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REVIEW ARTICLE

Neonatal asphyxia – predicting its occurrence and neurodevelopment of children after hypothermia treatment in the context of machine learning models – literature review

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Abstract

Introduction and Objective. Perinatal asphyxia (PA) is a condition of impaired blood gas exchange which, if persistent, leads to progressive hypoxemia and hypercapnia. PA is characterized by high neonatal mortality or neurodevelopmental disorders in the child's later life. PA is closely related to hypoxic-ischemic encephalopathy (HIE), which is a complication of perinatal hypoxia. In recent years, there has been a growing interest in the use of machine learning (ML) and artificial intelligence (AI) in medicine. The development of machine learning models can improve patient care by applying them to diagnosis, prognosis, decision support, and treatment recommendations.

Review Methods. The data for the article was found using the Web of Science, PubMed, Scopus and Google Scholar websites which were thematically selected for work.

Brief description of the state of knowledge. Currently, no sufficiently effective prophylactic and therapeutic methods can prevent HIE or death in newborns with PA. Hypothermia is currently the only available method that seems to improve the prognosis in neonates with PA; however, it is not completely effective. In recent years, research has been conducted in the use of machine learning models to predict the occurrence of neonatal asphyxia, based on the occurrence of specific risk factors. Additionally, research has been carried out on the use of neuroimaging in predicting the neurodevelopmental condition of children after neonatal asphyxia.

Summary. Presently, there are no preventive and therapeutic methods that can prevent HIE or death in newborns with severe perinatal hypoxia. In addition to basic knowledge about asphyxia, the review presents issues that could become the beginning of future research in the use of machine learning in neonatology.

Key words

neurodevelopment, neuroimaging, machine learning, neonatal asphyxia, predicting

INTRODUCTION AND OBJECTIVE

Perinatal asphyxia (PA) is a life-threatening condition of impaired blood gas exchange which, if persistent, leads to progressive hypoxaemia and hypercapnia [1]. PA is closely related to hypoxic-ischemic encephalopathy (HIE), which is a complication of perinatal hypoxia. In newborns born after 35 weeks of gestational age (GA), the frequency of HIE is estimated to be about 1.5 per 1,000 live births worldwide [2]. This rate varies depending on the advancement of perinatal care and is lower in developed countries [3].

In severe hypoxia, cellular oxygen metabolism is disturbed, leading to the depolarization of neurons and ischemia. In turn, ischemia causes a cascade of disorders, ranging from reduced availability of glucose needed for cellular metabolism to cell apoptosis [4]. As a result, asphyxia can cause permanent brain damage, which can lead to progressive disability or death. In addition, it is assumed that hypoxia in the perinatal period may be a factor triggering the development of Alzheimer's disease in adulthood [5]. Studies have shown changes in the expression of the presenilin 1 and 2 and amyloid protein precursor and β-secretase genes in neonates after asphyxia, similar to those observed in Alzheimer's disease [6].

The incidence of perinatal asphyxia has not decreased over the past decade, despite advances in the treatment of causes, and PA itself. Moreover, morality is still high. Neonatal asphyxia accounts for 30% -35% of all neonatal deaths worldwide [7]. According to the 2019 Levels and Trends in Child Mortality report, childbirth-related events, such as birth asphyxia or lack of breathing in childbirth, accounted for as much as 11% of all deaths worldwide among children under the age of 5 in 2018 [8]. Currently, no prophylactic and therapeutic methods can prevent HIE or death in newborns with PA.

The only currently available method that seems to improve the prognosis in newborns with PA is hypothermia. To date, this method of treatment has not been found to entirely prevent the development of neurodegeneration after perinatal

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asphyxia. A preliminary study was conducted to check whether the expression of genes related to the metabolism of amyloid protein precursor in peripheral lymphocytes, which after perinatal asphyxia pass to the brain, could be modified by hypothermia. In a preliminary study, hypothermia neither decreased nor increased changes in gene expression related to amyloid protein precursor processing in lymphocytes relative to controls [6].

