Sonographic and MRI findings in neonates following selective cerebral hypothermia

Zmiany w obrazie ultrasonograficznym i obrazie rezonansu magnetycznego mózgu u noworodków leczonych metodą selektywnej hipotermii.

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Abstract

Introduction: *Hypoxic ischemic insults during labor remain an important cause of brain injury in term and near-term neonates. Selective cerebral hypothermia is a potentially neuroprotective rescue therapy. Ultrasonography (US) and magnetic resonance imaging (MRI) are routinely used to visualize intracranial changes in neonatal hypoxic-ischemic injuries.*

Aim of the study: *We attempted to describe all pathological findings on US and MRI in the brains of our patients following selective cerebral hypothermia.*

Materials and methods: *Twenty-nine neonates with hypoxic-ischemic encephalopathy (HIE) following therapeutic cooling were assessed with cranial ultrasound (US) and magnetic resonance imaging (MRI). The findings were compared with the clinical outcome.*

Results: *Over one-fourth (27.6%) of the examined infants had a normal brain on MRI (with only 17.2% on US). Involvement of the basal ganglia and thalami was one of the most frequent findings in our material (9/29 = 31% on MRI, and 7/29-24.1% on US). Cerebral parenchymal hemorrhage was detected on MRI in as many as 7 (24.1%) and cerebellar parenchymal hemorrhage in 4 (13.8%) infants. The loss in the gray-white matter differentiation ('fuzzy brain'), usually transient on US, was observed in 79.3% of the neonates. Diffusion restriction in the callosal splenium (13.8%) and hyperechoic thalami and basal ganglia were strictly correlated to a significantly higher incidence of severe developmental delay.*

Conclusion: *Abnormalities on MRI and US were observed in 75% of newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia.*

Key words: **selective hypothermia** / **hypoxic-ischemic encephalopathy (HIE)** / / **ultrasound (US)** / **magnetic resonance imaging (MRI)** /

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Streszczenie

Wstęp: *Uraz niedotlenieniowo-niedokrwienny jest częstą przyczyną okołoporodowego uszkodzenia mózgu u noworodków, u których potencjalną, neuroprotekcyjną metodą leczenia jest selektywna hipotermia. Ultrasonografia (USG) i rezonans magnetyczny (MRI) są rutynowymi metodami obrazowania mózgu u noworodków ze zmianami niedotlenieniowo-niedokrwiennymi.*

Cel pracy: *Podjęłyśmy próbę opisania wszystkich zmian patologicznych wykrytych w badaniu USG i MRI mózgu u noworodków, które leczone były metodą selektywnej hipotermii.*

Materiał i metoda: *Przezciemiączkowe badanie ultrasonograficzne (USG) oraz badanie metodą rezonansu magnetycznego (MR) wykonano u 29 noworodków z encefalopatią niedotlenienieniowo-niedokrwienną (ENN) po zastosowaniu terapeutycznej hipotermii. Wyniki badań porównano z oceną kliniczną.*

Wyniki: *U ponad jednej czwartej badanych dzieci (27,6%) badanie MR mózgu było prawidłowe (w badaniu USG tylko u 17,2%). Zajęcie jąder podstawy i wzgórz było jednym z najczęstszych znalezisk w naszym materiale (9/29 = 31% w MR i 7/29 = 24.1% w USG). Krwawienie śródmózgowe wykryto w MR aż w 7 przypadkach (24,1%), a śródmóżdżkowe w 4 (13,8%). Brak zróżnicowaniu istoty szarej i białej ("fuzzy brain"), zwykle przemijające w obrazie USG, obserwowano u 79,3% noworodków. Restrykcja dyfuzji wody w płacie ciała modzelowatego (13,8%) oraz hiperechogeniczność wzgórz i jąder podstawy mózgu ściśle korelowały z istotnie częstszym występowaniem znacznego opóźnienia rozwoju.*

Wnioski: *Nieprawidłowy obraz MRI i US występuje u 75% noworodków z encefalopatią niedotlenieniowo-niedokrwienną leczonych metodą selektywnej hipotermii.*

Słowa kluczowe: **wybiórcza hipotermia** / **encefalopatia niedotlenieniowo--niedokrwienna (ENN)** / **ultrasonografia (USG)** / **rezonans magnetyczny (MR)** /

Background

Hypoxic ischemic insults during labor remain an important cause of brain injury in term and near-term neonates. A clinical manifestation of a brain injury is termed 'hypoxic ischemic encephalopathy' (HIE). Selective cerebral hypothermia is a potentially neuroprotective rescue therapy. Ultrasonography (US) and magnetic resonance imaging (MRI) are routinely used to visualize intracranial changes in neonatal hypoxic-ischemic injuries. US changes in HIE can be classified as peripheral and central [1].

