Characteristics and the clinical prognosis of epilepsy in patients with a diagnosis of tuberous sclerosis complex

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Summary

Aim: Epilepsy is the most common neurological problem in tuberous sclerosis complex (TSC). The aim of this study is to investigate the clinical features and prognosis of epilepsy associated with TSC and to determine the factors that may affect the course of epilepsy in TSC patients.

Material and Method: Our study included 21 TSC patients (11/10: M/F) aged between 1-14 years (7.5±4.2) and followed up for 9 months-10 years because of epileptic seizures. After epileptic seizures were classified as seizures with good and poor prognosis, they were statistically compared in terms of age at seizure onset, history of status and infantile spasms, initial treatment with vigabatrin, initial EEG findings, presence of autism or mental retardation or cognitive impairment, the number of cortical tubers and presence of astrocytoma.

Results: The age at seizure onset ranged between 3 days and 2.5 years. The most common seizure type in our patients was partial seizure and eight patients had infantile spasms and status epilepticus. As a result of follow-up, the prognosis was evaluated as poor in 11 and good in 10 patients. No statistical relationship was found between seizure prognosis and age at seizure onset (younger and older than 1 age), the history of status and infantile spasms, initial EEG findings, use of vigabatrin as the first drug, the presence of autism or mental retardation or cognitive impairment, the number and localization of cortical tubers and the presence of astrocytoma (p>0.05).

Conclusions: The prognosis of epilepsy in patients with TSC varies in each patient depending on several factors. For this reason close follow-up of these patients with clinical evaluation and EEG is required. (Turk Arch Ped 2013; 48: 123-130)

Key words: Epilepsy, prognosis, tuberous sclerosis complex

Introduction

Although many organs are affected in tuberous sclerosis complex (TSC), the most commonly involved organs include the brain, retina, kidneys, heart and skin (1,2,3,4). The diagnosis is made according to the diagnostic criteria of Roach which were revised in 1988 (5) (Table 1).

Although tuberous sclerosis complex is characterized with the triad of mental retardation, epilepsy and adenoma sebaceum, this triad is found only in 1/3 of the patients (6). Epilepsy is the most common neurological disorder observed in patients with TSC. Any kind of epileptic seizure may be observed in tuberous sclerosis complex and these seizures are generally resistant to anti-epileptic treatment (7). The characteristics of epilepsy in tuberous sclerosis complex have not been described yet.

Although there are some studies examining the clinical, electroencephalographic (EEG) and cranial MR findings affecting the prognosis of epilepsy, there is no consensus on this subject yet (8,9,10). This study aimed to investigate the characteristics of epileptic seizures and the clinical prognosis and to examine the factors which may affect the prognosis of epilepsy in patients with a diagnosis of epileptic TSC.

Material and Method

The files of 32 patients followed up with a diagnosis of TSC in our Pediatric Neurology Clinic between January 2001 and January 2012 were examined retrospectively and 21 epileptic (87.5%) TSC patients selected according the following criteria who could be reached by phone were included in the study. Patient selection criteria:
Table 1. Diagnostic Criteria in Tuberous Sclerosis Complex

<table>
<thead>
<tr>
<th>Major findings</th>
<th>Minor findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cortical tuber</td>
<td>1. Hypopigemented patch in the retina</td>
</tr>
<tr>
<td>2. Subependimal nodule</td>
<td>2. Hamartomatous rectal polyp</td>
</tr>
<tr>
<td>3. Giant cell astrocytome</td>
<td>3. Bone cyst</td>
</tr>
<tr>
<td>4. Hypomelanotic macules (ash-leaf sign)</td>
<td>4. Radial migration line in the brain withe matter</td>
</tr>
<tr>
<td>5. Shagreen patch</td>
<td>5. Multiple pits in the enamel</td>
</tr>
<tr>
<td>6. Adenoma sebaceum (Angiofibroma in the face) or fibrous plaia in the forehead</td>
<td>6. Gingival fibroma</td>
</tr>
<tr>
<td>7. Multiple retinal hamartomas</td>
<td>7. Extra-renal hamartoma</td>
</tr>
<tr>
<td>8. Ungual or periungual fibromas</td>
<td>8. Confetti skin lesions</td>
</tr>
<tr>
<td>9. Rhabdomyoma</td>
<td>9. Multiple renal cysts</td>
</tr>
<tr>
<td>10. Lymphangiomatosis in the lung or renal angiomyolipoma</td>
<td></td>
</tr>
</tbody>
</table>

