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Title	**High Intensity Focused Ultrasound for Non-Invasive Functional Neurosurgery**
Running Title	**Focused Ultrasound for Non-invasive Neurosurgery**
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Abstract	Transcranial magnetic resonance guided high intensity focused ultrasound implies a novel, non-invasive treatment strategy for various brain diseases. Nine patients with chronic neuropathic pain were treated with

selective medial thalamotomies. Precisely located thermal ablations of 4mm diameter were produced at peak temperatures of 53°C to 60°C under continuous visual MR-guidance and MR-thermometry. The resulting lesions are clearly visible on follow-up MRI. All treatments were well tolerated, without side effects or neurological deficits. This is the first report on successful clinical application of transcranial magnetic resonance guided high intensity focused ultrasound, portraying it as safe and reliable for non-invasive neurosurgical interventions

Introduction

For over 50 years researchers have been seeking for a way to perform non-invasive thermal ablation for brain treatments[1, 2]. Recent technical advances have made Magnetic Resonance guided High Intensity Focused Ultrasound (MRgHIFU) a firmly established modality for non-invasive surgery under closed loop image guidance and control throughout all steps of the intervention process[3-5]. MR-imaging allows for precise intraprocedural localization of the ablation target[6], definition and verification of safety margins for the ultrasound treatment, real-time monitoring of thermal ablation dynamics[7], and intra- and post-treatment assessment of intervention results. Thanks to its non-invasiveness MRgHIFU minimizes the risk of bleeding and infection and avoids collateral damage to non-targeted tissue[8]. In addition, it does not involve ionizing radiation. Transcranial application of MRgHIFU, therefore, promises to become an important new modality for neurosurgical interventions[9, 10] and is envisioned to enable novel treatment strategies against a variety of brain diseases[5, 11-13].

Based on our long-term clinical experience in functional neurosurgery of neuropathic pain with stereotactic interventions in the medial thalamus[14-16], we developed intervention processes to access ablation targets in the brain non-invasively, using transcranial MRgHIFU (tcMRgHIFU). Following preclinical studies with phantoms, biological tissues and human ex-vivo head preparations, a clinical phase I study was initiated to investigate the feasibility, reproducibility, accuracy and safety of tcMRgHIFU for functional neurosurgery. The study was approved by the ethics committee of the University and the State of Zurich.

Patients and Methods

Patients

Having obtained fully informed written consent nine patients scheduled for a selective central lateral thalamotomy (CLT)[16] against chronic therapy-resistant neuropathic pain were enrolled. Therapy-resistance was established by lack of efficiency of anti-epileptic and anti-depressant drugs. The first nine interventions encompassed patients aged 45 to 75 years suffering from pain in the face (3 patients), neck (1 patient), lower extremity (2 patients), upper extremity (2 patients) and hemibody (1 patient), of central (3 patients) or peripheral (6 patients) origin. The 9 causal lesions at the origin of the different neuropathic pain syndromes were amputation, nerve compression by disc prolapse or neurinoma, zoster infection, nerve trauma, brachial plexus avulsion and thalamic infarct. One additional patient suffered from idiopathic trigeminal neuralgia, and another from a neuropathic pain syndrome in the context of cervical dystonia. The duration of pain in these patients was between 1.5 and 17 years (mean: 7.5 years).

Surgery and Intraoperative Observations

The non-invasive neurosurgical interventions were performed in a clinical 3Tesla MR-system (Signa HDx, GE, Milwaukee, USA) using a clinical system for tcMRgHIFU surgery (ExAblate 4000, InSightec, Tirat Carmel, Israel) featuring a hemispheric 1024 element phased array transducer operating at 650kHz.

The fully shaved patient's head was immobilized within a MR-compatible frame (Radionics, Burlington USA) and carefully positioned in the helmet-like cavity of the ultrasound transducer (Fig 1). The space between transducer and head surface was sealed with a flexible membrane and filled with degassed water for ultrasound coupling. The water was circulating at 16°C for continuous scalp cooling. The

ablation target, i.e. the posterior part of the thalamic central lateral nucleus, was localized on 3D T1-weighted MR-images using the multiarchitectonic Morel atlas of the human thalamus and basal ganglia[17]. The coordinates of the sonication lesions were determined and entered into the planning software of the MRgHIFU system. Intrinsically, tcMRgHIFU sonications are not limited by trajectory restrictions and offer several degrees of freedom to taylor the sonication pattern for optimal target volume coverage: peak temperature, sonication duration and combination of multiple sonication lesions.

