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## **Use of diffusion-weighted magnetic resonance imaging for revealing hypoxic-ischemic brain lesions in neonates**

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*The article presents advantages of use of diffusion-weighted magnetic resonance imaging (DW MRI) for revealing hypoxic-ischemic brain lesions in neonates. The trial included 97 neonates with perinatal brain lesion who had been undergoing treatment at a resuscitation department or neonatal pathology department in the first month of life. The article shows high information value of diffusion-weighted images (DWI) for diagnostics of hypoxic-ischemic lesions in comparison with regular standard modes. In the event of no structural brain lesions of neonates, pronounced increase in signal characteristics revealed by DWI indicated considerable pathophysiological alterations. Subsequently, children developed structural alterations in the form of cystic encephalomalacia with expansion of cerebrospinal fluid spaces manifested with pronounced neurological deficit. DW MRI has been offered as a method of prognosticating further neurological development of children on early stages.*

**Key words:** *neonate, magnetic resonance imaging, diffusion-weighted image, hypoxic-ischemic lesion, brain.*

### **INTRODUCTION**

Due to intensive development of neonatal resuscitation care and progress in organization of effective developmental care, perinatal hypoxic-ischemic lesions of nervous system have become more widespread in the structure of infant morbidity in the last two decades. Statistical indicators also prove relevance of the issue. Mental disorders, nervous system and sense organs diseases take the leading position in the structure of incapacitation-resulting diseases; up to 60-70% of child morbidity causes are associated with perinatal pathologies [1]. Perinatal central nervous system lesions are one of the primary causes of somatic disorders, physical and neuropsychic development abnormalities in both infants and older children [2]. That is why an early non-invasive assessment of brain structures and cerebral blood flow condition is an issue of primary importance. The most widely used visualization method at the moment is neurosonography. This method is used to reveal intraventricular hemorrhages, cystic periventricular leukomalacia; however, it has low sensitivity in terms of revealing diffuse white matter alterations [3].

Magnetic resonance imaging (MRI) has been being used more often for brain examination in neonates in the last decade. Diffusion MRI is one of the most effective techniques of MR examination of brain tissue in the event of ischemic brain blood flow disorders [4]. Ischemic strokes constitute ca. 80% of all strokes. Ischemic strokes are caused by blood flow decline in a certain area of the brain [5]. Evaluation of diffusion processes plays an important role in early diagnostics of hypoxic-ischemic brain lesions in neonates.

Diffusion-weighted MRI (DW MRI) is a magnetic resonance imaging technique applied to obtain images of biologic tissues weighted by diffusion of water molecules on the microstructural level. DW MRI allows visualizing and measuring Brownian motion of water molecules. Signal intensity on diffusion-weighted images (DWI) expresses diffusion capability of water molecules in the target object's voxel. As long as biological tissues are structured, diffusion is not random. Water molecules move in intracellular and extracellular space, as well as in the membrane-spanning domain. Diffusion is restricted by cell membranes, vascular structures and axonal cylinders. Different restriction degree of free diffusion of water molecules is a potential source of image contrast.

Diffusion is isotropic if Brownian motion of water molecules is relatively unrestricted in all directions. Water motion is anisotropic if diffusion is restricted in one or several directions. E.g., diffusion in an adult brain's grey matter is almost completely isotropic, whereas diffusion in white matter (compact and orderly arrangement of myelinated axons and pathways) is anisotropic [6]. Thus, DWI displays Brownian motion in anatomical structures and allows assessing velocity of water molecules while providing high contrast between altered and the adjacent unaltered tissues [7]. DWI-revealed alteration of water molecules diffusion is measured by calculating the diffusion coefficient.

DW MRI is most successfully applied for diagnosing ischemic brain injuries. Such pathophysiological processes as hypoxia and ischemia result in membrane depolarization, membrane permeability and ion exchange alterations and ingress of water into cells. Cell swelling results in extracellular space compression and restriction of extracellular water diffusion, which lead to increase in DWI signal characteristics and low diffusion coefficients [6].

DW MRI is the most objective method of confirming perinatal brain injury in neonates and revealing hypoxic-ischemic alterations [8, 9].

