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Original Article

Preventive Antiepileptic Treatment in Tuberous Sclerosis Complex: A Long-Term, Prospective Trial

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ABSTRACT

Backgroud: Drug-resistant epilepsy is the main risk factor for future intellectual disability in patients with tuberous sclerosis complex. Clinical epileptic seizures are often preceded by electroencephalographic changes, which provide an opportunity for preventive treatment. We evaluated the neuropsychologic and epilepsy outcomes at school age in children with tuberous sclerosis complex who received preventive antiepileptic treatment in infancy.

Methods: We performed a prospective, nonrandomized clinical trial with 14 infants diagnosed with tuberous sclerosis complex in whom serial electroencephalographic recordings were performed and preventive treatment with vigabatrin initiated when active epileptic discharges were detected. An age-matched control group consisted of 31 infants with tuberous sclerosis complex in whom treatment with vigabatrin was given only after onset of clinical seizures. Results of clinical assessment of epilepsy and cognitive outcomes were analyzed.

Results: All patients in the preventive group (n = 14) and 25 of 31 patients in the standard treatment group were followed through minimum age five years, median 8.8 and 8.0 years in the preventive and standard groups, respectively. The median intelligence quotient was 94 for the preventive group when compared with 46 for the standard group ($P < 0.03$). Seven of 14 patients (50%) in the preventive group never had a clinical seizure when compared with one of 25 patients (5%) in the standard treatment group ($P = 0.001$).

Conclusions: This study provides evidence that preventive antiepileptic treatment in infants with tuberous sclerosis complex improves long-term epilepsy control and cognitive outcome at school age.

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Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder characterized by hamartomatous growths that may affect the brain, skin, retina, heart, kidneys, and lungs, which is due to mutation in either *TSC1* or *TSC2*.[1] Some TSC lesions, such as cardiac rhabdomyomas and cortical tubers, are often detected prenatally, whereas other lesions develop much later in life.[1,2] Neurological manifestations of TSC, including seizures and intellectual disability, are major issues in the care of infants and children with TSC and have significant impact on the quality of life of the patients and their families.[3] Epilepsy occurs in 70% to 90% of patients, typically beginning in the first year of life.[4] Refractory epilepsy is diagnosed in half of individuals with TSC and is predictive of development of intellectual disability, which occurs in 40% to 70% patients with TSC.[5-7]

Although new antiepileptic drugs (AEDs) continue to be developed, the percentage of patients with drug-resistant epilepsy remains stable.[8] Hence one approach that may lead to a better clinical outcome is early intervention with AEDs during the development of epilepsy (epileptogenesis). Epileptogenesis is a cascade of molecular and cellular events, which begins with a brain insult (injury, genetic predisposition, metabolic disease). It has been shown in both clinical and preclinical models that between the triggering factor and clinical seizure onset there is a latent period of epileptogenesis which may last for weeks or months.[9,10] Experimental and a few clinical studies have shown that the introduction of an antiepileptic treatment during epileptogenesis and before the start of clinical seizures may prevent epilepsy onset and lead to a reduction in drug-resistant epilepsy.[10-12]

In recent years the implementation of routine fetal echocardiography and the increased availability of fetal magnetic resonance imaging have made it possible to diagnose TSC in fetuses and newborns, before the onset of epilepsy.[13] This diagnosis has made it feasible for prospective studies of epileptogenesis and epilepsy prevention in TSC.[9] Analysis of the electroencephalographic (EEG) evolution and epilepsy characteristics enabled us to identify children with TSC at high risk of epilepsy and intellectual disability before clinical seizures appear.[14] In 2006, we initiated a prospective trial of EEG monitoring in infants with TSC, to enable a preventive approach to epilepsy management, using vigabatrin. In 2011, we reported the beneficial effect of preventive versus standard approach to epilepsy treatment on the neurodevelopmental outcome of children with TSC within the first 24 months of life.[12] Here we present the results of an extended, long-term, prospective follow-up of children diagnosed with TSC prenatally or in early infancy, who received preventive treatment, and compare their cognitive and epilepsy outcomes with those of patients who received routine treatment after onset of clinical seizures.

