



# Historical Patterns of Diagnosis, Treatments, and Outcome of Epilepsy Associated With Tuberous Sclerosis Complex: Results From TOSCA Registry

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**Background:** Epilepsy is the most common neurological manifestation in individuals with tuberous sclerosis complex (TSC). However, real-world evidence on diagnosis and treatment patterns is limited. Here, we present data from Tuberous Sclerosis registry to increase disease Awareness (TOSCA) on changes in patterns of epilepsy diagnosis, treatments, and outcomes over time, and detailed epilepsy characteristics from the epilepsy substudy.

**Methods:** Tuberous Sclerosis registry to increase disease Awareness (TOSCA) was a multicentre, international disease registry, consisting of a main study that collected data on overall diagnostic characteristics and associated clinical features, and six substudies focusing on specific TSC manifestations. The epilepsy substudy investigated detailed epilepsy characteristics and their correlation to genotype and intelligence quotient (IQ).

**Results:** Epilepsy was reported in 85% of participants, more commonly in younger individuals (67.8% in 1970s to 91.8% in last decade), while rate of treatments was similar across ages (>93% for both infantile spasms and focal seizures, except prior to 1960). Vigabatrin (VGB) was the most commonly used antiepileptic drugs (AEDs). Individuals with infantile spasms showed a higher treatment response over time with lower usage of steroids. Individuals with focal seizures reported similar rates of drug resistance (32.5–43.3%). Use of vagus nerve stimulation (VNS), ketogenic diet, and surgery remained low.

**Discussion:** The epilepsy substudy included 162 individuals from nine countries. At epilepsy onset, most individuals with infantile spasms (73.2%) and focal seizures (74.5%) received monotherapies. Vigabatrin was first-line treatment in 45% of individuals with infantile spasms. Changes in initial AEDs were commonly reported due to inadequate efficacy. TSC1 mutations were associated with less severe epilepsy phenotypes and more individuals with normal IQ. In individuals with TSC diagnosis before seizure onset, electroencephalogram (EEG) was performed prior to seizures in only 12.5 and 25% of subsequent infantile spasms and focal seizures, respectively.

**Conclusions:** Our study confirms the high prevalence of epilepsy in TSC individuals and less severe phenotypes with *TSC1* mutations. Vigabatrin improved the outcome of infantile spasms and should be used as first-line treatment. There is, however, still a need for improving therapies in focal seizures. Electroencephalogram follow-up prior to seizure-onset should be promoted for all infants with TSC in order to facilitate preventive or early treatment.

**Keywords:** epilepsy, registry, TOSCA, TSC, tuberous sclerosis complex

## INTRODUCTION

Epilepsy is a common manifestation of tuberous sclerosis complex (TSC), affecting 80–90% of individuals (1, 2). It usually presents during the first year of life with infantile (epileptic) spasms or focal seizures. Focal seizures remain the most frequent type after the first year of life, but individuals with TSC may develop almost all seizure types. In about two-thirds of individuals with TSC, seizures are refractory to anticonvulsant treatment (3), a much higher proportion than the 23% reported in the general epilepsy population (4). Epilepsy is associated with a wide range of TSC-associated neuropsychiatric disorders (TAND) including intellectual disability (ID), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD), as well as impaired health-related quality of life (HRQoL) (5–9).

Treatment options for TSC-associated epilepsy in the first year of life are specific to infantile spasms because of high rates and individuals' responsiveness to vigabatrin (VGB), a first-line treatment option. Antiepileptic drug (AED) recommendations in TSC after the age of 1 year are the same as in the general epilepsy population based on seizure types. Candidates for epilepsy surgery should be identified early in the course of the disease. Other non-pharmacological treatment options including ketogenic diet, and vagus nerve stimulation (VNS) should also

be considered early if the epilepsy is refractory (10). Evidence supports the use of mammalian target of rapamycin (mTOR)-inhibitors as adjunctive treatment to AEDs for treating focal epilepsy in TSC individuals, with a higher response rate in the younger subgroup aged below 6 years (11–13). Given the early onset, severity and significant impact of TSC-associated epilepsy on quality of life (QoL) (3, 5, 6), there is value in longitudinal population-based studies of detailed epilepsy characteristics.

The Tuberous Sclerosis registry to increase disease Awareness (TOSCA), which included individuals from 170 sites in 31 countries, was conceived to expand our understanding of different TSC manifestations, treatment patterns, and outcomes (14). Tuberous Sclerosis registry to increase disease Awareness consisted of a main study representing the diagnostic characteristics and associated clinical features, and six substudies, each focusing on specific TSC manifestations. In our initial publication, we reported characteristics of TSC-associated epilepsies (2). The key observations were (a) a typical onset pattern of focal seizures and infantile spasms in the first two years of life, (b), high rates of drug resistance in focal seizures compared to infantile spasms, and (c) a low proportion of individuals treated with non-pharmacological therapies, including epilepsy surgery. Here, we present data from the TOSCA final analysis, describing rates of epilepsy, treatment interventions, and outcomes over time. We also report findings

from the epilepsy substudy, a TOSCA research project, aimed at reporting more detailed epilepsy characteristics including time to epilepsy diagnosis, electroencephalogram (EEG) patterns, and therapies.

