Brain Edema
From the Laboratory Bench to the Bedside

Hong Kong Neurosurgical Society
Monthly Wednesday Morning Meeting
8th December 2010
Peter Woo
Chairman: Dr. KY Chan
Pathophysiology
The Role of Corticosteroids
Novel therapies
Pathophysiology
Swelling vs. Edema

Swelling: $\uparrow$ volume occupied by a given mass e.g. by a tumor, blood or edema.

Addition of a new constituent into the extracellular space of the brain i.e. requires active blood flow.

Brain Edema

Excessive accumulation of absolute cerebral tissue water content in the intracellular and/or extracellular spaces\(^1\).

ECS: 12-19% of brain volume\(^2\)

- Vasogenic
- Cytotoxic
- Interstitial (hydrocephalic)\(^4\)

\(^2\) Go KG. The normal and pathological physiology of brain water. Adv Tech Stand Neurosurg 1997;23:47-142
Starling’s Law and Brain Edema

Driving force

Hydrostatic pressure gradient + Osmotic pressure gradient

Permeability pore

Ion channels + Reverse pinocytosis
Endothelial tight juncitons

Astrocyte
# Causes of Brain Edema

<table>
<thead>
<tr>
<th>Vasogenic</th>
<th>Cytotoxic</th>
<th>Hydrocephalic (&quot;Interstitial&quot;)</th>
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<tbody>
<tr>
<td>Brain tumor</td>
<td>Vascular Early hypoxia Early ischemia</td>
<td>Obstructive</td>
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<tr>
<td>Vascular Late hypoxia Late ischemia</td>
<td>Traumatic</td>
<td>Communicating</td>
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<tr>
<td>Traumatic</td>
<td>Infection</td>
<td></td>
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<tr>
<td>Infection Meningitis Encephalitis Abscess</td>
<td>Metabolic Hyponatremia Hyperammonemonia Hyperbilirubinemia Diabetic ketoacidosis Uremia</td>
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</table>
Starling’s Principle of Edema Formation

- The driving force: the sum of the hydrostatic and the osmotic pressure gradients.
- The permeability pore: the passages through and between the BBB endothelial cells.

Vasogenic edema
- ↑ intraventricular pressure
- Trans-ependymal movement
- Paraventricular tissue
- Extracellular

Interstitial edema
- ↑ intraventricular pressure
- Trans-ependymal movement
- Paraventricular tissue
- Extracellular

Vasogenic edema
- Commonest type
- ↑ BBB permeability / BBB breakdown
- Trans-endothelial movement
- White matter
- Extra-cellular

Cytotoxic edema
- Failed ATP-ion pump
- Breakdown of ion gradients
- Trans-membranous movement
- Grey matter first
- Intracellular-Extracellular
Vasogenic Edema

- Primary disturbance: endothelial dysfunction
- Increased vascular permeability of the BBB.

Incompetent BBB

Influx of solutes and fluid through an incompetent BBB into the extracellular space

Tumor-related Brain Edema
Capillary ultrastructural abnormalities

Paracrine signal pathways
VEGF
NO
PGE$_2$

Aquaporin expression

Macrophage infiltration

Normal Capillary Ultrastructure

Normal tight junction

Smooth basal lamina
Normal

Normal TJ
Smooth BL
Normal sealing strands

Meningioma

Thinned endothelium + fenestrations
Increased number of pinocytic vesicles
FISH studies for GBM microvessels

- Decreased expression of function of adhesion proteins leads to tight junction opening and edema in astrocytomas and GBM\(^1\).
- Adenocarcinomas do not express occludin\(^2\).

Paracrine Signal Pathways: VEGF

VEGF binds to VEGFR-1 and -2
Tyrosine kinase mediated downstream cell signaling
↓
Stimulates tumor cell mitosis, angiogenesis and vascular permeability

- VEGF 1000 times more potent than histamine
- Upregulation of VEGF in edema associated tumors: GBM, meningiomas and metastases
- Phosphorylation of occludin impairing its function
- Topical application of VEGF induces endothelial fenestration

3 Stummer W. Mechanisms of tumor-related brain edema. Neurosurgical Focus 2007;22(5):E8 1-7
4 Roberts WG et al. Neovascularature induced by vascular endothelial growth factor is fenestrated. Cancer Res 1997;57:765-772
Phosphorylation of TJ Proteins

