

# Post-Traumatic Cerebral Edema

## Traumatic Brain Injury Mini-Symposium

4<sup>th</sup> Annual Research Retreat

UMASS Center for Clinical and Translational Science

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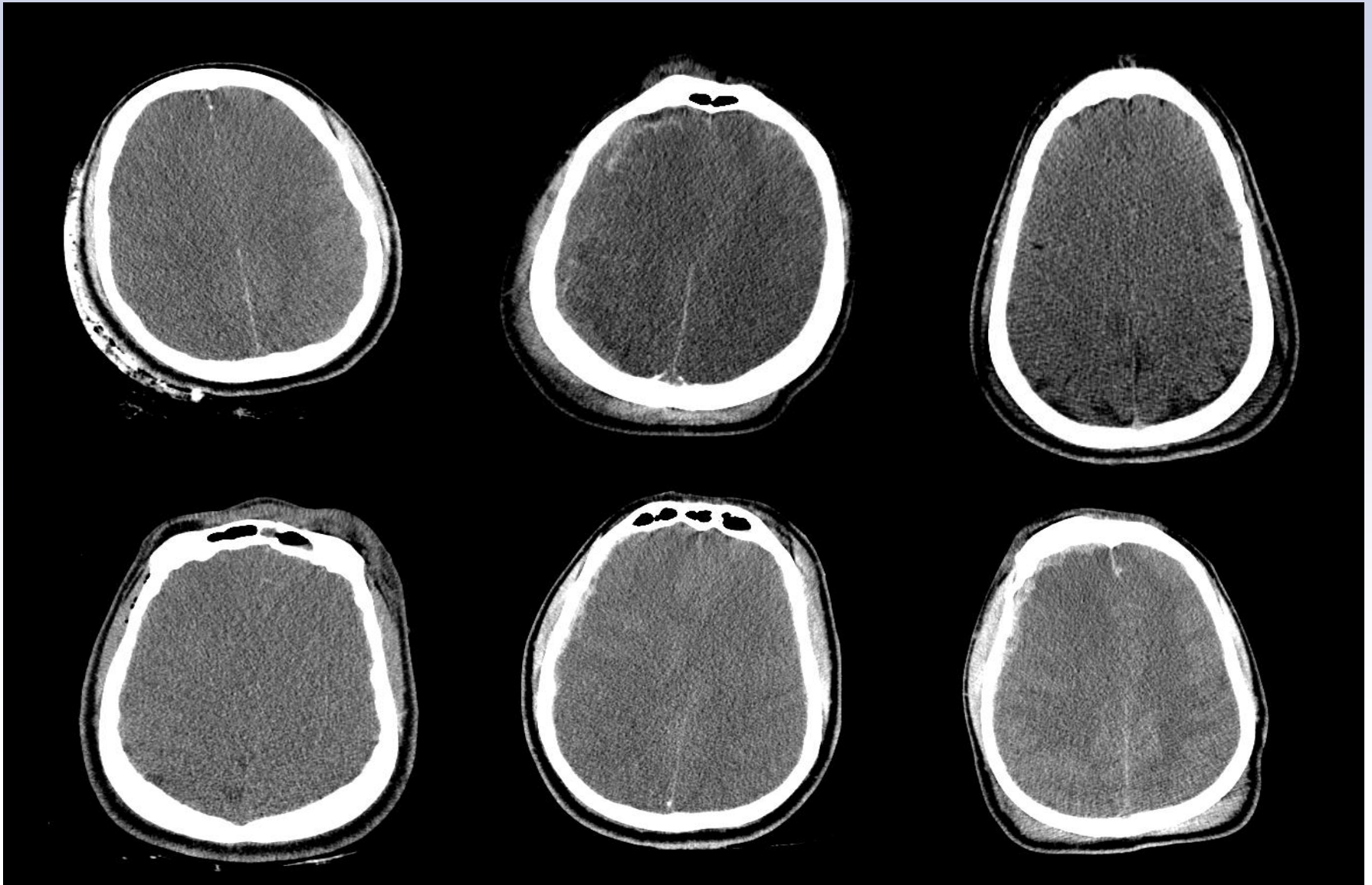
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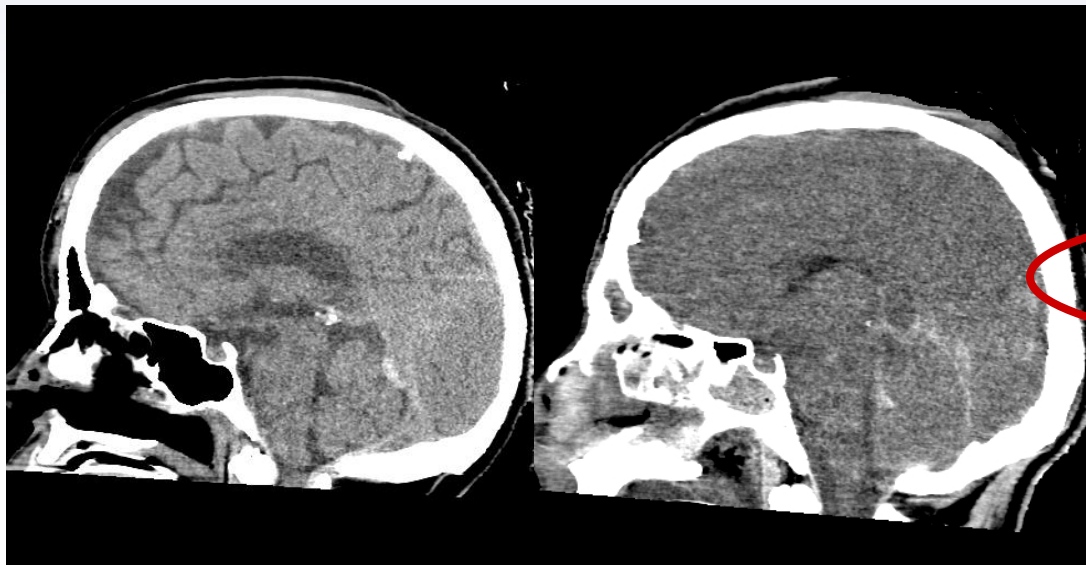
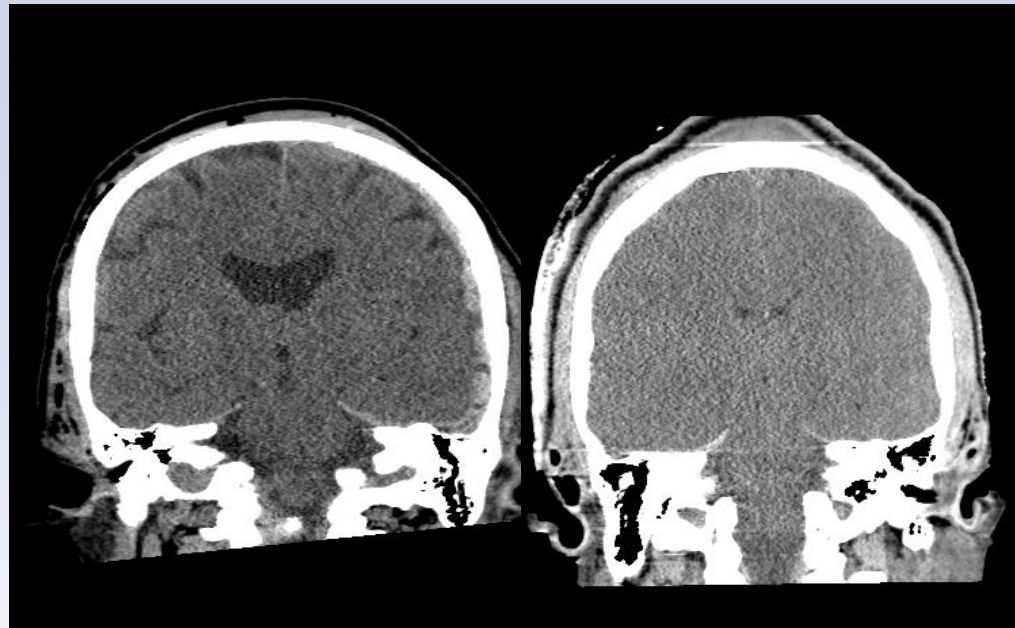
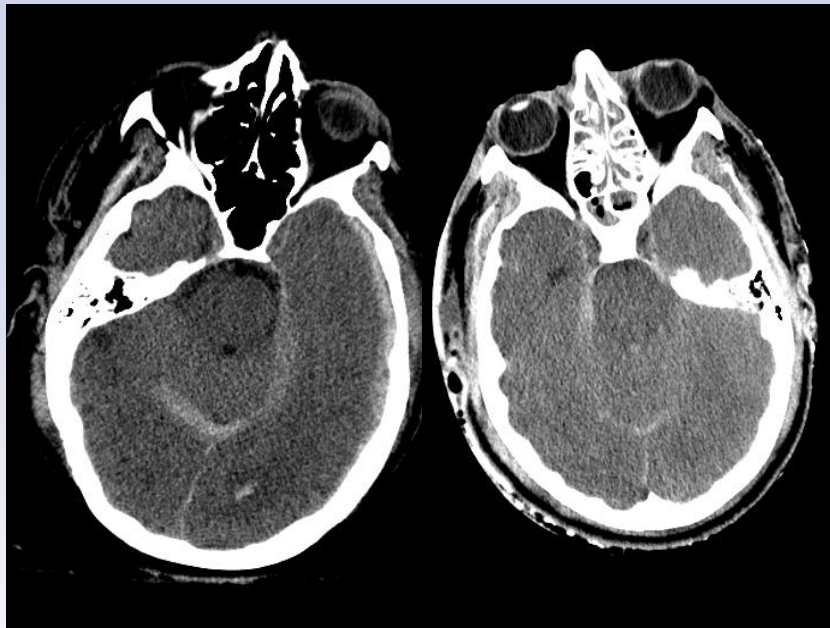


Disclosures: Worcester Foundation for Biomedical Research Grant 2011

# Outline

1. Clinical Implications of brain edema
2. Brain water homeostasis
3. Pathophysiology of brain edema
4. Aquaporin 4 Channels
5. CACNA1
6. Sulfonylurea receptor 1 (SUR1)
7. NKCC1
8. Clinical management and ongoing trials





*Modified Marshall CT grade:			
I	Diffuse Injury	No visible pathology	1
II	Diffuse Injury (with present cisterns, midline shift 0-5mm and/or small (<25cc) high or mixed density lesions	No lesions	2a
		Only one lesion	2b
		≥2 unilateral lesions	2c
		Bilateral lesions	2d
III	Diffuse injury and swelling	I – II + compressed or absent cisterns	3
IV	Diffuse injury and shift	I-III + midline shift >5mm	4
V	Evacuated mass lesion	Extradural	5a
		Subdural	5b
		Intracerebral	5c
		≥2 intra + extracerebral	5d
VI	Non-evacuated mass lesion >25cc)	Extradural	6a
		Subdural	6b
		Intracerebral	6c
		≥2 intra+extracerebral	6d

