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Early Extra-Uterine Growth Restriction in Very Low Birth Weight Neonates with Normal or Mildly Abnormal Brain MRI: Effects on 2-3 Years Neurodevelopmental Outcome

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Abstract: Extrauterine growth restriction (EUGR) is a common complication and a known risk factor for impaired development in very low birth weight (VLBW) preterms. We report a population of 288 patients with no or with low grade MRI lesions scanned at term equivalent age (TEA) born between 2012 and 2018. Griffiths mental development scale II (GMDS II) at 2 and 3 years, preterm complications and weight growth were retrospectively analysed. EUGR was defined for weigth z-score <10th percentile at TEA, 6 and 12 months of correct age or as z-score decreased by 1-point SDS from birth to TEA and from TEA to 6 months. Multivariate analysis showed that a higher weight z-score at 6 months is protective for global developmental quotient (DQ) at 2 years (OR 0.74; CI 95% 0.59-0.93; p=0,01). EUGR at 6 months was associated with worse locomotor, personal-social, language and performance DQ at 2 years and worse language and practical reasoning DQ at 3 years. In conclusion a worse weight z-score at 6 months of age seems to be an independent risk factor for significantly reduced GMDS in many areas. These results suggest to better invest on post-discharge nutritional, optimizing family nutritional education.

Keywords: preterm; extra-uterine growth restriction; EUGR; VLBW; neurodevelopment; weaning; nutritional education

1. Introduction

The survival rate in preterm babies, in particular for very low birth weight (VLBW, with birth weight <1500g) has drastically increased over the years [1,2,3]. However, the incidence of neurological sequelae like cerebral palsy, cognitive impairment and developmental co-ordination disorder has remained high due to increased survival at the lower gestational age [4,5,6]. Neurodevelopment can be affected by several neonatal complications in preterm babies.

Extrauterine growth restriction (EUGR) is a common complication in preterm infants [7] and is commonly considered a risk factor for poor development. It is defined as "cross-sectional" when the patient weights below a specific cut-off at a specific time-point [8] or “longitudinal” when there’s a

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growth deficit from birth concerning another defined time-point [9,10]. Its incidence varies from 13% to 97% in different populations and according to relative definitions [11]. In addition, Ehrenkranz RA et al. observed an increase on incidence of cerebral palsy, abnormal mental development index and psychomotor development index, and neurodevelopment impairment in patients with EUGR during NICU hospitalization in a large population of ELBW infants [12]. Furthermore, Guellec I et al. demonstrates an increased risk of cerebral palsy in "longitudinal" EUGR between birth and 6 months in a large population of preterms from the EPIPAGE study cohort [13]. Therefore, despite the influence of EUGR in neurodevelopment is widely shared, there is no univocal agreement on which definition and time-point better predict neurological outcome [10]. Furthermore, the most important studies do not consider MRI which is the gold standard to define the diagnosis including minor brain lesions often missed at ultrasound [14,15].

Major brain lesions like cystic periventricular leukomalacia (PVL), germinal matrix-intraventricular hemorrhage (GMH-IVH) complicated by periventricular hemorrhagic venous infraction (PVHI) or post-hemorrhagic ventricular distension (PHVD) and massive cerebellar hemorrhage (CBH) are strongly associated with important neurological impairment [16, 17, 18, 19, 20, 21, 22, 23, 24]. The role of minor lesions like low grade GMH-IVH, punctate white matter lesions (PWML) and micro CBH is still debated although some recent works seems to be associated with an impaired neurological development [25, 26, 27].

Furthermore, other neonatal complications can play a role in developing neurological sequelae in preterm babies, in particular hypoxia at birth [28], neonatal sepsis [29], necrotizing enterocolitis (NEC) [30, 31], bronchopulmonary dysplasia [32, 33, 34], surgical procedures [35, 36].

The primary aim of our study is to define if EUGR can be an independent prognostic factor for neurological outcome in VLBW preterm with negative or minor brain lesions at MRI. Furthermore, the secondary aim is to identify if there is a more sensitive time-point EUGR diagnosis more sensitive to better predict neurological outcomes.