**The research objective** is to demonstrate advantages of using DW mode of MR imaging in order to reveal spread and markedness of hypoxic-ischemic brain lesions in neonates, which allows predicting future development of neurologic impairment in a child. Early detection of pathophysiological alterations leading to structural and functional brain lesions in children is especially important in order to determine a set of therapeutic measures aimed at improving prognosis of the child's neurodevelopment.

## **PATIENTS AND METHODS**

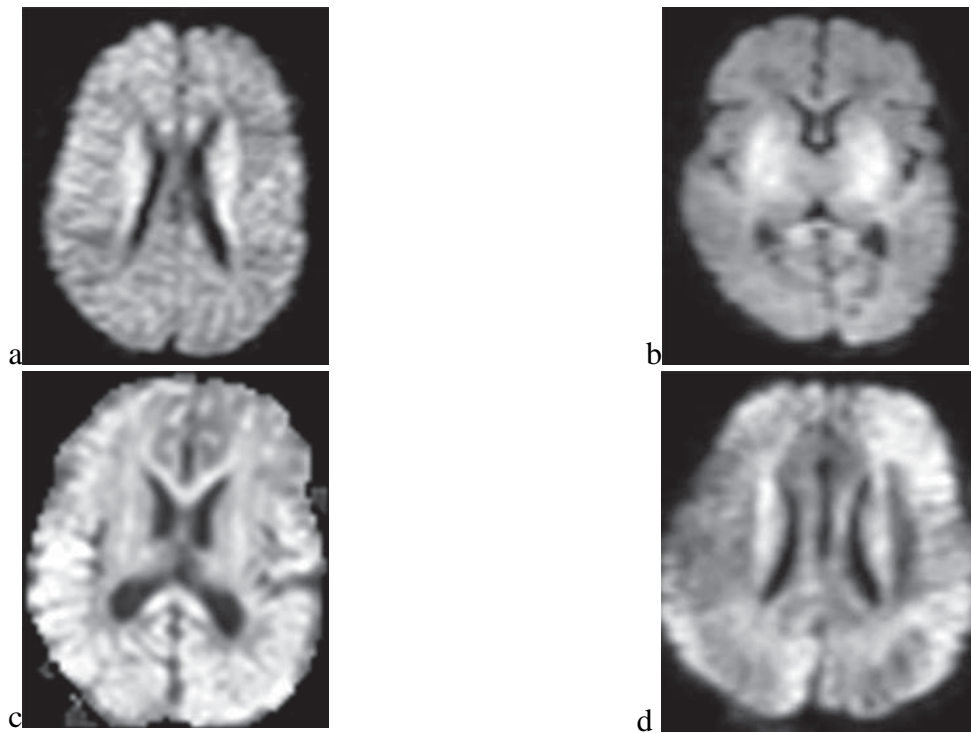
MRI was performed at the Krasnodar children's territorial clinical hospital (State Budgetary Healthcare Institution). The study involved 97 neonates with perinatal brain lesions treated at the intensive care and neonatal pathology units within the first month of life. Apart from the regular modes (T1- and T2-weighted imaging, FLAIR), 65 neonates of the main group also underwent DW mode of MRI. MR imaging did not involve diffusion MRI in the other 32 neonates (the control group). The children were examined with MR tomograph Panorama HFO-Philips (the Netherlands); magnetic field strength – 1.0 T, field-of-view (FOV) – 230x181x131 mm, slice thickness – 5 mm, b-factor – 2-5, max b-factor – 800 – 1 000; TR, TE – shortest. Parametric apparent diffusion coefficient (ADC) maps were generated for quantitative evaluation of water's diffusive properties within the tissue.

Anesthetic effect was achieved by inhalation of sevoflurane with apparatus Fabius MRI (Dräger, Germany). Safety of the study was secured by monitoring heart and respiratory rates, blood pressure and saturation with apparatus Datex-Ohmeda (USA). All children were characterized by adequate respiratory and heart activity throughout the study.