Materials and methods

Study design

All patients for this long-term, prospective, nonrandomized, controlled study were evaluated at the Department of Neurology and Epileptology, The Children's Memorial Health Institute, Warsaw, Poland. The design of the study was described earlier in the published article reporting outcomes achieved within the first 24 months of patients' life.[12] All children were diagnosed with TSC by the end of the second month of life according to criteria of Roach et al.[15] Children identified before 2006 were managed according to the standard epilepsy guidelines and received antiepileptic treatment with vigabatrin within a week after first clinical seizures were reported by caregivers or noticed by medical professionals (standard treatment group). In this group, EEG was routinely performed after seizure onset.

The infants recruited between 2006 and 2008 were offered a new approach and are included as the preventive group. The children were followed with serial one-hour video-EEG recordings and treatment with vigabatrin was introduced within a week after epileptiform discharges were observed and before any clinical seizure. The patients were treated with vigabatrin at a dose of 100 to 150 mg/kg/day. In this group, starting from the moment of TSC diagnosis, an EEG was performed every four to six weeks during the first 24 months of life, as currently recommended by Curatolo et al.[16] If no clinical seizures were detected by the end of the second year of life, the treatment was tapered and discontinued. Caregivers of all children were provided with thorough information regarding the typical TSC disease course and likelihood of seizures and trained in seizure recognition.

After having completed the prospective study (at age 24 months) described in an article published in 2011,[12] patients' caregivers were asked to participate in the current long-term prospective study. The protocol was approved by the Institutional Review Board of the Children's Memorial Health Institute, Warsaw, Poland, and written informed consent was obtained from the patients' caregivers. All children were followed up with at least annual visits as recommended by routine clinical management in patients with TSC.[17] The battery of clinical investigations included epilepsy assessment, neuropsychologic evaluation, and general pediatric examination.

End points

The primary end point of the study was the long-term neuropsychologic outcome assessed at age at least five years. To compare the results of neuropsychologic assessment with the previous results in the same cohort of patients with TSC,[12] neuropsychologic examination included the previously used tests validated for the Polish population: Wechsler Intelligence Scale for Children-Revised[18] or the Terman-Merrill or the Psyche-Cattell tests,[19] depending on the patients' age and cognitive skills. Raven's Progressive Matrices[20] were applied in one patient due to severe familial deafness.

The secondary end points included the incidence of clinical epilepsy and drug-resistant seizures, the percentage of seizure-free patients, patients with normalized EEG, and patients in whom AEDs could have been successfully withdrawn in both groups. Seizure remission at the last follow-up visit was defined as at least four months without seizures. Epilepsy was defined as drug-resistant if the patient continued to have two or more seizures per month despite the use of two or more antiepileptic therapies, including AEDs, ketogenic diet, vagus nerve stimulation, and epilepsy surgery. Polytherapy was defined as the use of two or more AEDs. After age 24 months, the EEGs have been performed in response to clinical conditions.

Statistical analysis

Interdependency of nominal variables was assessed using the chi-square test with "N−1" correction.[21] If the expected number of observations was lower than one, Monte Carlo simulation with one million replicates was implemented. Owing to small group sizes, it was difficult to estimate whether they comply with the assumptions of parametric tests; therefore comparison of median values between the groups was assessed using the Wilcoxon rank sum test. In cases of missing variables patients were excluded from comparisons. $P < 0.05$ was considered to be statistically significant.

