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Long-Term Neurodevelopmental Outcomes in Neonates with Perinatal Asphyxia in a High-Resource Country: A Single-Center Retrospective Analysis

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Highlights

What are the main findings?

- At five years of age, 31% of term and 21% of preterm children with a history of perinatal asphyxia showed age-appropriate development.
- Among term children, 31% had mild, 19% moderate, and 19% severe developmental delay, whereas among preterm children, 53% had mild, 16% moderate, and 11% severe developmental delay. In preterm children, these developmental outcomes may also be attributable to prematurity.

What are the implications of the main findings?

- Neurodevelopmental impairments are common in both term and preterm children following perinatal asphyxia, highlighting the importance of standardized long-term developmental follow-up.
- The wide range of outcomes, from age-appropriate development to severe developmental delay, underscores the need for improved risk stratification and larger prospective studies to better characterize long-term neurodevelopmental outcomes in children with a history of perinatal asphyxia.

Abstract

Background: Perinatal asphyxia is a critical condition resulting from various complications around birth. Despite advances in neonatal care reliable prediction of long-term neurodevelopmental outcomes remains challenging. Therefore, standardized clinical follow-up assessments are recommended to detect impairments early and provide optimal support. This study aimed to characterize five-year neurodevelopmental outcomes in children with a history of perinatal asphyxia treated at a tertiary neonatal care center in Austria. **Methods:** This retrospective analysis included infants with perinatal asphyxia, defined as umbilical artery pH < 7.0, admitted to the neonatal intensive care unit in Graz, Austria, between January 2004 and September 2020. The primary outcome was neurodevelopmental status at five years of age. This was assessed by trained clinicians during routine follow-up examinations and classified as age-appropriate development or mild, moderate, or severe developmental delay. Where feasible, the intelligence quotient was

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additionally quantified by certified psychologists using the standardized Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Demographic characteristics, causes of asphyxia, neonatal clinical course and short-term outcomes were also assessed. Data were extracted from the local electronic patient documentation system and analyzed descriptively. **Results:** Of 139 eligible neonates, 25 (18%) died. Five-year follow-up data were available for 35 (31%) of the 114 survivors; their median gestational age was 36.6 (IQR 31.3–39.3) weeks; 16 (46%) were term infants and 19 (54%) preterm infants. Hypoxic–ischemic encephalopathy was diagnosed in 19 (54%) infants. A total of 10 (29%) infants received therapeutic hypothermia, and 30 (86%) required invasive respiratory support. At five years, five (31%) term infants achieved age-appropriate development, while five (31%) had mild, three (19%) moderate, and three (19%) severe developmental delay. Among preterm infants, four (21%) showed age-appropriate development, whereas 10 (53%) had mild, three (16%) moderate, and two (11%) severe developmental delay. **Conclusions:** Developmental delay was common among both term and preterm infants assessed five years after perinatal asphyxia. However, the small cohort and incomplete follow-up limit the generalizability of these findings. Improved strategies for risk stratification, neuroprotective interventions and long-term developmental surveillance are warranted.

Keywords: neonate; preterm infants; term infants; perinatal asphyxia; neonatal resuscitation; long-term neurodevelopmental outcome; neonatal intensive care

1. Introduction

Perinatal asphyxia occurs in 1 to 6 per 1000 live births and accounts for approximately 23% of neonatal deaths, making it the third leading cause of neonatal mortality worldwide, according to the World Health Organization (WHO) [1,2]. Asphyxia results from various events in utero, during labor and immediately after delivery, including placental abruption, umbilical cord complications, meconium aspiration, and transplacental anesthetic transmission, affecting the respiratory drive and leading to a traumatic birth [3]. These events can impair oxygen delivery and tissue perfusion, leading to hypoxemia, acidemia, and multiorgan dysfunction, including hypoxic–ischemic encephalopathy (HIE) [4,5]. The diagnosis of perinatal asphyxia is based on a combination of clinical findings, including the Apgar score, umbilical cord blood gas analysis and a detailed neurological assessment, including scores like the Sarnat score for grading HIE [5]. HIE is one of the primary causes of severe neurological impairment in childhood and occurs in approximately 28% of infants affected by perinatal asphyxia [2,4]. Hypoxia-induced brain injury may result in acute complications such as seizures and impaired consciousness. In the long term, it is associated with an increased risk of permanent neurological impairments, including cerebral palsy, epilepsy and cognitive deficits [6].

Management of infants affected by perinatal asphyxia begins immediately after birth, with particular attention to appropriate monitoring, respiratory and cardiocirculatory support as well as adequate thermoregulation [7]. Therapeutic hypothermia is the standard of care for infants born at ≥36 weeks of gestation with moderate-to-severe HIE who meet established eligibility criteria [8]. When initiated within six hours after birth to a target core temperature of 33.5 °C, therapeutic hypothermia reduces brain injury and improves neurodevelopmental outcomes by reducing cerebral inflammation and free radical formation [9].

