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THE ROLE OF ADVANCED MAGNETIC RESONANCE IMAGING IN THE EVALUATION OF LONG-TERM CEREBRAL ALTERATIONS IN PATIENTS AFTER MILD TRAUMATIC BRAIN INJURY

Polina Angelova

Clinic of Neurosurgery, St. Georgi Hospital, Plovdiv, Bulgaria, p angelowa@abv.bg

Ivo Kehayov

Department of Neurosurgery, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria, dr.kehayov@gmail.com

Atanas Davarski

Department of Neurosurgery, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria, atanas.davarski@gmail.com

Aneta Petkova

Department of Neurosurgery, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria,

anisaluti@gmail.com

Grazia Diano

Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria, grazia.diano@gmail.com

Francesca Farino

Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria, francescafarino1@gmail.com

Abstract: Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality among people worldwide. It commonly results from high-velocity vehicle accidents, falls from heights, assaults and sport injuries. TBI can be classified as mild, moderate and severe depending on the score on the Glasgow Coma Scale (GCS). In terms of neurosurgical emergencies, accurate imaging diagnosis is essential. In these cases, computed tomography (CT) is the most widely used and readily available neuroimaging modality. Mild TBI (mTBI) presents approximately 90% of all head injuries. A great number of mTBIs are believed to cause only transient functional impairments to the brain due to the lack of sufficient radiological evidence on conventional CT and magnetic resonance imaging (MRI) scans. Generally, the diagnosis is based on the data obtained from the history and the neurological status. In some cases, categorized as "complicated mTBI", CT may present with visible focal contusions consistent with diffuse axonal injury or direct trauma. Although mTBIs are considered as relatively harmless to the brain, they still may lead to progressive cerebral impairments such as postconcussive syndrome, traumatic encephalopathy, sleeping disorders and even neurodegenerative diseases. The need for more detailed evaluation of subtle structural and functional brain changes in different areas of interest is made possible with the utilization of different types of advanced MRI techniques such as Susceptibility Weighted Imaging (SWI), Magnetic Resonance Spectroscopy (MRS), Diffusion Tensor Imaging (DTI) and resting state MRI (rsMRI). Their sensitivity is six-fold higher than conventional CT and MRI for detecting the number, size and location of microscopic structural alterations in patients with mTBI. The data obtained from these MRI sequences in the subacute and chronic stage of the injury can boost the knowledge and understanding about the mechanisms of neuronal damage following mTBI. Additionally, these cutting-edge imaging techniques can lead to more accurate diagnosis, thus resulting in optimal treatment and rehabilitation. Due to the its high incidence, disabling long-term posttraumatic cognitive and neurodegenerative sequelae, mTBI becomes a major social and public health issue. The aim of the current review is to look through the most commonly used advanced MRI techniques for evaluation of structural, functional and metabolic brain changes in patients after mTBI.

Keywords: Traumatic brain injury, Diffusion Tensor Imaging, fMRI, Susceptibility Weighted Imaging, Magnetic Resonance Spectroscopy

1. INTRODUCTION

Traumatic brain injury is a leading cause of morbidity and mortality among people worldwide and is a major neurosurgical and public health problem. (Frati et al., 2017) (<u>Tsitsopoulos, Hamdeh</u> and <u>Marklund</u>, 2017) TBI are classified based on the clinical presentation and the Glasgow coma scale (GCS) score. Patients with GCS score of 13 and more, loss of consciousness less than 30 minutes and posttraumatic amnesia less than 24 hours are classified as mild Traumatic Brain Injury (mTBI). (Mesfin, Gupta, Hays Shapshak et Taylor, 2020) (Toth, 2015) (Mild Traumatic Brain Injury Committee, 1993) Mild TBI represent approximately 90% of all head traumas. (Wang et al., 2018) It is a common condition among the elderly and young people, mostly athletes and military and is believed to