# Cerebral edema post-trauma

- Poor prognostic sign
- Class III (83.7%) and Class IV (93.8%) had severe disability, vegetative or dead
- >10 mm shift, Compressed basal cisterns, IVH, traumatic SAH = OR 2.0
- Absent cisterns OR 5.7 of death

# Physiological Consequences

- Intracranial hypertension
- Monro-Kellie Doctrine 1820
- Compression of venous outflow and CSF
- Decreased cerebral perfusion and secondary ischemic injury
- Compression of brain structures and clinical herniation

# Normal Brain Water Homeostasis

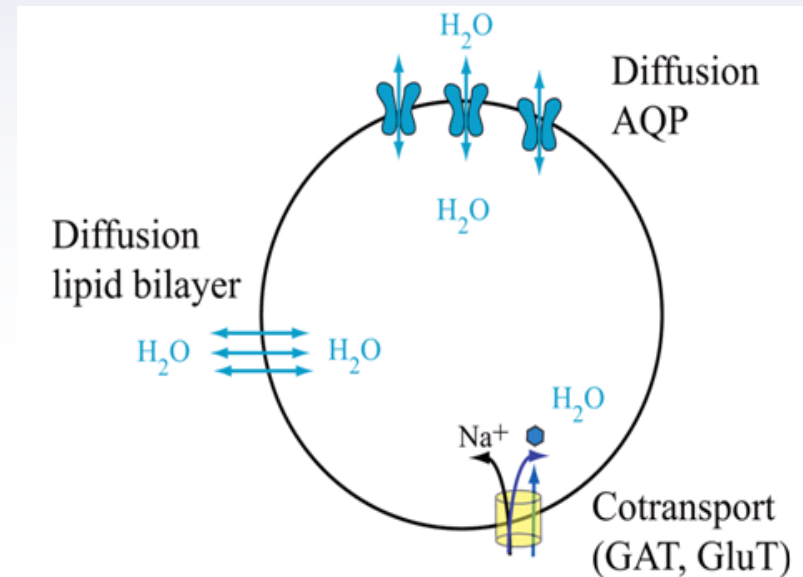
- Central osmoreception, osmolarity compensation, and cell volume regulation
- Compartments: blood in vessels, CSF in ventricular and subarachnoid space, ECF, and ICF in brain parenchyma
- BBB, Blood-CSF barrier and plasma membranes of neural cells
  - ECF – interactions between BBB, BCSFB and transporters on the membranes of neural cells, particularly astrocytes
  - CSF – choroid plexus secretion and drainage into dural sinuses, some flow from ECF to CSF
  - ICF – cellular metabolic activity and active transport of ions

# BBB AND BCSFB

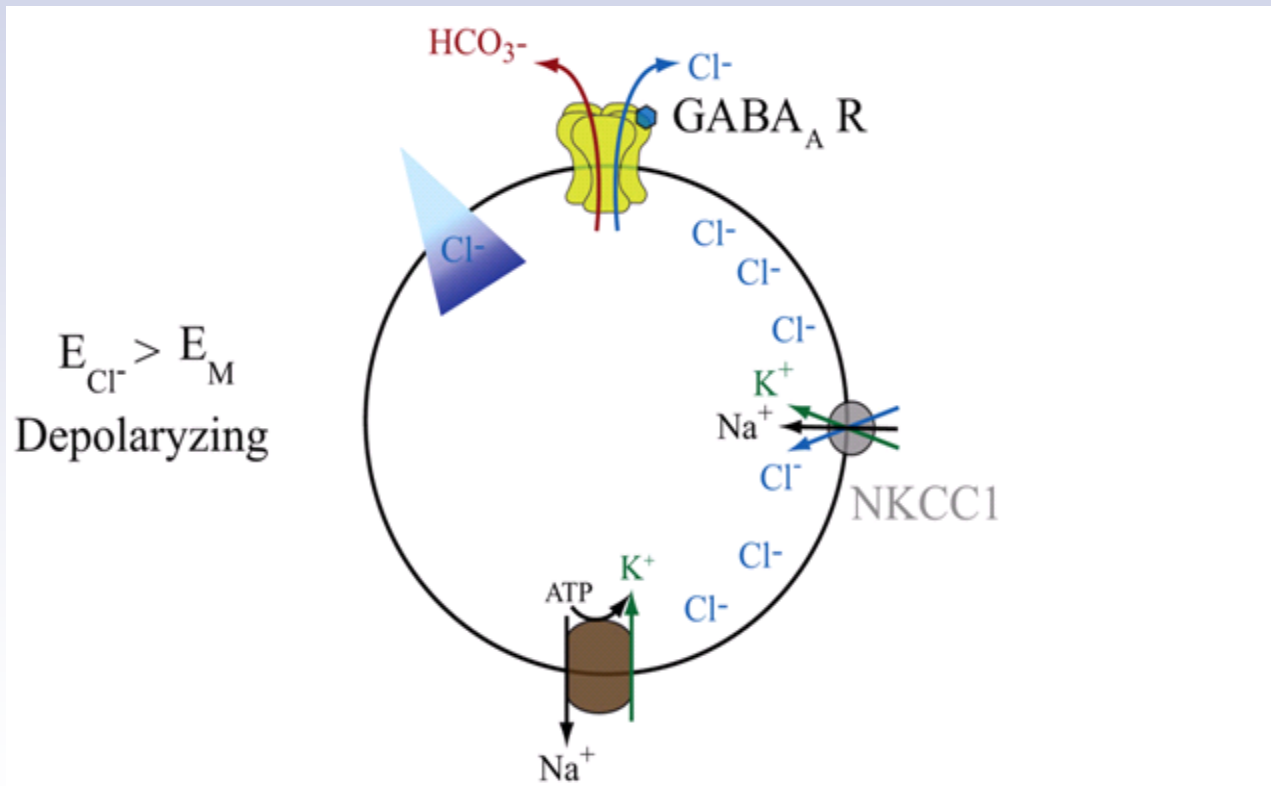
- Anatomic barriers and dynamic tissues expressing multiple transporters, receptors and enzymes
- Prevent free paracellular diffusion of polar molecules by complex morphological features such as Tight Junctions, adherens junctions in brain capillary endothelial cells in choroid plexus epithelium
- Specific transport proteins provide transport of nutrients, ions into CNS and removal of waste products
- Ion transporters and exchangers and ion channels
- Regulatory proteins possess kinase and phosphatase activity

# Cellular basis for volume distribution

- Water changes affect brain volume and intracranial pressure
- Changes in extracellular or intracellular content of osmolytes are coupled to movements of osmotically obliged water
- Normally, redistribution of water between ECF and ICF occurs modifying the volume of the neural cells but not the total brain volume
- This involves modification of the expression and activity of ion channels and transporters and by metabolic changes



# NEUROTRANSMITTER EFFECTS

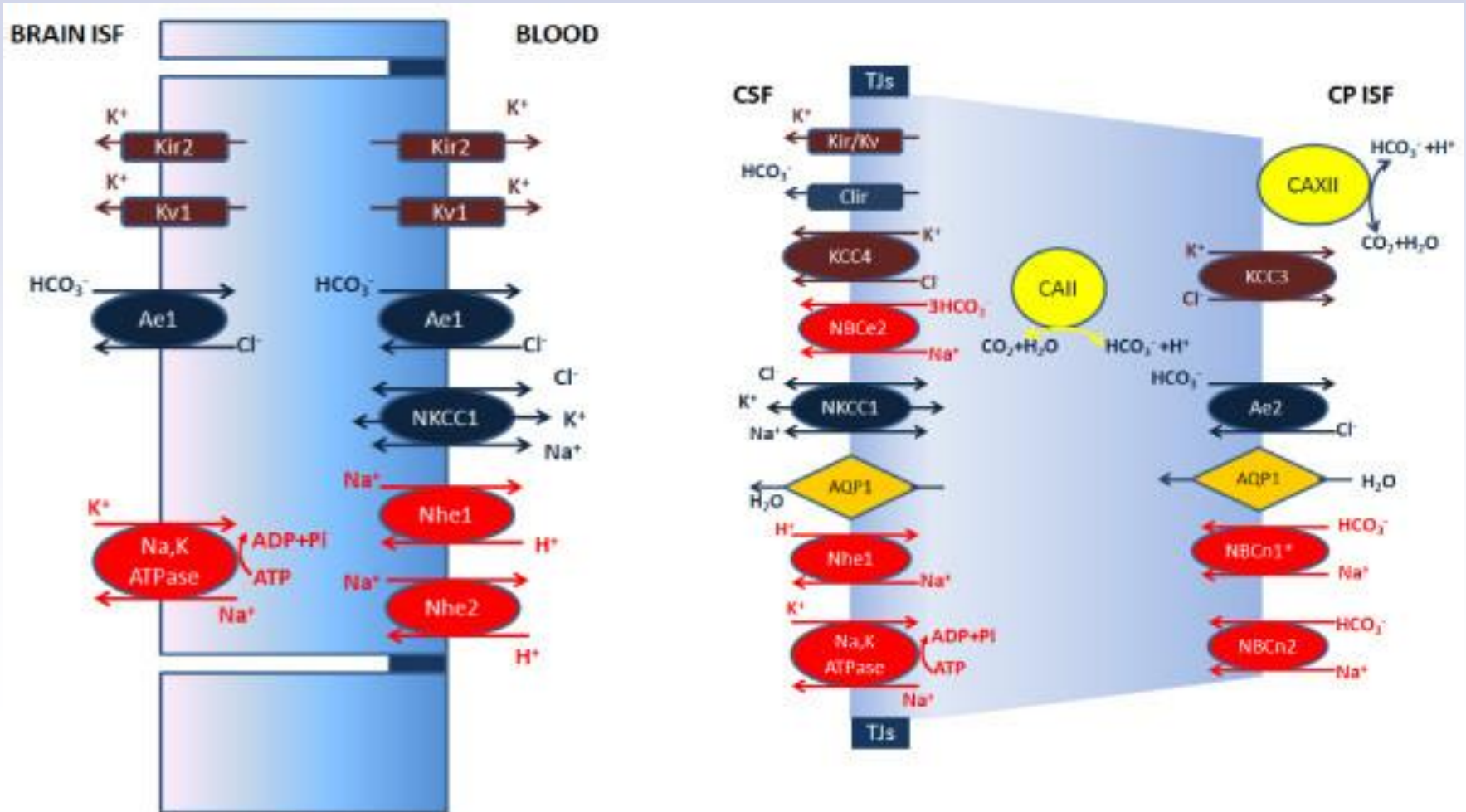


E.g. Neural activity determines isosmotic volume changes as a consequence of ionic fluxes across cell membranes during neuronal firing – cells counteract the volume change by Regulatory Volume increase and decrease

