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The impact of a newly established specialized pediatric epilepsy center in Tanzania: An observational study

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ABSTRACT

Purpose: This study evaluated the impact of a newly established clinic for the diagnosis of pediatric epilepsy in a resource-limited center (Ifakara, Tanzania).
Methods: Patients aged 0–18 years referred to the Pediatric Epilepsy Unit of Saint Francis Referral Hospital were recruited. Demographic and clinical data were collected through Kobo Toolbox and analyzed through a descriptive analysis..
Results: 143 patients were evaluated, and for 48 of them an EEG was recorded (abnormalities were detected in 80.85% of the cases). The diagnosis of epilepsy was confirmed in 87 patients. Focal epilepsy was diagnosed in 57 patients, generalized epilepsy in 24 patients, and forms of unknown onset in 6 patients. Epilepsy was excluded for 9 children. Etiologies included hypoxic-ischemic encephalopathy (39%), central nervous system infections (3.4%), and genetic diseases (3.4%). A specific epilepsy syndrome was diagnosed in 16 patients. 74 patients were under treatment; the most used antiseizure medication (ASM) was phenobarbital (43.36%), followed by carbamazepine (16.08%), sodium valproate (11.19%), phenytoin (2.8%), and lamotrigine (0.7%). Therapeutic changes were proposed to 95 patients, more frequently consisting of withdrawing phenobarbital (39.16%), switching to sodium valproate (27.97%), switching to or adjusting carbamazepine dosage (27.27%), and starting prednisone (2.8%). 76% of the patients with confirmed epilepsy achieved complete seizure freedom at the fourth follow-up consultation.
Conclusions: Our data depicted the epilepsy spectrum and highlighted the prognostic implications of improving the availability of ASMs such as sodium valproate and second- and third-generation ones in resource-limited countries.

1. Introduction

Data from community-based studies highlighted that the "epilepsy treatment gap" (ETG: the percentage of people with active epilepsy who are not being appropriately treated in each population at a given time) achieved in Sub-Saharan Africa (SSA) was 68.5%, with a downward trend over the years, resulting from the impact of various intervention programs [1,2]. The main limiting factors causing ETG included the lack of access to treatment due to economic and social costs and the inadequate training of specialized healthcare providers about the choice of optimal antiseizure medications (ASMs) targeted towards seizure semiology and aetiologies [1,2]. The impact of these limitations in resource-limited countries is probably higher for pediatric patients because of the major age-specific vulnerability to seizures and the more significant proportion of infantile morbidity and mortality [3].

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1.1. Objectives

This study evaluated the impact of a newly established specialized pediatric epilepsy center in a resource-limited region. This evaluation was realized through the following steps:

- Categorization of examined patients in terms of seizure/epilepsy types and epilepsy syndromes according to the International League Against Epilepsy (ILAE) Classification [4],
- Definition of a possible action program to reduce the ETG by:
  - Applying treatment guidelines based on the diagnosis and the available ASMs;
  - Educating the caregivers on how to care for a child or adolescent with epilepsy.

2. Material and methods

2.1. Study settings

2.1.1. Geographic location of the study

The study was conducted in Ifakara Town Council (Kilombero district, Morogoro region, Tanzania). According to the Population and Housing Census of 2012, the population of Ifakara Town included 106,424 people (52,148 males and 54,276 females), Kilombero District counted 407,880 people, and Morogoro region had a total population of 2,218,492 inhabitants [5]. Ifakara Town Council was involved in the Epilepsy Project led by *Comunità Solidali nel Mondo* Onlus with the partnership of the Saint Francis Referral Hospital (SFRH) and Saint Francis University College of Health and Allied Sciences (SFUCHAS). SFRH was founded in 1927 as a small dispensary, and throughout the years it has developed significantly, becoming a referral hospital in 2010. The hospital receives patients from the Kilombero, Ulanga, Mlimba, and Malinyi districts, serving more than 300 villages. In the outpatient department, about 90,000 patients are treated per year, and in the inpatient department, about 11,000.

2.1.2. Project background

At the beginning of 2022, Comunità Solidali nel Mondo Onlus launched a project intending to improve the quality of medical management of epilepsy, promote education, increase awareness, and fight the stigma of epilepsy. The project also aimed to find three epilepsy clinics (in Ifakara Town Council, Wanging'ombe District, and Mbeya City Council) with the support of the partners: SFUCHAS, SFRH, Inuka Rehabilitation Hospital, Simama, and Iyunga Roman Catholic Health Center. The goal was to develop *sustainable* clinics through a training project involving local healthcare professionals based on theoretical and practical activity in loco and followed by distance digital-mediated supervision. In April 2022, the first clinic was set up at SFRH in Ifakara, carried out by a team of Italian child neurologists as trainers and Tanzanian physicians with experience in child health care as trainees.

2.2. Data collection and analysis

Data were anonymously collected in a standardized digital sheet created on Kobo Toolbox (a free and open-source platform for collecting, managing, and visualizing data) [6]. Data were analyzed through descriptive statistics.

