MRS In Acute Brain Injury – What We Can Offer the Clinician Now

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SYNOPSIS

Imaging modalities such as CT and MRI are powerful tools to detect and assess focal injury such as hemorrhagic lesions and edema and brain swelling in severe injury. However, acute and chronic injury at a cellular level is sometimes difficulty to discern from normal features by anatomical imaging. **MRS** offers a unique non-invasive approach to assess injury at microscopic levels by quantifying cellular metabolites. The findings obtained with MRS in concussion and more severe head trauma are heterogeneous, reflecting the different time after injury, degree of injury and different physiologic and pathologic response of the brain to injury in individuals. The most important findings are that elevated **lactate** (and lipids) in apparently normal or close to normal tissue observed 2-5 days after injury are indicators of severe global hypoxic injury and poor outcome. Also, **N-acetylaspartate** (**NAA**), a marker for "healthy" neurons and axons, is generally reduced in traumatic brain injury signaling neuronal and axonal loss/damage. The extent of NAA reduction after injury is an objective and quantitative surrogate marker for the severity of injury and is useful for outcome prediction. In the cases of mild traumatic brain injury, **choline (Cho)** has been shown to be reflective of diffuse axonal injury.

Key Words: MR spectroscopy, metabolism, trauma, concussion, N-acetyl-aspartate, lactate, choline.

Traumatic brain injury (TBI)

Trauma syndromes: Closed head injury (aka traumatic brain injury – TBI) describes the constellation of neurological deficits associated with blows to head without any penetrating wound. Sub-classifications are based upon the nature of the physical insult – blast, pressure, motor vehicle accidents and falls, civilian, sports-related or military. The syndromes associated with TBI are graded by severity (mild, with no apparent abnormality on screening CT, moderate and severe) and degree of 'coma' (Glasgow coma score), as are the sequelae, 'outcome grades'

applied after 6 – 12 months. Longer-term outcomes include neuropsychological and psychiatric complications of post-traumatic stress disorder (PTSD). Better acute classification of TBI in the individual patient, which is important to clinical management, is becoming available as the range of neuro-imaging and recording techniques expands (Hunter JV et al. 2012).

Pathobiology: Biomechanical effects are broadly divided into focal – resulting in contusion ('bruising'), laceration (intra-cranial hemorrhage) - and diffuse, due to acceleration-deceleration forces causing diffuse axonal injury (DAI) and brain swelling (Ghajar J 2000; Giza CC and DA Hovda 2001; Werner C and K Engelhard 2007; Elkin BS et al. 2010; Johnson VE et al. 2013). Secondary effects include altered cerebral blood flow, oxygenation and metabolism, excitotoxicity, edema formation and free-radical release and other inflammatory processes contributing to the wide range of clinical patterns of TBI (Ross BD et al. 1998). Recognition of highly variable patterns of TBI is of importance to the neurologist designing clinical trials of therapy (Janowitz T and DK Menon 2010; Xiong Y et al. 2010; Kelso ML and JR Pauly 2011; Patterson ZR and MR Holahan 2012).

Genetics: TBI outcomes are the subject of genetic studies (Kurowski B et al. 2012): APOE e4 status being associated with worse outcome at all ages (Teasdale GM et al. 2005). Studies in a Drosophila model (Katzenberger RJ et al. 2013) seem poised to identify an array of genes contributing to the variable outcome after experimental TBI.

Neurochemical substrate: Abnormalities of cerebral glucose metabolism, pentose phosphate shunt, and cerebral ATP and mitochondrial energy metabolism, activation of phospholipase (Phillis JW and MH O'Regan 2004; Farooqui AA et al. 2006) and dysfunction of glutamate- glutamine-GABA (Faden AI et al. 1989; Giza CC and DA Hovda 2001; Johnson VE *et al.* 2013) have been defined in research studies of TBI. With the benefit of 20 years of clinical MRS research into human TBI (Kreis R et al. 1993; Cecil KM et al. 1998; Friedman SD et al. 1998; Ross BD *et al.* 1998; Friedman SD et al. 1999; Brooks WM et al. 2000; Brooks WM et al. 2001; Garnett MR et al. 2001; Govindaraju V et al. 2004; Shutter L et al. 2004; Cohen BA et al. 2007; Nakabayashi M et al. 2007; Gasparovic C et al. 2009; Vagnozzi R et al. 2010; Lin AP et al. 2012; Benarroch EE 2013; Kierans AS et al. 2014), we may add disruption of neurons and axons (manifested by abnormal NAA), myelin (Cho), osmoregulation (mI), neurotransmitter