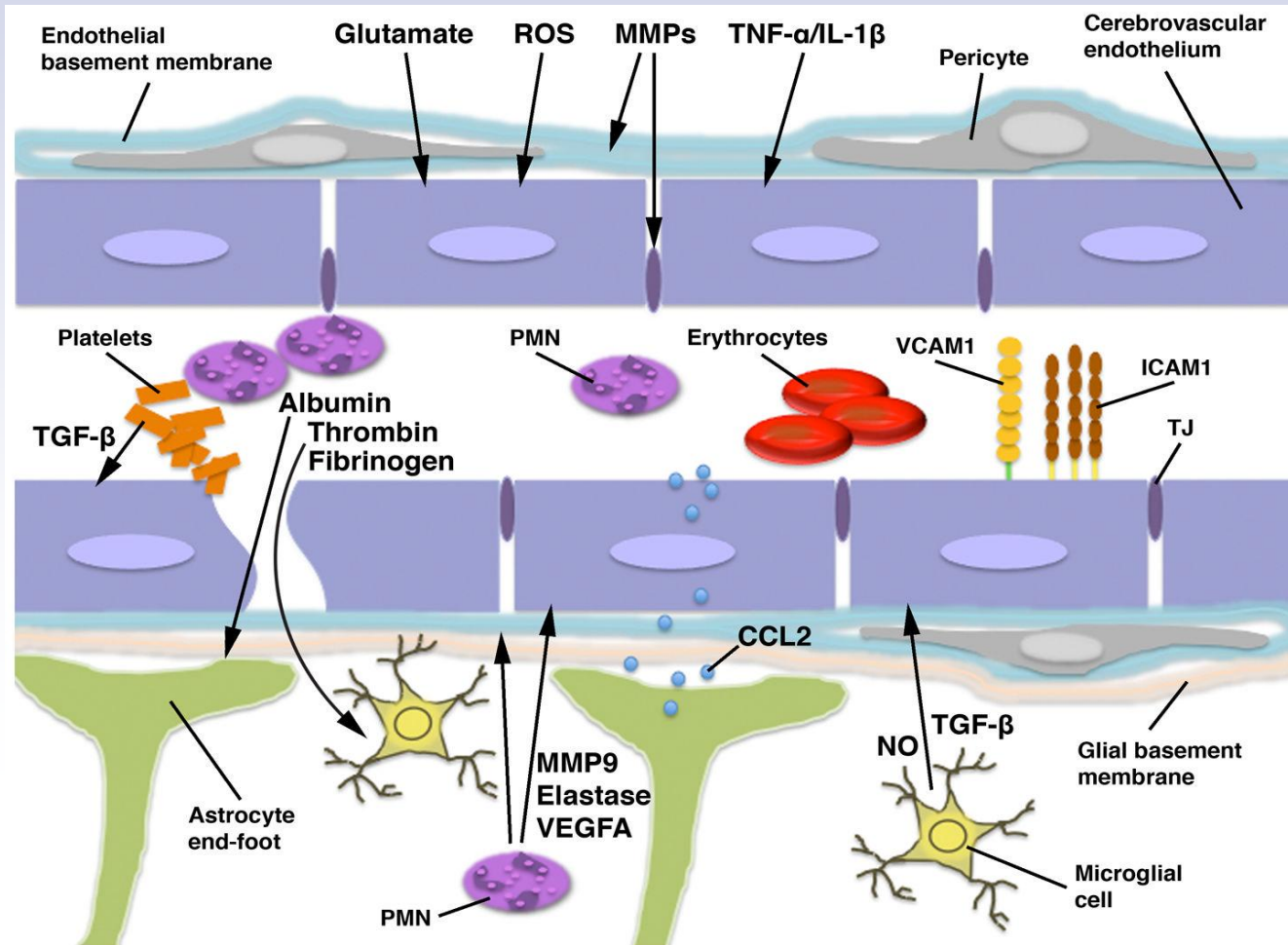
# WATER TRANSPORT

- Membrane-spanning transport proteins which can couple ion and substrate transport
  - K/Cl co-transporter in the choroid plexus
  - Na/K /Cl in the glia
  - Na coupled glutamate
  - Na/GABA
  - GLUT1 and 2
  - ATP binding cassette transporters (A $\beta$ , cholesterol efflux, Cs)
- Total water transported is the sum of co-transported and the osmotic components

# TRANSPORTERS



# PATHOPHYSIOLOGY: BBB/GLIOVASCULAR UNIT

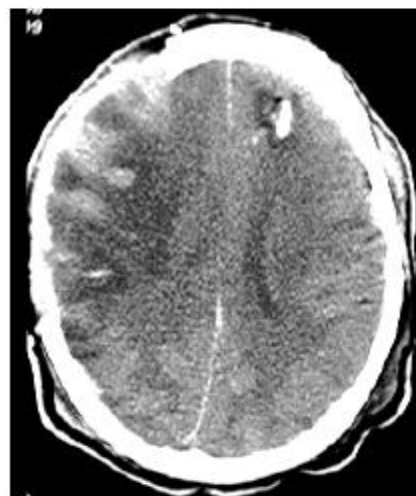


# CYTOTOXIC EDEMA

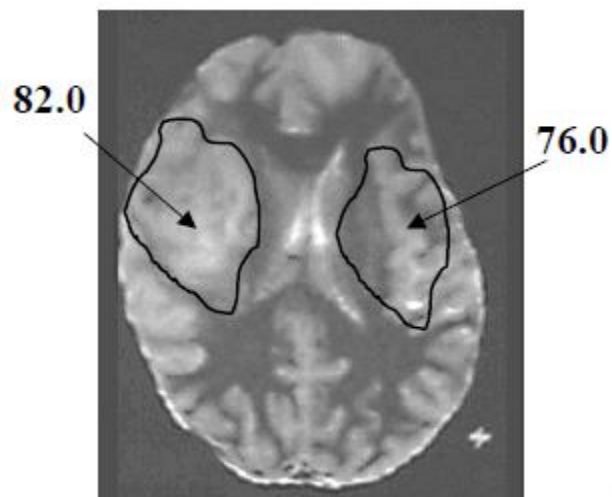
- Different pathologies lead to isosmotic cytotoxic swelling by different mechanisms:
  - Energy failure and dissipation of Na gradients - hypoxia/ischemia
  - Increase in intracellular K – ischemia, epilepsy, cortical spreading depression
  - Ammonium accumulation in hepatic encephalopathy
  - Dialysis dysequilibrium – changes in Urea/Osmolar gradient
- Changes in cell metabolism, pump and ion channel dysfxn
- Changes in ECF/ICF ion equilibrium alter neuronal function
- Role of Astrocytes/Glia - Astrocytes swell secondary to water fluxes across the membrane and to neighbor astrocytes through gap junctions



