Prognostic Factors for Mental Retardation in Patients with Tuberous Sclerosis Complex

Ping-Chen Chou and Yeu-Jhy Chang

Abstract-

Purpose: To analyze the prognostic factors for mental retardation in patients with tuberous sclerosis complex (TSC).

Methods: We retrospectively reviewed 35 in-patients with TSC in a medical center and analyzed the clinical features. 19 of 32 patients (59.4%) fulfilled the classical diagnosis of tuberous sclerosis. According to the diagnostic criteria of Roach et al., 30 patients had definite TSC and 5 patients possible TSC.

Results: Among the 35 patients, the mean age at diagnosis was 15.9±12.5 years, and the male-to-female ratio was 14:21. 11 of 30 patients (36.6%) had a family history of TSC. The most frequent CNS manifestations were seizures (32/35, 91.4%) and mental abnormality (12/32, 62.5%). The most common cutaneous manifestation was facial angiofibroma (27/35, 77.1%) and the most common seizure pattern was generalized tonic clonic seizures (22/32, 62.9%). Poor control of seizures (p=0.006) and the presence of cortical tubercles in imaging studies (p=0.03) were correlated statistically with mental abnormality. Poor control of seizures (15/32, 46%) was more common in generalized tonic clonic seizures than other seizure types (p=0.041). Twenty-six of 28 patients (92.8%) displayed the typical findings of cortical tubers and subependymal nodules on the brain CT or MRI.

Conclusion: Mental retardation in TSC was correlated with poor control of seizures and the presence of CNS lesions.

Key Words: Tuberous sclerosis complex, Mental retardation, Prognostic factors

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INTRODUCTION

In 1880, Bourneville[1] first described the cerebral manifestations of tuberous sclerosis applying the term sclérose tubéreuse to indicate a superficial resemblance of the lesions to potato. The diagnostic criteria for tuberous sclerosis complex (TSC) was revised in 1998 in the U.S. National Institutes of Health consensus conference[2]. TSC is a genetic disorder affecting cellular differentiation, proliferation, and migration early in development, resulting in a variety of hamartomatous lesions that may affect virtually every organ or system of the body. Poorly controlled seizures as well as certain types of seizures, including infantile spasms, are consid-

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ered to be a poor neurodevelopmental prognosis[3]. In this study, we investigated the prognostic factors and discuss how to reduce the morbidity of TSC.

METHODS

We retrospectively reviewed the medical records available for possible diagnosis of tuberous sclerosis complex between 1981 and 2002 at the Chang Gung Memorial Hospital. 19 of 32 patients (59.4%) fulfilled the classical diagnosis of tuberous sclerosis. According to the diagnostic criteria of Roach et al,[2] 30 patients had definite TSC and 5 patients had possible TSC.

The clinical parameters included family history, skin manifestations, seizure patterns, seizure control, and mental status. Mental retardation is evaluated by the criteria of DSM III-R[4]. Poor control of seizure was defined as seizures occurring more than 3 times each year[5]. Imaging studies, including brain computed tomography (CT) or magnetic resonance imaging (MRI), sonography of the liver, kidneys and the heart, were also reviewed.

Chi-square test was carried out for testing the significance of differences of proportions. The Fisher's exact test was performed while small sample size was observed. Two-sample t-test was used to determine the differences between independent means. A *p* value less than 0.05 was considered significant statistically.

RESULTS

35 patients fulfilled the diagnostic criteria of TSC with ages ranging from 5 to 50 years. The mean age at diagnosis was 15.9±12.5 years and the male-to-female ratio was 2:3. 11 of 30 patients (36.6%) had a family history of TSC. The most frequent manifestations were those of the skin (94.4%) and of the central nervous system (seizures 32/35, 91.4%; mental abnormality 12/32, 62.5%, Table 1).

Cutaneous manifestations included facial angiofibroma (27/35, 77.1%), hypomelanotic macules (20/35, 57.1%), shagreen patches (16/35, 45.7%), ungual fibromas (8/35, 22.9%) and confetti skin lesions (1/35, 2.8%). There were only two patients without skin features.

Seizure types were identified in 32 patients who had seizures. About two thirds of the patients had generalized tonic clonic seizures (22/32, 62.9%). Infantile spasm (6/32, 18.8%) was the next common form of seizure, followed by absence seizures (4/32, 12.5%) and complex partial seizure (5/32, 15.6%). Only three patients (8.6%) did not have a clinical history of seizures, and none of them had mental retardation. Two patients had a history of status epilepticus. The age of onset of seizures ranged from one month to 11 years with a peak between 1 and 4 years (13/26, 50%). Poor control of seizures (15/32, 46%) was more common in generalized tonic clonic seizures than other seizure types (p=0.041). All of the 12 patients with mental abnormality had a history of seizures. Ten patients with seizures (10/32, 31%) had a normal intelligence. Poor control of seizures (p=0.006) and the presence cortical tubercles on imaging studies (p=0.03) were significantly associated with mental abnormality. Mental abnormalities were not associated with seizure patterns, age of seizure onset, family history, and other clinical and laboratory findings.