2. Materials and Methods

All VLBW infants consecutively admitted to Neonatal Intensive Care Unit of IRCSS Giannina Gaslini Institute who underwent routine brain MRI at term-equivalent age from January 2012 to December 2018 were selected for the study. As per standard internal protocol, MRI scans were performed at term-equivalent age (TEA, between 38 and 42 weeks post menstrual age) as a part of the screening program for identification of prematurity-related lesions.“Feed and wrap” technique was used to perform the MRI [37]. The need for sedation (oral midazolam, 0,1 mg/kg) to prevent head motion was agreed with the neuro-radiologist case by case. Scans were performed with a 1.5 Tesla MR system (InteraAchieva 2.6; Philips, Best, The Netherlands) using a dedicated pediatric head/spine coil. Our institutional standard MRI protocol included 3 mm thick axial T2-weighted and T1-weighted images, coronal T2-weighted images, sagittal T1- weighted images, axial diffusion-weighted images (b value:1000 s/mm2) and axial SWI (susceptibility weighted imaging) that is the gold standard to identify hemosiderin and low-grade hemorrhage [38]. Patients with major brain lesions such as periventricular leukomalacia (PVL), periventricular hemorrhagic infarction (PVHI), post-hemorrhagic ventricular distention (PHVD) and massive-limited CBH [39] known to significantly affect neurological outcome were excluded or with congenital brain malformations were excluded from the present study. Patients with minor brain lesions such as low-grade GMH-IVH (I-II grade for Volpe’s Classification [20]), punctate white matter lesions (PWML), [26] or micro-CBH were included [21].

Demographic and clinical data of the enrolled patients were extracted from clinical charts. Collected data included: birth weight, gestational age, sex, mode of delivery, Apgar at 5th minute, diagnosis of neonatal complications (sepsis, NEC and BPD), need of major surgery, mother milk feeding at TEA. Neonatal sepsis was defined by the need for antibiotic therapy for clinical and laboratory findings suggesting blood infection. NEC was defined by clinical and imaging signs suggesting enterocolitis. BPD was defined by the need of any ventilatory support or O2 supplementation at 36 weeks. MRI data were collected and patients were divided into two groups:

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patients with normal MRI and patients with minor brain lesions, like those very mild hemorrhagic identified by Susceptibility Weighted Imaging [15, 38, 40].

Anthropometric data were collected by clinical charts of patients enrolled in our preterm follow-up service. During the hospital stay, weight was measured daily and after discharging it was collected at term-equivalent age (TEA), and 1, 3, 6, 9, and 12 months of correct age. We collected only weight at birth, at TEA, 6 and 12 months of corrected age. Z-scores of weight for age and sex were calculated for birth and TEA using INTERGROWTH-21strelatives charts for very preterm size at birth [41] and postnatal growth standard in preterm infants [42], while for 6 and 12 months of correct age, we used CDC Growth Charts, 2000 [43]. Patients who were lost in the follow-up phase or with incomplete anthropometric data were excluded from the present study.

The patients with birth weight z-score < 1,282 (<10° percentile) were considered small for gestational age (SGA). Extra-uterine growth restriction (EUGR) at TEA and 6 months was diagnosed by two different definitions: "cross-sectional" EUGR as a weight z-score < 1,282 (<10° percentile) and "longitudinal" EUGR as z-score decreased by 1-point SDS from birth to TEA and from TEA to 6 months [44]. A pathologic weight with z-score <1,282 (<10° percentile) was also defined as EUGR at 12 months of correct age.

The neurological development evaluation of patients was performed with Griffiths Mental Developmental Scales II (GMDS II) [45] at two years of corrected age and three years of chronological age. Patients lost in the follow-up phase were excluded from the study. Patients who did not perform only the 3-years assessment were included. These evaluations are part of routine follow-up service offered to all VLBW patients after discharge from the hospital. GMDS was administered by a 10-year experienced single operator blinded to MRI results. Raw numbers were converted into standardized development quotients (DQ). Total development quotients (DQ), relating to global development, were derived from the mean of the results of different areas of assessment: locomotor and gross motor skills (scale A); personal-social and adaptive behavior development (scale B); receptive/expressive language (scale C); fine motor function and hand-eye coordination (scale D); performance as precursors of reasoning and planning (scale E); practical reasoning (scale F, performed only at 3 years of age).Resulting values were used to evaluate the level of neurodevelopment: values below 70 define a developmental delay, values from 70 to 84 evidence borderline condition, and values above 84 are considered normal [45].