Differing VEGF Associations for Meningiomas and Gliomas*

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<tr>
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<th>Meningioma</th>
<th>Glioma</th>
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<tbody>
<tr>
<td>Correlation with VEGF mRNA and peri-tumoral edema</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>VEGF expression associated with tumor grade</td>
<td>N</td>
<td>Y (High grade x 50 more than low grade)</td>
</tr>
<tr>
<td>VEGF expression regulation</td>
<td>PDGF, EDGF, Estrogen</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>VEGF cell expression</td>
<td>All tumor cells</td>
<td>Peri-necrotic tumor cells</td>
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</table>

* References section
Aquaporins

- Transmembrane channel proteins highly selective for the transport of $\text{H}_2\text{O}$.
- Bidirectional flow.
- $\text{H}_2\text{O}$ transport by osmotic and hydrostatic gradients.

Distribution of Cerebral Aquaporins

Aquaporin-4

Endothelial astrocytic foot processes

AQP-4 Upregulation

Normal brain tissue

High grade glioma

Metastatic adenocarcinoma

Aquaporin-4 ameliorates Vasogenic Edema?
Bulk-flow in Tumor-related Edema

- Tumor associated edema propagates by bulk flow instead of simple diffusion.

- White matter resistance < grey matter

  - finger-like projections throughout white matter.

- Rate of edema fluid accumulation: \(0.5-3.2\text{ml/hour or 14-78ml/day}\)

- Speed of edema spread: \(1.9\text{mm/hour}\)


Brain Edema Fluid Resorptive Mechanisms medicated by AQP-4

Meningiomas and Peritumoral Edema

Up to 60% are associated with BE1.  

Risk factors:
- Size
- Location
- Histological subtype

Disintegration of the arachnoid layer between the tumor-brain interface
- Pial-cortical blood supply to tumor (?VEGF)

Meningiomas and Peritumoral Edema

Proposed mechanisms:
- Ischemia\(^1\)
- Venous congestion\(^2\)
- Excretory-secretory phenomena\(^3\)
- Hydrodynamic processes with leptomeningeal disintegration\(^4\)

Meningiomas and Peritumoral Edema

- Rare group of WHO Grade I meningiomas (3%): secretory
- Epithelial differentiation with intracellular inclusions of CCK, CEA, alpha-1 antitrypsin
- Incidence of surrounding edema 80%
- Edema encompassed the entire hemisphere in 64% of cases

“...arguably the greatest translational research contribution in the history of neurosurgery."  


Mice:
Circadian periodicity in brain uptake of fluorescein vs. reciprocal of adrenal corticosteroid rhythm.

Dogs and Galicich himself:
40mg dexamethasone via:
- Oral
- Intracarotid
- Intravenous
- Intramuscular

Cortisol levels same

October 1959:
Semicomatose hemiparetic patient with recurrent temporal GBM
→ improved limb power

Initial regimen: 10mg Q6h
Dose-response curve: maximum improvement with 4mg Q6h
Mechanisms of Action

- Not yet understood.
- ↓ edema formation. No effect on absorption.
- Increases capillary permeability within 1 hour.¹
- Reaches full effect within 24-72 hours.²

Promotion of BBB Stability
Astrocytes and Pericytes


Extra-GR pathways?
Arachidonic acid cascade
Peroxidative damage to cell membranes
Inhibits phospholipase A2
Single center double-blind RCT
96 patients with 8 weeks FU
Low dose (4mg/day) vs. high dose (16mg/day)

After 1 week: 4mg/day is as effective as 16mg/day in patients, with no impending signs of brain herniation, in terms of KPS.

Novel Therapies

- Corticotrophin-releasing factor (CRF)
  - Direct effect on BBB.
  - No ↑ in systemic adrenal corticosteroids.¹
  - Symptom improvement with reduced edema on MRI.²

- VEGF inhibitors

- COX-2 inhibitors
  - Rofecoxib as effective as dexamethasone in decreasing BBB permeability.⁴
  - Indomethacin improved KPS in 40% of patients.⁵

Stroke-related Brain Edema
Ionic edema occurs in the peri-infarct tissues i.e. in areas of perfused but severely ischemic tissues ("penumbra"). Relatively little edema within the infarct core.
Cytotoxic edema = Cellular edema = Oncosis = Oncotic volume increase