Machine learning (ML) techniques involve instructing computers to process data and make decisions. In machine learning, the model is based on examples provided as input data. Based on many examples, computers determine how to perform a mapping from features to labels to create a model that generalizes information in such a way that the task can be performed correctly with new, never-before-seen inputs [9]. In recent years, there has been a growing interest in the use of machine learning (ML) and artificial intelligence (AI) in medicine. The development of machine learning models can improve patient care by applying them to diagnosis, prognosis, decision support, and treatment recommendations [9]. Much of the research to date on the use of machine learning in paediatrics and neonatology has focused on paediatric neurodevelopment. Zhou et al. created a machine learning model using the Children Neuropsychological and Behavioural Scale-Revision 2016 for the differential diagnosis of autism spectrum disorder (ASD) and global developmental delay (GDD) [10]. Vassar et al. used machine learning to identify premature infants at risk of language disorders by analysing magnetic resonance imaging and white matter microstructure results in diffusion tensor imaging (DTI) [11], while Gschwandtner et al. used deep machine learning to create a model to estimate functional brain maturity in premature infants from EEG recordings [12].

OBJECTIVE

The current review aimed to try to answer the following questions in the context of the use of machine learning:

1) Is it possible to assess the chances of neonatal asphyxia and assess the degree of HIE before delivery based on maternal and fetal characteristics?
2) Does imaging, such as magnetic resonance imaging (MRI), have predictive value for neurodevelopmental delay in children with postnatal HIE?
3) Is it possible to predict the neurodevelopmental status of children after asphyxia treated with hypothermia based on imaging tests such as MRI?
4) Is it possible to predict abnormalities in neurodevelopment in children as young as 2 years based on MRI?

MATERIALS AND METHODS

Data for the article were searched using the Web of Science, PubMed, Scopus and Google Scholar platforms. The literature was reviewed twice. During the first review, 44 items were selected to present the current state of knowledge regarding neonatal asphyxia. Grey literature was also searched. After 2 months, the literature was reviewed again to find answers to the research questions. For this purpose, 37 items were searched including only original works published in the last 6 years. Ultimately, 5 studies were selected, of which the key results for the review are presented in Tables and discussed in the text of the review.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Types and risk factors of asphyxia. Figure 1 presents the types of asphyxia classified according to the severity of the course of asphyxia, and according to the time of onset of asphyxia. The severity of the course of asphyxia is clinically more important than the latter [13–15].

Figure 2 shows the risk factors for asphyxia. Antenatal, intrapartum and postpartum, maternal and foetal factors were distinguished. This is not a strict division, but a simplified diagram showing the most important causes of neonatal asphyxia [13, 14, 16–20].

Predicting the occurrence of neonatal asphyxia. Based on the risk factors listed in Figure 2 related to both maternal and child characteristics, it can be suspected that asphyxia will occur. In the study by D. Tesfa et al., the aim was to

