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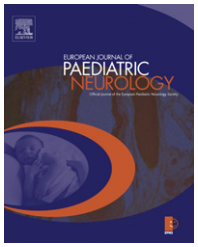

Original article

Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex

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ABSTRACT

Background: Epilepsy appears in 70–80% of patients with tuberous sclerosis complex, most commonly in the first year of age. Early manifestation of epilepsy is associated with drug-resistant epilepsy and mental retardation in more than 80% of patients. Clinical epileptic seizures are preceded by deterioration of EEG recording thus infants with high risk of epilepsy can be identified.

Aims: We hypothesized that preventative antiepileptic treatment of infants with multifocal activity on EEG might lower the incidence of drug-resistant epilepsy and mental retardation.

Methods: Forty-five infants with early diagnosis of tuberous sclerosis complex were included in the open-label study. They were divided in two groups: standard ($n = 31$) and preventative one ($n = 14$). In standard group the antiepileptic treatment was launched early, but after the onset of seizures. In preventative group medication was commenced when active epileptic discharges were seen on EEG, but before the onset of clinical seizures. Children were followed till the end of 2 years of age.

Results: At 24 months of age mental retardation was significantly more frequent and severe in "standard" vs "preventative" group (48% vs 14%; $p = 0.031$; mean IQ score 68.7 vs 92.3; $p < 0.05$). The "preventative" group was characterized by higher ratio of seizure-free patients (93% vs 35%; $p = 0.004$), lower incidence of drug-resistant epilepsy (7% vs 42%; $p = 0.021$) and lower number of patients requiring polytherapy (21% vs 55%; 0.039) than the "standard group.

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Conclusions: Preventative antiepileptic treatment of infants with tuberous sclerosis complex and high risk of epilepsy markedly improves their neurodevelopmental outcome and reduces the incidence of drug-resistant seizures.

1. Introduction

Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant disorder with an incidence of approximately 1 in 6000 livebirths,[1] that manifests itself with hamartomatous growths most commonly affecting the brain, skin, kidneys, heart, liver, eyes and lungs.[2] Molecular genetic studies have revealed two genes responsible for the development of clinical phenotypes: *TSC1* on 9q34 and *TSC2* on 16p13.[2]

Neurological manifestations, including seizures and mental retardation, are major morbidity causes in patients with tuberous sclerosis complex.[3] Epilepsy is the most common symptom appearing in 80 to 90% of patients, mainly in the first year of life.[3,4]

The prevalence of mental retardation is 40–70%[5–7] and severe or profound mental retardation (defined as IQ lower than 36) is reported in 30–45% of patients.[8,9] There is a strong association between mental retardation and epilepsy. In the large series of 160 patients from Mayo Clinic Gomez found that all patients with mental retardation had history of epilepsy, and none without seizures had mental retardation.[3] These findings were confirmed by recent studies.[7,10] Early onset of epilepsy in tuberous sclerosis complex, especially manifested by infantile spasms, is critically associated with severe forms of mental retardation.[5,6,7,10]

The earliest symptoms of TSC include heart tumors and cortical tubers, which can be seen even prenatally.[2] Introduction of routine fetal echocardiography and increasing availability of fetal MRI in recent years gave us a possibility to diagnose tuberous sclerosis complex very early and follow up these children prospectively.

We present the first unbiased, prospective study of a group of children diagnosed with tuberous sclerosis complex prenatally or perinatally and regularly seen from the first months of life. Analysis of their EEG evolution and epilepsy characteristics enabled us to identify the children with high risk of epilepsy and mental retardation. In this group of patients we introduced a novel approach to epilepsy management. Preventative antiepileptic treatment was given to infants with epileptic discharges on EEG before the onset of clinical seizures. We present results of first comparative study of "standard" and "preventative" approaches and their impact on neurodevelopmental outcome of children with tuberous sclerosis complex.

