (46%) had at least one brain lesion on MRI, while 37 (9%) had severe lesions. The most frequent lesion was IVH (28%), followed by WML (21%) and CBH (17%). Mild and severe IVH, moderate and severe WML and all grades of CBH were related to worst outcome at 3 years. In patients without lesions, small BPW and small TCD were associated with worse outcomes. No correlations were observed between TMS and outcome.

***Conclusion*:** We have observed that even mild brain lesions have a negative influence on neurological outcome at 3 years of age.

Keywords: Very low birth weight infants, preterm infants, neurodevelopmental outcome, white matter lesions, intraventricular hemorrhage, cerebellar hemorrhage, brain growth, total maturation score.

1. INTRODUCTION

Preterm birth affects around 10% of newborns, exposing them to higher risk of short- and long-term complications [1]. Very low birth weight infants (VLBW, birth weight <1500 gr) are the most fragile part of this population: notwithstanding progressive and constant rise in the quality of perinatal care and higher survival rates, frequency of adverse long-term neurodevelopmental outcomes in this population remained almost unchanged [2]. Both presence of overt brain lesions and more subtle developmental disturbances connected with preterm birth seem to contribute to these alterations [3].

In recent years the significant reduction of severe brain lesions, such as cystic periventricular leukomalacia (cPVL) or periventricular hemorrhagic infarction (PVHI), has been accompanied by the growing incidence of more subtle alterations. Brain magnetic resonance imaging (MRI) has become gold-standard for the visualization of brain lesions connected

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with prematurity [4], especially the ones that can hardly be diagnosed with brain ultrasound, as mild germinal matrix hemorrhage - intraventricular hemorrhage (GMH-IVH), small cerebellar hemorrhages (CBH) or punctate white matter lesions (PWML) [5-7]. Furthermore, brain MRI allows to carry out in a simple and reproducible manner linear measurements of different brain structures that correlate with brain growth and are potentially important for long-term outcomes [8, 9]. Finally, brain MRI performed at term-equivalent age in preterm infants can be used to evaluate the level of brain maturation both in infants with and without brain lesions [10, 11], but the potential importance of this parameter to the long-term follow-up is largely unknown.

Different classifications of prematurity-related brain lesions have been proposed in the literature: some of them are based entirely on cranial ultrasound, some require both MRI and ultrasound data (for example, to diagnose ventricular dilatation after GMH-IVH), and most studies lack routine usage of susceptibility-weighted imaging [9, 12-14].

Susceptibility-weighted imaging (SWI), a recently developed MRI sequence highly sensitive to hemosiderin deposits, can be useful for the diagnosis of hemorrhagic prematurity-related brain lesions (GMH-IVH and CBH), detecting even minor hemorrhages weeks after the insult [5, 6]. The use of SWI sequence in the assessment of outcome can be important, as the prognostic significance of mild GMH-IVH (corresponding to grades I and II of widely used Papile classification [12]) is still a matter of debate in the literature, and the precise definition of preterm groups can help to obtain solid results [15-18]. The same is true for CBH: while severe lesions easily diagnosed with brain ultrasound are often connected with negative neurodevelopmental outcome, there is no consensus in the literature about prognostic significance of milder lesions that are often diagnosed only on MRI [19-23].

PWML, a subtle form of white matter damage, presents an uncertain prognosis as well. In some cases, the follow-up of the patients is completely normal, while in other cases, neurodevelopmental alterations of various entity with both motor and cognitive components have been described [24-27]. Recent works stress the connection between the frontal localization of PWMLs and negative cognitive outcome [28, 29]. SWI sequence can detect hemorrhagic PWMLs (visible as punctate areas of decreased signal, SWI+), distinguishing them from lesions without hemosiderin (not visible, SWI-) [30, 31]. In previous studies, we have found evidence regarding the diversified clinical risk factors and different anatomical characteristics of SWI+ and SWI- PWMLs, suggesting that these two lesions could represent different nosological entities [32, 33]. We have therefore hypothesized that SWI+ PWMLs could have different neurodevelopmental consequences than SWI- PWMLs, and more specifically would not present worse outcome even when situated in the frontal part of the brain.

The aim of this study was to define the type and frequency of prematurity-related brain lesions in a modern cohort of VLBW infants using standardized MRI-based classification, evaluate brain growth and maturation parameters and describe their influence on neurological follow-up at 3 years of age.