Descriptive statistics were generated for the whole cohort; data were expressed as the mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. All collected demographic and clinical data were compared using the Chi-square or Fisher exact test and the Mann-Whitney U test for categorical and continuous variables. Univariate analysis determined the potential risk factors which were significantly associated with unsatisfactory scores in the GMDS (<85) at 2, and 3 years of CA. Logistic regression analysis was used for each variable, and odds ratios (ORs) were calculated with 95% confidence intervals (CIs). The absence of exposure to the factor or the variable that was less likely to be associated with the risk was used as a reference for each analysis. Multivariate analysis corrected for gestational age (GA) was then performed. The only variables that proved to be statistically or borderline significant in the univariate analysis (<0.08) were included in the model. The model which best fitted was based on the backward stepwise selection procedures, and each variable was removed if it did not contribute significantly. In the final model, a p-value of <0.05 was considered statistically significant, and all p-values were based on two-tailed tests. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS Inc. Chicago, IL).

The studies involving human participants were reviewed and approved by Giannina Gaslini Hospital, Genoa, Italy. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

3. Results

3.1. Main population description

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498 very low birth weights underwent brain MRIs from January 2012 to December 2018. Of these patients, 65 were excluded for severe brain lesions, 18 for incidental findings of brain malformations and congenital diseases, and 127 for incomplete follow-up or missing data.

The final population included 288 patients. GA mean was 28.9 ± 2.1 weeks (range 23-34.6), with a mean birth weight of 1097±255g (z-score -0,449 ± 1,09; range 435-1490g). 139 patients (48.3%) were male. The incidence of SGA was 21.5% (62 patients). 232 neonates were born by cesarean delivery (80.6%), mean Apgar score at 5 minutes was 8(range 2-10). About the major neonatal complications of preterm: incidence of sepsis was 37.5% (n 108), NEC was present in 30 patients (10.4%) of these 15 who underwent surgical treatment. A total of 36 patients (12.5%) underwent surgery before discharge (15 for NEC, 17 for patent ductus arteriosus, PDA). The MRI study at term age (TEA) showed that101 patients had low-grade lesions (35,1%). Of these 44 patients with low-grade IVH (15,3%), 47 had punctuate lesions of white matter (16.3%), 31 had micro-CBH (10,8%). At term age, only 17% (n 49) were fed by mother milk exclusively and 41% were fed only by formula milk. The mean weight at TEA was 2600 ± 598g (range 1140-4180g), the mean z-score for weight was -1.407±1.415, and 50% (n=144) had "cross-sectional" EUGR. The incidence of "longitudinal" EUGR was 43.8% (n=126). At 6 months of age, the mean weight was 6.81± 1.03 kg, z-score -1.24±1.29, the incidence of patients with "cross-sectional" EUGR was 46.2% (n=133), while the rate of "longitudinal" EUGR was 16,0% (n=46). At 12 months of age, the mean weight was 8.78± 1.16 kg, z-score -1.36±1.25, the incidence of patients with "cross-sectional" EUGR was 48.3% (n=139). (Table 1)

Table 1. Population features.

Whole population	**N= 288**
Gestational age (weeks)	28.9 ± 2.1
Birth Weight (g)	1097 ± 255 g (z-score -0,449 ± 1,09)
Small for gestational age (SGA)	62 (21,5%)
Male sex	139 (48,3%)
Cesarean delivery	232 (80,6%)
Apgarat 5 minutes	8± 1,2
Sepsis	108 (37,5%)
Necrotizing enterocolitis (NEC)	30 (10,4%)
Bronchodysplasia (BPD)	68 (23,6%)
Major Surgery	36 (12,5%)
NEC Surgery	15 (5,2%)
Patent Ductus Arteriosus Surgery	17 (5,9%)
Exclusive mother-milk feeding	49 (17%)
Exclusive formula feeding	118 (41%)
MRI low-grade lesions	101 (35,1%)
Low-grade intraventricular-hemorrhage (GMH-IVH)	44 (15,3%)
Punctate white matter lesions (PWML)	47 (16,3%)
Cerebellar micro-hemorrage (micro-CBH)	31 (10,8%)
Weight at term age TEA (g)	2600 ± 598 (z-score -1.407 ± 1.415)
"Cross-sectional" EUGR at TEA	144 (50%)
"Longitudinal" EUGR at TEA	126 (43,8%)