Peripheral brain abnormalities include changes in the grey-white matter differentiation (with or without loss of gray-white matter differentiation), and changes in the echogenicity of the cortex and subcortical white matter. Central brain abnormalities involve the deep gray matter (basal ganglia, thalami), hippocampus, dorsal brainstem and the periventricular white matter. Intraventricular and cerebellar bleeding, although uncommon, has also been described in term neonates with severe asphyxia. Application of Doppler studies in the hemodynamic evaluation of cerebral circulation in neonates treated with hypothermia in the first 72 hours of life significantly improves sensitivity and specificity of detecting post-hypoxic brain insults. A notably lowered (below 0.55) resistive index (RI) value of cerebral vessels is associated with poor clinical outcome [2, 3].

Material and methods

From December 2009 to May 2014, 29 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia were included in our study. The neonates were admitted to the NICU of Warsaw Medical University. The infants were recruited during the first 6 hours of life if they met the following entry criteria: gestational age of >36 weeks and birth weight of ≥2000g. The qualification was 3-staged. The first stage was based on the clinical/biochemical evaluation of neonatal condition just after birth. At that stage, criteria were met by neonates with at least one of the following: 1) Apgar score ≤5 at 10 minutes of life, 2) need for mechanical ventilation beyond 10 minutes after birth, 3) acidosis pH <7.0 in cord blood or in neonatal arterial blood taken in the first hour of life and/or base deficit ≥ -16 mmol/L in cord blood or in any blood sample taken in the first hour of life. During the second stage, neurological evaluation of the neonates was performed [lethargy, seizures, poor muscle tone, absence of sucking]. At the third stage, aEEG was done using the Cerebral Function Monitor. Written informed consent was obtained from all the parents. Exclusion criteria were: gestational age of <36 weeks, birth weight of <2000g, major congenital abnormalities, major mechanical head injuries, anal atresia, lack of written parental consent. As soon as the neonates met the entry criteria, the cool cap was applied and changed as required to maintain the rectal temperature [probe inserted 8 cm into the rectum] between 34-35°C. All infants were nursed in an open incubator. The temperature was regulated by servo-controlling using probe placed on the skin over the liver. The cooling procedure should be initiated during the first six hours of life. Unfortunately, in case of 9 neonates admitted from other hospitals, the cooling was started later, between hour 7-9 of life. All neonates had mildly to severely abnormal aEEG, which changed during treatment. Seven patients died. The cooling procedure was applied over the course of 72 hours. We analyzed 29 patients with known results of cranial US and MRI. The characteristics of the neonates are shown in Table I.

Cranial sonography was performed using a Philips HD 15XE machine with a 7.5-12 MHz sector probe. Standard images in coronal and sagittal planes were obtained via the anterior

Table I. Neonatal characteristics.

number of neonates	sex		gestational age [weeks]	birth weight [g]	Apgar		pH in the first hour	time of start [hours]	time discharge at home [days]
	M	F			5 min	10 min			
29	19	10	36 – 42 [mean 38.8]	1980 – 3990 [mean 3290]	0 – 8 [4]	0 – 8 [4.9]	6.60 – 7.45 [mean 6.79]	3 – 9 [mean 5.9]	13

Table II. Brain MRI findings in the study group.

MRI findings	Number of neonates	Percentage
Normal brain	8	27.6%
Involvement of basal ganglia and thalami	9	31.0%
Cortical involvement	4	13.8%
Involvement of callosal splenium	4	13.8%
Diffuse white matter involvement	4	13.8%
Cavitations	5	17.2%
Cerebral parenchymal hemorrhage	7	24.1%
Cerebellar parenchymal hemorrhage	4	13.8%
Bleeding to the ventricles, choroid plexi, subependymal	4	13.8%
Pericerebral/pericerebellar hemorrhage	3	10.3%
Venous sinus thrombosis	2	6.9%

Table III. US findings in the study group.