2. MATERIALS AND METHODS

2.1. Study Population

For the present study, all VLBW infants consecutively admitted to our NICU between January 2012 and September 2017 were retrospectively identified. Patients who had undergone brain MRI at term-equivalent age (TEA, between 37^{+0} and 41^{+6} weeks post-menstrual age) as a part of a routine screening program were selected and included in the study. In our department, brain MRI at TEA is a part of the neuroradiological screening protocol applied to all VLBW infants, as this population is known to be at high risk of brain lesions and adverse neurodevelopmental outcomes. Nevertheless, not all VLBW infants perform MRI for clinical (*e.g.* persistent clinical instability or death) or logistic (early transferal to other hospital or absence of parental consent) reasons: these patients were not included. Patients with known genetic syndromes or brain malformations were excluded from the study. The clinical data of the enrolled patients, including multiple gestations, intrauterine growth retardation, antenatal steroid course, type of delivery, birth weight, gestational age, gender, Apgar score at 5 minutes, need for intubation, presence of late onset sepsis (LOS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and of patent ductus arteriosus requiring treatment (PDA) were retrieved from clinical charts and department electronic database. This retrospective study was approved by the local ethics committee.

2.2. MRI Acquisition

MRI scans were performed at term-equivalent age during spontaneous sleep using the “feed and wrap” technique [34]. The need for sedation (oral midazolam, 0.1 mg/kg) to prevent head motion was agreed upon with the neuroradiologist based on the quality of images after the first sequence and the infant's state of arousal. Hearing protection was used in all patients, and heart rate and oxygen saturation were monitored noninvasively throughout the examination. MR imaging was performed on a 1.5 T MR scanner (InteraAchieva 2.6; Philips, Best, The Netherlands) using a dedicated pediatric head/spine coil. Our institutional standard MRI protocol included diffusion weighted imaging, 3 mm thick axial T2-weighted and T1-weighted images, coronal T2-weighted images, sagittal T1-weighted images and axial SWI. Informed consent that included statements about the significance and limitations of MRI at TEA was obtained in all cases.

2.3. Image Analysis

MRI scans of included subjects were independently reviewed by two neuroradiologists experienced in neonatal neuroimaging (performing more than 200 neonatal brain MRI per year, MS and DT) blinded to the clinical history of the patients, and the cases of disagreement were resolved by consensus. Prematurity-related brain lesions were classified as follows:

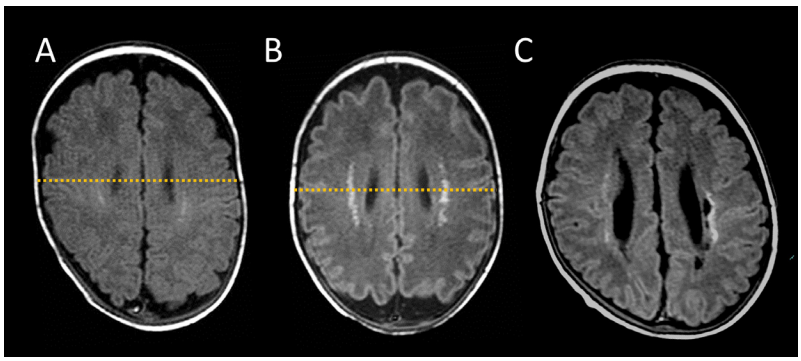

Fig. (1). Three grades of white matter lesions as seen on axial T1 sequences at term-equivalent age. **A**: Mild WML, punctate lesions situated only posteriorly to the midventricle line; **B**: Moderate WML, presence of punctate lesions situated anteriorly to the midventricle line; **C**: Severe WML, cystic periventricular leukomalacia. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

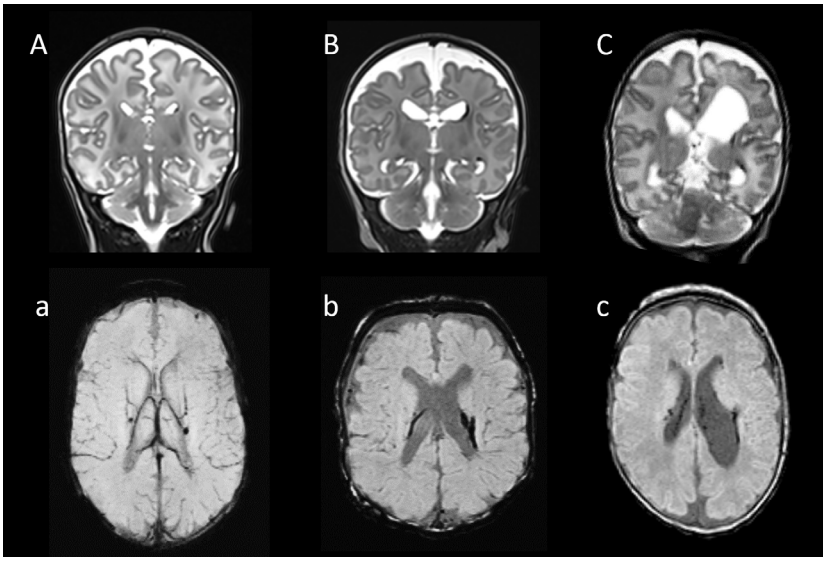

Fig. (2). Three grades of intraventricular hemorrhage as seen on coronal T2 (uppercase letters) and axial SWI (lowercase letters) sequences. A, a: Mild IVH, a hemosiderin deposit can be seen at the caudo-thalamic notch on the left on T2 and bilaterally on more sensitive SWI; B, b: Moderate IVH, ventricular dilatation is also present; C, c: Severe IVH, porencephalic cyst consequent to periventricular post-hemorrhagic infarction can be seen on the left. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

White matter lesions (WML, Fig. **1**):

- *Mild WML*: punctate white matter lesions (areas of high T1 and/or low T2 signal) not visible on SWI sequence situated posteriorly to the line dividing anterior and posterior halves of the lateral ventricles (midventricle line, adapted from Cayam-Rand *et al*. [29]) or punctate white matter lesions with signal loss on SWI independently of location;
- *Moderate WML*: presence of punctate white matter lesions without signal loss on SWI anteriorly to the midventricle line;
- *Severe WML*: cystic periventricular leukomalacia.