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Weight at 6 months (kg)	6.81 ± 1.03 (z-score -1.240± 1.29)
"Cross-sectional" EUGR at 6 months	133 (46,2%)
"Longitudinal" EUGR at 6 months	46 (16,0%)
Weight at 12 months (kg)	8.78± 1.16 (z-score -1.360± 1.25)
"Cross-sectional" EUGR at 12 months	139 (48,3%)

Data are reported in mean value ± SDS for continuous variables, absolute number, and percentage for categorical variables.

3.2. Neurological outcome and statistical analysis

About the long-term neurological outcomes, Global DQ evaluated with Griffiths scale II was pathologic or borderline (<85) in 56 patients of 288 at 2 years of age (19,4%). Considering separately the different rating areas of the Griffiths II scale, incidence of pathologic or borderline score was 23,6% for locomotor, 23,2% for personal-social; 44,1% for hearing and language,13,2% for hand-eye coordination, 24,3% for performance. At 3 years of age, global DQ Griffiths scale was pathologic or borderline in 100 of 262 patients (26 patients were lost in the follow-up phase) with an incidence of 38,2%. Considering separately the different rating areas incidence of pathologic or borderline score was 31,7 % for locomotor, 33,2% for personal-social; 53,0% for hearing and language, 31,6% for hand-eye coordination, 48,1% for performance, 38,5% for practical reasoning (Table 2).

Table 2. Griffith mental development scale II (GMDS) results at 2 and 3 years in the whole population for Global and sub-scales development quotient (DQ).

Pathologic or border line (<85) GMDS at 2y (n=288)	
Global DQ	56 *(19,4%)*
Locomotor (scale A)	68 *(23,6%)*
Personal-social (scale B)	67 *(23,2%)*
Language (scale C)	127 *(44,1%)*
Hand-eye coordination (scale D)	38 *(13,2%)*
Performance (scale E)	70 *(24,3%)*
Pathologic or border line (<85) GMDS at 3y (n= 262)	
Global DQ	100 *(38,2%)*
Locomotor (scale A)	83 *(31,7%)*
Personal-social (scale B)	87 *(33,2%)*
Language (scale C)	139 *(53,0%)*
Hand-eye coordination (scale D)	83 *(31,6%)*
Performance (scale E)	126 *(48,1%)*
Practicalreasoning (scale F)	101 *(38,5%)*

Considering the risk factors for worse neurological outcomes at 2 years, the univariate analysis showed that patients scoring below 85 on the Griffiths II scales had a lower weight z-score at 6 (-1,639 vs 1,140 p=0,03) and 12 months (-1,735 vs -1,264 p=0,03) than patients with normal results on the Griffiths assessment and the incidence of patients with "cross-sectional" EUGR at 6 months was higher even not statistically significant in patients with pathological or borderline global DQ at Griffiths (58,9 vs 43,5%; p=0,07). Furthermore, the incidence of surgical NEC appears to be higher in patients with pathological or borderline global DQ (10,7% vs 3,9%; p =0,08). Based on these data,

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multivariate analysis adjusted for gestational age showed that a higher z-score for weight at 6 months would be protective for global DQ deficit at 2 years of age (OR 0,74; CI 0,59-0,93; p=0,01) (Table 3).

Table 3. Univariate and Multivariate Analysis results for global development quotient at 2 years.

