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Original article

Seizures in preterm infants with germinal-matrix-intraventricular hemorrhage (GM-IVH): a retrospective monocentric study on predictors and neurodevelopmental outcome

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ABSTRACT

Aim: Germinal-matrix-intraventricular hemorrhage (GM-IVH) is a leading cause of seizures in preterm infants. This study aimed to analyze risk factors associated with seizures and to evaluate neurodevelopmental outcomes in preterm infants with GM-IVH and seizures.
Methods: We conducted a retrospective study from 2011 to 2019, identifying preterm infants with GM-IVH grades 2–4 through an electronic patient file system. Seizures were diagnosed based on clinical manifestations and abnormal EEG findings. Infants were grouped by the presence or absence of seizures, and associated comorbidities were compared. Neurodevelopmental follow-up was assessed at two years of age using the Mental Bayley Scales of Infant Development II (BSID-II). Outcomes of infants with seizures were compared to all tested preterm infants with birth weight <1500 g born between 2011 and 2019 (n = 195).
Results: A total of 34 preterm infants with GM-IVH grades 2–4 were included. Seizures occurred in 52.9 % of cases. Their occurrence was significantly associated with lower gestational age (mean 28.1 vs. 30 weeks, p = 0.04) and pneumonia (p = 0.003). Infants with seizures had significantly lower BSID-II Mental scores (n = 15) compared to those without seizures (86.3 ± 18.3 vs. 104.9 ± 8.5, p = 0.03). However, as these infants had a lower gestational age, we could not distinguish if they had a poorer outcome because of seizures or because of immaturity.
Conclusion: Seizures in preterm infants with GM-IVH were significantly associated with lower gestational age and pneumonia. Infections and inflammation may contribute to seizure development. Larger studies with continuous EEG monitoring are needed to validate these findings.

1. Introduction

1.1. Germinal matrix-intraventricular hemorrhage -pathophysiology

Germinal matrix-intraventricular hemorrhage (GM-IVH) is the most common neurological complication in preterm neonates on the neonatal intensive care unit (NICU) [1]. Studies from Australia and New Zealand found that 20 % of preterm infants <34 weeks of gestational age (GA) were affected [2], a Brazilian study found up to 34 % [3]. The pathomechanisms leading to GM-IVH involve vascular fragility and fluctuation in cerebral hemodynamics [4,5]. Additionally, inflammatory processes, often resulting from conditions such as maternal chorioamnionitis and early-onset neonatal sepsis, have been implicated in increasing the risk of vascular injury and subsequent bleeding [6,7].

The germinal matrix is a highly vascularized structure within the periventricular and subependymal region of the brain [1]. It begins to regress after 28 weeks of gestational age and is completely degraded at term age [8].

Findings from animal studies demonstrated that GM-IVH leads to brain injury through mechanisms such as iron overload, reactive oxygen species production and lipid peroxidation [9]. Additionally, GM-IVH in

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Abbrevitions

GM-IVH	germinal-matrix intraventricular hemorrhage
BSID	Bayley Scales of Infant Development
GMFCS	Gross Motor Function Classification System
DEGUM	German Society for Ultrasound in Medicine
aEEG	amplitude-integrated EEG
cEEG	conventional EEG
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
VACTERL	Vertebral defects, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, and Limb abnormalities
VP	ventriculo-peritoneal

the preterm brain leads to disruption of the periventricular zone which contains neuronal stem cells and therefore plays a crucial role for the development of glia cells, astrocytes and neurons [10,11]. Experimental data support that these pathomechanisms crucially contribute to long-term morbidity following GM-IVH [8].

1.2. Germinal matrix-intraventricular hemorrhage and seizures

GM-IVH does not only have a long-term negative impact on neurological development, but it is also the most common etiology of seizures in premature infants during the neonatal period [12–14]. Despite advances in neonatal intensive care, the precise mechanisms and risk factors contributing to seizures in neonates with GM-IVH remain incompletely understood.