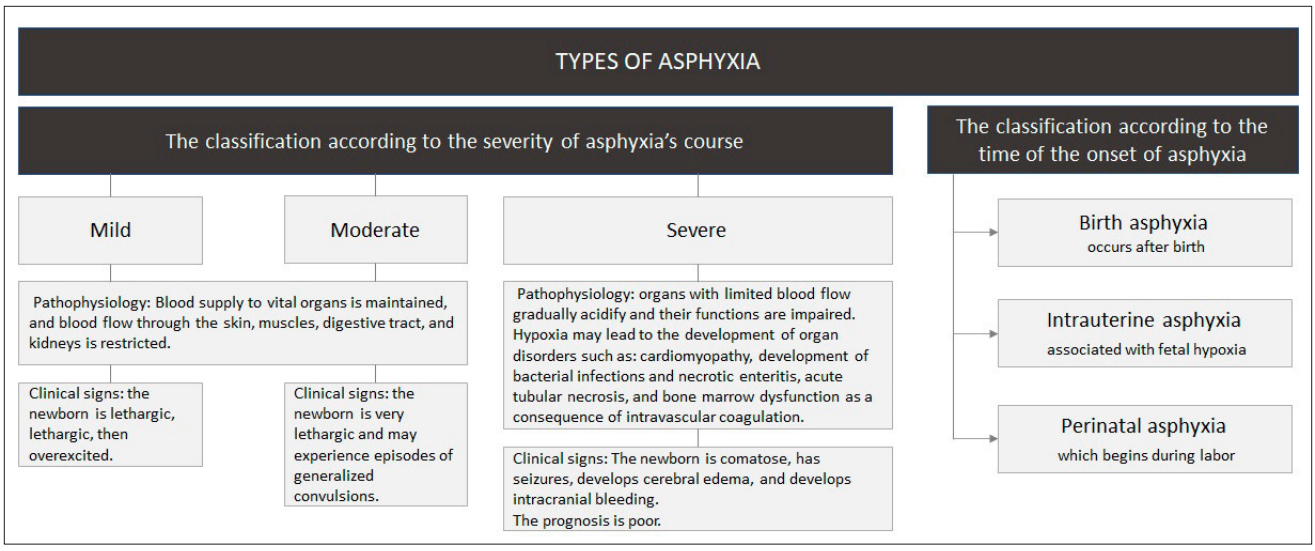

Figure 1. Types of asphyxia [13–15]

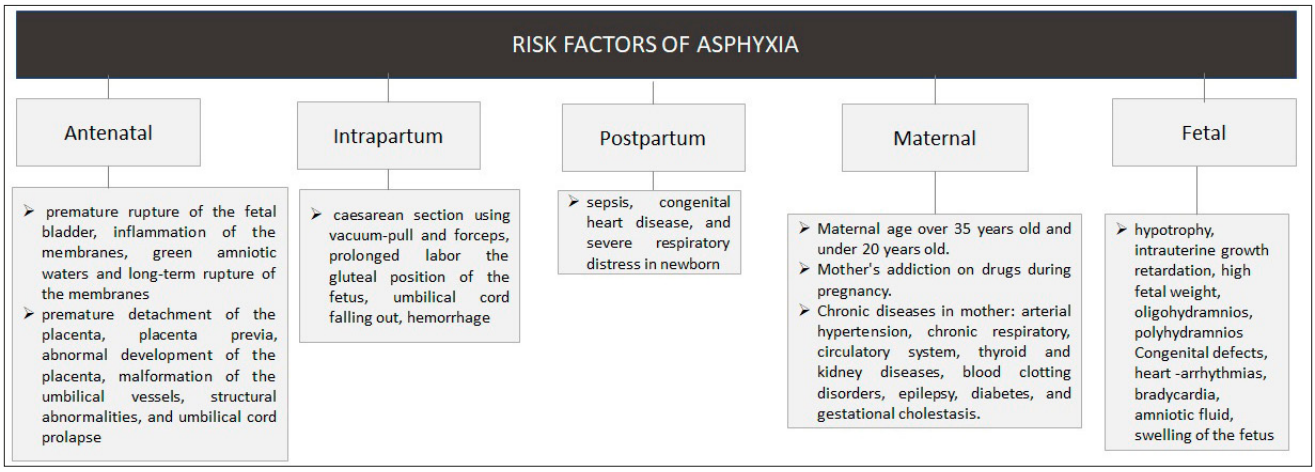

Figure 2. Risk factors of asphyxia [13, 14, 16–20]

develop a tool to predict perinatal asphyxia based on maternal and neonatal characteristics, i.e. premature rupture of the membrane, meconium aspiration, malpresentation, prolonged labour, preterm and tight nuchal cord in hospitals in the southern Gondar zone of northwestern Ethiopia [21]. The study developed and validated a clinically simplified prognostic risk assessment system for birth asphyxia without the need for advanced laboratory or imaging tests, and included 404 newborns born between June 2020 – June 2021, with a prevalence of perinatal asphyxia of 26.7% (108 newborns). To create an algorithm for predicting the occurrence of asphyxia, the statistical software EPI INFO windows (version 7 and R-software) were used. To identify potential prognostic determinants, bivariate and multivariate logistic regression and simple logistic regression were performed on a derived data set to investigate the relationship between each predictor and birth asphyxia. The probability of birth asphyxia was determined using each prognostic value determining the risk score [21]. In the cited study, premature membrane rupture, meconium aspiration syndrome (MAS), and a mother experiencing prolonged labour in the second stage had a high predictive value for neonatal asphyxia [21]. In the case of premature rupture of membranes, the fact that the interval between membrane rupture and birth is prolonged, increases the risk of amniotic membrane inflammation and early-onset neonatal sepsis [22]. The presence of meconium in the amniotic fluid can cause aspiration of amniotic fluid stained with meconium, which can lead to respiratory failure of the newborn, as evidenced, among others, by the results of imaging tests.