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be a progressive injury. (Gardner et al., 2018) Those patients are prone to repetitive injuries and are especially exposed to long-term complications. (Michel, Sambuchi and Vogt, 2019) (Manley et al. 2017) In 15% of the cases, there may be long-lasting neurobehavioral consequences like chronic progressive traumatic encephalopathy with persistent symptoms of headache, dizziness and nausea, concentration and memory problems, depression and anxiety. Sometimes sleeping disorders are observed. There is also an increased risk of neurodegenerative diseases following mTBI, such as Parkinson disease. (Toth, 2015) (Gardner et al., 2018) The speed, accessibility and accuracy in detecting traumatic intracranial hemorrhages made CT is the leading neuroimaging method of choice for acute evaluation of TBI patients. (Tsitsopoulos et al., 2017) CT also has the advantage in demonstrating presence of skull fractures, commonly assosiated with mTBI. (Bigler, 2015) However, in about 90% of the cases, mTBI is difficult to diagnose due to the lack of sufficient radiological evidence on the performed CT scans. The rest of the cases are CT-positive, with visible focal contusions. These cases are categorized as "complicated mTBI". (Toth, 2015) (Lannsjo, Backheden, Johansson, Af Geijerstam and Borg, 2013) In most of the cases, the lack of evidence of brain injury related to mTBI, has led to the increased use of other, more sensitive methods for neuroimaging, namely various MRI sequences such as Susceptibility Weighted Imaging, Magnetic Resonance Spectroscopy, Diffusion Tensor Imaging and resting state MRI. (Michel et al., 2019) (Manley et al. 2017) (Shenton et al. 2012)

The aim of the current paper is to provide analysis of the advantages and disadvantages of the different structural and functional MRI sequences in diagnosis and long-term evaluation of the brain changes in patients after sustained mTBI.

2. SUSCEPTIBILITY WEIGHTED IMAGING (SWI)

Susceptibility Weighted Imaging (SWI) utilizes the magnetic properties of iron for detecting microscopic bleeds developing as part of mTBI, particularly for diffuse axonal injury (DAI). (Toth, 2015) (Liu, Li, Tong, Yeom and Kuzminski, 2015) Diffuse axonal injury (DAI) is a type of TBI, caused by acceleration/deceleration forces, leading to diffuse shearing of axons. The most vulnearable to shear injury areas are the cerebral gray-white matter junction areas and midline structures such as corpus callosum and the brain stem. As a result, most DAI patients have multiple small hemorrhagic lesions located at the gray-white matter interface. (Frati et al., 2017) (Tsitsopouloset al., 2017) (Jang, 2020) Studies demonstrated that SWI is about 6 times more sensitive than conventional MRI for detecting the number, size and location of these microscopic hemorrhagic lesions in patients who suffered from mTBI. (Babikian et al., 2005) (Halefoglu and Yousem, 2016) (Xiong, Zhu and Zhang, 2014) SWI can also be helpful in detecting blood foci in the subcortical white matter, brainstem and intraventricular and subarachnoid hemorrhage, invisible on other type of imaging. Persistent hemosiderosis from traumatic bleedings is also best detected on SWI. (Halefoglu and Yousem, 2016)

3. DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is an advanced, specific MRI sequence, able to sensitively detect microstructural white matter (WM) changes in patients with TBI, while CT and conventional MRI can detect only macroscopic changes. DTI evaluates white matter damage by measuring the direction and amount of diffusion of water molecules along the white matter fibers that connect different parts of the brain. (Assaf and Pasternak, 2008) In healthy subjects, the direction of water molecules is parallel to the axons and this movement is called anisotropic diffusion. When the WM is damaged, the water diffusion is less parallel and appears to be equal in all directions. This is called isotropic diffusion. (Assaf and Pasternak, 2008) (Huisman, 2010) DTI has several indexes for measuring the WM integrity, but most commonly used amongst scientists is the fractional anisotropy (FA) which describes the direction of water molecules. FA is a measure, that range from 0 to 1. FA measured as 0 is a completely isotropic movement of water, like in the cerebrospinal fluid, and when it is closer to 1, there is an anisotropic movement of molecules along a single axis - the myelinated neuron. (Shenton et al, 2012) Mean Diffusitivity (MD) is the second, frequently used measure for evaluation of the mobility of water molecules. (Toth, 2015) As for mTBI, there are several areas of interested examined by DTI. The most common ones are corpus callosum (CC), internal and external capsule, centrum semiovale, corona radiata, corticospinal tracts, uncinate fascicle, inferior longitudinal fascicle, prefrontal cortex, mesencephalon and cerebral peduncles.

