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Malignant Cerebral Edema After Large Anterior Circulation Infarction: A Review

*Allison E. Arch, MD, MPH**
Kevin N. Sheth, MD, FAHA

Address
*Department of Neurocritical Care and Emergency Neurology, Yale University School of Medicine, 15 York Street, LCI Suite 710, New Haven, CT 06510, USA
Email: allison.arch@yale.edu

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Opinion statement

Malignant infarction implies a large middle cerebral artery (MCA) stroke that leads to rapid clinical deterioration and edema formation, and can be associated with hemorrhagic transformation, herniation, and poor functional outcomes, including death. Malignant edema is brain edema formation that occurs in the setting of large territory infarction. This review discusses the most recent efforts in diagnosis, prevention, and management of malignant edema in acute ischemic strokes.

Introduction

Malignant infarction implies a large middle cerebral artery (MCA) stroke that leads to rapid clinical deterioration and edema formation, and can be associated with hemorrhagic transformation, herniation and poor functional outcomes, including death. Malignant edema is the brain edema formation that occurs in the setting of large territory infarction (Fig. 1). The mortality rate in malignant infarction can be as high as 80 %, most commonly from transtentorial herniation following malignant edema formation [1, 2]. This is contrasted with the mortality rate of ischemic stroke of all subtypes, which is ~ 15 %, and with the mortality of MCA territory strokes in general, which ranges from 5 % to 45 % [3, 4]. Given the exceptionally high mortality rate associated with malignant edema formation, its prevention, early detection and treatment are a focus of great interest in stroke research.

Subtotal or complete MCA infarctions are common strokes, and occur in up to 10 % of anterior circulation stroke patients [5]. The etiology can be thrombotic or embolic, and the occlusion typically involves the inter-

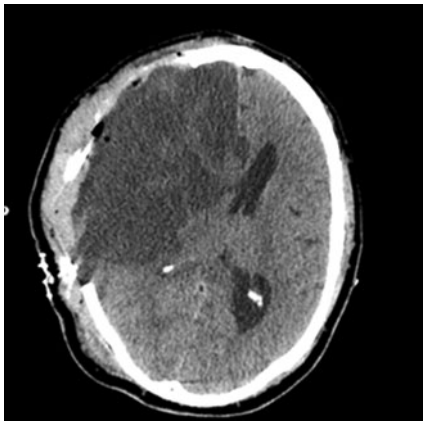

Figure 1. Malignant edema; computed tomography (CT) scan of a 56-year-old man with a large anterior circulation stroke, taken 48 hours after onset of symptoms and 24 hours after decompressive surgery. Note the significant midline shift and mass effect on the lateral ventricles.

nal carotid artery or the proximal MCA [6]. Initial stroke scale scores on the National Institutes of Health stroke scale (NIHSS) can exceed 16–20 if the dominant hemisphere is involved. Scores are typically greater than 15–18 in the nondominant hemisphere [7–9]. Progressive clinical deterioration occurs within 1–2 days, and malignant edema develops shortly thereafter and can occur up to 5 days poststroke [10].

Until recently, novel therapeutic targets for the treatment of malignant edema had not been identified. Treatment had largely focused on managing symptoms as they arise rather than on preventing edema from occurring [11]. However, multicenter clinical trials are now examining methods of edema prevention. Patient management may eventually shift toward early identification of malignant infarction and prevention of malignant edema rather than on symptomatic treatment. This review discusses the most recent efforts in diagnosis, prevention, and management of malignant edema in acute ischemic stroke.

Mechanism of edema formation

Edema formation is a complex and fluid process and does not fit perfectly into the well known categories of cytotoxic and vasogenic edema. These categories are helpful though, at understanding the basic processes that occur following brain injury in ischemic stroke.

Ischemic injury leads to alterations in ion gradients, primarily cessation of the primary active transport Na - K - ATPase channel. When this occurs, passive transporters attempt to maintain cellular processes. This leads to intracellular accumulation of sodium in neurons and glial cells, then cellular swelling in what is classically termed "cytotoxic edema," and eventually passage of water into the extracellular space [12•]. The hyperintense signal on diffusion-weighted MRI occurs due to this restriction of water diffusion into and out of cells. Endothelial cell dysfunction then occurs and the integrity of the blood-brain barrier (BBB) is disrupted. A vasogenic edema process then occurs as fluid leaks from the intravascular space. Patients are now also at risk of hemorrhagic transformation due to the increased permeability of the BBB [13].

