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Research Article

JOURNAL OF PEDIATRICS, PERINATOLOGY AND CHILD HEALTH

ISSN: 2641-7405

Low Grade Intraventricular Haemorrhage and Five-Year School Adaptation of Very Preterm Infants

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Abstract

Objectives: Intraventricular haemorrhage (IVH) is a frequent morbidity in the preterm infant's population. Low grade IVH's impact on neurodevelopment is not clear since data on the subject is contradictory. We aimed to study the effect of low grade IVH on school outcome at 5 years of age in a very preterm population.

Study design: Infants born preterm before 33 gestational weeks (GW) with low grade IVH or no IVH and followed in the LIFT (Loire Infant Follow Up Team) cohort with a school evaluation were included in the study. At least an ultrasound screening was performed during the first week of life for all infants. The school outcome is composed of the child's academic situation and of the teacher's evaluation of GSA (Global School Adaptation) score at 5 years.

Results: Among the 3206 infants with no IVH or low grade IVH during their initial hospitalisation, 2045 (64%) had a school evaluation at 5 years. No statistical difference on school outcome was found in a univariate analysis between infants without IVH, those with unilateral IVH and those with bilateral IVH (p = 0.542). There was no difference either after a set of logistic regressions for infants with no IVH, unilateral and for bilateral low grade IVH.

Conclusion: Low grade IVH seems to have no significant impact on 5-year neurodevelopment and academic abilities in our very preterm infant's population. This is an important result for clinicians and parents regarding prognosis of infants with neonatal low grade IVH.

Keywords: Intraventricular haemorrhage; Prematurity; Neurodevelopment; GSA score

Conflicts of interest: None

Introduction

Very preterm infants are at risk for numerous complications during initial hospitalization. One of them is intraventricular haemorrhage (IVH), which can result in significant neurodevelopmental impairment. Whereas progress in perinatal care during the last decades have led to a decreased mortality and morbidity in this high-risk population [1], neurological complications, in particular IVH remain a major concern for neonatologists.

IVH is the most common cerebral injury identified in preterm infants, with an incidence up to 32% in the most immature population [2] and results from a subependymal germinal matrix bleeding which can rupture into the lateral ventricles [3]. This bleeding occurs mostly during the first two weeks of life. It

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Citation: Apprioual Géraldine, Rozé Jean-Christophe, Rouger Valérie, Gascoin Géraldine, Nail Benallegue, Flamant Cyril. Low Grade Intraventricular Haemorrhage and Five-Year School Adaptation of Very Preterm Infants. Journal of Pediatrics, Perinatology and Child Health. 7 (2023): 134-141.

Received: June 19, 2023
Accepted: July 20, 2023
Published: July 31, 2023

Géraldine A, et al., J Pediatr Perinatol Child Health 2023
DOI:10.26502/jppch.74050157

is due to rich vascularity and vessels immaturity in this area, in addition to immature cerebrovascular autoregulation and coagulation disorders [4]. Several risk factors are well known for IVH, including gestational age (GA) and birth weight (BW) [5]. Other factors are implicated in the development of intraventricular haemorrhage, such as intrauterine infection, premature rupture of membranes, mode of delivery and absence of antenatal corticosteroid therapy [4,5].

Papile et al. [6] introduced a classification of IVH used to stratify IVH by severity. Grade I IVH is limited germinal matrix haemorrhage. Grade II IVH corresponds to intraventricular haemorrhage without ventricular dilatation. Grade III is IVH inducing ventricular dilatation and Grade IV is defined by intraventricular haemorrhage associated with intraparenchymal infarction. Grades I and II are considered as low grade IVH whereas grades III and IV are considered as high grade IVH [7].

High grade IVH is known to be a risk factor for poor neurodevelopmental outcome, during neonatal hospitalization [8] and in the long term [9]. The consequences of low grade IVH (grade I and II) are more uncertain which makes it more difficult to inform parents of very preterm infants about their prognosis in case of low grade IVH. A few studies, some of which published before the generalization of surfactant therapy, had shown an impact of low grade IVH on cognitive and school abilities compared with infants born at the same gestational age without IVH in very low birth weight infants (VLBW) population [10]. Payne et al. [11] have studied neurological outcome in a cohort of very preterm infants, comparing those with or without IVH [11]. In this study, at the age of 18 to 24 months of corrected age, no difference was found between preterm infants with low grade IVH and no IVH. In contrast, Patra et al. [12], in a cohort of 362 VLBW infants, have observed that infants with low grade IVH were more at risk for cerebral palsy, deafness and low cognitive scores compared to infants with no IVH [12]. Results of the studies conducted so far are contradictory, and very few are focused on neurodevelopmental status at school age and academic abilities.

