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Original article

A PREDICTIVE VALUE OF EARLY CLINICAL PARAMETERS FOR ABNORMAL BRAIN MRI SCAN IN NEONATES TREATED WITH THERAPEUTIC HYPOTHERMIA

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Abstract: **Introduction:** Brain MRI scans can predict neurodevelopmental outcomes in neonates treated with therapeutic hypothermia. It is a common clinical practice to perform brain MRI before discharge, but brain MRI scans performed at around four months of age have a better prognostic value for a long-term neurological outcome in asphyxiated neonates.

Aim: To identify which of three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) evaluated 10 days after therapeutic hypothermia could predict the primary outcome of an abnormal brain MRI.

Methods: We reviewed the medical records of neonates ≥ 36 completed weeks of gestation consecutively treated with therapeutic hypothermia who underwent brain MRI. Clinical parameters on day 10 after therapeutic hypothermia were correlated with brain MRI findings in the first 7-14 days of life. Logic regression analysis was performed using all three covariates of the clinical status, with an abnormal MRI as the primary outcome.

Results: Brain MRI was abnormal in 42 (51.85 %) neonates with the following distribution of brain injury patterns: abnormal signal in the basal nuclei in 6, an abnormal signal in the cortex in 16, an abnormal signal both in the cortex and basal nuclei in 20 neonates. Out of three analyzed clinical parameters, feeding difficulty ($P < 0.001$, OR 8.3, 95% CI 2.9 - 28.9) and a history of seizures ($P < 0.001$, OR 11.95, 95% CI 3 - 44.5) were significantly associated with an abnormal MRI.

Conclusion: Neonates who were capable of full oral feeding by day 10 after therapeutic hypothermia and had no history of seizures were unlikely to have an abnormal MRI. This may be used in selective planning of pre-discharge MRI in asphyxiated neonates.

Keywords: therapeutic hypothermia, clinical parameters, feeding difficulties, seizures, brain MRI.

INTRODUCTION

The neuronal injury after perinatal asphyxia is a process that lasts, rather than being an isolated, one-time event (1). The primary cell injury is a direct consequence of hypoxia and ischemia. During the primary injury the cerebral concentrations of energy-rich compounds, adenosine triphosphate, and phosphorus creatine are decreased, which causes cytotoxic edema and neuronal injury. The next stage is the reperfusion stage, where cellular edema subsides in approximately thirty minutes. Next comes the latent phase, in which oxidative cerebral energy metabolism is very close to normal and lasts around 6 hours after acute asphyxia. After the latent phase, secondary injury develops with extracellular accumulation of excitatory amino acids, free radicals, and induction of apoptosis and inflammatory activity with a final breakdown of oxidative metabolism and neuronal death. Therapeutic hypothermia is a standard neuroprotective therapy in asphyxiated neonates (2). The therapeutic window for the implementation of hypothermia corresponds to the latent phase of hypoxic-ischemic brain injury (3).

The brain magnetic resonance imaging (MRI) findings after perinatal hypoxia have a predictive value for the neurodevelopmental outcome. The common clinical practice is to perform brain MRI before discharge, but the studies of serial MRI findings following therapeutic hypothermia showed that brain MRI findings at around four months of age have the highest

correlation with a long-term neurodevelopmental outcome (4). Thus, in some cases, it might be better to prolong brain MRI to that age.

This study aimed to analyze a correlation between the clinical findings ten days after therapeutic hypothermia and the brain MRI findings which might lead to identifying neonates who should have a brain MRI performed before discharge and neonates in whom it is better to postpone the brain MRI scan to be more informative. This selective and targeted approach to the brain MRI evaluation of asphyxiated infants might be more useful.

MATERIAL AND METHODS

The medical records of 88 neonates ≥ 36 completed weeks of gestation consecutively treated with therapeutic hypothermia between December 2017 and December 2021 at Pediatric Clinic University Medical Center Sarajevo, Bosnia and Herzegovina were reviewed. Our research was conducted by the ethical standards of the Declaration of Helsinki and the ethical standards of the University Medical Center of Sarajevo, Bosnia and Herzegovina.

Both three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) and brain MRI scans were analyzed in 81 of the 88 neonates treated with therapeutic hypothermia. The medical records of the seven neonates who died were excluded. The therapeutic hypothermia for 72 h, initiated before 6 h of life was performed according to Bristol Royal Hospital's guidelines for therapeutic hypothermia in neonates. In all cases, prior to the initiation of therapeutic hypothermia parental consent was obtained.