1.2.1. Neurodevelopmental outcome of infants born preterm

Cerebral palsy and intellectual disability are common in preterm infants. The incidence of cerebral palsy in prematurely born infants ranged from 5.3 % (GA 27–31 weeks) to 8.8 % (GA 24–26 weeks) in the French EPIPAGE-2 study, including 3083 prematurely-born children at the age of 5 years [15]. High-grade GM-IVH, i.e. stage 3 and 4, increases the risk for cerebral palsy up to 26–30 % in preterm infants born before 30 weeks of GA [16,17]. In contrast, the impact of low-grade GM-IVH I and II on neurodevelopment remains controversial. While a recent Meta-analysis addressing the outcomes of preterm infants (GA <34 weeks) with GM-IVH up to three years of age, showed a slightly increased risk of neurodevelopmental impairment, including cerebral palsy and cognitive impairment [18], compared to preterm infants without GM-IVH, other studies could not confirm an increased risk of neurological impairment [19].

The potential effect of neonatal seizures in the context of GM-IVH on the neurodevelopmental outcome, especially in higher-grade GM-IVH, has not been studied so far. Understanding the interplay between these factors is crucial for improving clinical outcomes in this vulnerable population. Therefore, we conducted a retrospective monocentric analysis (2011–2019) to compare the neurodevelopmental outcome of preterm infants with GM-IVH with and without seizures at the age of 2 years.

2. Methods

2.1. Patient data acquisition

A targeted patient search was performed for the diagnoses “premature infant” and “intracranial hemorrhage” for the years 2011–2019 via our digital patient management system (Soarian, Siemens, Erlangen) as outlined in the Consort chart (Fig. 1) at the Department of Pediatrics, Friedrich-Alexander-University Erlangen-Nürnberg, Germany.

Cerebral imaging and EEG findings, as well as clinical data were taken from the medical records of interest. We compared preterm infants with GM-IVH and seizures to prematurely born infants with GM-IVH without seizures.

The following additional variables were included for analysis:

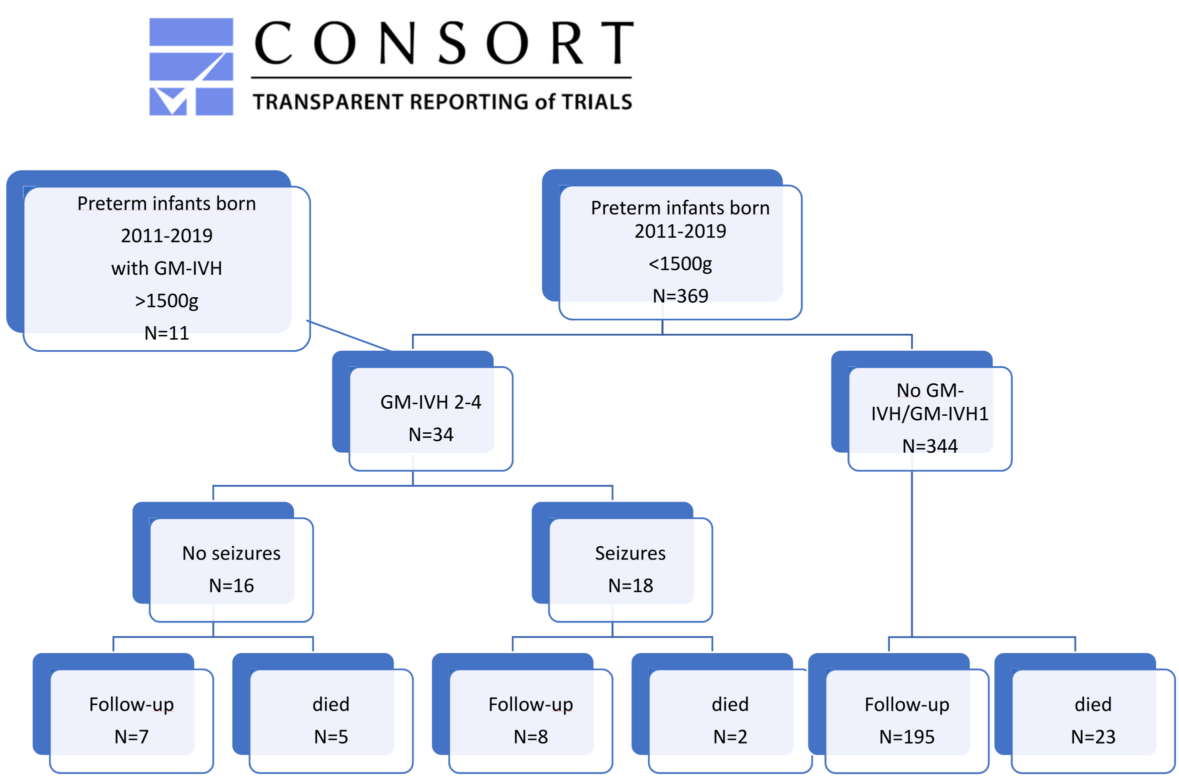

Fig. 1. Flow diagram of patient enrollment.

gestational age, birth weight, head circumference, multiple birth, respiratory distress syndrome, bronchopulmonary dysplasia, persistent ductus arteriosus, anemia, necrotizing enterocolitis, infection, pneumonia, sepsis, grade of intraventricular hemorrhage, occurrence of bilateral hemorrhage, number of EEGs, type of EEG (continuous vs. non-continuous), ventriculomegaly, ventriculo-peritoneal shunt (VP shunt) and mortality.