Admission CT



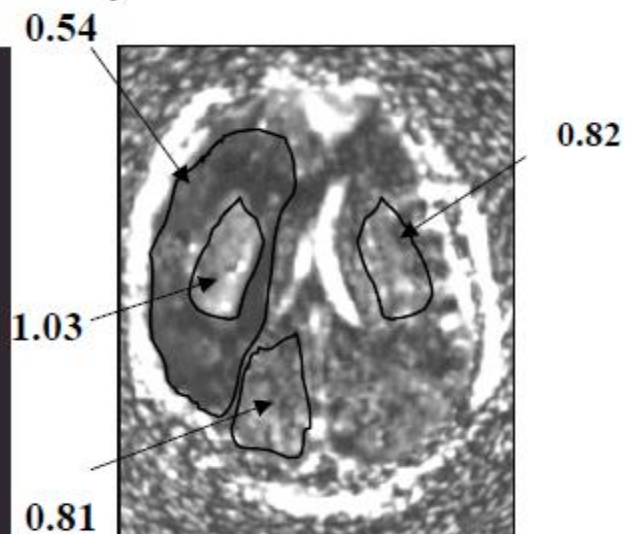
Day of study CT



Water Map



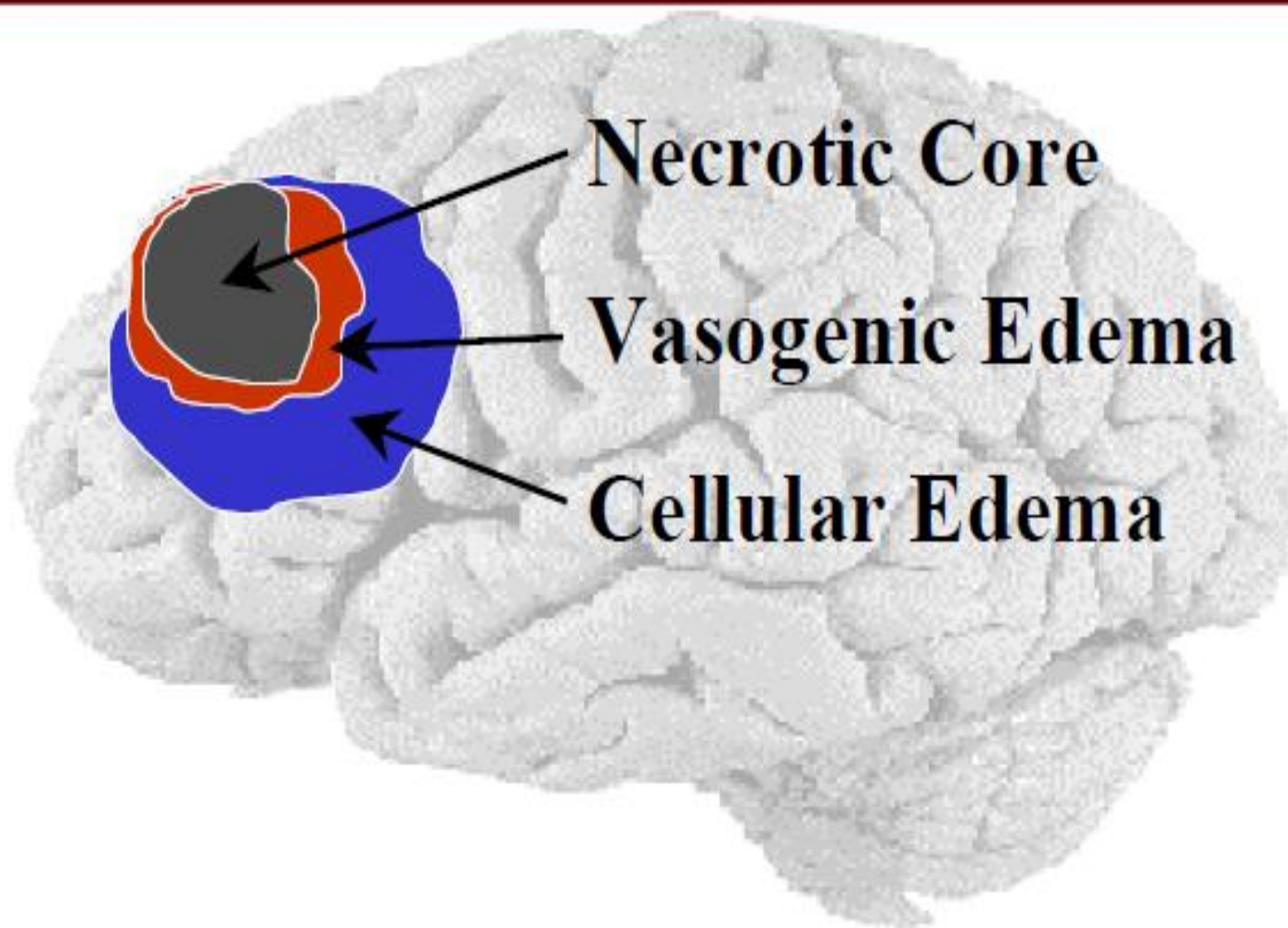
DWI MRI



ADC map

# Edema

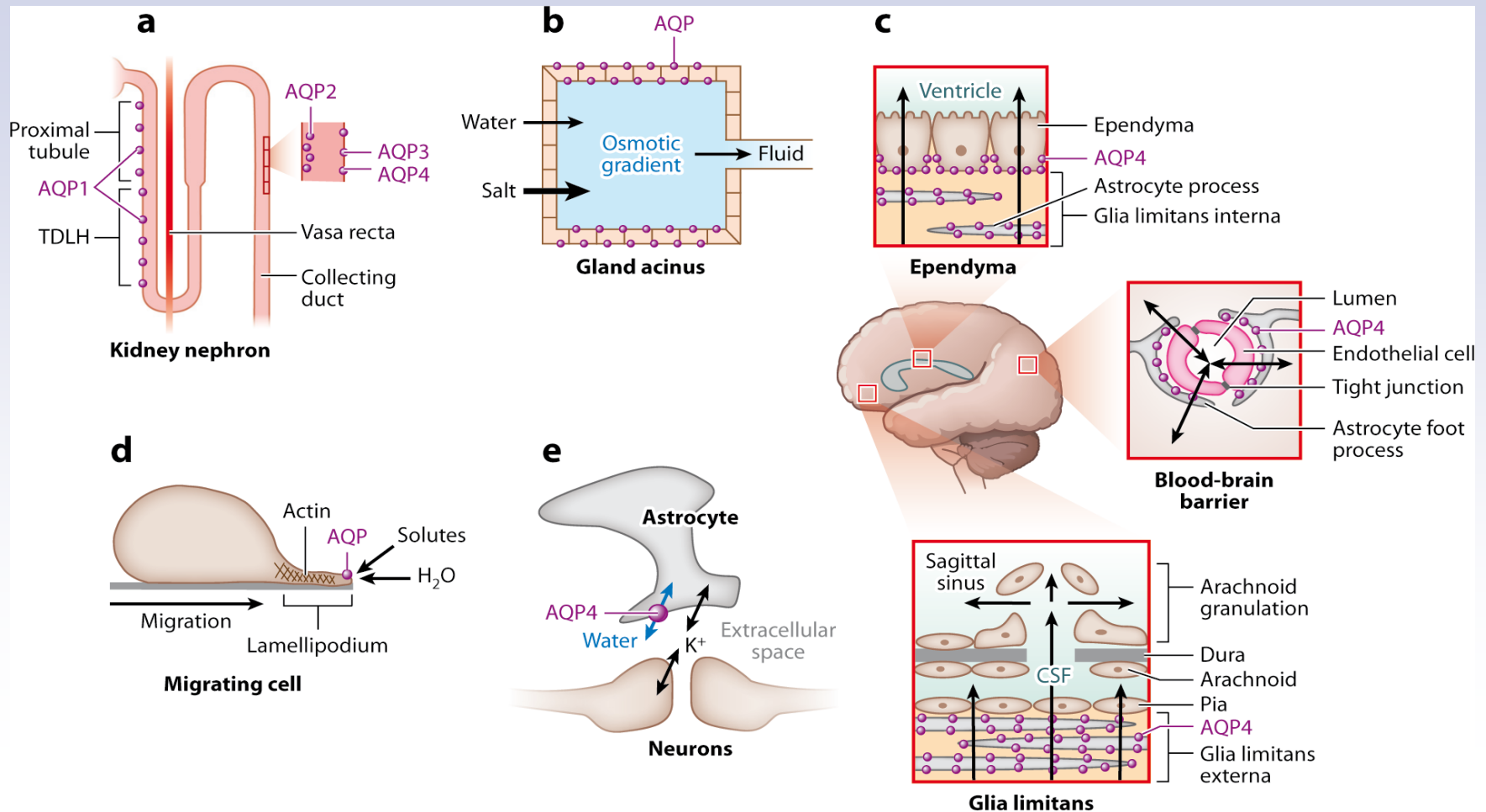
- Predominantly Cytotoxic edema in TBI
- MRI studies ADC decreased in perifocal and focal traumatic brain edema
- No evidence of BBB leakage at 24 hours
- Not related to CBF/ischemia
- Increased ADC in first 60 mins followed by decreased ADC from as early as 45 mins to 7 days post- injury
- Membrane depolarization activates ligand gated ion channels, triggers voltage gated channels
- Aquaporin-4 channels - water conducting protein in astrocyte foot processes adjacent to blood vessels



# AQUAPORIN CHANNELS

- Tetrameric water channels assembled at the cell membrane, or inside the cell (AQ6)
- 13 homologs in mammals, variable tissue distribution depending on physiological function and mediates movement of water and small solutes, such as glycerol across membranes according to osmotic gradient and differences in hydrostatic pressures
- 3 Functional Groups:
  - Water selective – AQP0,1, 2, 4, 5, 6 – permeable to water
  - Aquaglyceroporins - AQP3,7,8 – permeable to water, glycerol, urea
  - Neutral solute channels - AQP9 and 10 – water, glycerol, urea, purines, pyrimidines, and monocarboxylates
- CNS: AQP1,4,9 with AQP4 is the most abundant and expressed in borders between brain parenchyma and major fluid compartments

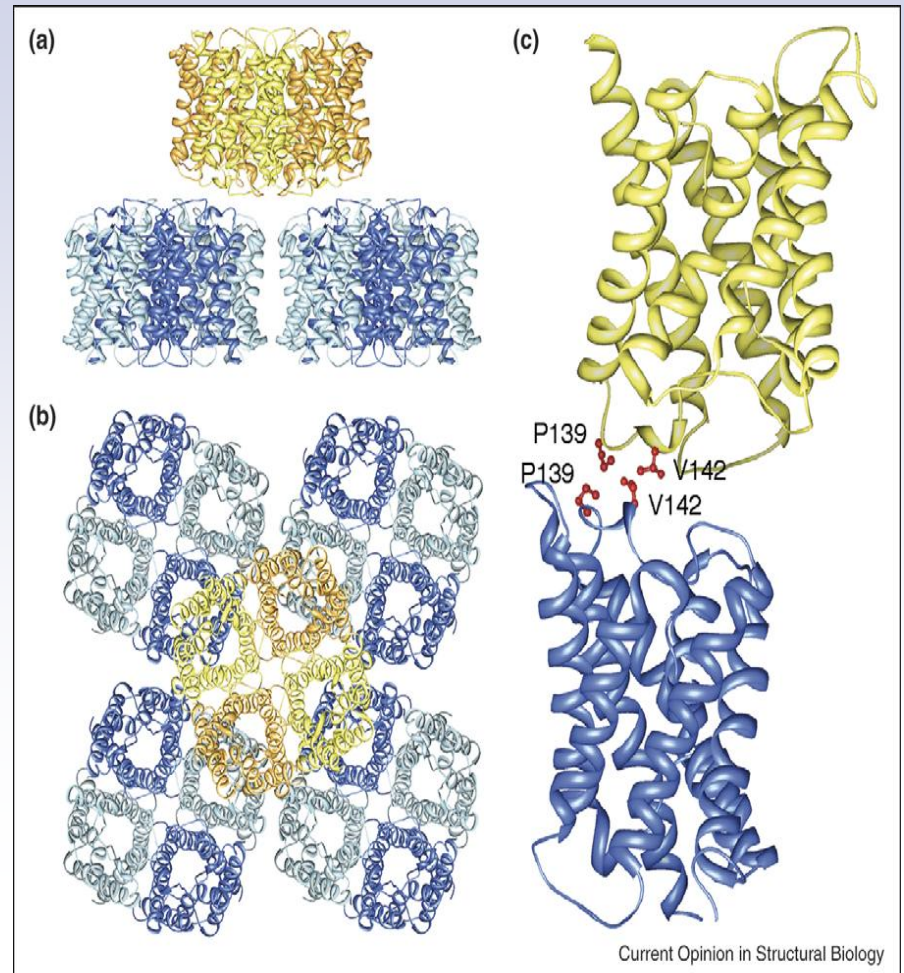
# ROLES OF AQPs



AR Verkman AS. 2012.  
 Annu. Rev. Med. 63:303–16

# Aquaporin 4 Channels

- bidirectional high capacity water channels
- expressed at astrocyte foot processes in the CNS
- blood-brain barrier/brain-CSF barrier
- Animal studies: AQP4 deficient mice had significantly reduced cerebral edema and better survival in a water intoxication model
- Human studies identified an AQP4 polymorphism associated with increased severity of cerebral edema after MCA occlusion



# AQP4

- Levels of expression are not constant but functionally regulated
  - Increased in brain regions where BBB is disrupted following injury, ischemia or tumor
- Regulated at level of RNA transcription and channel assembly
- Multiple phosphorylation sites and kinases have been implicated but the precise regulation of expression of these receptors remains unclear
- Brain water homeostasis – deficiency in mice reduces brain swelling in cytotoxic edema, and mediated by physiological neuronal activity
- But worsens outcome in vasogenic edema
- Likely facilitates redistribution and absorption of excessive brain fluid
- Functional Interplay between AQPs and Ion channels

# Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke

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ANDREW W. BOLLEN<sup>4</sup>, PAK CHAN<sup>2</sup> & A.S. VERKMAN<sup>3</sup>