Before the actual treatment phase of the tcMRgHIFU intervention it was confirmed that the thermal hot spot was centered in the target location. For this, several low power sonications of 10s to 20s duration were applied to induce peak temperatures of 39°C to 42°C. These temperatures are known to be below the ablation threshold but are easily visualized on MR-thermometry images to assess exact position and size of the hotspot and the overall safety profile of the applied sonication parameters[18] (Fig 2A).

During treatment several high power sonications were applied in an iterative process guided by MR-imaging and MR-thermometry. In order to induce local tissue ablation the acoustic power was stepwise increased from sonication to sonication to finally achieve a peak temperature at the target between 53°C and 60°C (Fig 2B). Typically, continuous wave sonications of 10s to 20s duration up to a maximum acoustic power of 1,200W and 800W, respectively, corresponding to 12,000J per sonication were applied.

Patients were fully awake and responsive during all stages of the intervention. The only medication administered before the procedure comprised an oral Benzodiazepine. In two cases a subcutaneous opiate injection was necessary

because of back pain due to lying motionless supine on the MR-table for an extended period of time. During the entire series of sonications, patients were monitored and questioned repeatedly to ensure their neurological integrity and to assess changes in pain quality, extension and intensity or other sensations experienced during the treatment.

Results

Selective CLT against chronic neuropathic pain have been applied in nine patients using the novel, non-invasive tcMRgHIFU technology. Patients were monitored continuously before, during and after each sonication period, were asked for their subjective experience (pain reduction, somatosensory improvements, vestibular feelings, par- and dysesthesias), and were examined to exclude any motor or somatosensory deficit. All treatments were well tolerated and no side effects or neurological deficits were observed. Operating at peak temperatures of 53°C to 60°C (except in the very first patient, where the peak temperatures were kept below 50°C for safety reasons) under closed-loop MR-guidance, precisely located lesions of 3mm to 5mm diameter were evident in 48h-postop MR-imaging. Pain relief two days after the interventions ranged from 30% to 100% (mean: 68%). Patients reported sonication effects during the procedure, such as pain relief (9 patients), somatosensory improvements (5 patients), vestibular feelings (5 patients), paresthesias (3 patients) or dysesthesias (7 patients) in and around the pain area. These symptoms were observed in some patients already at focal temperature below 50°C.

MR-imaging of the sonication lesions immediately following the intervention (in two patients) and 48h after the intervention (in all nine patients) revealed three concentric

zones on T2-weighted images (T2WI). They consist of a somewhat heterogeneous iso- to hypointense center (zone I) surrounded by a strongly hyperintense region (zone II). Zone II is sharply demarcated by a small hypointense rim towards an outer slightly fuzzy and irregularly shaped area (zone III) of lower hyperintensity (Fig 3A and 3B). This corresponds well to earlier studies on animal brains[6, 8]. The irregularly bordered outer zone III extends up to a maximum diameter of 10 to 12mm at 48h post intervention and represents the perifocal edema. It is best seen as diffusely hyperintense area on T2WI (Fig 3A and 3B).

Depending on the peak temperature achieved, the size of zone I immediately following the intervention and 48h postoperatively is 1 to 2mm in diameter on axial planes and 2 to 3mm in length on sagittal and coronal slices. The hyperintense zone II has a diameter of 3 to 4mm and a length of 4 to 5mm. These inner two zones I & II correspond most probably to the areas of coagulated and necrotic tissue[8] and are immediately and 48h postoperatively strongly hyperintense on isotropic diffusion images (Fig 3E and 3F), indicative of coagulation necrosis and cytotoxic edema. They are slightly hypointense on apparent diffusion coefficient maps and on T1WI, with a strong ring-enhancement of about 1 to 2mm thickness after administration of an intravenous contrast agent immediately after the intervention (Fig 3C), but almost no longer apparent at 48h follow-up (Fig 3D).

Previous reports based on in-vivo data in rabbit brain show that a thermal dose equivalent of 17min at 43°C (17 CEM 43°C) will result in 50% tissue damage[19]. In accordance with these findings, the total size of zone I & II as seen on T2WI (Fig 3A and 3B) after treatment matches exactly the area that accumulated more than 17 CEM 43°C on MR-thermometry images during treatment (Fig 2C).