Different tools are used to assess neurodevelopment in the preterm population. Among them, the Ages and Stages Questionnaire (ASQ) completed by parents is routinely used to assess the child in his own environment [13]. In this perspective, the Global School Adaptation (GSA) questionnaire was developed to evaluate school achievement and detect school difficulties at five years of age [14]. This easy tool is performed by the child's teacher and has been showed to be highly consistent with full-scale IQ scores in the preterm population [14].

The large regional LIFT (Loire Infant Follow Up Team) cohort gave us the opportunity to assess the possible impact of low-grade IVH on school outcome at 5 years of age.

Methods

Patients and sources

In this study, we included all surviving children born before 33 gestational weeks (GW), between March 2003 and December 2014, with at least one cranial ultrasound evaluation resulting in no or low grade IVH and enrolled in the regional multicentric LIFT cohort (Pays de Loire, France).

The LIFT network includes 23 maternities of which 3 neonatal intensive care units. It allows a long term follow up for children born preterm [15] with a screening for neurodevelopmental disabilities thanks to a standard assessment.

The LIFT cohort is registered with the French data protection authority in clinical research (Commission Nationale de l'Informatique et des Libertés or CNIL, No. 851117). Written consent was obtained from parents before children were included in the cohort.

Perinatal, demographic, neonatal and socioeconomic data were prospectively collected, in particular GA, sex, BW, antenatal corticosteroids, mode of delivery, multiple pregnancy, Apgar score, the course of hospitalization and parents' socioeconomic situation.

Cranial ultrasound evaluation

All children included in the study were evaluated by at least one cranial ultrasound, the first one was performed during the first week of life. IVH was ranked according to Papile's classification [6]. The most severe IVH grade was considered to classify each infant, and the unilateral/bilateral character of the disease was noted. Infants suffering from other cerebral lesions, as high grade IVH or Periventricular Leukomalacia (PVL) were excluded from the study.

GSA questionnaire and school outcome

The GSA questionnaire is an assessment tool, designed to evaluate academic and behavioural skills at five years of age [14]. The assessment is performed by the child's teacher at the age of 5 years (valid for two months either side of target age). This score has been shown to be correlated with the IQ evaluation at 5 years old in the very preterm population [14].

The GSA score is composed of twenty questions: six questions about linguistic competences, five questions about non-verbal abilities, eight questions about the child's behaviour in class and the 20th question asks the teacher's opinion about the child's adaptation to upcoming classes. Each question is worth 1 to 3 points (higher mark for best result), and the total score is obtained by summing the points. It has recently been shown that a non-optimal GSA score below the cut off of 48 points is predictive of a need for educational support at the age of seven [16].

Géraldine A, et al., J Pediatr Perinatol Child Health 2023
DOI:10.26502/jppch.74050157

All children included in the present study had a school evaluation at the age of five. Children were considered as having an optimal school outcome if they were enrolled in the expected class for their age with no need for special educational support and if they had an optimal GSA score > 48 at five years.

Statistical analysis

Descriptive values were reported as means with standard deviations for continuous variables, and number of subjects, frequencies and percentages for categorical variables. First, the neonatal characteristics and morbidities of the assessed population were compared to those of non-assessed population to check for comparability, with test using means comparisons. Second, the same analysis was performed between children with no IVH, unilateral and bilateral IVH.

Finally, tests were used to assess the effect of IVH on school outcome and GSA score at 5 y.o. Imputations were performed on infants followed in the LIFT Cohort but without school assessment at five years to reduce missing data. Multivariate analysis using four consecutive logistic regressions models was performed on complete cases and on imputed cases to adjust for clinically relevant characteristics (GA, BW z-score, gender, socioeconomical status, obstetrical data, head circumference and weight Z-scores at discharge and post-menstrual age at discharge).