2. Material and methods

2.1. Subjects

The study population for this prospective trial consisted of infants admitted to the Department of Neurology and Epileptology, The Children's Memorial Health Institute, Warsaw, Poland, with diagnosis of tuberous sclerosis complex established until the end of the second month of life according to criteria of Roach et al.[11] Most infants had multiple cardiac tumors revealed on prenatal echocardiography and subsequent neuroimaging and/or skin examination confirmed the diagnosis of TSC. Children presenting with seizures as a reason of referral were not enrolled in this study to avoid ascertainment bias. All the patients were followed-up at least till the end of 24 month of life.

2.2. Study design

We describe two groups of patients, according to the applied method of antiepileptic treatment: (1) a group with "standard" approach; medication with antiepileptic drugs was launched within a week after the onset of seizures (group S), and (2) a group with "preventative" treatment of epilepsy commenced within a week after appearance of active epileptic discharges on consecutive EEG, but before clinical seizures (group P). Both groups were followed prospectively till the end of 24th month of age.

Infants recruited between 2000 and 2006 were managed according to the standard epilepsy guidelines. The parents were informed about the tuberous sclerosis complex diagnosis and high risk of seizures and trained in seizures recognition. They were aware of contacting our study personnel as soon as they saw the seizures in order to facilitate early antiepileptic treatment.

The infants recruited between 2006 and 2008 were offered a new approach. Starting from the point when tuberous sclerosis complex diagnosis was established, electroencephalography was performed every 6 weeks and antiepileptic treatment was introduced as soon as epileptic discharges, defined as multifocal spikes, appeared on EEG. Patients with normal EEG recordings remained in follow up without antiepileptic medication.

In both groups of children, the antiepileptic drug of first choice was vigabatrin. The dosage regimen was 100–150 mg/kg per day. The visual field deficit is the well-recognized side effect of vigabatrin, but it cannot be adequately measured in infants and small children. In order to assess the impact of vigabatrin on vision in our patients, all children in P group and 16 children in S group underwent Visual Evoked Potentials (VEPs) examination before the introduction of vigabatrin and every 6 months during treatment.

All infants were seen every 6 weeks to assess the efficacy and safety of treatment. Follow-up neuropsychological assessment was performed in all infants at the age of 24 months.

The open-label study protocol was approved by the institutional bioethics committee of The Children's Memorial

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Health Institute, Warsaw, Poland, and written informed consent was obtained from the parents of the patients.

2.3. Outcome measures

The primary efficacy outcome for all study subjects was the result of neuropsychological evaluation at the age of 24 months.

Secondary efficacy outcomes included occurrence of epilepsy, age at epilepsy onset, morphology of seizures, number of seizure-free patients, drug resistance of epilepsy, number of patients with EEG normalization. Seizure freedom at the end of the study was defined as at least four-month period with no seizures. Epilepsy was considered as drug resistant if the patient continued to have two or more seizures per month despite the use of two or more antiepileptic drugs.[12]

2.4. EEGs evaluation

The EEG reports were assessed for the presence of disorganization of background activity, and focal, multifocal or generalized epileptic discharges. EEG was analyzed by an epileptologist who was blinded to the management of patients.

2.5. Neuropsychological assessment

All patients underwent neuropsychological evaluation based on Psyche-Cattell test at the age of 24 months by certified neuropsychologist blinded to the management of the patient. Patients were classified as intellectually normal when their score was 69 or more. Those with an IQ <69 were considered mentally retarded. Children with scores between 52 and 68 were classified as having mild mental retardation, those with score between 36 and 51 were classified as moderately retarded, and those with score 35 or less received a diagnosis of severe or profound mental retardation.

2.6. Statistical analysis

The statistical significant differences of the frequencies between the groups were assessed using the chi-square test for 2×2 tables. Depending on the number of observations in the table either regular Chi-square test was used, its corrected version, or the one with Yates correction.