## METHODS

Tuberous Sclerosis registry to increase disease Awareness was a multicentre, international disease registry. The study methods have been reported in detail previously (14). In the main study, general background information (i.e., demographic data, family history, pre-natal history, and disease features such as neurological and neuropsychiatric, renal, cardiovascular, pulmonary, dermatological, and others) were collected retrospectively at baseline (first inclusion visit) followed by prospective data collection during an observation period of up to 5 years. Follow-up visits were scheduled according to the standard practice of the site and per the treating physician's best judgement, but at minimum intervals of 12 months. Data were retrieved from clinical records, electronic medical records, individuals' questionnaires, and *ad-hoc* clinical databases. Research projects were designed to record additional, more detailed data related to specific disease manifestations [i.e., subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma, lymphangiomyomatosis, genetics, TAND, QoL, and epilepsy].

## Participants and Procedure

Individuals of any age who fulfilled clinical criteria for TSC diagnosis and a documented clinical visit for TSC within the past 12 months or newly diagnosed with TSC were enrolled in the main study. Investigators, specialized in epilepsy care, from 27 sites across nine countries (Belgium, France, Germany, Italy, Poland, Slovenia, Spain, Japan, and Turkey) participated in the epilepsy substudy.

Given the observational nature of the study, both diagnostic and treatment/management were performed according to local best practice. The study protocol, therefore, did not request any particular additional clinical or laboratory investigations.

Both main and substudy were designed and conducted according to the Guidelines for Good Clinical Practice and ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all individuals, parents, or guardians prior to enrolment, with prior endorsement by the local human research ethics committee.

## Data Analyses

From the main study, we present epilepsy characteristics, emphasizing changes in the rates of epilepsy diagnosis, treatment, and outcome over time. From the epilepsy substudy, we report characteristics [age of onset, frequency, tuber numbers, treatments and treatments outcomes, and intelligence quotient (IQ) level] of individuals with infantile spasms and focal seizures and correlated them to genotype. We report the impact of epilepsy characteristics and EEG foci on intellectual ability, date of EEG compared to the date of the seizure onset in individuals with focal seizures and infantile spasms with TSC diagnosis prior

to seizure onset, number of AEDs used at epilepsy diagnosis, and the reasons for changes in the AED regimen. Intellectual ability was categorized as normal (IQ > 70), mild ID (IQ 51–70), moderate ID (IQ 36–50), severe ID (IQ 20–35), and profound ID (IQ < 20). The response of individuals with infantile spasms was defined as follows: spasm-free + hypsarrhythmia resolved + normalized EEG or spasms free with disappearance of hypsarrhythmia, but persistent EEG anomalies. Efficacy in focal seizures was defined as >50% decrease in seizure frequency with rates of seizure freedom and response of >75%.

All eligible individuals enrolled in the TOSCA registry and epilepsy substudy, without any major protocol deviations, were included. As the study was observational in nature, primarily descriptive statistic methods were used. Continuous variables were evaluated quantitatively (frequency, mean, standard deviation, median, range), and categorical variables (presence/absence of a manifestation) were analyzed in terms of frequency distribution at baseline and at follow-up visits.

## RESULTS

### Findings From the Final Analysis of the Main Study

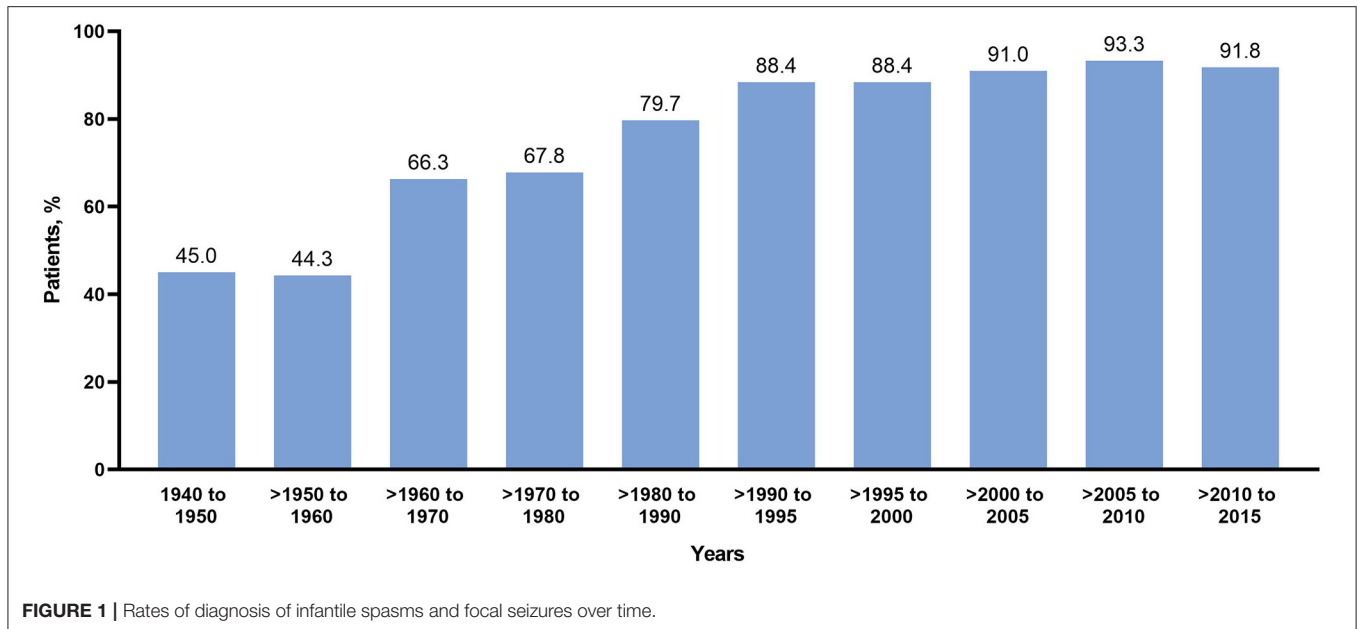
#### Clinical Characteristics of Epilepsy

Of the 2,211 individuals enrolled in the TOSCA main study, 1,879 (85%) were reported to have epilepsy. Of these, 942 (50.1%) were female and 937 (49.9%) were male (**Table 1**).