All neonates underwent a brain MRI before discharge. The brain MRI was performed using a 1,5-T magnet with T1- and T2- weighted imaging and the scans were interpreted by neuroradiologists. We used the categorization of the brain injury similar to the categorization described by Barkovich et al (6). This categorization is based on the recognition of two basic imaging patterns of hypoxic-ischemic brain injury, one in which the primary damage is to the basal nuclei and another in which the damage is primarily to the cortex (6–9). Injuries to both basal nuclei and cortex were considered 'severely abnormal'.

The three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) were evaluated 10 days after therapeutic hypothermia.

Data were analyzed by PASW Statistics 18. The clinical parameters between the groups were compared by X^2 test or t-test or Mann - Whitney test, as appropriate. The multivariate analysis was performed to determine which of the selected clinical parameters could predict an abnormal or severely abnormal MRI scan. Two-sided P-values ≤ 0.05 were regarded as significant.

RESULTS

We analyzed an MRI scan and three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) in 81 neonates treated with therapeutic hypothermia. MRI scans were performed at median postnatal age of 9 days (range 6 to 24 and 50% IQR 6 to 10). Ten days after completion of treatment with therapeutic hypothermia 45 neonates (55.55%) failed to achieve full oral feeding, 24 (29.63%) had a deviation in muscle tone (hypotonia or hypertonia) and 53 (65.43%) had a history of one or more seizures which required treatment with anticonvulsants. Brain MRI was abnormal in 42 (51.85%) neonates. 35 out of 45 neonates with feeding difficulties, 20 out of 24 neonates with a deviation in muscle tone, and 38 out of 53 neonates who had clinical seizures by day 10 after completion of therapeutic hypothermia had an abnormal MRI. Table 1. shows the predictive values of these three selected clinical findings evaluated for an abnormal MRI.

The brain MRI findings for all 81 neonates were: normal scan in 35, an abnormal signal in the basal nu-

Table 1. *Predictive value of three clinical parameters (oral feeding ability, deviation in muscle tone, history of clinical seizures) for abnormal brain MRI in 81 neonates treated with TH*

Clinical parameter evaluated 10 days after TH	*Abnormal MRI scan*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*P-value (OR,95%Cl)*
Inability of oral feeding (n = 45)	35	81	72	75	72	< 0.001 (8.3, 2.9 - 28.9)
Deviation in muscle tone (hypotonia/hypertonia) (n = 24)	20	48	87	83	55	0.004 (3.9, 1.6 - 9.8)
Hystory of clinical seizure (n = 53)	38	90	55	69	80	< 0.001 (11.9, 3 - 44.5)

Abbrevations: TH, therapeutic hypothermia; PPV, positive predictive value; NPV, negative predictive value, CI, confidence interval; OR odds ratio

Table 2. *Significance of clinical parameters for prediction of 'severely abnormal' brain MRI*

Clinical parameter	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*P-value (QR, 95%CI)*
Inability of oral feeding	83	54	38	92	0.013 5.5,1.3-21.5
Hystory of clinical seizure	92	36	39	95	0.032 9.5,1.2-78.5

Abbrevations: PPV, positive predictive value; NPV, negative predictive value, CI, confidence interval; OR odds ratio

clei in 7, abnormal signal in the cortex in 16, abnormal signal both in the cortex and in the basal nuclei in 23 neonates. MRI scans showing injury of both basal nuclei and cortex were considered 'severely abnormal'.

Univariate analysis showed that all three selected clinical parameters evaluated 10 days after completion of therapeutic hypothermia were significantly associated with abnormal brain MRI scans the inability of oral feeding (P < 0.001, OR 10.2, 95% CI 3.4 – 25.7), deviation in muscle tone (P < 0.001, OR 8.9, 95% CI 2.5 – 29.7) and a history of clinical seizures (P < 0.001, OR 12.5, 95% CI 3.4 – 41.7). When we performed the multivariate analysis, only feeding difficulty ($P < 0.001$, OR 8.3, 95% CI 2.9 - 28.9) and a history of seizure ($P < 0.001$, OR 11.95, 95% CI 3 - 44.5) was linked with an increased risk of abnormal brain MRI findings.

Out of 23 neonates with 'severely abnormal' MRI, 20 neonates had difficulties with oral feeding, and 22 had a history of seizures. When we repeated multivariate regression analysis with all three clinical parameters for the outcome of 'severely abnormal' brain MRI, feeding difficulty and a history of seizures were again associated with the outcome, with negative predictive values of 92% and 95%, respectively (Table 2).