US findings	Number of neonates (total: 29)	Percentage (%)
Acute peripheral brain abnormalities		
Loss in the gray-white matter differentiation (with or without cerebral edema, fuzzy view)	23	**79.3**
Global increase in cerebral echogenicity 'bright brain"	**12**	**41.0**
Acute central brain abnormalities		
Involvement of basal ganglia and thalami	**7**	**24.1**
Periventricular white matter hyperechogenicities	**3**	**10.3**
Other acute findings		
Bleeding to the ventricles, subependymal	**6**	**20.7**
Cerebellar parenchymal hemorrhage	**1**	**3.5**
Cerebral parenchymal hemorrhage	**6**	**20.7**
Sinus thrombosis	**1**	**3.5**
Long-term changes in US		
Cerebral atrophy	**2**	**6.9**
Cavitations (multicystic encephalopathy)	**2**	**6.9**
Lenticulostriate vasculopathy	**5**	**17.2**
Doppler findings		
RI <0.55	**14**	**48.3**
Normal brain	**5**	17.2

fontanelle. To exclude IVH II posterior fontanelle was used. The mastoid fontanels were used to visualize the posterior fossa, midbrain and cerebellar hemorrhages. In order to improve the sensitivity and specificity for brain injury, Doppler evaluation of the blood flow in the anterior cerebral artery (ACA) was performed during each US examination. The ACA was visualized in the sagittal plane using the anterior fontanelle, where signals from the inferior point of the corpus callosum on the artery were recorded. The measurements of peak systolic and end-diastolic velocities (S and D), and RI were calculated from at least four beats of an optimal quality. The resistive index of Pourcelot was calculated using the following formula: S-D/S. In most newborns, the US evaluation of the brain and cerebral circulation was performed during the first three days of life, every 12 hours (during the head check-up after the cool cap was removed). The first cranial US using the anterior fontanelle was done upon admission to NICU, before hypothermia was applied. MR examinations were performed between the ages of 5 days and 5 weeks at the Department of Diagnostic Imaging of the Institute of Mother and Child with the use of GE Signa HDxt 1.5T scanner according to the routine protocol for newborns. Six of these babies were examined in the MR compatible incubator after its introduction into the clinical practice.

Results

The results of brain US and MRI in the newborns after hypothermia are presented in table II and III. The percentages do not sum to 100% because more than one type of injury was found in some neonates.

The follow-up is provided to all newborns at the Follow-up Department. The neurodevelopmental delay was estimated using the Bayley Scale at the age of 12 months and will be published in our next paper.

Discussion

In our paper, we attempted to describe all pathological findings on US and MRI in the brains of our patients (including hemorrhages, corpus callosum lesions, sinus thrombosis and lenticulostriate vasculopathy), as we are of the opinion that all of them – and not just those classically attributed to hypoxia-ischemia – contribute to deteriorated prognosis and outcome in these children. We found no abnormalities in the brains of more than one-fourth of the examined neonates on MRI (27.6%), and only 17.2% on US. This observation is similar to that of Sarkar et al. who described normal findings in 26% of neonates after selective head cooling [4]. These authors stated that hypoxic–ischemic brain lesions detected on MRI were more frequent and more severe in newborns treated with selective head cooling than in those with whole body cooling. In this second group of patients, normal brain MRIs were described in 55% of the cases [4]. Lower rates of normal brain image on US are the result of changes which regress in the subsequent days of life, for example 'fuzzy brain', and are no longer visible on MRI. Cranial sonographic changes in the earlier phase (within 2 days of the insult) in neonates treated with selective head cooling, are indecisive because microvascular changes and cell reaction develop over a period of at least 48 hours. Thus, the earliest and the most common change observed on US in the first 48 hours of life is the loss of the gray-white matter differentiation (with or without cerebral edema, 'fuzzy brain'), which we noted in 79.3% of the neonates (Figure 1). Similarly, such early changes are reported in the literature also by other authors [1, 5, 6]. In some of the neonates the changes regressed after day 7 of life, whereas global increase in cerebral echogenicity – the 'bright brain' – was noted in the remaining 41% of the cases. Increased cerebral echogenicity was accompanied by an extensively reported in the literature change, known as the parasagittal cerebral injury or watershed injury in the regions of hypovascularity. In reports of other authors, the phenomenon called the 'bright brain", which is fully developed by day 2 or 3 of life, has a high sensitivity (88-100%) for death or severe disability [1, 7]. In our study, the 'bright brain' on US was detected in 12 children: 1 neonate died, 6 children (50%) were diagnosed with severe developmental disorders (cerebral palsy,), 3 develop normally, and loss of observation was noted in the remaining 2 cases.