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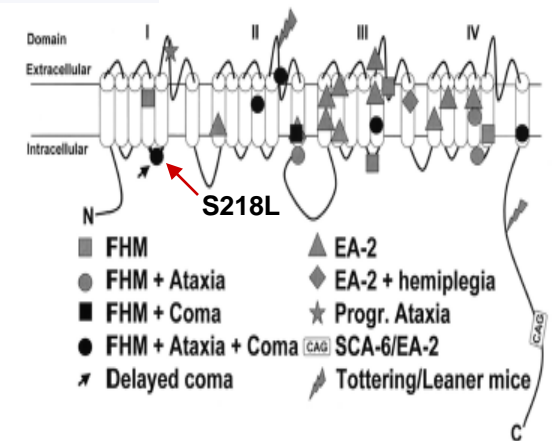
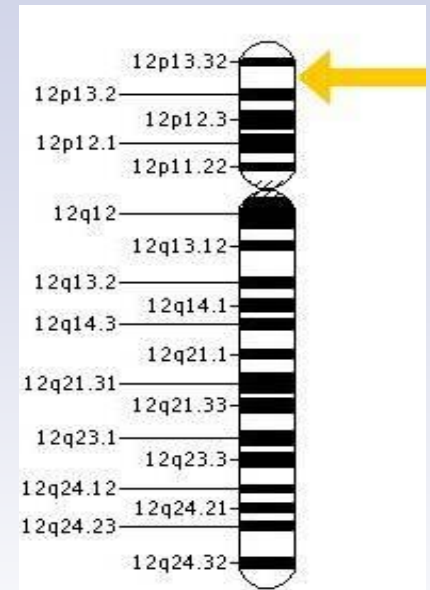
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- Human studies
- DNA analysis of 188 ethnically diverse cohort
- Identified 4 novel single nucleotide polymorphisms
- I128T, D184E, I205L and M224T
- Reduced water permeability

# CACNA1 gene mutation

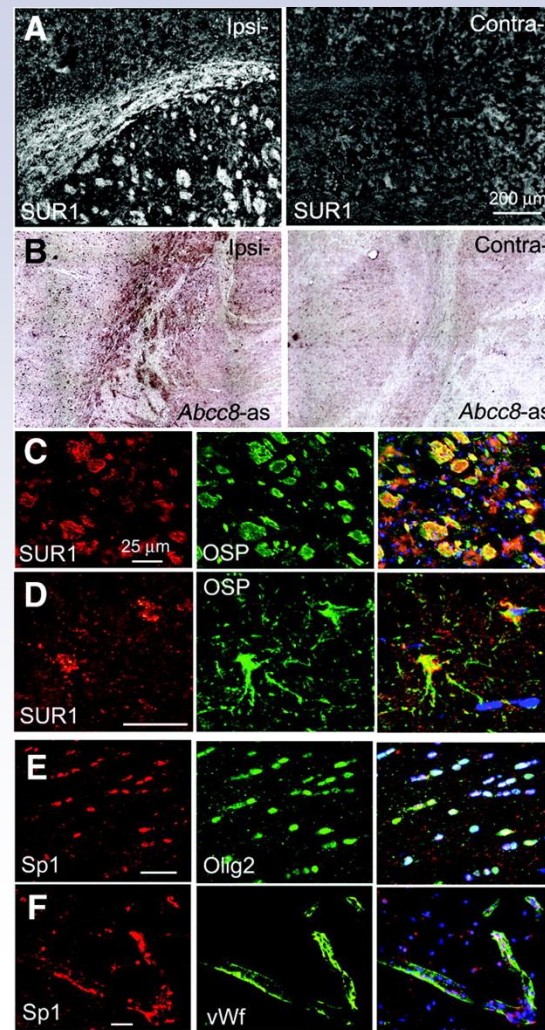
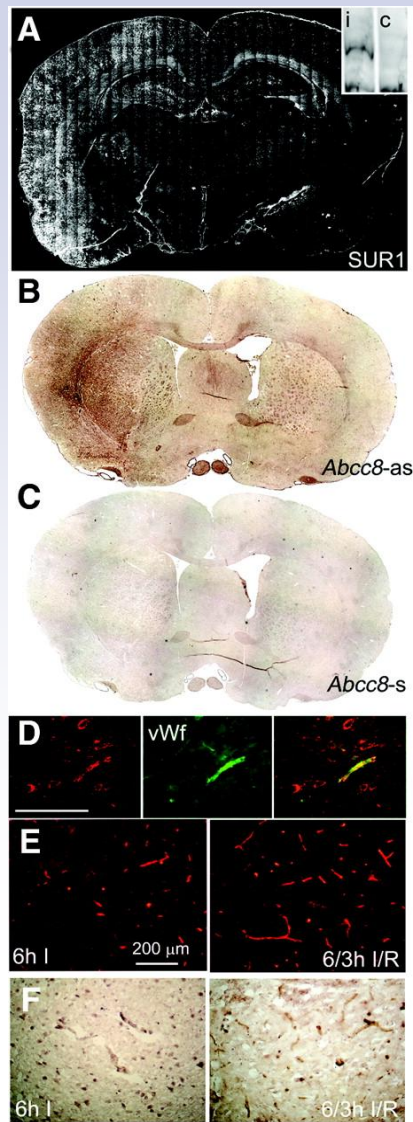
- Ion conducting pore forming  $\alpha 1A$  subunit of voltage dependent P/Q type neuronal calcium channels
- Involved in modulating neurotransmitter release like glutamate, monamines
- Missense mutation (C-to-T/Serine for Lysine at codon 218) in small intracellular loop between 4th and 5th transmembrane segments of first domain of  $\alpha 1A$  subunit
- S218L mutation has been found in patients with familial hemiplegic migraine, seizures and delayed cerebral edema after trivial head trauma
- Lowers threshold of cortical spreading depression, enhancing excitotoxicity



# SULFONYLUREA 1 RECEPTOR

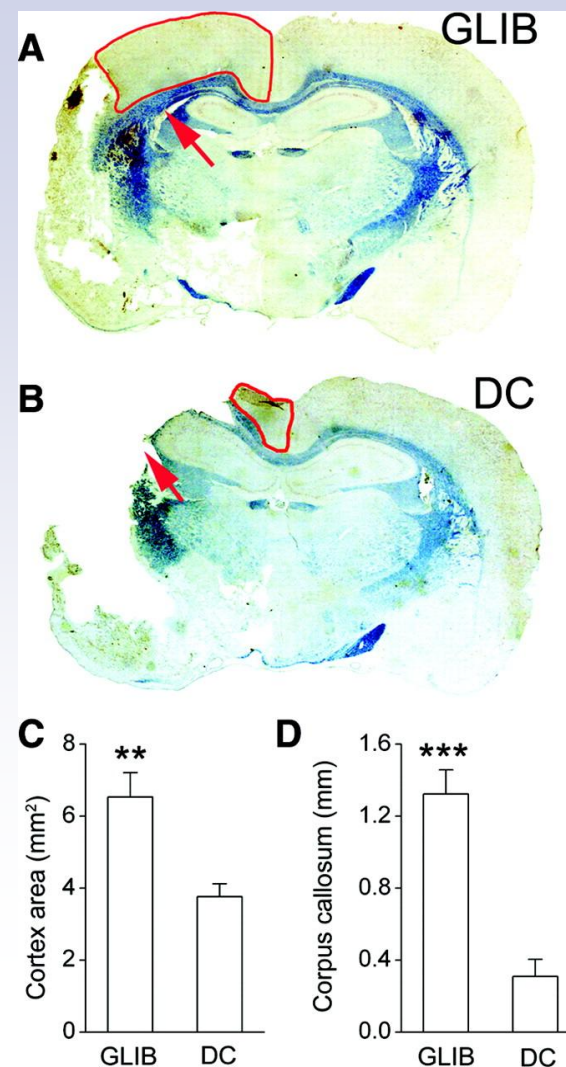
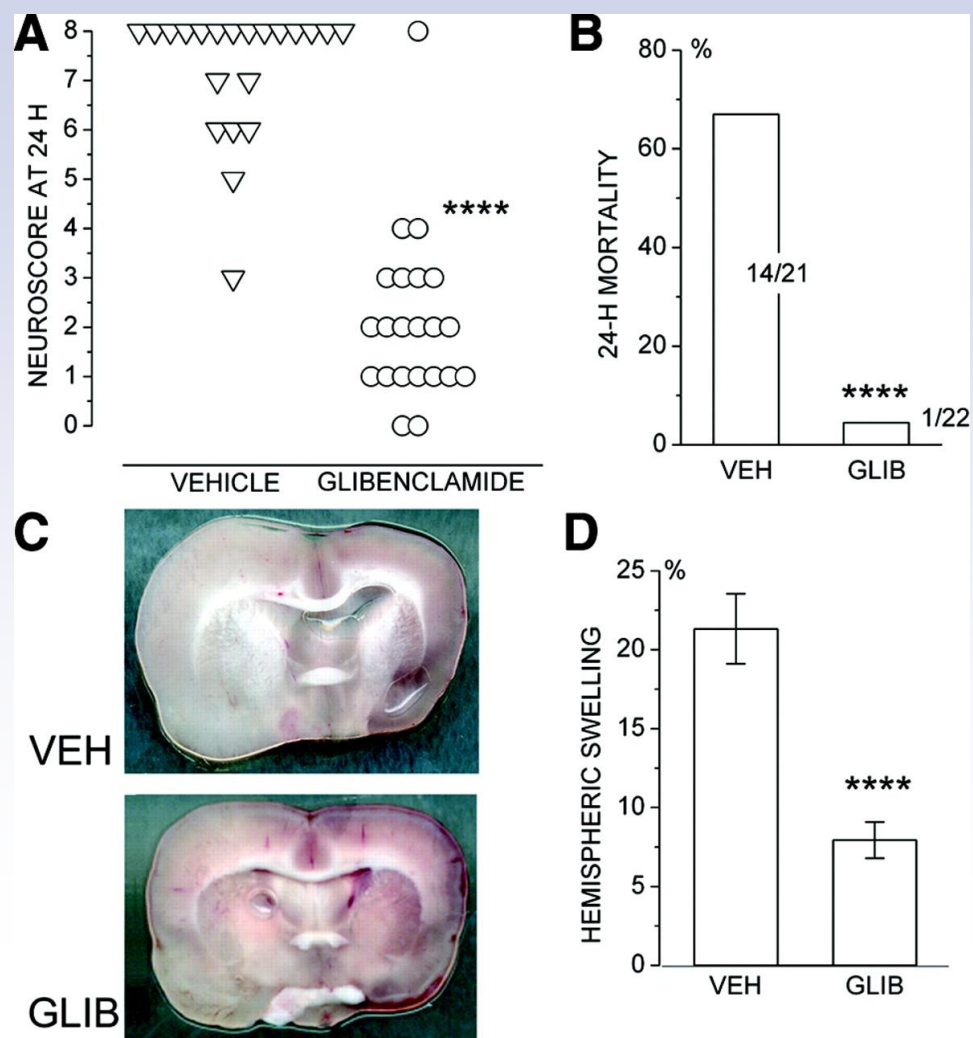
- SUR1 regulatory subunit involved in forming pore forming subunits of K-ATP channels
- Regulates SUR1/TRPM4 a nonselective cation channel that requires calcium and is activated by ATP depletion
- Causes cell depolarization and cell blebbing cytotoxic edema
- Glibenclamide/Glyburide is an antagonist

