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Research Paper

Association Between Seizures and Neurodevelopmental Outcome at Two and Five Years in Asphyxiated Newborns With Therapeutic Hypothermia

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ABSTRACT

Objective: To investigate the association between the presence and severity of seizures in asphyxiated newborns and their neurodevelopmental outcome at ages two and five years.
Methods: Retrospective data analysis from a prospectively collected multicenter cohort of 186 term-born asphyxiated newborns undergoing therapeutic hypothermia (TH) in 11 centers in the Netherlands and Belgium. Seizures were diagnosed by amplitude-integrated electroencephalography (EEG) and raw EEG signal reading up to 48 hours after rewarming. Neurodevelopmental outcome was assessed by standardized testing at age two and five years. Primary outcome was death or long-term neurodevelopmental impairment (NDI) including cerebral palsy. Associations were calculated using univariate and multivariate logistic regression analyses adjusting for Thompson score and a validated brain magnetic resonance imaging (MRI) score.
Results: Seventy infants (38%) had seizures during TH or rewarming, and 44 (63%) of these needed two or more antiseizure medications (ASMs). Overall mortality was 21%. Follow-up data from 147 survivors were available for 137 infants (93%) at two and for 94 of 116 infants (81%) at five years. NDI was present in 26% at two and five years. Univariate analyses showed a significant association between seizures and death or NDI, but this was no longer significant after adjusting for Thompson and MRI score in the multivariate analysis; this was also true for severe seizures (need for two or more ASMs) or seizures starting during rewarming.
Conclusion: The presence or severity of seizures in newborns undergoing TH for hypoxic-ischemic encephalopathy was not independently associated with death or NDI up to age five years after adjusting for several confounders.

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Introduction

Neonatal seizures are frequently encountered in infants suffering from hypoxic-ischemic encephalopathy (HIE) caused by perinatal asphyxia. Studies have shown that the occurrence of seizures and the seizure burden (SB) within the first days of life in these infants are associated with an increased risk of neurodevelopmental impairment (NDI). Except for a recently published large cohort study on SB and neurological outcome at 18 months, the majority of published studies were performed in the era before hypothermia treatment was introduced.[1-3] Nowadays therapeutic hypothermia (TH) treatment has been implemented as standard of care in most high-income countries, and its application reduces the SB and improves neurodevelopmental outcome in infants with HIE.[4,5]

Previous studies investigating the association of neonatal seizures with outcome in neonates suffering from HIE may have been influenced by methodologic weaknesses.[5-19] First, some studies investigated this association only with clinically diagnosed seizures without electroencephalographic (EEG) confirmation.[13,15] As many seizures in neonates exist in the absence of any clinical manifestation, these results may not be reliable.[20,21] Second, some studies only assessed the association between seizures and magnetic resonance imaging (MRI) abnormalities instead of neurodevelopmental outcome.[6,9,16,19] Finally, none of the studies adjusted the analyses for severity of encephalopathy before TH using the Thompson score, or assessed the neurodevelopmental outcome beyond the follow-up period of two years. Outcome assessment of NDI is more reliable at more advanced ages.

It is essential for clinicians and caregivers to know whether the presence and/or severity of neonatal seizures in HIE during TH or the onset of seizures during rewarming are associated with long-term outcome. Therefore, the aim of this study was to assess if the presence of seizures (as diagnosed by aEEG combined with a raw EEG signal reading), the seizure severity, or the presence of seizures during rewarming was associated with neurodevelopmental outcome at both two and five years in infants with HIE and treated with TH.

Methods

Study design and participants

This is a retrospective study of prospectively collected data from a large observational multicenter study, the "PharmaCool study."[22] In the PharmaCool study investigators assessed the pharmacokinetics and pharmacodynamics of commonly administered drugs during TH in infants suffering from HIE caused by perinatal asphyxia. The original study was conducted between December 2009 and December 2014. A total of 10 Dutch and two Belgian neonatal intensive care units participated. All newborns undergoing TH were eligible for inclusion. According to national protocol, term newborns (gestational age $\geq$37 weeks) were treated with TH within six hours after birth to a core temperature of 33.5°C for 72 hours if they met the criteria of perinatal asphyxia and ensuing encephalopathy defined by a Thompson score $\geq$7. Thereafter, patients were slowly rewarmed to normothermia. Exclusion criteria were congenital hepatic or renal pathology and absence of central venous or arterial access for blood sampling. The institutional review board of each participating center approved the study, and parents provided signed informed consent. All 189 participants of the original PharmaCool study were included in the current study. The original study was funded by a Project Grant from The Netherlands Organization for Health Research and Development ZonMw, Priority Medicines for Children Grant number: 40-41500-98-9002.