Notably, most authors describe only strictly hypoxic-ischemic findings in their papers dealing with patterns of brain injury and hypothermia [8]. In contrast, we describe all pathological findings in the brains of our patients (including hemorrhages), because we believe that all of them - and not just those classically attributed to hypoxia-ischemia - contribute to a worse prognosis and outcome in these children. Li et al. reported hemorrhages in their paper but did not comment on them [8]. In our study, cerebral parenchymal hemorrhage was detected on MRI in as many as 7 neonates (24.1%) (Figure 2 a, b) and cerebellar parenchymal hemorrhage in 4 (13.8%) infants (Figure 3 a). The sensitivity of the US method to detect cerebellar and surrounding bleedings, despite using additional acoustic windows (i.e. mastoid fontanels), remains relatively low, with only 3.5% in our study, whereas detection of cerebral parenchymal hemorrhages on US correlated well with MRI results (20.7% vs. 24.1%). Especially cerebellar injury in recent years has been rated as highly relevant in the context of developmental disorders, particularly autism [9]. Bleeding to the ventricles and subependymal hemorrhage, although uncommon, has also been described in term neonates with HIE [6]. We noted an overestimation, especially of intracranial hemorrhages (MRI-13.8%; US-20.7%), in our patients with hyperechogenicity of the basal ganglia region.

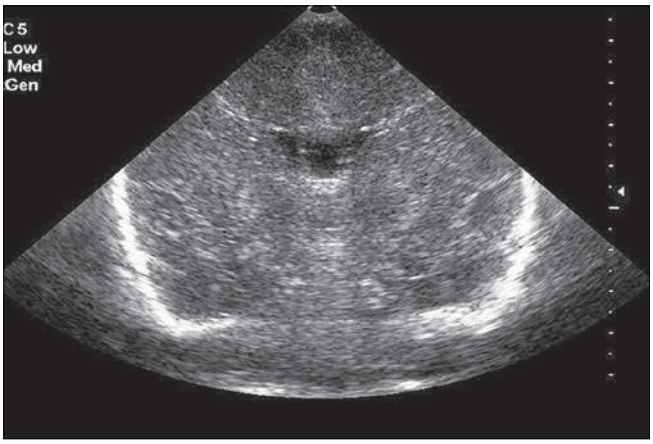

Figure 1. US. 'Fuzzy brain' with difficult to recognize sulci (coronal view)s.

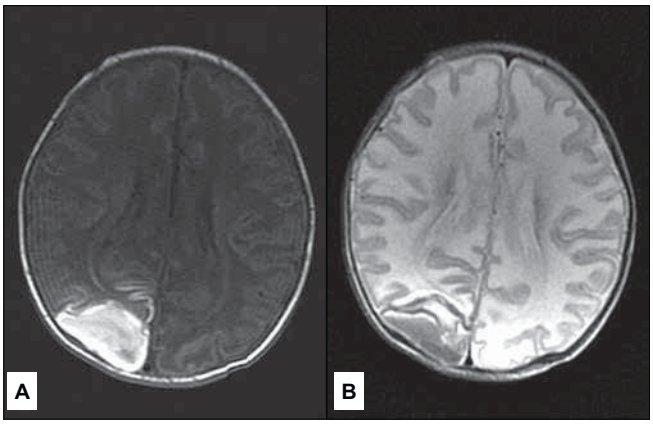

Figure 2. A neonate with a diffuse bilateral white matter injury and supratentorial hemorrhage on the right side.
A. SE/T1-weighted image shows hyperintense bleeding and hypointense signal from the damaged white matter.
B. FSE/T2-weighted image. Hemorrhage of mostly low signal intensity and hyperintense white matter.

The involvement of the basal ganglia and thalami was the most frequent finding in our material (9/29 = 31% in MRI - Figure 4 a, b, c, and 7/29 = 24.1% in US) and was associated with cortical injury only in 3 cases. The cortex was involved in 4 cases altogether (13.8%). In the material of Sarkar et al. the situation is reversed in the group of newborns with selective head cooling: damage to the cerebral cortex was the most common (with or without the accompanying damage to the basal ganglia and thalami – 70%), while basal ganglia were affected in 47% of the cases (with or without cortical injury) [7]. Hyperechoic basal ganglia and thalami is an early, clearly visible sonographic indicator of a primary necrotic process and appears on day 2 as a few hyperechoic columns in the coronal section through the deep gray matter (Figure 5) [5]. In contrast, decreased echogenicity of the basal ganglia is noted in that early phase. Cerebral palsy was detected in 6 patients with hyperechogenic thalami.