The level of statistical significance was set at $p < 0.05$ for all analyses performed with two-tailed tests. Analyses were performed with SPSS 17.0.

Results

Of the 3206 infants screened by cranial ultrasound with no haemorrhage or low grade IVH during their neonatal hospitalisation, 2528 were enrolled in LIFT cohort, of which 2045 children (64%) had a school evaluation at 5 years, and 483 children did not have a school evaluation and were therefore excluded (Figure 1).

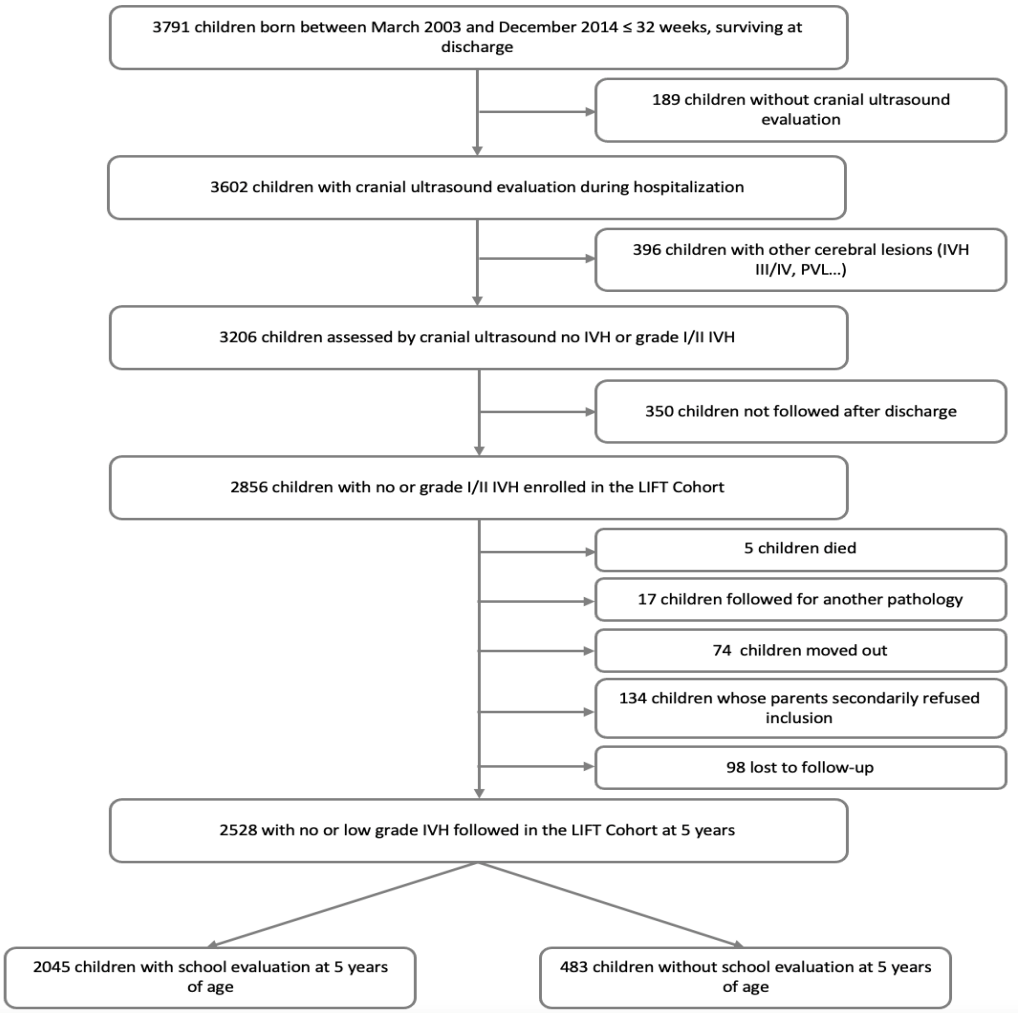

Figure1: Flow Chart.

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Table 1: Neonatal characteristics and morbidities on children with a school evaluation at 5 years in comparison with those not assessed (N = 3206).