Definite diagnosis: two major or one major + two minor criteria
Suspicious diagnosis: one major + one minor criteria
Possible diagnosis: one major or two minor criteria
retardation in the developmental milestones according to age were defined as developmental delay if the clinical evaluation was also compatible.

To determine the risk factors which may affect the prognosis of seizures the patients who were classified as good and poor prognosis groups were statistically compared in terms of the age of onset of seizures, a history of status, presence of infantile spasm, initial EEG findings, location of the epileptic activity on EEG, intellectual and cognitive development levels, the number and locations of cortical tubers and presence of astrocytoma.

The study was initiated after obtaining approval from the ethics committee of Medeniyet University, Göztepe Education and Research Hospital.

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL) program. The Chi-square test was used for comparison of categorical variables. A p value below 0.05 was considered significant.

Results

The ages of 21 patients included in the study ranged between 1 and 14 years (7.5±4.2 yıl) and outpatient follow-up times ranged between 9 months and 10 years (5.3±3.9 years). Consanguineous marriage was found in 8 patients (38%) and a known history of TSC was found in 7 patients (35%). When the cutaneous findings of the patients were evaluated, depigmented nevus was found in 20 patients (95.2%), adenoma sabaceum was found in 14 patients (66.6%), fibrous plaqua in the forehead was found 5 patients (23.8%) and “Shagreen” patch was found in 4 patients (19%). Among other findings of the disease, rhabdomyoma in the heart was found in 3 patients (14.3%) and retinal astrocytoma was found in one patient (4.7%). When 7 patients (33.3%) who had renal involvement were examined, renal angiomyolipoma was found in five (23.8%) and renal cyst was found in two (9.5%).

When DSM-IV psychiatric assessments and intellectual or developmental tests of the patients were examined, it was found that 12 patients (57.1%) had an intellectual or cognitive development below normal and two patients (9.5%) had autism (Table 2).

Epilepsy characteristics: The age of onset of seizures ranged between the newborn period and 2.5 years of age and was mostly below the age of one (76.1%). Three patients had seizures in the newborn period (14.2%). The first seizure was partial in 9 patients (42.8%), diffuse tonic-clonic in 6 patients (28.5%), infantile spasm in 5 patients (23.8%) and atonic in one patient (4.7%). It was observed that 7 of these seizures (33%) developed during a period of fever. In the follow-up, partial seizures were observed in 20 of the patients (95.2%), infantile spasms were observed in 8 patients (38%), diffuse tonic-clonic seizures were observed in three patients (14.2%), atonic seizures were observed in three patients (14.2%) and absence seizures were observed in one patient (4.7%). Although status epilepticus developed during the clinical course in 8 of the patients (38%), it was found that seizures lasted shorter than 5 minutes in the majority of the patients (16 patients (76.1%)).

When epilepsy treatments of the patients were examined, it was found that three patients used drugs other than vigabatrin throughout the follow-up and one of these patients was using carbamazepine and the other two patients were using carbamazepine plus valproic acid. While valproic acid was used in 8 of the patients as the initial antiepileptic drug, phenobarbital was used in 6 patients and vigabatrin was used in 6 patients as the initial drug. In three of the patients, epileptic seizures were under control with monotherapy throughout the follow-up period. Our only patient in whom drug treatment was discontinued is being followed up without seizure for one year since the discontinuance of treatment.