Seizures and antiseizure medications

All infants were continuously monitored with amplitude-integrated EEG (aEEG) using one or two channels following a standardized national hypothermia protocol. Recording started when the infant was admitted to the neonatal intensive care unit and was continued until 48 hours after rewarming. Seizures were diagnosed by assessing the aEEG pattern combined with a raw EEG signal recording. The presence of seizures (or status) was assessed and noted in the anonymized study files (CRF) every day by the attending physician, who was trained in the interpretation of aEEG and raw EEG signal reading. Also, the type, number, and dose of the antiseizure medications (ASMs) prescribed were noted each day up until the fifth day. Medical files were carefully studied to assess if benzodiazepine medication (e.g., midazolam) was used as an ASM or a sedative. Based on the known association with seizures starting during the rewarming period and poor outcome, we also collected these data for further analysis.

All infants were subjected to at least one full-lead EEG registration at 48 hours after admission, and if needed multiple full-lead EEG registrations were performed. The full-lead EEG registrations were assessed by both experienced pediatric neurologists and neurophysiologists.

As part of the clinical protocol, all neonates underwent an MRI scan of the brain after rewarming. MRI scans were assessed according to a previously validated MRI scoring system.[23] All MRI scans were centrally assessed by a team of highly experienced neuroradiologists and neonatologists unaware of the patients' history. Scans were performed according to national TH protocol between days 4 and 8 of life. Timing of MRI scan was not influenced by seizure onset.

Outcome definition

As part of routine care following TH for HIE, a standardized outpatient follow-up visit was performed at age two years including a neurological examination by a trained neonatologist and a Bayley Scales of Infant and Toddler Development test (third edition, Dutch Language [BSID-III-NL]) by a trained developmental specialist.[24] In the presence of cerebral palsy (CP), the level of CP was classified using the Gross Motor Function Classification System (GMFCS).[25] NDI was defined as a test score ≤ -1 S.D. below the reference mean BSID-III-NL composite cognitive score or composite motor score (i.e., a score <85 points), a GMFCS score of $\geq$2, a hearing loss requiring aids, or cerebral visual impairment (blind or abnormal visual acuity). Furthermore, as part of routine care, a standardized follow-up visit was performed at age five years, using the Wechsler Preschool and Primary Scale of Intelligence-III and the movement Assessment Battery for Children 2. A neurological examination was again included. NDI at five years was defined as having either Full Scale Intelligence Quotient <85 of the Wechsler Preschool and Primary Scale of Intelligence-III, movement Assessment Battery for Children 2 total raw score <5, a GMFCS score of $\geq$2, a hearing loss requiring aids, or cerebral visual impairment (blind or abnormal vision). All outcome assessments were performed blinded for the research questions. For statistical analyses, the binary outcomes of interest at ages two and five years were the combined outcome death or NDI and its separate components. As a sensitivity analysis we also assessed the association of the presence of seizures with the cognitive outcome at both ages.

Statistical analyses

Data were analyzed using R statistical software (Version 4.03 for Windows) and R Studio (integrated development for R, Boston, 2015) (R studio desktop 2022.07.02). Descriptive statistics summarized the patient characteristics and outcome parameters depending on their distribution as mean (±S.D.) or median (minimum–maximum). To minimize missing data, the principal investigator of each center was contacted for any details needed. When data could not be retrieved and there was >5% missing data that was assumed to be missing at random, multiple imputation was performed on the dataset. For the dependent variables, passive imputation was used after checking possible correlations for each variable. Multiple imputations results were checked for imputation errors, with convergence plots, strip plots, and checking individual datasets.[26] First, the association between seizures and/or number of ASMs needed and the outcome of interest was analyzed using univariate logistic regression analyses expressed as odds ratios (ORs) and its 95% confidence intervals (CIs). Second, a multivariate logistic regression analysis was performed adjusting for the Thompson score as a measure of HIE disease severity. Finally, a third multivariate logistic regression model was analyzed including the (total) MRI score by Weeke et al.[23] combined with the Thompson score[27] after birth as potential confounders. A sensitivity analysis was performed to test the robustness of the analyses by assessing the association between the long-term outcomes and the onset of seizures during rewarming and the presence of severe seizures defined as needing treatment with two or more ASMs. Although the majority of the participating centers used the BSID-III-NL for assessing neurodevelopmental outcome, in case another version of the BSID was used, a correction as previously described was performed to compensate for discrepancies between these scales.[28,29]