2.2. Diagnosis of GM-IVH and seizures

GM-IVH was diagnosed via standardized cerebral ultrasound which was performed according to the DEGUM recommendation on day of life 1, 3 and 7 [20]. GM-IVH was classified according to the Papile classification system [21]. "High-grade GM-IVH" was defined as GM-IVH 3 and 4. Seizures were diagnosed by a clinical seizure-suspicious event and a pathological interictal or ictal conventional EEG (range 30min – 1h), validated by a pediatric neurologist. The EEG was video-assisted and based on a conventional EEG with 8 active electrodes according to the international 10-20 system of electrode placement, modified for neonates (F1, F2, C3, C4, T3, T4, O1, O2), combined with amplitude-integrated EEG (aEEG) in accordance to the recommendations of the American Clinical Neurophysiology Society Guideline from 2011 (23). EEGs were considered to be pathologic if there were electrographic seizures or if focal or multifocal sharp wave discharges were detected. Continuous EEG recording was not routinely established in the analysed time period and only available in selected cases. The EEGs were evaluated by an experienced child neurologist. The standard treatment for seizures in preterm infants was phenobarbital as a first line therapy. In cases in which seizures persisted and the EEG remained pathological, levetiracetam was added as a co-medication. We included all seizures occurring from birth until hospital discharge.

2.3. Diagnosis of infection, sepsis and pneumonia

The diagnosis of infection was made by clinical signs of infection and if antibiotic treatment was continued for more than 3 days, CRP >5 mg/l. Sepsis was diagnosed based on the presence of a positive blood culture. Pneumonia was defined as the need for mechanical ventilation with concomitant detection of pathogens in the tracheal aspirate of preterm infants, radiologic signs of respiratory distress syndrome as well as elevated CRP, elevated leucocytes or leucopenia and thrombopenia. For pneumonia and sepsis, the temporal association with the occurrence of seizures and date of collection was verified. The diagnoses of pneumonia and sepsis were independently reviewed and confirmed by two board-certified neonatologists (i.e., FF, PM).

2.4. Neurodevelopmental outcome

At the age of two years, neurodevelopment was assessed by clinical neurological examination and by using the Mental Bayley Scales of Infant Development II. Postneonatal epilepsy was defined as the presence of seizures after discharge from the hospital and antiseizure medication at the age of 2 years.

2.5. Statistical analysis

The statistical analysis was performed using Graph Pad Prism version 9 (Graph Pad Software, Boston, Massachusetts, USA) and SPSS version 21 (IBM, Armonk, New York, USA) software programmes. Categorical variables were analysed by the Chi-square-Test and Exact Fisher Test. Results are given as mean ± SD unless stated otherwise. Statistical tests were considered significant at $p < 0.05$.

Ethical statement

Our retrospective study was approved by the institutional ethics committee of the medical faculty of the University of Erlangen-Nürnberg (request no.416_20Bc).

3Results

Our retrospective study included 34 preterm infants with a gestational age (GA) of 23–35 weeks (mean GA 29.2 ± 3.4). Twenty-three infants were very-low-birth-weight, and 11 patients had a birth weight >1500 g (Fig. 1). Among these infants, 18 had GM-IVH 3 and 4, 16 infants were diagnosed with GM-IVH 2 (Table 1). Neonatal seizures were observed in 18 infants (52.9 %). Table 1 presents the characteristics of patients classified into seizure and non-seizure groups: Infants with seizures had a significantly lower gestational age and lower birthweight (28.1 ± 3.0 weeks, 1006 ± 299g) compared to those who had no seizures (30.3 ± 3.6 weeks, 1502 ± 591g, p = 0.03, p = 0.02, shown in Table 1). The seizures occurred in the neonatal period (postnatal day 1–24), the mean time of onset was 7.6 ± 5.6 postnatal days.