FA and MD are sensitive markers for detecting changes in the WM integrity in patients with TBI. They are known to be inversely related. DTI results indicate FA reduction in most regions, as well as increased MD. (Shenton et al, 2012) Some studies show that there is a difference in the value of FA and MD depending on when the MRI is performed at the acute, subacute or chronic phase of the trauma. For example, FA and MD can be both reduced within the first 24 hours after the trauma. These results indicate cytotoxic axonal edema and may correlate with poor outcome. A week after the trauma, in most cases the FA is decreased and the MD in increased. (Bazarian, Zhu,

Blyth, Borrino and Zhong, 2012) (Lawrence et al., 2019) DTI can also be post-processed for creating tractographies of different fiber tracts, connecting remote areas of the brain, commonly affected by TBI. (Huisman, 2010)

4. RESTING STATE MRI (RSMRI)

When a person is not actively engaged in goal-directed activities, the brain is considered to be "resting". This resting brain is the base for the rsMRI examination. RsMRI is a type of functional MRI (fMRI), which studies the changes of the relative levels of oxyhemoglobin and deoxyhemoglobin. These changes across anatomically distinct brain regions can be detected by this examination and the approach is called blood oxygen level–dependent (BOLD) imaging. The change in the BOLD signal is the cornerstone of fMRI. This allows the study of brain networks and their interactions with other brain areas and networks. (Lv et al., 2019)

Scientific data have shown that the explored brain regions form active "default" brain function networks, when the healthy individual is awake and resting, whereas it is relatively hypoactive during performing specific cognitive tasks. These networks are conjoint and called default mode network (DMN), which is the most common to be examined with rsMRI. (Mak et al., 2017) (Raichle et al., 2001)

The DMN is particularly vulnerable to TBI. This is because it consists of brain areas, connected by networks passing through the midline, which is susceptible to shear injury. The shear forces are the main mechanism for the mTBI occurence. (Sheth, Rogowska, Legarreta, McGlade and Yurgelun-Todd., 2020) Except the DMN, there are other networks, like the anterior cingulate cortex, thalamic, frontoparietal, orbitofrontal, visual and motor-striatal, which have also been reported as susceptible to mTBI. The results from the rsMRI can show alterations in the connectivity, either increasing or decreasing, depending on the examined network. (Sheth et al., 2020) (Palacios et al., 2017)

5. MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Magnetic Resosance Spectoscopy (MRS) is an advanced MRI sequence, able to detect areas in the brain with compromised metabolism. Brain metabolism may be disturbed due to different conditions like epilepsy, ischaemic strokes, neurodegenerative disorders, depression and other mental diseases, as well as TBI, especially mTBI. (Eisele, Hill-Strathy, Michels and Rauen, 2020) (Rhodes, 2017)

When performing MRS, there are several areas of interest of brain matter that are being examined. Some of them are corpus callosum, anterior cingulum, frontal lobe, superior longitudinal fasciculus, brain stem, gray matter in the interhemispheric fissure. (Gasparovic et al., 2009) (Sivák et al., 2013) MRS allows measurement of different metabolites in the brain matter of these areas of interest, like N-acetylaspartate (NAA), choline, creatine and glutamate. There are several others, which are useful for detecting brain alterations in patients with non-traumatic diseases. (Xiong et al, 2014) (Eisele et al., 2020) (Rhodes, 2017) (Dager, Corrigan, Richards, and Posse, 2008) The result after applying MRS on TBI patients, show that there are specific deviations on levels of the mentioned above metabolites. NAA is a marker, found in neurons only in the brain, both in gray and white matter, so its presence in reference range shows neuronal integrity. Reduced levels of NAA indicate loss or damage of neurons, caused by the al, 2014) (Rhodes, 2017) (Carpentier mTBI. (Xiong et et al., 2006) The second, most commonly studied metabolite is chlorine. Studies show that increase in the chlorine levels demonstrate a neuron cell membrane breakdown, or a demyelination. (Xiong et al, 2014) (Rhodes, 2017) Changes in the levels of creatine, which is a marker of normal metabolism in nerve cells, indicate cell death, as caused by disease, ischemia or TBI. These results are controversial. It is said to be gradually reduced in the course of mTBI development over time. (Rhodes, 2017) Other studies found that creatine levels after mTBI increased in the white, but not in the gray brain matter, (Kirov et al., 2013) which makes the examination of creatine after TBI questionable. (Stovell et al., 2017)

As they are useful for research purposes, the results from MRS should be consider variable, according to the age of the patient and the time from the TBI to the scan. (Xiong et al, 2014)

6. CONCLUSION

When evaluating a TBI patient, CT has been proved to be the method of choice in the acute trauma phase because it is cheap, accessible and fast to perform in terms of emergency. However, CT and conventional MRI have limited possibilities for detecting subtle structural brain matter changes after mTBI, especially DAI. Because of that, in the subacute and chronic stage after the trauma, advanced MRI techniques may be performed. They are able to evaluate the structural and functional deviations in white and grey matter in different areas of interest in the brain. These neuroimaging modalities can demonstrate the presence and location of brain matter changes, as well as the functional capacity of these areas, compared to healthy individuals. The various MRI sequences can help us diagnose mTBI more precisely and evaluate the different diagnostic and therapeutic procedures. In the long-term,

patients` condition can be followed-up, thus we can assess the effect of the mTBI on cognitive functions and their role in the development of different psychiatric and neurodegenerative diseases.