**TABLE 1** | Demographics and characteristics of individuals with TSC and epilepsy.

Characteristics	Individuals
<b>No. of individuals with epilepsy, n (%)</b>	1,879 (85.0)
<b>Sex, n (%)</b>	
Male	937 (49.9)
Female	942 (50.1)
<b>Age of individuals in years, n (%)</b>	
≤2	257 (13.7)
>2 to ≤5	282 (15.0)
>5 to ≤9	311 (16.6)
>9 to ≤14	276 (14.7)
>14 to ≤18	126 (6.7)
>18 to ≤40	499 (26.6)
≥40	128 (6.8)
<b>Type of epilepsy, n (%)</b>	
Infantile spasms	735 (39.1)
Focal seizures	1,343 (71.5)
Other seizures	537 (28.6)
<b>Median (range) age at diagnosis, years</b>	
Infantile spasms	<1 (0–30)
Focal seizures	1 (0–66)
<b>Genetic analysis</b>	
<b>Individuals with mutational analysis data available, n (%)</b>	849 (45.2)
TSC1	155 (18.3)
TSC2	587 (69.1)
No mutation identified	107 (12.6)

SD, standard deviation.



Focal seizures were reported in 1,343 individuals (71.5%), while infantile spasms were reported in 735 (39.1%). Five hundred and thirty-seven individuals (28.6%) were reported to have other seizure types. The median age at diagnosis was 1 year (range 0–66) for focal seizure and <1 year (range 0–30) for infantile spasms, respectively. Genetic data were available for 849 individuals with epilepsy; 587 (69.1%) had pathogenic mutations in the *TSC2* gene, while 155 (18.3%) had mutations in the *TSC1* gene. In 107 individuals (12.6%), no mutations were identified.

### Epilepsy Diagnosis, Treatment, and Outcome Patterns Over Time

Epilepsy diagnosis was more common in younger individuals, ranging from 67.8% in the 1970s to 91.8% in the last decade (Figure 1, Table 2). The rates of infantile spasms diagnosis increased from 24.6% in the 1960s to about 41.4% from the 1990s. The rates of focal seizures diagnosis increased from 29.6% in the 1950s to about 84% in 2000s (Figure 1).

More than 93% reported treatment for infantile spasms or focal seizures after 1960 (Table 2). Vigabatrin was the most commonly used AEDs in TSC individuals with infantile spasms and focal seizures in any year, with usage increasing over time and a clear shift after the late 1990s (>1950–1960: 33 and 50%; >1960–1970: 37.5 and 42.3%; >1970–1980: 40.7 and 50.9%; >1980–1990: 68.2 and 61.8%; >1990–1995: 62.9 and 66.7%; >1995–2000: 83.3 and 77.1%; >2000–2005: 86.2 and 69.1%; >2005–2010: 88.1 and 73.3%; >2010–2015: 91.2 and 76.9%). In contrast, usage of steroids for infantile spasms was at a peak (reported in 33.9%) between 1990 and 1995, decreasing thereafter (>1995–2000: 16.7%; >2000–2005: 13.8%; >2005–2010: 14.2%; >2010–2015: 10.0%).

Epilepsy surgery for infantile spasms was reported in only one of 66 individuals (1.5%) between 1980 and 1990. Epilepsy surgery

appeared as an alternative treatment for infantile spasms since 2000 and reached a peak in recent years (8.0% during 2005 and 2010). In individuals with focal seizures, use of the ketogenic diet was first reported in two individuals (1.5%) in 1980 with more regular use since 1995. Use of VNS was first reported in the late 1980s in patients with infantile spasms. Use of VNS showed a peak at the beginning of the 2000s (reported in 6% of individuals with infantile spasms and 7.8% in those with focal seizures), but there was a clear decrease thereafter. In contrast, the ketogenic diet showed a slow increase since its first use in this cohort but did not exceed 9% for infantile spasms and 12% for focal seizures. The use of mTOR inhibitors was reported in 17.1% of individuals with infantile spasms and 18.1% of individuals with focal seizures between 2010 and 2015.

Over time, individuals with infantile spasms responded better to treatment than those with focal seizures (Table 2); those with infantile spasms achieved a high response rate with a plateau since the late 1990s. This correlated to an increased use of VGB and a decreased use of steroids (Figure 2, Table 2). Outcome of focal seizures did not vary much since the 1960s, plateauing between 56 and 64% (Table 2).

### Findings From the Epilepsy Substudy

A total of 162 individuals (65 adults and 97 children) from 27 sites across nine countries were enrolled into the epilepsy substudy; 74 (45.7%) were males and 88 (54.3%) were females. The median age at enrolment was 14 years (range 2–63 years). Median duration of epilepsy prior to enrolment was 12 years (range 1–63 years).

Information about the type of treatment at epilepsy diagnosis was available in 68 of 71 individuals with infantile spasms and in 88 of 94 of those with focal seizures; 52 individuals (73.2%) with infantile spasms and 70 (74.5%) with focal seizures received monotherapies, while 16 (22.5%) with infantile spasms and 18 (19.1%) with focal seizures received polytherapies.