TABLE 1.
Clinical Characteristics in the Preventive Group

Patient ID	Gender (Age of Last Observation (Years))	TSC Mutation	Last EEG	Age at the Last EEG (Years)	Onset of Antiepileptic Treatment (Months)	Clinical Seizure Onset (Months)	Seizure Type	AED(s) Used at the Last Visit	Age at Withdrawal of AED(s) (Years)	Seizure Frequency at the Last Observation	Age at the Last Psychologic Evaluation (Years)	IQ at the Last Evaluation
1	Female (9.5)	*TSC2*	F, G	9.5	3.5	5.5	Focal	VGB, VPA, LAC + everolimus	-	4-5/day	9	25
2	Female (7.5)	*TSC2*	Normal	7.5	2.5	Never	-	Withdrawn	3.5	-	6.5	93
3	Female (8.5)	*TSC2*	F, G	8.5	3	6	Focal	VGB, VPA, TPM + sirolimus	-	4-5/day	9	21
4	Female (9.75)	nt	F	9.5	2.5	114	Focal	VGB	6 (Reintroduced at 9.5 years)	4-5/week	9.5	83
5	Male (7)	*TSC2*	F, G	7	5	5.25	Focal	Withdrawn	6.5	Remission	7	109
6	Male (10)	*TSC2*	F	10	4	Never	-	Withdrawn	8	-	6	103
7	Male (9.5)	nt	Normal	9.5	7	Never	-	Withdrawn	3	-	9.5	89
8	Female (8.5)	*TSC1*	F	8.5	4	4.5	Focal	VGB, VPA, TPM, CLB	-	Every second day	8.5	100
9	Male (8.5)	*TSC1*	Normal	8.5	9	10	Focal	Withdrawn	5	Remission	8.5	119
10	Male (11.5)	nt	G	11.5	15	17	Focal	VGB, VPA	-	2-3/week	11	42
11	Male (9.5)	*TSC1*	Normal	9.5	29	Never	-	Withdrawn	5	-	7	100
12	Female (9)	nt	No data	2	Never	Never	-	-	-	-	8	Normal IQ*
13	Female (7)	nt	F	5.5	Never	Never	-	-	-	-	7	Normal IQ*
14	Female (7)	*TSC2*	F	7	Never	Never	-	-	-	-	5	95

Abbreviations:
AED(s) = Antiepileptic drug(s)
CLB = Clobazam
EEG = Electroencephalography
F = Focal discharges
G = Generalized discharges
IQ = Intelligence quotient
LAC = Lacosamide
nt = Not tested
TPM = Topiramate
TSC = Tuberous sclerosis complex
VGB = Vigabatrin
VPA = Valproic acid

* Parents of these patients refused to control neuropsychologic development. However, these children have never developed seizures and were not preventatively treated with VGB. On the basis of a phone interview, these patients attended regular primary school and did not experience cognitive problems in everyday life.

TABLE 2.
Clinical Characteristics in the Standard Treatment Group

Patient ID	Gender (Age at the Last EEG (Years))	TSC Mutation	Result of the Last EEG	Epilepsy Onset (Months)	AED(s) Used at the Last Visit	Age at Withdrawal of AED(s) (Years)	Seizure Type	Seizure Frequency at the Last Observation	Age at the Last Psychologic Evaluation (Years)	IQ at the Last Evaluation
1	Male (7.5)	*TSC2*	F	2.5	VGB, VPA, LTG	-	Focal	Every 2 weeks	7	12
2	Female (5.5)	*TSC2*	F	3	VGB, VPA	-	Focal	Several times per months	5.5	46
3	Male (9)	nt	F	3	OXC	-	Focal	Remission	9	27
4	Female (8)	nt	F	8	VPA, CLB, tiagabine	-	Focal	Daily	9	10
5	Male (5.5)	*TSC2*	G	5	LTG, TPM, OXC	-	Focal	Every 2 weeks	4	57
6	Male (6.5)	*TSC2*	Normal	8	Withdrawn	6	Focal	Remission	5.5	121
7	Male (9)	*TSC2*	Normal	5	Withdrawn	6.5	Generalized	Remission	5.5	98
8	Female (9)	*TSC2*	Normal	25	VGB, OXC	-	Focal	Remission	6	90
9	Male (10)	nt	Normal	7	VGB	-	Focal	Remission	11	94
10	Female (10)	*TSC2*	F	1	VGB, LEV, TPM + everolimus	-	Focal	Daily	9	29
11	Male (7)	*TSC2*	F	5	VPA	-	Generalized	Remission	8	27
12	Female (8.5)	nt	F, G	7	VGB, VPA	-	Focal	Remission	6	30
13	Female (8)	NMI	F, G	7	VGB, VPA, CLZ	-	Focal	Daily	8	38
14	Male (9)	*TSC2*	Normal	3	Withdrawn	10.5	Generalized	Remission	4.5	55
15	Male (7)	*TSC2*	F	16	VGB	-	Generalized	Remission	10	47
16	Male (10)	NMI	G	9	VGB, VPA + everolimus	-	Generalized	Several times per month	5	72
17	Male (7.5)	*TSC2*	F	22	VGB	-	Generalized	Remission	6.5	103
18	Female (6)	*TSC1*	G	15	VPA, CLZ	-	Generalized	Every 3-4 days	5.5	27
19	Female (8)	*TSC2*	F	10	Withdrawn	5.5	Focal	Remission	9	100
20	Male (8)	*TSC1*	F	12	VGB, VPA, TPM, OXC	-	Focal	Daily	7.5	10
21	Male (9.5)	nt	F	11	VGB	-	Focal	Sporadic	10	44
22	Male (9.5)	nt	F	36	CBZ	-	Focal	Remission	10.5	62
23	Male (5)	*TSC2*	F	10	VGB, VPA + sirolimus	-	Generalized	Remission	5	51
24	Male (5.5)	*TSC1*	Normal	-	-	-	-	-	7.5	44
25	Male (7.5)	*TSC2*	Normal	6	VGB, LTG	-	Focal	Daily	7.5	27