Other ion channels have also been studied in edema formation. NKCC1 is an active transporter involved with the Na - K - Cl channel. It mediates sodium entry into cells and is activated following ischemic injury, representing a potential target for therapeutic intervention [14]. Aquaporin-4 (AQP4) is the most abundant water channel in the brain and is involved in edema formation after strokes [15]. The SUR1/TRPM4 channel is activated after ischemic injury, which results in the influx of cations and cellular swelling. There is evidence that this channel is upregulated following stroke, and it has become an important target to inhibiting edema formation. SUR1/TRPM4 channel activation leads to upregulation of an extracellular protease called matrix metalloproteinase-9 (MMP-9) [16]. An increase in MMP-9 occurs early after cerebral ischemia and is associated with the loss of microvascular integrity. Vascular permeability then occurs with the subsequent extravasation of serum components leading to brain edema. Inhibiting SUR1/TRPM4 may inhibit MMP-9 activation, thereby helping to prevent edema formation. These enzymes and channels are proposed targets for pharmacologic interventions to prevent malignant edema.

Diagnosis

Clinical and molecular markers

The goal in malignant edema management is to predict when it will occur or to diagnosis it early so that intervention can be timely and effective. A 2008 systematic review attempted to do this by identifying predictors of development of fatal brain edema in patients with MCA infarction. Twenty-three articles were included in this meta-analysis. The authors found a total of 12 statistically significant predictors of life-threatening malignant edema. The most significant were infarct size, involvement of other vascular territories other than MCA, low perfusion levels in other vascular territories, and hemorrhagic transformation [17]. Increasing age was also cited as a predictor of malignant edema formation, although a more recent analysis did not demonstrate this effect [18].

Decreased consciousness is a predictor of neurologic deterioration in ischemic stroke and leads to a 50 %–70 % likelihood of mortality despite maximal medical management [19]. A drawback to these clinical predictors is that it can take days to fully appreciate the size of the stroke, to see hemorrhagic transformation, or to witness increased lethargy. By that time it can be too late to effectively intervene.

Perhaps a more effective tool would be finding a molecular brain marker that could immediately predict which patients will suffer from malignant edema. A study in 2005 tried to determine which molecular markers of endothelial damage could predict brain edema following a large hemispheric stroke. Forty patients with malignant MCA infarction and 35 controls with massive MCA infarctions were matched by stroke severity. Malignant infarction was defined by neurologic deterioration combined with midline shift and compression of the basal cisterns on CT. On admission, plasma concentrations of multiple potential biomarkers were measured, including glutamate, glycine, gamma-aminobutyric acid, IL-6, IL-10, TNF-alpha, MMP-9, and cellular fibronectin (c-Fn). Both MMP-9 and c-Fn were significantly

higher in patients with malignant MCA infarction, with c-Fn, an antigen which mediates the interaction between the endothelium and red blood cells, having the highest accuracy overall [20].

These and other biomarkers have been the subject of many studies on both the early diagnosis of stroke in the acute setting, and also on predicting outcome, hemorrhagic transformation, and malignant edema. Timely tests for these biomarkers do not currently exist but may become available as more data links their levels to the formation of malignant edema [21•]

Imaging

There is ongoing debate over which imaging modality best identifies malignant edema following stroke. CT scan is fast and usually readily available. Recent studies have focused on perfusion CT (PCT) imaging to predict the development of malignant MCA infarction. A 2011 study using clinical signs of herniation to define malignant MCA infarction found that the best predictor of a malignant course was the ratio of cerebral blood volume (CBV) to CSF volume on PCT. Fifty-two patients were included in this study. When the imaging was done on admission, the CBV:CSF ratio had a sensitivity, specificity, positive and negative predictive values all greater than 95 % for malignant stroke [22].

Increased blood-brain barrier permeability on PCT has also been associated with malignant infarction [23, 24]. In addition, MRI within 6 hours of symptom onset has been studied. A prospective cohort study found that a diffusion-weighted imaging (DWI) lesion volume >82 ml predicted malignant infarction with a high specificity of 98 % but a low sensitivity of 52 % [25].

In clinical practice, there is not one imaging technique that is used to predict fatal outcomes in stroke. This may be due to a number of factors. PCT is widely available in acute care settings, but it has a number of potential pitfalls. It has a high false negative rate in stroke, particularly in smaller infarcts. There are also known stroke mimics such as tumor, and the PCT software varies across institutions which can limit its precision [26]. On the other hand, rapid MRI scans are not readily available in many institutions, and they can be cumbersome, expensive and sometimes unsafe or unfeasible in certain patients.

