Subarachnoid Hemorrhage-Induced Hydrocephalus in Rats

Shuichi Okubo MD, PhD; Richard Keep PHD; Ya Hua MD; Jennifer Strahle MD; Guohua Xi MD
Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan

Background and Purpose

Acute hydrocephalus is a common complication after aneurysmal subarachnoid hemorrhage (SAH). Hydrocephalus can result in increased intracranial pressure that may lead to decreased cerebral blood flow and clinical deterioration [1]. Hydrocephalus portends a worse prognosis in patients with aneurysmal SAH [2]. Few studies have investigated acute hydrocephalus after SAH in animal models. Here we report a rat model of acute hydrocephalus after SAH induced by endovascular perforation.

Methods

SAH was induced by endovascular perforation in adult male Sprague-Dawley rats (n=36). Sham rats (n=8) underwent the same procedure without perforation [3]. MRI was performed 24 hours after SAH and the volume of the ventricular system and extent of T2* hypointensity lesions were measured. We defined hydrocephalus as ventricular volume greater than +3 standard deviations above the mean in sham animals. SAH grade was determined and brains were used for histology, immunohistochemistry, Perls' staining for iron and Western blot analysis [4]. Ventricular wall damage was defined as percentage of ependymal surface disruption.

Results

All surviving rats (n=27) after SAH had ventricular enlargement (33.6±4.7 vs. 13.5±1.4 mm^3 in sham animals, $p<0.01$). Ventricular volume correlated with SAH severity ($r=0.48$, $p<0.05$). 12 of 27 SAH rats demonstrated hydrocephalus and all had intraventricular blood accumulation. Rats with hydrocephalus had more severe ventricular wall damage (7.4±1.2%) than the sham animals (0.6±0.2%, $p<0.01$) and rats without hydrocephalus (1.1±0.2%, $p<0.01$). Periventricular iron deposition was observed and heme oxygenase-1 (HO-1; heme handling), Iba-1 (microglia) expression were markedly increased in hydrocephalus rats.

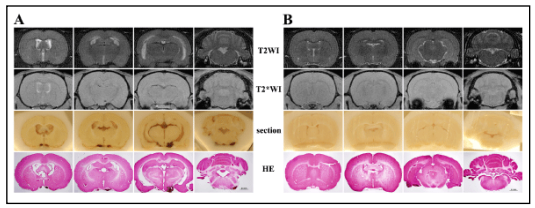

Fig. 2. Ventricular volume 24 hours after endovascular perforation or sham procedure (A). Correlation of ventricular volume and SAH grade at 24 hours (B). Coronal T2* images of sham and SAH animals with or without hydrocephalus at 24 hours. Rats with hydrocephalus have a larger hypointensity volume than the sham animals or rats without hydrocephalus (C). Hematoxylin and eosin staining of sham and SAH animals with or without hydrocephalus. Note the presence of intraventricular hemorrhage in the hydrocephalic rat. Boxes show intact ependyma (sham, SAH without hydrocephalus) and disrupted ependyma with intraventricular hemorrhage (SAH with hydrocephalus). SAH animals with hydrocephalus have more ventricular wall damage compared to sham or SAH animals without hydrocephalus (D). *p<0.05 and #p<0.01. Values are mean±SEM. Scale bar=200μm. SAH-subarachnoid hemorrhage; HC-hydrocephalus.