The precision of tcMRgHIFU targeting was calculated by comparing the centers of the zone II on T2WI 48 h postoperatively and presurgical stereotactic coordinates of the ablation targets. So far, for nine targets in five patients the median / mean ± standard deviation are: dorso-ventral 0.5 / 0.61 ± 0.56mm ; (ii) antero-posterior 1.5 / 1.16 ± 0.57mm; (iii) medio-lateral 0.5 / 0.96 ± 0.87mm.

Discussion

The preliminary findings of our ongoing clinical phase I study on nine patients indicate that tcMRgHIFU is a safe, reliable and precise modality for non-invasive neurosurgical interventions for the first time and highlight the potential of this novel technology. All treatments could be safely performed and successfully executed to the planned endpoints owing to closed-loop high-field MR-image guidance. The sonication protocol allows for optimal target coverage: (i) by applying multiple sonication lesions, and (ii) by freely choosing the position of the sonication lesions without trajectory restrictions. Being non-invasive, all treatments were performed on fully awake patients as an outpatient procedure. Although pain relief was immediate in all treated patients, prior studies of thalamotomy have suggested that such relief might be transient. Our previous results with radiofrequency CLT on a large series of patients[16] demonstrate long term (mean follow-up 3 years 9 months) pain relief between 50% and 100% in 53% of patients. Follow-up MRI studies (as implemented here), physiological tests (quantitative EEG with spectral analysis and source localization), as well as clinical examinations (pain questionnaire, visual analog scale and neurological examination by independent observer) are planned at 3 and 12 months postoperatively to document in detail the long term post-sonication evolution of the patients.

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References

1. Lynn JG, Zwemer RL, Chick AJ. The Biological Application of Focused Ultrasonic Waves. Science (New York, N.Y. 1942;96:119-120
2. Fry WJ, Barnard JW, Fry EJ et al. Ultrasonic lesions in the mammalian central nervous system. Science (New York, N.Y. 1955;122:517-518
3. Jolesz FA, Hynynen K, McDannold N, Tempany C. MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. Magnetic resonance imaging clinics of North America. 2005;13:545-560
4. Fennessy FM, Tempany CM, McDannold NJ et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols. Radiology. 2007;243:885-893
5. Jolesz FA, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. J Magn Reson Imaging. 2008;27:391-399
6. Chen L, Bouley D, Yuh E et al. Study of focused ultrasound tissue damage using MRI and histology. J Magn Reson Imaging. 1999;10:146-153
7. Chung AH, Jolesz FA, Hynynen K. Thermal dosimetry of a focused ultrasound beam in vivo by magnetic resonance imaging. Med Phys. 1999;26:2017-2026
8. Chen L, Bouley DM, Harris BT, Butts K. MRI study of immediate cell viability in focused ultrasound lesions in the rabbit brain. J Magn Reson Imaging. 2001;13:23-30

9. Hynynen K, McDannold N, Clement G et al. Pre-clinical testing of a phased array ultrasound system for MRI-guided noninvasive surgery of the brain--a primate study. Eur J Radiol. 2006;59:149-156

10. Jagannathan J, Sanghvi NT, Crum LA et al. High-intensity focused ultrasound surgery of the brain: part 1--A historical perspective with modern applications. Neurosurgery. 2009;64:201-210; discussion 210-201

11. Hynynen K, Clement G. Clinical applications of focused ultrasound-the brain. Int J Hyperthermia. 2007;23:193-202

12. Tachibana K, Feril LB, Jr., Ikeda-Dantsuji Y. Sonodynamic therapy. Ultrasonics. 2008;48:253-259

13. Frenkel V. Ultrasound mediated delivery of drugs and genes to solid tumors. Advanced drug delivery reviews. 2008;60:1193-1208

14. Jeanmonod D, Magnin M, Morel A. Thalamus and neurogenic pain: physiological, anatomical and clinical data. Neuroreport. 1993;4:475-478

15. Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain. 1996;119 (Pt 2):363-375

16. Jeanmonod D, Magnin M, Morel A, Siegemund M. Surgical control of the human thalamocortical dysrhythmia: I Central lateral thalamotomy in neurogenic pain. Thalamus & Related Systems. 2001;1:71-79

17. Morel A. Stereotactic Atlas of the Human Thalamus and Basal Ganglia: Informa Healthcare, 2007

18. Hynynen K, Vykhodtseva NI, Chung AH et al. Thermal effects of focused ultrasound on the brain: determination with MR imaging. Radiology. 1997;204:247-253

19. McDannold N, Vykhodtseva N, Jolesz FA, Hynynen K. MRI investigation of the threshold for thermally induced blood-brain barrier disruption and brain tissue damage in the rabbit brain. Magn Reson Med. 2004;51:913-923

Figure Captions:

Fig 1. Patient prepared for transcranial MRgHIFU intervention.

