Epilepsy may be the major risk factor of mental retardation in children with tuberous sclerosis: A retrospective cohort study

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ABSTRACT

Mental retardation (MR) is one of the most common cognitive comorbidities in children with tuberous sclerosis, and there are enormous studies about its risk factors. The genetic difference and the severity of epilepsy are the two main factors, but their weight in the occurrence of MR is still unclear. Two hundred twenty-three patients with tuberous sclerosis who received intelligence assessment, genetic mutation analysis, and the epilepsy severity assessment were included in our study. Genotype–neurocognitive phenotype correlations and epilepsy–neurocognitive phenotype correlations were analyzed by binary logistic regression analysis. No statistical significant result was found on genotype–neurocognitive phenotype correlations, which contrasted the previous report. The prevalence of MR was 50.0% for the patients with tuberous sclerosis complex-1 (TSC1) mutation, 54.5% for TSC2 (p = 0.561), 54.7% for patients with protein-truncating (PT) and 50.0% for patients with nontruncating (NT) (p = 0.791), and 54.3% for patients with family history and 53.7% for patients without family history (p = 0.748). Statistical significant results were found on epilepsy–neurocognitive phenotype correlations, both on E-chess score (p = 0.01) and the occurrence of infantile spasms (p = 0.014), which was consistent to the previous study. For children with tuberous sclerosis, instead of genetic factors, epilepsy may play the main role for the presence of mental retardation. Patients with mental retardation tend to have earlier seizure attack, take more AEDs, have more seizure types, and have higher seizure frequency. Among the four cognitive functions in Denver II, social ability and language ability are more vulnerable to be influenced than fine and gross motor ability.

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1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder. As a birth defect, its clinical manifestations are complex and diverse, including a series of neuropsychiatric disorders in behavioural, cognitive, and psychological aspects [1]. At present, these aspects of abnormalities have been listed as a separate complication, known as tuberous sclerosis associated with neuropsychiatric disorders (TAND) [1–3]. Among them, mental retardation is one of the most common neuropsychiatric disorders, affecting 44%–70% patients [4–10], and its impact on quality of life can be lasting and detrimental. Previous studies on risk factors for mental retardation in tuberous sclerosis have proved that it mainly associated with genotype [11,12], cortical tubers [13,14], and epilepsy [15]. Among them, the impact of cortical tubers on cognitive function has been widely studied. (18)F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging ((18)F-FDG PET/MRI) and diffusion tensor imaging (DTI) have been used as further aid in predicting the likelihood of epilepsy in tubers of different lesion types [13], and patients with cystic tubers whose mutation region is in TSC2 are more likely to present mental retardation [16]. Besides, present study shows that early intervention can improve the prognosis of neuropsychiatric development [17]. However, the first peak of mental development was infancy [18], but the tubers develop gradually as children grow, and during infancy, they are not fully developed [19]. Therefore, despite their relationship, it may only be a signal of mental retardation but not the cause. Therefore, the cause of MR falls to the other two factors and we planned to analyze their correlations and then try to give some indicators for the early intervention.

We collected the data of 639 children from 0 to 14 years old diagnosed with tuberous sclerosis in the Paediatric Department of Chinese PLA General Hospital from 2011/9 to 2016/9. According to the inclusion and exclusion criteria, a total of 223 patients were enrolled, all undergoing gene test, the assessment of mental development and severity of epilepsy. We used early childhood epilepsy severity scale (E-chess) [20], which was designed by Cambridge University, to analyze the severity of epilepsy in the children with tuberous sclerosis. We further assessed the impact of an epileptic syndrome, infantile spasms, which was not included in E-chess score, on children’s cognitive development. Through this study, we also planned to help better identifying the potential
mechanisms of mental retardation and to provide more evidences for further intervention.