2y GMDS GLOBAL DQ	**<85**	**≥ 85**	
N	56	232	Total 288
z-score 6 month	-1,639 ± 1,582	-1,140 ± 1,188	p=0,03
z-score 12 month	-1,735 ± 1,56	-1,264 ± 1,155	p=0,03
Surgical NEC	6 (10,7%)	9 (3,9%)	p=0,08
"Cross-sectional" EUGR at 6 months	33 (58,9%)	101 (43,5%)	p=0,07
Multivariate analysis (corrected for GA):			
z-score 6 month	***OR 0,74 (CI95% 0,59-0,93)***		***p=0,01***

Univariate and Multivariate Analysis corrected for gestational age (GA); Global development quotient (DQ) at 2 years Griffith Mental Development Scale. Data are reported in mean value ± SDS for continuous variables, absolute number, and percentage for categorical variables. Odds ratios (OR) were calculated with a 95% confidence interval (CI). All p-values were based on two-tailed tests.

The same analysis was performed separately for the different rating areas of the Griffiths II scale. Results of multivariate analysis are resumed in Table 4. Considering the locomotor area (Scale A) the multivariate analysis showed that "cross-sectional" EUGR at 6 months (OR 1.96; CI 95% 1.10-3.47; p=0.02), punctate white matter lesions (PWML) (OR 2,33; CI95% 1,15-4,71; p=0,02) and major surgery during NICU stay (OR 3.79; CI 95% 1.69-8.49; p=0.001) were a negative prognostic factor. For Personal-Social area (Scale B) "cross-sectional" EUGR at 6 months (OR 1,94; CI 95%; 1,12-3,37; p=0,02) and NEC (OR 2,6; CI 95% 1,14-5,92; p= 0,02) are the major risk factors. Considering the hearing and language areas (Scale C), multivariate analysis identified higher gestational age (OR 0,5; CI 95% 0,27-0,92; p=0,02) and higher birth weight z-scores (OR 0,31; CI 95% 0,12-0,81; p=0,02) as protective factors, while the presence of NEC (OR 2,48; CI 95% 1,07-5,71; p=0,03) and "cross-sectional" EUGR at 6 months (OR 1,87; CI 1,05-3,29; p= 0,02) were also confirmed as negative prognostic factors. NEC was also a negative prognostic factor (OR 3,98; CI1,66-9,55; p=0,002)for the assessment of hand-eye coordination (Scale D). Lastly, male sex(OR 2,01; CI 95% 1,13-3,57; p=0,02); major surgery (OR 4,07: CI 95% 1,78-9,33; p=0,001), white matter punctate lesions at MRI (OR 2,03; CI 95% 1,00-4,14; p=0,05), and "longitudinal" EUGR at 6 months (OR 2,10; CI 95% 1,03-4,30; p= 0,04) seemed to be negative prognostic factor relatively to the performance area (Scale E) (Table 4)

Table 4. Multivariate Analysis for different Griffith Mental Development subscales at 2 years.

2y GMDS Locomotor DQ		
Major surgery	OR 3.79 (CI 95% 1.69-8.49)	p=0,001
"Cross-sectional" EUGR at 6 months	***OR 1.96 (CI 95% 1.10-3.47)***	***p=0,02***
Punctate white matter lesions (PWML)	OR 2,33 (CI 95% 1,15-4,71)	p=0,02
2y GMDS Personal-social DQ		
"Cross-sectional" EUGR at 6 months	***OR 1,94 (CI 95% 1,12-3,37)***	***p=0,02***
NEC	OR 2,60 (CI 95% 1,14-5,92)	p=0,02
2y GMDS Language DQ		
Gestational age (GA)	OR 0,50 (CI 95% 0,27, 0,92)	p=0,02
NEC	OR 2,48 (CI 95% 1,07-5,71)	p=0,03

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"Cross-sectional" EUGR at 6 months	***OR 1,87 (CI 95% 1,05-3,29)***	***p=0,02***
Weight z-score at birth	OR 0,31 (CI 95% 0,12-0,81)	p=0,02
2y GMDS Hand-eye coordination DQ		
NEC	OR 3,98 (CI 95% 1,66-9,55)	p=0,002
2y GMDS Performance DQ		
Male sex	OR 2,01 (CI 95% 1,13-3,57)	p=0,02
Punctate white matter lesions (PWML)	OR 2,03 (CI 95% 1,00-4,14)	p=0,05
Major surgery	OR 4,07 (CI 95% 1,78-9,33)	p=0,001
"Longitudinal" EUGR at 6 months	***OR 2,10 (CI 95% 1,03-4,30)***	***p=0,04***

Multivariate Analysis corrected for gestational age (GA) for different Griffith Mental Development subscales at 2 years. Odds ratios (OR) were calculated with a 95% confidence interval (CI). All p-values were based on two-tailed tests.