Abbreviations:
AED(s) = Antiepileptic drug(s)
CBZ = Carbamazepine
CLB = Clobazam
CLZ = Clonazepam
EEG = Electroencephalography
F = Focal discharges
G = Generalized discharges
IQ = Intelligence quotient
LEV = Levetiracetam
LTG = Lamotrigine
NMI = No mutation identified
nt = Not tested
OXC = Oxcarbazepine
TPM = Topiramate
TSC = Tuberous sclerosis complex
VGB = Vigabatrin
VPA = Valproic acid

TABLE 3.
Comparison of Intellectual and Epilepsy Outcomes at the Last Follow-Up Visit in the Preventive and Standard Group

Group Characteristics	Standard Group (n = 25)	Preventive Group (n = 14)	*P* Value
Median IQ at last observation (mean)	46 (52.8)	94 (81.6)	<0.03
Median IQ at the last observation in patients treated with AED(s) (mean)	46.5 (53.2)	93 (80.4)	<0.04
Patients with intellectual disability, n (%)	18 (72)	3 (21)	0.003
Patients with intellectual disability among patients treated with AED(s), n (%)	17 (71)	3 (21)	0.02
Patient with moderate, severe, and profound intellectual disability, n (%)	15 (60)	3 (21)	0.02
Patients with epilepsy	24 (96)	7 (50)	0.001
Patients requiring epilepsy polytherapy (≥2 AEDs), n (%)	13 (52)	4 (29)	0.16
Patients with drug-resistant epilepsy, n (%)	10 (40)	4 (29)	0.5
Mean number of AEDs in use	1.6	0.9	<0.04
Patients in whom AEDs were withdrawn, n/N (%)	4/24 (17)	6/11 (55)	<0.03
Patients with normal EEG, n (%)	7 (28)	4 (31)	0.86

Abbreviations:
AED(s) = Antiepileptic drugs
EEG = Electroencephalography
IQ = Intelligence quotient

Results

Patient characteristics

All 14 children recruited between 2006 and 2008, who had been offered preventive treatment based on the observations of EEG abnormalities completed long-term follow-up. Their baseline characteristics were described previously.[12] The preventive group included eight girls and six boys. The age of patients at the last follow-up ranged from seven to 11.5 years (median: 8.8, mean: 8.8) in the preventive group (Table 1). In the standard treatment group, 25 patients from the initially included 31 completed the long-term observation. In three patients it was not possible to collect information about any of the studied outcomes. In the remaining three patients, all attempts of contact were unsuccessful. There were eight girls and 17 boys in the standard treatment group. The age of patients ranged from five to 10 years (median: 8.0, mean: 7.8) at the last follow-up (Table 2). *TSC1* versus *TSC2* mutations were similarly distributed in both groups (three patients with *TSC1* and six with *TSC2* in preventive and three with *TSC1* mutation and 14 with *TSC2* in standard group; $P > 0.3$). In the remaining patients in both groups genetic testing was not performed or no mutation was identified (Tables 1 and 2).