The differentiation between mild and moderate WML was based on the connection evidenced by Cayam-Rand and colleagues between the frontal localization of punctate white matter lesions and negative cognitive outcomes [29]. As our previous experience suggest the presence of a nosological difference between SWI+ and SWI- punctate white matter lesions [33], we have hypothesized that SWI+ PWMLs would not present worse outcome even when situated in the frontal part of the brain.

Intraventricular hemorrhage (IVH, Fig. **2**):

- *Mild IVH*: hemosiderin depositions in the caudo-thalamic notch and/or alongside lateral ventricle walls seen as areas of signal loss on SWI sequence without continuity suggestive of veins [5]; no persistent ventricular dilatation (lateral ventricle diameter ≤10 mm);
- *Moderate IVH*: as previous, but with signs of persistent ventricular dilatation (lateral ventricle diameter >10 mm) and/or necessitating ventricular drainage;
- *Severe IVH*: periventricular post-hemorrhagic infarction.

IVH classification was based on that of Papile *et al.* as adapted to MRI with SWI by Parodi *et al.*, uniting in the same group of "mild IVH" infants with what is usually referred to as GMH-IVH grade 1 and GMH-IVH grade 2 due

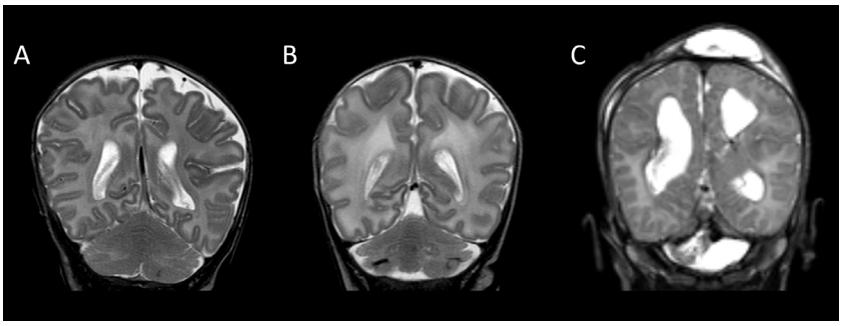

Fig. (3). Three grades of cerebellar hemorrhage on coronal T2 sequences. **A**: Mild CBH, punctate hemorrhage seen in the left cerebellar hemisphere; **B**: Moderate CBH, bilateral limited cerebellar hemorrhage; **C**: Severe CBH, massive bilateral hemorrhage destroying major part of cerebellar parenchyma. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

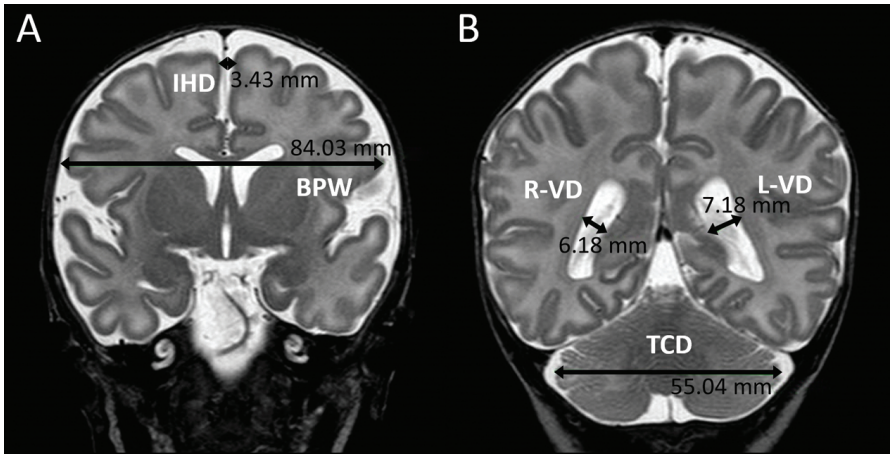

Fig. (4). Linear brain measurements were performed on coronal T2 scan. **A**: IHD and BPW measured at the level of the third ventricle, cochlea, and basilar artery; **B**: R-VD, L-VD and TCD measured at the level of the ventricular atrium. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

to similar pathogenesis and neurodevelopmental consequences [5, 12, 17, 18].