Regarding the neurological outcome at 3 years of age, the Griffiths II scale was applied only in 262 patients of the 288 because 26 patients were lost in the follow-up phase. The univariate analysis showed a major incidence of Griffiths score <85 in the male babies (60% vs 43,2%; p= 0,01), and patients with NEC (17% vs 7,4%; p=0,02), while normal Griffiths had a higher incidence in patients born by cesarean delivery (76% vs 85,2%; p=0,05). Based on these data, the multivariate analysis adjusted for gestational age showed that only male sex (OR 1,94; CI 95% 1,16-3,24; p=0,01) and NEC (OR 2,55; CI 95% 1,11-5,86; p=0,03) was independent negative prognostic factors for worse global DQ at 3 years. (Table 5)

Table 5. Univariate and Multivariate Analysis results for global development quotient at 3 years.

3y GMDS GLOBAL DQ	**<85**	**≥ 85**	
N	100	162	Total 262
Male sex	60 (60%)	70 (43,2%)	p=0,01
Caesarean delivery	76 (76%)	138 (85,2%)	p=0,05
NEC	17 (17%)	12 (7,4%)	p=0,02
Multivariate analysis (corrected for GA):			
Male sex	OR 1,94 (CI 95% 1,16-3,24)		p=0,01
NEC	OR 2,55 (CI 95% 1,11-5,86)		p=0,03

Univariate and Multivariate Analysis corrected for gestational age (GA); Global development quotient (DQ) at 3 years Griffith Mental Development Scale. Data are reported in mean value ± SDS for continuous variables, absolute number, and percentage for categorical variables. Odds ratios (OR) were calculated with a 95% confidence interval (CI). All p-values were based on two-tailed tests.

Considering separately the areas of Griffith II at 3 years, multivariate analysis showed that the protective prognostic factors for locomotor area (Scale A) was higher gestational age at birth (OR 0,88; CI 95% 0,77-1; p=0,06) while male sex was a negative prognostic factor (OR 1,82; CI 95% 1,07-3,10; p=0,03). Male sex was also a negative prognostic factor (OR 2,18; CI 95% 1,28-3,72; p=0,004) for personal-social area (Scale B) while cesarean delivery seemed to be a protective factor (OR 0,47; CI 95% 0,25-0,91; p=0,02).About hearing and language area (Scale C)"cross-sectional" EUGR at 6 months (OR 1,63; CI 95% 0,99-2,68; p= 0,05) and male sex (OR1,88; CI 95% 1,14-3,10; p=0,01) seemed to be the only negative prognostic factors. Regarding hand-eye coordination (Scale D) and performance (Scale E) the major risk factors seemed to be male sex (OR 4,17; CI 95% 1,78-9,76; p=0,001 - OR 2,39; CI 95% 1,44-3,97; p=0,001 respectively)and NEC (OR 4,17; CI 95% 1,78-9,76; p=0,001 - OR 4,31; CI 95% 1,63-

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11,35; p=0,003 respectively). For practical reasoning (Scale F) only "longitudinal" EUGR at 6 months (OR 2,07; CI95% 1,02-4,17; p= 0,04) and NEC (OR 4,47; CI 95% 1,84-10,85; p=0,001) seems to be significative (Table 6).

Table 6. Multivariate Analysis for different Griffith Mental Development subscales at 3 years. .