Results

Patient characteristics and patient flow

Three infants of the 189 included were excluded because of congenital malformations (Figs 1 and 2). The patient characteristics and incidence of seizures are shown in Table 1. All infants were assessed by aEEG and EEG as mentioned. MRI was performed in the first week of life in 83% of cases; in 17% of cases MRI was performed within the first 14 days because of clinical factors.

Of the 186 eligible infants, 70 (38%) infants developed seizures during the first four days after birth, and 44 (63%) of those 70 infants with seizures needed two or more ASMs. A total of 15 infants suffered seizures during rewarming. Thirty-nine infants (21%) died during initial admission; none died during the five-year follow-up period. The outcome assessment at age two years was incomplete for 31 (21%) infants, of whom none were diagnosed with any form of CP. In total 10 (7%) infants were lost to follow-up. Analyses of the patient characteristics of the survivors assessed at follow-up versus those lost to follow-up showed no significant differences (Supplementary Table 1).

In 27% of the infants, the BSID scores needed to be converted from either the second Dutch edition to the (currently used) third Dutch edition or from previously used American norms to (currently used) Dutch norms. Follow-up at age five years was standard of care in six of the 11 participating centers. Therefore, in total 116 of the 147 (79%) potential patients were eligible for the five-year follow-up assessments. The five-year outcome assessment was incomplete for 22 (19%) infants; again none of these infants showed signs of CP. In total 22 (19%) infants were lost to follow-up. Analyses of the patient characteristics of the survivors assessed at follow-up versus those lost to follow-up showed no significant differences (Supplementary Table 2). NDI was present in 26% of the survivors at both two- and five-year follow-up.

Association with outcomes at ages two and five years

The univariate analyses at age two years showed that a diagnosis of seizures occurring during the first four days was significantly associated with the combined outcome death or NDI (OR 5.18, 95% CI 2.68 to 9.99), and its component death (OR 5.44, 95% CI 2.51 to 11.8), or NDI in survivors (OR 2.62, 95% CI 1.10 to 6.26). These associations remained significant after adjusting for the Thompson score, but not after adjusting for the Thompson and the brain MRI score (Table 2). Also, no significant association was found for the presence of seizures and the cognitive outcome (adjusted OR [aOR] 1.25, 95% CI 0.32 to 4.93).

The univariate analyses at age five years showed that a diagnosis of seizures occurring during the first four days was significantly associated with the combined outcome death or NDI (OR 2.90, 95% CI 1.19 to 7.06), and its component death (OR 3.14, 95% CI 1.33 to 7.39), but not NDI in survivors (Table 2). The only association remaining significant after adjusting for the Thompson score was the outcome death (aOR 3.10, 95% CI 1.10 to 8.77). After adjusting for both the Thompson and MRI score, none of the associations were statistically significant (Table 2). Again, no significant association was found for the presence of seizures and the cognitive outcome (aOR 1.27, 95% CI 0.28 to 5.78).

In the univariate analyses, the use of two or more ASMs as a proxy for the more severe seizures was significantly associated with the combined outcome death or NDI (OR 8.76, 95% CI 3.87 to 19.8), and its component death (OR 10.2, 95% CI 4.55 to 22.7), whereas the outcome NDI showed no difference at age two years. Adjusting for the Thompson score did not change these associations. After adjusting for both confounders, the Thompson and the brain MRI score, the associations with long-term outcomes were no longer statistically significant.