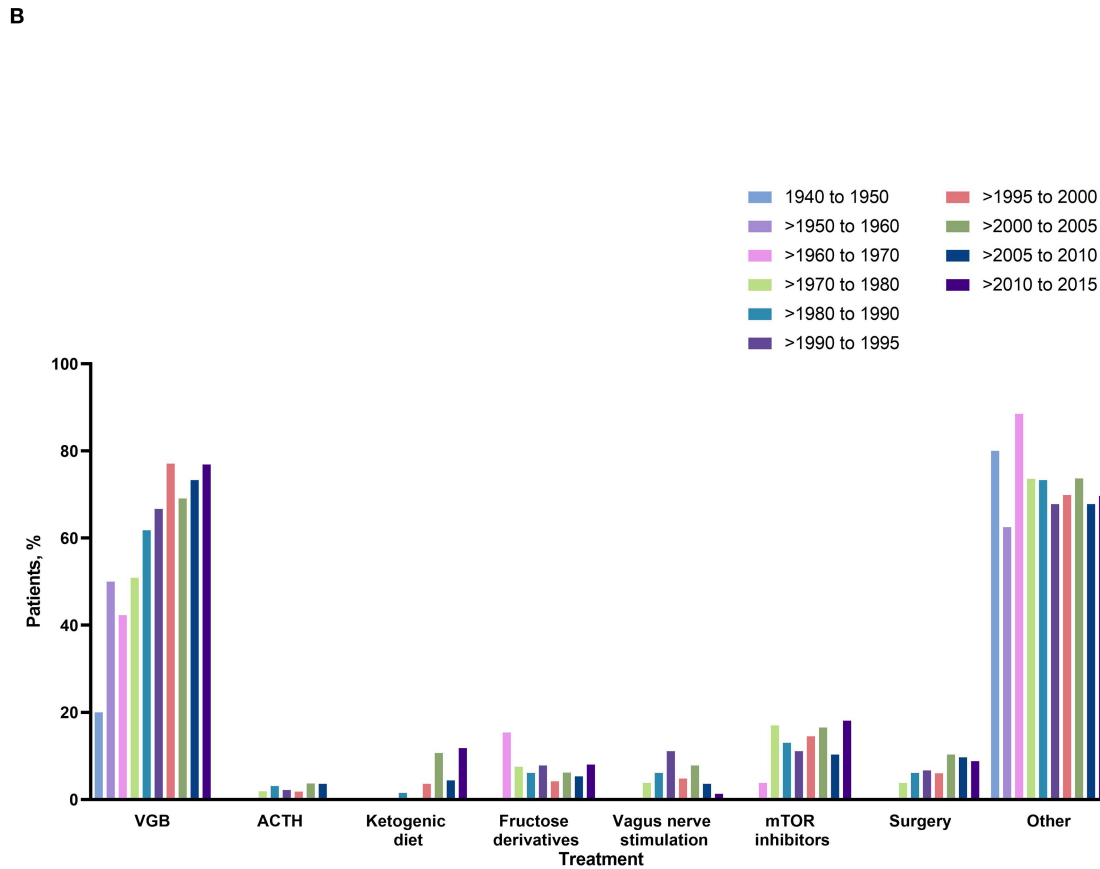
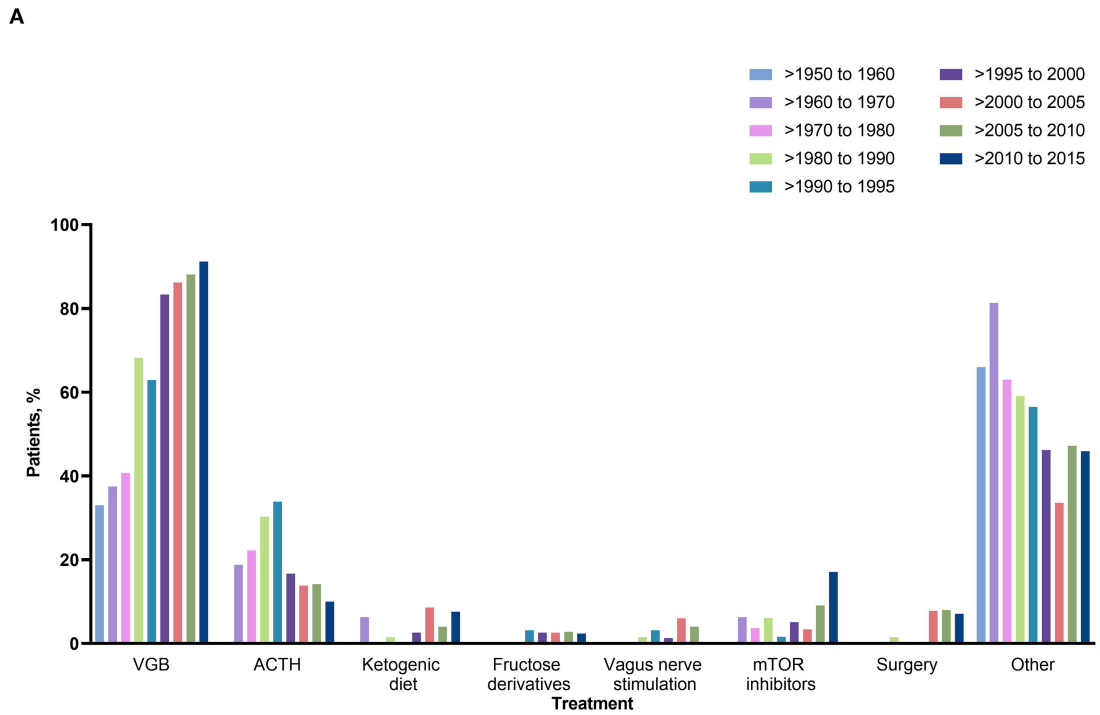
**TABLE 2 |** Rates of epilepsy and treatments over time among individuals with TSC and epilepsy.