Outcomes of infants diagnosed with perinatal asphyxia vary widely, ranging from age-appropriate development and mild developmental delay to severe neurological impairments, cerebral palsy, seizures or death, especially in infants with severe HIE [10,11]. Developmental follow-up assessments are essential in severely affected infants to monitor the progression and extent of impairment over time and to ensure optimal guidance for the child and parents [12]. In infants with milder involvement, cognitive deficits may only emerge after toddlerhood as cognitive demands increase [13]. Therefore, continued observation is important to assess the developmental status and to provide appropriate educational and therapeutic support for the child in later life [14]. The most commonly used neurodevelopmental assessment tools performed at two years of age are the Griffiths Scales of Child Development and the Bayley Scales of Infant and Toddler Development [11]. At five to six years of age, children are evaluated by standardized intelligence tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) evaluates verbal comprehension, visual–spatial ability, fluid reasoning, working memory, and processing speed and provides a full-scale IQ value. Diagnostic testing is particularly important to assess a child's cognitive and behavioral abilities and provides decision support on whether a child is ready for school entry [15,16].

Despite broad early follow-up studies, evidence on the neurodevelopmental outcomes of children at five years of age after perinatal asphyxia across different gestational age groups remains limited [17]. Assessments at five years enable a more reliable evaluation of cognitive function and school readiness than assessments during infancy. Therefore, this study aimed to characterize long-term developmental outcomes at five years of age in infants affected by perinatal asphyxia (umbilical artery pH < 7.0), integrating cognitive performance and developmental impairment. Outcomes were stratified by gestational age to evaluate potential differences between term and preterm infants.

2. Methods

2.1. Study Design

This retrospective analysis included infants diagnosed with perinatal asphyxia who were admitted to the tertiary neonatal intensive care unit (NICU) at the Medical University of Graz. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (ethics committee number: 36-130-ex 23/24).

2.2. Participants and Data Collection

Infants admitted to the NICU of the Medical University of Graz between January 2004 and September 2020 were initially identified using the International Classification of Diseases, 10th Revision (ICD-10) codes for severe perinatal asphyxia (P21.0), corresponding to a 1-min Apgar score of 0–3, mild and moderate perinatal asphyxia (P21.1), corresponding to a 1-min Apgar score of 4–7, and unspecified perinatal asphyxia (P21.9) [18]. To ensure a uniform definition of perinatal asphyxia across the study cohort, medical records were subsequently reviewed to verify eligibility based on a documented umbilical artery pH < 7.0, which served as a surrogate marker of perinatal asphyxia. All pH measurements were performed on confirmed arterial samples using a calibrated blood gas analyzer. Additionally, ten infants were excluded a priori because of incomplete clinical data. The reasons for exclusion were an unavailable umbilical artery pH (n = 8) and initial postnatal management at an external hospital (n = 2). Surviving children with available neurodevelopmental assessments at five years of age were included in the long-term follow-up analysis.

Data were extracted from electronic medical records in the openMEDOCS documentation system (Steiermaerkische Krankenanstaltengesellschaft, Graz, Austria) and anonymously stored in Microsoft Excel (Version 16, Microsoft Corporation, Redmond, WA, USA).

2.3. Outcome Parameter

The primary outcome was neurodevelopmental status at five years of age in children with a history of perinatal asphyxia, defined based on the Apgar score according to ICD-10 criteria and an umbilical artery pH < 7.0. Neurodevelopmental outcomes were assessed by trained clinicians during routine follow-up examinations. At our center, all infants who received therapeutic hypothermia were scheduled for developmental follow-up until six years of age, irrespective of gestational age or subsequent clinical course. Infants with mild HIE were selectively referred for developmental follow-up if additional risk factors or clinical concerns were present, including small-for-gestational-age status, abnormalities on cranial ultrasound or brain MRI, additional complications during the clinical course, neonatal seizures, or prematurity. However, five-year outcome data were not available for all infants treated with therapeutic hypothermia, as some families were unable to attend the follow-up visits.

Developmental assessments were primarily performed by neonatologists. When indicated, additional standardized assessments were conducted by psychologists, occupational therapists, and speech and language therapists. Based on the clinical assessment documented in the medical records, neurodevelopmental outcomes were categorized as age-appropriate development or mild, moderate, or severe developmental delay. This classification reflected the clinical impression and was not based on a predefined standardized assessment scale. The presence of cerebral palsy, epilepsy, and microcephaly was also documented.

Standardized developmental testing for children with a history of perinatal asphyxia, including the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), was introduced at our center in 2019. Prior to this, standardized assessments were performed selectively in children with additional risk factors, particularly prematurity. Consequently, standardized test results were available only for a subset of children and were not obtained consistently throughout the study period. Where available, the full-scale IQ was assessed by certified psychologists using the third or fourth edition of the WPPSI. IQ testing was performed independently of the clinically assigned neurodevelopmental outcome category.

Data were stratified by gestational age into preterm (delivered <37+0) and term infants. Preterm infants were further classified as moderate-to-late preterm infants (MLPIs), born ≥32+0 and <37+0 weeks of gestation, very preterm infants (VPIs) born ≥ 28+0 and <32+0 weeks of gestation and extremely preterm infants (EPIs) <28+0 weeks of gestation. Demographic and perinatal characteristics included gestational age, sex, birthweight, birth length, head circumference, Apgar score, umbilical artery pH, and mode of delivery. Moreover, causes of asphyxia and the neonatal clinical course were also assessed, including therapeutic hypothermia, respiratory support, catecholamine requirement, seizures, hypoglycemia, renal, hepatic or cardiovascular dysfunction and HIE. Length of hospital stay and short-term outcomes at hospital discharge, including in-hospital mortality, were also analyzed. Mortality was assessed in the entire eligible cohort (n = 139).

