Aphasia Following MR Guided Focused Ultrasound Thalamotomy (MRGFUST) Lesioning of The Ventral Intermediate Nucleus (Vim) in A Patient with Essential Tremor (ET): The Importance of Adhering to The Diagnosis of Exclusion Principle and Distinguishing Between Cortical and Thalamic Etiologies

Michael Horowitz, Youseff Al-Saghir, Ronnie Bond, Tarek Al-Saghir

Introduction

Essential tremor (ET) remains the most common adult movement disorder with a prevalence of approximately 5%. This condition, worsened by intention (kinetic movement), presents with uni- or bilateral involuntary 6-12 Hz shaking of the extremities, trunk, head and vocal cords making it difficult for individuals to carry out activities of daily living. Common ET treatments included orthotic compensatory devices, medications, implanted deep brain stimulation and thalamotomy. Over the last several years, thalamotomy using MRI guided focused ultrasound destruction of the ventral intermediate nucleus (Vim) has gained favor due to its high rate of effectiveness, low complication rate, and non-invasive implementation.

While ET is associated with subtle disturbances in language, manipulation of the Vim using stimulation and thalamotomy has been associated with language worsening and in some cases a fluent type of aphasia. It is not clear if such worsening is due to Vim changes or changes in surrounding thalamic nuclei and tracts [1]. This case report documents development of aphasia in a patient treated with MRGFUST of the left Vim less than 24 hours prior to symptom onset and stresses the importance of complete neurologic and imaging evaluation prior to making a presumptive diagnosis.

Clinical History

A 74 year old right handed obese man (BMI 42.2) with a past medical history significant for sleep apnea, hypertension, hyperlipidemia and medications that included amlodipine, atorvastatin and telmisartan was referred for neurosurgical intervention due to a several year history of incapacitating bilateral upper extremity essential tremor (ET) that failed to be adequately controlled with oral medical therapy. The patient was evaluated and scheduled for MRI Guided Focused Ultrasound Thalamotomy lesioning (MRGFUST) of the left thalamic ventral intermediate nucleus (Vim) to treat his dominant arm and hand movement disorder. If successful, the patient planned to undergo right Vim lesioning at a future date to manage his left upper extremity ET.

The patient underwent left Vim MRGFUST (TARGET: x = 14.5 mm left lateral from third ventricle mid sagittal plane; y = 6.1 mm anterior to the PC; z = 2 mm superior to the AC-PC line). Five total sonications each ranging between. 10-15 seconds were applied reaching a maximum energy of 12.7kJ, maximum power of 910W and maximum temperature of 56/58 degrees Celsius. The procedure was completed without incident and the patient experienced immediate cessation of his right upper extremity ET upon exiting...
the treatment suite. The immediate post procedure MR image of the thalamic lesion showed the expected T2 signal change in the region of the left Vim. (Figure 1). Subsequent analysis of the left Sylvian fissure and supraclinoid region suggested no significant elevations in temperature from transiting energy.

The patient was discharge home 3 hours later with no neurologic deficits and instructed to begin a tapered regimen of Decadron the next day to manage normal perilesional edema. Upon awakening the next morning (18 hours after procedure completion) the patient’s wife found him collapsed by the bedside. He exhibited right sided weakness and was unable to speak or follow commands. Emergency Services transferred the patient to a local hospital where a head CT showed no abnormalities aside from the expected left Vim region hypodensity (Figure 2).

In view of his recent thalamotomy, a diagnosis of thalamic aphasia (TA) was issued. The patient was administered 20 mg IV dexamethasone and transferred to the treating neurosurgeon’s institution. Upon arrival at our hospital the patient demonstrated a National Institute of Health Stroke Score (NIHSS) of 13 with global aphasia (deficits in fluency, comprehension and repetition) and mild lethargy. No other focal deficits could be identified. Right upper extremity tremor was absent. A repeat emergent CT showed evolving left temporal lobe hypodensity (Figure 3a). MRI showed the expected Vim signal change without evidence for significant edema extension or hemorrhage. The left temporal lobe, however, demonstrated restricted diffusion on DWI imaging suggesting a left middle cerebral artery thromboembolic event and an immediate CT arteriogram (CTA) confirmed a near total left MCA bifurcation occlusion with evidence for collateral reconstitution of the more distal MCA branch vessels (Figure 3). A CT perfusion study (CTP) suggested a left hemispheric defect with Core and Penumbra measuring 0 cc and 28 cc, respectively (Figure 4).