Cerebellar hemorrhage (CBH, Fig. **3**):

Hemosiderin depositions within the cerebellum are seen as foci of signal loss on SWI sequence, without continuity suggestive of veins [6]:

- *Mild CBH*: punctate cerebellar hemorrhage with maximum diameter <5 mm;
- *Moderate CBH*: limited cerebellar hemorrhage, an intermediate form ranging between 5 mm and one-third of cerebellar parenchyma;
- *Severe CBH*: massive cerebellar hemorrhage, involving more than one-third of cerebellar parenchyma.

Further, linear parameters of brain growth characterizing dimensions of brain structures and subarachnoid spaces were evaluated by a trained operator (MM), as described in the literature (Fig. **4**) [8]:

- biparietal width (BPW);
- interhemispheric distance (IHD);
- transcerebellar diameter (TCD);
- right and left ventricular diameters (R-VD and L-VD)

Finally, MR sequences of neonates included in the study were reviewed by a trained operator (MM) to qualitatively assess brain maturation using a previously validated scoring system [10]. Briefly, four parameters were considered related to the progressive maturation of myelination and cortical infoldings and the progressive involution of periventricular glial cell migration bands and germinal matrix tissue. A single score was determined for each of the four parameters (value ranges 1 to 7 for myelination, 1 to 6 for cortical infoldings, 1 to 4 for germinal matrix, and 1 to 4 for bands of migrating cells). The total maturation score was then calculated as the sum of the four different scores.

Interobserver reliabilities (calculated as intraclass correlation coefficients based on 20 scans assessed by 2 operators, MM and AP) were >0.92 for linear brain measurements and >0.91 for total maturation score, while intraobserver reliabilities (calculated as intraclass correlation coefficients based on 20 scans assessed a month apart by the same operator, MM) were >0.93 for linear brain measurements and >0.95 for total maturation score.

2.4. Follow-up

In our hospital, all VLBW infants are offered a standardized follow-up that includes regular pediatric evaluations and neurodevelopmental assessment, including GMDS at 1, 2

and 3 years of age. Additional specialistic visits and specific rehabilitation interventions are carried out when clinically necessary. For the purpose of the current study, neurodevelopmental evaluation of the patients was performed using the Griffiths Mental Developmental Scales (GMDS) [35] at three years of age by a single operator with 10 years of experience who was blinded to the MRI results. Raw numbers were converted to standardized development quotients (DQ): total DQ, global development; A, gross motor skills; B, adaptive behavior, and social functioning; C, receptive/expressive language; D, fine motor function and hand-eye coordination; E, performance, and F, practical reasoning. Values below 70 were defined as pathologic, from 70 to 79 as at limit, from 80 to 89 as below the mean and from 90 on as normal. Patients too severely impaired to perform GMDS were assigned DQ values of 50.

2.5. Data Analysis

Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois, USA). Descriptive statistics were generated for the whole cohort and data were expressed as mean and standard deviation (SD) for continuous variables. Absolute or relative frequencies were calculated and reported for categorical variables. Differences between groups were evaluated with Student t test or Mann Whitney U test for continuous variables and with χ^2 or Fisher's exact test for categorical variables.

To evaluate the influence of different brain lesions on the outcome, patients were divided into groups based on the type and grade of the lesion. Mean DQ values (total and 6 subscales) were compared between patients with three grades of lesions and patients with normal MRI (control group); between-group comparison was then performed among patients with different grades of white matter lesions.

Multivariate analysis was performed to evaluate the role of different grades of WML as a possible risk factor for pathologic values of total DQ at 3 years of age, after accounting for gestational age, BPD and ROP treated with laser. The results were reported as odds ratio (OR) with their 95% confidence intervals (CI).

Finally, possible correlations between linear measures of brain growth (BPW, TCD) and outcome were evaluated. As BPW and TCD strongly depend on corrected gestational age at MRI, we have performed an adjustment procedure to mitigate this influence. Linear regression model was used to calculate predicted BPW at given gestational age based on the part of the population without brain lesions, and the difference between the predicted and observed values was used for further calculations. Difference corresponding to the 10^{th} percentile in patients without lesions was used as a cut-off between small BPW and normal BPW. Mean DQ values at 3 years of age were compared between patients with small BPW and normal BPW, separately for groups of patients with and without brain lesions. The same adjustment procedure and comparison between groups were then performed for TCD.

A p-value <0.05 was considered statistically significant and all p-values were based upon two-tailed tests.

3. RESULTS

During the study period, 473 VLBW infants were admitted to the Neonatal Intensive Care Unit of IRCSS Istituto Giannina Gaslini. Of them, 47 deceased before TEA, while the parents of 18 infants refused MRI for logistic or personal reasons. One patient was excluded because of complex brain malformation. In the remaining population of 407 infants, GA ranged between 23 and 34 weeks (mean 28.4 ± 2.2) and birth weight between 435 and 1495 g (mean 1066 ± 263). Thirty-six percent of infants were born from multiple pregnancies, 23% were born by vaginal delivery, and female/male ratio was 1.2. Detailed clinical characteristics of patients included in the study are listed in Table **1**.