HIE severity was classified according to the Sarnat classification as mild (stage I), moderate (stage II), or severe (stage III) [2]. This classification was used to grade the severity of neonatal encephalopathy but not to assess subsequent neurodevelopmental outcomes. Since 2010, therapeutic hypothermia at our center has been performed in accordance with an institutional guideline. Eligibility criteria include a gestational age ≥36 weeks,

a birthweight > 1800 g, a postnatal age < 6 h, and the absence of severe intracranial hemorrhage or major congenital malformations. In addition, infants must meet at least one criterion for perinatal asphyxia (10-min Apgar score <5, postnatal resuscitation lasting more than 10 min, umbilical artery pH < 7.0, arterial pH < 7.0 within the first 60 min of life, or arterial base deficit >15 mmol/L) and at least one criterion for encephalopathy (altered level of consciousness, abnormal muscle tone, abnormal reflexes, clinical seizures, abnormal amplitude-integrated electroencephalography (aEEG) findings).

2.4. Statistics

Statistical analyses were performed using Microsoft Excel (Version 16, Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics (Version 29, IBM Corp., Armonk, NY, USA). Primary outcome data were analyzed descriptively using absolute and relative frequencies. Developmental outcomes, as well as the occurrence of cerebral palsy, epilepsy, and microcephaly, were compared between term and preterm infants using Fisher's exact test. Demographic characteristics and secondary outcomes were summarized as medians and interquartile ranges (IQR) for continuous variables and absolute and relative frequencies for categorical variables. Baseline characteristics were compared between children who completed the five-year follow-up and those lost to follow-up. The Mann–Whitney U test was used to compare continuous variables and the chi-square test for categorical variables. Fisher's exact test was used instead if any expected cell count was below 5. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Bar charts were used to visualize the results.

3. Results

In total, 13,130 infants were admitted to the NICU between January 2004 and September 2020. Of these, 357 infants had a documented diagnosis of perinatal asphyxia. After excluding 208 infants with an umbilical artery pH ≥ 7.0 and 10 infants with incomplete medical records, a total of 139 infants were eligible for inclusion in the study (Figure 1).

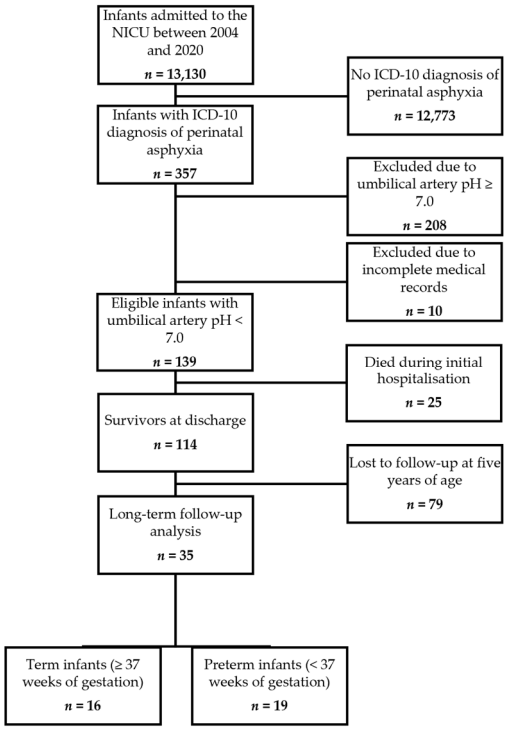


Figure 1. Flowchart.

Of 139 infants eligible, 25 (18%) died during initial hospitalization after birth. Five-year neurodevelopmental follow-up data were unavailable for 79 (69%) of the 114 survivors. The remaining 35 children (31% of survivors) were included in the primary outcome analysis. Demographic and perinatal characteristics are summarized in Table 1. Table 2 presents a comparison of baseline characteristics between children who completed the five-year follow-up and those lost to follow-up.

Table 1. Demographic characteristics, place of birth and mode of delivery of included infants.

	Total ***n*** **= 35**	**Term** ***n*** **= 16**	**Preterm** ***n*** **= 19**	**EPIs** ***n*** **= 3**	**VPIs** ***n*** **= 7**	**MLPIs** ***n*** **= 9**
Gestational age, weeks	36.6 (31.3–39.3)	39.4 (38.6–40.0)	31.9 (29.7–34.1)	26.3 (24.6–27.3)	30.1 (29.7–31.3)	34.1 (33.0–36.6)
Female sex	17 (49)	7 (44)	10 (53)	3 (100)	4 (57)	3 (33)
Birthweight, g	2605 (1560–3365)	3408 (2899–3850)	1560 (1260–2335)	595 (460–750)	1500 (1260–1900)	2335 (1560–2920)
Birth length, cm	49 (42–51)	51 (49–53)	43 (39–48)	32 (28–34)	40 (39–43)	48 (43–51)
Head circumference, cm	32 (28–34)	34 (33–36)	29 (27–31)	21 (20–21)	28 (27–30)	31 (31–33)
Apgar score at 1 min	2 (1–4)	3 (1–5)	2 (1–3)	2 (0–2)	3 (1–4)	2 (1–3)
Apgar score at 5 min	6 (4–7)	5 (4–7)	6 (4–7)	6 (4–6)	6 (4–7)	4 (4–6)
Apgar score at 10 min	7 (6–8)	7 (6–8)	7 (6–8)	6 (4–7)	7 (7–9)	7 (5–8)
Umbilical artery pH	6.90 (6.78–6.95)	6.89 (6.79–6.95)	6.90 (6.77–6.94)	6.89 (6.84–6.94)	6.92 (6.88–6.98)	6.82 (6.71–6.92)
Mode and place of delivery						
SVD	5 (14)	3 (19)	2 (11)	1 (33)	0 (0)	1 (11)
VED	1 (3)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
ElCD	2 (6)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
EmCD	27 (77)	10 (63)	17 (90)	2 (67)	7 (100)	8 (89)
Hospital with NICU	24 (69)	8 (50)	16 (84)	2 (67)	5 (71)	9 (100)
Hospital without NICU	10 (29)	8 (50)	2 (11)	0 (0)	2 (29)	0 (0)
Out-of-hospital birth	1 (3)	0 (0)	1 (5)	1 (33)	0 (0)	0 (0)