Electroencephalogram findings: While no epileptic activity was found on EEG in five (23.8%) of our patients, partial epileptic activity was found in 14 patients (66.6), hypsarhythmia was found in 8 patients (38%), diffuse epileptic activity was found in 2 patients (9.5%) and

| Table 2. Distribution of the patients with a diagnosis of tuberous sclerosis according to presence of autism and intellectual-cognitive development levels |
|-----------------------------------------------|----------------|----------------|
| Autism/intellectual-cognitive development level | Number of patients | %  |
| Autism (-) / normal                          | 7              | 33.3 |
| Autism (+)                                   | 2              | 9.5  |
| Autism (-) / *growth retardation (+)         | 3              | 14.2 |
| Autism (-) / *mental retardation (+)         | 9              | 42.8 |
|    Mild mental retardation                    | 4              |      |
|    Moderate mental retardation                | 2              |      |
|    Severe mental retardation                  | 1              |      |

*For patient below the age of 6
**For patients aged 6 years and older
multifocal epileptic activity was found in 2 patients (9.5%) (Table 3).

Cranial MR imaging findings are given in Table 3. Cortical tuber was found in 20 patients (95.2%), subependimal nodule was found in 18 patients (85.7%), astrocytoma was found in 5 patients (23.8%) and white matter involvement was found in 2 patients (9.5%). Heterotopy was not observed in any patient.

The seizure prognosis was considered as poor in 11 of the patients and good in 10. Although seizures occurred rarely in three of the patients, the seizure prognosis was considered poor, since status which led to monitoring in the intensive care unit occurred. However, presence of status was not found to be a risk factor for poor prognosis. In patients who had infantil spasms, the epileptic seizure prognosis was observed to be poorer, but this difference was not statistically significant. No statistically significant difference was found between the patients whose age of the onset of seizures was one year and younger and above one year in terms of the prognosis of epilepsy. Initial EEG findings, the number of cortical tubers on cranial MR imaging, tubers being bilateral or regional and presence of astrocytoma had no effect on the prognosis of epilepsy. While frequent complex partial seizures continued in 2 of 5 patients who had astrocytoma, the seizures occurred as status in one patient. In two patients the seizures had a good prognosis. No difference was found between the patients who were found to have autism or cognitive developmental-intellectual retardation and the patients who had no autism and whose cognitive developmental-intellectual development were normal in terms of the prognosis of epileptic seizures (Table 4).

Discussion

The most common neurological finding in tuberous sclerosis complex is epilepsy which has been reported with a rate of 80-90% (7,15,16,17,18,19,20). Although presence and prognosis of seizures in patients with tuberous sclerosis

