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ORIGINAL ARTICLE

The relationship of neuroimaging findings and neuropsychiatric comorbidities in children with tuberous sclerosis complex

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attention-deficit–hyperactivity disorder;
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tuberous sclerosis complex

Background/Purpose: To clarify the relationship between neuroimaging findings, neuropsychiatric comorbidities, and epilepsy in patients with tuberous sclerosis complex (TSC) in Taiwan.
Methods: Medical records from 32 patients with TSC were retrospectively reviewed, including mutational analysis, neuroimaging findings, electroencephalogram findings, and neuropsychiatric comorbidities.
Results: Of these patients, six (18.75%) were diagnosed to have autism spectrum disorders (ASD), and 10 (31.25%) were diagnosed to have attention-deficit–hyperactivity disorder. In the latter patients, there were no differences in the regional distribution of tuber burden. In addition to a high prevalence of cystic-like tubers, tubers in insular and temporal areas were associated with ASD. Nonsense mutations in the *TSC2* gene group had a correlation with autistic behavior. In 26 (81.25%) patients with a history of epilepsy, infantile spasms and partial seizures were the predominant type of epilepsy. Most of them developed seizures prior to age 1 year.

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Conclusion: ASD is a common comorbidity in TSC. Cortical tubers in the temporal lobe and insular area were associated with ASD. The presence of cystic-like tubers on magnetic resonance imaging may also offer a structural marker for ASD in TSC.

Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder that is inherited as an autosomal dominant trait and occurs in 1 in 6000—10,000 live births.[1] However, two-thirds of patients with TSC have sporadic mutations.[1] Two genes, *TSC1* on 9q34 and *TSC2* on 16p13.3, coding for the proteins hamartin and tuberin, respectively, have been found to be related to TSC. Their mutations in humans may cause abnormal tissue growth and differentiation affecting multiple organs in patients, including the brain, eyes, heart, lung, kidneys, and skin.[1] Clinical manifestations in patients with TSC may have variable age-related changes. Some presentations may occur at an earlier age, such as renal angiomyolipomas, which appear after age 1 year,[1,2] and some may appear at a later stage, such as ungual fibroma, which mostly appears after age 15 years.[1] Cardiac rhabdomyomas in children with TSC may appear in the fetus and almost always regress spontaneously in infancy.[3] Pulmonary involvement mostly occurs in women and the onset of pulmonary symptoms is in adulthood.[4]

The major findings of TSC in the central nervous system consist of cortical tubers, subependymal nodules, and subependymal giant-cell astrocytomas (SEGA).[5] Epilepsy is found in about 90% of all TSC patients and tubers are believed to be epileptogenic. Seizures usually start in early childhood in most of the cases. Of these, complex partial seizures and infantile spasms are the most common seizure types.[1,6]

In the past decade, there has been a dramatic increase on research concerned with neuropsychiatric comorbidities in patients with TSC.[7—12] Autism spectrum disorders (ASD) have been shown to be more frequent in patients with TSC than in the normal population.[13] Several studies have noted the relationship between tubers in temporal lobe and the development of autism in TSC.[7,9]Although tubers in the temporal lobe are considered to be associated with autism, there are some other risk factors, such as total tuber counts,[10] temporal lobe epileptiform discharge[7] and earlier age of seizure onset.[14] Another common neuropsychiatric problem, attention-deficit—hyperactivity disorder (ADHD), is also very common in patients with TSC. About 30—60% of patients with TSC have symptoms related to ADHD.[11] Although the exact pathogenetic mechanisms of these comorbidities are still unknown, the commonly accepted hypothesis is that the damage resulting from tubers cause cognitive and emotional impairment in these patients.[15] However, there has been little research focused on the relationship between cystic-like tubers and neuropsychiatric comorbidities.[7,16]

Therefore, in this study, we reviewed 32 TSC patients, followed up in our hospital, to determine the relationship among neuropsychiatric comorbidities, seizures, *TSC* gene mutations, and tuber characters.

Methods

We reviewed medical records of patients with TSC followed up at the National Taiwan University Hospital, Taipei, Taiwan. The data analyzed included: neuroimaging findings; electroencephalogram findings; *TSC1* and *TSC2* mutations; mentality; neuropsychiatric comorbidities (such as ASD and ADHD); seizure history; and other neuropsychological assessments. Neuropsychological tests, including the Child Behavior Checklist, Leiter's parent rating scale, Wechsler intelligence scale for children, Wechsler adult intelligence scale, and Bayley Scales of Infant and Toddler Development II, were performed to evaluate the cognitive conditions of patients. The Institutional Ethical Committee of the National Taiwan University Hospital approved this cross-sectional study. The patients were classified into three groups according to the results of neuropsychiatric tests: normal development, borderline development, and intellectual disability. Categories were chosen based on: (1) normal development for intelligent quotient $>$ 80 on the Wechsler intelligence scales for children and adults; (2) borderline development for scores 70—80; and (3) intellectual disability for scores $<$ 70.

The *TSC1* and *TSC2* gene mutations were analyzed using denaturing high-performance liquid chromatography, followed by direct sequencing if any abnormalities were found. The mutations of *TSC1* and *TSC2* genes were divided into four categories: missense, nonsense, frameshift, and large deletion.

Brain magnetic resonance imaging (MRI) studies were reviewed by one pediatric neuroradiologist (S.S.F.P.) without knowing the results of neuropsychological assessments and electroencephalogram findings. MRI studies consisted of pre- and post-contrast T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences. The following features were analyzed: the presence of cystic-like tubers; numbers and sites of tubers (frontal, parietal, temporal, mesiotemporal, insular, occipital, and cerebellar); and SEGA by using fluid-attenuated inversion recovery sequences with sections of 4—5 mm thickness and 1-mm gap covering whole brain.

SPSS software version 18 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The associations between the presence of cystic-like tubers, *TSC* gene mutations, and ASD were also analyzed with the Fisher exact test. Analysis of the number and locations of tubers and neuropsychiatric comorbidities was performed using the Mann—Whitney *U* test. Kruskal—Wallis test was applied for the analysis of statistic difference in mentality category and age of seizure onset. A p value $<$ 0.05 was considered to be significant.