Bronchopulmonary dysplasia, persistent ductus arteriosus and development of hydrocephalus requiring a VP-shunt implantation were more frequent in the seizure group, but the difference between the two groups did not reach statistical significance. Pneumonia with detection

Table 1
Characteristics of preterm infants with GM-IVH with/no seizures.

	All infants (N = 34)	No seizures (N = 16)	Seizures (n = 18)	
GA (weeks), mean (SD)	29.2 (3.4)	30.3 (3.6)	28.1 (3.0)	**P = 0.03**
Birth weight (g), mean (SD)	1240 (526)	1502 (591)	1006 (299)	**P = 0.02**
Head circumference (cm), mean (SD)	27.1 (3.7)	28.8 (3.7)	25.7 (3.1)	P = 0.09
Multiple birth (n)	13 (38.2 %)	6 (37.5 %)	7 (39.9 %)	P = 0.18
Respiratory distress syndrome (N)	23 (67.6 %)	10 (62.5 %)	13 (72.2 %)	P = 0.41
Bronchopulmonary dysplasia (N)	3 (8.8 %)	0	3 (16.7 %)	P = 0.14
Persistent ductus arteriosus (N)	10 (29.4 %)	3 (18.8 %)	7 (39.9 %)	P = 0.18
Anemia (N)	23 (67.6 %)	9 (56.3 %)	14 (77.8 %)	P = 0.23
Necrotizing enterocolitis (NEC, N)	6 (17.6 %)	2 (12.6 %)	4 (22.2 %)	P = 0.66
Infection, clinical (N)	30 (88.3 %)	12 (75.0 %)	18 (100 %)	**P = 0.04**
Pneumonia with positive tracheal aspirate (N)	8 (23.5 %)	0	8 (55.5 %)	**P = 0.003**
Sepsis (N)	3 (8.8 %)	0	3 (16.7 %)	P = 0.14
GM- IVH 2 (N)	16 (47.1 %)	8 (50.0 %)	8 (44.4 %)	P = 0.90
GM-IVH 3	13 (38.2 %)	6 (37.5 %)	7 (38.9 %)	
GM_IVH 4	5 (14.7 %)	2 (18.5 %)	3 (16.7 %)	
GM-IVH bilateral (N)	23 (67.6 %)	11 (64.7 %)	12 (70.6 %)	P = 0.50
EEG/no EEG	25 (73.5 %)/9	7 (53.8 %)/16	18/18 (100 %)	P > 0.001
Number of EEGs, mean (SD)	10 (4.5)			
Continuous EEG	7 (28 %)	1 (6.2 %)	6 (33.3 %)	
Ventriculomegaly (N)	15 (44.1 %)	5 (31.3 %)	10 (55.6 %)	P = 0.14
VP shunt (N)	5 (14.7 %)	1 (6.7 %)	4 (22.2 %)	P = 0.23
Mortality (N)	7 (20.6 %)	5 (31 %)	2 (11.1 %)	P = 0.15

Metric variables were compared with the unpaired *t*-test, categorical variables with the Chi-Square Test and Exact Fisher Test. SD: standard deviation, N: number of patients.
The percentage refers to the number of patients in the column.

of bacterial pathogens was a significant risk factor for seizures (p = 0.003). The grade of GM-IVH or a bilateral GM-IVH was not decisive for the development of seizures (Table 1).

3.1. Seizures in preterm infants with GM-IVH grade 2

In the group of preterm neonates with GM-IVH grade 2, eight out of 16 (50 %) developed neonatal seizures. These infants had a significant lower gestational age and lower birth weight compared to those without seizures (27.1 ± 2.6 vs. 32.3 ± 1.7, p = 0.01, 977 ± 333 g vs. 1813 ± 305, p = 0.01, shown in Table 2). However, no other significant differences in comorbidities or pre-existing risk factors were observed between preterm infants with GM-IVH grade 2 and seizures compared to those without seizures (Table 2).

3.2. Seizures in preterm infants with high-grade GM-IVH

Neonatal seizures were diagnosed in 10 out of 18 (55.6 %) preterm neonates with high-grade IVH. In contrast to the group of patients GM-IVH grade 2, there were no significant differences in gestational age and birth weight between infants with and those without seizures. However, seizures were significantly associated with pneumonia (p = 0.003, Table 3).