3y GMDS Locomotor DQ		
Gestational Age (GA)	OR 0,88 (CI 95% 0,77-1)	p=0,06
Male sex	OR 1,82 (CI 95% 1.07-3,10)	p=0,03
3y GMDS Personal-social DQ		
Male sex	OR 2,18 (CI 95% 1,28-3,72)	p=0,004
Caesarean delivery	OR 0,47 (CI 95% 0,25-0,91)	p=0,02
3y GMDS Language DQ		
"Cross-sectional" EUGR at 6 months	***OR 1,63 (CI 95% 0,99-2,68)***	***p=0,05***
Male sex	OR 1,88 (CI 95% 1,14-3,10)	p=0,01
3y GMDS Hand-eye coordination DQ		
NEC	OR 4,17 (CI 95% 1,78-9,76)	p=0,001
Male sex	OR 1,80 (CI95% 1,04-3,10)	p=0,03
3y GMDS Performance DQ		
NEC	OR 4,31 (CI 95% 1,63-11,35)	p=0,003
Male sex	OR 2,39 (CI 95% 1,44-3,97)	p=0,001
3y GMDS Practical Reasoning DQ		
NEC	OR 4,47 (CI 95% 1,84-10,85)	p=0,001
"Longitudinal" EUGR at 6 months	***OR 2,07 (CI 95% 1,02-4,17)***	***p=0,04***

Multivariate Analysis corrected for gestational age (GA) for different Griffith Mental Development subscales at 3 years. Odds ratios (OR) were calculated with a 95% confidence interval (CI). All p-values were based on two-tailed tests.

4. Discussion

EUGR is already considered a risk factor for worse global mental development [7, 8, 9, 10, 11, 12]. We showed that better weight z-score at 6 months is protective for pathologic-border line GMDS at 2 years of age (Table 3). "Cross-sectional" EUGR at 6 months seemed to be associated with a worse neurodevelopment for some areas of GMDS at 2 and 3 years in particular: 2y locomotor, 2y personal-social, 2-3y language (Table 4, 6). "Longitudinal" EUGR from TEA to 6 months of CA was associated with a worse GMDS in 2y performance and 3y practical reasoning (Table 4, 6). The 6 months' time-point was not taken into consideration in recent existing studies, in particular Zozaya et al. that compared "longitudinal" and "cross-sectional" EUGR at 36 weeks of CA [8] or De Rose et al that compared 48 definitions of EUGR, 24 "cross-sectional" and 24 "longitudinal" at different time points from births to TEA [10]. Furthermore, the above mentioned studies didn't consider MRI data as an influencing factor for outcome.

A result similar to ours was published by Guellec I at al. as part of the EPIPAGE study. They demonstrated an association between "longitudinal" EUGR from birth to 6 months of age and cerebral palsy at 5 years in patients born AGA and cognitive deficiency-school difficulties in SGA at 5-8 years even if not significantly [13]. This study too, although extremely cited didn't consider lesions or no lesions studied with MRI to predict neurological follow-up.

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Our results reinforce attention not only to EUGR but to post-discharge growth focusing again on the feeding problems of VLBW preterms. Indeed, although there are evidence-based recommendations on VLBW nutrition in hospitals [46], little is known about optimal nutrition after discharge and also the introduction of solid foods (referred to as weaning) guidelines.

Regarding post-discharge nutrition, in our center, we recommend mother milk feeding. Exclusive post-discharge breastfeeding is rarely possible in our preterm babies so the initial indication is to feed with unfortified mother milk by bottle for a hydric quotient of 160 up to 200 ml/kg per day. In the absence of breastmilk, a post-discharge formula is prescribed for an energy quotient of between 120 and 140 kcal/kg/day until TEA and 3000 g of weight are reached, then it is replaced with common formula milk for an energy quotient of between 110 and 130 kcal/kg/day. These intakes are adjusted and individualized based on weight growth in the last hospital weeks and the first few post-discharge weeks and depending on the presence of co-morbidities. Unfortunately, mother milk was available in 59% but only 17% were exclusively fed by mother milk at 40 weeks of CA in our population, a poor result similar to others [47]. There is a large consensus that mother milk represents the best choice due to its well-known positive effects on neurodevelopment and body composition [46, 48, 49, 50, 51]. The role of mother milk fortification and the choice of better formula milk after discharge is still controversial. As a matter of fact, two quite recent Cochrane meta-analysis did not provide evidence that fortification of mother milk after hospital discharge or use of post-discharge formula (enriched in protein, LCPUFA, and micronutrients) are able to affect differently growth rates and neurodevelopmental outcomes [52, 53, 54]. Furthermore, as regards nutrition in the immediate post-discharge period, the only intervention showing encouraging results is to support and educate families to promote mother milk feeding [47].