REFERENCES

- Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci.34(1):51-61.
- Babikian, T., Freier, M.C., Tong, K.A., Nickerson, J.P., Wall, C.J., Holshouser, B.A., Burley, T., Riggs, M.L., & Ashwal, S. (2005). Susceptibility weighted imaging: neuropsychologic outcome and pediatric head injury. Pediatr Neurol. 33(3):184-94.
- Bazarian, J.J., Zhu, T., Blyth, B., Borrino, A., & Zhong, J. (2012). Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. Magn Reson Imaging. 30(2):171-80.
- Bigler, E.D. (2015). Chapter 31. Kobeissy FH (Ed.). Neuropathology of Mild Traumatic Brain Injury: Correlation to Neurocognitive and Neurobehavioral Findings. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton (FL): CRC Press/Taylor & Francis.
- Carpentier, A., Galanaud, D., Puybasset, L., Muller, J.C., Lescot, T., Boch, A.L., Riedl, V., Cornu, P., Coriat, P., Dormont, D., & van Effenterre, R. (2006). Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". J Neurotrauma. 23(5):674-85.
- Dager, S. R., Corrigan, N. M., Richards, T. L., & Posse, S. (2008). Research applications of magnetic resonance spectroscopy to investigate psychiatric disorders. Topics in magnetic resonance imaging : TMRI, 19(2), 81– 96.
- Eisele, A., Hill-Strathy, M., Michels, L., & Rauen, K. (2020). Magnetic Resonance Spectroscopy following Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis on the Potential to Detect Posttraumatic Neurodegeneration. Neurodegener Dis. 20(1):2-11.
- Frati, A., Cerretani, D., Fiaschi, A.I., Frati, P., Gatto, V., La Russa, R., Pesce, A., Pinchi, E., Santurro, A., Fraschett, F., & Fineschi, V. (2017). Diffuse Axonal Injury and Oxidative Stress: A Comprehensive Review. <u>Int J Mol</u> <u>Sci</u>. 18(12): 1 - 20.
- Gardner, R.C., Byers, A.L., Barnes, D.E., Li, Y., Boscardin, J., & Yaffe, K. (2018). Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. Neurology. 90(20):e1771-e1779.
- Gasparovic, C., Yeo, R., Mannell, M., Ling, J., Elgie, R., Phillips, J., Doezema, D., & Mayer, A.R. (2009). Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: an 1H-magnetic resonance spectroscopy study. J Neurotrauma. 26(10):1635-43.
- Halefoglu, A.M., & Yousem, D.M. (2018). Susceptibility weighted imaging: Clinical applications and future directions. World J Radiol. 10(4):30-45.
- Huisman, T.A. (2010). Diffusion-weighted and diffusion tensor imaging of the brain, made easy. Cancer Imaging. 10 Spec no A(1A):S163-71.
- Jang, S.H. (2020). Diagnostic Problems in Diffuse Axonal Injury. Diagnostics (Basel). 10(2):117.
- Kirov, I.I., Tal, A., Babb, J.S., Lui, Y.W., Grossman, R.I., & Gonen, O. (2013). Diffuse axonal injury in mild traumatic brain injury: a 3D multivoxel proton MR spectroscopy study. J Neurol. 260(1):242-52.
- Lannsjö, M., Backheden, M., Johansson, U., Af Geijerstam, J.L., & Borg, J. (2013). Does head CT scan pathology predict outcome after mild traumatic brain injury? Eur J Neurol. 20(1):124-9
- Lawrence, T. P., Steel, A., Ezra, M., Speirs, M., Pretorius, P. M., Douaud, G., Sotiropoulos, S., Cadoux-Hudson, T., Emir, U. E., & Voets, N. L. (2019). MRS and DTI evidence of progressive posterior cingulate cortex and corpus callosum injury in the hyper-acute phase after Traumatic Brain Injury. Brain injury, 33(7), 854–868.
- Liu, C., Li, W., Tong, K.A., Yeom, K.W., & Kuzminski, S. (2015). Susceptibility-weighted imaging and quantitative susceptibility mapping in the brain. J Magn Reson Imaging. 42(1):23-41.
- Lv, H., Wang, Z., Tong, E., Williams, L.M., Zaharchuk, G., Zeineh, M., Goldstein-Piekarski, A.N., Ball, T.M., Liao, C., & Wintermark, M. (2018). Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know. AJNR Am J Neuroradiol. 39(8):1390-1399.
- Mak, L.E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S.H., & Milev, R. (2017). The Default Mode Network in Healthy Individuals: A Systematic Review and Meta-Analysis. Brain Connect. 7(1):25-33.
- Manley, G., Gardner, A.J., Schneider, K.J., Guskiewicz, K.M., Bailes, J., Cantu, R.C., Castellani, R.J., Turner, M., Jordan, B.D., Randolph, C., Dvořák, J., Hayden, K.A., Tator, C.H., McCrory, P., & Iverson, G.L. (2017). A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med. 51(12):969-977.