Results of brain image studies are summarized in Table 2. Among 28 patients who had CT/MRI, 26 patients (92.8%) displayed the typical CT or MRI findings, including cortical tubers and subependymal nodules. Two patients with seizures had normal CT/MRI findings.

Table 1. *Clinical manifestations of 35 patients with tuberous sclerosis complex*

Clinical features	Patient number (%)
Mean diagnosis age (year)	15.9±12.5
Male and female (ratio)	14:21 (2:3)
Family history	11/30 (36.6%)
Skin manifestations	33/35 (94.4%)
Facial angiofibroma	27/35 (77.1%)
Hypomelanotic macules	20/35 (57.1%)
Shgreen patches	16/35 (45.7%)
Ungual fibroma	8/35 (22.9%)
Confetti skin lesions	1/35 (2.8%)
Non- skin lesions	2/35 (5.6%)
Seizure	32/35 (91.4%)
Poor control	15/32 (46%)
Seizure types	
Generalized tonic clonic seizure	22/32 (62.9%)
Infantile spasm	6/32 (18.8%)
Complex partial seizure	5/32 (15.6%)
Absence seizure	4/32 (12.5%)
Mental abnormality	12/32 (62.5%)

Table 2. *Imaging studies of 35 patients with tuberous sclerosis complex*

Findings of examinations	Patient number (%)
Renal echo	
Angiomyolipoma	4/12 (33.3%)
Multiple renal cysts	6/12 (50%)
Pelvic ectasis	4/12 (33.3%)
Liver echo	
Harmatoma	1/ 3 (33.3%)
Hemangioma	1/ 3 (33.3%)
Echocardiography	
Ventricular septal defect	1/11 (9%)
CT/MRI	
Cortical tubers	7/28 (25%)
Subependymal nodules	25/28 (89.2%)

DISCUSSION

Seizures, the most common presenting symptom, occur in 74 to 98% of patients with TSC (91.4% in our cases) and are often medically intractable[6-9]. The incidence of mental retardation in our patients is 62.5% that is slightly higher than other reports (between 52% and 55%)[4,10,11]. This result might be due to an older mean diagnostic age in our patients (15.9±12.5 years). As our series, Webb[10], documented that all those with mental abnormality had a history of seizures. It has been postulated that the earlier the onset of seizures, the poorer the prognosis for intellectual outcome[11]. The presence of infantile spasm is strongly associated with poor mental development[3].

Katsuyaki et al[12] reviewed their longitudinal experience with 47 children who had the West syndrome. Infantile spasm evolved into symptomatic generalized epilepsy in 27 patients (57%), into partial epilepsy in nine (19%), and into a mixture of generalized and partial seizures in 11 (23%)[12]. The prognosis with regard to seizure control and social integration was most favorable in the group that developed partial epilepsy[12]. Because our patients had a wider and older age distribution and the incidence of infantile spasm accounts only for 18.8%, age distribution may be the main factor leading to generalized tonic clonic seizures which have a statistically significant correlation with poor control of seizures rather than infantile spasm.

The association between the age at onset of seizures (younger than 6 months) and the moderate to profound mental retardation in patients with TSC is not independent but reflects the age distribution of infantile spasm[3]. Our analysis showed that the age at onset of seizures was not significantly associated with poor mental development. The mental abnormality is correlated with poor control of seizures. The white spots of TSC on CT or MRI are often the first evidence of the disease[13,14]. A few recent studies have reported negative CT or MRI findings in a small percentage of patients with TSC[15]. Tubers are found in 95% of patients with tuberous sclerosis[16] and in 92.8% in our study. Cortical tuber count in MRI was considered a biomarker correlating with the intractable seizures and mental retardation[16-20]. The number, size and perhaps the location of the dysplastic cortical lesions shown in MRI tend to correlate with the severity of neurologic dysfunction[17]. We also found that the presence of cortical tubers on brain CT or MRI was associated with the presentation of mental retardation. However, the imaging results are not recommended to predict the neurological outcome of an individual patient[21].

In our study, there are only two patients diagnosed as TSC without skin features. Further evaluations of suspected TSC by skin lesions may be worthwhile. Most children do not have facial angiofibromas or ungual fibromas at the time of diagnosis. However, typical hypomelanotic macules can be recognized by most clinicians who are knowledgeable[21]. A dermatological evaluation can be useful when the skin lesions are atypical or when the diagnosis of TSC is uncertain[21].

The mean diagnostic age of our patients is 15.9± 12.5 year. The awareness of TSC usually rises from the classic triad, i.e. mental retardation, seizure and adenoma sebaceum[22,23]. Since complications of neurological involvement are the most common causes of mortality and morbidity an improvement for early diagnosis of TSC can be made, including education of the general population. Early diagnosis is important for a better outcome because there is a good correlation between control of the seizures and the degree of mental retardation[24].

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