Weaning is likely to be crucial for infantile nutrition and neurodevelopment [55, 56] although there is a wide variability in time of introduction, micronutrients supplementation and types of foods proposed center by center [57]. In our population weaning was started at 6 months of postnatal age (PA) according to ESPHGAN indications [58]. In literature, different timing for weaning was proposed mainly derived from observational studies [59, 60, 61]. The few randomized controlled trials (RCT) do not report significant differences in weight growth when weaning is started at 4 vs 6 months of correct age [62] or at 13 vs 17 weeks of age where an improvement in length at 12 months of age was the only achievement [63]. Only one recent RCT found that starting weaning in VLBW at 10-12 weeks of CA instead of 16 -18 weeks of CA had positive effects on weight z-score at 6 months [64]. None of these RCTs considered neurodevelopment as the primary outcome. The efficacy on the growth of this "early weaning policy" is still controversial with poor evidence as observed in different cohort studies [65, 66] but it seems to be safe without increased risk of obesity [62, 67] and food allergy or atopic dermatitis [68]. A recent systematic review guided by the Italian Societies of Pediatrics (SIP), Neonatology (SIN), and Paediatric Gastroenterology, Hepatology and Nutrition (SIGENP) tried to draw up recommendations for weaning in preterm infants and recommended to start between 5 and 8 months of postnatal age consider the limit of 3 months of CA to ensure the acquisition of developmental skills [69]. Based on our data and what is reported in the literature, we speculate that an early weaning policy at about 3 months of correct age when developmental skills are acquired (i.e., between about 4 and 6 months of PA depending on GA) will be safe and could improve weight gain at 6 months and consequently the neurological outcome of VLBW patients.

Data about the type of food proposed in weaning in preterm are lacking so the guidelines used for term babies are those used for preterms too [58, 70]. Interestingly Cochrane systematic review reports a decrease in risk of undernutrition and growth improvements when the family of term babies received adequate nutritional education although the effects on neurodevelopment remain uncertain [71]. A similar study was conducted in preterms families without convincing evidence although we can speculate that similar effects can be reached in preterm [72]. Proposing adequate nutritional education to families of preterm infants may improve the growth and neurodevelopment of these patients.

Lastly, other well-known risk factors like GA [4, 5, 6], male sex [73, 74], NEC [30, 31], and major surgeries [35, 36] were identified and confirmed by our study as risk factors for worse GMDS in

different areas. About MRI findings, in our population, PWML was confirmed to be a risk factor for worse GMDS, in particular for locomotor development (scale A) and performance (scale E) at 2 years, in agreement with previous findings [27, 75].

The strengths of our study are the large population of VLBW studied up to 3 years of age and the comparisons between two groups, one with absolute no brain lesion (at MRI) and the other with minor lesions whose long term clinical significance remain not widely studied.

5. Conclusions

Our study confirms that extrauterine growth retardation affects neurological outcomes in preterm infants. EUGR diagnosed at 6 months of corrected age seems to have a major negative impact on many areas of neurological development, more than those deriving from minor brain lesions almost exclusively diagnosed with MRI. Only Periventricular White Matter Lesions show a significantly negative effect like EUGR although it was restricted to locomotor development and performance and, exclusively, at 2 years follow-up. At 3 years of age EUGR at 6 months maintains a negative effect on language and practical reasoning. We believe it is appropriate to focus more on post-discharge nutritional help, optimizing family nutritional education.

Supplementary Materials: ***Table 1:*** population features; ***Table 2***: Griffith mental development scale II (GMDS) results at 2 and 3 years in the whole population for Global and sub-scales development quotient (DQ). ***Table 3***: Univariate and Multivariate Analysis results for global development quotient at 2 years. ***Table 4:*** Multivariate Analysis for different Griffith Mental Development subscales at 2 years. ***Table 5***: Univariate and Multivariate Analysis results for global development quotient at 3 years. ***Table 6***: Multivariate Analysis for different Griffith Mental Development subscales at 3 years

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Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required.

Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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