3.3. Antiseizure medication (ASM) in preterm neonates with GM-IVH

Phenobarbital was the first-line treatment in all infants (n = 34, 100 %). In 14 out of 18 patients (77.8 %), an additional antiseizure medication (levetiracetam in 12 out of 14 patients) was administered. The remaining two patients received midazolam and clonazepam respectively. The group receiving the additional medication had a slightly lower gestational age compared to patients on phenobarbital monotherapy (27.3 ± 2.4 vs. 30.8 ± 3.9), however this difference was not statistically significant. The antiseizure medication (ASM) was continued after discharge from the hospital in 15/18 (83.3 %) infants.

Table 2
Characteristics of preterm infants with GM-IVH 2 with/no seizures.

	No seizures (N = 8)	Seizures (N = 8)	
GA (weeks), mean (SD)	32.3 (1.7)	27.1 (2.6)	**P = 0.01**
Birth weight (g), mean (SD)	1815 (305)	977 (333)	**P = 0.01**
Head circumference (cm), mean (SD)	30.6 (2.3)	25.3 (3.8)	**P = 0.03**
Multiple birth (n)	2 (25 %)	4 (50 %)	P = 0.3
Respiratory distress syndrom(N)	5 (62.5 %)	5 (62.5 %)	P = 0.7
Bronchopulmonary dysplasia (N)	0	1 (12.5 %)	P = 0.50
Persistent ductus arteriosus (N)	2 (25 %)	3 (37.5 %)	P = 0.64
Anemia (N)	4 (50 %)	6 (66.7 %)	P = 0.30
Infection, clinical (N)	7 (87.5 %)	8 (100 %)	P = 0.50
Pneumonia with positive tracheal aspirate (N)	0	2 (25 %)	P = 0.47
Sepsis (N)	0	2 (25 %)	P = 0.23
Ventriculomegaly (N)	1	4 (50 %)	P = 0.23
VP shunt (N)	0	1 (12.5 %)	P = 0.6
Mortality (N)	0	1 (11.1 %)	P = 0.56

Metric variables were compared with the unpaired *t*-test, categorical variables with the Chi-Square Test and Exact Fisher Test.
SD: standard deviation, N: number of patients.
The percentage refers to the number of patients in the column.

Table 3
Characteristics of preterm infants with GM-IVH 3 and 4 with/no seizures.

	No seizures (N = 8)	Seizures (N = 10)	
GA (weeks), mean (SD)	28.3 (4.0)	28.7 (3.3)	P = 0.42
Birth weight (g), mean (SD)	1188 (686)	1030 (285)	P = 0.26
Head circumference (cm), mean (SD)	26.4 (4.1)	26.0 (2.6)	P = 0.41
Multiple birth (N)	4 (50 %)	3 (30 %)	P = 0.5
Respiratory distress syndrom(N)	5 (62.5 %)	8 (80 %)	P = 0.38
Bronchopulmonary dysplasia (N)	0	2 (20 %)	P = 0.29
Persistent ductus arteriosus (N)	1 (12.5 %)	4 (44.4 %)	P = 0.23
Anemia (N)	65 (66.7 %)	7 (77.8 %)	P = 0.38
Infection, clinical (N)	5 (62.5 %)	10 (100 %)	P = 0.07
Pneumonia with positive tracheal aspirate (N)	0	6 (60 %)	**P = 0.01**
Sepsis (N)	0	1 (10 %)	P = 0.56
Ventriculomegaly (N)	4 (50 %)	5 (50 %)	P = 0.52
VP shunt (N)	1 (12.5 %)	3 (30 %)	P = 0.38
Mortality (N)	5 (62.5 %)	1 (10 %)	**P = 0.03**

Metric variables were compared with the unpaired *t*-test, categorical variables with the Chi-Square Test and Exact Fisher Test.
SD: standard deviation, N: number of patients.
The percentage refers to the number of patients in the column.

The duration of treatment was highly variable (244.5 ± 226.4 days, range 53–925 days).

3.4. Infection in preterm infants with GM-IVH

Infection was diagnosed in 25 of 34 patients (73.5 %). 3 of them (8.8 %) had a positive blood culture. 23.5 % (8/34) of infections were pneumonias –caused by staphylococci, E. coli and pseudomonas aeruginosa. In 3 cases coagulase-negative staphylococci were isolated. Neonates with a positive blood culture or tracheal aspirate had a lower mean gestational age compared to those with negative findings (29.9 + 3.5 weeks vs 27.3 + 2.5 weeks, p = 0.01). The time interval between seizures and positive tracheal aspirate was 7.2 ± 7.04 days. Sepsis was detected in the three affected children on day 2, day 7 and in one child on day 43 after the onset of the seizure, so that we only assume a temporal connection in the first-mentioned cases.