(glutamate), lipid, phospholipid (macromolecules), high energy ATP and PCr metabolism, as well as neuroinflammation with microglial activation.

Systemic contributions: Endocrine imbalance (Rothman MS et al. 2007; Sterns RH and SM Silver 2008; John CA and MW Day 2012) with either inappropriate ADH secretion or hypernatremic, hyperosmolar states, cardiac arrest with hypoxic encephalopathy, and systemic hypoxia and acidosis may complicate cerebral response to TBI and directly impact MRS diagnosis.

Diagnostic MRS findings: Infants, young children and adults show different, yet distinct, MRS patterns after TBI. Mild traumatic brain injury (mTBI), currently defined as being associated with no abnormality on CT screening at admission, has been reported to show consistent reduction in the neuronal marker NAA and the ratio NAA/Cr in frontal white matter; recovery of NAA/Cr is delayed by 10-15 days compared to recovery from subjective neurological symptoms. Thus, MRS after proven concussion establishes new guidelines for 'return to play', setting this interval at 2 -3 weeks, compared to clinical symptoms, which may resolve within 5 – 7 days.

Published studies after moderate to severe TBI are infrequent (except in infant shaken baby syndrome - see below)– partly a reflection of the convenience and speed of CT and the reluctance to move seriously ill patients to an MR scanner. It has been demonstrated (Kreis R *et al.* 1993; Ross BD *et al.* 1998) that 100% of such patients exhibit abnormal MRS with several distinct patterns of neurochemical disturbance: hypoxic-ischemic: hypo-osmolar: hyper-osmolar: neuronal-axonal injury. Longitudinal MRS studies confirm consistency of these disparate neurochemical responses. MRS was correlated with GCS measured at the time of MRS examinations; Rancho Outcome Score (ROS) was aligned with the earlier MRS findings; reduced NAA with increased amounts of both lactate and free lipid were predictive of poor outcome. MRS was predictive of outcome after TBI in infants and children (Shutter L *et al.* 2004). Several studies (Haseler LJ et al. 1997; Ashwal S et al. 2006) confirm the diagnostic value of MRS abnormalities in shaken baby syndrome – loss of NAA is severe, as is the rapid accumulation of 'lipid' resonances in the MR spectrum. In this unique setting the resonances labeled 'lipid' are more likely macromolecules of the phospholipid series supporting earlier identification of phospholipase activation after brain trauma (Haseler LJ *et al.* 1997; Farooqui

AA *et al.* 2006). Note that "macromolecules" (MM I – VI) which contribute broad resonances to the irregular baseline of the short echo time MR spectrum offer valuable additional chemical information in several neuropathologies, from stroke to multiple sclerosis (Graham GD et al. 2001; Mader I et al. 2001; Seeger U et al. 2003).

Supportive MRS findings: Elevated 'choline' (Cho) post TBI may be interpreted as 'myelin damage' or diffuse axonal injury (Ross BD *et al.* 1998). Elevated myoinositol (mI) and glutamate+ glutamine (Glx) has been reported in the putamen of adult mTBI (Kierans AS *et al.* 2014).

Summary: MRS has demonstrated diagnostic value early and late after mTBI and appears reliably predictive of outcome after mild, moderate - severe TBI in both adults and infants.

References

Ashwal S, Holshouser BA, Tong KA. 2006. Use of advanced neuroimaging techniques in the evaluation of pediatric traumatic brain injury. Dev Neurosci 28:309-326.