Characteristics	1940 to 1950 N = 20	>1950 to 1960 N = 61	>1960 to 1970 N = 104	>1970 to 1980 N = 183	>1980 to 1990 N = 265	>1990 to 1995 N = 172	>1995 to 2000 N = 241	>2000 to 2005 N = 323	>2005 to 2010 N = 461	>2010 to 2015 N = 380
<b>Individuals ever had epilepsy, n (%)</b>	9 (45.0)	27 (44.3)	69 (66.3)	124 (67.8)	212 (79.7)	152 (88.4)	213 (88.4)	294 (91.0)	430 (93.3)	349 (91.8)
<b>Type of epilepsy<sup>a</sup></b>										
Infantile spasms	0	4 (14.8)	17 (24.6)	29 (23.4)	70 (33.0)	63 (41.4)	80 (37.6)	122 (41.5)	178 (41.4)	172 (49.3)
Focal seizures	5 (55.6)	8 (29.6)	27 (39.1)	57 (46.0)	135 (63.7)	93 (61.2)	168 (78.9)	246 (83.7)	361 (84.0)	243 (69.6)
Other seizures	4 (44.4)	19 (70.4)	42 (60.9)	66 (53.2)	79 (37.3)	64 (42.1)	52 (24.4)	54 (18.4)	84 (19.5)	73 (20.9)
<b>Infantile spasms</b>										
Individuals received treatment, n (%)	0	3 (75.0)	16 (94.1)	27 (93.1)	66 (94.3)	62 (98.4)	78 (97.5)	116 (95.1)	176 (98.9)	170 (98.8)
<b>Type of treatment, n (%)<sup>b</sup></b>	–									
VGB	–	1 (33.3)	6 (37.5)	11 (40.7)	45 (68.2)	39 (62.9)	65 (83.3)	100 (86.2)	155 (88.1)	155 (91.2)
ACTH	–	0	3 (18.8)	6 (22.2)	20 (30.3)	21 (33.9)	13 (16.7)	16 (13.8)	25 (14.2)	17 (10.0)
Ketogenic diet	–	0	1 (6.3)	0	1 (1.5)	0	2 (2.6)	10 (8.6)	7 (4.0)	13 (7.6)
Fructose derivatives	–	0	0	0	0	2 (3.2)	2 (2.6)	3 (2.6)	5 (2.8)	4 (2.4)
Vagus nerve stimulation	–	0	0	0	1 (1.5)	2 (3.2)	1 (1.3)	7 (6.0)	7 (4.0)	0
mTOR inhibitors	–	0	1 (6.3)	1 (3.7)	4 (6.1)	1 (1.6)	4 (5.1)	4 (3.4)	16 (9.1)	29 (17.1)
Surgery	–	0	0	0	1 (1.5)	0	0	9 (7.8)	14 (8.0)	12 (7.1)
Other	–	2 (66.7)	13 (81.3)	17 (63.0)	39 (59.1)	35 (56.5)	36 (46.2)	39 (33.6)	83 (47.2)	78 (45.9)
<b>Treatment outcome, n (%)</b>										
Resolved spontaneously	–	0	1 (6.3)	0	2 (3.0)	7 (11.3)	0	2 (1.7)	9 (5.1)	1 (0.6)
Controlled	–	3 (100.0)	9 (56.3)	19 (70.4)	44 (66.7)	43 (69.4)	69 (88.5)	99 (85.3)	138 (78.4)	137 (80.6)
Not-controlled	–	0	5 (31.3)	3 (11.1)	14 (21.2)	8 (12.9)	7 (9.0)	12 (10.3)	26 (14.8)	31 (18.2)
Unknown	–	0	1 (6.3)	5 (18.5)	6 (9.1)	4 (6.5)	2 (2.6)	3 (2.6)	3 (1.7)	1 (0.6)
<b>Focal seizures</b>										
Individuals received treatment, n (%)	5 (100.0)	8 (100.0)	26 (96.3)	53 (93.0)	131 (97.0)	90 (96.8)	166 (98.8)	243 (98.8)	360 (99.7)	238 (97.9)
<b>Type of treatment<sup>b</sup></b>										
VGB	1 (20.0)	4 (50.0)	11 (42.3)	27 (50.9)	81 (61.8)	60 (66.7)	128 (77.1)	168 (69.1)	264 (73.3)	183 (76.9)
ACTH	0	0	0	1 (1.9)	4 (3.1)	2 (2.2)	3 (1.8)	9 (3.7)	13 (3.6)	9 (3.8)
Ketogenic diet	0	0	0	0	2 (1.5)	0	6 (3.6)	26 (10.7)	16 (4.4)	28 (11.8)
Fructose derivatives	0	0	4 (15.4)	4 (7.5)	8 (6.1)	7 (7.8)	7 (4.2)	15 (6.2)	19 (5.3)	19 (8.0)
Vagus nerve stimulation	0	0	0	2 (3.8)	8 (6.1)	10 (11.1)	8 (4.8)	19 (7.8)	13 (3.6)	3 (1.3)
mTOR inhibitors	0	0	1 (3.8)	9 (17.0)	17 (13.0)	10 (11.1)	24 (14.5)	40 (16.5)	37 (10.3)	43 (18.1)
Surgery	0	0	0	2 (3.8)	8 (6.1)	6 (6.7)	10 (6.0)	25 (10.3)	35 (9.7)	21 (8.8)
Other	5 (100.0)	5 (62.5)	23 (88.5)	39 (73.6)	96 (73.3)	61 (67.8)	116 (69.9)	179 (73.7)	244 (67.8)	166 (69.7)
<b>Treatment outcome, n (%)</b>										
Resolved spontaneously	0	0	0	0	0	1 (1.1)	1 (0.6)	2 (0.8)	6 (1.7)	0
Controlled	3 (60.0)	5 (62.5)	18 (69.2)	30 (56.6)	75 (57.3)	50 (55.6)	106 (63.9)	139 (57.2)	212 (58.9)	134 (56.3)
Not-controlled	2 (40.0)	3 (37.5)	7 (26.9)	21 (39.6)	52 (39.7)	39 (43.3)	54 (32.5)	98 (40.3)	137 (38.1)	100 (42.0)
Unknown	0	0	1 (3.8)	2 (3.8)	4 (3.1)	0	5 (3.0)	4 (1.6)	5 (1.4)	4 (1.7)