# SUR1 is transcriptionally upregulated in white matter.



Simard J M et al. Stroke 2010;41:531-537

# Glibenclamide improves 24-hour end points in a stroke model with 6-hour I/R.



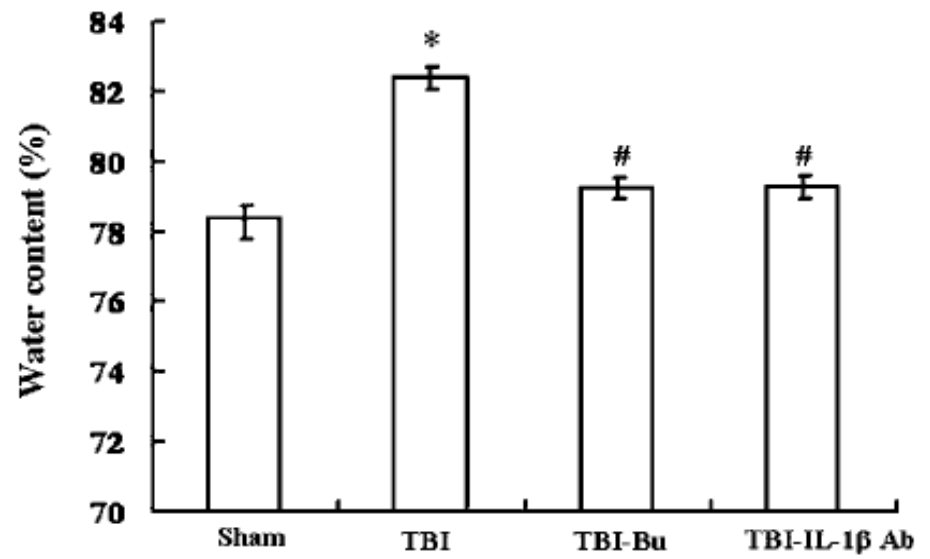
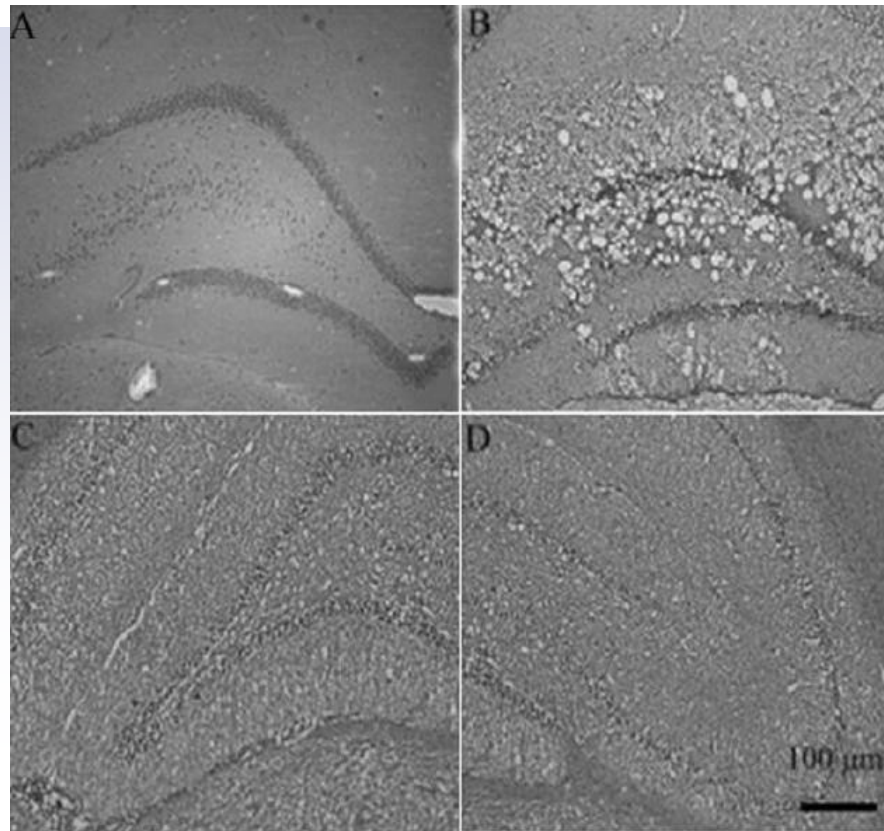
Simard J M et al. Stroke 2010;41:531-537

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# NKCC1

- Co-transporter protein
- Expressed in the luminal surface of endothelial cells
- Modulates Cl<sup>-</sup> in neurons, glia, etc
- Upregulated in ischemia
- Mediated by Glutamate and K<sup>+</sup> – that stimulate NKCC1 activity in neurons and neuroglia

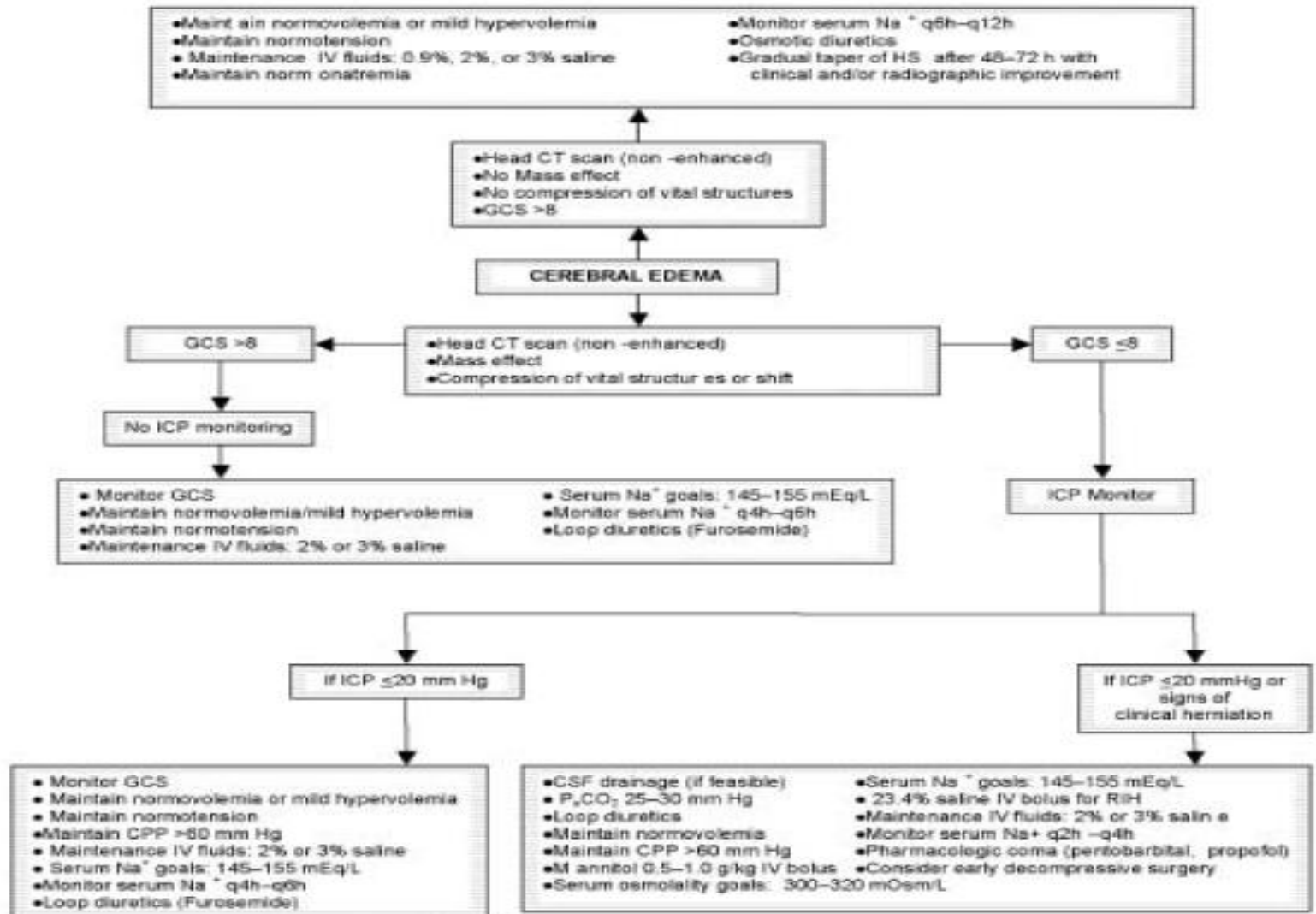
# Bumetanide administration attenuated traumatic brain injury through IL-1 overexpression



**Figure 3:** Photomicrographs showing morphology of hippocampal neurons in rats of sham control (A), TBI (B), TBI with bumetanide (15 mg/kg, i.v.) treatment (C) or TBI with IL-1 $\beta$  antibody (5  $\mu$ l, i.c.v.) (D). As compared to the control group, rats with TBI showed neuronal swelling and shrinkage, followed by neuronal loss 24 hours after TBI. Administration of bumetanide and IL-1 $\beta$  significantly attenuated this TBI-induced neuronal loss

[Neurol Res 2007; 29: 404–409]

# CURRENT THERAPIES



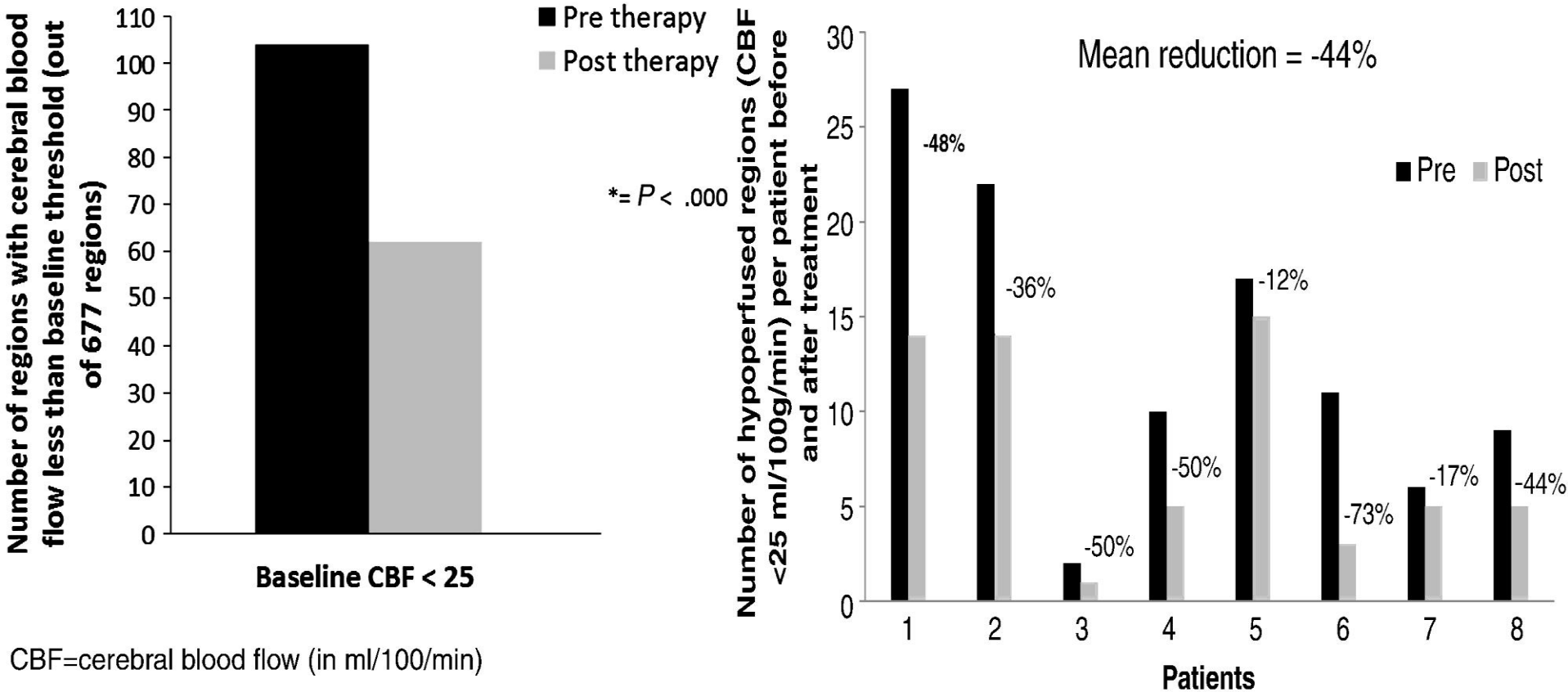
# Effect of osmotic agents on regional cerebral blood flow in traumatic brain injury☆☆☆