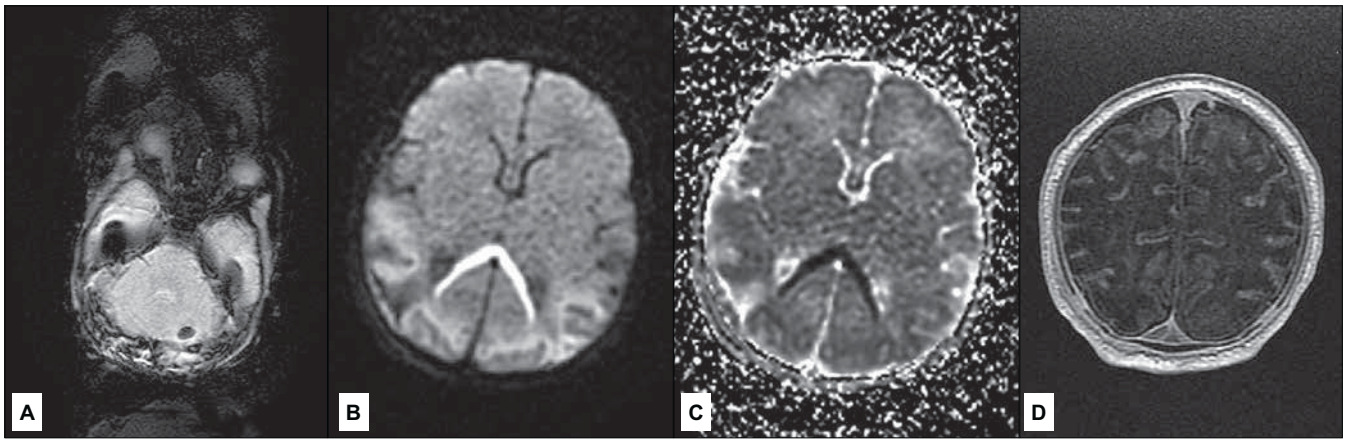

Figure 3. A newborn with cerebellar hemorrhage in the left hemisphere (**A** – SWI sequence), involvement of the corpus callosum (**B** – hyperintensity of the callosal splenium on DWI sequence; **C** – corresponding ADC map showing callosal hypointensity as confirmation of true diffusion restriction) and venous sinus thrombosis (**D** – FSPGR/3D/T1-weighted image after gadolinium administration – hypointense filling defect in the confluence of sinuses).

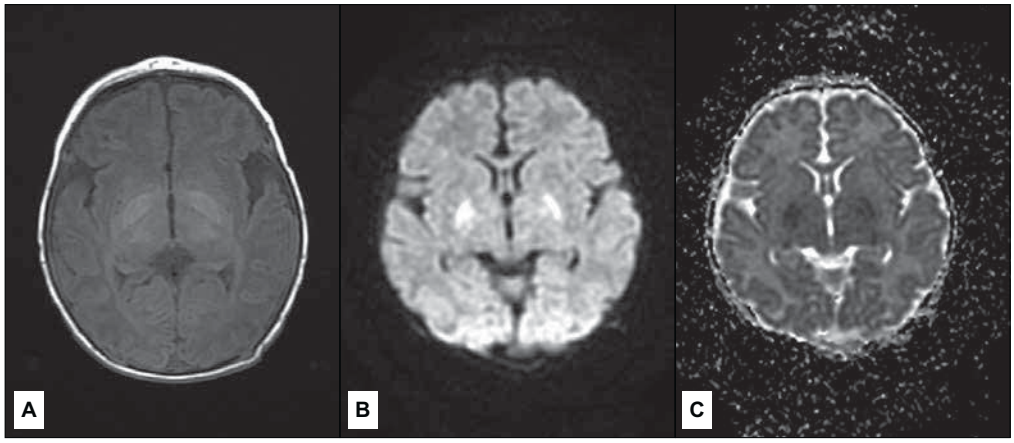

Figure 4. A neonate with acute asphyxia presenting as T1-hyperintensity in the basal ganglia (**A**) and diffusion restriction (**B –** DWI sequence, **C** – ADC map).

