New Insight into Mechanism of Epileptogenesis with Dynamic T1 Contrast Perfusion MRI in Calcified Neurocysticercosis

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Introduction: Neurocysticercosis is the commonest cause of seizures and epilepsy in the endemic regions of the world including India. Usually degenerating cysts in the brain result in acute symptomatic epilepsy as well as chronic epilepsy in these patients. Calcified lesions are considered the end stage of the disease and regularly referred to as inactive neurocysticercosis. A number of studies are available in the hospital settings as well in screening of population in the endemic regions where CT and MRI have been used to study the disease burden where calcified lesions form a large percentage of total lesions with different stages of the cysts.

Importance of calcified lesions was realized when Nash et al published their seminal work showing calcified lesions with edema and ring enhancement in patients who presented with seizures[1]. Since then a number of papers have been published describing the similar findings. Gupta et al demonstrated scolex in the calcified lesions using phase corrected gradient echo MRI and postulated that the release of antigen from the viable calcified lesions results in perilesional edema and seizures[2,3]. They have also demonstrated perilesional gliosis around calcified lesions as a cause of chronic epilepsy in these patients. It is well known that a large number of asymptomatic subjects have calcified lesions and number of patients with calcified lesions don't show perilesional edema or gliosis on MRI. This makes it amply clear that disease manifestations associated with calcified lesions and its associated mechanisms are not yet clearly understood.

Dynamic contrast enhanced (DCE) MRI has been extensively used in the evaluation of intracranial mass lesions as it helps in grading of gliomas and predicting the response to radiation and chemotherapy[4,5]. DCE has been used to measure the angiogenesis in brain infection and have also shown correlation with MMP-9 a marker of blood brain integrity. We selected cases from the ongoing imaging survey to quantify the disease burden in the swine farming community who had single calcified lesions on CT as well on T2 star weighted angiography (SWAN) with corrected phase and perfusion MRI as additional sequence with an aim to quantify the perfusion indices to look for the differences between asymptomatic and symptomatic subjects if any and correlate these indices with blood MMP-9 and ICAM expression.

Material and Methods: We selected 30 cases with single calcified lesion irrespective of whether they were having seizures or were asymptomatic

***Data acquisition*:** All patients underwent both conventional and DCE-MRI on a 3 Tesla scanner (Signa HDxt, General Electric, Milwaukee, USA) using a 12 channel head coil. DCE-MRI was performed using a three dimensional spoiled gradient recalled echo (3D-SPGR) sequence [TR/TE/flip angle/ number of excitation(NEX)/slice thickness/ field of view (FOV)/matrix size=5.0ms/2.1ms/10°/0.7/6mm/240×240mm/128×128mm, number of phases=32]. At the fourth acquisition, Gd-DTPA-BMA (Omniscan, GE Healthcare, USA) was administered intravenously through a power injector at 5ml/sec, followed by 30ml saline flush. A series of 384 images in 32 time points for 12 slices were acquired (Temporal resolution: 6.03sec). Prior to 3D SPGR, two inversion recovery FSE (TR/TE/NEX/slice thickness/FOV/matrix size= 940ms/8ms/0.75/6mm/240×240mm/128×128mm) with inversion time 800 and 1600ms were performed for the same slice position to quantify voxel wise tissue T_{10}.

***MRI data processing and quantitative analysis*:** Voxel wise tissue T_{10} was calculated from two inversion recovery sequences. Quantitative analysis of concentration time curve was performed for calculation of cerebral blood volume (CBV) and cerebral blood flow (CBF). Pharmacokinetic model was implemented for permeability (k^{trans} & Kep) and leakage (v_e) calculation. Corrected CBV map was generated by removing the leakage effect of the disrupted BBB[6]. For the calculation of perfusion indices ROIs ($10mm^2$) were drawn on the lesion. Relative CBV (rCBV) and CBF (rCBF) were quantified by placing ROI on normal contra-lateral portion of the brain.

Enzyme linked immunosorbent assay kit (R&D Systems, Minneapolis, USA) was used to quantify human soluble intra-cellular adhesion molecules (sICAM), and MMP-9expression in the serum of these patients, taken before the MRI on the same day.