Michael T. Scalfani MSCI<sup>a</sup>, Rajat Dhar MD<sup>a,b</sup>, Allyson R. Zazulia MD<sup>a,c</sup>,  
Tom O. Videen PhD<sup>a,c</sup>, Michael N. Diringer MD, FCCM<sup>a,b,\*</sup>

<sup>a</sup>Department of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA

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<sup>c</sup>Department of Radiology, Washington University School of Medicine, St Louis, MO 63110, USA



# Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II):



Guy L Clifton, Alex Valadka, David Zygun, Kathy Harshman, Adam Conley, Ava Puc, James N Scott, Howard Yonas, David O O

## Summary

Age (years)
GCS score 5-8
GCS score 3-4
Non-reactive pupils*
Surgical lesion removed in first 24 h after injury
Prehospital hypotension†
Prehospital hypoxia‡
Injury severity score
Abbreviated injury severity score for head
Positive blood alcohol§
First temperature (°C)¶

	Hypothermia (n=52)	Normothermia (n=45)	p value
Serum sodium (mmol/L)	143 (5)	143 (6)	0.80
Serum potassium (mmol/L)	3.6 (0.3)	3.8 (0.2)	0.0005
Blood urea nitrogen (mmol/L)	4.3 (2.9)	3.9 (1.4)	0.28
Serum creatinine (µmol/L)	74 (36)	72 (18)	0.66
Prothrombin time (s)*	15 (2)	14 (3)	0.73
Partial thromboplastin time (s)†	34 (7)	31 (5)	0.004
Haemoglobin (g/L)	110 (10)	110 (10)	0.28
Platelet count (cells per µL)‡	189 (77)	209 (74)	0.2
Serum magnesium (mmol/L)§	0.8 (0.1)	0.8 (0.1)	0.46
Partial pressure of brain oxygen <6 mm Hg	19 (39%)	18 (45%)	0.55
Partial pressure of arterial carbon dioxide (mm Hg)¶	36 (4)	37 (2)	0.75
Partial pressure of arterial carbon dioxide <30 mm Hg	43 (83%)	28 (62%)	0.02
Serum glucose (mmol/L)	7.6 (2.0)	7.1 (0.6)	0.12

Data are mean (SD) or number (%). Mean values were calculated for each patient who had a value recorded from the time of admission until discharge from the intensive care unit. Mean values are not corrected for the duration of intensive care stay or the number of values collected for each patient. \*Data missing for 11 patients in the hypothermia group and 12 in the normothermia group. †Data missing for two patients in the hypothermia group. ‡Data missing for two patients in the hypothermia group. §Data missing for one patient in the hypothermia group. ¶Not corrected for temperature (alpha stat).

**Table 4: Laboratory findings**

Data are mean (SD) or number (%). GCS=Glasgow coma scale. \*Data missing for three patients in the hypothermia group and one in the normothermia group. †Data missing for four patients in the hypothermia group and two in the normothermia group. ‡Data missing for four patients in the hypothermia group and two in the normothermia group. §Data missing for 23 patients in the hypothermia group and 16 in the normothermia group. ¶Data missing for one patient in the normothermia group.

**Table 1: Demographics and baseline characteristics**

haematomas (n=28)							
Hypothermia (n=15)	5 (33%)	0.44 (0.22-0.88)	0.02	2 (13%)	0.35 (0.08-1.50)	0.16	
Normothermia (n=13)	9 (69%)	..	..	5 (39%)	..		

Data are number (%). RR=relative risk.

**Table 2: Outcome and mortality rates**

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ght be *Lancet Neurol* 2011; 10: 121-29

Died			
p value	n (%)	RR (95% CI)	p value
..	20 (21%)	..	..
0.67	12 (23%)	1.30 (0.58-2.89)	0.52
..	8 (18%)	..	..
..	13 (19%)	..	..
0.09	10 (27%)	2.88 (0.87-9.57)	0.08
..	3 (9%)	..	..
..	7 (25%)	..	..

# Pentobarbital Coma For Refractory Intra-Cranial Hypertension After Severe Traumatic Brain Injury: Mortality Predictions and One-Year Outcomes in 55 Patients

*Gary T. Marshall, MD, Robert F. James, MD, Matthew P. Landman, MD, Patrick J. O'Neill, PhD, MD, FACS, Bryan A. Cotton, MD, FACS, Erik N. Hansen, MD, John A. Morris, Jr., MD, FACS, and Addison K. May, MD, FCCM, FACS*

**TABLE 1.** Injury Severity and Mortality for All TBI Patients

Patient Group	All Head Injury AIS $\geq 3$ (n = 4,934)	ICP Monitor Placed (n = 611)	Pentobarbital Coma (n = 55)
Mean ISS	26.8 $\pm$ 12.3	37.0 $\pm$ 11.2	38.0 $\pm$ 9.7
Mean AIS head	3.8 $\pm$ 0.8	4.7 $\pm$ 0.6	4.8 $\pm$ 0.4
Mortality	17.3%	33.2%	60%

**TABLE 2.** ICP and Selected Laboratory Data for Patient with RICH Treated With PBC (n = 55)

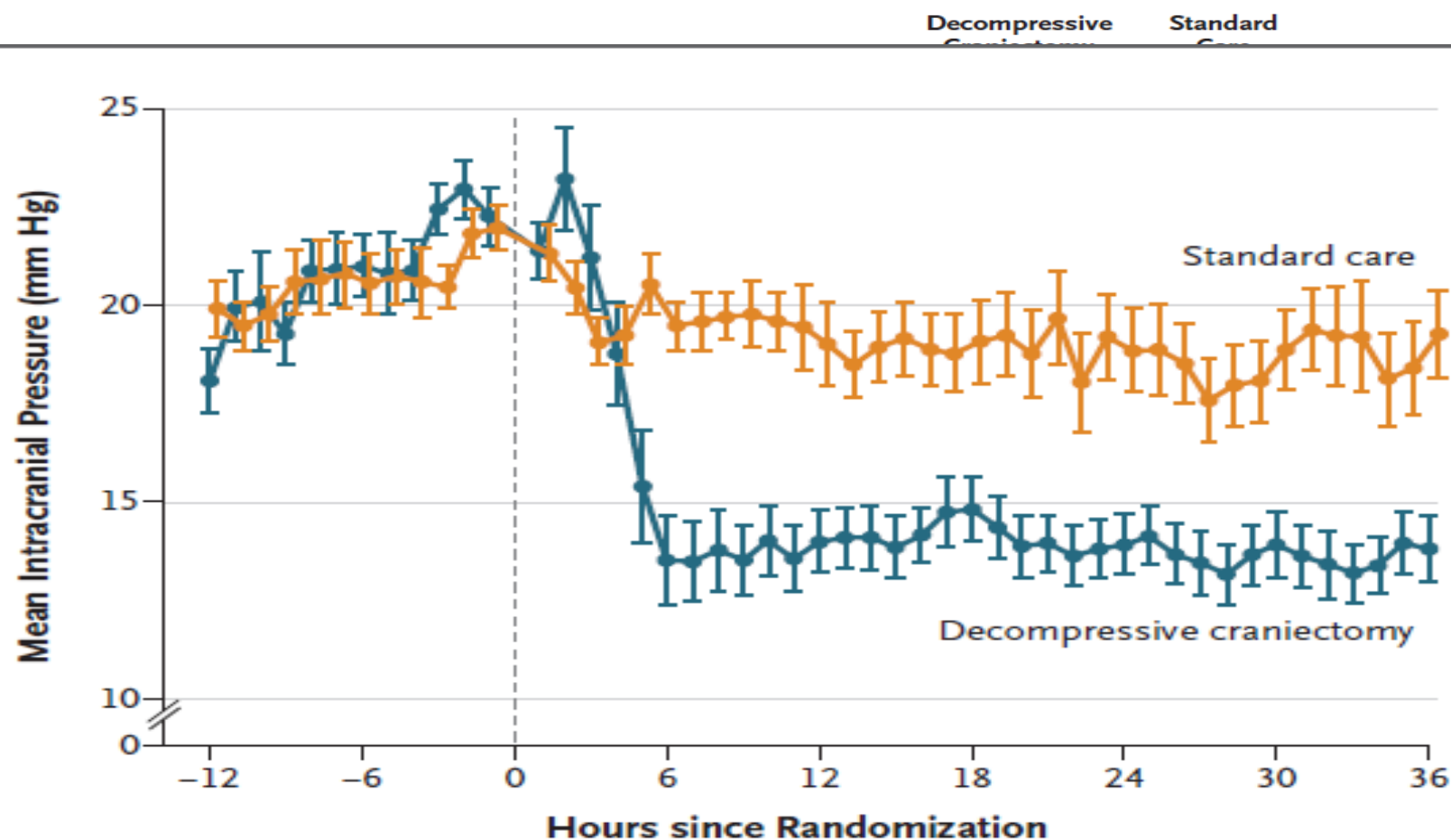
	Median	Interquartile Range
Opening pressure at ICP monitor placement	25 mm Hg	18–40
Highest ICP before pentobarbital	51 mm Hg	40–64
Lowest CPP before pentobarbital	40 mm Hg	30–47
Sodium before pentobarbital	149 mmol/L	144–155
Osmolarity before pentobarbital	314 mOsm/L	305–321

**TABLE 4.** Functional Outcome at 1 Year in 19 of 22 Survivors

Glasgow Outcome Score	Description	Criteria	Patients at 1 Yr (n)
5	Good recovery	Able to return to work or school	8 (42%)
4	Moderate disability	Able to live independently; unable to return to work or school	5 (26%)
3	Severe disability	Able to follow commands; unable to live independently	0 (0%)
2	Vegetative state	Unable to interact with environment; unresponsive	6 (32%)
1	Dead		0 (0%)

**Table 1. Baseline Characteristics of the Patients.\***

D



**Figure 1. Intracranial Pressure before and after Randomization.**

Shown are the mean measurements of intracranial pressure in the two study groups during the 12 hours before and the 36 hours after randomization. The I bars indicate standard errors.