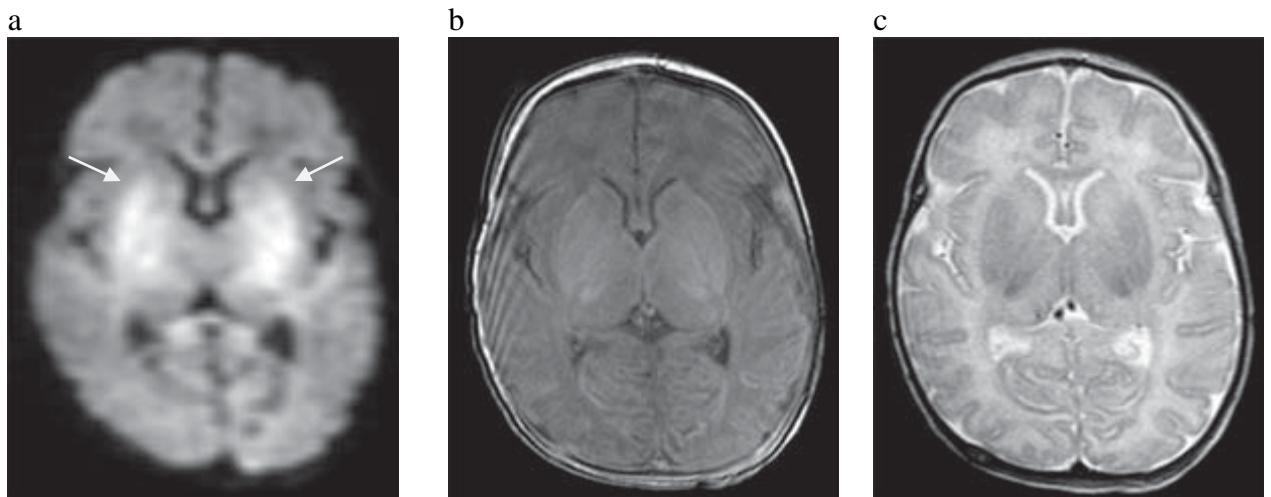
## **RESULTS**

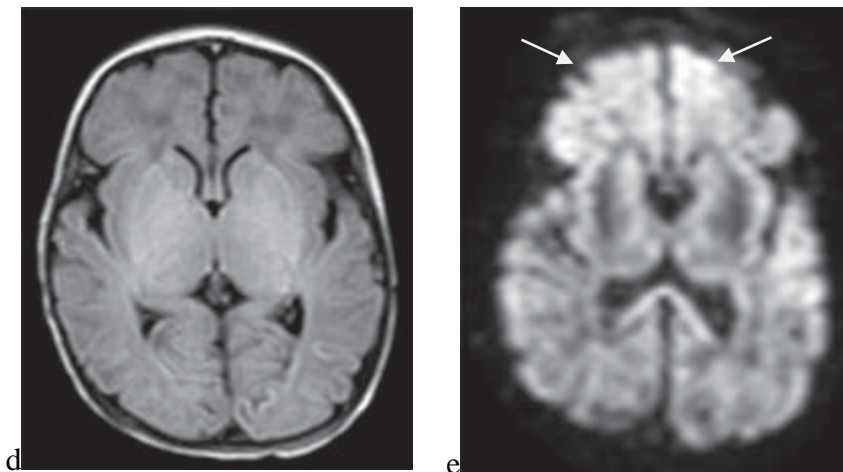
The following alterations were revealed by DW MRI (65 main group neonates): diffuse hypoxic-ischemic brain lesions (26; 40%; pic. 1), ischemic foci of varying localization (9; 14%; pic. 2),

**Pic. 1.** Magnetic resonance imaging. Diffusion-weighted images: periventricular leukomalacia (a), encephalomalacia (basal ganglia) (b), diffuse encephalomalacia (subcortical necrosis, periventricular necrosis – c, d).



**Pic. 2.** Magnetic resonance imaging (MRI) of a 6-day-old neonate's brain. Encephalomalacia (basal ganglia (shown with arrows)): diffusion-weighted images (a), T1-weighted images (b), T2-weighted images (c), FLAIR (d). Pic. e: MRI of the neonate's brain (27<sup>th</sup> day of life). Encephalomalacia (basal ganglia (shown with arrows)). Diffusion-weighted images. Later – formation of spastic-kinetic cerebral palsy.





intracranial hemorrhages (11; 17%), delayed myelination (7; 10.7%) and abnormal brain development (6; 9%). No structural pathology was revealed in 6 (9%) children (tb.).