As the event was a wakeup stroke, the patient’s last known normal (LKN) was greater than 4.5 hours making him ineligible for IV thrombolytic therapy. The patient’s NIHSS was 13. Taking into consideration that he had no significant

Figure 1: Immediate post thalamotomy coronal MRI showing expected new left thalamic Vim region signal change (arrow)

Figure 2: Axial CT scan of the brain upon presentation to outside hospital ER. Expected small left thalamic post thalamotomy hypodensity is identified (arrow). Left MCA territory shows no hypodensity suggestive of MCA stroke.

Figure 3: (3a) CT head upon transfer from outside ER showing early left MCA distribution hypodensity (arrow) (3b Top) Axial MR images of brain show left MCA distribution restricted diffusion (arrows) and expected left thalamic Vim signal change secondary to procedure (arrowhead); (3b Bottom) CTA showing occluded left M1/M2 (blue arrow).

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weakness, a CTA that suggested distal MCA collateral flow, a CT that demonstrated hypodensity, and MR DWI changes involving a portion of the temporal lobe tissue that was consistent with a physiologic arterial occlusion distal to the M1 bifurcation, a decision was made to not pursue endovascular thrombectomy for fear of compromising existing collateral flow with procedure related thromboemboli. The risks of potentially procedurally inducing a more proximal occlusion or distal shower embolization of patent vessels were felt to outweigh the benefits of thrombus retrieval. Concern was also present for a reperfusion hemorrhage in the CT hypodensity. The patient was instead admitted to the hospital and managed with antiplatelet medication (Plavix 300 mg load followed by 75 mg daily; Aspirin 81 mg daily) and permissive hypertension. On post stroke day #1 a repeat head CT demonstrated left temporal lobe hypodensity that matched the previous day’s CT and DWI findings (Figure 5).

NIHSS was 10 and the patient was nodding appropriately to simple questions and following simple commands. He remained expressively aphasic aside from an occasional verbal “yes/no” to simple questions. EKG and Cardiac Echocardiography revealed atrial flutter and aortic stenosis with a calcified aortic valve (Figure 6). The patient was discharged post stroke day #5 to a rehabilitation center on apixaban with a discharge NIHSS was of 14.

Discussion
MR Guided Focused Ultrasound Thalamotomy (MRGFUST) Using MR Guided High Intensity Focused Ultrasound (MRgHIFU)

MRGFUST treatment of ET exploits the capabilities of MRgHIFU. This technology uses electric fields applied to piezoelectric crystals to generate ultrasonic (US) energy waves (Exablate device, Insightec Inc, Tirat Carmel, Israel). These waves, emitted from up to 1000 separate sources, are focused on a single convergent point (the
therapeutic target) using x,y and z coordinates identified on a contemporaneously acquired MR image. A target specific temperature spike is created by the convergent US waves. By heating the selected tissue target to approximately 57 degrees Celsius, protein denaturation and tissue death is achieved. Tissue surrounding the target is exposed to non-convergent energy waves that generate lower, non-lethal temperatures. This treatment step is termed “sonication”. Destruction of the thalamic Vim nucleus yields significant reduction/elimination of upper extremity disordered movement in patients suffering from ET.

Cortical Aphasia (CA)

Language is most often a product of the dominant hemisphere which in most individuals is located on the left side of the brain. The temporal lobe (Wernicke’s Area Brodmann 21, 22) and frontal lobe (Broca’s Area Brodmann 44, 45) are responsible for auditory comprehension and spoken language execution, respectively. To function in concert, these areas must communicate with one another via a white matter pathway called the arcuate fasciculus (Figure 8). Brain injury can cause deficits in communication based upon the portion of the brain that has been compromised.