<table>
<thead>
<tr>
<th>No</th>
<th>Cortical tuber Number location</th>
<th>Subependimal nodule</th>
<th>Astrocytoma</th>
<th>Initial EEG</th>
<th>Follow-up EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiple</td>
<td>Very extensive in the right</td>
<td>+</td>
<td>No EA</td>
<td>No EA</td>
</tr>
<tr>
<td>2</td>
<td>Multiple</td>
<td>Extensive</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>EA yok, sağ FST, Right F</td>
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<tr>
<td>3</td>
<td>9</td>
<td>bIF right P, bi T</td>
<td>+</td>
<td>Right F</td>
<td>Right F, right T, right FTP</td>
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<tr>
<td>4*</td>
<td>Multiple</td>
<td>left F, biT and biO</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>No EA, biT</td>
</tr>
<tr>
<td>5</td>
<td>Multiple</td>
<td>biF, biP, biO</td>
<td>+</td>
<td>No EA</td>
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</tr>
<tr>
<td>6</td>
<td>Multiple</td>
<td>Extensive</td>
<td>+</td>
<td>No EA</td>
<td>No EA, No EA</td>
</tr>
<tr>
<td>7*</td>
<td>12</td>
<td>biF, biP, right T</td>
<td>+</td>
<td>+</td>
<td>No EA</td>
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<tr>
<td>8</td>
<td>8</td>
<td>Extensive</td>
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<td>No EA</td>
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<tr>
<td>9</td>
<td>Multiple</td>
<td>Extensive</td>
<td>+</td>
<td>No EA</td>
<td>EA yok, EA yok, No EA</td>
</tr>
<tr>
<td>10*</td>
<td>None</td>
<td></td>
<td>+</td>
<td>No EA</td>
<td>biF</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>Extensive</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>biF</td>
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<tr>
<td>12</td>
<td>12</td>
<td>Extensive</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>biT, No EA</td>
</tr>
<tr>
<td>13*</td>
<td>14</td>
<td>biF, left T, biP</td>
<td>+</td>
<td>Extensive</td>
<td>No EA, left FPT, No EA</td>
</tr>
<tr>
<td>14*</td>
<td>Multiple</td>
<td>biF, biP</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>Right TP, right T</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>Extensive</td>
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<td>Hipsarrhytmia</td>
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<td>+</td>
<td>Right TPO</td>
<td>biSP</td>
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<td>17</td>
<td>Multiple</td>
<td>biF, biP, right T</td>
<td>+</td>
<td>Left central</td>
<td>biSP</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>Left F</td>
<td>+</td>
<td>Hipsarrhytmia</td>
<td>MF</td>
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<tr>
<td>19</td>
<td>6</td>
<td>biF, left P, right O</td>
<td>+</td>
<td>Marked MF in the left</td>
<td>Marked biTP biTO in the left</td>
</tr>
<tr>
<td>20</td>
<td>Multiple</td>
<td>biF, biT, biO</td>
<td>+</td>
<td>Extensive</td>
<td>No EA, No EA</td>
</tr>
<tr>
<td>21</td>
<td>1</td>
<td>Right F</td>
<td></td>
<td>Hipsarrhytmia</td>
<td>biTO, right FS</td>
</tr>
</tbody>
</table>

*a right F KD, † venous anomaly, *White matter involvement positive, F: Frontal; S: Central, P: Parietal; T: Temporal; O: Occipital; KD: Cortical dysplasia, EA: Epileptic Activity; F: Frontal; S: Central, P: Parietal; T: Temporal; O: Occipital; MF: Multifocal
complex affect the quality of life substantially, there is no consensus on the prognosis of seizures yet (15,21). In this study, we investigated the characteristics of epileptic seizures, the prognosis of seizures and the factors which may affect the prognosis of seizures in a group of patients with a diagnosis of epileptic TSC. It has been reported that seizures in tuberous sclerosis complex frequently start in the first year of life and the most common seizure types in this disease include partial seizures and infantile spasm (18,20,21,22). Hence, the most common seizure type in

| Table 4. Factors which affect the prognosis of epilepsy in patients with a diagnosis of tuberous sclerosis |
|---------------------------------------------------|-----------------------------------|-------------------|---|
| **Age at the time of the first seizure**          | **Good prognosis s (%)** | **Poor prognosis s (%)** | **p** |
| One year and younger (n:16)                       | 7 (43.8)                        | 9 (56.3)           | 0.52 |
| Above one year of age (n:5)                       | 3 (60)                          | 2 (40)             |     |
| First seizure in association with fever (n:7)     | 3 (42.9)                        | 4 (57.1)           | 0.76 |
| First seizure without fever (n:14)                | 7 (50)                          | 7 (50)             |     |
| Histroy of status positive (n:8)                  | 4 (50)                          | 4 (50)             | 0.864|
| Histroy of status negative (13)                   | 6 (46.2)                        | 7 (53.8)           |     |
| Histroy of infantil spasm positive (n:8)          | 3 (37.5)                        | 5 (62.5)           | 0.466|
| Histroy of infantil spasm negative (n:13)         | 7 (53.8)                        | 6 (46.2)           |     |
| First antiepileptic drug                          |                                 |                   | 0.22 |
| Vigabatrin (n:7)                                  | 2 (28.6)                        | 5 (71.4)           |     |
| Other than vigabatrin (14)                         | 8 (57.1)                        | 6 (42.9)           |     |
| Location of EA on EEG                             |                                 |                   | 0.7  |
| Right                                             | 2 (33.3)                        | 4 (66.7)           |     |
| Left                                              | 2 (50)                          | 2 (50)             |     |
| No EA or localized finding                        | 6 (54.5)                        | 5 (45.5)           |     |
| First EEG                                         |                                 |                   | 0.44 |
| Normal                                            | 4 (66.7)                        | 2(33.3)            |     |
| Focal or extensive EA                             | 3 (50)                          | 3 (50)             |     |
| MF or Hipsarrhytmia                               | 3 (33.3)                        | 6 (66.7)           |     |
| Number of cortical tubers (s: 20 patients)        |                                 |                   | 0.232|
| 1-6                                               | 0 (0)                           | 3 (100)            |     |
| 7-12                                              | 3 (50)                          | 3 (50)             |     |
| Multiple                                          | 6 (54.5)                        | 5 (45.5)           |     |
| Location of tubers (s: 20 patients)               |                                 |                   | 0.426|
| Extensive bilateral                               | 6 (54.5)                        | 5 (45.5)           |     |
| Right                                             | 1 (20)                          | 4 (80)             |     |
| Left                                              | 2 (50)                          | 2 (50)             |     |
| Astrocytoma positiver (s:5)                       | 2 (40)                          | 3 (60)             | 0.696|
| Astrocytoma negative (s:16)                       | 8 (50)                          | 8 (50)             |     |
| Autism /mental or developmental level             |                                 |                   | 0.537|
| Autism (-) / normal (s:7)                         | 4 (57.1)                        | 6 (42.9)           |     |
| Autism (+) or mental retardation-developmental retardation (s:14) | 3 (42.9) | 8 (57.1) |     |