2. Methods

We collected the data of 639 patients with tuberous sclerosis at the Paediatric Department of Chinese PLA General Hospital from 2011/9 to 2016/9. Fig. 1 shows the flowchart of patient screening, and Table 2 shows the inclusion and exclusion criteria. For all the included patients, it would be 2–3 years from the first onset of epilepsy to the epilepsy severity assessment date. Basic assessments included a structured clinical history detailing gender, age of onset, family history, frequency of seizures, seizure patterns, time period over which seizures occurred, number of seizure types, number of AEDs used, and the effect of the AEDs. In addition, standardized and validated psychological measures were used to assess mental development level, Raven’s Standard Progress Matrices (SPM) for children equal to or older than 6 years old, and Denver Development Screening Test II (Denver II) for children below 6 years old. Because of their younger age and the difference of scale, we classified the patients’ cognitive development into mental retardation positive and negative according to the score. For children below 6 years old, if the Denver II result was normal on development scale, we classified the patients’ cognitive development into mental retardation negative, otherwise positive. For children equal to or older than 6 years of age, if the score of SPM was more than 70, we then would record it as mental retardation negative; otherwise positive. All the diagnosis of mental retardation was done by the senior experts.

All children and their parents were genotyped on TSC1/TSC2 point mutation, TSC2 large fragment deletion and rearrangement mutation. Genetic testing was performed after obtaining informed consent from the respective guardians of patients. It was carried out at the Molecular Pathology Centre of Affiliated Hospital of the Air Force Institute or Beijing Genomics Institute using venous blood samples. High-throughput sequencing results were validated on Sanger sequencing, wherever necessary. All of the detected mutations would require pathogenicity assessment. First, the reported mutations would be screened by accessing Leiden Open Variation Databases (LOVD) (http://chromium.lovd.nl/LOVD2/TSC/home.php). If the mutation was not detected in one genetic testing center, we would do it in another center. The patients who were not found to have mutations or whose mutations had been identified as genetic polymorphisms would be excluded from our study, because according to the current study, their mutations may be mosaic on TSC1/TSC2, and including these patients may lead to biases [21]. Patients with more than 1 mutation would be excluded because it was not clear which sites caused the disease. Some of the nonreported missense mutations were evaluated using the PolyPhen Website (http://genetics.bwh.harvard.edu/pph2/) to predict pathogenicity. Mutation type, mutant exons and nucleotides were also recorded. To further study the effect of specific mutation domains on neuropsychology, the mutation domains were described in our study, including TSC1: Rho activating domain, tuberin interaction domain (TID), coi-coi domain (CCD), and ezrin-radixin-moesin (ERM); TSC2: hematin interaction domain (HID), alternative splice sites, transcription activating domain (TAD), GTPase-activating protein (GAP), and calmodulin-bind domain (CaMD). As for family history, it would be confirmed by both clinical data and their genotype. Mutations were additionally classified into protein-truncating (PT, nonsense, frame-shift, splice site, and large deletions of at least one exon) and nontruncating (NT, missense, and small in-frame deletions and insertions) mutations.

The severity of the epilepsy was measured by the E-chess on general [20]. Early childhood epilepsy severity scale was designed by the University of Cambridge in 2008, and it can reflect the severity of epilepsy in patients with tuberous sclerosis more systematically. It includes five parts, frequency of seizures, time period over which seizure occurred, number of seizure types, number of anticonvulsants used, and the effect of the AEDs. Additionally, considering the dramatic impairment of infantile spasms (IS), we particularly compared the level of cognitive developments of patients with and without IS. There were 223 patients who met all the criteria above. Data analysis was performed using SPSS 24. Genotype–neurocognitive phenotype correlations and epilepsy–neurocognitive phenotype correlations were analyzed by binary logistic regression analysis. In the study, the two-tailed test for $p < 0.05$ was considered statistically significant. GraphPad Prism 7 and Photoshop CS6 were used to draw the figures.

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the PLA General Hospital. Consent was obtained from all the patients in our study including the use of all their clinical data and genetic testing reports.

3. Results

Basic information of the patients was listed in Table 1. There were 120 in 223 patients (53.8%) presenting mental retardation, consistent with previous studies of 44–70% [4–10]. Among them, 70 (38.3%) were male and 50 (41.7%) were female. The age between patients with and without mental retardation showed no statistical difference.

3.1. Genotype–neurocognitive phenotype correlations

Patients with different genotypes presented no difference in cognitive development. Accounting for 13.5% of the included patients,

![Fig. 1. The flowchart of patient screening.](image-url)
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