At five years corrected age, the univariate analysis and multivariate analysis correcting for the Thompson score showed a significant association between the use of two or more ASMs and the combined outcome and its component death (Table 3). However, the outcome NDI in survivors was not associated with the number of used ASMs in both analyses. After adjusting for both the

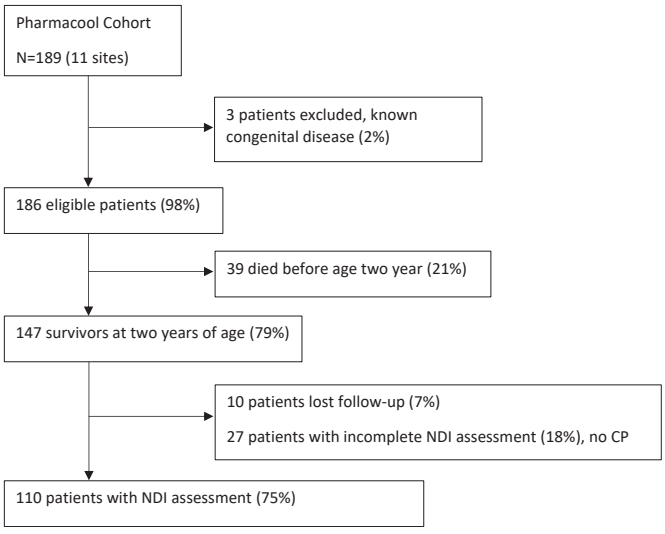

FIGURE 1. Flow diagram of patient selection at age two years.

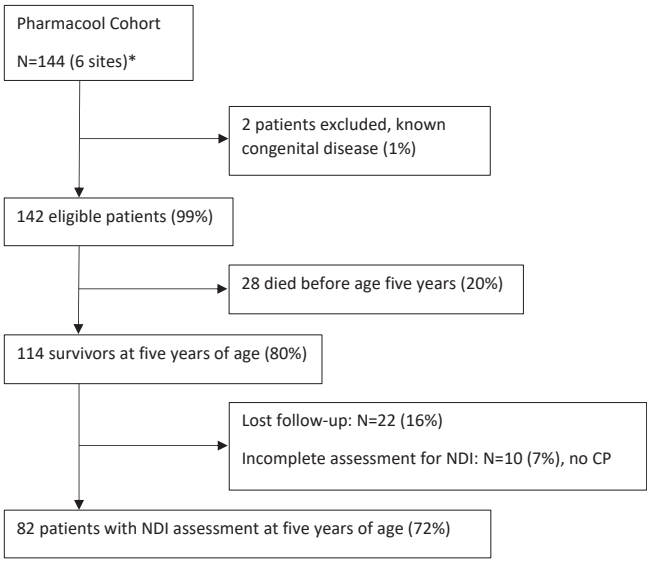

FIGURE 2. Flow diagram patient selection at age five years. *Six sites of the Pharmacool performed standardized neurodevelopmental assessment at age five years.

TABLE 1.
Patient Characteristics

Characteristics	Two Years (N = 186)	Five Years (N = 142)
Clinical Characteristics		
Male	116 (61%)	90 (63%)
Gestational age (weeks)	40 (36-42)	40 (36-42)
Birth weight (g)	3400 (2090-5070)	3365 (2090-5070)
Apgar at 1 minute	1 (0-9)	1 (0-9)
Apgar at 5 minutes	3 (0-10)	3 (0-10)
Apgar at 10 minutes	5 (0-10)	5 (0-9)
pH (at admittance)	6.98 (6.53-7.38)	6.98 (6.53-7.38)
Thompson score	9 (3-19)	9 (3-19)
Seizures*	70 (38%)	50 (35%)
Adverse aEEG background	44/172 (26%)	32/133 (24%)
nr. ASMs ≥2	44 (24%)	33 (23%)
nr. ASMs ≥3	14 (8%)	9 (6%)
nr. ASMs = 4	4 (2%)	2 (1%)
Seizures during rewarming	15/163 (9%)	11/123 (9%)
Outcome		
Combined outcome	68/149 (46%)	49/110 (45%)
Death	39/186 (21%)	28/142 (21%)
NDI in survivors assessed	29/110 (26%)	21/82 (26%)
CCS/WIPPSI	101 (54-143)	100 (59-144)
CMS/mABC2	104 (52-132)	8 (2-15)
GMFCS ≥2	14/137 (10%)	4/77 (5%)
Vision	4/137 (3%)	0/89 (0%)
Hearing	3/135 (2%)	0/89 (0%)

Abbreviations:
aEEG = Amplitude-integrated encephalography
CCS = Composite cognitive score
CLV = Continuous extremely low voltage
CMS = Composite motor score
GMFCS = Gross Motor Function Classification System
mABC2 = Movement Assessment Battery for Children-2
NDI = Neurodevelopmental impairment
nr. ASMs = Number of antiseizure medications
WPPSI = Wechsler Preschool and Primary Scale of Intelligence-III
Median (min-max).
Adverse aEEG background defined as abnormal burst suppression/CLV/flat trace.
Combined outcome = death or NDI.
* During first five days after birth.

