INVITED COMMENTARY

Commentary on “Midline Shift Greater than 3 mm Independently Predicts Outcome After Ischemic Stroke”

Rajat Dhar*

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When large regions of the brain are subject to prolonged cerebral ischemia, for example, in the setting of large vessel occlusion, tissue infarction triggers a biologic cascade that results in brain water accumulation [1]. This cerebral edema involves the infarct region as well as surrounding tissue. The main consequence of stroke-related edema is an increase in hemispheric volume resulting in a compartmental pressure gradient between the two hemispheres, as well as the supratentorial and infratentorial spaces. The rise in pressure is initially attenuated by compensatory mechanisms that attempt to maintain the stability of total intracranial volume; these include the displacement of blood and cerebrospinal fluid (CSF) from the affected hemisphere. This can be visualized early after stroke by effacement of sulci along the hemispheric convexity, and later by effacement and displacement of the ventricular system. In fact, the global volumetric effects of edema can be quantified by measuring the total CSF displaced from the supratentorial space in the hours to days after stroke [2]. Progression of cerebral edema after hemispheric stroke will result in midline shift when this capacity for compensation is exhausted and compartmental pressure rises. Ultimately, this pressure gradient can result in herniation with severe clinical deterioration. Greater intracranial reserve (CSF volume as a ratio of cranial volume), a measure of this capacity for compensation, has been shown (similar to older age) to be

protective against complications relating to edema formation [3]. Those patients with stroke who develop midline shift and deterioration have less reserve and greater CSF displacement measurable by the 24-h mark, a time when midline shift is often still minimal [4]. Furthermore, given that the majority of edema and consequent CSF displacement occurs in the hemisphere ipsilateral to the stroke, the ratio of CSF remaining in that hemisphere relative to the volume in the contralateral hemisphere can be used as a dynamic early biomarker of edema that is significantly lower in those destined to develop midline shift [5].

Despite the emergence of quantitative biomarkers of edema that assess early CSF displacement or progressive hypodensity within the infarct (a marker of lesional water accumulation, termed net water uptake [NWU]) [6], midline shift remains the most accepted radiographic measure of cerebral edema. It can be measured manually and relatively simply from routine brain imaging and has long been used as a marker of imminent deterioration in the setting of hemispheric mass lesions, including large strokes [7]. Several decades ago, Ropper [8] related the degree of midline shift to a reduction in the level of arousal. He suggested that horizontal displacement of the pineal body of more than 3 mm was associated with drowsiness, progressing to stupor and coma as the shift increased further. In experimental models, the degree of midline shift has also been correlated with hemispheric swelling and poststroke water accumulation [9]. Midline shift can lead to secondary brain injury, not only worsening ischemia within the affected hemisphere but also causing compression of the contralateral hemisphere and brainstem, with potential for additional morbidity and, ultimately, mortality from herniation [10]. In the

*Correspondence: dharr@wustl.edu
Division of Neurocritical Care, Department of Neurology, Washington University in Saint Louis School of Medicine, 660 S Euclid Avenue, Campus Box 8111, Saint Louis, MO, USA

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absence of decompressive hemicraniectomy, the outcome of patients with stroke who develop midline shift and deterioration is extremely poor [11]. However, the independent contribution of edema and midline shift to stroke outcomes is clouded by the strong correlation of this complication with larger stroke volume and higher stroke severity, with both being powerful predictors of edema and poor outcome [12]. Prior studies have suggested that edema volume is an independent indicator of poor outcome across a broad spectrum of hemispheric strokes (even those without midline shift) but have relied on advanced image analysis [13, 14].

The present collaborative study by McKeown et al. [15] provides additional data on the relationship between degree of midline shift and stroke outcome by analyzing several stroke cohorts with a total of almost 2000 patients (with one third of these patients having underwent thrombectomy). Their analysis clearly demonstrates that patients who develop midline shift have worse outcomes, independent of key clinical factors including National Institutes of Health Stroke Scale (NIHSS), reperfusion treatments, and infarct volume. Moreover, their data suggest that a threshold of 3 mm distinguishes those with milder degrees of edema without functional consequences from those with severe edema resulting in a significant impact on recovery. Their findings were true for the thrombectomy and nonthrombectomy subgroups, although the impact of reperfusion itself was not clearly delineated and remains the topic of ongoing studies [16, 17]. A recent meta-analysis of participants in several clinical trials found that reperfusion therapy was associated with increased midline shift in those with a very large core volume [18].

As with many studies of edema, a key limitation is that midline shift was assessed at varying time points, determined by study protocols, as well as there being differences in which patients had follow-up imaging and when it was performed. Timing is key for a dynamic evolving process such as edema: although midline shift can develop within 24 h of stroke onset, it reaches its peak around 48–72 h after stroke. It can therefore be insensitive to malignant edema when measured too early, despite significant early swelling (as assessed by other volumetric or densitometric biomarkers) and patients still being at risk for subsequent deterioration. Although relatively rare, we found that 3 of 20 patients who developed malignant edema resulting in death or requiring decompressive surgery in one cohort had no measurable midline shift at 24 h but had significant edema measurable by volumetric CSF tools [19].

The authors propose that their findings support the use of midline shift as a surrogate end point for clinical trials of antiedema therapy. Evaluation of imaging data

from the pilot GAMES-RP (Glyburide Advantage in Malignant Edema and Stroke - Remedy Pharmaceuticals) trial of intravenous glyburide in large hemispheric stroke found that midline shift (measured by using magnetic resonance imaging performed at 72–96 h after treatment onset) was significantly reduced in those receiving glyburide [20]. However, despite a reduction in mortality, there was not a significant improvement in functional outcome associated with this treatment effect; this could be due to the imbalanced impact of hemicraniectomy on outcome. A further analysis of study data demonstrated that lesional NWU, a densitometric biomarker of edema, was also reduced in parallel to a reduction in midline shift with glyburide treatment [21]. This does suggest a promising biologic signal and has led to a large multicenter study of this agent to reduce edema, with midline shift as one of the key secondary end points [22]. Ultimately, although midline shift will remain the most used bedside assessment of severe edema in patients with stroke, it is unlikely to be the most sensitive or dynamic biomarker for understanding edema or treatment effects [23]. Assessing edema with dynamic measures that detect earlier effects in a larger proportion of patients promises to unlock even greater mechanistic and therapeutic insights, as demonstrated in several recent studies using NWU [17, 24]. The next challenge of imaging edema is making these more sensitive biomarkers accessible to clinicians and researchers to apply in large cohort studies and clinical trials and ultimately exploring whether they can provide more actionable insights at the bedside [25].

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Conflict of interest

The author has nothing to disclose.

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