Abbreviations: ElCD, elective cesarean delivery; EmCD, emergency cesarean delivery; EPIs, extremely preterm infants (<28 weeks of gestation); MLPIs, moderate-to-late preterm infants (≥32+0 and <37+0 weeks of gestation); NICU, neonatal intensive care unit; SVD, spontaneous vaginal delivery; VED, vacuum extraction delivery; VPIs, very preterm infants (≥28+0 and <32+0 weeks of gestation). Data are presented as median (interquartile range) or *n* (%).

Table 2. Comparison of baseline characteristics between children who completed the five-year follow-up and those lost to follow-up.

	Five-Year Follow-Up ***n*** **= 35**	**Lost to Follow-Up** ***n*** **= 79**	***p*-Value**
Gestational age, weeks	36.6 (31.3–39.3)	39.0 (36.5–40.3)	**0.002**
Birthweight, g	2605 (1560–3365)	3080 (2500–3450)	**0.043**
Apgar score at 1 min	2 (1–4)	3 (2–5)	**0.022**
Apgar score at 5 min	6 (4–7)	7 (5–7)	**0.007**
Apgar score at 10 min	7 (6–8)	8 (7–9)	**0.016**
Umbilical artery pH	6.90 (6.78–6.95)	6.92 (6.81–6.95)	0.262
HIE	19 (54)	25 (32)	**0.036**
Therapeutic hypothermia	10 (29)	19 (24)	0.609

Seizures	10 (29)	11 (14)	0.072
Birth period 2004–2009	11 (31)	24 (30)	0.911
Birth period 2010–2014	16 (46)	26 (33)	0.191
Birth period 2015–2020	8 (23)	29 (37)	0.145

Abbreviations: HIE, hypoxic–ischemic encephalopathy. Data are presented as median (interquartile range) or *n* (%). *p*-values were calculated using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables. Statistically significant *p*-values ($p < 0.05$) are highlighted in bold.

3.1. Five-Year Outcome Analysis

Thirty-five infants with a median gestational age of 36.6 weeks (IQR 31.3–39.3) were included in the five-year outcome analysis. Sixteen (46%) infants were born at term. Among preterm infants, 9 (47%) were classified as MLPIs, 7 (37%) as VPIs and 3 (16%) as EPIs. Five-year neurodevelopmental outcomes are presented in Table 3 and Figure 2.

Table 3. Five-year neurodevelopmental outcomes of children with a history of perinatal asphyxia according to gestational age at birth.

	Total ***n* = 35**	**Term** ***n* = 16**	**Preterm** ***n* = 19**	**EPIs** ***n* = 3**	**VPIs** ***n* = 7**	**MLPIs** ***n* = 9**
Age-appropriate development	9 (26)	5 (31)	4 (21)	0 (0)	1 (14)	3 (33)
Mild developmental delay	15 (43)	5 (31)	10 (53)	2 (67)	3 (43)	5 (56)
Moderate developmental delay	6 (17)	3 (19)	3 (16)	0 (0)	3 (43)	0 (0)
Severe developmental delay	5 (14)	3 (19)	2 (11)	1 (33)	0 (0)	1 (11)
Cerebral palsy	5 (14)	2 (13)	3 (16)	1 (33)	1 (14)	1 (11)
Epilepsy	2 (6)	1 (6)	1 (5)	0 (0)	0 (0)	1 (11)
Microcephaly	9 (26)	3 (19)	6 (32)	2 (67)	1 (14)	3 (33)

Abbreviations: EPIs, extremely preterm infants (<28 weeks of gestation); MLPIs, moderate-to-late preterm infants (≥32+0 and <37+0 weeks of gestation); VPIs, very preterm infants (≥28+0 and <32+0 weeks of gestation). Developmental categories are mutually exclusive. Cerebral palsy, epilepsy, and microcephaly may coexist with any developmental category. Data are presented as *n* (%).

