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Neuroimaging correlation with neurological severity in tuberous sclerosis complex

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ABSTRACT

Objective: To delineate the relationship between neurological severity and neuroimage of lesion load including specific topography of supratentorial cortical tubers and white matter lesions in tuberous sclerosis complex (TSC).

Methods: Twenty-five TSC patients more than 2 years of age who underwent conventional and fluid-attenuated inversion recovery sequence (FLAIR) magnetic resonance imaging (MRI) were retrospectively studied. Neurological severity score was designated for three items: seizure, developmental delay and/or mental retardation, and autism. A neuroimaging scoring system was designed to evaluate the load of the cerebrum lesions with respect to location and size of cortical tubers and white matter lesions based on FLAIR MRI.

Results: A linear trend was observed between MRI lesion score and neurological severity score ($r = 0.511$; $p = 0.009$). The lesion score in the left temporal lobe has positive correlation to neurological severity score ($r = 0.609$; $p = 0.001$).

Conclusions: The brain lesion load was positively correlated with neurological prognosis in TSC patients. Patients with larger lesion load in the left temporal lobe may be correlated with increased neurological severity in right-handed patients with TSC.

1. Introduction

Tuberous sclerosis complex (TSC) often exhibit neurological manifestations such as epilepsy, developmental delay, mental retardation, autism and other neurological symptoms.[1,2] Neurological status may be affected by the number or specific location of cortical tubers or white matter lesions.[3–6] Fluid-attenuated inversion recovery sequence (FLAIR) magnetic resonance imaging (MRI) is more sensitive than T1-weighted and T2-weighted MRI for imaging cortical tubers and white matter lesions.[7] Several reports have examined the relationship between neuroimaging features and neurological prognosis.[3–8] Although the cerebral cortical tuber is believed to be a biomarker of neurological outcome[3] and the positive trend between numbers of traditional MRI detected cortical tubers and clinical manifestations had been firstly demonstrated about 20 years ago by Roach et al.,[4] the relationship between neuroimaging composites of cortical tubers and white matter

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lesions in the cerebrum and their causing neurological manifestations also requires further study. Although neurological variables have been compared to neuroimaging findings separately, no clinical neurological scoring system has been developed for TSC patients. This study proposes a system to delineate the relationship between neurological severity score and supratentorial neuroimaging lesion load including both cortical tubers and white matter lesions.

2. Materials and methods

The subjects of this study were a cohort of TSC patients consecutively treated during the previous 21 years at a tertiary university-based hospital in Taiwan. Subjects met established revised diagnostic criteria for TSC.[9] All patients had undergone brain MRI studies including T1, T2 and FLAIR imaging during December 2004 and December 2006. Patients were excluded if they were less than 2 years of age, had less than 1 year of follow-up history and incomplete clinical information. Medical records were reviewed for history of early developmental milestone, seizure (age of onset, pattern, frequency and treatment), mental retardation, autism as diagnosed by *Diagnostic and statistical manual of mental disorders, Forth Edition* (DSM IV), right or left handedness and family history of TSC or epilepsy. Intractable seizure was defined as failure of more than two first-line antiepileptic drugs, history of more than one seizure per month (average) for 18 months and no more than three consecutive months seizure–free during the study interval.[10]

Size, number and topography of cerebral cortical tubers and white matter lesions were examined for associations with neurological manifestations. Neurological severity was scored as follows: 1 point if seizure, developmental delay and/or mental retardation, or autism were noted. The points for the three manifestations were totaled to produce a neurological severity score.

Brain MRI, including T1-weighted, T2-weighted and FLAIR, with/without contrast and with section thickness of 4 or 5 mm in all sequences, were reviewed by an experienced pediatric neuroradiologist and a pediatric neurologist who were blind to the clinical characteristics of the subjects. In cases where they produced different neuroimaging scores, they reviewed the MRI together until they reached a consensus. The cortical tubers and white matter lesions on the bilateral frontal, parietal, temporal and occipital lobes were visually counted on FLAIR images. The following criteria were used to classify the lesions—(1) cortical tuber: localized abnormal signal intensity within cortical gyri, possibly causing cortical thickening, gyral expansion, and a less distinct gray–white matter junction; (2) transmantal white matter lesion: straight or curvilinear bands with signal intensity extending from the ventricle wall toward the tuber or normal cortex; (3) wedge-shaped white matter lesion: triangular signal intensity with apex near the ventricle and base of the cortex; (4) white matter nodular lesion: isolated conglomerate signal intensity foci within the white matter (Fig. 1).[11,12]

To establish a MRI lesion scoring system, the size of lesions larger than 5 mm in greatest diameter were counted and scored as follows: 1 point for cortical tuber on each separated gyrus, 2 points for cortical tuber occupying two adjacent gyri crossing sulcus; 1 point for one transmantal white matter lesion, 1 point for nodular white matter lesion (5–10 mm) and 2 points for wedge-shaped white matter lesion (≧10 mm). The points for cortical tubers and white matter lesions in each brain region were added to produce a regional lesion score. The number of protruding subependymal nodules was also counted on T1-weighted and T2-weighted MRI images.

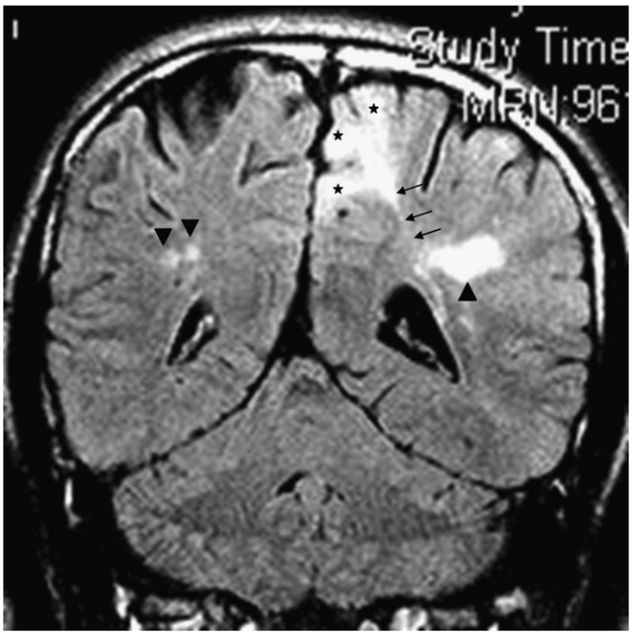

Fig. 1 – FLAIR MRI of lesion load score in TSC patients: each cortical tuber (★) on the separate gyrus was scored as 1, each transmantal white matter lesion (←) was scored as 1, each nodular white matter lesion (▼) was scored as 1, and each wedge-shaped white matter lesion (▲) was scored as 2.

The relationships between clinical variables and MRI findings were assessed by Fisher's exact test, Pearson's correlation and simple linear regression analysis. Distribution of regional MRI lesion score was compared by *t*-test. To analyze the relationship between clinical variables and regional MRI lesion score, Mann–Whitney rank-sum test was used. All reported *p*-values are two-sided; values less than 0.01 were considered statistically significant. Statistical analyses were performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL).

3. Results

Twenty-five patients (14 males and 11 females) were studied. Age range was 2–29 years (mean age ± SD: 11 ± 7.4 years). Two had family history of TSC, three had a family history of epilepsy without TSC, and one was an adopted child with unknown family history. All were right-handed. Of the 25 subjects, 23 (92%) had seizures, 16 (64%) had developmental delay, 14 (56%) had mental retardation and 5 (20%) had autism. Of the 23 seizure patients, 11 (48%) had intractable