In patients with MAS, ultrasound can reveal alveolar-interstitial syndrome or B-line in the non-consolidating area. In addition, in the study of Liu et al., lung consolidation with air bronchogram was found in all patients; pleural line anomalies and A-line atrophy were also found in all patients, some of whom were diagnosed with atelectasis and pleural effusion [23]. Confirmation that prolonged labour at an expensive stage may have a high predictive value determining the assessment of the risk of neonatal asphyxia may be provided by the study by Altman et al., in which newborns with prolonged second stage of labour had statistically significantly lower values in the 5-minute Apgar scale (<7 and <4 points in Apgar jumps) than newborns in whom labour was not prolonged [24].

To sum-up, based on the study by Tesfa et al., premature membrane rupture, meconium aspiration syndrome (MAS) and prolonged second stage of labour have a high predictive value in predicting neonatal asphyxia, which can be used in the development of further machine learning algorithms. This is also emphasized by Tesfa et. al and other authors. However, Tesla et al. looked at a single centre in a low-income country; therefore, the results of the study need to be externally validated before being used in another context.

F. Darsareh et al. used a machine learning model to identify risk factors for perinatal asphyxia [25] in a retrospective study including 8,888 women who gave birth between January 2020 – January 2022. 4.3% (380 newborns) were identified with perinatal asphyxia. Maternal chronic hypertension, maternal anaemia, diabetes, drug addiction, gestational age, newborn weight, newborn gender, preeclampsia, placenta abruption, parity, IUGR, meconium amniotic fluid, mal-presentation, and delivery method were considered to be statistically significant predisposing factors for asphyxia. Socio-demographic factors, however, were not associated with neonatal asphyxia. F. Darsareh and others used 8 machine learning models: Logistic regression, Decision Tree Classifier, Random Forrest Classification, XGBoost Classification, Permutation Classification, Feed Forward Deep Learning, Light GBM (LGB), Feed Forward Deep Learning and Support Vector Machines (SVM). Of the above models, Random Forrest Classification proved to be the most accurate algorithm for predicting perinatal asphyxia [25].

The limitation of the study by F. Darsareh et al. was that the study was conducted in only one hospital and, for a machine learning model, a relatively small number of subjects to allow the Random Forrest Classification to be used in clinical practice. It is unknown whether a different model would be more accurate in predicting neonatal asphyxia if the study were performed on more patients.

Neuroimaging in the diagnosis of neonatal asphyxia. The choice of treatment and the development of particular patient care for neonatal asphyxia depends on the effectiveness of available diagnostic methods and prognostic tools. It is important to be aware of the limitations of individual methods, therefore integrating information obtained from different tests may be appropriate in some clinical situations [26].

Cranial ultrasound (cUS) enables an inexpensive bedside examination which is routinely performed in newborns with pre-existing neonatal asphyxia. Despite its common

use, in itself it has little prognostic value due to, *inter alia,* low sensitivity and dependence on the operator, because the assessment of changes in neonatal asphyxia is subjective [26]. Cranial Doppler ultrasound provides a more objective measurement of blood flow in the cerebral arteries and resistance [27].

Due to the popularization of a more efficient and sensitive tool, such as MRI, the importance of CT in the diagnosis of HIE has decreased with time. The use of CT is mainly limited to very specific situations, such as suspected intracranial haemorrhage, when it is more sensitive than ultrasound and faster to perform than MRI [28]. With this in mind, conventional magnetic resonance imaging is considered a standard tool in the assessment of brain damage resulting from HIE asphyxiation in neonates and their potential pathway of development. Newer MRI techniques are also being investigated, including T2*-weighted gradient images and sensitivity-weighted imaging (SWI), which allow for the detection of both calcifications and haemorrhages, a direct result of TH treatment in neonatal asphyxia in up to 38% of patients. However, at the moment, the use of these MRI techniques is still limited in the diagnostic process of HIE after perinatal asphyxia [29].

Therapeutic hypothermia in the treatment of neonatal asphyxia. Management of a child with asphyxia includes resuscitation, general measures, such as fluid therapy or antibiotic therapy in specific clinical situations, and hypothermia. New treatments are still being developed. In recent years, it has been indicated that natural compounds with neuroprotective properties, such as melatonin, can be used in the treatment of encephalopathy caused by asphyxia [30].