- Mesfin, F.B., Gupta, N., Hays Shapshak, A., & Taylor, R.S. (2020). Diffuse Axonal Injury. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; PMID: 28846342.
- Michel, B.F., Sambuchi, N., & Vogt, B.A. (2019). Impact of mild traumatic brain injury on cingulate functions. Handb Clin Neurol. 166:151-162.
- Mild Traumatic Brain Injury Committee, A. C. o. R. M. (1993). Head Injury Interdisciplinary Special Interest Group Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation. 83: 86-87.
- Palacios, E.M., Yuh, E.L., Chang, Y.S., Yue, J.K., Schnyer, D.M., Okonkwo, D.O., Valadka, A.B., Gordon, W.A., Maas, A.I.R., Vassar, M., Manley, G.T., & Mukherjee, P. (2017). Resting-State Functional Connectivity Alterations Associated with Six-Month Outcomes in Mild Traumatic Brain Injury. J Neurotrauma. 34(8):1546-1557.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America. 98(2), 676–682.
- Rhodes, C.J. (2017) Magnetic resonance spectroscopy. Science Progress. 100(3), 241-292
- Shenton, M.E., Hamoda, H.M., Schneiderman, J.S., Bouix, S., Pasternak, O., Rathi, Y., Vu, M.A., Purohit, M.P., Helmer, K., Koerte, I., Lin, A.P., Westin, C.F., Kikinis, R., Kubicki, M., Stern, R.A., & Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. Brain Imaging Behav. 6(2):137-92.
- Sheth, C., Rogowska, J., Legarreta, M., McGlade, E., & Yurgelun-Todd, D. (2020). Functional connectivity of the anterior cingulate cortex in Veterans with mild traumatic brain injury. Epub. PMID: 32853657.
- Sivák, Š., Bittšanský, M., Grossmann, J., Nosál', V., Kantorová, E., Siváková, J., Demková, A., Hnilicová, P., Dobrota, D., & Kurča, E. (2014). Clinical correlations of proton magnetic resonance spectroscopy findings in acute phase after mild traumatic brain injury. Brain Inj. 28(3):341-6.
- Stovell, M. G., Yan, J. L., Sleigh, A., Mada, M. O., Carpenter, T. A., Hutchinson, P. & Carpenter, K. (2017). Assessing Metabolism and Injury in Acute Human Traumatic Brain Injury with Magnetic Resonance Spectroscopy: Current and Future Applications. Frontiers in neurology, 8, 426.
- Toth, A. (2015). Chapter 24. Kobeissy FH (Ed.). Magnetic Resonance Imaging Application in the Area of Mild and Acute Traumatic Brain Injury: Implications for Diagnostic Markers? In:, editor. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton (FL): CRC Press/Taylor & Francis.
- <u>Tsitsopoulos, P.P., Hamdeh, S.A., & Marklund, N</u>. (2017). Current Opportunities for Clinical Monitoring of Axonal Pathology in Traumatic Brain Injury. <u>Front Neurol</u>. 8: 599.
- Wang, S., Hu, L., Cao, J., Huang, W., Sun, C., Zheng, D., Wang, Z., Gan, S., Niu, X., Gu, C., Bai, G., Ye, L., Zhang, D., Zhang, N., Yin, B., Zhang, M. and Bai, L. (2018). Sex Differences in Abnormal Intrinsic Functional Connectivity After Acute Mild Traumatic Brain Injury. Frontiers in neural circuits, 12, 107.
- Xiong, K.L., Zhu, Y.S., & Zhang, W.G. (2014). Diffusion tensor imaging and magnetic resonance spectroscopy in traumatic brain injury: a review of recent literature. Brain Imaging Behav. 8(4):487-96.