The involvement of the splenium of the corpus callosum in term neonates has been rarely described so far, either as an infrequent (2/30 = 6.7% [10]) or a frequent finding (10/34 = 29% [11]). In our study it was detected in 4 children (13.8%) who showed diffusion restriction in the callosal splenium (Figure 3 b, c). Similarly to Takenouchi et al., callosal lesions in our material were correlated to the diffuse white matter injury, which was not present in the remaining newborns. Callosal injury with restricted diffusion was correlated to a significantly higher incidence of death or severe developmental delay as compared to newborns without callosal lesions [11]. In 4 of our patients, the above mentioned changes in corpus callosum correlated with significantly lowered (<0.55) RI registered in ACA in the first days of life (Figure 6). All patients survived and 3 developed cerebral palsy (one child was discharged to receive hospice care at home and one child with spasticity was referred to a Neurology Clinic). Although corpus callosum is not classically recognized as an epileptogenic structure, injury to this structure has been found to correlate with epilepsy in follow-up examinations [12]. Multicystic encephalopathy constitutes the rarest form of hypoxic-ischemic injury in neonates, most often term ones, and is associated with poor prognosis. In our material, cystic lesions were observed in as many as 5 children (17.2% in MRI). One case of regression of the cystic changes in the brain, with normal psychomotor development so far, over the observation period of >2 years, has been reported [13].

Venous sinus thrombosis was detected as an additional pathology in 2 neonates from our study group (6.9%) (Figure 3d). This entity – which may coexist with hypoxic-ischemic changes – is very rarely recognized, and its prevalence is often underestimated [9], while in our study the frequency of its occurrence was high.

Signs of cytotoxic cerebral edema, followed by the loss of cerebral autoregulation, are observed in cases of prolonged hypoxia, also in Doppler US, what is manifested by significantly decreased RI and PI values. Low RI values in both arteries, ACA and MCA, were significantly associated with an adverse outcome. The results analysis conducted by Seibert et al. showed the RI to be lower than 0.6 in neonates with psychomotor disturbances [14]. However, other publications revealed the number of deaths and children with impaired development to correlate better with RI <0.55 (also RI <0.5 in a study by Gray et al.), which is consistent with our findings [3, 15]. In our study, RI <0.55 was noted in 48.3% of patients in the first days of life: 1 neonate died, 3 children develop normally and 6 demonstrate signs of impaired neurological development.

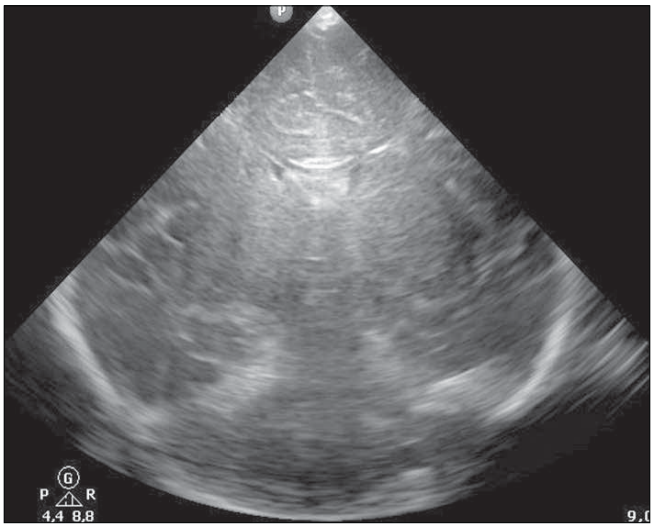

Figure 5. US. Thalami with hyperechoic columns (coronal view).

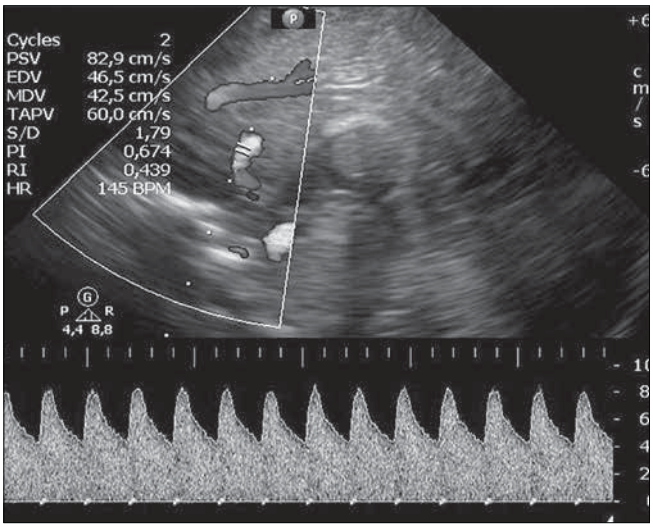

Figure 6. US. Color Doppler evaluation shows a high cerebral blood flow velocity with very low RI in ACA, RI-0.44 (sagittal view).