3.1. Prematurity-related Brain Lesions

Consensus was reached about the presence and grade of brain lesions in all cases. Two hundred and twenty VLBW infants out of 407 (54%) had normal term-equivalent age MRI, while 187 patients presented at least one prematurity-related brain lesion. Thirty-seven patients (9% of VLBW) had severe brain lesions. The most frequent brain lesion was germinal matrix - intraventricular hemorrhage, found in 113 patients (28%): 74 infants had mild, 15 moderate and 24 severe IVH. Eighty-six patients (21%) had white matter lesions (WML): 53 had mild, 20 moderate and 13 - severe WML. Finally, 70 patients (17%) had cerebellar hemorrhage: 48 had mild, 18 moderate and 4 severe CBH.

Sixty-eight patients (17% of VLBW) had more than one lesion: the most frequent association was IVH and CBH (33 patients), followed by IVH and WML (19 patients), while only two patients had WML and CBH; 14 patients presented all three types of lesions.

3.2. Linear Brain Measurements

Evaluation of linear brain measurements was performed for 396 out of 407 patients, while in the remaining 11 patients, coronal T2 sequence was not performed for technical reasons, or the quality of the sequence was not sufficient for the evaluation. In patients without prematurity-related brain lesions (n=213) mean BPW was 79.6 ± 5.8 mm, IHD 3.0 ± 1.5 mm, TCD 52.6 ± 4.9 mm, and R-VD and L-VD 5.2 ± 1.3 mm and 5.2 ± 1.6 mm, respectively. In patients with brain lesions (n=183), mean BPW was 78.3 ± 6.6 mm, IHD of 3.1 ± 1.7 mm, TCD of 49 ± 7.1 mm, and R-VD and L-VD 7.2 ± 4.6 mm and 7.6 ± 6.6 mm respectively.

3.3. Neurological Outcome at 3 Years of Age

Two hundred and seventy-five patients have completed GMDS at 3 years of age. Remaining 132 patients did not perform centralized GMDS mainly due to logistic reasons: part of the families with infants born at our hospital reside far away from the main city of the region and have chosen to proceed with controls at local health institutions. No significant

Table 1. Patient characteristics in the whole cohort.

Characteristic	Cohort (n=407)
Gestational age at birth in weeks, mean (SD)	28.4 (2.2)
Birth weight in gr, mean (SD)	1066 (264)
Male gender, n (%)	185 (45.4)
Intrauterine growth retardation, n (%)	100 (24.6)
Complete antenatal steroid treatment, n (%)	295 (72.5)
Multiple birth, n (%)	144 (35.4)
Caesarean section, n (%)	307 (75.4)
Apgar score at 5 minutes, median (range)	8 (0-10)
Need for intubation, n (%)	258 (63.4)
Inotropic support, n (%)	32 (7.9)
Patent ductus arteriosus requiring treatment, n (%)	214 (52.6)
Late onset sepsis, n (%)	169 (41.5)
Bronchopulmonary dysplasia, n (%)	75 (18.4)
Retinopathy of prematurity, n (%)	162 (39.8)

Abbreviations: SD: standard deviation.

Table 2. Mean developmental coefficient values on Griffiths scale at 3 years of age in patients with different types and grades of brain lesions.

-	N	Total DQ (mean ± SD)	Scale A (mean ± SD)	Scale B (mean ± SD)	Scale C (mean ± SD)	Scale D (mean ± SD)	Scale E (mean ± SD)	Scale F (mean ± SD)
Intraventricular Hemorrhage								
Severe IVH	15	69.6 ± 18.8*	67.6 ± 16.6*	70.4 ± 20.1*	68.4 ± 18.0*	72.3 ± 20.7**	70.7 ± 22.3^{+}	68.6 ± 18.3^{+}
Moderate IVH	8	83.9 ± 26.2	80.6 ± 26.3	85.6 ± 23.6	84.6 ± 27.0	81.8 ± 25.1	82.9 ± 28.1	83.1 ± 27.9
Mild IVH	40	81.6 ± 12.5**	83.5 ± 14.0**	85.6 ± 13.1^{+}	77.0 ± 13.8^{+}	83.6 ± 14.3**	81.1 ± 13.4**	82.2 ± 16.1*
White Matter Lesions								
Severe WML	8	61.0 ± 16.1*	54.9 ± 5.9*	64.1 ± 19.5*	65.6 ± 19.4*	63.1 ± 20.7*	60.3 ± 19.0*	63.0 ± 20.0*
Moderate WML	8	71.8 ± 11.3*	64.5 ± 10.9*	71.4 ± 11.1*	70.9 ± 16.0^{+}	75.8 ± 16.3^{+}	70.8 ± 12.4**	73.0 ± 15.5**
Mild WML	36	83.4 ± 14.8	84.9 ± 15.6^{+}	85.0 ± 15.4^{+}	81.2 ± 16.4	86.6 ± 14.9	83.8 ± 16.9	83.6 ± 17.1^{+}
Cerebellar Hemorrhage								
Severe CBH	2	65.0 ± 21.2	65.0 ± 21.2	65.0 ± 21.2	65.0 ± 21.2	65.0 ± 21.2	65.0 ± 21.2	65.0 ± 21.2
Moderate CBH	11	72.6 ± 17.4**	75.1 ± 19.8^{+}	76.2 ± 17.2^{+}	70.8 ± 22.3^{+}	77.0 ± 17.0^{+}	70.3 ± 14.5*	70.6 ± 19.1**
Mild CBH	29	79.5 ± 15.0**	79.4 ± 17.3**	83.1 ± 16.3^{+}	76.9 ± 15.3^{+}	81.4 ± 14.6**	78.2 ± 14.7^{+}	81.4 ± 18.6^{+}
No Brain Lesions	146	88.3 ± 12.0	89.7 ± 13.7	90.5 ± 13.6	84.8 ± 15.9	90.2 ± 12.6	86.6 ± 13.0	89.7 ± 13.8