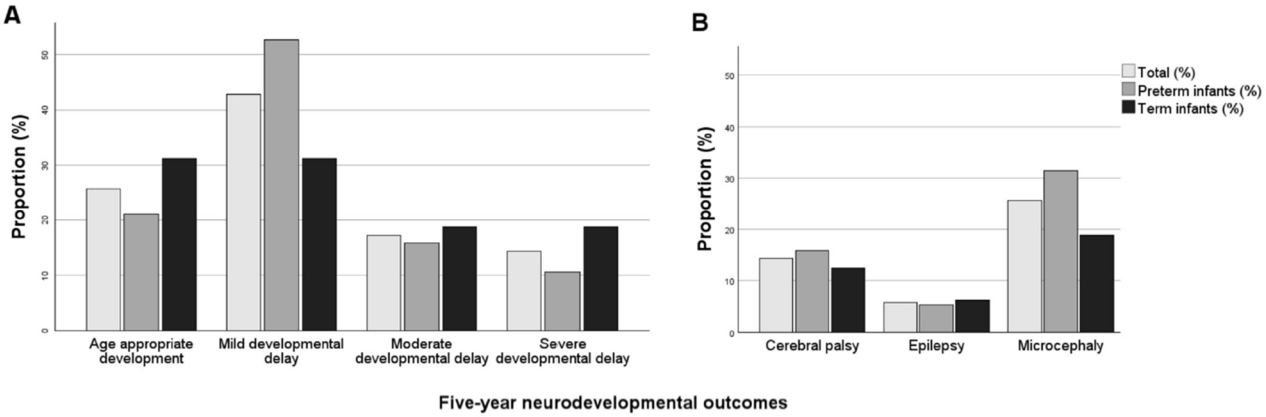


Figure 2. Five-year neurodevelopmental outcomes of children born preterm or at term with a history of perinatal asphyxia. (**A**) neurodevelopmental long-term outcome; (**B**) neurological long-term outcome.

Five-year developmental outcome did not differ significantly between children born at term and those born preterm (age-appropriate development, $p = 0.700$; mild developmental delay, $p = 0.306$; moderate developmental delay, $p = 1.000$; severe developmental

delay, $p = 0.642$). Among the children included in the primary outcome analysis, neurodevelopmental assessment using the WPPSI was performed in 10 children (two born at term and eight born preterm) and revealed a median IQ of 95 (IQR 85–105), with individual scores ranging from 76 to 114 (Table 4).

Table 4. Clinical characteristics and full-scale IQ scores of children assessed using the WPPSI.

Gestational Age	Umbilical Artery pH	HIE (Stage)	Therapeutic Hypothermia	Five-Year Developmental Outcome	IQ Score
24+4	6.84	no	no	mild developmental delay	85
26+2	6.97	no	no	mild developmental delay	87
28+2	6.90	no	no	mild developmental delay	107
30+1	6.88	no	no	moderate developmental delay	82
30+1	6.96	no	no	moderate developmental delay	76
31+6	6.98	no	no	age-appropriate development	105
32+2	6.95	no	no	mild developmental delay	86
32+5	6.68	no	no	age-appropriate development	114
38+4	6.95	no	yes	age-appropriate development	103
41+2	6.99	yes (stage I)	yes	age-appropriate development	104

Abbreviations: HIE, hypoxic–ischemic encephalopathy; IQ, intelligence quotient. WPPSI, Wechsler Preschool and Primary Scale of Intelligence. Children are listed in ascending order of gestational age, expressed as weeks + days. HIE severity was classified according to the Sarnat classification.

3.2. Causes and Associated Risk Factors of Perinatal Asphyxia

In the study cohort ($n = 35$), the most frequent cause of perinatal asphyxia was placental abruption, observed in 11 (31%) infants. Prolonged labor occurred in three (9%) and meconium aspiration in four (11%) of all infants. Documented umbilical cord complications included nuchal cord in two cases (6%) and velamentous cord insertion in one (3%). Delivery-related complications, such as shoulder dystocia were identified in one (3%) infant. Regarding antenatal risk factors, preeclampsia was present in the mothers of two (6%) infants, whereas placental insufficiency was documented in one (3%) and chorioamnionitis in one (3%) pregnancy. Additionally, maternal uterine rupture occurred in one case (3%). Other causes of perinatal asphyxia were reported in eight (23%) infants. When comparing term and preterm infants, term infants more frequently experienced meconium aspiration and prolonged labor whereas placental abruption and preeclampsia were more common among preterm infants. Other causes of asphyxia were similarly distributed between the two groups.

3.3. Clinical Course During NICU Hospitalization

The frequencies of therapeutic interventions, mechanical ventilation, medication use, organ involvement, seizures, and hypoglycemia are shown in Table 5. The incidence of renal dysfunction increased with decreasing gestational age. Likewise, the duration of hospitalization increased with decreasing gestational age, with preterm infants requiring longer hospital stays than term infants. Hypoglycemia also occurred more frequently in preterm than in term infants, with the highest rate observed in the VPI group.

Table 5. Clinical course during hospital stay in infants with perinatal asphyxia.