3.5. Outcome

3.5.1. Mortality in preterm infants with GM-IVH

The overall mortality in our preterm GM-IVH cohort was 20.6 % (n = 7, Fig. 1 and Table 1 which was higher number compared to our cohort of VLBW (n = 23, 6.7 %, Fig. 1). Notably, only a single infant (GA 24 weeks) died from severe brain edema as a direct consequence of GM-IVH grade 4. One infant with a gestational age of 24 weeks died from respiratory failure, while two infants with a GA of 25 and 28 weeks died due to sepsis, NEC and multiorgan failure. Another infant with a gestational age of 28 weeks died because of multiorgan failure, but in this case as a consequence of severe asphyxia with an umbilical cord blood pH of 6.7. One child had VACTERL association with pulmonary atresia and renal failure. One child died at the age of 13 month due to sepsis and short bowel syndrome.

3.5.2. Neurodevelopmental outcome of infants born preterm with GM-IVH

We were able to conduct a follow-up on 15 out of 27 (55.6 %) surviving infants, who underwent a neurodevelopmental examination and the Mental Bayley Scales of Infant Development (BSID II) at a mean age of 23.8 ± 1.9 months.

Preterm infants with seizures had lower scores on the Mental Developmental index (MDI) (N = 8, 86.3 ± 18.3) compared to preterm infants without seizures (N = 7, 104.9 ± 8.5) (Fig. 2). The difference was significant ($p = 0.03$). 53.33 % in the seizure group had an MDI score below 85. In the overall group of preterm infants <1500g we found 29 % who had an MDI Score below 85. For infants with GM-IVH who did not experience seizures, the outcome was favorable with no infants with an MDI below 85.

One child (6.7 %) without seizures developed cerebral palsy GMFCS (Gross Motor Function Classification System) 3, while three patients (20 %) in the seizure group had cerebral palsy ($p = 0.60$, Exact Fisher test). None of the children without seizures developed post-neonatal epilepsy, but three patients with neonatal seizures had epilepsy at the age of two years ($p = 0.25$, Exact Fisher test). One infant, born at 25 weeks of gestation, developed BNS epilepsy at six months after the antiseizure medication was discontinued. This child also developed bilateral spastic cerebral palsy and could not be assessed with the Bayley Mental Scales due to severe developmental delay at the age of two years. Instead, the Griffith Scales were used, revealing a developmental index of 63.

4. Discussion

This study identifies pneumonia and lower gestational age as significant clinical risk factors for neonatal seizures in preterm infants with GM-IVH. Additionally, we observed that seizures were associated with poorer neurodevelopmental outcomes, although this finding was confounded by the significantly lower gestational age of infants with seizures. The frequent use of second-line antiseizure medication and the lack of continuous EEG monitoring highlight the current diagnostic and therapeutic challenges in this population.

4.1. Role of gestational age

The mean gestational age of preterm infants with neonatal seizures in our study was 28.0 weeks, compared to 30.3 weeks in infants without seizures. This supports the known association between lower gestational age and seizure risk. A previous study similarly reported a mean GA of 25.0 weeks in infants with seizures and 27.0 weeks in those without [13]. While the absolute gestational ages differ, both studies highlight that seizure occurrence is more common among the most immature infants.

When comparing preterm infants with GM-IVH grade 2 to those with grades 3 and 4, we observed that lower gestational age, lower birth weight, and smaller head circumference were associated with an increased risk of seizures in the grade 2 group. Other factors like bronchopulmonary dysplasia, anemia and PDA did not show the same association. In contrast, the high-grade GM-IVH group had a more homogenous and overall lower gestational age compared to the preterm infants with GM-IVH 2. Mortality was higher in infants with GM-IVH than in the overall cohort of preterm infants, however the main causes of death were sepsis or respiratory failure and not the consequences of GM-IVH.