Note: N=275; 28 patients had more than one type of lesion of the same grade and were included in both groups. *$p < 0.001$, **$p < 0.005$, +$p < 0.05$ *vs.* patients without brain lesions.

differences were observed in mean gestational age (28.6 ± 2.5 weeks), rate of multiple births (34.8%) or intrauterine growth retardation (21.2%), median Apgar score at 5 minutes (8), presence of IVH (29.5%), WML (22.7%), CBH (15.1%), severe brain lesions (9.8%), or other significant short-time outcomes between patients with and without follow-up at 3 years.

Among patients who completed GMDS, 53 (19%) had developmental quotient (DQ) below normal (<70), 31 had at limit values (70-79), 79 patients had values below the mean (80-89), and 112 infants had normal values (≥90). The presence of brain lesions, even mild ones, was associated with lower mean DQ values (Table **2**) when compared to patients without lesions, with statistically significant differences for all types and grades of lesions except mild WML and moderate IVH (in the latter case probably due to small number of patients with highly variable Griffiths values). We have further observed significant differences in general and motor outcomes between patients with mild WML and moderate WML (Table **3**).

Table 3. Mean developmental coefficient values on Griffiths scale at 3 years of age in patients with different grades of white matter lesions.

-	Mild (n=36)	Moderate (n=8)	Severe (n=8)	*p* Value Mild *vs.* Moderate	*p* Value Moderate *vs.* Severe	*p* Value Mild *vs.* Severe
Total DQ, mean ± SD	83.4 ± 14.8	71.8 ± 11.3	61.0 ± 16.1	**.02**	.05	**.002**
Scale A, mean ± SD	84.9 ± 15.6	64.5 ± 10.9	54.9 ± 5.9	**.001**	.08	**.0001**
Scale B, mean ± SD	85.0 ± 15.4	71.4 ± 11.1	64.1 ± 19.5	**.01**	.23	**.004**
Scale C, mean ± SD	81.2 ± 16.4	70.9 ± 16	65.6 ± 19.4	.10	.33	**.03**
Scale D, mean ± SD	86.6 ± 14.9	75.7 ± 16.3	63.1 ± 20.7	**.03**	.08	**.003**
Scale E, mean ± SD	83.8 ± 16.9	70.7 ± 12.4	60.2 ± 19	**.02**	.06	**.002**
Scale F, mean ± SD	83.6 ± 17.1	73 ± 15.5	63 ± 20	.10	.23	**.01**

Table 4. Multivariate analysis for white matter lesions as a possible risk factor for pathological Scale A (motor) DQ values at 3 years of age.

White Matter Lesions	OR (95% CI)	*p*-value*
Mild	2.40 (0.79; 7.32)	0.12
Moderate	9.74 (1.86; 50.94)	**0.007**
Severe	50.40 (7.26; 631)	**0.0001**

Note: *corrected for gestational age, BPD and severe ROP.

Table 5. Mean developmental coefficient at 3 years of age in infants without brain lesions with small *vs.* normal BPW.

-	Small BPW (n=14)	Normal BPW (n=129)	*p* Value
Total DQ, mean ± SD	82.9 ± 8.7	89.2 ± 12.1	**0.02**
Scale A, mean ± SD	87.7 ± 15.3	90.1 ± 13.5	0.43
Scale B, mean ± SD	88.9 ± 17.8	91 ± 13	0.62
Scale C, mean ± SD	75.1 ± 15.5	86.1 ± 15.6	**0.02**
Scale D, mean ± SD	86.6 ± 10.4	90.7 ± 12.7	0.14
Scale E, mean ± SD	79.1 ± 11.6	87.7 ± 12.8	**0.02**
Scale F, mean ± SD	84.4 ± 12.8	90.5 ± 13.7	0.06

Multivariate analysis (corrected for gestational age, BPD and severe ROP) showed that moderate and severe WML were significant risk factors for unfavorable outcomes at 3 years of age expressed as DQ <70 (Table **4**).