	Total $n = 35$	Term $n = 16$	Preterm $n = 19$	EPIs $n = 3$	VPIs $n = 7$	MLPIs $n = 9$
Therapeutic hypothermia	10 (29)	9 (56)	1 (5)	0 (0)	0 (0)	1 (11)
Mechanical ventilation	30 (86)	13 (81)	17 (89)	3 (100)	6 (86)	8 (89)

Duration of mechanical ventilation, days	6 (4–8)	6 (3–8)	6 (4–8)	6 (4–14)	7 (4–8)	6 (2–7)
Inhaled nitric oxide	1 (3)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Catecholamine use	21 (60)	7 (44)	14 (74)	1 (33)	6 (86)	7 (78)
Seizures	10 (29)	5 (31)	5 (26)	0 (0)	3 (43)	2 (22)
Hypoglycemia	8 (23)	3 (19)	5 (26)	1 (33)	3 (43)	1 (11)
Renal dysfunction	17 (49)	6 (38)	11 (58)	2 (67)	4 (57)	5 (56)
Elevated liver enzymes	25 (71)	11 (69)	14 (74)	2 (67)	6 (86)	6 (67)
Hospital stay, days	26 (13–44)	15 (11–24)	37 (24–65)	120 (105–232)	49 (36–65)	27 (22–34)

Abbreviations: EPIs, extremely preterm infants (<28 weeks of gestation); MLPIs, moderate-to-late preterm infants (≥32+0 and <37+0 weeks of gestation); VPIs, very preterm infants (≥28+0 and <32+0 weeks of gestation). Data are presented as median (interquartile range) or *n* (%).

Among the 10 infants (median gestational age 39.1 (IQR 38.6–40.0)) who received therapeutic hypothermia during the neonatal period, four (40%) infants demonstrated age-appropriate development at five years, four (40%) had mild developmental delay, and two (20%) had severe developmental delay. In comparison, among the 25 infants (median gestational age 33.0 (IQR 30.1–37.1)) who did not receive therapeutic hypothermia, five (20%) showed age-appropriate development, 11 (44%) had mild, six (24%) moderate and three (12%) severe developmental delay.

3.4. Short-Term Outcome at Discharge

HIE was diagnosed in 19 (54%) of the 35 infants. Table 6 presents the distribution of HIE severity according to the Sarnat classification across gestational age groups.

Table 6. Severity of hypoxic–ischemic encephalopathy (HIE) classified by the Sarnat score and stratified by gestational age.

	Total ***n* = 35**	**Term** ***n* = 16**	**Preterm** ***n* = 19**	**EPIs** ***n* = 3**	**VPIs** ***n* = 7**	**MLPIs** ***n* = 9**
HIE	19 (54)	11 (69)	8 (42)	1 (33)	3 (43)	4 (44)
HIE stage I (including I/II)	13 (68)	7 (64)	6 (75)	1 (100)	2 (67)	3 (75)
HIE stage II (including II/III)	5 (26)	3 (27)	2 (25)	0 (0)	1 (33)	1 (25)
HIE stage III	1 (5)	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: EPIs, extremely preterm infants (<28 weeks of gestation); MLPIs, moderate-to-late preterm infants (≥32+0 and <37+0 weeks of gestation); VPIs, very preterm infants (≥28+0 and <32+0 weeks of gestation); HIE, Hypoxic–ischemic encephalopathy. Intermediate stages (I/II and II/III) were grouped with the respective lower grade for analysis. Data are presented as *n* (%). Percentages for HIE refer to all infants in the respective gestational age group, whereas percentages for individual HIE stages refer only to infants diagnosed with HIE within that group. Percentages may not sum to 100% due to rounding.

Cranial magnetic resonance imaging (cMRI) was performed in 7 (20%) infants from the follow-up cohort at a median age of 8 days (range 5–16 days). Findings were unremarkable in one (14%) infant. Among the remaining six (86%) infants, extra-axial intracranial hemorrhage was identified in three (50%) cases, and one (17%) infant showed residual hemorrhage in the form of hemosiderin deposits. Hypoxic–ischemic brain lesions were detected in one (17%) infant, while another exhibited cerebral edema.

3.5. Mortality

Among the 139 eligible infants, 25 (18%) died during NICU hospitalization. The median age at death was 2 days (range 1–7 days). The mortality was 14% (12 of 86) among

term infants and 25% (13 of 53) among preterm infants (n = 53), reaching 40% (4 of 10) in the extremely preterm subgroup. The most frequent cause of death was multi-organ failure, occurring in 12 (48%) infants, frequently in combination with intraventricular hemorrhage. Six (24%) infants sustained severe hypoxic–ischemic brain injury, after which care was redirected to palliative measures. Additional causes of death included isolated cardiovascular or pulmonary failure and therapy-refractory status epilepticus.

4. Discussion

This study describes five-year neurodevelopmental outcomes in children born at term or preterm who were treated for perinatal asphyxia in a tertiary neonatal care center in Austria. In this retrospective cohort, 25 of 139 eligible infants (18%) died during neonatal hospitalization. Five-year neurodevelopmental follow-up data were available for 35 of the 114 survivors (31%). Developmental delay was identified in 26 of the 35 children assessed (74%), with mild delay being the most common finding. No statistically significant differences in neurodevelopmental outcomes were observed between children born at term and those born preterm, although the small sample size and incomplete follow-up limit interpretation.