Therapeutic lowering of body temperature, depending on the temperature range used, can be divided into: slight, moderate and deep hypothermia. To reduce the extent of neurological complications in neonates with asphyxia, mild hypothermia is the standard treatment. The body temperature is maintained in the range of 33 – 34 degrees Celsius, and the newborn's body temperature should not be allowed to fall below 33 degrees Celsius. The 2 most common methods are selective head cooling (SHC) and whole-body cooling (WBC) [31]. Indications for therapeutic hypothermia and criteria preventing the implementation of therapy are presented in Figure 3 [31, 32, 33].

The therapeutic use of hypothermia in hypoxic-ischemic encephalopathy (HIE) is due to its neuroprotective function. Hypothermia lowers levels of excitatory neurotransmitters, reduces acidosis, slows metabolism and cerebral blood flow, and increases the synthesis of vasoconstrictors, such as thromboxane A2. In addition, it inhibits neuronal apoptosis by down-regulating p53 protein levels, regulating anti-apoptotic Bcl-2 proteins, mitogen-activated protein kinases, caspase pathways and cold-induced RNA binding proteins [34]. Clinical trials evaluating the long-term effects of hypothermia in HIE found that newborns with PA treated with hypothermia were less likely to develop neurological disorders, cerebral palsy or disability, than those who were not treated with hypothermia.

When using hypothermia, the time of its implementation, appropriate qualification of patients for treatment and quick organization of transport of the newborn to a centre with appropriate equipment are important [32].

Predicting the neurodevelopmental status of children after hypothermia treatment based on imaging studies

Figure 4 presents 5 selected studies, in which one of the objectives was to determine the predictive power of neuroimaging in neurodevelopmental delay in children aged 2 years who had asphyxia of the newborn, and were treated with therapeutic hypothermia. From the above original studies, the following data were selected: results of neurodevelopmental delay, number of newborns treated with the hypothermia cooling method. All 5 studies in Figure 4 excluded patients with life-threatening congenital malformations, syndromic disorders, neurometabolic diseases, or other alternative diagnoses of encephalopathy that were evident within 6 hours of birth [35–39]. Therapeutic hypothermia was used based on the clinical condition of the newborns following the accepted standards of neonatal medical care. To determine the neurodevelopment of a child at the age of 2 years, the Bayley-II scale was used in the study conducted by Apaydin et al., and the Bayley-III scale was used in the others. The MRI examinations listed in the Figure 4 (mainly in sequences T1, T2, DWI) were performed within the first 2 weeks of life of the newborns. In interpreting imaging results, the timing of MRI scan performance is of paramount importance, as injury patterns vary greatly during the first weeks after birth, depending on the imaging

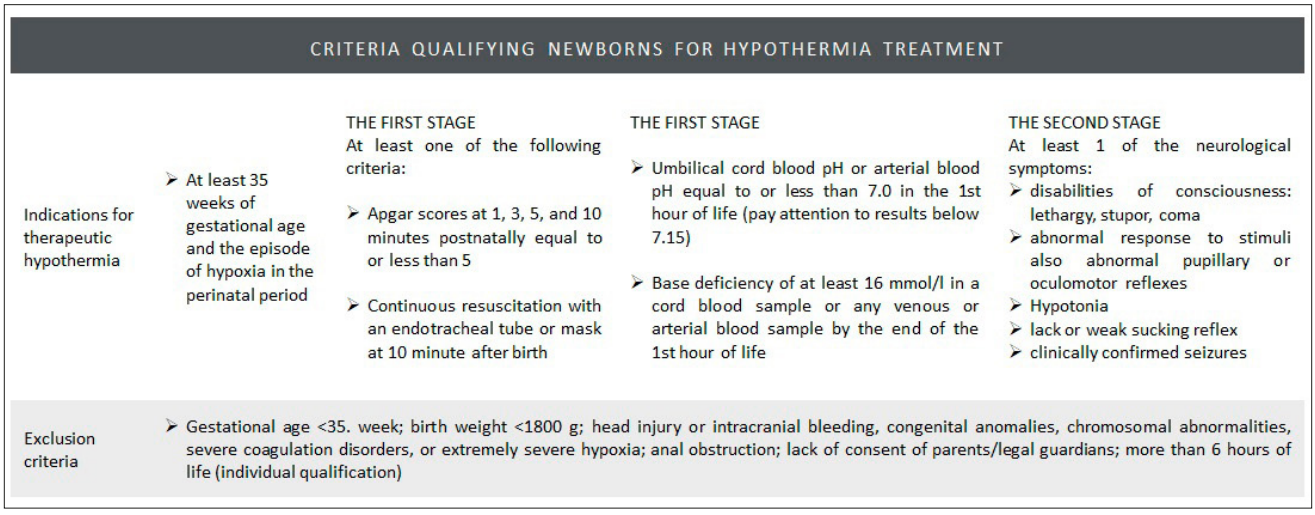

Figure 3. Criteria qualifying newborns for hypothermia treatment [31, 32, 33]