Cell

[Na\(^+\)] 14
[K\(^+\)] 157
[Ca\(^-\)] 0

Blood

[Na\(^+\)] 142
[K\(^+\)] 5
[Ca\(^-\)] 103

H\(_2\)O

ICM: Glial or neuron?
Edema and the Ischemic Brain

Cytotoxic edema ➔ Ionic ➔ Vasogenic

Primary drivers: \([\text{Na}^+]\)
Secondary participants: \(\text{H}_2\text{O}, [\text{Ca}^-]\)

↑ Sulfonylurea receptor-1 (SUR-1) regulated \(\text{NC}_{\text{Ca-ATP}}\) channel

↑ NKCC

↑ Aquaporin

↑ Transient receptor potential channel (TRPC)

\([\text{Na}^+]\)

\([\text{K}^+]\)

\([\text{H}_2\text{O}]\)


Scanning Electron Microscopy of Freshly Isolated Rat Astrocytes after NaN₃-induced ATP depletion

Neuron / astrocyte Necrotic Cell Death

$[\text{Na}^+]$ electrical gradient still preserved $\because$

- ICS $>>$ ECS
- $[\text{K}^+]$ bound to -ve charged intracellular proteins

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Cytotoxic edema ➔ Ionic ➔ Vasogenic

Ionic edema involves abnormal $[\text{Na}^+]$ transport with normal exclusion of protein by the “intact” BBB.

Precedes vasogenic edema by $\geq 6$ hours.

Endothelial dysfunction: breakdown of the BBB allowing passage of macromolecules e.g. albumin.

# Brain Edema Imaging Techniques

<table>
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<tr>
<th>Edema/ MRI sequence</th>
<th>DWI</th>
<th>ADC</th>
</tr>
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<tbody>
<tr>
<td>Cytotoxic</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Vasogenic</td>
<td>↑</td>
<td>↑</td>
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</tbody>
</table>

Ischemia-induced Vasogenic Edema

- Uncoupling of TJ: interendothelial gaps
- Endothelial cell retraction
- Phosphorylation of TJ proteins
- Basement membrane degradation

Blood

Brain

VEGF

Thrombin

MMP-9

MMP-2


Ischemia-induced Vasogenic Edema

**Driving force**
- Hydrostatic pressure gradient
- Osmotic pressure gradient

**Permeability pore**
- BBB breakdown

**Systemic BP**
- ICP
- All osmotically active molecules

**Astrocyte**
Timing of Decompressive Craniectomy?

Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial

Jeannette Hofmeijer, L Jaap Kappelle, Ale Algra, G Johan Amelink, Jan van Gijn, H Bart van der Worp, for the HAMLET investigators*

“...surgical decompression reduces case fatality and poor outcome... within 48 hours of stroke onset....no evidence...when it is delayed up to 96 hours after stroke onset.”

Early Decompressive Craniectomy?

**Vasogenic edema stage**
- BBB violated
- ↓ICP → ↑CPP
- Hydrostatic pressure major contributor to edema formation

**Ionic edema stage**
- BBB intact
- Hydrostatic pressure less important for edema formation
Intracerebral Hemorrhage

Hematoma retraction

- Few hours

Coagulation cascade
Thrombin induced BBB disruption

- 24-48 hours

RBC lysis
Hb and other degradation products
Inflammatory reaction

Peri-hematomatal Edema Not Associated with Ischemia

CBF in the ICH vicinity remains close to normal.1

Peri-hematomatal edema zone ATP levels up to 8 hours after ictus: normal.4


Peri-hematomatal Edema

**Vasogenic**
- Thrombin induced interendothelial gaps.
- Release of $\text{Fe}^{2+}$ released from heme. Catalyst for lipid peroxidation → free radical damage to endothelial cells

**Cytotoxic**
- Degradation products
  - $\text{Hb}$ inhibits $\text{Na/K} \text{ ATPase}$ activity.
  - Bilirubin disrupts ion transport and mitochondrial activity.
- Oxy-hb: vasospasm

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Iron chelator
- Can cross the BBB
- ↓ Hb induced Na/K ATPase inhibition
- ↓ Fe induced lipid peroxidation

↓ ICH brain edema in rats after intra-peritoneal deferoxamine infusion


Subarachnoid Hemorrhage

- Global cerebral edema
- 7-12% of SAH
- Significant independent predictor of mortality and poor outcome (adjusted OR 2.5).
  Death at 3 months 40% vs. 18%\(^1\).
- RBC degradation components
- Hyponatremia

Vasogenic edema

BBB breakdown

Global Ischemia

Vasospasm

“3H” therapy (loss of autoregulation)

↓ CBF

↑ ICP

↑ ICP

SAH

Cytotoxic edema

Ionic edema

Steroids for Stroke?