DISCUSSION

Currently, there are several clinical scoring systems in the early neonatal period proposed for the prediction of neurological outcomes after therapeutic hypothermia (10, 11). Many of these tests incorporate feeding ability and history of seizures, which appear to be significant predictors of neurodevelopmental outcomes following perinatal asphyxia (12, 13). The clinical assessment immediately after the therapeutic hypothermia treatment may result in false prediction due to the postponed removal of medication or impaired neuronal activity because of a briefly preceding hypoxic-ischemic incident and delaying clinical examination is more informative (14). Our study suggests that deferring clinical evaluation until ten days after therapeutic hypothermia completion provides significant prognostic information on neurodevelopmental outcomes.

The brain MRI scans after therapeutic hypothermia assure that there is no other pathology (e.g. hemorrhage, ischemia, congenital anomalies,…) and have a prognostic value. Early MRI abnormalities may not represent the final pathology, but the injury that is still evolving and studies show that delaying brain MRI scans to 4 months of age has the highest correlation with a long-term neurodevelopmental outcome (4). In our study, the negative predictive values of oral feeding ability and a history of seizures ten days after the completion of therapeutic hypothermia for prediction of 'severely abnormal' MRI were 92% and 95%. respectively. This signifies that neonates who attain oral feeding and have no history of seizures are unlikely to have severe changes on brain MRI. According to our results, brain MRI scans before discharge in such cases are not necessary and can be postponed to a period of life when MRI scans are more informative regarding the long-term neurodevelopmental outcome.

In conclusion, oral feeding ability and history of clinical seizures 10 days after completion of therapeutic hypothermia may be used for a selective and targeted approach to the brain MRI evaluation of the asphyxiated neonates. This approach may be more useful since delayed brain MRI scans are more informative in terms of long-term neurodevelopmental outcomes.

Abbreviations

MRI — magnetic resonance imaging
CI — confidence interval
NPV — negative predictive value
OR — odds ratio
PPV — positive predictive value
TH — therapeutic hypothermia;

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Sažetak

ZNAČAJ RANIH KLINIČKIH PARAMETARA U PREDIKCIJI MRI NALAZA NA MOZGU KOD NOVOROĐENČADI LEČENIH TERAPIJSKOM HIPOTERMIJOM

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Uvod: Nalaz MRI mozga ima prediktivnu vrednost za neurorazvojni ishod kod novorođenčadi lečenih terapijskom hipotermijom. Uobičajena klinička praksa je da se uradi MRI mozga pre otpusta, ali MRI mozga u dobi od oko 4 meseca života ima bolju prognostičku vrednost za dugoročni neurološki ishod kod novorođenčadi sa asfiksijom.

Cilj: Identifikovati koji od odabranih kliničkih parametara (sposobnost oralnog hranjenja, mišićni tonus, konvulzije) procenjeni 10 dana nakon terapijske hipotemije mogu predvideti primarni ishod abnormalnog MRI mozga.

Metode: Pregledali smo medicinsku dokumentaciju novorođenčadi ≥ 36 navršenih sedmica gestacije koja su uzastopno lečena terapijskom hipotermijom i bila podvrgnuta MRI mozga. Klinički parametri 10 dana nakon terapijske hipotermije bili su u korelaciji sa nalazima MRI mozga učinjenim u prvih 7-14 dana života. Urađena je logička regresiona analiza korištenjem sve tri kovarijante kliničkog statusa, sa abnormalnim MRI nalazom kao primarnim ishodom.

Rezultati: MRI mozga je bio abnormalan kod 42 (51,85%) novorođenčadi sa sledećom distribucijom obrazaca oštećenja mozga: abnormalni signal u bazalnim jedrima kod 6, abnormalni signal u korteksu kod 16, abnormalni signal i u korteksu i bazalnim jedrima kod 20 novorođenčadi. Od tri analizirana klinička parametra, samo poteškoće pri hranjenju ($P < 0,001$, OR 8,3, 95% CI 2,9 - 28,9) i konvulzije ($P < 0,001$, OR 11,95, 95% CI 3 - 44,5) su bili značajno povezani sa abnormalnim MRI nalazom.

Zaključak: Novorođenčad koja su bila sposobna za potpuno oralno hranjenje do 10. dana života nakon terapijske hipotermije i nisu imala konvulzije, imala su malu verovatnost da će imati abnormalni nalaz MRI mozga. Ovo se može koristiti u selektivnom planiranju MRI mozga pre otpusta kod asfiksiranih novorođenčadi.

Ključne reči: terapijska hipotermija, klinički parametri, poteškoće pri hranjenju, napadi, magnetna rezonanca mozga.

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