The head is immobilized within a stereotactic frame. The transducer is positioned using a 3-axis mechanical positioner. The flexible membrane seals the space between patient head and transducer, which is filled with degassed water. The bore of the 3T MR-scanner is visible in the background.

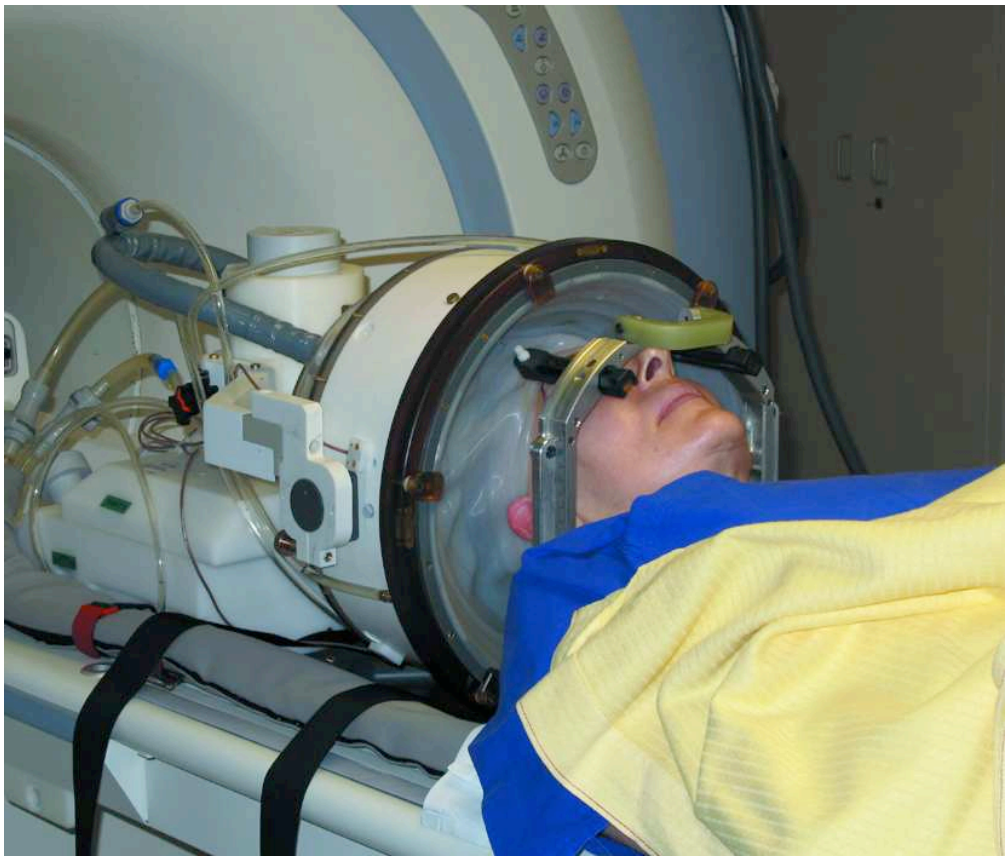
Fig 2. MR-image guidance of transcranial MRgHIFU intervention.