ACTH, adrenocorticotropic hormone; mTOR, mammalian target of rapamycin; VGB, vigabatrin.

<sup>a</sup>Individuals may have more than one type of epilepsy.

<sup>b</sup>Individuals may have received treatment as monotherapy or as combination therapy.



**FIGURE 2 |** Types of intervention over time in individuals with **(A)** infantile spasms and **(B)** focal seizures. ACTH, adrenocorticotropic hormone; mTOR, mammalian target of rapamycin; VGB, vigabatrin.

Changes of the initial antiepileptic treatment were reported in 64 (90.1%) individuals with infantile spasms and 64 (68.1%) with focal seizures. Most frequently reported reasons for change of treatment were partial or lack of efficacy of the first therapy. Vigabatrin was used as first-line therapy in individuals with infantile spasms in less than half of cases (45.1%) and was the most frequent second line treatment option (62.5%, **Table 3**).

### Characteristics of Epilepsy in TSC by Genotype

Of 63 individuals with available genetic data, 10 had pathogenic mutations in *TSC1* and 53 had pathogenic mutations in *TSC2*. Median age of epilepsy onset was 8 years in individuals with pathogenic variants in *TSC1* and <1 year in those with pathogenic variants in *TSC2*.

Infantile spasms were not reported in individuals with *TSC1*, but in 16 individuals (30.2%) with *TSC2*. Focal seizures were reported for most individuals (90% of *TSC1* individuals and 69.8% of *TSC2* individuals). The median frequency of focal seizures per week was 3.5 in individuals with pathogenic variants in *TSC1* and 1 in individuals with pathogenic variants in *TSC2*. MRI showed a mean number of three tubers in individuals with *TSC1* and 9.2 tubers in in *TSC2*.

Focal seizures were controlled with treatment in 60% of individuals with *TSC1* compared with only 22.6% of those with *TSC2*. Infantile spasms were controlled with treatment in 28.3% of individuals with *TSC2*.

### Association of Epilepsy Foci With IQ Level

The association between epilepsy and IQ was examined in 102 individuals at baseline (69 had normal intellectual ability and 33 had various degrees of ID). Regarding IQ and focal spikes on last EEG recording, EEG showed temporal focal spikes in 52.3% of individuals with normal IQ and frontal focal spikes in 68% of individuals with moderate to severe ID.

### Correlation of IQ Level and Genotype

Sixty-two of 102 individuals showed normal IQ level. The IQ level was normal in 70% of individuals with *TSC1* and in 20.8% of those with *TSC2*; moderate ID was found in 20% of individuals with *TSC1* and in 22.6% of those with *TSC2*; severe ID was observed in 15.1% of individuals with *TSC2*, but none of those with *TSC1*.

### EEG in Individuals With TSC Diagnosis Before Seizures Onset

Diagnosis of TSC was established in 28 individuals before seizure onset. In this group, 16 individuals developed infantile spasms and 12 developed focal seizures. Median age at first EEG was 6 months in individuals with infantile spasms and 11 months in those with focal seizures. The first EEG was performed in 12.5% of individuals before the onset of infantile spasms and in 25% of individuals before the onset of focal seizures. Electroencephalogram was performed the same day seizures occurred in 18.8 and 16.7% of individuals with infantile spasms and focal seizures, respectively. In the remaining cases, 68.8 and 58.3%, EEG was performed after the onset of infantile spasms and focal seizures, respectively.

## DISCUSSION

This study provides final data or information on epilepsy characteristics in a large cohort of TSC individuals who participated in the TOSCA registry and in the epilepsy substudy.

Findings from the main study emphasize the changes in both diagnosis and treatment patterns of TSC-associated epilepsies over time. Overall, a diagnosis of epilepsy was reported in approximately 85% of all individuals with TSC included, equally affecting both sexes. Infantile spasms were reported in about 39% of individuals with a median age of <1 year at diagnosis, and focal seizures in two-thirds of the individuals with a median age of 1 year at diagnosis. These findings were consistent with our previous report and also with other studies (2, 3, 15–17).