Previous studies have reported similar findings regarding severe developmental delay following perinatal asphyxia. Blommaert et al. documented long-term neurodevelopmental outcomes in 63 children with a history of HIE who were treated with therapeutic hypothermia, reporting severe developmental delay in 14% and cerebral palsy in 14% of these children at five years of age [19]. These proportions were numerically similar to those observed in the present study, whereas age-appropriate development was reported in 52% of their cohort and 26% in the present study. These descriptive comparisons should be interpreted cautiously because of differences in outcome definitions and cohort characteristics. Blommaert et al. included only infants born at ≥35 weeks of gestation. Furthermore, all infants in their cohort received therapeutic hypothermia, compared with only 29% in the present cohort [19]. Similarly, Cainelli et al. reported a median full-scale IQ of 100 (IQR 87–110) in 40 children with a history of HIE treated with therapeutic hypothermia and found no significant differences compared with healthy controls [20]. Compared with the present study, the IQ values reported by Cainelli et al. were slightly higher. However, their cohort consisted exclusively of infants born at > 36 weeks of gestation and excluded children with major neurological impairments such as cerebral palsy or epilepsy [20]. In contrast, Murray et al. compared 46 infants with HIE to a healthy control cohort at five years of age and demonstrated significantly lower full-scale IQ scores in the HIE group. The median WPPSI IQ in the HIE group was 99 (IQR 94–124), which was higher than that observed in the present study [21]. Additionally, Dzikiene et al. reported a mean IQ of 87 (SD 16.9) in 32 children with a history of perinatal asphyxia assessed at 8 to 9 years of age, which was significantly lower than that of healthy controls and also lower than the median IQ observed in the present study; notably, none of the children in their cohort had received therapeutic hypothermia during the neonatal period [22]. Overall, the present findings are broadly consistent with those reported in previous cohorts although differences in gestational age, treatment strategies, inclusion criteria, and outcome assessments limit direct comparisons. This underscores the need for standardized diagnostic criteria, uniform treatment protocols and structured long-term follow-up assessments to improve the comparability across future studies and ultimately optimize care for affected infants.

A particular strength of the present study is the inclusion of preterm infants, a population that has been underrepresented in previous studies on long-term outcomes following perinatal asphyxia. Accordingly, Robertsson Grossmann et al. investigated long-

term outcomes following HIE treated with therapeutic hypothermia, including late preterm infants. Their results demonstrated that all included infants born <36 weeks of gestation experienced adverse outcomes, suggesting that prematurity may aggravate the consequences of perinatal asphyxia [13]. Notably, the benefits of therapeutic hypothermia demonstrated in term infants may not extend to preterm infants. In a randomized controlled trial involving infants born at 33–35 weeks of gestation with moderate or severe HIE, Faix et al. found that therapeutic hypothermia did not reduce the risk of death or moderate-to-severe disability at 18–22 months and may even have increased mortality [23]. Therapeutic hypothermia is therefore not recommended in infants born before 35 weeks of gestation [8]. Although the neurodevelopmental outcomes did not differ significantly between term and preterm infants in the present study, adverse outcomes and the need for intensive therapeutic interventions tended to be more frequent among preterm infants. For example, none of the EPIs and only 14% of VPIs achieved age-appropriate development, compared with 31% of term infants. Likewise, the need for mechanical ventilation, administration of catecholamines and the duration of hospitalization appeared to increase with prematurity. These findings are consistent with those of Logitharajah et al., who reported more severe outcomes in preterm infants (≤36+0 weeks of gestation) with perinatal asphyxia than term infants. Their documented mortality rate (30%) and incidence of cerebral palsy (26%) among preterm infants were higher than those observed in term infants of the present study [24]. In contrast, Lademann et al. reported comparable long-term neurodevelopmental outcomes between preterm and term infants at the age of two years using the Bayley Scales of Infant Development; however, their analysis was restricted to late preterm infants (LPIs) [25]. Although age-appropriate development was numerically less frequent among children born preterm, the small subgroups and the absence of a control group without perinatal asphyxia preclude conclusions regarding the independent contribution of asphyxia to neurodevelopmental outcomes in this population. Prematurity, particularly among VPIs and EPIs, is a major determinant of neurodevelopmental outcome, as one third of children born before 27 weeks of gestation have moderate or severe disability at the age of 5 years [26]. Consequently, prospective studies focusing on preterm infants with perinatal asphyxia and HIE are warranted to improve our understanding of gestational age-specific risks and to optimize management strategies in this particularly vulnerable population.

The beneficial effects of therapeutic hypothermia in term infants with moderate-to-severe HIE, are well established [27]. Follow-up examinations at 6 to 7 years of age have shown that therapeutic hypothermia is associated with reduced mortality and a lower rate of cerebral palsy [8]. In recent years, however, the use of therapeutic hypothermia has increasingly expanded to infants with mild HIE. Van Oldenmark et al. demonstrated a marked increase in the use of therapeutic hypothermia for mild HIE over the past 15 years, but found no clear reduction in adverse outcomes or mortality [28]. In an observational study, Montaldo et al. reported reduced MRI-defined brain injury in infants with mild HIE treated with therapeutic hypothermia, suggesting a potential neuroprotective effect [29]. A subsequent pilot randomized controlled trial by the same group found no improvement in cerebral magnetic resonance biomarkers with therapeutic hypothermia in mild HIE; however, infants in the hypothermia group were more severely affected at study entry [30]. These conflicting results highlight the need for further research on both short- and long-term neurodevelopmental outcomes in infants with mild HIE [17]. Notably, Reiss et al. observed that a substantial proportion of infants with mild HIE, who did not receive therapeutic hypothermia developed neurological abnormalities, raising the question of whether selected infants with mild HIE could benefit from therapeutic hypothermia [31]. Nevertheless, the present descriptive findings should be interpreted with

caution, as our study was neither designed nor powered to evaluate the efficacy of therapeutic hypothermia, and treatment allocation was not randomized. Consequently, the presented data do not allow conclusions regarding treatment efficacy.