(A) Thermal map on axial plane at the level of the third ventricle. Thermal maps are refreshed at intervals of 3 to 5s to monitor localization and dynamics of temperature rise during sonication and subsequent temperature relaxation during cooling period. The blue circle delineates the planned sonication target in the posterior part of the central lateral thalamic nucleus. The red cross marks the pixel with the highest temperature at the end of sonication. The three wedge shaped forms are placed by the operator to balance background noise in thermal calculations. **(B)** Red: temperature evolution during a therapeutic sonication of 12s duration using 850W in the voxel of highest temperature. Time resolution 4s, monitored cooling period aftersonication 30s. Green: temperature evolution of average temperature of the neighbouring voxels around the temperature maximum. **(C)** Red circle: Contour line of thermal dose corresponding to 17 CEM 43 C (see text) at the target location superimposed on the T2 weighted MR image (T2WI) obtained 48h after treatment. **(D)** Stereotactic reconstruction of MRgHIFU-guided CLT. The outline of the lesion (dotted circle) corresponds to the extent of zone II (3 to 5mm diameter) seen on axial T2WI taken 48h postoperatively. The location of the CLT is determined by projecting the corresponding atlas map (6.3mm dorsal to intercommissural plane) onto the T2WI using the position of the posterior commissure (black cross) for anteroposterior alignment. Scale bars = 4mm. For abbreviations see reference 17.

Fig 3. Post treatment MR-images.

(A), (C), (E) Axial T2WI, post contrast T1WI and isotropic diffusion tensor image, respectively, of patient #2, obtained immediately after treatment with transcranial MRgHIFU. Two sonication lesions of 3-5mm diameter were placed into the right posterior part of the central lateral nucleus of the thalamus (for image description see text).

(B), (D), (F) Axial T2WI, post contrast T1WI and isotropic diffusion tensor image, respectively, of patient #3, obtained 48h after treatment with transcranial MRgHIFU. One sonication lesion was placed bilaterally in each of the posterior parts of the central lateral thalamic nuclei (for image description see text).



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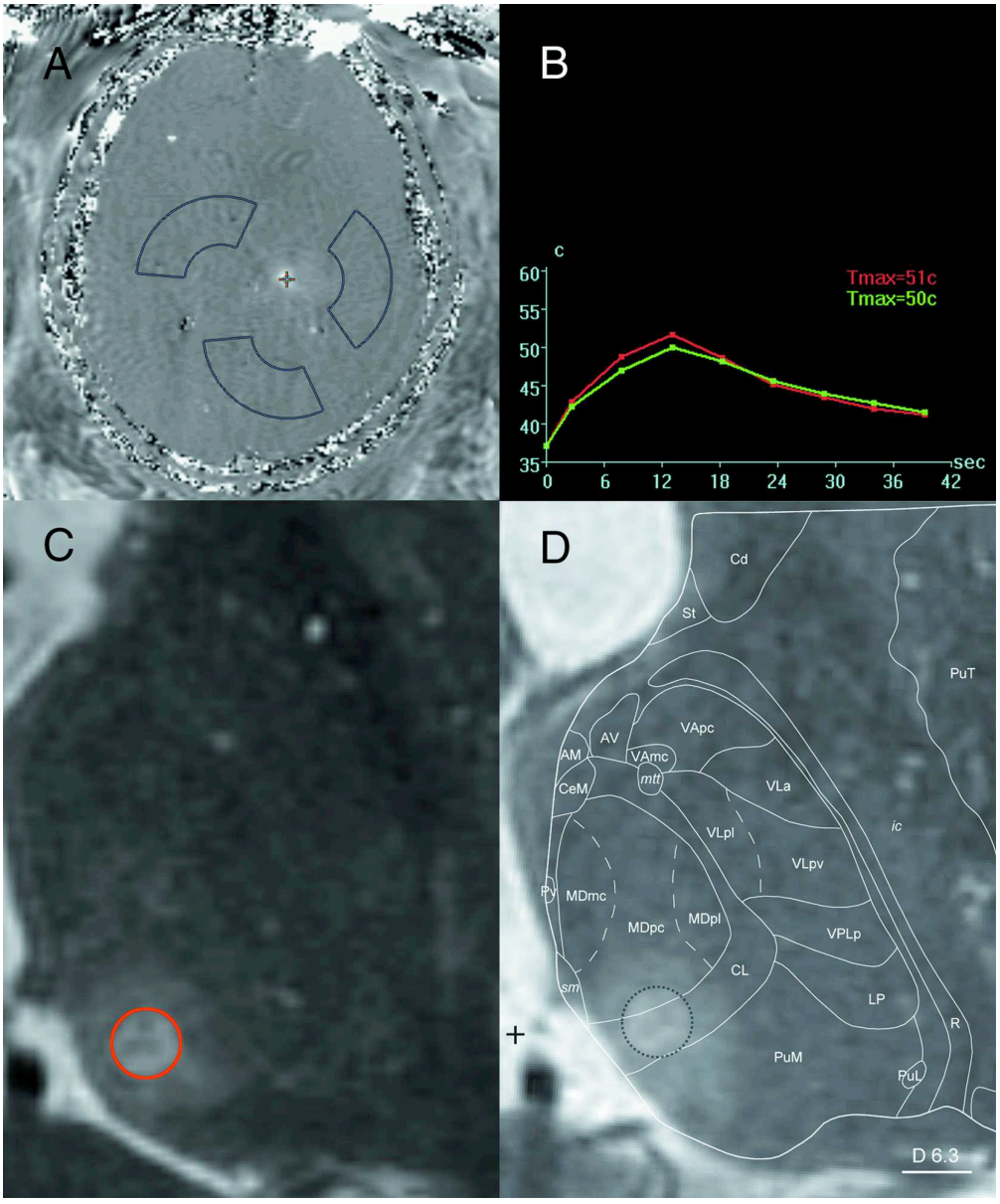