More large-scale studies are needed regarding imaging modalities, biochemical markers, and other markers that will help guide clinicians to determine which patients with MCA infarctions will develop a malignant course. In the future, clinicians will likely combine biomarker serum tests with rapid imaging in order to best determine which patients are at risk for worse outcomes.

Neuroprotective strategies

While vessel opening with thrombolytics remains the primary initial goal in stroke, efforts to combine this with neuroprotective strategies have come to the forefront in stroke research. Tissue injury in stroke leads to a cascade of biochemical events that result in neuronal cell death and edema formation. Neuroprotective efforts to prevent the ensuing damage have been studied with mixed results. To date there have been many successful molecules reported in experimental and animal models, but most all have failed in clinical trials [27, 28]. However, currently there

are some exciting new neuroprotection trials, which are already enrolling patients with ischemic strokes.

MMP-9

- As mentioned above, MMP-9 is an enzyme that is activated in acute stroke, and functions to promote BBB disruption and edema formation. High levels are a negative prognostic factor in acute stroke, and peak levels are found at 24 hours poststroke. Animal models have demonstrated that inhibiting MMP-9 leads to reduced stroke volumes [29].
- The common antibiotic minocycline has been shown to have many neuroprotective properties including inhibiting MMP-9. It was demonstrated to be safe in two small clinical trials. It was also shown to lower levels of MMP-9 in stroke patients. Efficacy data are now needed, using function or mortality as outcomes [30, 31].
- Edaravone, a free-radical scavenger, has also been shown to inhibit MMP-9. It is commonly given in Japan and China in combination with thrombolytic therapy in acute ischemic stroke. Its effect on preventing malignant edema in humans is so far unknown [32, 33].

Glyburide

- Glibenclamide (glyburide in U.S.) is a selective inhibitor of the sulfonylurea receptor 1 (Sur1) on the SUR1/TRPM4 channel, which leads to decreased edema formation by inhibiting activation of MMP-9.
- A retrospective observational trial found that glyburide led to improved functional outcomes in ischemic stroke patients with diabetes. An additional retrospective analysis showed a decreased risk of hemorrhagic transformation following stroke. These patients were taking glyburide prior to their stroke and were continued on it during their poststroke hospitalization [34, 35].
- A phase I trial with glyburide in stroke has been completed with results pending.
- The Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) trial is an ongoing randomized, multicenter, prospective, double-blind trial studying the effects of glyburide in patients with acute, severe, anterior circulation ischemic stroke. The primary outcomes are 90-day functional outcome and the need for decompressive surgery. Patients are currently being enrolled (clinicaltrials.gov NCT01794182).

Hypothermia

- Hypothermia as a neuroprotective agent following cardiac arrest has been well established, and is becoming standard care for certain disease states in the U.S. So far there have been only preliminary studies in ischemic stroke. The proposed mechanism of hypothermia is multifold, and includes inhibiting neurotransmitter release, decreasing inflammatory markers such as MMP-9, disrupting apoptotic

pathways, and decreasing free radical generation. All serve to minimize edema formation [36, 37].

- The Intravascular Cooling in the Treatment of Stroke 2/3 Trial (ICTuS2/3) is currently recruiting patients into a large multicenter trial to determine whether the combination of thrombolysis and hypothermia is superior to thrombolysis alone for the treatment of acute ischemic stroke (clinicaltrials.gov NCT01123161). Its relative safety was demonstrated in phase I trials [38, 39].

Corticosteroids

- Corticosteroids are not routinely used as a neuroprotective strategy in malignant MCA infarction. They have not been found to improve functional outcomes in survivors or to prevent death. These conclusions are based on a systematic review of eight randomized trials including 466 people [40]. It should be noted that the trials were small and under-powered, and their results could not be pooled because the outcome scales differed.

Progesterone

- Progesterone exhibits neuroprotective effects by rebuilding the BBB and decreasing edema formation. Most research to date has focused on its use in traumatic brain injury, where it has been show to decrease 30-day mortality in a phase II randomized trial. Stroke data has so far been limited to animal models [41, 42].

Aquaporin 4

- Aquaporin-4 (AQP4) is a glial water channel expressed in astrocyte processes adjacent to cerebral capillaries. It has high water permeability and facilitates both cytotoxic and vasogenic edema formation. The role of AQP4 has been explored in several animal models, but human data is lacking [43].
- To date there are few AQP4 inhibitors that have been identified for clinical development. Vascular endothelial growth factor (VEGF) is closely related to AQP4 though, and researchers are starting to examine the role of VEGF in edema formation [44, 45].