Benarroch EE. 2013. Microglia: Multiple roles in surveillance, circuit shaping, and response to injury. Neurology 81:1079-1088.

Brooks WM, Friedman SD, Gasparovic C. 2001. Magnetic resonance spectroscopy in traumatic brain injury. J Head Trauma Rehabil 16:149-164.

Brooks WM, Stidley CA, Petropoulos H, Jung RE, Weers DC, Friedman SD, Barlow MA, Sibbitt WL, Jr., Yeo RA. 2000. Metabolic and cognitive response to human traumatic brain injury: a quantitative proton magnetic resonance study. J Neurotrauma 17:629-640.

Cecil KM, Hills EC, Sandel ME, Smith DH, McIntosh TK, Mannon LJ, Sinson GP, Bagley LJ, Grossman RI, Lenkinski RE. 1998. Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. J Neurosurg 88:795-801.

Cohen BA, Inglese M, Rusinek H, Babb JS, Grossman RI, Gonen O. 2007. Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. Am J Neuroradiol 28:907-913.

Elkin BS, Shaik MA, Morrison B. 2010. Fixed negative charge and the Donnan effect: a description of the driving forces associated with brain tissue swelling and oedema. Philos Trans A Math Phys Eng Sci 368:585-603.

Faden AI, Demediuk P, Panter SS, Vink R. 1989. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 244:798-800.

Farooqui AA, Ong WY, Horrocks LA. 2006. Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders. Pharmacol Rev 58:591-620.

Friedman SD, Brooks WM, Jung RE, Chiulli SJ, Sloan JH, Montoya BT, Hart BL, Yeo RA. 1999. Quantitative proton MRS predicts outcome after traumatic brain injury. Neurology 52:1384-1391.

Friedman SD, Brooks WM, Jung RE, Hart BL, Yeo RA. 1998. Proton MR spectroscopic findings correspond to neuropsychological function in traumatic brain injury. AJNR Am J Neuroradiol 19:1879-1885.

Garnett MR, Corkill RG, Blamire AM, Rajagopalan B, Manners DN, Young JD, Styles P, Cadoux-Hudson TA. 2001. Altered cellular metabolism following traumatic brain injury: a magnetic resonance spectroscopy study. J Neurotrauma 18:231-240.

Gasparovic C, Yeo R, Mannell M, Ling J, Elgie R, Phillips J, Doezema D, Mayer A. 2009. Neurometabolite Concentrations in Gray and White Matter in Mild Traumatic Brain Injury: A 1HMagnetic Resonance Spectroscopy Study. J Neurotrauma.

Ghajar J. 2000. Traumatic brain injury. Lancet 356:923-929.

Giza CC, Hovda DA. 2001. The Neurometabolic Cascade of Concussion. J Athl Train 36:228-235.

Govindaraju V, Gauger GE, Manley GT, Ebel A, Meeker M, Maudsley AA. 2004. Volumetric proton spectroscopic imaging of mild traumatic brain injury. AJNR Am J Neuroradiol 25:730-737.

Graham GD, Hwang JH, Rothman DL, Prichard JW. 2001. Spectroscopic assessment of alterations in macromolecule and small-molecule metabolites in human brain after stroke. Stroke 32:2797-2802.

Haseler LJ, Arcinue E, Danielsen ER, Bluml S, Ross BD. 1997. Evidence from proton magnetic resonance spectroscopy for a metabolic cascade of neuronal damage in shaken baby syndrome. Pediatrics 99:4-14.

Hunter JV, Wilde EA, Tong KA, Holshouser BA. 2012. Emerging imaging tools for use with traumatic brain injury research. J Neurotrauma 29:654-671.

Janowitz T, Menon DK. 2010. Exploring new routes for neuroprotective drug development in traumatic brain injury. Sci Transl Med 2:27rv21.

John CA, Day MW. 2012. Central neurogenic diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormone, and cerebral salt-wasting syndrome in traumatic brain injury. Crit Care Nurse 32:e1-7; quiz e8.