Research topic	Number of newborns in the study	Years of research	Inclusion criteria for the study	Number of newborns treated with hypothermia	Brain MRI findings	The predictive power of neuroimaging for neurodevelopmental delay (in 2 year old children)	Results for neurodevelopmental delay
1. Apaydın, U., Erol, E., Yıldız, A., et al. The use of neuroimaging, Prechtl's general movement assessment and the Hammersmith infant neurological examination in determining the prognosis in 2-year-old infants with hypoxic ischemic encephalopathy who were treated with hypothermia. Early Human Development, 2021; 163: 105487.	47; 18(Female); 29 (Male)	2014-2018	Term birth (gestational age > 37 weeks) and presenting with asphyxia	47	7–14 days after hypothermia	The sensitivity and specificity in determining the Psychomotor Developmental Index (PDI) score were 97% and 100%, respectively, for MRI; The sensitivity and specificity in determining the Mental Developmental Index (MDI) score were 95% and 85.7%, respectively, for MRI	7 patients (with grade III HIE) had an MDI or PDI score (Bayley II score) <85 points, which indicates neurodevelopmental delay.
2. Sweetman D, Kelly L, Hurley T, et al. Troponin T correlates with MRI results in neonatal encephalopathy. Acta Paediatr. 2020; 00: 1-5.	54; 14(Female); 40 (Male); 4 deaths	no information about	Term birth (gestational age > 37 weeks) and presenting with asphyxia	27	45 newborns; 1-7 days after hypothermia	Day 1 troponin T significantly correlated with BSID III cognitive score. Infants who had an abnormal MRI brain scan had significantly higher troponin T levels on day 2 and 3	3 patients (with grade III HIE) had a Bayley-III score below normal
3. Lally PJ, Montaldo P, Oliveira V, et al. Magnetic resonance spectroscopy assessment of brain injury after moderate hypothermia in neonatal encephalopathy: a prospective multicentre cohort study. Lancet Neurol. 2019;18(1):35-45.	223; 99 (Female); 124 (Male); Mild HIE N=37; Moderate HIE N=163; Severe HIE N=23	29.01.2013-25.06.2016	term and near-term infants (36–43 weeks' gestation) with neonatal encephalopathy who received therapeutic hypothermia	216	4–14 days after birth	190 (85%) had Bayley-III at a median age of 23 months; in relationship between each of the MRI measures with the continuous neurodevelopmental outcome scores from Bayley-III individually, all 9 were significantly associated with these scores (all p<0·0001). MRI had a sensitivity of 71% (95% CI 52–86) and specificity of 88% (82–93)	190 patients: 31 (16%) had an adverse neurodevelopmental outcome (death or moderate or severe disability). Mild HIE N=1 ; Moderate HIE N=17; Severe HIE N=13
4. Alderliesten T, de Vries LS, Staats L, et al. MRI and spectroscopy in (near) term neonates with perinatal asphyxia and therapeutic hypothermia. Arch. Dis. Child Fetal Neonatal Ed. 2017;102(2):F147-F152.	88; 22 deaths	no information about it	Term birth (gestational age >= 36 weeks) and presenting with asphyxia	88	within 7 days after birth	In infants with an adverse outcome, ADC values of the basal ganglia and thalamus were significantly lower, and lactate/N-acetylaspartate ratios were significantly higher than in infants with a normal outcome.	7 had an adverse neurodevelopmental outcome
5. Parmentier CEJ, Lequin MH, et al. Additional Value of 3-Month Cranial Magnetic Resonance Imaging in Infants with Neonatal Encephalopathy following Perinatal Asphyxia. J. Pediatr. 2023;258:113402.	63; 39 (Female), 24 (Male)	09.2003-04.2020	Term birth (gestational age >36 weeks) and presenting with asphyxia	28	<14 days after birth and repeated at 2-4 months after birth because of neonatal MRI abnormalities	MRI variables such as Total Score not including 1H-MRS (Proton magnetic resonance spectroscopy), Deep Gray Matter Damage Score not including 1H-MRS, and Cerebellar Damage Score had predictive value in determining neurodevelopmental delay	The Dutch version of the BSID-III (Bayley-III-NL), or 18-24 months using the Griffiths Mental Development Scales when a Bayley-III-NL wasn't performed. 23 patients had adverse outcome including 7 treated with hypothermia