Miscellaneous

- Several other targets for intervention have been identified in animal models and are theoretically plausible as targets for pharmacologic therapy. In one example cited above, the NKCC1 transporter is involved in the Na-K-Cl channel and is inhibited by the drug Bumetanide. Human trials are needed to study this agent further [46].

Treatments

Malignant edema can lead to increased intracranial pressure (ICP) and cause significant morbidity and mortality. When the ICP is elevated, there are

numerous management strategies for lowering it. The American Academy of Neurology (AAN) Stroke Guidelines currently recommend the same initial tools as those used in traumatic brain injury and intracranial hemorrhage, including hyperventilation, hypertonic saline and osmotic diuretics, intraventricular drainage of CSF, and decompressive surgery [47].

ICP measurement

- Initial signs of clinical deterioration from malignant edema include headache, vomiting, and alteration in mental status. As the ICP increases the patient may have papilledema; Cushing's trial of bradycardia respiratory depression, and hypertension; ophthalmoparesis; asymmetric pupils; and finally fixed and nonreactive pupils. These signs represent an emergency situation where timely intervention is critical.
- Increased ICP is not directly correlated with herniation and death. Poor outcomes can occur in the settings of a "normal" ICP as well, the mechanism of which is still being studied. It may be that local tissue shifts are a more essential process than globally increased ICP. A stroke or other lesion can result in tissue shift and cause herniation. This can occur from local edema and would not necessarily manifest as increased ICP.
- In patients with traumatic brain injury, evidence does not suggest that tight control of ICP leads to improved outcomes. Basing treatment decisions on the clinical examination plus neuroimaging findings is just as effective as ICP monitoring with goal intracranial pressures less than 20 mm Hg [48]. The same is likely true in malignant infarction patients. Frequent neurological exams in an ICU setting combined with serial imaging studies can be used instead of ICP monitors. Despite this, in tertiary care settings with access to neurosurgeons, ICP monitors such as external ventricular drains (EVDs) are often placed and can provide useful information in addition to the clinical exam and neuroimaging.

Osmotic agents

- Mannitol and hypertonic saline are the two osmotic agents most commonly used in the U.S. to decrease ICP. They work by drawing water back into the vasculature where it can be excreted by the kidneys. An additional proposed mechanism is that mannitol also leads to vasoconstriction, thus reducing blood volume and decreasing ICP [49]. Despite being widely used for decades, there are few randomized controlled trials evaluating the use of osmotic agents in stroke patients.
- A Cochrane review of mannitol in stroke found only three randomized trials and concluded that there was not enough evidence to support its use in stroke patients. The outcomes of disability, death, or change in clinical condition were not different between mannitol-treated groups and controls [50].
- For hypertonic saline, a 2013 meta-analysis of 23.4 % saline in neurocritical care settings found a >50 % reduction in raised ICP

following administration of this high osmolarity solution. Eleven clinical studies were included in the analysis but there was only 1 small randomized study, and most of the included patients had actually suffered a subarachnoid hemorrhage or TBI, not an ischemic stroke [51].

- There are few head-to-head studies comparing mannitol and hypertonic saline. A meta-analysis published in 2011 found that hypertonic saline solutions were more effective than mannitol in controlling episodes of elevated ICP. In 112 patients with 184 episodes of elevated ICP, the overall relative risk in favor of hypertonic saline was 1.16 (1.00–1.33). Only nine of these patients were ischemic stroke patients, though [52].
- A more recent small study compared 20 % mannitol with 23.4 % saline in nine ischemic stroke patients who deteriorated clinically and had >2 mm midline shift on imaging. Neither agent led to changes in cerebral blood flow or blood volume [53].
- In clinical practice, both mannitol and hypertonic saline are acceptable as first line agents for treating malignant edema. While their benefit has yet to be shown in the literature—particularly with mannitol—they are both likely effective.
- Mannitol can be nephrotoxic, so hypertonic saline is a better choice in patients with renal insufficiency. The mannitol dose can range between 0.5 gm/kg and 2 gm/kg, with higher doses given in worse situations. Hypertonic saline can worsen congestive heart failure and should be used with caution in those patients. It typically comes in 1.5 %, 3 %, and 23.4 % solutions. In emergency situations, a small volume dose of 23.4 % is often used.