Thompson and MRI score, none of the outcomes at interest showed an independent association with the number of ASMs administered.

The univariate and multivariate analyses correcting for the Thompson score showed a significant association between the onset of seizures during rewarming and the combined outcome death or NDI at age two years (OR 16.9, 95% CI 3.73 to 76.8; aOR 14.5, 95% CI 2.93 to 72.1, respectively). The univariate and multivariate analyses correcting for the Thompson score at age five years also showed a significant association between the onset of seizures during rewarming and the combined outcome death or NDI (OR 15.1, 95% CI 1.95 to 116.3; aOR 12.4, 95% CI 1.49 to 102.9, respectively). After correcting for both Thompson score and the brain MRI score, none of the outcomes were associated with seizures during the rewarming period.

Discussion

This is the first study assessing the association between neonatal seizures and the outcomes mortality and neurodevelopment up to age five years in infants suffering from HIE due to perinatal asphyxia and treated with TH. The univariate analyses showed a significant association between the presence and severity of seizures and the long-term outcome or demise at ages two and five years. Most of these outcomes remained statistically significant after adjusting for the Thompson score. However, adjusting for both the Thompson score and brain damage assessed on MRI, none of the association analyses remained significant.

Previous studies have shown an association between MRI abnormalities with neuronal injury and the presence of neonatal seizures.[30,31] Our current study results, investigating long-term clinical outcomes, did not confirm this association of seizures as an independent risk factor for neuronal injury. Seizures are bursts of abnormal and uncontrolled neural activity, leading to increasing metabolic demand, triggering neuronal glycolysis and increasing energy depletion. It is plausible that neonatal seizures might secondarily exacerbate neuronal injury in an already energy-depleted and injured brain due to the initial perinatal asphyxia.[32] However, it is important to acknowledge that these studies by design are not able to differentiate between a direct causal effect of seizures on acquired brain injury and the presence of seizures as merely a reflection of disease severity. Unraveling whether epilepsy augments brain damage after HIE is important and has a direct clinical impact, because treatment with antiepileptic drugs is not without risks and might, in some cases, outweigh the benefits. Although neonatal seizures are regarded as an emergency neonatal condition that needs to be treated immediately, evidence of benefit of treating infants with HIE with ASM is scarce, and many of these drugs may also have an impact on long-term development.[33,34] The drugs reported in our study cohort (e.g., midazolam) were only prescribed at the time to treat seizures and not as sedatives.

In addition to scoring the absence or presence of seizures, we also performed a more detailed analysis looking at seizures during rewarming and the use of multiple antiepileptic drugs.

A recent publication demonstrated that the presence of seizures during rewarming was associated with an increased risk for death or disability at two years.[5] These infants presented with a predominantly suppressed background EEG and basal ganglia-thalamic MRI injury pattern, suggesting the presence of a severe insult at birth. This finding is in line with our results where the presence of seizures during rewarming was significantly associated with the combined outcome death or NDI at age two years and the outcome death, even after adjusting for the Thompson score.

We were able to assess both the two- and five-year outcomes of this cohort. To date, no other study investigated the association

TABLE 2.
Association Between Seizures and Long-Term Outcome at Ages Two and Five Years