The mortality rate observed in the present analysis (18%) was similar to that reported in previous studies. For example, Blommaert et al. reported a mortality rate of 15% [19]. Although mortality rates in high-resource settings have improved considerably over recent decades, perinatal asphyxia remains associated with substantial mortality. In contrast, markedly higher mortality rates continue to be reported from low-income countries. In a Ugandan cohort, Namusoke et al. reported a mortality rate of 26% among infants with HIE during the first week of life, with approximately two-thirds classified as Sarnat stage III HIE [32]. Similarly, a cohort from Ethiopia reported a mortality rate of 33% among infants with perinatal asphyxia over a median follow-up of 15 days [33]. Current evidence suggests that therapeutic hypothermia alone does not substantially improve outcomes in low-income countries. Instead, strengthening hospital infrastructure and ensuring adequate supportive care may improve survival and long-term neurodevelopmental outcomes in these regions [34]. These findings highlight the persistent burden of perinatal asphyxia and emphasize the need for further studies to improve mortality rates and long-term outcomes across different healthcare settings.

Strengths and Limitations

A strength of this study is the inclusion of 139 eligible infants with perinatal asphyxia over a 16-year observation period, at a tertiary single-center cohort. The inclusion of both term and preterm infants, including very and extremely preterm infants, together with the stratification of therapeutic interventions and outcomes across gestational age groups, provides insights into the clinical course and long-term developmental outcomes following perinatal asphyxia. Neurodevelopmental assessment at five years of age allows the identification of cognitive and functional difficulties that may not be apparent during infancy or toddlerhood.

Several limitations should also be acknowledged. The most important is the incomplete follow-up: five-year neurodevelopmental follow-up data were available for only 31% of survivors (69% lost to follow-up), introducing potential risk of selection bias. Because developmental surveillance was scheduled routinely only for infants treated with therapeutic hypothermia and was otherwise selective, children with a more complicated neonatal course may be overrepresented (Table 2). Consequently, the reported long-term outcomes may not fully reflect those of the entire study population. In addition, only survivors entered the neurodevelopmental analysis, introducing survivor bias. Second, developmental categories were based on clinical assessments documented during routine follow-up rather than a uniform standardized assessment protocol, potentially leading to observer bias and limiting the consistency of classification as well as the comparability with other studies. Formal cognitive assessment using the WPPSI included only ten children, two born at term and eight born preterm. This imbalance may have introduced bias, as additional morbidities associated with prematurity could have influenced the full-scale IQ scores. The selective availability of testing and the small, heterogeneous subgroup limit the interpretation and generalizability of the IQ findings. In addition, the Sarnat classification was developed for term and near-term infants and has not been validated in preterm infants, particularly those born before 32 weeks of gestation. HIE staging in VPIs and EPIs should therefore be interpreted with caution. Case identification relied on ICD-10 coding followed by confirmation of an umbilical artery pH < 7.0, potentially excluding infants with perinatal asphyxia who were not appropriately coded or lacked a documented pH value. Furthermore, clinical management of infants with perinatal asphyxia evolved over the 16-year study period, particularly with the introduction of therapeutic

hypothermia. This time effect may have influenced both the outcomes and their assessment. Comparisons between children who received therapeutic hypothermia and those who did not are therefore subject to confounding by indication, gestational age and treatment era and cannot establish treatment efficacy. Moreover, prematurity itself is a major determinant of neurodevelopmental outcome, and the impairments observed in preterm children, particularly in VPIs and EPIs, cannot be attributed exclusively to perinatal asphyxia. Information on parental education, socioeconomic status and participation in early intervention programs was not available, although these factors are known to influence developmental outcome. Finally, the small follow-up cohort limits statistical power, particularly for comparison between gestational age subgroups, while the retrospective single-center study design limits the generalizability of the findings.

5. Conclusions

At five years of age, neurodevelopmental impairment was common among children with a history of perinatal asphyxia. Although developmental outcomes varied considerably, mild developmental delay was the most common finding. However, the small cohort and incomplete follow-up limit the generalizability of these results. Additionally, long-term outcomes in preterm infants cannot be attributed to perinatal asphyxia alone, as prematurity itself is an additional determinant of neurodevelopmental outcome. Structured long-term developmental surveillance and larger prospective multicenter studies are warranted.

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Abbreviations

aEEG	amplitude-integrated electroencephalography
cMRI	cranial magnetic resonance imaging
ElCD	elective cesarean delivery
EmCD	emergency cesarean delivery
EPIs	extremely preterm infants
HIE	hypoxic–ischemic encephalopathy
ICD-10	International Classification of Diseases, 10th Revision
IQ	intelligence quotient
IQR	interquartile range
LPIs	late preterm infants

MLPIs	moderate-to-late preterm infants
NICU	neonatal intensive care unit
SVD	spontaneous vaginal delivery
VED	vacuum extraction delivery
VPIs	very preterm infants
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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