In our study, epilepsy diagnosis rates, especially diagnosis of infantile spasms, were higher in younger individuals (67.8% in 1970s to 91.8% in last decade). Since infantile spasms were reported as the seizures types of West syndrome by William West in 1841 (18), followed by Gibbs and Gibbs' description of the characteristic EEG pattern of hypsarrhythmia in 1952 (19), clinicians have made remarkable progress in recognizing this syndrome. The first proposal of classification of patients with epilepsies in syndromes published in the "Guide Bleu" (Blue Guide) in 1984 added to this knowledge (20). In addition, the better recognition of infantile spasms in TSC and their focal nature might have changed the delineation of focal seizures and infantile spasms in the recent years. Although we believe that there was an improvement in the diagnosis of infantile spasms and that this major improvement in clinical epileptology guarantees earlier and better seizure and developmental outcomes. We should be cautious about the concept of an increased rate of epilepsy diagnosis because older individuals in TSC clinics often have a lower rate of epilepsy as they present with angiomyolipoma or being the parent of a child with TSC.

Our data showed a better treatment response rate in individuals with infantile spasms over time, but not in those with focal seizures. This seems to be due to VGB specificity in infants with West syndrome and its growing usage since the 1990s. A decrease in the use of steroids after VGB also clearly shows the specific efficacy of VGB and the lack of a need to add steroids as practiced in infantile spasms due to other etiologies (21). Vigabatrin is an established first-line therapy for individuals with infantile spasms (10, 22). This precision medicine approach in individuals with infantile spasms in TSC is a major example of how an early diagnosis of TSC can help to better target the therapy and to avoid therapeutic failures and ineffective polytherapies. In addition, VGB is recommended as first-line treatment for focal seizures in individuals with TSC in the first year of life (10), aiming to prevent transition into infantile spasms. However, its use for focal seizures in older individuals does not seem to be superior to other AEDs licensed for focal seizures. Indeed, there has been no change in responder rates for focal seizures for the past 45 years despite availability of over 30 new AEDs (23, 24). This finding is also in line with the high percentage of drug resistance reported in individuals with TSC-associated focal seizures in recent reports (3, 25). Despite the

**TABLE 3** | Initial and change in the treatment and reason for change in the epilepsy substudy.

	Infantile spasms	Focal seizures
<b>Number of individuals</b>	71 (43.8)	94 (58.0)
<b>Type of initial treatment reported at the epilepsy diagnosis</b>		
Monotherapy	52 (73.2)	70 (74.5)
VGB	32 (45.1)	33 (35.1)
ACTH	8 (11.3)	2 (2.1)
Other	12 (16.9)	33 (35.1)
Polytherapy	16 (22.5)	18 (19.1)
GABAergics and other	5 (7.0)	3 (3.2)
<b>Change of first treatment</b>	64 (90.1)	64 (68.1)
Median time from first to second treatment, days	214.0 (0–5,480)	288.0 (0–8,402)
<b>Type of second treatment</b>		
VGB	40 (62.5)	31 (48.4)
ACTH (steroids)	10 (15.6)	3 (4.7)
Ketogenic diet	1 (1.6)	0
Fructose derivates	1 (1.6)	1 (1.6)
Vagus nerve stimulation	0	0
mTOR inhibitors	0	0
Other	42 (65.6)	49 (76.6)
<b>Reason for change of drugs</b>	62 (96.9)	62 (96.9)
Partial efficacy	20 (31.3)	24 (37.5)
No efficacy	20 (31.3)	18 (28.1)
Side effects	1 (1.6)	4 (6.3)
Other	21 (32.8)	16 (25.0)

ACTH, adrenocorticotropic hormone; mTOR, mammalian target of rapamycin; VGB, vigabatrin. Values are expressed as n (%) unless otherwise mentioned.

high response to VGB in individuals with infantile spasms, it was not always the first therapy in individuals with infantile spasms (only 45% received VGB as first-line monotherapy). This finding is unexpected, especially in epilepsy centers, but emphasizes the need for more education about the use of individualized treatment options for specific etiologies.

Surprisingly, other non-pharmacological therapies such as VNS and the ketogenic diet were not used in this highly drug resistant population (range 1.5–8.6%). This might be due to the lack of randomized controlled trials in both therapies and evidence often based on retrospective small series (26) from one hand and the lack of expertise in both therapies on the other hand. The use of VNS in this cohort decreased during recent years after a peak in the 2000 and might be still underused although recommended as last resort in patients with refractory seizures.

Early evaluation for epilepsy surgery candidates in individuals with drug resistant TSC-associated epilepsies should be performed in expert centers in order to prevent/minimize developmental consequences of ongoing seizures (27). In our study, only a few individuals had epilepsy surgery. However, we did not ask in the study protocol how many had undergone pre-surgical evaluation.

Epilepsy surgery shows a relevant rate of 8–10% in our study but might not reflect yet the number of patients that were good candidates for epilepsy surgery and that can benefit

from such therapy. Additionally, not all of the epilepsy centers participating in the study were also surgery centers trained in TSC-associated epilepsy. Therefore, additional training and education are needed and additional collaboration with expert surgery centers should be established for individuals with drug-resistant epilepsy with TSC in order to promote early identification of surgery good candidates.

Individuals with TSC and epilepsy are prescribed with multiple AEDs or undergo multiple surgical procedures to manage epileptic seizures (28, 29). However, we have observed in our epilepsy substudy that a large number of individuals were initiated on AED monotherapies as recommended by the ILAE (International League Against Epilepsy). This might be related to the use of VGB in the first year of life in both infantile spasms and focal seizures or epilepsy combining both seizure types.