The distribution of the quantitative variables was checked using Shapiro–Wilks and Kolmogorov–Smirnov tests. In case of non-normally distributed variables they were summarized by range and median. The differences between the groups were checked using Kolmogorov–Smirnov test.

Two-tailored p-value less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Demographic data

Thirty one patients (17 girls and 14 boys) were enrolled to S group and 14 patients (8 girls and 6 boys) were enrolled to P group. In all patients, 24-month-long follow-up was completed. Twenty-five patients in S group and 7 in P group underwent mutational analysis.

There were 6 patients with TSC1 mutation and 17 with TSC2 mutation in S group. In 2 cases in this group no mutation was identified. There was a similar proportion of TSC1/TSC2 mutations found in P group, with 2 and 5 patients, respectively.

3.2. EEG evaluation

3.2.1. Standard treatment group

In S group, EEG was routinely performed after seizure onset. In 6 patients, however, EEG was recorded before the onset of seizures demonstrating normal pattern in all recordings.

EEG recorded after the onset of seizures in S group showed hypsarrhythmia in 7 cases (23% of all patients in this group; 32% of patients with epilepsy), generalized multiple spikes or spike-wave activity in 8 cases (26%; or 36%, respectively), or localized spikes in 7 patients (23%; or 32%, respectively). Despite antiepileptic treatment, only in 2 patients (6% or 9% of patients with epilepsy) EEG turned to normal in the first two years of life.

3.2.2. Preventative group

In P group, EEG was performed every 6 weeks starting from the enrollment visit, till the end of 24-month follow-up. In 4 patients (29%), EEG remained normal throughout the study. In 10 patients initial EEG was normal and then deterioration was shown. Median age at epileptiform discharges onset in this group was 4 months. In 8 (57%) cases localized spikes and spike-wave activity was recorded, in 1 (7%) patient generalized polyspike activity, and in 1 (7%) patient hypsarrhythmia was recognized. In these patients, preventative antiepileptic treatment with vigabatrin was introduced. Preventative approach was associated with significantly higher number of patients whose EEG turned out to be normal at the age of 2 years ($p = 0.0007$ comparing whole S and P groups; or $p = 0.0001$ comparing only treated patients within P and S group) (Tables 1–3).

Table 1 – Electroencephalography findings in both groups of patients.

	Standard care group ($n = 31$)	Preventative group ($n = 14$)	p-Value
Patients with epileptiform discharges on EEG	22 (71%)	10 (71.4%)	Not significant
Patients with hypsarrhythmia	7/31 (22.6%) 7/22 with epilepsy	1/14 (7.1%) 1/10 with epileptic EEG	$p = 0.405$ $p = 0.378$
Normal EEG at the age of 24 months	11/31	12/14	$p = 0.005$*
Patients whose EEG turned to normal			
Whole group	2/31	8/14	$p = 0.0007$*
Pts receiving AEDs	2/22	8/10	$p = 0.0001$*

AED, antiepileptic drug.
*Statistically significant values.

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Table 2 – Clinical findings and characteristics in patients with standard approach (S group).

