Malignant MCA Infarction: Pathophysiology and Imaging for Early Diagnosis and Management Decisions

Wolf-Dieter Heiss

Max Planck Institute for Metabolism Research, Cologne, Germany

Key Words

Malignant MCA infarction · Ischemic tissue damage · Penumbra · Brain edema · CT-hypodensity · DW-MRI-lesion · PET tracer accumulation · Decompressive hemicraniectomy

Abstract

Background: Malignant middle cerebral artery infarction is a devastating condition, with up to 80% mortality in conservatively treated patients. The pathophysiology of this stroke is characterized by a large core of severe ischemia and only a relatively small rim of penumbra. Due to the fast development of irreversible morphological damage, cytotoxic edema occurs immediately in a large portion of the ischemic territory. The subsequent damage of the tight junctions leads to the breakdown of the blood brain barrier and vasogenic brain edema, resulting in space-occupying brain swelling. The progressive vasogenic edema reaches its maximum after 1 to several days and exerts a mechanical force on surrounding tissue structures leading to midline shift and tentorial herniation and finally brain stem compression and death. **Summary:** Early severe neurological symptoms – hemiparesis, gaze deviation, higher cortical signs – followed by headache, vomiting, papillo edema and reduced con-

sciousness may predict the deleterious course. Imaging supports the suspected diagnosis with hypodense changes on CT extending beyond 50% of the MCA territory. The size of the probably infarcted tissue and a midline shift on CT as well as the size of the lesion on diffusion-weighted MRI are predictive of a malignant course. Reduction of cerebral blood flow below a critical value and volume of irreversible tissue damage detected by positron emission tomography in the early hours after the stroke are indicative of progression to malignant infarction with increased intracranial pressure (ICP) and decreased tissue oxygen tension observed by multimodal neuromonitoring in the later course. Treatment options of malignant infarction include general measures to limit the extent of space-occupying edema, but these therapies have not been efficacious. Only surgical intervention with decompressive hemicraniectomy (DHC) was successful in relieving the effects of increased ICP and of the deleterious shifts of brain tissue. Several controlled clinical trials have proven the efficacy of DHC with a significant decrease in mortality and improved functional outcome. However, DHC must be performed early and with a large diameter, regardless of the age of patients, but in patients beyond 60 years, the higher likelihood of resulting severe disability should be taken into consideration. **Key Messages:** Malignant MCA in-

farction can be predicted early with a high sensitivity by neuroimaging. The early diagnosis is mandatory for DHC, which was shown to reduce mortality and improve functional outcome in several controlled clinical trials.

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Introduction

Ischemia involving large portions of a hemisphere may cause space-occupying cerebral edema leading to rapid neurological deterioration. The most serious condition involving the whole territory of the middle cerebral artery was termed ‘malignant MCA infarction’ [1] and it manifests itself with a severe hemispheric syndrome including hemiparesis, gaze deviation and higher cortical signs combined and followed by headache, vomiting, papillo edema and reduced consciousness. The life-threatening edema develops usually 1 to several days after the stroke and may cause midline shift, transtentorial herniation and death in up to 80% within the first week [2]. The annual incidence of this devastating condition is 10–20 per 100,000 people [3], females are more often affected and younger patients are more susceptible due to decreased potentially compensatory space within the intracranial cavity [4].

Evolution of Tissue Damage

The energy demand of the brain is rather high and therefore sufficient blood supply must be maintained constantly. If the normal cerebral blood flow is reduced below a certain level, reversible functional failure occurs; a further decrease of CBF below a lower level leads to irreversible morphological damage [5]. The tissue with perfusion values in the range between these limits is called the ‘ischemic penumbra,’ which is characterized by the potential for functional recovery without morphological damage, provided that local blood flow can be reestablished within a certain time window that is dependent on the residual flow [6].

During the acute phase at flows below the threshold of energy metabolism required for maintenance of basic housekeeping (~20% of preocclusion values) in the core tissue, injury is a direct consequence of the ischemia-induced energy failure. The disturbance of the energy-dependent ionic pumps leads to increase in intracellular sodium and extracellular potassium concentrations as well as calcium influx into cells. With the disturbed ionic equilibrium,

water is transported into the cells causing osmotic swelling. The final result is terminal depolarization of cell membranes; it is established within a few minutes after the onset of severe ischemia.