In patients without brain lesions, small BPW was associated with significantly lower mean DQ values for total score and sub-scales C and E (Table **5**).

On the contrary, within the patients with brain lesions, small BPW did not cause significant reduction in mean DQ values at 3 years of age (Supplementary Table **1**).

Small TCD was associated with significantly lower mean DQ values on scales A and C in patients without lesions (Table **6**) and with a highly significant reduction in DQ values in all subscales in patients with brain lesions (Table **7**).

3.4. Total Maturation Score

No significant differences were observed in total maturation score between patients with prematurity-related brain lesion and infants without brain lesions (Table **8**).

No correlation was observed between TMS and outcome at 3 years of age in our population. Interestingly, among the infants with IVH we have observed a trend for higher GMDS scores with lower values of B component of TMS ("bands of migration cells"), corresponding to earlier stages of maturation. This difference was though not statistically significant (Table **9**).

Table 6. Mean developmental coefficient at 3 years of age in infants without brain lesions with small *vs.* normal TCD.

-	**Small TCD (n=13)**	**Normal TCD (n=130)**	***p* Value**
Total DQ, mean ± SD	83 ± 11.4	89.1 ± 11.9	0.055
Scale A, mean ± SD	81.5 ± 12.5	90.6 ± 13.5	**0.009**
Scale B, mean ± SD	84.2 ± 16.1	91.5 ± 13	0.15
Scale C, mean ± SD	75 ± 15.7	86 ± 15.6	**0.02**
Scale D, mean ± SD	89.4 ± 14.7	90.4 ± 12.4	0.80
Scale E, mean ± SD	85.8 ± 13.7	87 ± 12.9	0.94
Scale F, mean ± SD	83.4 ± 13.8	90.6 ± 13.5	0.08

Table 7. Mean developmental coefficient at 3 years of age in infants with brain lesions with small *vs.* normal TCD.

-	**Small TCD (n=39)**	**Normal TCD (n=87)**	***p* Value**
Total DQ, mean ± SD	69.8 ± 16.4	82.3 ± 15.0	**<0.0001**
Scale A, mean ± SD	70.1 ± 17	83.2 ± 15.9	**<0.0001**
Scale B, mean ± SD	72.1 ± 18	84.9 ± 15.2	**<0.0001**
Scale C, mean ± SD	67.8 ± 17.8	79.9 ± 16.4	**<0.0001**
Scale D, mean ± SD	72.8 ± 16.9	85.1 ± 16	**<0.0001**
Scale E, mean ± SD	70.3 ± 17.6	82 ± 16.7	**<0.0001**
Scale F, mean ± SD	69.5 ± 16.9	82.5 ± 18.2	**<0.0001**

Table 8. Total maturation score in patients with different grades of IVH and WML and in infants without brain lesions.

-	**TMS, Mean ± SD**	***p* Value *vs.* no Lesions**
IVH		
Mild	12.0 ± 0.93	0.14
Moderate	12.6 ± 1.21	0.49
Severe	11.6 ± 1.19	0.10
WML		
Mild	12.2 ± 0.93	0.80
Moderate	12.2 ± 1.20	0.49
Severe	13.2 ± 1.47	0.09
No lesions	12.2 ± 1,17	-

Table 9. Mean developmental coefficient at 3 years of age in infants with IVH and different stages of brain maturation relative to bands of migration cells.

Stage of Maturation	**DQ at 3 Years, Mean ± SD**	***p* Value *vs.* B1**
B1, broad band with additional narrower bands	83.7 ± 9.2	-
B2, broad band alone	79.5 ± 15.1	0.59
B3/4, narrow band alone / no band seen	75.6 ± 13.5	0.27

4. DISCUSSION

In the present study, we have observed that an important share of our population (46% of all VLBW infants) presented at least one brain lesion on magnetic resonance imaging performed at term-equivalent age. This number seems to be higher than what was reported in similar studies [9, 36]. Possible cause for this difference is the higher sensitivity of the protocols used in our center to low-grade hemorrhagic lesions (GMH-IVH and CBH): the SWI sequence, highly sensitive to the deposits of hemosiderin, is considered a gold standard for the diagnosis of brain hemorrhagic lesions but is not always included in the protocols for brain neonatal imaging [5, 6]. Indeed, the prevalence of severe brain lesions in our population is similar to cited studies: 9% *vs.* 10% in the study by Kidokoro *et al*. [9] and 6% in the study by Neubauer *et al*. [36].

Potential role of low-grade hemorrhagic brain lesions on the neurodevelopmental outcome is still a matter of debate in the literature. Some studies show a negative influence of low-grade GMH-IVH, while others do not report significant differences with the control group [15, 17, 18, 37]. As most studies are based on ultrasound diagnosis of GMH-IVH known to have low sensitivity towards low-grade lesions, it is possible that the difference is due to recruitment bias: the patients with unseen low-grade GMH-IVH could have been included among controls [5]. The same seems to be true for low-grade CBH, with the prognosis being largely unknown [21, 23, 38].