Male sex	Assessed (N = 2045)	Not assessed (N = 1161)	p value
	1078 (52.7%)	**603 (51.9%)**	**0.672**
Gestational age, mean (weeks) ± SD	29.0 ± 1.82	29.2 ± 1.80	0.023
Antenatal corticosteroid therapy	1316 (64.4%)	712 (61.3%)	0.088
Multiple pregnancy	668 (32.7%)	314 (27.0%)	< 0.001
Caesarean section	950 (46.4%)	512 (44.1%)	0.198
Apgar < 7 at M5	197 (9.6%)	121 (10.4%)	0.473
Maternal hypertension	348 (17.0%)	202 (17.4%)	0.783
Birth weight Z-score ± SD	-0.18 ± 1.01	-0.13 ± 1.02	0.17
Weight Z-score at discharge ± SD	-1.01 ± 1.04	-0.83 ± 1.28	< 0.001
Birth head circumference Z-score ± SD	-0.08 ± 1.28	-0.11 ± 1.30	0.606
Head circumference Z-score at discharge ± SD	-0.29 ± 1.06	-0.25 ± 1.11	0.406
Post-menstrual age at oxygenotherapy discontinuation (weeks) ± SD	30.0 ± 2.44	30.1 ± 2.50	0.422
Post-menstrual age for exclusive enteral feeding (weeks) ± SD	33.7 ± 3.54	33.7 ± 3.44	0.867
Post-menstrual age at discharge (weeks) ± SD	37.8 ± 2.19	37.7 ± 2.30	0.047
Respiratory status			
- No oxygenotherapy (O_2) support	1118 (54.7%)	648 (55.8%)	0.016
- O_2 support < 28 days	692 (33.8%)	401 (34.5%)	
- O_2 support > 28 days without BPD*	176 (8.6%)	67 (5.8%)	
- O_2 support > 28 days with BPD	59 (2.9%)	45 (3.9%)	
Socioeconomic status			
- High	474 (23.2%)	144 (12.4%)	< 0.001
- Intermediate	1288 (63.0%)	782 (67.4%)	
- Low	252 (12.3%)	198 (17.1%)	
- Unknown	31 (1.5%)	37 (3.2%)	
*BPD : Bronchopulmonary dysplasia			

Among the population of 3206 children with no IVH or low grade IVH, those with school evaluation at 5 years old (N = 2045) were compared with others (N = 1161) (Table 1). Children assessed at 5 years of age were born at an earlier term (29.0 vs. 29.2 GW, p = 0.023), were more likely to be born from a multiple pregnancy (32.7% vs. 27.0% p < 0.001), to have a worse respiratory outcome (p = 0.016) and a worse weight Z-score at the end of the hospitalization (-1.01 vs. -0.83, p < 0.001). These infants were also more often born in families with a high socioeconomic status (p < 0.001). There was otherwise no difference on maternal, neonatal characteristics and complications of prematurity.

Characteristics of the children included in the study were compared according to their neurological status (no IVH, unilateral low grade IVH and bilateral low grade IVH) (Table 2). As compared with the others, children with bilateral low grade IVH had a significantly lower gestational age (p < 0.001), a lower Apgar score at M5 (p = 0.004), had a longer neonatal hospitalization with a higher post-menstrual age at discharge (p = 0.014) and had a lower head circumference Z-score at discharge (p = 0.027). Infants with a unilateral low grade IVH were less likely to be born by a cesarean section (p = 0.001), had a higher birth weight z-score (p = 0.036) and had higher risk for bronchopulmonary dysplasia (p = 0.032) as compared to the others.

Table 3 shows the impact of low grade IVH on school achievement at the age of five. In this univariate analysis, incidence of optimal school outcome was not significantly different between children with neonatal unilateral or bilateral low grade IVH and children without low grade IVH (p = 0.542) and mean for GSA score was also not different according to their neurological status (p = 0.405).

Four consecutive logistic regressions were performed on complete cases (Figure 2) and imputed cases (Figure 3). This multivariate analysis showed no statistical difference between infants with bilateral low grade IVH, unilateral low grade IVH or no IVH.

Géraldine A, et al., J Pediatr Perinatol Child Health 2023
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Table 2: Neonatal characteristics and morbidities of children without IVH, low grade unilateral IVH and low grade bilateral IVH (N = 2528).