# NOVEL THERAPIES

**Table 1** Novel targets to treat cerebral edema

	NKCC1	SUR1/TRPM4	Vasopressin-receptor
Location	Neurons, neuroglia, endothelium, choroid plexus	Neurons, neuroglia, endothelium	Basolateral membrane of the cells lining the collecting ducts of the kidneys
Activation	ATP	Depletion of ATP	Vasopressin
Specific antagonist	Bumetanide	Glyburide (glibenclamide)	Conivaptan
Function	Loads sodium and chloride into cells to maintain level of $[Cl^-]_i$	Conducts monovalent cations	Absorption of free water in collecting tubule of kidney

- NKCC1 – cotransporter inhibited by bumetanide
- SUR1/TRPM4 – nonselective cation channel causing depolarization and cell blebbing, upregulated in TBI, ischemia - NCT01268683
- Decreases absorption of water in collecting tubules – FDA approved for euvolemic hyponatremia

## A pilot study of the role of CACNA1 and AQP4

Raphael Carandang, MD<sup>1,3</sup>; Susanne Muehlschlegel, MD, MPH<sup>1,2,3</sup>; Cynthia Ouillette, RN<sup>1</sup>; Wiley Hall, MD<sup>1,3</sup>; Robert H. Brown Jr. MD DPhil, PhD<sup>1</sup>

<sup>1</sup>Departments. of Neurology, <sup>2</sup>Anesthesia/Critical Care and <sup>3</sup>Surgery, University of Massachusetts Medical School, Worcester, MA



### BACKGROUND

Cerebral edema is a significant predictor of poor outcome in traumatic brain injury. The pathophysiology, cellular mechanisms and predictors of post-traumatic edema are still unelucidated. Cytotoxic mechanisms and Blood-CSF-Brain barrier dysfunction are involved and secondary ischemia, loss of ion homeostasis and neurotransmitter excitotoxicity have been implicated. Current treatments are of unproven benefit particularly for functional outcome so there is an urgent need to investigate the pathophysiology, identify predictors and develop new medical therapies. The exponential growth in genetic information has led to studies that have implicated specific genes and channels in the pathophysiology of post-traumatic injury edema.

### CANDIDATE GENES

CACNA1 gene on chromosome 19p13 encodes for the main ion conducting, pore forming  $\alpha 1A$  subunit of voltage dependent P/Q type neuronal calcium channels and is involved in modulating release of neurotransmitters including monoamines and glutamate. A missense mutation (C-to-T that substitutes serine for lysine at codon 218 of the first domain of the  $\alpha 1A$  subunit) has been reported in patients with familial hemiplegic migraine, early seizures and delayed fatal cerebral edema from minor trauma (ESCEATH). Animal studies have reported it lowers the threshold for cortical spreading depression, affecting calcium homeostasis and enhancing neurotransmitter excitotoxicity.

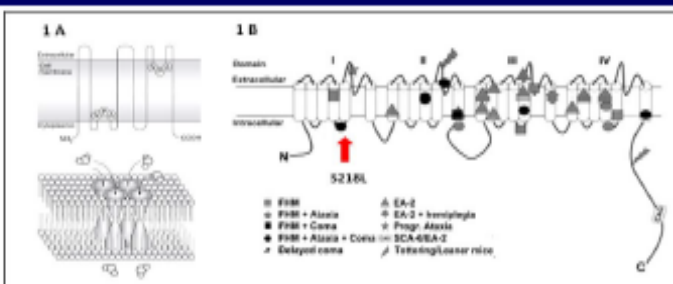


Figure 1A. Aquaporins have six transmembrane domains and two extracellular loops that form a water-transporting pore. (from Nat Clin Pract Endocrinol Metab 2006; 4: 627-634) Figure 1B. Localization of the novel S218L mutation in the 1A subunit of the P/Q-type calcium channel causing delayed cerebral edema and coma after a minor head trauma (arrow). The mutation is located in the small cytoplasmic between the fourth and fifth segments of the first domain of the protein. (from Kore ES et al. Ann Neurol 2001; 49: 753-760)

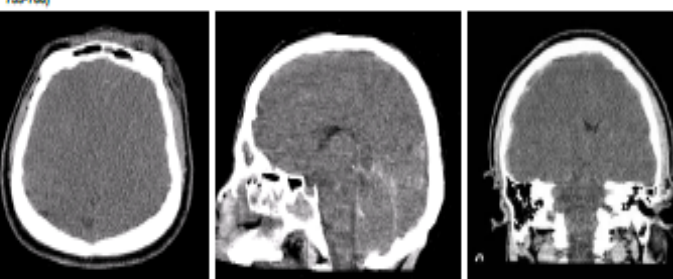


Figure 2. CT scan with diffuse cerebral edema and brainstem herniation. Note obliteration of cisterns and absence of grey-white differentiation

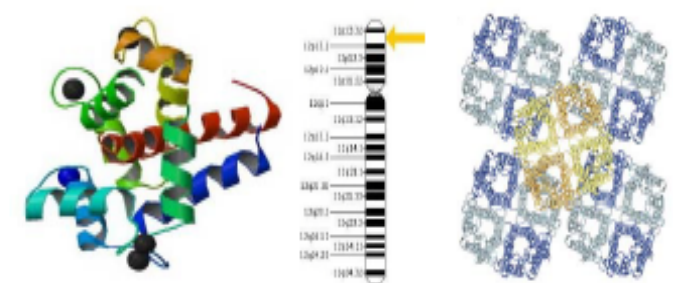
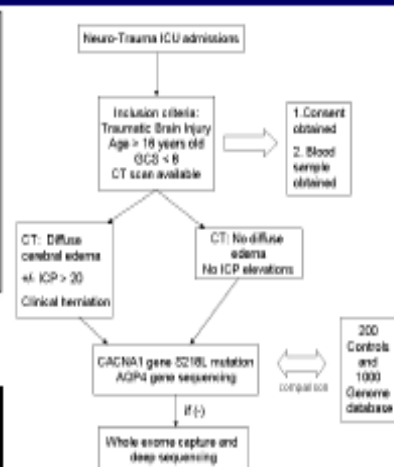


Figure 3. CACNA1 gene, Chromosome 19p13, Aquaporin crystallography model.



### SUMMARY

We hypothesize that The CACNA1 gene missense mutation S218L and AQP4 polymorphisms will be over-represented in patients with post-traumatic cerebral edema. Our Specific Aim is to perform full exon sequence analysis of these two genes in 20 well-defined cases of excessive cerebral edema. Our long term goal is to systematically investigate genetic variants as determinants of risk of excessive cerebral edema. It is hoped that this will further elucidate secondary mechanisms of injury specifically in the formation of post-traumatic edema and lead to targeted therapies in the future.

### Disclosures

#### Financial support:

- Dr. Carandang: Worcester Research Foundation Grant 2011
- Dr. Muehlschlegel: American Heart Association Scientific Development Grant 09302030002
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Aquaporin-4 gene on chromosome 18q11.2-12.1 encodes the Aquaporin-4 protein (AQP4) water channel which is a bidirectional high capacity water channels expressed in astrocytic foot processes in the central nervous system at the blood-brain barrier and brain-cerebrospinal fluid barrier and is thought to be critical for brain water homeostasis. Experimental studies showed that AQP4 deficient mice had significantly reduced cerebral edema and better survival in a water intoxication model. Recent human studies have identified an AQP4 polymorphism associated with increased severity of cerebral edema following MCA occlusion.

### METHODS

Severe TBI Patients admitted to the Neurotrauma ICU will be screened; CT scans reviewed for diffuse cerebral edema. Consent will be obtained and blood samples drawn for DNA extraction. Gene mutation analysis will be performed with full exon sequencing of AQP4 and CACNA1 genes. To validate identified mutations, we will cross-reference the 1,000 Genome Database and use Taqman primers to amplify the novel variants in a set of 200 controls. Results from cases and controls will be analyzed with the Pearson chi-square.

### References

- Manley GT et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. Nature Med 2003; 9: 159-163
- Kieffer I. et al. The role of aquaporin-4 polymorphisms in the development of brain edema after middle cerebral artery occlusion. Stroke 2008; 39: 1333-1335
- Stam A. et al. Early seizures and cerebral edema after intracranial trauma associated with the CACNA1A S218L mutation. J Neuro Neurosurg Psych 2009; 8: 1125-9

# Hypothesis and Specific Aims

- The CACNA1 gene missense mutation S218L and AQP4 polymorphisms will be over represented in patients with post-traumatic cerebral edema
- Perform full exon sequence analysis of these 2 genes in 20 well defined cases of excessive cerebral edema

# Research Design and Methods

- Clinical Cohort and Phenotype
  - Prospective outcome study of moderate to severe TBI
  - Data points, Functional outcomes 3 & 12 months
- Blood samples
  - DNA extracted from white blood cells
- Gene Mutation analysis (Dr. Brown's lab)
  - Full sequencing of all exons of the AQP4 and CACNA1 genes
  - Cross-reference with 1,000 genome database
  - Use Taqman primers to amplify novel variants in 200 controls

# Conclusion

- Traumatic Cerebral edema has severe clinical consequences
- Highly predictive of death and poor outcome
- Normal Brain function necessitates the maintenance of a highly regulated electrical osmotic microenvironment
- BBB and BCSFB are complex barrier systems that include multiple ion channels and co-transporters

# Conclusion

- Vasogenic edema results from barrier breakdown and initiates multiple pathways of damage
- Cytotoxic edema is the major component of post-traumatic cerebral edema
- Aquaporin 4 channels modulate cytotoxic edema and may attenuate vasogenic edema
- Current treatments include Osmotherapy, Pentobarbital coma, Hypothermia and surgical therapies but trials are negative

# Conclusion

- Possible therapies developed from channel modulators some are in ongoing clinical trials
- Multiple therapy trials

# FUTURE DIRECTIONS

- Better outcome studies
- Surgical trials
- Channel research
- AQP4 and human genetic studies
- Imaging studies/Perfusion studies
- Microdialysis/PET/SPECT
- New Therapies



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**THANK YOU!**  
**Worcester Foundation**