In our study, both mild IVH and mild CBH were related to lower values on Griffiths scale at 3 years of age. Several pathophysiologic mechanisms could be involved in the process. Preclinical studies suggest that damage to germinal matrix can alter the development of brain cortex [39]; it has also been shown that even non-complicated GMH-IVH can be associated with the reduction of gray matter volume at term-equivalent age [40]. On the other hand, even small amounts of blood degradation products seem to alter proliferation and differentiation of oligodendrocyte progenitors [41] and can damage white matter through microglia activation [42]. Indeed, our group has observed microstructural changes of white matter associated with worse neurodevelopmental outcome at 2 years of age, in patients with low-grade GMH-IVH [43]. In this case the pathological process could involve passage of blood degradation products from the ventricle to the periventricular white matter. Finally, several papers have evidenced alterations in cerebral oxygenation and cerebral blood flow as measured with near-infrared spectroscopy in preterm infants with low-grade GMH-IVH [44, 45], with alterations lasting as long as weeks. Even the perfusion of the cortical and deep gray matter seems to be altered in patients with low-grade GMH-IVH [46], suggesting a new possible mechanism of disturbing normal brain development. In case of cerebellar hemorrhage, a negative influence of hemosiderin deposits on cerebellar development has been described in the literature, probably *via* free radical damage to the cerebellar cortex [23, 47].

White matter lesions were observed in 21% of our population: the major part was affected by punctate white matter lesions (mild and moderate WML), while only 3% presented cystic periventricular leucomalacia (severe WML). Recent literature has shown that anterior punctate white matter lesions are related to negative neurodevelopmental outcome [28, 29], and our work seems to confirm this finding. Indeed, only moderate and severe WML (non-hemorrhagic anterior punctate white matter lesions and cystic periventricular leucomalacia) were related to significantly lower values on Griffiths scale at 3 years of age, with higher risk for pathologic values on multivariate analysis.

We have furthermore observed that among infants without brain lesions small BPW was associated with significantly lower mean DQ values for total score and sub-scales related to language and performance, while small TCD was associated with significantly lower mean DQ values on scales related to gross motor skills and language. Similar results were observed by other authors: Kidokoro *et al*. noted worse cognitive outcome in preterm infants with small BPW [9], while Dewan *et al*. observed correlations between BPW and developmental index, TCD and mental developmental index at 2 years of corrected age [48]. Other authors have observed that even without brain lesions the reduction of either TCD or BPW was associated with the reduction of mental developmental index at 2 years of age [49, 50].

We have not evidenced significant correlations between TMS and outcome at 3 years of age. Intriguingly, we have observed a non-significant trend for higher GMDS scores with lower values of B component of TMS ("bands of migration cells") among the infants with IVH. It could be interesting to explore if the major presence of cells migrating from germinal matrix to the cortex could be a positive sign after an intraventricular hemorrhage, but the design of our study did not allow to draw significant conclusions on the matter.

The main limitations of our study are its retrospective design and high specificity of studied population (VLBW), so the extension of the results to other patient groups of different gestational ages could not be applicable. This is important to keep in mind as, for example, punctate white matter lesions could be found in infants of different gestational ages, including term [30, 51]. Furthermore, the use of magnetic resonance imaging at term-equivalent age limits our diagnostic capacity, as some lesions, for example, a part of non-hemorrhagic punctate white matter lesions, could disappear before term [26].

Among strong points of our work, we could name a vast population with homogenic strategies of treatment, imaging and follow-up. Furthermore, the availability of SWI sequence for all scans has allowed us to identify with high precision even low-grade hemorrhages. Finally, the follow-up performed at 3 years of age is known to correlate better with long-term outcome when compared to 2-year evaluation frequently used in this type of study.

CONCLUSION

In conclusion, in a vast population of preterm infants with the very low birth weight we have observed a high

share of brain lesions visible on term-equivalent age MRI. The lesions were related to negative neurodevelopmental outcomes at 3 years of age. Our data suggest that term-equivalent MRI can have an important role in verifying the presence and type of brain lesions connected with prematurity, to promptly identify at-risk patients and to direct them as soon as possible toward highly needed programs of stimulation, habilitation and rehabilitation.

LIST OF ABBREVIATIONS

BPW = Biparietal Width

CBH = Cerebellar Hemorrhage

DQ = Developmental Coefficients

IVH = Intraventricular Hemorrhage

TCD = Trans-cerebellar Diameter

TMS = Total Maturation Score

WML = White Matter Lesions

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective observational study was approved by the local ethics committee of the IRCCS Istituto Giannina Gaslini, Genoa, Italy.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent that included statements about the significance and limitations of MRI at TEA was obtained in all cases.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest related to the manuscript.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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