Cognitive outcome

Preventive group

In the preventive group the median age at the last neuropsychologic assessment was 8.3 years (range: five to 11) (Table 1). The median intelligence quotient (IQ) score in the preventive group was 94 (Table 3). Three of 14 patients (21%) had moderate or severe intellectual disability with IQ scores of 42, 25, and 21 (Table 1). Two of 14 caregivers refused IQ assessment. However, these two children never developed evidence of epileptogenesis or seizures, were not treated with vigabatrin or other AEDs, and were reported to have normal cognitive development, attending regular primary school without special needs.

Standard group

In the standard treatment group the median age at the last neuropsychologic assessment was 7.5 years (range: four to 10) (Table 2). The median IQ score in the standard group was 46 (Table 3). Eighteen children (72%) were diagnosed with intellectual disability, including three patients (12%) with mild, six (24%) with moderate, six (24%) with severe, and three (12%) with profound intellectual disability.

Comparison of preventive and standard group

The long-term neuropsychologic outcome was significantly better in the preventive group than in the standard treatment group (median IQ 94 versus 46; $P < 0.03$). Furthermore, significantly fewer patients had intellectual disability (21%) when compared with the standard approach cohort (72%; $P = 0.003$). These differences were also observed when comparing patients treated with AEDs (due to EEG abnormalities or clinical seizures) (Table 3).

Epilepsy outcome

Preventive group

EEG and epilepsy data for the preventive group are summarized in Fig and Table 1. EEG data at the last follow-up visit were available for 13 patients. One patient had no EEG results after age 24 months; the patient was seizure-free from birth untill the last follow-up visit at age nine years. At the last EEG recording, four of 13 patients (31%) had a normal EEG recording, five (38%) displayed focal discharges, three (23%) exhibited both focal and generalized discharges, and one (8%) only had generalized abnormalities. Seven of 14 patients (50%) never had clinical seizures during follow-up, including three who received preventive treatment during the first 24 months of life, one who received treatment due to EEG abnormalities at age 29 months, and three who had neither EEG abnormalities nor seizures (Fig). In the other seven patients (50%), despite the introduction of preventive vigabatrin treatment, clinical seizures occurred. In six children these occurred within the first two years of life, and in one patient, at age 9.5 years, after vigabatrin had been discontinued (Fig). At the time of last observation, five of 14 children (36%) still suffered from seizures, including four of 14 (29%) who had drug-resistant epilepsy. Among the patients in whom antiepileptic treatment was initiated (11 patients, 79%), AEDs were successfully withdrawn in six (six of 11; 55%) (Fig and Table 1). At the last follow-up visit, only five patients (five of 14; 35%) in this group required antiepileptic treatment.

Standard group

In the standard treatment group seven children (28%) had a normal EEG, thirteen (52%) exhibited focal discharges, two (8%) displayed both focal with generalized discharges, and three (12%) had generalized abnormalities at the last observation (Table 2). Only one patient (4%) in the standard group never developed clinical seizures. The remaining 24 children (96%) developed epilepsy, and 11 of these children (44%) suffered from active seizures at the last visit, including 10 patients (40%) with drug-resistant epilepsy (Table 2).