Le and Lui have published an excellent aphasia review which will be summarized below [2]. Eight types of CA have been described. These can be divided into two main categories, fluent and non-fluent. The former is analyzed by observing speech rate and syntax. The latter is judged by identifying an individual’s ability to understand written and spoken words. A third language quality that must be noted is an individual’s ability to repeat written or spoken words (repetition).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>FLUENCY</th>
<th>COMPREHENSION</th>
<th>REPEITION</th>
<th>LESION LOCATION</th>
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<tr>
<td>Wernicke</td>
<td>Yes</td>
<td>Impaired</td>
<td>Unable</td>
<td>Brodmann 21</td>
</tr>
<tr>
<td>Transcortical Sensory</td>
<td>Yes</td>
<td>Impaired</td>
<td>Able</td>
<td>Around and isolating</td>
</tr>
<tr>
<td>Conduction</td>
<td>Yes</td>
<td>Intact</td>
<td>Unable</td>
<td>Arcuate Fasciculus</td>
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<tr>
<td>Anomic</td>
<td>Yes</td>
<td>Intact</td>
<td>Able</td>
<td>Brodmann 39</td>
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</table>

Fluent aphasias are categorized as:

Non-fluent aphasias are categorized as:

<table>
<thead>
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<th>TYPE</th>
<th>FLUENCY</th>
<th>COMPREHENSION</th>
<th>REPEITION</th>
<th>LESION LOCATION</th>
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<tbody>
<tr>
<td>Broca</td>
<td>No</td>
<td>Intact</td>
<td>Unable</td>
<td>Brodmann 44, 45</td>
</tr>
<tr>
<td>Transcortical Motor</td>
<td>No</td>
<td>Intact</td>
<td>Able</td>
<td>Around and sparing Brodmann 44, 45</td>
</tr>
<tr>
<td>Mixed Transcortical</td>
<td>No</td>
<td>Impaired</td>
<td>Able</td>
<td>Brodmann’s 21, 44,45, and Arcuate fasciculus</td>
</tr>
<tr>
<td>Global</td>
<td>No</td>
<td>Impaired</td>
<td>Unable</td>
<td>MCA territory</td>
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Thalamic Aphasia (TA)

According to Crosson there are several corticothalamic relationships that can affect language by engaging cortical task responsiveness, controlling the passage of information from one cortical area to another, influencing focus on task relevant information and affecting the selection of one language unit or another in the expression of a concept [3]. Injuries (usually vascular infarcts/hemorrhages) that affect the ventral anterior nucleus of the dominant thalamus and/or the posterior portion of the dominant thalamus (Pulvinar) can disrupt the above corticothalamic communications thus causing language deficits (Figure 9).

While there can be considerable variability in how patients with TA present and progress, the most common symptom is semantic (word meaning) paraphasia (language error that leads to the production of unintended words, phrases or syllables when speaking) (SP). Many identify this as “naming difficulty” with the patient having the inability to attach a meaning to a word. Examples would be saying “pants” when meaning to say “shirt” or saying “wife” when meaning to say “husband”. Patients with TA often have fairly intact auditory comprehension, reading and repetition although comprehension of phrases may be adversely affected. Non-fluent aphasias and other deficits can be exhibited [3]. Unlike cortical aphasia, TA generally recovers within days to weeks.

The Vim Nucleus:

The Vim nucleus of the thalamus is the most commonly targeted thalamic nucleus for the treatment of drug resistant refractory tremors. This neuronal collection is defined by Hassler as a part of the motor thalamic nuclei with a wedge

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Aphasia Following Thalamotomy

MRGFUST uses the combined energy of convergent ultrasound energy beams to heat a target within the brain thus rendering it permanently inactive [5-7]. Treatment of ET uses this modality to destroy the Vim nucleus. The Vim nucleus receives input from the cerebellar dentate nucleus and relays this information to the motor and premotor cortex. Destruction of the Vim using MRGFUST leads to tremor reduction or cessation in the patient’s contralateral upper extremity.

According to Elias, et al, adverse events following MRGFUST in 56 treated patients included gait disturbance, paresthesia/numbness and weakness. One patient (1.7%) suffered a transient ischemic attack 6 weeks after undergoing therapy [8]. In 2023, Cosgrove, et al, published five-year follow up results in patients who underwent 77 MRGFUST treatments [9]. These authors noted 0% serious adverse events at 5-year follow-up. Those adverse events that were documented at follow-up were mild or moderate and included paresthesia (10%), imbalance (8%), unsteadiness (3%), gait disturbance (3%), limb weakness (3%), dysmetria (3%), dysgeusia (3%), slow movements (1%) and the sensation of head pressure (1%). Neither Elias nor Cosgrove reported any episodes of aphasia.