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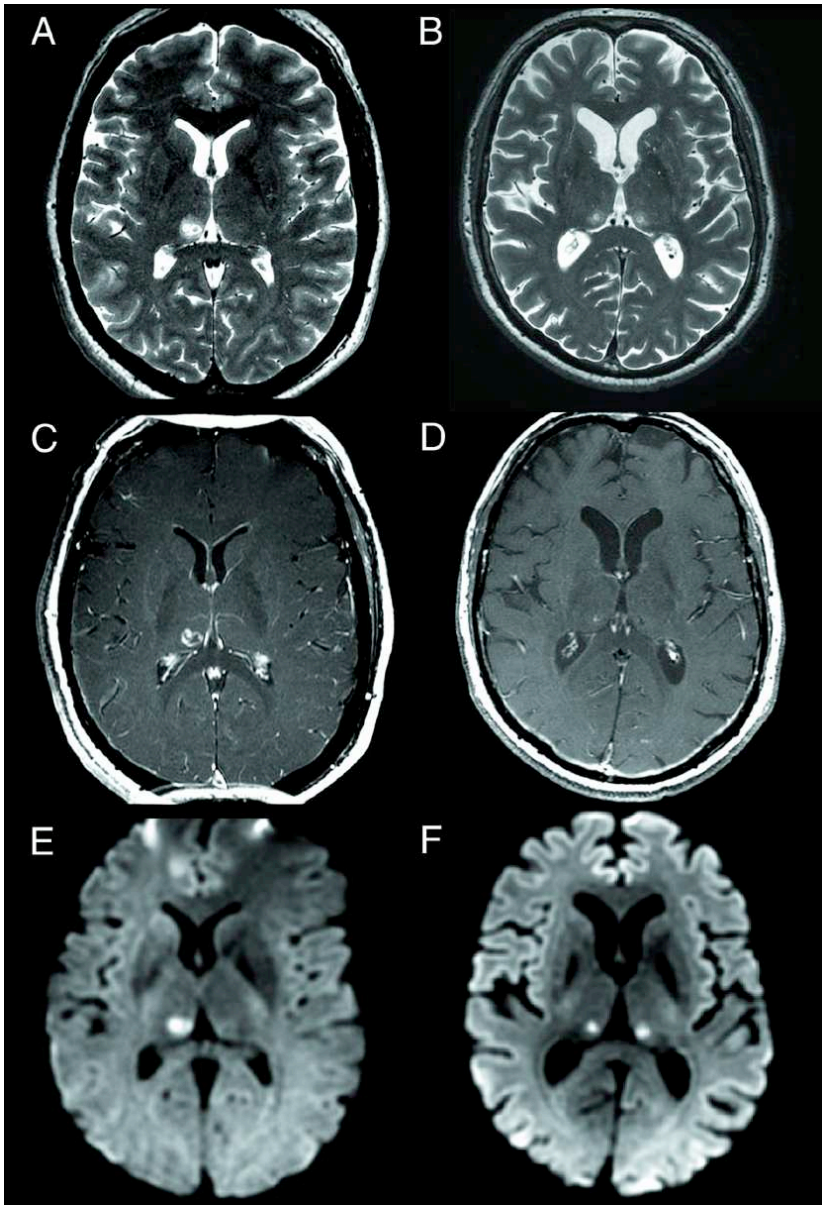

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