Our results also showed the increased use of disease-modifying treatment with mTOR inhibitors. The efficacy of this therapy was reported in late 2010 and its use in case of failure of initial treatment could be the rational approach. Its use increased and reached 18% in the last reports from the TOSCA study in 2015, showing the need for more efficient therapies in focal seizures associated with TSC. This increased use of approved mTOR inhibitor, everolimus, and the wider evaluation of surgery candidates in the management of TSC-associated focal seizures and in some individuals with drug-resistant infantile spasms might improve responder rates in



the future and could help to achieve a better cognitive TAND outcomes.

In our substudy, in infants with TSC diagnosis prior to seizure onset, EEG was performed mainly after the onset of clinical seizures, both for infantile spasms (in 68.8%) and focal seizures (in 58.3%). Curatolo et al. recommended in 2012 (22) and later in 2018 (10) to use EEG in infants with TSC before seizure onset to early identify individuals at high risk of developing epilepsy. This was also reported in the international recommendations (guidelines) in 2013 (30), based on studies showing that TSC individuals who were diagnosed and treated before the onset of seizures had less severe epilepsy and better neurodevelopmental outcomes (31). Abnormal EEG patterns and/or in some instances subclinical seizures recorded on the EEG should urge the use of AED therapy without waiting for the onset of overt clinical seizures. The results of the research project are in contrast with these recommendations and emphasize the need for more information for clinicians about the key role of sequential EEG recordings to early recognize individuals at high risk of developing early onset seizures and preventive AED treatment. Parents should be educated to recognize seizures earlier and most importantly EEG recordings should be performed—with an ultrasound of cardiac rhabdomyoma, pre-natal, or post-natal MRIs—in cases with family history of TSC with signs of TSC or with cutaneous hallmarks of TSC.

The place of this pre-symptomatic diagnosis strategy for epilepsy in TSC and the preventive therapy might be better implemented after the recent validation of this approach with the first results of the EPISTOP study (32, 33). Individuals receiving early preventive treatment showed a later epilepsy onset and a less severe epilepsy compared to those receiving standard therapy started after the onset of clinical seizures. The cognitive outcome might need further validation and longer follow-up (32, 33).

Our data show no significant correlation between the spikes focus and the IQ levels as for frontal or temporal focus. More severe cognitive but mainly psychiatric disorders as ASD are reported with temporal lesions (34). However, we did not report ASD testing and TAND results were mostly missing.

Finally, our study showed that individuals with *TSC1* had less severe phenotypes than those with *TSC2*. This finding is in accordance with the literature (3, 25, 35), but, importantly, we were able to validate it on a very large cohort probably less biased than mono-center studies and smaller series. A higher proportion of individuals with *TSC1* had normal IQ levels than those with *TSC2*. Compared to individuals with *TSC2*, they had fewer numbers of tubers, later onset of epilepsy, and higher rates of controlled seizures. The tuber load, usually higher in individuals with *TSC2*, might have a role in creating more complex and diffuse abnormal networks, with fewer regions showing normal brain cortex, leading more frequently to drug resistant epilepsy and higher rates of co-morbidities.

In conclusion, our study highlights that despite the improvement in diagnosis and in some aspects of treatment of TSC-associated epilepsy over time, especially for infantile spasms, there are still some major improvements to be made. Better epilepsy control is urgently needed, mainly for focal seizures. A more targeted use of available therapies and the

promotion of innovative therapies and of evaluating surgery candidates should continue. Despite the established guidelines, the need for further education of clinicians in order to provide earlier diagnosis of epilepsy based on serial EEGs before the onset of seizures in patients with TSC should be promoted and to use VGB as first monotherapy for infantile spasms established as the first line therapy. Pre-seizure diagnosis will also help to use timely or even preventive therapies and could be a major step toward changing the natural history of epilepsy in individuals with TSC. Finally, the use of new targeted therapies such as mTOR inhibitors, or cannabidiol (36), and earlier and better definition of candidates for epilepsy surgery may lead to better outcomes, especially for focal seizures where the seizure control rates have plateaued in the last decade.

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## DATA AVAILABILITY STATEMENT

Novartis supports the publication of scientifically rigorous analysis that is relevant to patient care, regardless of a positive or negative outcome. Qualified external researchers can request access to anonymized patient-level data, respecting patient informed consent, contacting study sponsor authors. The protocol can be accessed through EnCePP portal <http://www.encepp.eu/> (EU PAS Register Number EUPAS3247).

## ETHICS STATEMENT

The study protocol and all amendments were reviewed and approved (if applicable) by independent ethics committee/institutional review board for each center: National Hospital Organization Central Ethics Committee; Gazi University Clinical Research Ethics Committee; Independent Multidisciplinary Committee on Ethical Review of Clinical Trials; Peking Union Medical College Hospital; Commissie Medische Ethiek UZ Brussel; CNIL (Commission Nationale de l'Informatique et des Libertés), CCTIRS (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé); Comité Etico Investigación Clínica de Euskadi (CEIC-E); Consejería de Salud y Bienestar Social, Dirección General de Calidad, Investigación, Desarrollo e Innovación, Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; Research Ethics Committee of the University of Tartu (UT REC); Ethikkommission der Medizinischen Universität Graz; North Wales REC—West; Regionala Etikprövningsnämnden i Göteborg; REK—Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk; Komisja Bioetyczna przy Instytucie Pomnik Centrum Zdrowia Dziecka; Ethikkommission bei der Ludwig-Maximilians-Universität München; Hokkaido University Hospital Independent Clinical Research Institutional Ethics Committee; Medical Juntendo University Institutional Ethics Committee; National Center for Chile Health and Development of IRB; Osaka University

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