While Elias and Cosgrove did not identify any instances of TA following MRGFUST targeting the Vim nucleus, reports of TA following thalamotomy and deep brain stimulation (DBS) for movement disorders (ET and Parkinson’s Disease) are reported. Alomar, et al’s 2017 meta-analysis of 2,320 patients who underwent thalamotomy revealed a 19.8% incidence of speech difficulty with 15% of those treated unilaterally and 40.6% of those treated bilaterally exhibiting speech impairment [10]. After thalamotomy for ET alone, 4.5% of unilaterally treated and 13.9% of bilaterally treated patients reported disturbances, with higher rates recorded in patients treated using DBS.

MRGFUST and Cortical TIA/Stroke

Review by the manufacturer (Insightec Inc., Miami, Florida, USA) of neurologic events within 30 days of FUS events has identified three reported ischemic events (2 strokes, 1 TIA) one of which was reported by Elias (8). Interestingly, rather than being a risk for stroke, MRGFUS has been considered as a potential experimental treatment for ischemic stroke using the technology’s ability to perform sonothrombolysis. In vitro and in vivo animal studies has demonstrated this capability [11].

MRGFUS by design causes tissue denaturation and coagulation [11]. For this reason, the question of whether or not transmitted non-convergent MRGFUST generated energy waves could have damaged the MCA and been responsible for the left temporal lobe stroke reported in this case report was raised. Engineers at Insightec, Inc. reviewed the treatment plan used for the case discussed in this report. This analysis, as mentioned in the above clinical history section revealed no heating near the left MCA or the left intracranial supraclinoid internal carotid artery.

Cardiac Risk Factors for Stroke

Approximately 25% of ischemic strokes are cardioembolic in origin with atrial arrhythmias and valvular disease responsible for the majority of such events [12-14]. Aortic stenosis predisposes patients to enhanced thrombin activation, increased platelet activation, and reduced fibrinolysis in the valve area [15-18]. Atrial flutter, which has an 80% association with intermittent atrial fibrillation, predisposes patients to development of thrombus within the left atrial appendage which can embolize to the intracranial circulation [19, 20]. In the authors’ opinion, the subject of this report most likely suffered a right MCA thrombembolic
stroke that was directly related to his AF and/or aortic valvular disease. As mentioned above, prior to this event he was naïve to antiplatelet and anticoagulant medications. Over 15,000 MRGFUS have been performed to date. If the number of associated cerebral ischemic events is isolated to the 4 cases mentioned in this report, the incidence would be 0.027%. This incidence is far below the US annual incidence of adult stroke which approximates 0.3% (795,000/258,000,000).

Conclusion
The authors describe a patient who, 18 hours after undergoing successful left MRGFUST for ET, presented to his local ER with an unremarkable brain CT and new onset aphasia yielding an initial diagnosis of TA secondary to dominant hemisphere Vim lesioning. Further evaluation following transfer to his treating neurosurgeon revealed an exam that was more consistent with global aphasia. Imaging demonstrated a left MCA distribution ischemic event that was managed with supportive care and antiplatelet medications. Post stroke cardiac evaluation documented aortic stenosis, aortic valve calcification and new onset atrial flutter, each of which are significant stroke risk factors. Retrospective evaluation of the MRGFUST ET treatment plan showed no significant risk for MCA or ICA damage generated by transiting ultrasonic energy waves. Literature review found only one prior published example of an ischemic injury presenting 6 weeks following MRGFUST while a manufacturer’s review identified two more (3 known reported total cases). If these numbers are accurate, the cumulative incidence of stroke over the last several years following MRGFUST is far lower than the annual incidence of stroke in US adults (0.027% vs 0.3%).

The above case report reinforces the importance of fully evaluating a patient with neurologic signs and symptoms to diagnose and appropriately treat the true etiology for the disease process. Automatically assuming that a postsurgical clinical change is related to the procedure itself runs the risk of misdiagnosing and subsequently mismanaging the adverse condition.

Declarations
Author Responsibilities

Competing Interests
The authors have no competing interests

Ethics approval
This article reports the outcomes following a surgical intervention on a human participant. The subject has been de-identified and both the patient and his family have provided informed written consent to be included as a part of this report. All procedures performed are standard of care and FDA approved.

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Availability of data and materials
All data has been provided in the Manuscript’s Results section. Any additional deidentified information can be obtained through the corresponding author (MH)

References