Johnson VE, Stewart W, Smith DH. 2013. Axonal pathology in traumatic brain injury. Exp Neurol 246:35-43.

Katzenberger RJ, Loewen CA, Wassarman DR, Petersen AJ, Ganetzky B, Wassarman DA. 2013. A Drosophila model of closed head traumatic brain injury. Proc Natl Acad Sci U S A 110:E4152-4159.

Kelso ML, Pauly JR. 2011. Therapeutic targets for neuroprotection and/or enhancement of functional recovery following traumatic brain injury. Prog Mol Biol Transl Sci 98:85-131.

Kierans AS, Kirov II, Gonen O, Haemer G, Nisenbaum E, Babb JS, Grossman RI, Lui YW. 2014. Myoinositol and glutamate complex neurometabolite abnormality after mild traumatic brain injury. Neurology 82:521-528.

Kreis R, Ernst T, Ross Bd. 1993. Absolute quantitation of water and metabolites in the human brain. II. Metabolite concentrations. J Magn Reson 102:9-19.

Kurowski B, Martin LJ, Wade SL. 2012. Genetics and outcomes after traumatic brain injury (TBI): what do we know about pediatric TBI? J Pediatr Rehabil Med 5:217-231.

Lin AP, Liao HJ, Merugumala SK, Prabhu SP, Meehan WP, Ross BD. 2012. Metabolic imaging of mild traumatic brain injury. Brain Imaging Behav 6:208-223.

Mader I, Seeger U, Weissert R, Klose U, Naegele T, Melms A, Grodd W. 2001. Proton MR spectroscopy with metabolite-nulling reveals elevated macromolecules in acute multiple sclerosis. Brain 124:953-961.

Nakabayashi M, Suzaki S, Tomita H. 2007. Neural injury and recovery near cortical contusions: a clinical magnetic resonance spectroscopy study. J Neurosurg 106:370-377.

Patterson ZR, Holahan MR. 2012. Understanding the neuroinflammatory response following concussion to develop treatment strategies. Front Cell Neurosci 6:58.

Phillis JW, O'Regan MH. 2004. A potentially critical role of phospholipases in central nervous system ischemic, traumatic, and neurodegenerative disorders. Brain Res Brain Res Rev 44:13-47.

Ross BD, Ernst T, Kreis R, Haseler LJ, Bayer S, Danielsen E, Bluml S, Shonk T, Mandigo JC, Caton W, Clark C, Jensen SW, Lehman NL, Arcinue E, Pudenz R, Shelden CH. 1998. 1H MRS in acute traumatic brain injury. J Magn Reson Imaging 8:829-840.

Rothman MS, Arciniegas DB, Filley CM, Wierman ME. 2007. The neuroendocrine effects of traumatic brain injury. J Neuropsychiatry Clin Neurosci 19:363-372.

Seeger U, Klose U, Mader I, Grodd W, Nagele T. 2003. Parameterized evaluation of macromolecules and lipids in proton MR spectroscopy of brain diseases. Magn Reson Med 49:19-28.

Shutter L, Tong KA, Holshouser BA. 2004. Proton MRS in acute traumatic brain injury: role for glutamate/glutamine and choline for outcome prediction. J Neurotrauma 21:1693-1705.

Sterns RH, Silver SM. 2008. Cerebral salt wasting versus SIADH: what difference? J Am Soc Nephrol 19:194-196.

Teasdale GM, Murray GD, Nicoll JA. 2005. The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. Brain 128:2556-2561.

Vagnozzi R, Signoretti S, Cristofori L, Alessandrini F, Floris R, Isgrò E, Ria A, Marziali S, Marziale S, Zoccatelli G, Tavazzi B, Del Bolgia F, Sorge R, Broglio SP, McIntosh TK,

Lazzarino G. 2010. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. Brain 133:3232-3242.

Werner C, Engelhard K. 2007. Pathophysiology of traumatic brain injury. Br J Anaesth 99:4-9.

Xiong Y, Mahmood A, Chopp M. 2010. Neurorestorative treatments for traumatic brain injury. Discov Med 10:434-442.