Cases: No/ gender/age at diagnosis	TSC criteria fulfilled at enrollment	Seizure onset (months)	Time from seizure to treatment onset (days)	Seizure type	Antiepileptic drugs	Seizure outcome	EEG outcome	Neuropsychological evaluation at 24 months of age
1, M, 1/12	MCT, SEN, SEGA, CT	2.5	5	IS + PMS	VGB, VPA, LEV, TPM, VNS	PMS remain, IS – ceased	Multifocal discharges	48
2, F, 1/12	SEN, CT, HM	4	7	IS, PMS	VGB, VPA	PMS remain, IS – ceased	Localized discharges	90
3, M, prenatal	MCT, HM, SEN, CT, SEGA	5	2	IS, PMS	VGB, VPA, ACTH, TPM	IS, PMS	HS	36 (severe hypoacusis)
4, F, 2/12	MCT, HM, CT, SEN, SEGA	5	1	IS, PMS	VGB, VPA, TPM, ACTH	PMS remain, IS - ceased	Multifocal discharges	41
5, F, prenatal	MCT, HM, SEN SEGA	8	7	PMS	VGB,	PMS	Localized discharges	78
6, M, 2/12	HM, SEN, CT, SEGA	5	5	PMS	VGB, VPA	PMS	Multifocal discharges	55
7, F, 1/12	MCT, HM, SEN,	No	NA	No	No	Seizure-free	normal	99
8, M, 1/12	HM, SEN, CT, SEGA	4	3	IS, PMS	VGB, VPA, ACTH	PMS remain, IS ceased	Multifocal discharges	37
9, F, 2/12	MCT, SEGA	No	NA	No	No	Seizure-free	Normal	111
10, F, prenatal	MCT, SEN, CT	2	3	PMS	VGB, VPA	PMS	Localized discharges	24
11, F, 1/12	MCT, CT	6	6	PMS	VGB	PMS	Multifocal discharges	63
12, M, 1/12	MCT, HM,	3	3	IS, PMS	VGB, VPA, ACTH	PMS remain, IS ceased	Multifocal discharges	39
13, F, 2/12	MCT, HM,	5	5	IS, PMS	VGB, VPA	PMS remain, IS ceased	Multifocal discharges	55
14, M, 2/12	MCT, HM, SEN, CT	2	7	IS, PMS	VGB, VPA, ACTH, TPM	IS, PMS	HS,	38
15, F, 1/12	MCT, HM, SEGA	4	5	PMS	VGB, VPA, ACTH	PMS	Multifocal discharges	42
16, M, 2/12	MCT, HM,	10	5	PMS	VGB, TPM	PMS	Localized discharges	70
17, M, prenatal	MCT, HM, SEN, CT	2,5	6	IS, PMS	VGB, TPM	IS, PMS	Multifocal discharges	38
18, M, 1/12	MCT, HM, SEGA, CT, SEN	2	5	PMS	VGB, VPA	Seizure-free	Multifocal discharges	61
19, F, 2/12	MCT, SEN	No	NA	No	No	Seizure-free	Normal	93
20, F, 1/12	MCT, SEN	5	7	IS	VGB, VPA	Seizure-free	Normal	81
21, M, 2/12	MCT, HM	9	5	PMS	VGB	Seizure-free	Multifocal discharges	74
22, F, 2/12	MCT, CT	No	NA	No	No	Seizure-free	Normal	89
23, M, 1/12	MCT, CT, SEN	15	7	PMS	VGB	PMS	Multifocal discharges	67
24, F, 1/12	HM, CT, SEN	No	NA	No	No	No	Normal	97
25, F, 2/12	HM, CT	No	NA	No	No	No	Normal	94
26, M, 1/12	MCT, CT, HM, SEN	No	NA	No	No	No	Normal	91
27, F, 2/12	MCT, CT	10	5	PMS	VGB	Seizure-free	Normal	97

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Table 2 (*continued*)

Cases: No/ gender/age at diagnosis	TSC criteria fulfilled at enrollment	Seizure onset (months)	Time from seizure to treatment onset (days)	Seizure type	Antiepileptic drugs	Seizure outcome	EEG outcome	Neuropsychological evaluation at 24 months of age
28, F, 1/12	CT, SEN, HM	No	NA	No	No	No	Normal	106
29, M, 1/12	MCT, HM, CT	7	6	PMS	VGB, TPM	PMS	Multifocal discharges	96
30, F, 1/12	MCT, HM, SEGA	No	NA	No	No	No	Normal	92
31, M, 1/12	MCT, SEGA, SEN, CT	2	5	PMS, IS	VGB, VPA, TPM, CBZ	PMS	HS	28

M, male; F, female; MCT, prenatally found multiple cardiac tumors; HM, hypomelanotic macules (3 or more); CT, cortical tubers; SEN, subependymal nodules; SEGA, subependymal giant cell astrocytoma; IS, infantile seizure; PMS, partial motor seizures; VGB, vigabatrin; VPA, valproic acid; LEV, levetiracetam; TPM, topiramate; NVS, nerve vagus stimulator; CBZ, carbamazepine; ACTH, adrenocorticotropic hormone; NA, not applicable.

