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Editorial

Understanding the metabolite–function relationship after cardiac arrest

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of coma.[1] Depending on the extent and severity of brain damage following CA, coma duration can extend beyond first week, necessitating accurate and reliable prognostication methods. Current guidelines recommend delaying prognostication, particularly after targeted temperature management, and relying on multi-modal paradigm instead of single tests or findings.[2,3]

Despite their safety and feasibility, conventional MRI measures have not been proven the most reliable prognostic markers in comatose survivors of CA. Qualitative Diffusion Weighted Imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) assessments,[4–6] as well as quantitative Apparent-Diffusion Coefficient (ADC) based measurements[7–10] suffer from poor discriminatory qualities. Variability in MRI measures also complicates reliable prediction of poor neurologic prognosis.[11]

After achieving some success in correlations with clinical outcome in traumatic brain injury (TBI)[12] and neonatal hypoxic-ischemic encephalopathy populations,[13] Proton Magnetic Resonance Spectroscopy Imaging (MRSI) has been attempted in a small number of cases after CA.[14–16] MRSI is a noninvasive tool to assess metabolic concentrations in the brain, reflecting a composite of neuronal density and viability, glial density, membrane injury, potential ischemic changes and metabolic crisis. MRSI employ voxel selection methods to focus on particular regions of brain, and thus multivoxel MRSI with larger brain volume may be preferred if time permissible.

In the current issue of *Resuscitation*, Quintard et al.[17] published their findings on comatose (Glasgow Coma Scale, GCS <9) patients after OHCA. Exclusion criteria included death before 7 days, neurologic and traumatic etiologies of CA and inability to receive an MRI. 40 of the initial 111 eligible patient cohort received Structural MRI and Multivoxel MRSI on 1.5-T using the point-resolved proton spectroscopy sequence and other standard parameters at a mean of 7 days post-arrest. The voxel was placed in a region covering the head of striatum to the thalamus. After excluding images of 11 additional patients due to quality, visual qualitative analysis using the FLAIR-DWI scoring[4] on conventional MRI and the concentration of metabolites, *N*-acetylaspartate (NAA at 2.0 ppm), Choline (Cho at 3.2 ppm), and Creatinine and phosphocreatine (Cr at 3.0 ppm) in the lenticular cores and thalami were estimated on MRS sequences of 29 patients. The worst value of bilateral lenticular cores and thalami were taken and area under the curve (AUC) was computed. Unfavorable outcome was defined as Cerebral Performance Category (CPC) scores >2 at 6 months.

Of 21/29 (72%) patients with unfavorable outcome, 17/21 (81%) died during hospital stay with 3 additional deaths by 6 months. Patients in favorable outcome category were younger and had improved GCS score (range 9–12) at the time of MRI (Median 7 days) since admission, compared to unfavorable group (range 3–6). The qualitative MRI scoring i.e. FLAIR-DWI scores in the deep nuclei were significantly higher (i.e. worse) in the unfavorable outcome group. Further, NAA/Cr ratios in lenticular cores were significantly lower in the unfavorable category, while there was no significant difference between groups in NAA/Cr ratios in the thalamus. Multivariate model including the Simplified Acute Physiology Score II on day 1 post-arrest, GCS at time of MRI, FLAIR–DWI scores for deep nuclei, and worst NAA/Cr in lenticular cores, had the greatest AUC of 0.95 (95% Confidence Intervals CI, 0.87–1.00), with a specificity of 100% (CI, 63–100%) and a sensitivity of 90% (CI, 70–99%).

NAA is involved in the regulation of neuronal protein and lipid synthesis, osmotic maintenance, and membrane transport. NAA exists in CNS structures exclusively and has consequently been used as a specific marker of neuronal viability.[14] Serial MRSI has demonstrated that the degeneration of neurons extends to axons and dendrites before affecting myelin sheaths in the subacute and chronic phase after anoxic brain injury.[15] Reduction of NAA in gray matter has shown correlations with poorer neuropsychological performance at 6 months after TBI.[18] After CA, day 7 MRSI showed higher sensitivity over structural MRI; there was a significant NAA reduction and presence of lactate peaks in the cerebral cortex, with normal appearance on DWI.[14]

The largest study so far on MRS after CA[6] is a prospective, observational cohort study (part of the MRI-COMA study) done in 14 centers in France, Italy, and Belgium. Included were 150 adult patients who had been unconscious for at least 7 days post-arrest and had an interpretable multimodal MRI. NAA/Cr ratios in the thalami and pons were significantly lower in patients with unfavorable outcomes (CPC >2, N = 117/150) than in patients with favorable outcomes. The AUC of NAA/Cr in thalami reached 0.85 (0.77–0.92) for 100% specificity, but sensitivity could only reach 30% (21–40). The thalamic and pons MRSI had a predictive accuracy similar to qualitative FLAIR/DWI scores. The study showed superiority (AUCROC curve 0.95, 95% CI 0.91–0.98) of whole-brain white matter fractional anisotropy over conventional MRI and MRSI in predicting unfavorable outcomes at 6 months.

Despite earlier reports demonstrating early cortical involvement, both studies chose deep grey nuclei as they are less prone to voxel placement issues. It is noteworthy that in earlier MRS studies on CA, phylogenetically newer CNS structures (i.e. cerebral cortex, caudate,

and putamen) were typically more severely compromised than the globus pallidus and other diencephalic-derivative, older structures, like the thalami and the gray nuclei of the brain stem.[18] The thresholds in Quintard et al.[17] study for NAA/Cr thalami have not been provided, so comparison with the study above was not possible.

There were few obvious caveats in the study design by Quintard et al.[17] First, the majority of patients (71%) in the unfavorable group underwent withdrawal-of-care, with no patients achieving CPC 3 and only one with CPC of 4 at 6 months. This likely precluded meaningful associations between metabolites concentration levels and clinical severity of injury. Second, motor response rather than pupillary reflexes were chosen for the model. Recent data[19] and meta-analysis[3] have demonstrated bilateral absence of pupillary reflexes beyond 5–7 days to have better specificity with lowest false-positive rates for poor outcomes. Lastly, there were significant differences between GCS scores obtained at the time of MRI between favorable (median 10 [9–12]) and unfavorable groups (Median 3 [3–6]). Future studies should consider excluding patients from the analysis that showed marked improvement in neurological exam at time of MRI.

There have also been technical challenges with MRSI. Despite allowing several days for stabilization in the ICU, the authors could only obtain interpretable MRSI in 73% of their patients, highlighting the fact that obtaining research quality MRI scans is arduous.

Pending normal population data for metabolite levels in the brain, standard space approaches to analyze data are preferable. In TBI, it has been demonstrated that high-resolution metabolite maps can be generated using echo-planar based MRS methods and patient data can then be compared statistically to control populations.[20] Additionally, it will be interesting to study longitudinal changes in NAA levels, as the extent of recovery of the NAA peak may be associated with the severity of clinical injury.

The key challenge to widespread and routine use of this method is the need to establish a unified scanning protocol that accounts for consistency in MRS voxel placement, establishment of sensitivity to motion, among other potential sources of variance. Finally, an initiative by investigators to provide a detailed description of the protocols for imaging and analysis would facilitate effective comparisons.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

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Sachin Agarwal*
Neurocritical Care, Department of Neurology, Columbia University Medical Center, New York, NY, United States

Frank A. Provenzano
Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University Medical Center, New York, NY, United States

* Corresponding author at: 177 Ft. Washington Avenue, Floor: 8-300, New York, NY 10032, United States.
E-mail address: sa2512@columbia.edu (S. Agarwal).

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