Outcome	Seizures		Univariate Analyses			Multivariate Model Adjusted for Thompson			Multivariate Model Adjusted for Thompson and Weeke		
	Yes	No	OR	95% CI	*P* Value	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value
Age Two Years											
Combined	42/62 (68%)	26/87 (30%)	5.18	(2.68-9.99)	<0.01	5.39	(2.58-11.2)	<0.01	2.01	(0.77-5.26)	0.15
Death	27/70 (39%)	12/116 (10%)	5.44	(2.51-11.8)	<0.01	5.76	(2.38-13.9)	<0.01	1.97	(0.49-7.89)	0.33
NDI in survivors	15/35 (43%)	14/75 (19%)	2.62	(1.10-6.26)	0.03	2.29	(1.05-4.98)	0.04	1.53	(0.66-3.59)	0.32
Age Five Years											
Combined	24/44 (55%)	29/74 (39%)	2.90	(1.19-7.06)	0.02	2.29	(0.89-5.87)	0.08	0.98	(0.30-3.25)	0.98
Death	16/50 (32%)	12/92 (13%)	3.14	(1.33-7.39)	<0.01	3.10	(1.10-8.77)	<0.01	0.94	(0.13-6.53)	0.95
NDI in survivors	8/28 (29%)	17/62 (27%)	1.18	(0.42-3.31)	0.76	0.96	(0.32-2.82)	0.93	0.67	(0.21-2.16)	0.50

Abbreviations:
aOR = Adjusted odds ratio
BSID-III-NL = Bayley Scales of Infant and Toddler Development test (third edition, Dutch Language)
CI = Confidence interval
GMFCS = Gross Motor Function Classification System
MRI = Magnetic resonance imaging
NDI = Neurodevelopmental impairment, defined as a test score ≤ -1 S.D. below the reference mean BSID-III-NL composite cognitive score or composite motor score (e.g., a score <85 points), a GMFCS score of ≥ 2, a hearing loss requiring aids, or cerebral visual impairment (blind or abnormal vision)
OR = Odds ratio
Weeke = Weeke MRI score

between seizures and long-term outcome up to age five years. The majority of the analyses performed in this study showed similar results at both two and five years. The only difference between two and five years was the lack of an association between the presence of seizures during the first four days or during rewarming and the outcome NDI in survivors. We can only speculate on the reason of these differences between the two- and five-year outcomes. The number of publications reporting the five-year outcome of infants after TH for HIE is scarce, making it difficult to compare our rates of NDI in survivors with those of other cohorts.[35,36] Nevertheless, the incidence of NDI at five years in the group of infants who had seizures seems low compared with the two-year outcome, suggesting a lack of power to detect a possible difference at five years. Six of the 11 participating centers in the Pharmacool performed the standard five-year follow-up, and these six centers included 76% (144 of 189) of the Pharmacool participants; this may have resulted in selection bias explaining the observed difference between two- and five-year outcomes. The fact that no differences were seen between those infants included in the analysis and those lost to follow-up is reassuring but does not completely rule out bias. Given this uncertainty regarding the five-year outcome, more studies with follow-up continued after age two years are needed.

The impact of neonatal seizures during TH on long-term outcome or degree of hypoxic-ischemic damage visible on MRI in asphyxiated infants has been a matter of debate fueled by small studies that were heterogeneous in methodology, timing of assessment, and definitions of outcome.[5-19] These studies showed conflicting results with six showing a significant association between seizures and long-term outcomes,[5,6,8,9,19] whereas nine studies not showing. There may be several explanations for this lack of consistency. First, in contrast to our multicenter prospective study, most reports had small samples sizes (median number of patients 49) and were performed in a single-center setting using retrospective data.[7-14] Second, these studies only assessed mortality till discharge home or developmental outcome up to two years.[5-9,11,14-19] Finally, the majority of the studies did not adjust the association under investigation for the Thompson score or MRI result, which, based on the results of our study, may lead to different results.[6-8,15] In contrast to our study, Alharbi et al. assessed the association of the SB instead of the presence of seizures with

TABLE 3.
Association Between Number of Antiseizure Medications and Long-Term Outcome at Ages Two and Five Years

