Early prediction of gross hemorrhagic transformation by MRI cluster analysis after embolic stroke in rat

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Introduction The incidence of hemorrhagic transformation (HT) during the first 36 hours after stroke is significantly higher in patients receiving tPA than in placebo treated patients (0.6% vs 6.4%), and 61% of the patients with symptomatic HT died within three months[1]. A method to assess the risk of HT after ischemic stroke would improve the safety of thrombolytic therapy. No precise predictors of HT have been identified. CT can diagnose hemorrhage once it has occurred[2], however, it cannot predict HT unless high-dose contrast-enhanced CT is used[3]. MRI obtained at 3h after MCAo in rat moderately predicts HT[4-5]. In this study, a two-dimensional (2D) cluster plot method that employs ADC_w and T_{1sat} maps is shown to predict HT in a rat model of embolic stroke with a high degree of specificity and accuracy.

Materials and Methods Male Wistar rats (300-350g) subjected to embolic stroke were randomly divided into two groups with (n=12) or without (n=10) the combination treatment with tPA and GPIIb/IIIa inhibitor at 4h after stroke. MRI measurements were performed using a 7-Tesla system. DWI and T_{1sat} measurements were performed from 1h to 3h, and at 24h, as well as 48h after embolization for all animals. All animals were sacrificed at 48h after MCAo. Coronal sections were cut and stained with H&E for the evaluation of hemorrhage. Gross hemorrhage was defined as blood evident to the unaided eye on the H&E stained sections and confirmed by microscopy. MRI maps of T_{1sat} and ADC_w were analyzed as a 2D cluster plot to segment the cerebral tissue into normal area and ischemic area with and without brain-blood barrier (BBB) disruption.

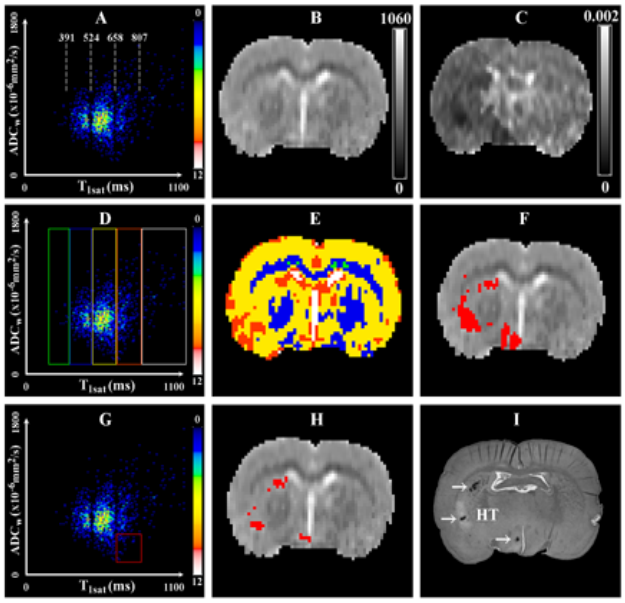

Fig.1 A 2D cluster plot (A) of T_{1sat} map (B) vs ADC_w map (C) from a treated rat. The structure of the 2D plot along the T_{1sat} axis naturally separated into clusters (D). These clusters according to their T_{1sat} values were transposed back onto the T_{1sat} image, as a theme image (E). The image (F) used a restricted cluster with $ADC_w<6.0x10^{-4}s/mm^2$. Using the conditions of $658ms<T_{1sat}<807ms$ and $ADC_w<6.0x10^{-4}s/mm^2$ (G), the cluster identified three regions (H) reflecting gross HT measured in the histological section of rat brain at 48h after onset of embolic MCAo (I).

Results A 2D cluster plot (Fig.A) of T_{1sat} (Fig.B) versus ADC_w (Fig.C) maps, acquired at 2h after onset of ischemia, from a treated rat shows various clusters according to their T_{1sat} values (Fig.D) which were transposed back onto the T_{1sat} map as a theme image (Fig.E). Clusters with $391ms<T_{1sat}<524ms$ and $524ms<T_{1sat}<658ms$ encompassed the normal WM and GM, respectively. From the theme image, we assume that the cluster with $658ms<T_{1sat}<807ms$ contained abnormal tissue (red color in Fig.E). Fig.F presents the back-transposed image by cluster with $ADC_w<6.0x10^{-4}s/mm^2$ only. With conditions of $658ms<T_{1sat}<807ms$ and $ADC_w<6.0x10^{-4}s/mm^2$ (Fig.G), the cluster clearly identifies three regions noted in red within the coronal section, as shown in Fig.H. Comparing to the histological section at 48h after MCAo (Fig.I), the three regions identified by the 2D cluster plot accurately predicted the gross HT areas both in size and location inside of the rat brain at 48h after stroke without any imaging contrast agent intervention. Using H&E staining, we found that 4 control rats and 3 treated rats showed gross hemorrhage. For all rats with gross hemorrhage, the acute T_{1sat}-ADC_w 2D cluster plot using individual threshold values predicts regions of gross hemorrhage histologically measured at 48h. The histologically measured areas of hemorrhage for all rats are $0.30\pm0.27mm^2$, while the corresponding T_{1sat}-ADC_w 2D cluster plot areas are $0.80\pm0.55mm^2$. The positions of gross HT tissue between T_{1sat}-ADC_w 2D cluster plot and histological measurements were within 3 pixels (approximately 0.75mm). The 2D cluster plot using 24h and 48h MRI maps failed to identify the gross hemorrhagic region histologically measured at 48h after stroke.

Discussion The 2D cluster plot consists of two MRI parameters T_{1sat} and ADC_w that respond early to stroke. The T_{1sat} is related to the apparent forward transfer rate of magnetization (k_f) between macromolecular protons and free water protons, which is sensitive to BBB disruption in the rat model of embolic stroke[5]. DWI has been employed in the early diagnosis of stroke. Since all gross hemorrhage were predicted by cluster analysis at 2h, this implies that changes in tissue which lead to HT arise prior to two hours after the onset of stroke. In the present study, we show that without contrast agent intervention, the 2D cluster plot analysis using T_{1sat} and ADC_w maps predict gross HT as early as at 2h after the onset of embolic stroke. This suggests that MRI can be employed to predict gross HT early (2h) after stroke onset by its own intrinsic contrast mechanisms.

References

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