	No IVH	Low grade unilateral IVH	Low grade bilateral IVH	p value
	N = 2228	N = 135	N = 165	
Gestational age, mean (weeks) ± SD	29.1 ± 1.77	28.5 ± 2.04	28.2 ± 2.10	< 0.001
Male sex	1170 (52.5%)	69 (51.1%)	95 (57.6%)	0.42
Antenatal corticosteroid therapy	1446 (64.9%)	80 (59.3%)	105 (63.6%)	0.401
Multiple pregnancy	730 (32.8%)	38 (28.1%)	47 (28.5%)	0.304
Caesarean section	1067 (47.9%)	47 (34.8%)	64 (38.8%)	0.001
Maternal hypertension	397 (17.8%)	16 (11.9%)	28 (17.0%)	0.204
Apgar < 7 at M5	194 (8.7%)	15 (11.1%)	27 (16.4%)	0.004
Birth weight Z-score ± SD	-0.20 ± 1.01	-0.02 ± 0.93	-0.14 ± 1.06	0.036
Weight Z-score at discharge ± SD	-0.99 ± 1.15	-0.98 ± 1.04	-1.19 ± 0.99	0.082
Birth head circumference Z-score ± SD	-0.09 ± 1.27	-0.09 ± 1.30	-0.11 ± 1.37	0.267
Head circumference Z-score at discharge ± SD	-0.27 ± 1.08	-0.31 ± 1.14	-0.51 ± 0.97	0.027
Post-menstrual age at oxygenotherapy discontinuation (weeks) ± SD	30.1 ± 2.4	30.2 ± 3.0	29.8 ± 3.3	0.469
Postmenstrual age for exclusive enteral feeding (weeks) ± SD	33.7 ± 3.4	33.6 ± 3.8	34.0 ± 4.2	0.483
Post-menstrual age at discharge (weeks) ± SD	37.8 ± 2.2	38.1 ± 2.5	38.3 ± 2.1	0.014
Respiratory status				
- No oxygenotherapy (O_2) support	1213 (54.4%)	57 (42.2%)	79 (47.9%)	0.032
- O_2 support < 28 days	766 (34.4%)	56 (41.5%)	59 (35.8%)	
- O_2 support > 28 days without BPD*	180 (8.1%)	14 (10.4%)	18 (10.9%)	
- O_2 support > 28 days with BPD	69 (3.1%)	8 (5.9%)	9 (5.5%)	
Socioeconomic status				
- High	495 (22.2%) 1394 (62.6%)	35 (25.9%)	37 (22.4%)	0.767
- Intermediate	304 (13.6%)	79 (58.5%)	108 (65.5%)	
- Low	35 (1.6%)	18 (13.3%)	18 (10.9%)	
- Unknown		3 (2.2%)	2 (1.2%)	

Table 3: Impact of low grade unilateral/bilateral IVH at 5 years of age (N = 2528).

	No IVH N = 2228	Low grade unilateral IVH N = 135	Low grade bilateral IVH N = 165	p value
GSA score (mean) ± SD	48.3 ± 8.5	47.5 ± 8.7	47.6 ± 8.4	0.405
Optimal school evaluation*	1026 (57.1%)	63 (55.8%)	70 (52.2%)	0.542

* Optimal school evaluation: children enrolled in the expected class for they age with no need for special educational support or optimal GSA score at 5 years (GSA score > 48)