Decompressive surgery

- Decompressive surgery is currently the final treatment strategy that exists for malignant cerebral edema.
- The rate of craniectomy following ischemic stroke increased from 3.9 in 1999–2000 to 14.5 in 2007 2008. This increase is likely from the publication of multiple randomized controlled trials in 2007, which demonstrated improved survival and functional outcomes of surgical decompression after malignant infarction [54•].
- The AAN guidelines currently recommend surgical decompression for malignant edema as effective and potentially lifesaving [47].
- Mortality following surgical decompression in stroke is around 44 % in those >60 years of age. It is significantly less at 24 % in patients aged 18–59 years. This difference between age groups is largely erased when adjusting for factors such as length of stay, total hospital charges, chronic comorbidities, and medical complications [54•]. It is therefore not age itself that increases mortality but rather confounding variables that tend to be associated with age. These factors need to be taken into consideration when deciding whether to take a patient for decompressive surgery.

Table 1. Randomized controlled trials of decompressive surgery following malignant middle cerebral artery (MCA) stroke

Trial	Ages (y)	Number included	Intervention	Primary outcome measures	Results
DECIMAL	18–55	38 total Surgery: 20 Controls: 18	Surgery within 30 h after symptom onset	mRS score ≦3 at 6 mo and 1 y	6 mo: 25 % vs 5.6 % (P=0.18) 1 y: 50 % vs 22 % (P=0.10)
DESTINY	18–60	32 total Surgery: 17 Controls: 15	Surgery between 12 and 36 h	30-day mortality and mRS ≦ 3 at 6 mo	Mortality: 12 % vs 53 % (P=0.02) mRS 6 mo: 47 % vs 27 % (P=0.23)
HAMLET	18–60	64 total Surgery: 32 Controls: 32	Surgery within 96 h	Mortality and mRS score of 4–6 at 1 y	Mortality: 22 % vs 59 % (P=0.002) mRS 1 y: 75 % both groups (P=1)
Zhao, et al.	18–80	47 total Surgery: 24 Controls: 23	Surgery within 48 h	Mortality and mRS >4 at 6 mo	Mortality: 12.5 % vs 70 % (P=0.001) mRS 6 mo: 33 % vs 83 % (P=0.001)

DECIMAL early Decompressive Craniectomy In Malignant Middle Cerebral Artery Infarction, *DESTINY* Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery, *HAMLET* the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial, *mRS* modified Rankin score

- The DECIMAL, DESTINY, and HAMLET trials are the randomized controlled trials on surgical decompression for malignant infarction (Table 1). Each enrolled patients between the ages of 18–60 years. When the data were pooled, 93 patients were included in the analysis. The number needed to treat to prevent mortality was two, but this was irrespective of functional outcome. The number needed to treat to survive with a modified Rankin score of ≤3 was 4 [7–9, 55].
- Despite the low NNT numbers, if a patient survives their initial malignant infarction and decompressive surgery, there is still a significant chance they will have a poor functional outcome at 6 months [56•].
- A more recent RCT enrolled patients up to the age of 80 and showed similar outcomes to the pooled analysis above in a subgroup analyses of patients between the ages of 60–80 (Table 1) [57]. Studies are ongoing to evaluate the benefit of decompressive surgery in patients older than 60 years [58].
- Surgery was performed within 48 hours of stroke onset in the above trials. It is possible that with earlier diagnosis and intervention, outcomes can be improved. More studies are needed in order to determine this.

Conclusions

Malignant edema in large ischemic infarctions leads to high morbidity and mortality rates. This occurs despite treatment strategies that have existed for decades, namely osmotic diuretics, hypertonic saline, and decompressive surgery. A more thorough understanding of the pathophysiology of malignant edema is critical for determining new potential pharmacologic targets for edema prevention. This is starting to occur, and animal models studying

potential targets are plentiful. More recently, large multicenter clinical trials have started recruiting patients in order to study neuroprotective agents to prevent edema. The ICTuS 2/3 and GAMES-RP trials are two such examples, studying hypothermia and glyburide administration, respectively, following large strokes.

Decompressive surgery is effective at reducing poor outcome in malignant stroke patients. The mortality rate following surgery is still high, however, and when patients survive surgery they have a significant chance of poor long-term functional outcome. Instead of treating patients with surgery, our goal going forward should be to discover ways at predicting when malignant edema may occur so that we can prevent it from occurring in the first place. Then, early detection can combine with neuroprotection in order to offer patients with large strokes a multimodal management strategy. The ongoing studies of serum biomarkers, neuroimaging strategies, and neuroprotection are exciting and should offer innovative new strategies for patients with malignant infarctions.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Allison E. Arch declares that she has no conflicts of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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