Table 3 – Clinical findings and characteristics in patients with preventative approach (P group).

Cases: No/gender/ age at diagnosis (months)	TSC criteria fulfilled at enrollment	Epileptic discharges onset (months)	Seizure onset (months)	Seizure type	Antiepileptic drugs	Seizure outcome	EEG outcome	Neuropsychological evaluation at 24 months of age
1, F. 1/12	MCT, HM, SEN, SEGA, CT	3.5	5	IS + PMS	VGB, VPA, LEV, TPM	PMS remain, IS – ceased	Normal	68
2, F. 1/12	SEN, CT	2.5	No	No	VGB	Seizure-free	Normal	101
3, F. 1/12	MCT, HM, SEN, CT	3	6	PMS	VGB, VPA, ACTH, TPM	Seizure-free	Localized discharges	71
4, F. 1/12	MCT, HM,	2.5	No	No	VGB	Seizure-free	Normal	84
5, M. 1/12	MCT, HM,	5	5	PMS	VGB, VPA	Seizure-free	Normal	110
6, M. 2/12	MCT, HM, SEN, CT	4	No	No	VGB	Seizure-free	Normal	94
7, M. prenatal	MCT, HM, SEN,	7	No	No	VGB	Seizure-free	Normal	98
8, F. 2/12	MCT, HM, SEN, CT	4	4.5	PMS	VGB	Seizure-free	Normal	58 (severe familial hypoacusis)
9, M. prenatal	MCT, HM, SEN, CT	9	10	PMS	VGB	Seizure-free	Normal	132
10.M 1/12	SEN, CT	15	17	PMS	VGB, VPA	Seizure-free	Localized discharges	88
11. M 1/12	MCT, SEN, CT	No	No	No	No	Seizure-free	Normal	97
12. F. 1/12	MCT, HM, SEN, CT	No	No	No	No	Seizure-free	Normal	96
13. F 1/12	MCT, HM, SEN, CT	No	No	No	No	Seizure-free	Normal	100
14. F 1/12	MCT, HM, SEN, CT	No	No	No	No	Seizure-free	Normal	95

M, male; F, female; MCT, prenatally found multiple cardiac tumors; HM, hypomelanotic macules (3 or more); CT, cortical tubers; SEN, subependymal nodules; SEGA, subependymal giant cell astrocytoma; IS, infantile seizure; PMS, partial motor seizures; VGB, vigabatrin; VPA, valproic acid; LEV, levetiracetam; TPM, topiramate; ACTH, adrenocorticotropic hormone.

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3.3. *Epilepsy outcomes*

Seizures developed in 22 (71%) patients in S group and in 6 (43%) patients in P group ($p = 0.072$) Mean time between the onset of seizures and treatment initiation in S group was 5 days (ranging from 1 day to 7 days).

In P group, seizures developed only in patients with previous EEG deterioration. All these patients had vigabatrin started before the onset of seizures. In patients with normal EEG, no seizures were recorded. Median age at onset of seizures in S group was 5.0 months (range from 2 to 15 months) and 5.5 months (range from 4 to 17 months) in P group ($p = 0.138$).

In P group epilepsy was much better controlled. At the end of the study, in P group only 1 of 6 patients with epilepsy (17%) presented with active epilepsy, while in S group, 20 out of 22 children (91%) were still experiencing seizures ($p = 0.0003$).

In P group, 3 patients required two or more antiepileptic drugs to control seizures, while in S group, polytherapy was necessary in 17 children ($p = 0.039$).