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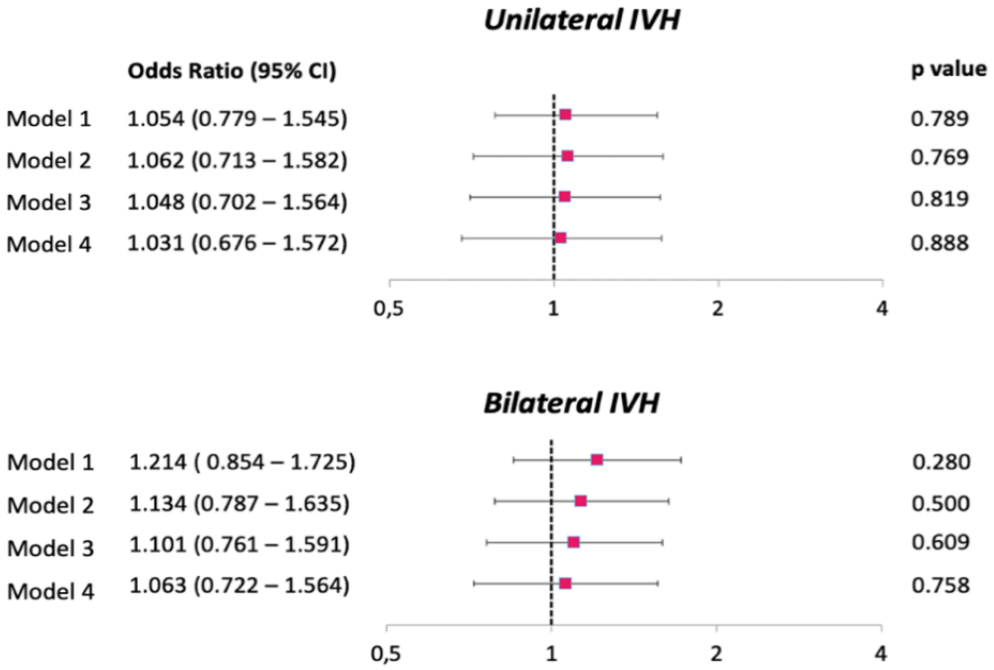

Figure 2: Multivariate analysis of the association between school outcome and unilateral/bilateral low grade IVH (complete cases). Model 1 is not adjusted. Model 2 is adjusted on GA, BW Z-score and economic status. Model 3 is adjusted on those included in model 2 and obstetrical data. Model 4 is adjusted on those included in model 3 and GA at discharge.

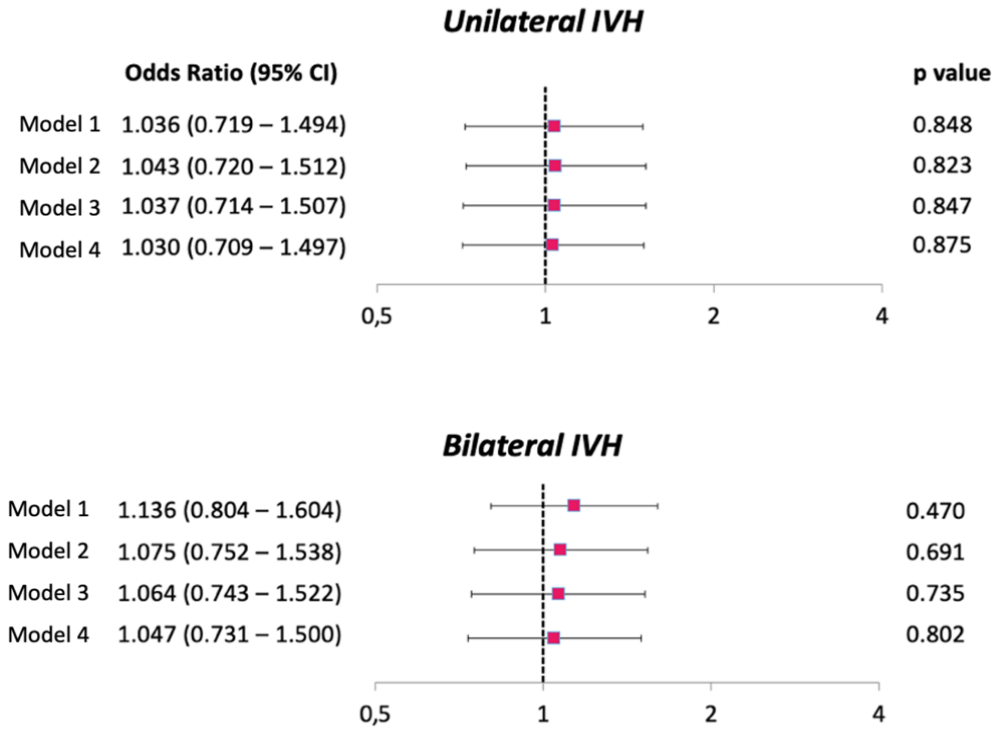

Figure 3: Multivariate analysis of the association between outcome and unilateral/bilateral low grade IVH (imputed cases). Model 1 is not adjusted. Model 2 is adjusted on GA, BW Z-score and economic status. Model 3 is adjusted on those included in model 2 and obstetrical data. Model 4 is adjusted on those included in model 3 and GA at discharge.