Outcome	AEDs ≥2		Univariate Analyses			Multivariate Model Adjusted for Thompson			Multivariate Model Adjusted for Thompson and Weeke		
	Yes	No	OR	95% CI	*P* Value	aOR	95% CI	*P* Value	aOR	95% CI	*P*Value
Age Two Years											
Combined	33/62 (53%)	35/87 (40%)	8.76	(3.87-19.8)	<0.01	5.88	(2.47-14.0)	<0.01	1.81	(0.48-6.87)	0.38
Death	24/70 (34%)	15/116 (13%)	10.2	(4.55-22.7)	<0.01	5.89	(2.42-14.4)	<0.01	0.50	(0.09-2.59)	0.41
NDI	9/35 (35%)	20/75 (27%)	2.32	(0.88-6.14)	0.08	1.90	(0.69-5.28)	0.21	1.22	(0.38-3.90)	0.74
Age Five Years											
Combined	22/44 (50%)	31/74 (42%)	4.50	(1.62-12.5)	<0.01	3.11	(1.05-9.21)	0.04	1.08	(0.25-4.57)	0.92
Death	17/50 (34%)	11/92 (12%)	9.47	(3.73-24.1)	<0.01	3.10	(1.10-8.78)	<0.01	0.94	(0.13-6.53)	0.95
NDI	5/28 (18%)	20/62 (32%)	1.15	(0.33-4.03)	0.82	1.08	(0.28-3.76)	0.98	0.68	(0.16-2.86)	0.59

Abbreviations:
AED = Antiepileptic drug
aOR = Adjusted odds ratio
ASMs = Antiseizure medications
BSID-III-NL = Bayley Scales of Infant and Toddler Development test (third edition, Dutch Language)
CI = Confidence interval
GMFCS = Gross Motor Function Classification System
NDI = Neurodevelopmental impairment, defined as a test score ≤ -1 S.D. below the reference mean BSID-III-NL composite cognitive score or composite motor score (e.g., a score <85 points), a GMFCS score of ≥ 2, a hearing loss requiring aids, or cerebral visual impairment (blind or abnormal vision)
OR = Odds ratio

long-term outcome data in a cohort study and showed that an increased total SB was independently associated with worse cognitive and language scores at 18 months, after adjusting for the exposure to ASMs and severity of brain injury on MRI.[3] In our study no association was found for the combined outcome death or NDI, its separate components, or the cognitive outcome at ages two and five years. The difference between their reported conclusions and our results might be explained by several factors: (1) the MRI Weeke score assessed in our study to describe the cerebral hypoxic-ischemic injury differed from the score Alharbi et al. used, (2) the outcome assessment at 18 months can differ to a large extent from neurodevelopmental outcome at two or five years, and (3) the continuous full-lead EEG assessment or the SB algorithm was not available in our cohort. Future large cohort studies should investigate if total SB measurements are more sensitive in assessing the effects of seizures on neurodevelopmental outcome.

Several strengths and limitations of this study need to be discussed. First, the strength of our study is that we assessed the long-term outcome at both two and five years in a large multicenter cohort of asphyxiated infants undergoing TH. Second, the data were collected prospectively at the time, and only seizures diagnosed by aEEG combined with a raw EEG signal reading were taken into account. All MRI and outcome assessments were performed as standard of care for the predefined time points, and all assessments were blinded for the current research question.[29]

Regarding the limitations of our study, the SB could unfortunately not be assessed in a standardized or automated/objective manner as not all original aEEG data were available for analyses. As a proxy for seizure severity, we therefore used the number of ASMs prescribed. Furthermore, during the study period a study demonstrated the importance of treatment of subclinical seizures. We cannot exclude that units have changed their policy of seizure treatment based on this publication.[37] It remains unknown if and how these factors may have influenced the analyses. Another limitation of this study was the need for multiple imputation for some of the missing data, and the need to convert the BSID scores in a subgroup of the infants. Although we used previously published conversion methods, we cannot exclude that over- or underestimation of the outcome results occurred.

Conclusion

This study in infants undergoing TH for HIE due to perinatal asphyxia showed no independent association of either the presence or severity of seizures with either demise or the presence of NDI or cognitive impairment up to age five years after adjusting for HIE severity and brain MRI abnormalities. After correcting for both Thompson score and the brain MRI score, none of the outcomes were associated with seizures during the rewarming period.

CRediT authorship contribution statement

J.F. Langeslag: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Writing – original draft. **W. Onland:** Conceptualization, Formal analysis, Writing – review & editing. **F. Groenendaal:** Conceptualization, Writing – review & editing. **L.S. de Vries:** Conceptualization, Writing – review & editing. **A.H. van Kaam:** Conceptualization, Writing – review & editing. **T.R. de Haan:** Conceptualization, Formal analysis, Writing – review & editing.

Declaration of competing interest

No disclosures were reported.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.01.023.

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