**Table.** Structural brain pathology detected with magnetic resonance imaging

Structural brain pathology	Main group (n=65)	Control group (n=32)
Hypoxic-ischemic brain injuries:		
- ischemic foci of varying localization;	9	-
- subcortical ischemia;	6	-
- periventricular ischemia;	11	-
- ischemia in the area of basal ganglia and thalamus;	4	-
- diffuse encephalomalacia:	2	-
a) marked diffuse increase in signal characteristics;	3	-
b) polycystic encephalomalacia;	-	3
- enlargement of external cerebrospinal fluid spaces and/or ventricular system	-	10
Intracranial hemorrhages	11	5
Delayed myelination	7	4
Abnormal brain development	6	3
Structural pathology not detected	6	7
Total	65	32

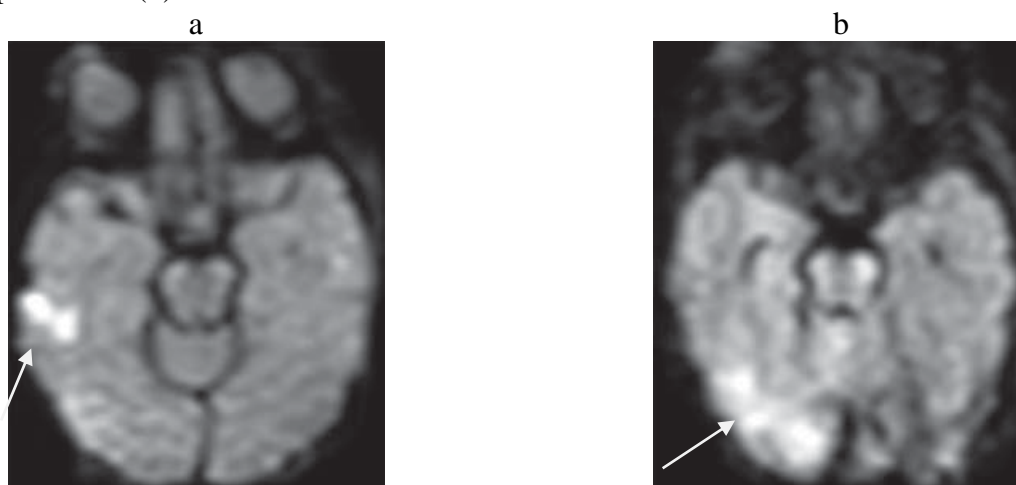
Increase in DWI signal characteristics, primarily in periventricular area (see pic. 1a) was observed in 11 children from the group of neonates with diffuse hypoxic-ischemic brain injuries; in 6 children it was observed in subcortical zone, in 4 children – in the area of basal ganglia and thalamus (see pic. 1b). Five children had diffuse hypoxic-ischemic brain injuries and marked increase in DWI signal characteristics in periventricular and subcortical zones (see pics. 1c, 1d) developing into cystic encephalomalacia. It should be noted that hypoxic-ischemic brain injuries of various markedness were revealed in all neonates with intracranial hemorrhages. Hypoxic-ischemic alterations (DWI) characterized by increase in signal characteristics were also registered in 6 neonates (86%) with delayed myelination and 4 neonates (67%) with abnormal brain development.

At DWI, the tissue with restricted diffusion appears brighter (ischemic zone), whereas the tissue with less restricted diffusion appears darker (see pics. 1, 2) [9]. Each DWI voxel has intensity expressing diffusion freedom degree for water in the corresponding localization.

Pic. 2 (a-d) shows brain images of a 6-day-old neonate in different pulse sequences clearly demonstrating DWI advantages.

DWI (pic. 3) shows neonates' brain ischemic foci of varying localization.