4.2. Consequences of GM-IVH in the preterm brain

GM-IVH contributes to brain injury through multiple pathways. Experimental studies in rodents have shown that hemoglobin and thrombin increase pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β, and promote oxidative stress, damaging oligodendrocyte precursor cells [22]. These cells differentiate into oligodendrocytes, white matter astrocytes, and GABAergic neurons, particularly in the thalamus and cortex. Consequently, GM-IVH disrupts myelination. These findings from animal studies are supported by MRI diffusion tensor imaging(DTI) studies in preterm infants, which demonstrate reduced myelination in preterm infants affected by GM-IVH [23].

4.3. Influence of inflammation

Our analysis indicated a significant association between seizures and

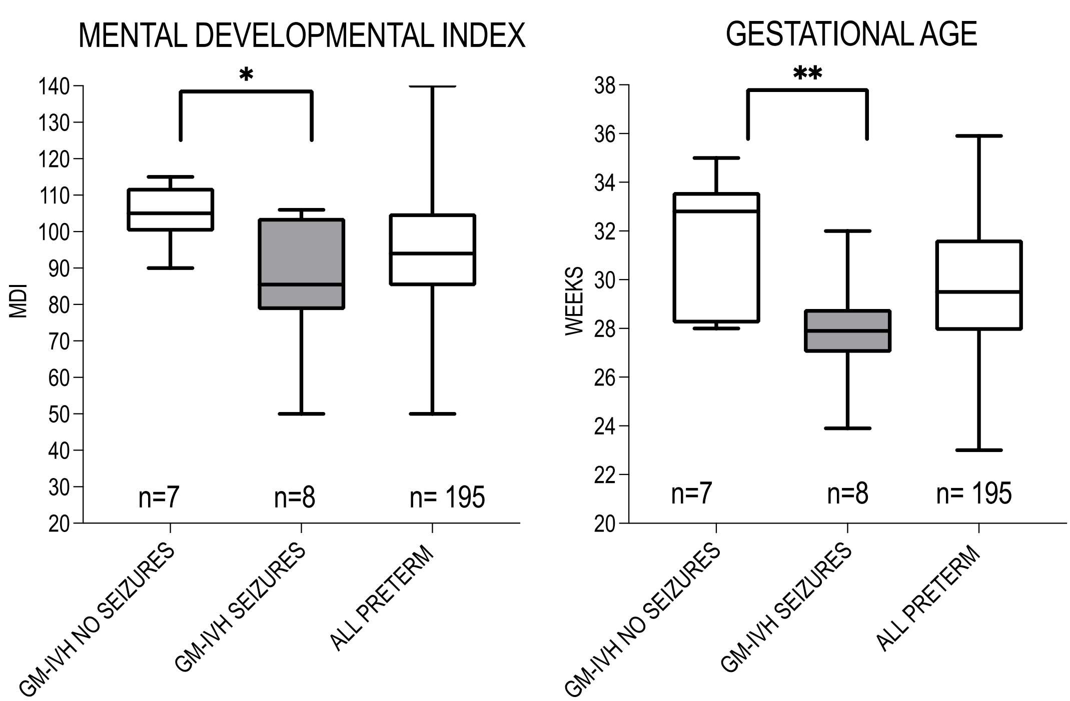

Fig. 2. Cognitive development of preterm infants with GM-IVH with/without seizures.

pneumonia in preterm infants with GM-IVH, especially in high-grade hemorrhage. Although NEC and sepsis were more frequent among infants with seizures, these associations were not statistically significant. Experimental data support these findings: in an LPS-induced brain injury model in preterm sheep, white matter injury and EEG disturbances occurred to a greater extent [24]. Similarly, LPS infusion in mice increased seizure susceptibility [25]. In clinical studies, premature infants with periventricular leukomalacia had a 4.6-fold increased seizure risk if sepsis or NEC were also present [26]. Furthermore, the presence of microorganisms in the placenta has been linked to neonatal seizures in very preterm infants [27]. These data support our hypothesis that inflammation may contribute to seizure development. Additionally, pneumonia likely increases the risk of hypoxia and hyperoxia due to complex respiratory management. Both conditions can be monitored via near-infrared spectroscopy (NIRS) [28], but their specific impact on seizure development remains poorly studied. While the role of hypoxia is well established—particularly in term infants with hypoxic-ischemic encephalopathy [29,30]—the precise relationship between oxygenation disturbances (e.g., pO_2 and pCO_2 variability) and seizures in preterm infants warrants further investigation. Hypoxia leads to a failure of the Na-K-ATPase in neurons, resulting in depolarization, calcium influx, and glutamate release, which collectively increase neuronal excitability [31].

