WHITE PAPER: A GUIDE TO UNDERSTANDING LARGE HEMISPHERIC INFARCTION
Large Hemispheric Infarction (LHI) represents a minority of strokes, yet is responsible for a disproportionately large share of stroke-related morbidity and mortality.

The principal reason for such poor prognosis is that LHI’s have a high likelihood of developing life-threatening cerebral edema (brain swelling). Space-occupying edema is the leading cause of death in LHI, and in survivors it contributes to poor neurological outcomes and permanent disability.

This White Paper examines LHI, and describes some of the steps being taken to address this devastating disease.

A LARGE UNMET MEDICAL NEED

Stroke is one of the leading causes of death and disability in the world, but not all strokes are the same. For example, of the estimated 795,000 strokes a year in the U.S., approximately 74% are termed “ischemic strokes” – those that occur as a result of an obstruction within a blood vessel supplying blood to the brain. This paper focuses on a specific type of ischemic stroke called Large Hemispheric Infarction (LHI).

LHI makes up as many as 14% of all strokes (19% of ischemic strokes). In the U.S., for example, that represents about 110,000 incidents each year. While the overall mortality rate for strokes is about 8% to 10%, the mortality rate for LHI ranges from 40% to 80%. Importantly, few effective treatment options exist for LHI patients -- the most common treatments for ischemic stroke, like tissue plasminogen activator (tPA) and mechanical thrombectomy, are of uncertain value and, in the case of thrombectomy, not recommended for LHI patients.

Putting aside the catastrophic effects on LHI victims and their families, the financial and manpower/resource burdens on already strained healthcare systems are enormous. Costs associated with caring for these patients run into the several billions of dollars.

WHAT IS LHI AND WHAT MAKES IT UNIQUE?

LHI is defined as an ischemic stroke affecting the total or sub-total territory of the middle cerebral artery (MCA), involving the basal ganglia at least partially, with or without involvement of the adjacent (i.e., anterior cerebral artery or posterior cerebral artery) territories. As the name suggests, this is a large ischemic stroke with a significant amount of injured brain tissue.

LHI MAKES UP ABOUT

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The hallmark of LHI is the high likelihood of the evolution of clinically significant, life threatening cerebral edema. Among anterior circulation strokes, clinically significant edema is relevant only to LHI (Hacke et al. 1996). This high risk of life-threatening edema is related to the vessel affected by the occlusion, along with insufficient collateral bloodflow, which together result in a large volume of unsalvageable, dead tissue. This initiates a cascade that disrupts the blood-brain barrier, allowing fluid leakage into the brain i.e. swelling.

This swelling can further compromise arterial inflow to surrounding tissues, causing more ischemic damage and enlargement of the infarct, and frequently results in brain herniation and death. Clinical characteristics comprise secondary deterioration of
neurological symptoms, particularly a disturbance of consciousness and further clinical signs of brain stem herniation, like pupillary dilation. The prognosis for these patients is frequently poor, with case fatality as high as 40% to 80% (Hacke et al. 1996, Berrouschot et al. 1998).

The terminology surrounding the evolution of life threatening edema in LHI has been confusing, often conflating the prospectively-defined population at-risk, with those retrospectively defined as having suffered life threatening edema. The comingled terms include, for example, malignant cerebral edema and malignant infarction, MCA infarction and LHI (Wijdicks et al. 2014, Torbey et al. 2015).

The term ‘malignant MCA infarction’ was first introduced in 1996 to describe this severe MCA syndrome with typical clinical symptoms, following a uniform clinical course and ending in transtentorial herniation (Hacke et al. 1996). Adopting the clarification of Torbey et al. (2015), LHI refers to the condition at presentation, whereas “malignant MCA infarction” refers to the syndrome, frequently observed in the LHI population, in which clinically significant edema that ultimately can lead to transtentorial herniation has formed.

IDENTIFICATION OF LHI PATIENTS

Identifying a patient with LHI requires quantification of the extent of ischemic damage i.e. the stroke lesion volume. There are three common methods of estimating lesion volume, discussed below.

Diffusion-weighted magnetic resonance imaging (DW-MRI) is considered the “gold standard” in assessing lesion size. Thomalla et al. (2010) defined the threshold lesion size of 82 cm³ by DW-MRI with 98% specificity for predicting life threatening edema in LHI.

While DW-MRI is very precise, as a practical matter it is not available to many centers treating stroke or it is not available at a point in the assessment protocols to be routinely useful in this regard (Lee et al. 2015, Roladan-Valdez et al. 2014). Accordingly, MRI is rarely used in the normal, early-stage triage process to estimate lesion size, and would only very rarely be used to diagnose LHI early in its course.