*ki kare test; s: hasta sayısı
EA: Epileptik aktivite
our patients was partial seizure and seizures started in the
first year of life in 76%. Infantile spasm which has been
reported with a rate of 25-69% was found in 38% of our
patients (21,23,24,25,26).

In a study in which EEG changes were examined in 361
patients with epileptic TSC, presence of epileptic activity
on EEG (35% focal, 10% diffuse, 22% hypsarrhythmia)
was found with a rate of 78% (27). Although this rate was
found to be 76% in our study (focal epileptic activity 66.6%,
hypsarrhythmia 38%, diffuse and multifocal epileptic activity
9.5%), focal findings were observed more frequently.

Three types of nodular lesion have been defined in
patients with tuberous sclerosis complex: cortical tubers,
subcortical heterotopic nodules and subependimal giant
cell astrocytoma (28). It has been reported that cortical
tubers are observed with a rate of 82-100% (29) and
subependimal nodules are observed with a rate of 50-
100% (10,30). When the cranial MR imaging findings of our
patients were examined, it was found that the frequencies
of cortical tuber (95%) and subependimal nodule (85%) were
compatible with the literature. Giant cell astrocytoma
which is the predominant tumor of tuberous sclerosis
complex and has been reported to be observed with a rate
of 6-9% (31,32) was observed with a slightly higher rate in
our patient group (24%).

Intellectual development is frequently affected in
tuberous sclerosis complex and mental retardation has been
reported with a rate of 50-55% (20,21,25,33,34). Autism is
another neurological disorder which has been reported to
be observed with a rate of 30-50% in TSC patients and
which affects the quality of life negatively in these patients
(35,36). In our study, intellectual and cognitive development
levels were found to be below normal in 57% of the patients
which was compatible with the literature, whereas autism
was found with a lower rate (9.5%). This difference was
thought to have arised from the sample size.

It was reported that resistant seizures developed in 65%
of the patients and remission occured in 34% (remission:
no seizures for at least one year) at the end of the follow-up
period in a study in which 248 patients with epileptic TSC
were followed up for 5.5 years (21). In another study, the
remission rate for seizures was reported to be 14%, but
exacerbation was observed in 25% of these patients in the
follow-up (15). At the end of 9 month-10 year-follow-up, it
was found that seizures had a good prognosis in 47.6% of
our patients and seizures were controlled in 38%. Although
interpretation is not possible, since the results may vary
according to follow-up times and sample size, we can say
that the response to epilepsy treatment in our patients was
not very different compared to the literature.