Drug-resistant epilepsy was also more frequently observed in S group: 13 patients (42%) in this group vs 1 child (7%) in P group ($p = 0.021$) (Table 4).

3.4. *Neuropsychological assessment*

Mental retardation was observed only in patients with epilepsy. It was significantly more frequent in S than in P group (15 patients, 48% vs 2 patients, 14%) ($p = 0.031$). At the age of 24 months, IQ score of patients in S group was significantly lower than in P group: mean 68.7 (range from 24 to 111) vs 92.3 (range from 58 to 132) ($p < 0.05$). Median values were 74 and 95.5, correspondingly.

In S group, intellectual disability was also significantly more severe than in P group. Severe and profound intellectual disability was found in 2 (6%) patients and moderate in 8 (26%) patients in S group. No patient in P group presented with severe/profound or moderate disability ($p = 0.043$) (Fig. 1, Table 4).

Table 4 – Comparison of seizure severity and mental outcome in standard and preventative treatment groups.

	Standard care group ($n = 31$)	Preventative group ($n = 14$)	p-Value
Number of patients with epilepsy	22 (71.0%)	6 (42.9%)	0.072
Median age at epilepsy onset (months)	5.0	5.5	0.138
Patients with infantile spasms	11 (35.5%)	2 (14.3%)	0.151
Patients requiring epilepsy polytherapy	17 (54.8%)	3 (21.4%)	0.039*
Patients with drug-resistant epilepsy	13 (41.9%)	1 (7.1%)	0.021*
Seizure-free patients at the age of 24 months	11 (35.4%) 2/22 with epilepsy	13 (92.9%) 5/6 with epilepsy	0.004* 0.0003*
Mean IQ score at the age of 24 months	68.7 Median 74.0 (Range 24–111)	92.3 Median 95.5 (Range 58–132)	$p < 0.05$*
Patients with intellectual disability at the age of 24 months	15 (48.4%)	2 (14.3%)	0.031*
Patients with mild intellectual disability at the age of 24 months	5 (16.1%)	2 (14.3%)	0.876
Patients with moderate, severe, and profound intellectual disability at the age of 24 months	10 (32.4%)	0 (0%)	0.036*

IQ, intellectual quotient.
*Statistically significant values.

4. Discussion

This is the first study showing the beneficial effect of preventative antiepileptic treatment on intellectual outcome and epilepsy severity in children with high risk of epilepsy. Our study population consisted of infants with tuberous sclerosis complex and thus was homogenous in regard to etiology of epilepsy. Mental retardation is common in tuberous sclerosis complex and for parents receiving the diagnosis in their child, it is the most overwhelming symptom of the disease.

Several interrelated factors, including onset and type of epilepsy, cortical tubers number and load, TSC1 or TSC2 mutation, and others, are believed to account for mental retardation in this disorder.[5,7] Our two groups of patients did not differ in the initial tuberous sclerosis complex symptoms, demographic data, and TSC1/TSC2 mutation ratio.

The most striking fact is that vast majority of patients, who did not develop epilepsy, do not also develop mental retardation.[3,5,8,9] On the other hand, in epileptic patients, especially in those with history of infantile spasms, mental retardation is recognized in 80–100%.[5,13]

In our study, we were successful to reduce the percentage of patients with epilepsy by use of preventative antiepileptic treatment. Consequently, only 14% of patients in this group presented with intellectual disability and none had moderate or worse mental retardation at the age of 24 months. However, as learned from other reports such treatment should be maintained at least till the end of the second year of life.[14]

Several studies show[12,15] that the longer the duration of seizures from the onset to cessation, the greater the risk of mental retardation. It is worth to note, that in our traditionally treated patients, those with epilepsy received antiepileptic drug in one week after the onset of seizures as latest and still 15 out of 22 patients with epilepsy (68%) developed mental retardation. Sixty-eight per cent, however, is less than previously reported in series of patients in whom the treatment lag was longer.[3,5,13] This is in conjunction with the study of Bombardieri et al.,[15] who found that implementation of VGB as early as within a week from the onset of seizures resulted in better cognitive outcome than delayed treatment. However, in their group of patients, still 70% presented with mental retardation.