Arguments For...

- Animal studies: Cats: MCA infarction volume ↑ x6-fold size in controls. Rats: pretreatment ↓ brain H\textsubscript{2}O content in global ischemia.


- For ICH, only 3 studies. Only 159 patients.

Arguments Against...

- Cochrane Review: Several RCTs No beneficial effect. ↑ risk of complications.

Traumatic Brain Injury-related Edema
Brain Contusion

Rapid edema formation / “Malignant cerebral edema”

- Early (within 12-48 hours)
  \[ \uparrow \text{ICP} \]
  Contusion center

- Delayed (several days)
  ICP static
  Peri-contusional area: white matter


Cytotoxic edema
But often not severe enough to cause early mass effect
But [Na\(^+\)], [K\(^+\)], [Cl\(^-\)] not altered up till 12 hours post-trauma

Rapid disruption of the cell membrane
Homogenization of ICS and ECS contents

Vasogenic
But often delayed 24-48h after injury

Blood

Products of cellular metabolism e.g. FFA

[Na\(^+\)], [K\(^+\)], [Cl\(^-\)]

[Idiogenic osmoles\(^-\)]

Other Mechanisms for TBI related-Edema

Ischemia:  
↓ ATP

Traumatic membrane depolarization:  
Neurotransmitter release

PG release from injured vessels / platelets:  
↑ capillary permeability  
Vasoconstriction → ischemia

Indomethacin COX-2 inhibitor → limits vasogenic edema?


Aquaporin-4 in TBI Edema

- Role unknown
- Contusion core: ? ↑¹ OR ↓²
- Peri-contusional tissue: ? ↓¹ OR ↑²
- New drug target?
  Acetazolamide reversibly inhibits AQP-4 → limits cytotoxic edema.

Steroids for TBI?

Largest multi-center, international RCT.
239 centers, 49 countries.

IV methylprednisolone vs. placebo.
Loading dose of 2gm over 1 h then 48h maintenance dose.

Increased risk of death at 2 weeks (RR 1.18, p=0.001)\(^1\) and 6 months (RR 1.15, p= 0.001).\(^2\)

No increased risk of disability at 6 months.


General Management of Brain Edema

- Proper head and neck position
- Airway protection and ventilation
- Meticulous BP control
- Normothermia
- Tight glucose control / nutritional support
- Pain control and sedation
- Seizure prophylaxis
- Osmotherapy: mannitol; the hypertonic saline debate
- Loop diuresis
- Cerebral metabolic suppression
<table>
<thead>
<tr>
<th>Predominant edema type</th>
<th>Intra-axial Brain Tumors</th>
<th>Ischemic Stroke</th>
<th>Brain Contusion</th>
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<tbody>
<tr>
<td>Time transition from Ionic to Vasogenic edema (hours)</td>
<td>Vasogenic</td>
<td>Ionic-vasogenic</td>
<td>Ionic-vasogenic</td>
</tr>
<tr>
<td>Primary disturbance</td>
<td>Inter-endothelial gapping</td>
<td>↓ cellular [Na(^+)] extrusion</td>
<td>(&gt;6)</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Hydrostatic pressure</td>
<td>Osmotic-hydrostatic pressure</td>
<td>Osmotic-hydrostatic pressure</td>
</tr>
<tr>
<td>VEGF</td>
<td>✔ ✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>AQP-4</td>
<td>✔ ✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>✔ ✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>✔ / ✗</td>
<td>✗</td>
<td>✔</td>
</tr>
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</table>


Conclusions

Brain edema, irrespective of underlying origin, is a major cause of mortality and death.

Full understanding of the pathophysiology of brain edema has yet to be achieved.

An ideal agent that selectively prevents the formation or promotes the absorption of edema fluid with minimal side effects has yet to be discovered.

Agents targeting VEGF and AQP-4 are possible candidates.
Different VEGF Associations for Meningiomas and Gliomas