Although the factors which affect the prognosis of
seizures were examined by other investigators previously,
there is no consensus on this subject. While it was reported
that onset of seizures below the age of 1 year in a study
and below the age of 6 months in another study might be
a risk factor for poor prognosis (8,15), Park ve ark. (37)
reported that onset of seizures below the age of one
was not related with poor prognosis as also reported in
our study. It has been reported that presence of infantile
spasm was a risk factor for resistant seizures in some
studies (8,21). Although the seizures of our patients who
were found to have infantile spasm showed a poorer
prognosis, the difference was not statistically significant.
This may be explained by the fact that some of our patients
who had some partial seizures other than infantile spasm
also showed a treatment-resistant seizure prognosis. In
addition, it has been reported in the literature that there is
no relation between infantile spasm and seizure prognosis
(37). Our findings suggest that seizure type and duration in
TSC patients alone are not significant in the prognosis in
terms of epilepsy.

It has been reported that cognitive functions would have
a better prognosis with vigabatrin treatment initiated in the
early period by early control of seizures in TSC patients
(38). However, we found no effect of initial vigabatrin
treatment on the prognosis of seizures in our TSC patients.

In a study conducted in 2003 with a small number of
TSC patients, presence of multifocal findings on EEG
was reported to be an indicator of poor prognosis (15).
This finding was supported by another study which was
conducted with 30 TSC patients in 2011 and showed the
relation between severe epileptic activity and poor seizure
prognosis (8). In the same year, Park et al. (37) reported
the presence of a relation between epileptic activity
found on the initial EEG and seizure prognosis. When the
initial EEG findings of our patients were examined, good
seizure prognosis was observed in 67% of the patients
with a normal initial EEG and poor seizure prognosis was
observed in 67% of the patients who had severe findings
including multifocal epileptic activity and hypersrhythmia
on the initial EEG. However, no statistically significant relation
was found between our initial EEG findings and localization
of epileptic activity and seizure activity.

In the literature, the relation between epilepsy and
cortical tuber in TSC is one of the subjects which draws
much attention (7,8,34,39). It is thought that tubers are
epileptogenic, but the molecular basis of epileptogenesis
in cortical tubers is not known exactly (40,41). There are
different views about cortical tuber and epilepsy prognosis
(8,34,37,39). Some investigators have reported that there
is a relation between the number of cortical tubers and
seizure prognosis, while others have reported that tuber
load (tuber/brain ratio) rather than the number of tubers
has an effect on seizure control (8,9,39). A different view is
that there is no relation between the number of tubers and
epilepsy prognosis as concluded in our study (42).

It has been proven that giant cell astrocytoma which
is the most common brain tumor observed in TSC is
epileptogenic (7). However, it has been reported that giant cell astrocytoma increases the frequency of seizures in some studies (31). Frequent complex partial seizures continued in 2 of 5 patients in whom we found astrocytoma, while seizures occurred as status in one. In two patients, seizures showed a good prognosis. In our study, it was found that presence of astrocytoma on cranial MRI was not a risk factor for seizure prognosis.

Many studies have defended that there is a relation between mental retardation and seizure prognosis (8,21). It has been reported that intellectual and cognitive development retardation are observed in presence of resistant epilepsy in TSC patients. On the other hand, seizures have been reported to show a good prognosis in 82% of TSC patients who have a normal intellectual level (8,21). In our study, good seizure prognosis was found in 57% of our patients who had normal intellectual and cognitive development level and no statistically significant relation was found between seizure prognosis and intellectual or cognitive development level.

Although the epileptic seizure characteristics in our patients were not markedly different from the ones reported in the literature, it appears that it is not possible to predict the seizure prognosis according to clinical and laboratory findings. Conclusively, seizure prognosis varies according to different factors for individual TSC patients. Therefore, these patients should be monitored closely considering not only certain criteria, but all factors together. However, large-scale multi-center prospective studies which do not have the limitations of our study are needed to make healthier interpretations.

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References