**Pic. 3.** Magnetic resonance imaging. Diffusion-weighted images. Brain ischemic foci (shown with arrows): ischemic focus in the right temporal lobe (a), ischemic focus in the right temporal and occipital lobes (b)



MRI without DWI (32 control group neonates) revealed cystic encephalomalacia manifestations (3; 9%), enlargement of external cerebrospinal fluid spaces and ventricular system (10; 31%), intracranial hemorrhages (5; 16%), delayed myelination (4; 12%) and abnormal brain development (3; 9%). No structural pathology was revealed in 7 (22%) children. Revealed enlargement of external cerebrospinal fluid spaces and ventricular system, along with cystic encephalomalacia manifestations, results from hypoxic-ischemic brain injuries. Neonates with posthemorrhagic noncommunicating hydrocephalus were considered children with intracranial hemorrhages, whereas neonates with congenital hydrocephalus were considered children with abnormal brain development.

The table shows advantages of using DW for brain MRI in neonates. DWI revealed hypoxic-ischemic alterations in 56 children of the main group (86.1%). Enlargement of external cerebrospinal fluid spaces and/or ventricular system was observed in all 22 neonates (33.8%) of the main group with diffuse encephalomalacia, periventricular ischemia or subcortical ischemia. Cystic stage of brain lesion in the form of periventricular or subcortical cysts or multicystic alterations was detected in 9 children. In the other children of the main group cerebral ischemia was DWI-expressed only with increase in signal characteristics. The earlier the study, the less manifested was enlargement of cerebrospinal fluid spaces, which is why it was possible to determine hypoxic-ischemic brain alterations by intensity of signal characteristics. A more marked increase in signal characteristics resulted in better manifested brain structural alterations in the end.

MR imaging without DWI revealed hypoxic and ischemic alterations in the form of enlargement of external cerebrospinal fluid spaces and ventricular system, cystic encephalomalacia and intracranial hemorrhages in 18 children of the control group (56%). Cystic stage of brain lesion in the form of periventricular or subcortical cysts or multicystic alterations was detected in 3 children of this group. MR imaging revealed enlargement of external cerebrospinal fluid spaces in 1/3 of control group neonates; however, DWI is essential to specify spread and markedness of hypoxic-ischemic brain injuries.

Detectability of hypoxic-ischemic brain alterations in neonates is significantly higher in case of DWI neurovisualization than when standard modes are used; this indicates clear advantages of DW MRI.

## DISCUSSION

DW MR imaging yields much more information on localization and markedness of hypoxic-ischemic brain injuries in neonates than regular MRI. In the event of increase in signal characteristics in T2-weighted images or reduction in T1-WI on an early stage, a hypoxic-ischemic brain injury may only be suspected; spread and intensity of its manifestations can be specified only by applying DW MRI.

One and the same intensity of central nervous system lesion results in registration of different morphological alterations in clinical presentation (muscular hypotonia, reduction in tendon and physiologic reflexes) and neurosonography [10]. That is why DW MRI is essential for reliable assessment of a child's condition. Structural alterations cannot be visualized (no cysts, enlargement of cerebrospinal fluid spaces) within the first 2-3 weeks of life even if the hypoxic-ischemic brain injury is marked, whereas DWI allows detecting a considerable increase in signal characteristics – diffuse encephalomalacia progressing into cystic encephalomalacia marked by enlargement of cerebrospinal fluid spaces (hydrocephalus ex vacuo). False normalization stage in the 2<sup>nd</sup>-3<sup>rd</sup> month of life is especially dangerous. It is characterized by reduction in neuronal losses and intensity of neurologic disorders, general condition improvement, increase in motion activity and recovery of muscular tonus and tendon reflexes progressing into the stage of spastic phenomena [11].

Correct assessment of a neonate's condition and prediction of further neurologic impairment development require localization, size of the hypoxic-ischemic brain injury, and rate of increase in signal characteristics (DWI). It is important to reveal perinatal lesion of central nervous system on early stages of a child's development (in neonatal period) in order to select therapeutic measures to cover the whole period of child's rehabilitation and improve his/her further neurodevelopment.

MRI is an accessible method of examination in territorial, regional and several district centers. Some neonates are transferred from district centers to territorial and regional centers for the second stage of developmental care; this increases the method's accessibility. Safety of the study is secured by monitoring heart and respiratory rates, blood pressure and saturation.

## CONCLUSION

DW MRI is an objective method of detecting hypoxic-ischemic brain injury. Use of such a method of neurovisualization as DW MRI allows assessing condition of neonates correctly on early stages and arranging a set of therapeutic measures aimed at decreasing neurologic impairment and improving children's quality of life in time.

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