***Statistical analysis*:** Mann-Whitney U-test was used to look for statistically significant differences between symptomatic and asymptomatic subjects, using ICAM and MMP-9 expression and various DCE indices. Spearman's correlation was calculated to check the correlation of ICAM and MMP-9 expression with DCE indices.

Results: On Mann-Whitney U-test, **a**mong all the DCE indices, ICAM and MMP-9 expression, only Kep, v_e and MMP-9 expression were significantly higher in symptomatic patients as compared to asymptomatic ones. On Spearman's correlation it was found that MMP-9 expression correlated well with K_{ep}, V_e and also with K^{trans} upto a certain extent but ICAM expression did not correlated with any of the DCE indices.

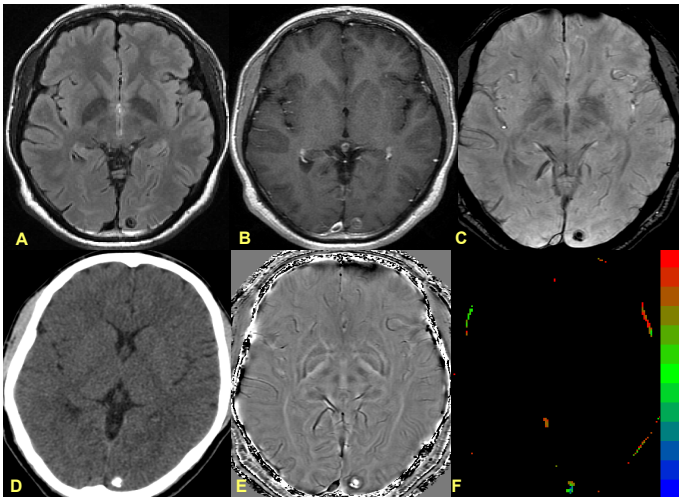

Fig.1 Showing A-F, T2 FLAIR, POST CONTRAST T1, SWAN, CT, Phase and RGB-K_{ep} map of a 29-yrs-old male , presented with seizures

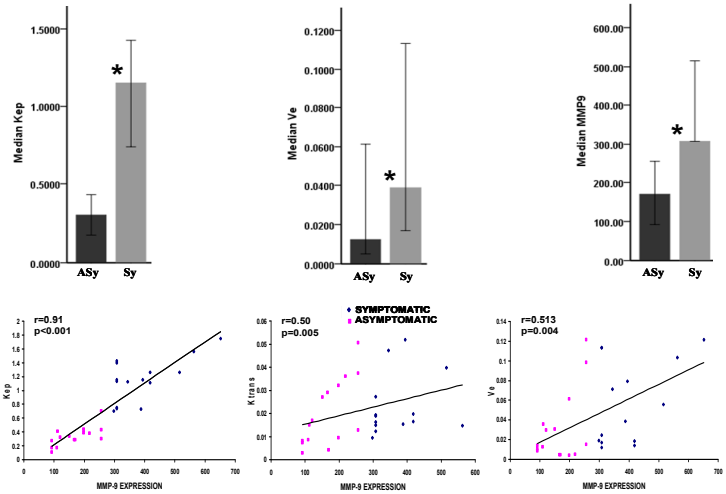

Fig.2 Bar diagrams showing significant differences in DCE metrices and MMP-9 expression between symptomatic (Sy) and asymptomatic (Asy) patients. Error bars represent 95% confidence interval. Below are the correlation scatter plots of DCE metrices with MMP-9 expression

Conclusion: Our results indicate that it is possible to differentiate symptomatic from asymptomatic subjects using DCE MRI. The strong correlation of the Kep with serum MMP-9 suggests that the degree of BBB disruption is significantly different in these groups and Kep may be used as a surrogate marker for its differentiation.

References: 1-Nash et al. *Lancet Neurol* 2008;7: 1099–105; 2- Gupta et al. *Epilepsia* 2002;43:1502-8; 3- Chawla et al. *Clin Radiol*. 2002 Sep;57:826-34; 4- Haris et al. *JCAT* 2008;32:955-65; 5- Bobek-Billewicz et al. *Folia Neuropathol*, 2010;48:81-924; 6-Singh et al. *J Magn Reson Imaging* 2007;26 :871-80