Recently, data is accumulating that the cognitive manifestations in epilepsy are associated with epileptic discharges recorded on EEG.[10,16–18] Prolonged duration of continuous epileptic activity is considered to be deleterious for

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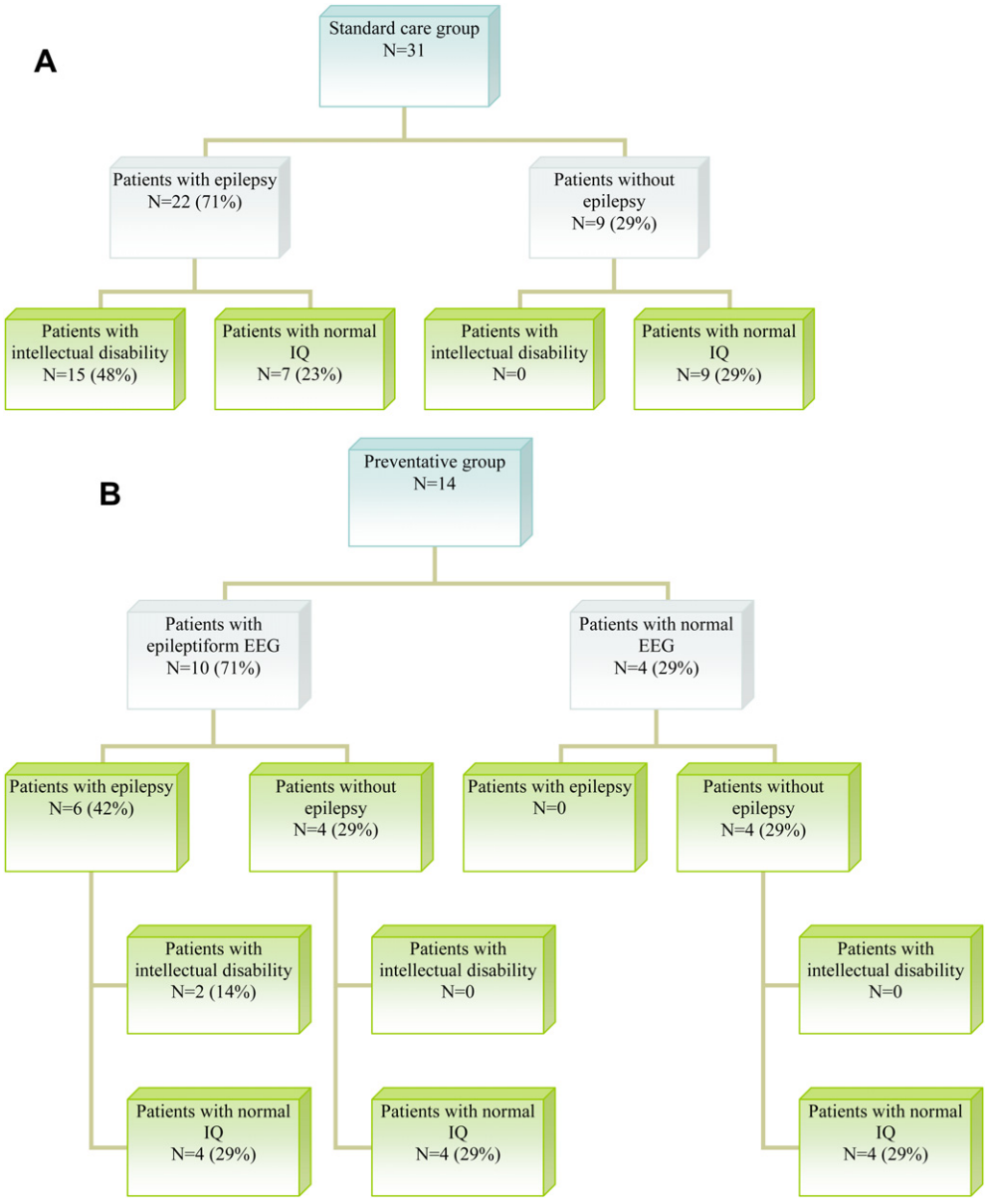