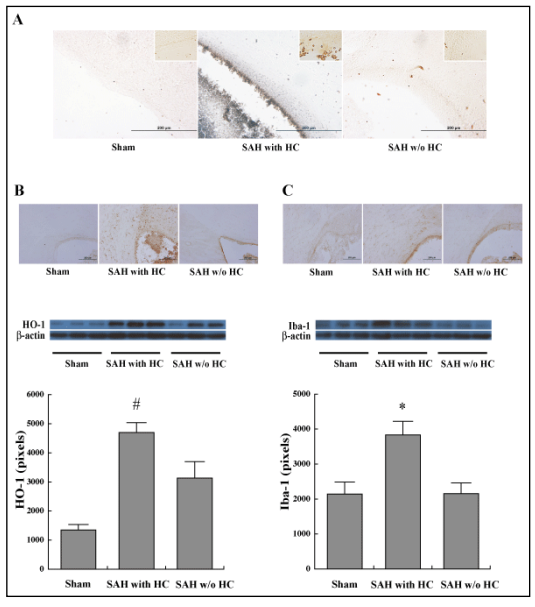

Fig. 1. Coronal T2 and T2* images, photomicrographs and hematoxylin and eosin sections 24 hours after endovascular perforation (A) or sham procedure (B). HE: hematoxylin and eosin staining. Note the enlarged ventricles in (A).

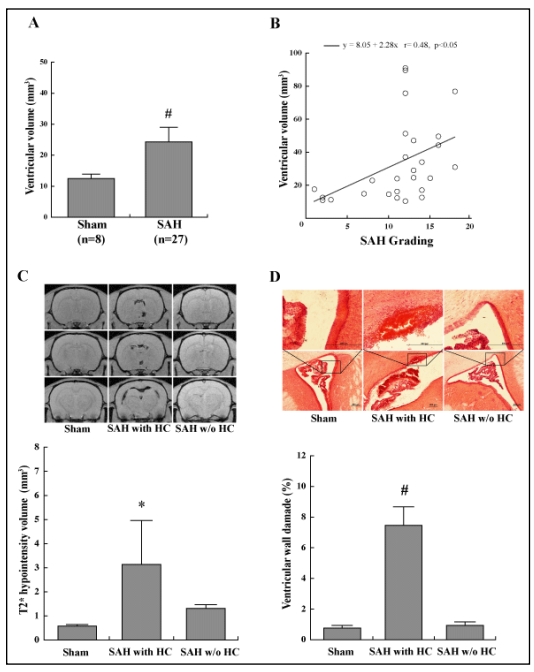

Fig. 3. Perls' reaction (with 3,3'Diaminobenzidine, DAB, enhancement) showed iron-positive cells in ependyma and subependyma in hydrocephalic SAH rats but not sham and non-hydrocephalic rats. The inserts show DAB staining alone (A). Periventricular HO-1 immunoreactivity of sham and SAH animals with or without hydrocephalus. Western blot analysis demonstrated higher HO-1 levels in SAH animals with hydrocephalus compared with sham controls (#p<0.01; n=3-4) (B). Periventricular Iba-1 (microglia marker) immunoreactivity of sham and SAH animals with or without hydrocephalus. Western blot analysis demonstrated higher Iba-1 levels in hydrocephalic SAH rats compared with SAH animals without hydrocephalus and sham controls (*p<0.05; n=3-4) (C). Scale bar=200μm. Values are mean ± SEM. SAH-subarachnoid hemorrhage; HC-hydrocephalus.

Conclusions

SAH causes ventricular enlargement in a rat endovascular perforation model, with hydrocephalus occurring in 44% of animals at 24 hours. Rats with hydrocephalus had more severe SAH, intraventricular hemorrhage and greater ventricular wall damage. This model may be useful for determining the mechanisms underlying SAH-induced hydrocephalus and the efficacy of potential therapeutics.

References

1. Del Bigio MR. Neuropathological changes caused by hydrocephalus. Acta Neuropathol. 1993;85:573-585
2. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. Stroke. 1989;20:747-753
3. Lee JY, Keep RF, He Y, Sagher O, Hua Y, Xi G. Hemoglobin and iron handling in brain after subarachnoid hemorrhage and the effect of deferoxamine on early brain injury. J Cereb Blood Flow Metab. 2010;30:1793-1803
4. Chen Z, Gao C, Hua Y, Keep RF, Muraszko K, Xi G. Role of iron in brain injury after intraventricular hemorrhage. Stroke. 2011;42:465-470

Sources of Funding

This study was supported by grants NS-039866, NS-057539 and NS-073595.