During the subsequent subacute phase, the irreversible damage expands into the areas around the core where flow ranges between 25 and 35% of preocclusion values until after several hours (usually approximately 6 h) the lesion has extended over all the area with critically reduced blood supply. A multitude of electrical and biological disturbances interact in the progression of irreversible cell damage in ischemia (review in [7]); peri-infarct spreading depression like depolarization play an important role in triggering and continuously stimulating this molecular/biochemical cascade of cell injury (reviews in [8]) and contribute to the growth of the infarct. Most of the biochemical and molecular processes suspected as potential key factors in the propagation of ischemic damage (review in [7]) still cannot be assessed in humans.

The transfer of the concept of the penumbra and of the progression of ischemic damage into imaging modalities is difficult, as most markers used in experimental studies necessitate invasive procedures. In order to follow these pathophysiologic changes, noninvasive imaging modalities are required, which provide quantitative maps of several important physiologic variables, including regional cerebral blood flow (rCBF), regional cerebral blood volume and regional cerebral metabolic rate of oxygen and glucose, and up to now only positron emission tomography (PET) is able to measure these variables repeatedly. Early PET studies in stroke have identified various tissue compartments within a brain territory compromised by ischemia (review in [9]). These PET studies allow the classification of 3 regions within the disturbed vascular territory: the core of ischemia with a flow <12 ml/100 g/min usually showing a transition into necrosis; a penumbra region with a flow between 12 and 22 ml/100 g/min of still viable tissue but with uncertain chances for infarction or recovery; and a hypoperfused area (>22 ml/100 g/min) not primarily damaged by the lack of blood supply. It has to be kept in mind that the condition of the tissue is changing with time; the extent of the penumbra and its conversion into infarction is a dynamic process, and irreversible damage spreads from the core of ischemia to its border.

Finally, a delayed phase of tissue injury evolves, which may last for several days or even weeks, in which secondary phenomena – vasogenic edema, inflammation, programmed cell death – may contribute to further progression of tissue damage.

Brain Edema

Ischemic brain edema can be differentiated into 2 pathophysiologically different types: an early cytotoxic type, followed after some delay by a late vasogenic type of edema. The cytotoxic type of edema is initiated at flow values close to 30% of control when stimulation of anaerobic metabolism causes an increase of brain tissue osmolality and, hence, an osmotically obliged cell swelling. At flow values below 20% of control, failure of the Na⁺/K⁺ pump leads to an influx of Na⁺ and progressive loss of the ionic gradient, resulting in membrane depolarization further enhancing intracellular osmolality and the associated cell swelling. In the absence of blood flow, cell swelling occurs at the expense of the extracellular fluid volume, leading to the shrinkage of the extracellular compartment, but not to a change in the net water content. The shift of fluid is reflected by a decrease of the apparent diffusion coefficient (ADC) of water, which is the reason for the increase of signal intensity in diffusion-weighted MRI (DW-MRI) [10]. However, if some residual blood flow persists, water is taken up from the blood and the net tissue water content increases. After vascular occlusion, this increase starts within a few minutes after the onset of ischemia and it causes a gradual increase in brain volume.

With the evolution of tissue necrosis and the degradation of basal lamina, the blood-brain barrier breaks down [11], and after 4–6 h, serum proteins begin to leak from the blood into the brain. This disturbance initiates a vasogenic type of edema, which further enhances the water content of the tissue. The exact mechanism through which ischemic injury disrupts the BBB is not fully understood, though active pinocytosis by endothelial cells appears to occur early, with the disruption of the tight junctions becoming a later feature [12]. Additionally, several ischemia-induced mediators including matrix metalloproteinases, nitric oxide synthase, vascular endothelial growth factors and thrombin might be involved. Reestablishment of recirculation in areas of the infarcted tissue might contribute to the flow of water through the ruptured blood-brain barrier [13]. Vasogenic edema reaches its peak at 1 to several days after the onset of ischemia and may cause an increase of tissue water by more than 100%. Vasogenic edema, in contrast to the early cytotoxic type of edema, is isoosmotic and accumulates mainly in the extracellular compartment. This reverses the narrowing of the extracellular space and explains the ‘pseudonormalisation’ of the signal intensity observed in DW-MRI [14]. However, as the total tissue water content is in-

creased at this time, the high signal intensity in T2-weighted images clearly differentiates this situation from a ‘real’ recovery to normal.