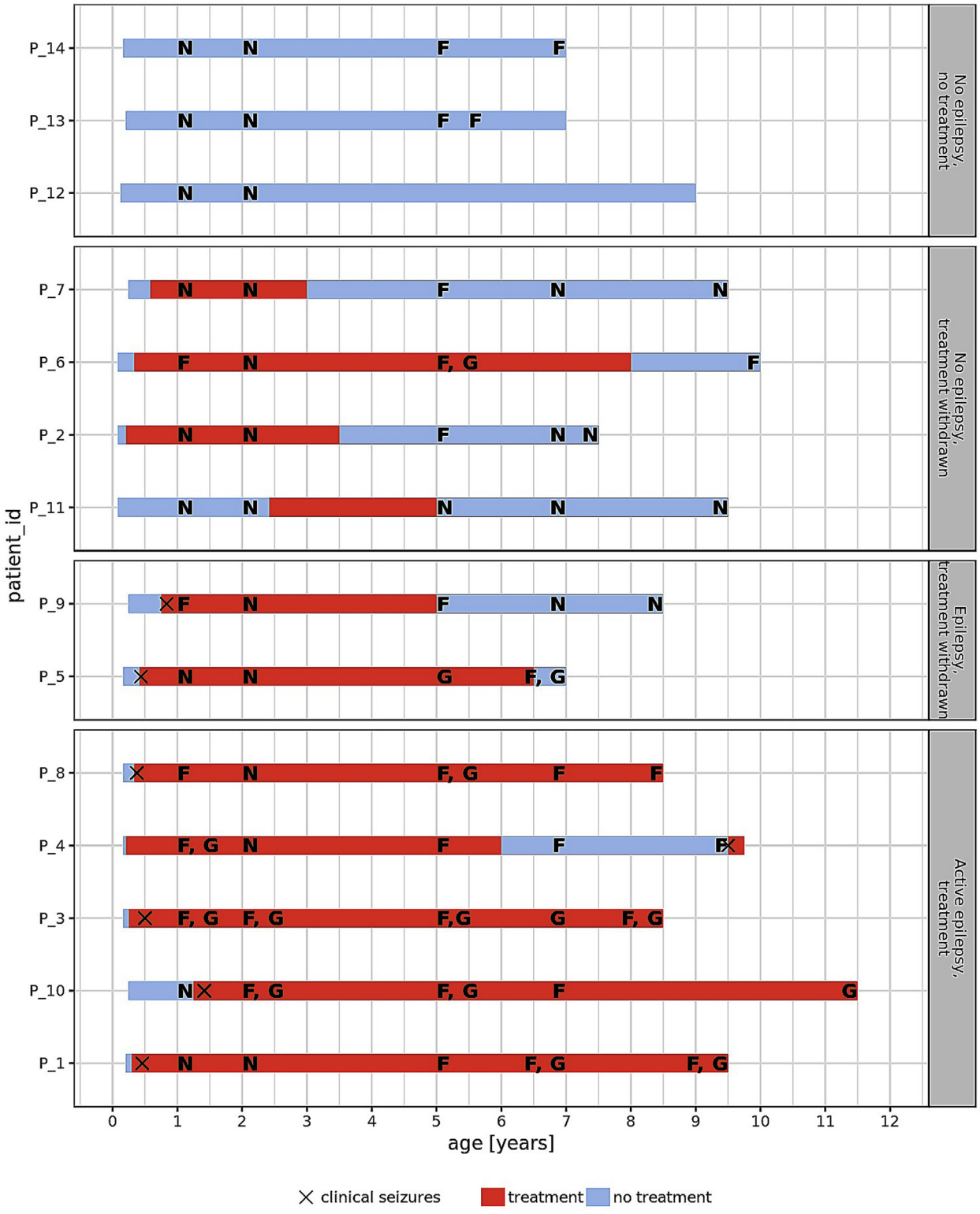

FIGURE. History of epilepsy, antiepileptic treatment, and electroencephalographic (EEG) results in the preventive group. EEG results are presented at twelfth and twenty-fourth months, fifth and seventh years, and last available EEG. F = Focal discharges; G = Generalized discharge; N = Normal EEG. The color version of this figure is available in the online edition.

Among the patients with epilepsy, successful AED withdrawal was possible in four (17%) of 24 children at a median age of 6.25 years (mean age: 7.1 years). Twenty of 25 patients (80%) required antiepileptic treatment at the last follow-up visit.

Comparison of preventive and standard group

At the last follow-up visit, significantly more children treated according to a standard approach had developed clinical seizures compared with patients in the preventive care (96% versus 50%;

$P = 0.001$); however, there was no significant difference in the incidence of drug resistance or seizure remission between the groups ($P = 0.5$ and 0.2, respectively) (Table 3). Children in the preventive group had a higher likelihood of successful AED(s) withdrawal in a long-term perspective (55% versus 17%; $P < 0.03$), and the number of utilized AEDs was lower in the preventive group than in the standard treatment group (mean: 0.9 versus 1.6; $P < 0.04$) (Table 3).

Safety

No significant adverse events due to treatment were observed. Special attention has been paid to visual field examination. However, owing to young age and insufficient attention of the examined the visual field examination was feasible in only three and one patient receiving vigabatrin during the study in preventive and standard group, respectively. In all cases results of the assessment were normal.