Figure 4. Results of imaging studies and neurodevelopmental status of children after neonatal asphyxia treated with hypothermia [35–39]

modality used. MRI, including DWI and 1H-MRS performed immediately after therapeutic hypothermia (i.e., 4–5 days after birth) is optimal for the diagnosis and prognosis of newborns with HIE, as diffusion abnormalities peak at 3–5 days post-partum, and pseudonormalization of DWI and 1H-MRS occurs at the end of the first week after the onset of HIE [40].

Different scoring systems were used to determine brain lesions in MRI of patients which did not affect the ability to compare study results, as it was shown that different scoring systems developed to quantify brain lesions in neonatal magnetic resonance imaging were able to predict neurodevelopmental outcomes in infants after HIE (Fig. 4) [40].

In the Apaydin et al. study and the Sweetman et al. study, all patients who had the highest HIE grade had delayed psychomotor and mental development, regardless of the type of brain structure damaged on MRI and although they were treated with hypothermia. This was supported by the fact that neurodevelopment is abnormal in 100% of newborns with stage III HIE [33]. However, in the Lally et al. study, of the patients with severe HIE (N=23) who received therapeutic hypothermia, 43% (N=10) had a normal Bayley-III score and 57% (N=13) had an abnormal score. Based on this, it can be assumed that hypothermia treatment may also improve the neurodevelopment of newborns with the highest degree of HIE. In addition, in the study of Alderliesten et al., as many as 92% (N=81) and in the study of 5–75% (N=21) of children treated with hypothermia after neonatal asphyxia, obtained a normal result in the Bayley-III test at the age of 2 years, which is consistent with the knowledge that hypothermia has a neuroprotective effect [34].

SUMMARY

Currently, there are no preventive and therapeutic methods that can prevent HIE or death in newborns with severe perinatal hypoxia. However, before birth, maternal and foetal characteristics are known which allows prediction of the occurrence of neonatal asphyxia, and refer pregnant women to give birth in specialized centres where therapeutic hypothermia is available or where the journey to such a centre is short.

In recent years, scientific research has been conducted to use predictive models for predicting the occurrence of neonatal asphyxia, based on the occurrence of specific risk factors. However, an algorithm that would numerically estimate the chance of neonatal asphyxia has not yet been used in clinical practice. Research on the use of machine learning in neonatology will certainly take a few more years, but the introduction of such an asphyxia calculator into

clinical practice in the future would facilitate the work of both obstetricians and neonatologists, and would also enable parents to be made aware of their child's condition earlier, and thus provide an opportunity for better child development. It is also worth emphasizing that such an asphyxia calculator should be subject to geographical validation to improve the accuracy of predicting the occurrence of asphyxia in a given area.

The limitation of the current review in the context of the research question – is it possible to predict the neurodevelopmental status of children after hypothermia treatment based on imaging tests? was that not all authors of the studies presented in Table 4 provided the number of children with neurodevelopmental delay depending on the degree of HIE and whether they were treated with hypothermia. Additionally, no studies were found aimed at developing models for predicting the neurodevelopmental status of children after neonatal asphyxia, either treated or untreated with hypothermia.

Further research on the use of machine learning in neonatology would be worth focusing on the development of models thanks to which, based on:

1) maternal and foetal characteristics, the chances of developing HIE and the possible degree of HIE could be determined;
2) maternal characteristics, foetal characteristics and expected degree of HIE, it would be possible to predict the child's neurodevelopmental status depending on the use of therapeutic hypothermia;
3) time between delivery and the use of neuroprotective strategies, the chances for normal development of the child after HIE can be determined.
4) and based on neuroimaging, it would be possible to predict the chance for normal development of children both treated with hypothermia and those not treated.

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