Fig. 1 – Intellectual outcome in children of our cohort of 45 infants with early diagnosis of tuberous sclerosis complex, depending on the approach to epilepsy management. (A) Antiepileptic treatment introduced within 1 week after clinical seizures appearance; 52% of patients presented with normal IQ at the age of 24 months; (B) antiepileptic treatment was introduced when epileptic activity appeared on EEG recording and before the onset of clinical seizures; 86% of patient presented with normal IQ at the age of 24 months.

intellectual outcome in young children.[16,18] Primec et al.[19] showed that three weeks of hypsarrhytmia significantly increases the risk of mental retardation in infants with epilepsy. It was shown by Philippi et al.[20] in their retrospective study that hypsarrhytmia is preceded by gradual deterioration of EEG over a period of 3–6 weeks. They called this clearly distinguishable prehypsarrhytmic EEG pattern a "point of no return", as if not treated, all the children who reached it, later developed West syndrome with mental retardation. The authors introduced antiepileptic treatment in 4 children in this prehypsarrhytmic period, despite no clinical seizures being observed, and none of them developed West syndrome. In our study, preventative antiepileptic treatment markedly reduced the risk of mental retardation.

Philippi et al.[20] showed also that hypsarrhytmia preceded the onset of infantile spasms for up to 26 days. This means that even if antiepileptic treatment was introduced at the day of seizure onset, the child might be as far as 3–10 weeks ahead of "point of no return" for mental deterioration. Our findings indirectly provide further support for these statements, as the median age of epilepsy onset was 5.5 months, and median age at the onset of epileptiform discharges on EEG was 4 months. Moreover, damage to the brain made by constant epileptic activity not only results in neuronal loss and disturbed

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myelination and maturation, but also may induce the expression of multidrug resistance gene thus leading to the development of drug-resistant epilepsy.[21] As shown in our study, preventative antiepileptic treatment lowers risk of drug-resistant epilepsy which confirm the results of similar studies on preventative treatment from animal models.[22]

Cortical tubers in tuberous sclerosis complex show reduced inhibition by gamma-aminobutyric acid (GABA)[23] and vigabatrin, an analogue of GABA, has been shown to be particularly effective in treating infantile spasms owing to this etiology.[24,25] This drug was proposed as the first-line medication for infantile spasms as well as partial seizures in tuberous sclerosis complex.[15,24] Vigabatrin is considered to be relatively safe in children, with the exemption of a specific side effect of peripheral visual field defect occurring in about 15% of treated patients.[26] However, Guzzetta et al.[27] found no visual impairment in infants with West syndrome, treated with VGB. As the percentage of patients receiving antiepileptic drugs in our two groups of patients did not differ, we believe that we offered the preventative antiepileptic treatment only to those children who without treatment would develop epilepsy on further follow up.

In conclusion, our study shows that in children below 2 years of age treatment with vigabatrin may markedly improve the neuropsychological outcome in tuberous sclerosis complex if commenced after the deterioration of EEG, but before the onset of seizures.

At present we recommend to carry out neuroimaging and skin examination in every child suspected of having tuberous sclerosis complex, especially in newborns with multiple cardiac tumors. If the diagnosis is confirmed, serial EEG recordings should be performed to identify infants with high risk of epilepsy. In those infants, antiepileptic treatment with vigabatrin should be introduced and continued till the end of the second year of age.

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