Discussion

This is the first long-term prospective study to show the beneficial effect of an epilepsy prevention strategy implemented during infancy on the neurodevelopmental and epilepsy outcome in school-aged children. It is well established that the earlier the onset of seizures, the poorer the epilepsy and neurodevelopmental outcome.[3,5,22] Our previous study and later reports confirmed that early serial EEG monitoring should be a routine in infants with TSC to identify those at high risk for epilepsy.[12,23,24] Serial video-EEG monitoring, used in our study, is a preferable method of patient assessment because of subtle presentation of focal seizures, which are commonly missed by parents of children with TSC.[14,24]

In our initial report, we showed that preventive treatment in infants improved neurodevelopmental outcome in children at age two years.[12] Our current results suggest that the effect is sustained. At school age, intellectual disability was diagnosed in 72% patients receiving standard antiepileptic treatment and in 21% children treated preventively.

The risk of developing clinical seizures by school age was 96% in the group receiving standard antiepileptic treatment and 50% in children who were treated preventively. The published risk of developing clinical seizures due to TSC varies between 70% and 90%.[4,25] However, there are few long-term prospective studies of patients diagnosed with TSC in early infancy. In our preventive group, the risk of developing clinical seizures by school age was lower than not only that in the comparative standard group but also those in other published TSC cohorts.[5,25,26]

Epilepsy associated with TSC is usually characterized as severe and drug-resistant.[25] About 40% to 60% patients suffer from infantile or epileptic spasms, and nearly two-thirds of the patients require multiple AEDs.[5,25,27] Our standard group recapitulated this scenario: 40% presented with drug-resistant epilepsy and 80% required antiepileptic treatment at school age. It should be highlighted that, at the time of study entry, the caregivers received detailed training on how to recognize first clinical seizures and were asked to refer to us immediately after first alarming events. Thus, children in this standard treatment group received antiepileptic treatment earlier than the patients who are diagnosed with TSC after seizures.[28,29] Our findings indicate that early TSC diagnosis is crucial for long-term epilepsy outcome. Early diagnosis also facilitates preventive treatment, and such an approach in our study resulted in a significant change of epilepsy characteristics: only 35% of children at school age required antiepileptic treatment and 29% developed drug-resistant epilepsy.

We did not observe adverse events from preventive treatment. The most serious complication of vigabatrin is visual field constriction, observed in 6% to 32% treated patients and possibly related to the cumulative vigabatrin dose.[30-33] Because of the young age of our patients at the last follow-up visit and the high incidence of intellectual disability in the standard group, a detailed visual field examination was not feasible in the majority of our patients. However, although the patients in the preventive group received vigabatrin earlier than the children in the standard group, the likelihood of medication withdrawal was significantly higher in the preventive group. Accordingly, patients in the preventive group were exposed to the possible adverse events of vigabatrin shorter than those in the standard treatment group.

Intellectual disability and drug-resistant seizures are major factors that negatively influence the quality of life of patients with epilepsy and their families.[34] Drug-resistant epilepsy is the most important socioeconomic burden associated with epilepsy.[35] We provide the first evidence that this burden might be significantly reduced with epilepsy-preventive strategies.

The main limitations of our study are its open-label design and the relatively low number of enrolled patients. Moreover, the two groups were not followed in parallel, as it was not possible for the caregivers to accept standard treatment while preventive strategy was implemented in our site. An important confounder in analysis is lack of *TSC* testing in all patients, because children with *TSC2* mutation generally have greater cognitive disability.[25,26]

The need for a randomized comparison of the standard and preventive approach in larger cohorts is addressed by two large studies on epilepsy prevention in patients with TSC: EPISTOP funded by 7th Framework Programme of European Commission (ClinicalTrials.gov Identifier: NCT02098759) (www.epistop.eu) and PREVENT in the United States (ClinicalTrials.gov Identifier: NCT02849457). Both projects are focused on the first two to three years of life. Our study indicates that these observations should be extended.

Conclusions

Our study is the first to document the long-term safety and efficacy of preventive antiepileptic treatment in children with TSC. We showed that preventive antiepileptic treatment introduced in infancy reduces the risk of clinical seizures, the number of required AEDs, and intellectual disability in school-aged children with TSC.

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