Edema leads to midline shift, a sign the uninjured hemisphere is compressed. Since the brain is three dimensional, it likely will, if enlarged enough, push down on the brain stem, causing herniation and death. The above images are of an LHI patient who developed edema that was severe enough to push the brain midline over more than 1.5cm. The patient subsequently died.
Computed tomography (CT) perfusion uses special x-ray equipment and a contrast agent to provide a reasonably reliable lesion volume with fewer availability and logistical concerns than MRI. To the downside, it is not widely used outside of the larger centers for triaging patients, and it suffers from concerns over time needed and additional radiation (Lee et al. 2015).

The most commonly available and used imaging modality in estimating lesion size is non-contrast CT (standard of care at all centers) using Alberta Stroke Program Early CT score (ASPECTS), which is a 10-point quantitative topographic CT scan score. Previously, estimates such as a hypodensity on Non Contrast head CT (NCCT) of >33% of the MCA territory was used to determine LHI. However, ASPECTS represents a reproducible grading system to assess early ischemic changes in patients with acute ischemic stroke of the anterior circulation and has thus, on the whole, replaced the 33% rule. While ASPECTS is not a measure of lesion size per se, in general, a lower score is correlated with larger size and it is used this way in clinical practice (Schröder et al. 2014). In general, ASPECTS scores of <6 represent a high likelihood of a large lesion size i.e., LHI.

CLINICAL TREATMENT OF LHI

As recognized by the American Heart Association and the Neurocritical Care Society, the unique clinical course of LHI, involving life-threatening edema, warrants separate guidelines to manage this population, as distinct from the broader ischemic stroke population (Wijdicks et al. 2014; Torbey et al. 2015).

While treatment of ischemic stroke focuses on reperfusion, this is of uncertain value and may, in fact, be harmful in LHI. Improved outcomes from reperfusion in ischemic strokes are believed to result from restoring blood flow to ischemic, but salvageable tissue (Lee et al. 2015, Powers et al. 2015, Ionita et al. 2009), whereas the large amount of non-salvageable tissue in LHI not only supports the onset of life-threatening edema, but also makes reperfusion less likely to improve outcomes (Mlynash et al. 2011, Yoo et al. 2009, Sanak et al. 2006). Accordingly, the management of LHI focuses on clinically significant edema, which is unique to LHI.

In fact, the primary reason LHI patients are placed in neurological intensive care units, or neuro ICUs – where patients are treated with 24/7 personalized care from a team of advanced critical care trained doctors, nurses and other neurological specialists – is to closely monitor them for signs and symptoms of brain edema.

THE PRIMARY REASON PATIENTS ARE PLACED IN NEUROLOGICAL INTENSIVE CARE UNITS IS TO CLOSELY MONITOR THEM FOR SIGNS AND SYMPTOMS OF BRAIN EDEMA.

The two common reperfusion strategies for ischemic stroke are the use of thrombolytic therapies, tPA, and mechanical thrombectomy devices. Reperfusion, however, has been suggested to promote the development of clinically significant edema (Bell et al 1985; Koudstaal et al. 1988; Pillai et al. 2009; Nielsen et al. 2012). It has also been noted that the use of rtPA may aggravate the development of edema (Rudolf et al. 1998) and recanalization of LHI patients provides no benefit (Goyal et al. 2011). Notably, AHA Guidelines recommend thrombectomy only in patients with an ASPECTS score ≥6 (Powers et al. 2015), clearly excluding LHI patients.

The evidence suggesting LHI patients should be excluded from reperfusion strategies, along with the unique pathophysiology of edema in the LHI population, has caused LHI to become recognized as a unique condition by the medical community. In fact, the American Heart Association has issued separate guidelines for the management of clinically significant cerebral edema following infarction (Wijdicks et al. 2014), which occurs exclusively in LHI, among anterior circulation strokes (Hacke et al. 2014).
More specifically, the guidelines issued by the Neurocritical Care Society outline the overall distinct management approaches required by the unique pathophysiological progression of LHI (Torbey et al. 2015).

Decompressive Craniectomy (DC) has improved the bleak outlook for LHI patients who have progressed to "malignant infarction." In a pooled analysis of three prospective trials, DC was found to significantly reduce poor outcome and case fatality in patients who were randomized within 48 hours of stroke onset. However, numerous factors limit the usefulness of DC in LHI patients, including limited eligibility for surgery among patients who are gravely ill and have serious co-morbidities. Additionally, DC is a highly invasive procedure, involving two separate surgeries and all the inherent associated risks and adverse consequences (Sarov et al. 2010; Durga et al. 2011; Waziri et al. 2007; Kurland et al. 2014). Also, DC is of uncertain utility in patients >60 years of age, due to a high incidence of severe disability, as reported by Jüttler et al. (2014).

From a physiologic and clinical perspective, preventing swelling is preferable to decompressing the already swollen brain. DC does not stop swelling – it can only allow space for the brain to continue swelling outward.