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Discussion

In this large prospective French cohort of very preterm infants, we found no difference at 5 years on school difficulties between children with low grade IVH and children with normal cranial ultrasound screening during the neonatal period. These results could constitute an important element to bring to parents of very preterm infants at the time of diagnosis and may help the clinician to specify the later prognosis of infants who present a low grade intraventricular haemorrhage.

Data regarding low grade IVH in literature is controversial and most studies are targeted on neonatal outcome or short-term outcome with a 18-24 months neurodevelopmental assessment. In a recent meta-analysis by Mukerji et al. [17] comparing infants with low grade IVH to infants with no IVH, and infants with high grade IVH to infants with low grade IVH, the authors found a gradual risk for neurodevelopmental impairment at 18-24 months according to the severity of the IVH. Infants with low grade IVH were more at risk for the composite outcome of death or neurodevelopmental impairment than children with no IVH. An Australian retrospective cohort, including 332 extremely preterm infants with neonatal low grade IVH found an increased rate of neurosensory impairment (developmental delay, severe cerebral palsy or bilateral blindness) at 2 to 3 years of corrected age [18]. These studies are of interest because they provide information about neurodevelopmental outcome in case of low grade IVH neonatal diagnosis, but they are limited in time without further cognitive assessment and school adaptation.

Another recent Australian retrospective cohort by Legge et al. [19] evaluated the neurodevelopmental impact of low grade IVH on a longer term (5 and 8 years). They included 450 newborns < 30 gestational weeks, 15% of whom were diagnosed with intraventricular haemorrhage. No difference was found on Full Scale IQ at 5 years between children affected by low grade IVH and their unaffected matched peers. The 8-year evaluation did not show either any decrease in Full Scale IQ, children with low grade IVH even had better scores than their unaffected peers, which could be explained by the possible impact of early interventions on this specific population [19].

In our study, the unilateral/bilateral character of the low grade IVH did not seem to have an impact on the school outcome of the children. Infants suffering from bilateral low grade IVH had similar overall results than infants with unilateral low grade IVH and infants without IVH. While it is well known that infants with bilateral grade IV IVH have a worse outcome than unilateral grade IV IVH [20], the impact of bilateral low grade IVH compared to unilateral low grade IVH was not shown until now to the best of our knowledge.

One of the strengths of our study is related to the large population-based cohort, with an assessment at school age for more than sixty percent of the children included. The children assessed at 5 years of age were mostly similar to those not included (not assessed or lost to follow-up after their hospital discharge), except that they were born at an earlier term, had a better respiratory outcome and were less likely to be from a lower socio-economic class. Another strength of this study is the statistical analysis using multiple imputations, allowing to reduce the missing data and increasing the size of the sample. Furthermore, in this article, we showed an absence of difference between uni- or bilateral low

IVH, which is an information not widely discussed in the literature. However, our study is retrospective and observational with all the limitations inherent to this type of study, especially the risk of confounding factors, which was managed by a set of logistic regressions. In addition, the cranial ultrasound evaluation was not standardized, with potential differences in terms of postnatal age at the time of the cranial ultrasound, number of ultrasound evaluations during the hospital stay, and the ultrasound operator (radiologist or neonatologist), according to the different centres included in the LIFT cohort.

The neurodevelopmental assessment at the age of five allows for a more accurate evaluation than the earlier evaluation because it takes into consideration the acquisition of academic skills and analyses some behavioural and social skills. However, this evaluation is still limited since it takes place before the learning of reading and writing. There might be a benefit to extend the follow-up and evaluate infants later in childhood to screen for more subtle difficulties.

Conclusion

In this very preterm population, no impact of low grade IVH was found on a 5-year school outcome, both for unilateral and bilateral IVH. This is an important factor for the clinician to provide to parents of a very preterm infant diagnosed with low grade intraventricular haemorrhage. Further studies are nevertheless needed to sharpen the possible impact of each grade of intraventricular haemorrhage on neurodevelopmental outcome.

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