Rate of FLAIR signal evolution depends on depth of ischemia and time: predicting ischemia age

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Introduction

A substantial proportion of ischemic stroke patients have unknown stroke onset time. An example is the 'wake-up' stroke in which patients awake with stroke symptom. Wake-up stroke patients constitute approximately 25% of ischemic stroke. Since the stroke onset is uncertain, these patients have been precluded from therapeutic intervention. This undesirable situation has motivated efforts in finding imaging surrogate markers of lesion age, which in turn might identify patients who are still within the therapeutic time windows. It has been reported that DWI lesion may appear within minutes of ischemia, while FLAIR (or T2) signal increase over the course of first hours after stroke onset. To this end, a DWI/FLAIR mismatch method (positive DWI and negative FLAIR) has been explored to identify patient within 3 or 4.5 hours window. Despite some level of success, controversial findings have been reported using this approach [1, 2]. This inconsistency has been attributed to different patient population that median NIHSS were not the same. We hypothesize that the evolution of the FLAIR signal depends on both the depth of ischemia and elapsed time after stroke onset. To test this hypothesis, we evaluated the rate of FLAIR signal change in stroke patients who were sequentially imaged. Moreover, we incorporate this information and develop a model to predict ischemic age.

Materials and Methods

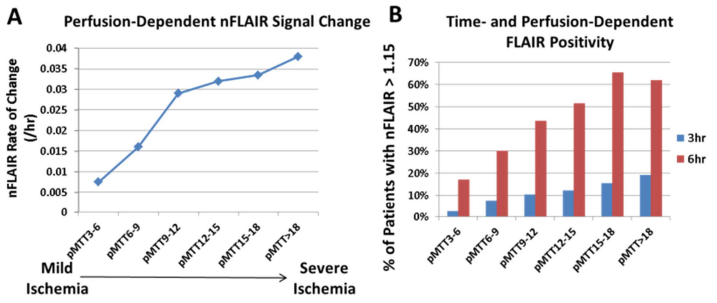

Fig 1. (A) nFLAIR rate of change (/hr) from tp1 (~3hr) to tp2 (~6hr). (B) % of patients with FLAIR positivity (nFLAIR>1.15).

Ischemic stroke patients with witnessed stroke onset were sequentially imaged with FLAIR, ADC and PWI (MTT) at <3hr (tp1), ~6.5hr (tp2) after stroke onset. FLAIR signal intensity (SI) and ADC were normalized to the median of contralesional hemisphere (nFLAIR & nADC). White matter disease and old strokes were manually outlined and excluded. MTT prolongation (pMTT) was computed as pMTT=MTT-median(contralateral MTT). Regions of stable ischemia (pMTT change between tp1 and tp2 was within +/- 3 seconds) were stratified based on six increments of pMTT ranging from mild to severe ischemia. Rates of nFLAIR change between two time-points (shown in units per hour) were measured between 3-6hr for each pMTT increment. Percent of patients with FLAIR positivity (defined as: nFLAIR > 1.15) at 3 and 6 hr was calculated for each pMTT increment.

Ischemia age prediction A generalized linear model (GLM) was used to construct a prediction model for ischemia age. Using this model, we have tested 1)whether FLAIR or ADC signal change, or both signal changes significantly correlate with lesion age; 2) what range of pMTT may yield a more reliable predition of lesion age. Six different ROIs were defined as pMTT>=4, 6, 8, 10, 12, 14 seconds for each patient. Mean nFLAIR and nADC were obtained from these ROIs. For each ROI, three GLM models, 1)Model 1: t=a0+a1*nFLAIR; 2) Model 2: t=a0+a2*nADC; and 3) Model 3: t=a0+a1*nFLAIR+a2*nADC were tested. In these models, t is the ischemia age, nFLAIR and nADC are the mean nFLAIR and mean nADC in a specific ROI, respectively. Finally, the predicted ischemia age was compared with the known true age to evaluate the prediction accuracy. Prediction error (PE) was defined as PE=Predicted age-actual age.

Results

41 patients were imaged at 2.6 hr, 6.2 hr after stroke onset. Between tp1 and tp2, rates of SI change for nFLAIR progressively increased with increasing severity of ischemia (Fig A). The % of patients with FLAIR positivity increased between 3 and 6 hr and with increasing severity of ischemia (Fig, B). Model 1 showed a significant association between nFLAIR and t ($p<0.05$), while the association between nADC and t did not reach statistical significance in model 2 ($P>0.05$). The significant association between nFLAIR and t remains in model 3, suggesting that nFLAIR is an independent predictor of ischemia age after controlling for nADC. Given that only nFLAIR is significantly associated with t, only model 1 was used to predict ischemia age in each ROI. We have found that the median absolute PE (in hours) and interquartile range [IQR] were 1.75 [1.15, 2.12], 1.56 [0.87,2.07], 1.5 [0.85,2.07], 1.1 [0.41, 1.93], 1.19 [0.54, 1.88], 1.20 [0.33,2.00] for ROI1 to 6, respectively. It is apparent that prediction of ischemia age is more reliable in a moderate to severe ischemic region (ROI4, 5, and 6). The prediction accuracy results corroborates with the finding that nFLAIR rate of change is high in large pMTT region. In other words, if nFLAIR signal change rate is small in a mildly hypoperfused region, the prediction model will be more subjective to the effects of noise. Our hypothesis and findings also explain the discrepancy reported in the literature. The low NIHSS patient cohort may have a slower FLAIR signal evolution when compared to a patient group with high NIHSS. In this case, it is not surprising to find negative FLAIR in patients with mild ischemia, who may have lesion age >4.5hrs.

Discussion and Conclusions

Rates of FLAIR change and FLAIR positivity were influenced by both time from stroke onset and depth of ischemia. FLAIR signal change has a significant association with ischemia age. We have found that the lesion age prediction is more reliable in moderate to severe ischemia. Encouraging results on lesion age prediction using a GLM model have been obtained (the median absolute prediction error is about 1hour across all patient). Further technical refinement are needed to improve the prediction accuracy.

References

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