AJNR

Reply:

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AJNR Am J Neuroradiol 2008, 29 (2) 215-216
doi: https://doi.org/10.3174/ajnr.A0941
http://www.ajnr.org/content/29/2/215.1

Stenoses in Idiopathic Intracranial Hypertension: To Stent or Not To Stent?

I read with great interest the paper entitled "Reversibility of Venous Sinus Obstruction in Idiopathic Intracranial Hypertension" recently published in the *American Journal of Neuroradiology* by Rohr et al.[1] This paper presents the case histories of 3 patients with idiopathic intracranial hypertension (IIH) and venous outflow stenoses. The first patient had an initial resolution of her symptoms after insertion of a stent into the transverse sinus, but the symptoms recurred and a restenosis was noted just upstream from the stent. This patient was later treated with insertion of a shunt tube. In the second and third cases, the patients were treated with insertion of a shunt, with the venous stenoses in the second patient improving after the insertion. On the basis of these cases, the authors suggest that the elevated venous pressure in IIH is caused by the collapse of the sinuses.[1] They go on to assert that insertion of a stent should be reserved for fixed stenoses and should not be used for dynamic stenoses. This suggestion is proposed because, logically, if the raised pressure in the CSF has caused the collapse of the venous sinus, then the elevated venous pressure cannot also be the cause of the raised CSF pressure. I wish to discuss whether the cause-and-effect relationship, as outlined, is the only one possible given the data as presented.

Most patients with IIH have morphologic stenoses in the venous outflow.[2] Many of these stenoses reduce the outflow by more than 70% in area and would be deemed significant if found on the arterial side of the vascular tree. Direct manometry has shown the pressure gradients across these stenoses to average 24 mm Hg,[3] which would also suggest that these stenoses were significant by the usual criteria. Finally, I have measured the arterial inflow and venous outflow in 21 patients with IIH and stenoses and found, on average, a 13% reduction in the sagittal sinus outflow as a percentage of the inflow in IIH.[4] This indicates that 140 mL/min bypasses the dominant outflow stenosis via the collateral vessels,[4] again suggesting significance.

Can we reconcile the apparent significant nature of the stenoses with the fact that they occur secondary to the CSF pressure? Intracranial pressure (ICP) is dependent on a balance between the production and reabsorption of CSF. Davson et al[5] modeled the relationship between ICP and the formation and reabsorption of CSF showing that,

$$ICP = R_{out} \times FR_{CSF} + P_{SS}$$

where R_{out} is the resistance of CSF outflow, FR_{CSF} is the formation rate of CSF, and P_{SS} is the sagittal sinus pressure. In a report by King et al[3] in which they studied 21 patients with IIH, a mean CSF pressure of 27 mm Hg and sagittal sinus pressure of 22 mm Hg gave a CSF-superior sagittal sinus (SSS) gradient of 5 mm Hg, which is in the normal range (2–6 mm Hg). Rearranging Davson's equation, we find that the CSF-SSS pressure gradient is equal to the product of the CSF rate of production and the resistance to flow across the arachnoid granulations, ie,

$$ICP - P_{SS} = R_{out} \times FR_{CSF.}$$

Malm et al[6] used a technique of constant flow to measure FR_{CSF} and showed it to be normal in this condition. If the gradient and the rate of formation are normal, then the R_{out} must also be normal in IIH. Therefore, the elevated venous pressure is the sole variable effecting the elevation in CSF pressure despite itself being secondary to the elevated CSF pressure. This finding indicates that a feedback loop must exist in which both the CSF and venous pressures are cause and effect. It follows that this condition could be treated by attacking either side of the feedback loop (ie, reducing the CSF pressure with placement of a shunt or stent into an overly compliant transverse sinus will break the loop). Thus, I believe that the assertion by Rohr et al[1] that placement of a stent should not be offered to patients who have IIH and collapsible stenoses is not necessarily correct. The only proviso is that the stent must support all of the compliant sections of the venous system or the stenosis will recur (well documented by the authors in patient 1). Ultimately, whether the front-line treatment of IIH associated with collapsible venous outflow is stent placement or shunt insertion will depend on the relative morbidity of these procedures and their long-term rates of success.

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DOI 10.3174/ajnr.A0804

Reply:

Because venous sinus stenoses in idiopathic intracranial hypertension (IIH) can be reversed by lowering the intracranial pressure, I believe that these stenoses are caused primarily by elevated intracranial pressure. I think there might, furthermore, be a feedback mechanism in IIH such that an increase in intracranial pressure (due to impaired absorption of CSF?) leads to stenoses of the transverse sinuses and that these stenoses lead to an increase in intravenous pressure proximal to the stenoses (which can be measured directly by a catheter). This again could hamper absorption of CSF, leading to a further increase in pressure. (In theory, pressure would then rise infinitely, but in reality it does not. Therefore, the mechanisms must be somewhat more complex.) We saw cases of secondary intracranial hypertension demonstrating narrowing of large segments of the intracranial sinuses, whereas in IIH, there seems to be a predilection for the development of the stenoses in the lateral parts of the transverse sinuses. Therefore, patients with IIH probably have some pathoanatomic change in this region of the sinus ("vulnerable segments" may be secondary to hormonal changes).

I agree with Bateman that patients might profit from stent angioplasty, which interrupts the feedback mechanism. However, the problem is—as he stated and as our first patient demonstrated—that stent angioplasty might be necessary for all the "vulnerable" segments of the intracranial sinuses. Moreover, we probably tackle only a part of the problem with this procedure. On the other hand, there might be a subgroup of patients with IIH who have fixed sinus stenoses (eg, originating in venous sinus thrombosis) predisposing them for stent angioplasty. We have to prove though that these groups of patients really exist.

I also think there is a need for a randomized controlled multicenter trial in which the performance of stent angioplasty versus shunt surgery procedures is compared in patients with pharmacore-

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.

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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]

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DOI 10.3174/ajnr.A0798