At present, no satisfactory pharmacotherapy is available to reduce the formation of edema associated with LHI. Mannitol is an osmotic agent that is approved for reducing intracranial pressure and is used to reduce brain swelling, although AHA guidelines (Jauch et al. 2013; Wijdicks et al. 2014) state that the effect of mannitol in patients with ischemia-related brain swelling is unknown.

Glucocorticoids e.g., Decadron (Dexamethasone), are similarly approved for the treatment of cerebral edema, but AHA guidelines recommend that corticosteroids not be administered (Jauch et al. 2013; Wijdicks et al. 2014). Accordingly, no hospitals use corticosteroids in LHI.

Given that most therapies for ischemic stroke do not address the unique characteristics of LHI, or may even be harmful, there is a clear and urgent need for innovative medical strategies to prevent or mitigate malignant progression in LHI.

**THIS COULD BE THE FUTURE OF LHI TREATMENT**

Remedy Pharmaceuticals has developed a drug, CIRARA™, to address edema that can develop as part of CNS-related injuries and conditions – LHI being one such example.

CIRARA reduces the formation of edema by closing the Sur1-Trpm4 channel, a novel nonselective cation channel that is expressed in the central nervous system only under conditions of ischemia, hypoxia, and trauma (Chen and Simard 2004; Chen et al. 2003; Simard et al. 2006) discovered by Dr. J. Marc Simard.

**CIRARA REDUCES THE FORMATION OF EDEMA BY CLOSING THE Sur1-Trpm4 CHANNEL THAT IS EXPRESSED IN THE CENTRAL NERVOUS SYSTEM FOLLOWING INJURY**

Sur1-Trpm4 channel opening, which is triggered by depletion of ATP, results in cytotoxic edema and oncotic cell death (Simard et al. 2007). If the cell involved in the above pathophysiological sequence is a microvascular endothelial cell, these mechanisms result in formation of space-occupying edema (Simard et al. 2006; Simard et al. 2007). Brain edema formation through this mechanism is a serious complication and can lead to mechanical compression of adjacent brain structures, herniation, and death.

Additionally, it can impair regional cerebral blood flow, resulting in further ischemia.

CIRARA is a high-specificity inhibitor of Sur1-Trpm4 channels and thus specifically targets a key mechanism involved in development of edema, reducing the formation of edema and secondary damage resulting from edema in
multiple models of LHI with treatment delays of up to 10 hours following LHI. CIRARA is an intravenous (IV) formulation designed to rapidly reach and maintain steady-state therapeutic levels in acute CNS patients. CIRARA is suitable for both bolus injection and for continuous infusion.

PHASE 2 STUDY SHOWS THE POTENTIAL OF CIRARA IN TREATING LHI

In a randomized, double-blind, placebo controlled phase 2 study of CIRARA conducted at 18 leading U.S. sites in LHI patients, edema-related deaths were cut by 90% (2% in the CIRARA group versus 22% in placebo patients. p=0.01). This resulted in 90-day all-cause mortality being cut by 53% (17% versus 36%. p=0.06). In patients ≤70 years old, 90-day mortality was cut an astounding 66% (11% versus 33%. p=0.04). The extent of edema, as measured by average midline shift of the brain, was halved (8.8mm in placebo vs. 4.4mm in CIRARA-treated patients, p=0.0006).

CIRARA is a patented, high affinity inhibitor of Sur1-Trpm4 channels, which are upregulated following ischemia and trauma. Opening of these channels can lead to edema, midline shift, increased intracranial pressure, and brain herniation, culminating in permanent disability or death.

Sur1-Trpm4 channels were discovered by University of Maryland neurosurgeon Dr. J. Marc Simard, scientific founder and board member of Remedy Pharmaceuticals. CIRARA is suitable for intravenous delivery at the bedside or even in an ambulance. CIRARA uses our proprietary, patented MPD™ technology.

Edema contributes to the high mortality and morbidity of LHI. Central Nervous System-related edema occurs not just in LHI, but in many other CNS-related injuries and conditions, i.e., subarachnoid hemorrhage, intracerebral hemorrhage, contusional traumatic brain injury, spinal cord injury, as well as numerous other CNS conditions and injuries. CIRARA is a treatment for all these indications.

CIRARA is an investigational drug and is not approved by FDA.

ABOUT REMEDY PHARMACEUTICALS

Remedy Pharmaceuticals, Inc. is a privately-held, clinical stage pharmaceutical company focused on developing and bringing lifesaving treatment to people affected by acute central nervous system (CNS) edema – including large hemispheric infarction as well as other ischemic injuries and neurological disorders.

For more information on LHI and CIRARA, please go to: RemedyPharmaceuticals.com