Conclusions

Abnormalities on MRI and US were observed in 75% of newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia.

The involvement of basal ganglia and thalami and cerebral parenchymal hemorrhage are the most frequent MRI findings in newborns with hypoxic-ischemic encephalopathy and these findings correlate very well with US images.

Among the sonographic changes, 'fuzzy brain' is the phenomenon that is most frequently observed in hypoxic-ischemic encephalopathy.

No MRI/US correlations between the intraventricular, subependymal and cerebellar hemorrhage were found.

Oświadczenie autorów

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References

1. Ilves P. Sonographic Changes in Hypoxic-Ischemic Encephalopathy. Miscellanea on Encephalopathies – A Second Look http://www.intechopen.com/download/pdf/35734: (access: 2012.04.25).
2. Stark JE, Seibert JJ. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. *J Ultrasound Med.* 1994, 13 (8), 595-600.
3. Jongeling BR, Badawi N, Kurinczk JJ, [et al.]. Cranial ultrasound as a predictor of outcome in term newborn encephalopathy. *Pediatr Neurol.* 2001, 26 (1), 37-42.
4. Sarkar S, Donn SM, Bapuraj JR, [et al.]. Distribution and severity of hypoxic-ischemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling. *Arch Dis Child Fetal Neonatal Ed.* 2012, 97 (5), 335-339.
5. Govaert P, de Vrie L. Asphyxia. In: An atlas of neonatal brain sonography. Eds. *Govaert P, de Vrie L. London,* 2010, 269-270.
6. Cassia GS, Faingold R, Bernard Ch, Sant'Anna GM. Neonatal Hypoxic-Ischemic Injury: Sonography and Dynamic color Doppler sonography perfusion of the brain and abdomen with pathologic correlation. *AJR.* 2012, 199 (W), 743-752.
7. Babcock DS, Ball W Jr. Postasphyxial encephalopathy in full-term infants: US diagnosis. *Radiology.* 1983, 148 (2), 417-423.
8. Li J, Funato M, Tamai H, [et al.]. Predictors of neurological outcome in cooled neonates. *Pediatr Int.* 2013, 55 (2),169-176.
9. Bekiesinska-Figatowska M, Helwich E, Rutkowska M, [et al.]. Magnetic reso-nance imaging of the neonates in the MR compatible incubator. *Arch Med Sci.* in press.
10. Boichot C, Walker PM, Durand C, [et al.]. Term neonate prognoses after peri-natal asphyxia: Contributions of MR imaging, MR spectroscopy, relaxation times, and apparent diffusion coefficients. *Radiology.* 2006, 239 (3), 839-848.
11. Takenouchi T, Heier LA, Engel M, Perlman JM. Restricted diffusion in the cor-pus callosum in hypoxic-ischemic encephalopathy. *Pediatr Neurol.* 2010, 43 (3), 190-196.
12. Mulkey SB, Yap VL, Swearingen CJ, [et al.]. Quantitative cranial magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy. *Pediatr Neurol.* 2012, 47 (2),101-108.
13. Bekiesińska-Figatowska M, Borszewska-Kornacka MK, Antczak-Marach D, Szczepanik E. [Regression of cystic lesions on brain MRI in a child with hypoxic-ischemic encephalopathy treated with selective head cooling]. *Ginekol Pol.* 2013, 84 (2), 151-156. [Polish].
14. Seibert JJ, McCowan TC, Chadduck WM. Duplex pulsed Doppler US versus intracranial pressure in neonate: Clinical and experimental studies. *Radiology.* 1989, 171 (1), 155-159.
15. Gray PH, Tudehope DI, Masel JP. Perinatal hypoxic-ischemic brain injury: prediction of outcome. *Dev Med Child Neurol.* 1993, 35 (11), 965-973.