AJNR

A Positive Correlation Between α-Glutamate and Glutamine on Brain ^{1}H-MR Spectroscopy and Neonatal Seizures in Moderate and Severe Hypoxic-Ischemic Encephalopathy

Yonglin Pu, Ankur Garg, Rodney Corby, Jia-Hong Gao, Chao-Mei Zeng, Yonglin Pu and Qing-Feng Li

AJNR Am J Neuroradiol 2008, 29 (2) 216
doi: https://doi.org/10.3174/ajnr.A0798
http://www.ajnr.org/content/29/2/216

sistant IIH. In such a study, subgroups of patients with fixed and reversible stenoses should be analyzed separately. Until then, I do not favor performing stent angioplasty in patients with reversible stenoses.

A. Rohr
Department of Neuroradiology
University of Schleswig-Holstein Campus Kiel
Kiel, Germany

DOI 10.3174/ajnr.A0941

A Positive Correlation Between α-Glutamate and Glutamine on Brain ^{1}H-MR Spectroscopy and Neonatal Seizures in Moderate and Severe Hypoxic-Ischemic Encephalopathy

Cerebral metabolic disturbances during seizures and hypoxic-ischemic events in patients with hypoxic-ischemic encephalopathy (HIE) can lead to excessive synaptic and extracellular concentrations of glutamate with concomitant and subsequent neuronal cell injury or death.[1,2] Multiple studies also suggest that the increased glutamate concentration in the brain can induce seizures.[2] Therefore, glutamate is intimately involved in the pathogenesis of the seizures. However, there is no evidence, to our knowledge, that shows a relationship between the severity of neonatal seizures in HIE and the concentration of glutamate in the human brain. We reanalyzed the data published in 2000 in the *American Journal of Neuroradiology*[1] that showed an increased detectability of α-brain glutamine/glutamate (Glx) in neonatal HIE and found a positive correlation between the severity of seizures and peak-area ratio of α-Glx/creatine and phosphocreatine (TCr) in neonates with moderate and severe HIE.

Study subjects included 7 normal neonates as a control group (2–4 days old; mean age, 3 days; mean gestational period, 39.3 weeks; and mean birth weight, 3.386 kg; group 1), 14 neonates with mild-to-moderate HIE without seizures (2–7 days old; mean age, 3.2 days; mean gestational period, 37.8 weeks; and mean birth weight, 2.730 kg; group 2), and 7 neonates with moderate and severe HIE and seizures (2–7 days old; mean gestational period, 39.6 weeks; and mean birth weight, 3.250 kg; group 3). The types of seizures included subtle seizures in 2 subjects, clonic seizures in 2 subjects, and generalized tonic seizures in 3 subjects.[3] The seizures were graded according to their severity and frequency[4] from grade 1 to grade 3. Grade 1 was defined as occasional and transient seizures. Grade 2 was defined as repeated seizures (<3 seizures per day) with each seizure lasting less than 3 minutes. Grade 3 was defined as repeated seizures (>3 seizures per day) with each seizure lasting more than 3 minutes.

The peak areas of α-Glx and TCr were measured at 3.75 ppm and 3.02 ppm, respectively, on the point resolved spectroscopy sequence (TR of 2000 ms; TE of 135 ms, with averages of 250 ms). The spectral volume of interest of 18 cm^3, placed in the center of the brain, included the basal ganglia, the centra semiovale, and the thalami, as well as parts of the lateral and third ventricles. The selection of the spectral volume of interest was done because several studies in human neonates with severe perinatal asphyxia have shown that the basal ganglia and thalami are more sensitive to anoxia.[5,6] Because the CSF concentration of glutamate can be used to estimate the level of glutamate concentration in the extracellular compartment of the brain,[7] inclusion of the ventricles in the volume of interest would not affect the quantification of the extracellular concentration of glutamate with ^{1}H-MR spectroscopy. Furthermore, it is much easier to perform shimming in the central part of the brain. The data were described as median/range.

On initial ^{1}H-MR spectroscopy studies, which were performed at 2 to 7 days of age, the level of the peak-area ratio of α-Glx/TCr in group 3 (0.5/2.42; $n = 7$) was significantly higher than in group 1 (0.00/0.12; $n = 7$) and in group 2 (0.00/0.33; $n = 14$; both $P < .01$). The difference of the level was not statistically significant between groups 1 and 2. The level of the peak-area ratio of α-Glx/TCr in group 3 was positively correlated with the grade of seizures (Spearman rank correlation, $r = 0.769$; $P < .05$; $n = 7$). In neonates with grade-1 seizures, the ratios were 0.38, 0.38, and 0.5 ($n = 3$). In neonates with grade-2 seizures, the ratios were 0.5 and 0.5 ($n = 2$). In neonates with grade-3 seizures, the ratios were 0.5 and 2.8 ($n = 2$).

On the follow-up ^{1}H-MR spectroscopy study performed in 4 neonates in group 3 at 13.0 to 16.5 days of age, the seizure symptoms subsided, and the level of the peak area ratio of α-Glx/TCr decreased from 0.500/0.00 to 0.330/0.110 after supportive treatment in 3 neonates of group 3. However, 1 neonate of group 3 still had seizures, a high level of the peak area ratio of α-Glx/TCr of 1.0, and died 2 days after the follow-up ^{1}H-MR spectroscopy study.

Our reanalysis demonstrated that the Glx peak at its α-region is increased in the basal ganglia, centra semiovale, thalami, and part of the lateral and third ventricles in all neonates with seizures and HIE. It also established a positive correlation between the detectability of α-Glx and the severity of the seizures. These findings are consistent with the notion that glutamate plays an important role in the pathogenesis of epilepsy that has been documented by previous studies.[2]

References

1. Pu Y, Li QF, Zeng CM, et al. **Increased detectability of alpha brain glutamate and glutamine in neonatal hypoxic-ischemic encephalopathy.** *AJNR Am J Neuroradiol* 2000;21:203–12
2. Chapman AG. **Glutamate and epilepsy.** *J Nutr* 2000;130:1043S–45S.
3. Zupanc ML. **Neonatal seizures.** *Pediatr Clin N Am* 2004;51:961–78
4. Cramer JA, French J. **Quantitative assessment of seizure severity for clinical trials: a review of approaches to seizure components.** *Epilepsia* 2001;42:119–29
5. Barkovich AJ. **MR and CT evaluation of profound neonate and infantile asphysia.** *AJNR Am J Neuroradiol* 1992;13:959–72
6. Schneider H, Ballowwitz L, Schachinger H, et al. **Anoxic encephalopathy with predominant involvement of basal ganglia, brain stem and spinal cord in prenatal period.** *Acta Neuropathol* 1975;32:287–98
7. Cataltepe O, Towfighi, J, Vannucci RC. **Cerebrospinal fluid concentration of glutamate and GABA during perinatal cerebral hypoxia-ischemia and seizure.** *Brain Res* 1996;709:326–30

Yonglin Pu
Ankur Garg
Rodney Corby
Jia-Hong Gao
Department of Radiology
University of Chicago
Chicago, Ill
Chao-Mei Zeng
Yonglin Pu
People's Hospital
Peking University
Beijing, China
Qing-Feng Li
Wei-Hai-Jin-Hai-Wan Hospital
Wei-Hai, Shandong, China

DOI 10.3174/ajnr.A0798