4.4. Antiseizure medication in preterm infants with GM-IVH

Phenobarbital was the WHO-recommended first-line therapy for neonatal seizures during our study period (2011–2019) and remains endorsed by the International League Against Epilepsy (ILAE)- Task Force on Neonatal Seizures [32,33]. In our cohort, most infants required second-line treatment with levetiracetam, particularly those of lower gestational age. This reflects clinical observations from other studies, such as Herzberg et al., who found a limited response of 68 % to ASM in preterm infants with GM-IVH [34]. A further study on preterm infants treated with levetiracetam as a first line therapy reported that a greater proportion of infants required three ASMs—including topiramate and phenytoin [35]. These findings underscore the high prevalence of refractory seizures in this population and highlight the need for further pathophysiological research.

4.5. Role of EEG in seizure diagnosis

Recent studies emphasize that many seizures in preterm infants with GM-IVH are electrographic-only and would go undetected without continuous conventional EEG (cEEG) monitoring [36,37,38]. However, a meta-analysis found that most studies still rely on intermittent cEEG or aEEG monitoring, possible due to logistical challenges of implementing cEEG in critically ill preterm neonates [39]. Furthermore, the presence of microorganisms in the placenta has been linked to neonatal seizures in very preterm infants [27]. In our study, cEEG was not available in all patients and could not be analysed retrospectively, likely leading to underdiagnosis of subclinical seizures. Nevertheless, the seizure detection rate in our cohort was comparable to those reported in studies using aEEG. For example, Shah et al. [38] reported seizures in 62.5 % of preterm infants with high-grade GM-IVH using aEEG, while Vesoulis et al. [37] found seizures in 48 % of preterm infants regardless of GM-IVH presence. While cEEG remains the gold standard for neuromonitoring in preterm infants, aEEG -although less sensitive (30–50 %)- is established as a preferred method in many NICUs [40]. Both aEEG and cEEG require expert interpretation, which limits widespread use. Looking ahead, artificial-intelligence and specialized algorithms hold promise for improving neuromonitoring and the detection of neonatal seizures in the future [41].

4.6. Neurodevelopmental outcome

Preterm infants with GM-IVH and seizures showed significantly lower MDI scores (−1 SD), but this was confounded by a lower gestational age in this group. Thus, it remains unclear whether seizures independently worsen neurodevelopmental outcomes or reflect the consequences of extreme prematurity and its comorbidities (e.g., BPD). To our knowledge, previous studies have not specifically addressed this question, highlighting the need for prospective, matched-control studies.

In our cohort, the rates of cerebral palsy in the seizure group were not significantly higher compared to previous studies on preterm infants with similar gestational ages [15,16,42] The rate of postneonatal epilepsy was 16 %. This number is consistent with the findings from Pisani et al., who found epilepsy in 9 of 58 children at 30 months [43]. These data suggest that neonatal seizures associated with GM-IVH are predominantly acute symptomatic events that do not necessarily lead to epilepsy. While the prognosis regarding postneonatal epilepsy is generally favorable, cognitive impairment remains a significant neurological concern following preterm birth.

4.7. Limitations and perspective

The main limitation of our study is the small sample size, which results from its single-center, retrospective design. While this reduces significance and statistical power, it ensures a homogeneous cohort in terms of clinical care and diagnostic protocols. A UK-based study showed high variability in neonatal seizure management across NICUs, with 18 different guidelines across 68 units [44], underlining the value of consistent single-center data.

Importantly, we focused on seizures due to a single etiology—GM-IVH—unlike many previous studies that combined heterogeneous neonatal populations. However, only 15 of 27 surviving infants completed neurodevelopmental follow-up, underscoring the need for more complete follow-up and family engagement strategies. Although we aimed to assess the impact of seizures on developmental outcomes, the significantly lower gestational age in the seizure group precludes causal interpretation. Larger, multicenter studies with consistent EEG use and matched patient cohorts will be needed to clarify the impact of seizures on long-term outcomes in preterm infants with GM-IVH.

5. Conclusion

Infections and Inflammation may significantly contribute to the development of seizures in preterm infants with GM-IVH. Premature infants with GM-IVH and infections might have a special risk for seizures and should undergo continuous EEG-Monitoring. Studies with larger cohorts of infants and continuous EEG-monitoring are required to confirm our findings.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used DeepL Translate in order to translate parts of the text in English. After using this tool, the author(s) reviewed and edited the content as needed and take (s) full responsibility for the content of the publication.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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