Progressive brain edema following ischemic stroke exerts a mechanical force on surrounding tissue structures. This occurs within the fixed volume of the intracranial cavity, and is therefore at the expense of other compartments, namely the vasculature and cerebrospinal fluid space. Once accommodative mechanisms are exhausted, intracranial pressure (ICP) starts to rise. Consequently, cerebral blood flow is compromised, with failure of autoregulation and worsening ischemia. Rising ICP may then result in tissue shifts, with midline shift and transtentorial and uncal herniation leading to progressive brainstem dysfunction.

Imaging

Imaging plays a central role in the prediction of the development of malignant infarctions and is essential for early therapeutic interventions (reviews [4, 15]).

CT

In most institutions, CT is the first diagnostic procedure performed in acute stroke and is essential for the differentiation of ischemia from other causes. Within the first few hours after onset of symptoms, CT shows attenuation changes within the grey matter resulting in the loss of grey-white matter differentiation at the cortex, loss of distinction of basal ganglia and of the insular ribbon. With development of early edema, cortical sulci disappear and hypo-attenuation develops in the white matter. An extension of these early hypodense changes beyond 50% of the MCA territory predicted malignant infarction with a sensitivity of 61% and a specificity of 94% [16, 17]. An infarct volume of >220 ml as well as midline shift of >3.9 mm were predictive of severe brain edema and herniation [18]. The risk of malignant course can be estimated by ASPECTS (Alberta Stroke Program Early CT score), where 7 was the cutoff score to determine progression to malignant infarction with 50% sensitivity and 86% specificity [19]. On CT-perfusion (PCT) maps the early involvement of more than two thirds of the MCA territory predicted malignant course with high sensitivity (92%) and specificity (94%) [20]. PCT can also assess increased blood-brain-barrier permeability, which leads to malignant infarction [21]. The involvement of additional vas-

cular territories [22, 23] and carotid occlusion [24] additionally predicted a fatal outcome. The extent of collateral circulation to the ischemic territory can be analyzed by CT angiography: a collateral score of less than 2 derived from these images was shown to be an independent predictor of malignant brain edema in addition to an NIHSS score of >18 [25].

MRI

MRI, especially diffusion-weighted imaging (DWI), is more sensitive than CT for the early detection of ischemic lesions. A DWI lesion volume of 145 ml was predictive of malignant infarction (100% sensitivity, 94% specificity) [26], but the determination of this cortical volume is dependent on the threshold of the reduction of the ADC used for DWI evaluation: using an ADC cutoff value of 80% compared to contralateral healthy tissue, a volume of >82 ml within 6 h of symptoms onset predicted malignant infarction with high specificity (98%) but low sensitivity (52%) [27]. Follow-up examination after 24 h improves sensitivity to 79%, while specificity-positive predictive value and negative predictive value remained unchanged [28]. The addition of a measure for brain atrophy could further increase the positive predictive value of the DWI lesion size [29].

Imaging of Flow and Tissue Viability

Quantitative measures of cerebral blood flow might be used to determine the critical thresholds of ischemia and the size of developing infarcts. Early single photon emission computed tomography (SPECT) with 99m-technetium-ethyl-cysteinate predicted malignant MCA infarction more accurately than CT changes or clinical symptoms [30]. PET of 11C-flumazenil (FMZ) can be used to assess rCBF (early distribution) and irreversible neuronal damage (reduced tracer accumulation). In 34 patients with ischemic changes in >50% of the MCA territory in early CT scans, results of FMZ-PET performed within 24 h after stroke were compared with recordings from probes of tissue oxygen pressure, ICP and microdialysis placed into the ipsilateral frontal cortex [31]. The early PET measurements demonstrated larger volumes of ischemic core (mean 144.5 vs. 62.2 ml) and of irreversibly damaged tissue (157.9 vs. 47.0 ml) in patients with malignant course (i.e. progressive edema formation with midline shift) than in patients with benign course. Mean ce-

rebral blood flow values within the ischemic core were significantly lower and the volume of the ischemic penumbra was smaller in the malignant than in the benign group. In patients with malignant course, cerebral perfusion pressure dropped to <50 mm Hg 52 h (mean) after onset of symptoms; subsequently, tissue oxygen pressure dropped and glutamate increased, indicating secondary ischemia responsible for extension of infarction. These findings indicate that PET studies could be used to predict the development of malignant infarction, whereas multimodal neuromonitoring detects secondary infarction of peri-infarct tissue once it occurs.

PET and SPECT studies help to determine thresholds for tissue viability and to elucidate pathophysiological changes leading to space-occupying infarction, but are not suited for the selection of patients for invasive treatment in the clinical setting. Therefore, the selection of patients for surgical therapy is based on CT (infarction >50% of MCA territory, ASPECT score 7 or lower, PCT deficit in 2/3 of MCA territory) or MRI (DWI total lesion volume of >145 ml or cortical lesion volume of >82 ml within 6 h).

Treatment

Recently, guidelines for the management of patients with malignant MCA infarction were published [4, 15], and therefore, only recent advances in the therapy of malignant infarction are reviewed in the following. Of the general conservative measures, only hypothermia showed some beneficial effects: hypothermia reduces postischemic hyperperfusion, delayed postischemic hypoperfusion, blood brain barrier disruption, brain edema and volume of neuronal damage after focal cerebral ischemia in animal models [32]. In patients with malignant MCA infarction, maintaining core temperature at 33°C for 48–72 h reduced mortality to 44% with an outcome on Barthel Index of 70 at 3 months [33]. In comparison to decompressive hemicraniectomy (DHC), hypothermia is less effective: mortality with hypothermia was 47% compared to 12% with DHC [34]. In combination with hemicraniectomy, hypothermia may have an additional beneficial effect (slightly improved outcome after 6 months without additional side effects) [35], but a controlled study is still in progress [36].

Osmotic therapy is used to reduce existing edema and minimize tissue shifts, but studies with hypertonic saline solutions, mannitol and glycerol, which all were effective in reducing at least transiently intracranial pressure, did

not significantly improve outcome [37–39]. Also, steroids failed to improve functional outcome or reduce mortality [40]. However, osmotherapy may be beneficial to bridge the time to surgical intervention.

DHC

The consequences of space occupying edema due to malignant infarction with shift of tissue to the contralateral side (midline shift), to the posterior fossa (tentorial herniation) and finally leading to compression of the brain stem and death can be mitigated only by creating additional space for the edematous brain to expand by DHC. After the first description of the effect of this procedure [41], numerous case reports and case series have indicated potential benefits especially with respect to survival rates in patients with malignant infarction (reviews in [4, 15, 42, 43]). Based on these results, several prospective randomized trials were performed [44–46], which taken alone did not result in significantly improved clinical outcome. A pooled analysis of these 3 trials provided evidence that DHC is a life-saving procedure, increasing the chances of survival from 29 to 78% [47], but an improvement in functional outcome of survivors (dichotomized to mRS 0–3 vs. 4–6) was not observed. This poor clinical outcome with increased survival rates was especially demonstrated in patients beyond the age of 60: decrease in mortality rate from 70% in control patients to 33% in DHC, but survival with poor neurological status (mRS4 32 vs. 15%, 28 vs. 13% mRS5, only 7 vs. 3% for mRS3) [48]. Similar results were observed in a nationwide survey of DHC in Japan [49]. However, contrary to expectations, DHC in the dominant hemisphere was not

associated with worse outcomes [42, 50]. It was shown repeatedly that early DHC performed within 24 h after onset of symptoms significantly reduced mortality and improved outcome 6 and 12 months after stroke [44, 45]. DHC performed 48 h after stroke onset might not have a beneficial effect on mortality or clinical outcome [51]. Additionally, the size of the hemicraniectomy is important and a diameter of DHC of at least 12 cm is recommended in most studies. Pre- and postoperative perfusion CT hemodynamic parameters were associated with mortality and the improvement of PCT parameters after DHC was related to favorable outcome [52]. Recent meta-analyses including newer controlled trials [51, 53, 54] confirmed the results of previous studies: DHC significantly decreases mortality and improves functional outcome for malignant infarction in patients aged 18–80, although with a nonsignificant increase in the proportion of major disability especially among aged survivors. Therefore, DHC should be recommended to improve survival after malignant infarction regardless of patient age, but in patients older than 60 years, the wishes of patients and family should be taken into consideration, since the likelihood of resulting severe disability is rather high. Improved imaging procedures – perfusion and angio CT, PW and DW-MRI, PET – early after stroke may help to select patients who will develop malignant infarction and therefore will especially benefit from early DHC. Controlled studies to prove this concept and the effect on hemodynamic parameters [52] are urgently needed.

Disclosure Statement

None.

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