2.3. Study design

Patients referred consecutively to the newly established pediatric epilepsy unit of SFRH between April 2022 and November 2022 were recruited. Inclusion criteria were as follows: 1) clinical suspect or confirmed diagnosis of epilepsy; 2) age between 0 and 18 years. The patients were recruited through a media campaign on radio, television, and social networks or referred from pediatric and physiotherapy departments. All patients underwent a medical consultation during which anamnestic data were collected, a neurological assessment was performed, and a diagnosis was made according to ILAE criteria [7]. EEG recording was obtained according to the minimum standards required by ILAE and the International Federation of Clinical Neurophysiology [8]. Therapeutic choices were realized according to local drug availability and affordability for the family. An ad-hoc diagnostic and therapeutic algorithm was built and followed to easily guide the clinical characterization of patients and the establishment of therapeutic schedules according to the local affordability and availability of ASMs (Fig. 1).

After the first evaluation, the patients attended our clinic monthly, except those prescribed prednisone, who were examined weekly. We adopted the Clinical Global Impression Scale (CGI) [9], and specifically the CGI-Improvement (CGI-I) component [9], to describe the change in patients' condition at each consultation compared with the period before the first visit to our clinic. At every follow-up visit, each patient was considered to have: (a) a CGI-I score of 1 if seizure control was achieved since the last consultation; (b) a CGI-I score of 2 if seizure frequency was reported to be reduced compared with the frequency at admission; (c) a CGI-I score of 4 no difference in seizure frequency was noticed; (d) a CGI-I score of 6 if seizures increased. There was no chance to benefit from therapeutic drug monitoring (TDM) because of the unavailability of laboratory reagents. The study obtained ethical approval from the National Institute for Clinical Research (NIMR) of Tanzania (NIMR/HQ/R.8a/Vol.IX/4219).

3. Results

3.1. Cohort composition, risk factors, and comorbidities

The enrolled cohort included 143 patients, 82 males (57.34%) and 61 females (42.66%). Demographic and general clinical data are summarized in Table 1. Most enrolled patients (77.72%) came from villages in the surrounding regions. All of them were previously considered to have epilepsy or suspected epilepsy, with no other designation.

Caregivers reported neurodevelopmental delay in 93 patients (65.03%), mainly consisting of motor delay (56.64%), language delay (51.75%), social delay (42.66%), and academic skills delay (25.87%).

Risk factors for epilepsy covered different areas and were summarized in Table 1. As regards comorbidities, 46 patients (32.17%) were found to have an intellectual disability, 45 patients (31.47%) were diagnosed with cerebral palsy, 24 children (16.78%) under the age of four were found to present with a neurodevelopmental delay, and 12 patients (8.39%) were diagnosed with autism spectrum disorder (ASD).

3.2. Epilepsy phenotype

The diagnosis of epilepsy was confirmed in 87 patients (60.8%), whereas 47 patients (32.87%) were considered patients with possible or probable epilepsy and were kept on follow-up, and for nine patients (6.29%) the diagnosis of epilepsy was excluded. Fig. 2A shows the seizure types and their frequency. Remarkably, at the first evaluation, almost half the patients with confirmed epilepsy (42 patients, 48.27%) reported having seizures more than once per month, and 14 patients (16.1%) referred multiple episodes per day, whereas only 3.44% were seizure-free in the last year. Among the cases with a confirmed diagnosis of epilepsy, focal

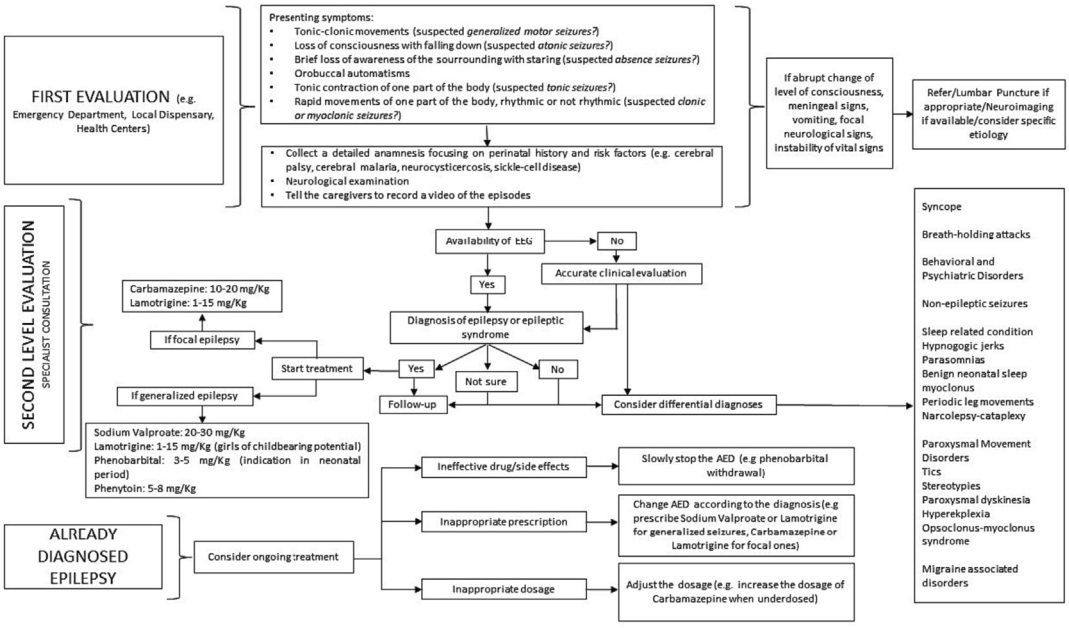

Fig. 1. The proposed algorithm for diagnosing and managing epilepsy that was built for resource-limited epilepsy centers and used in the present study.

Table 1
Demographic and anamnestic data of the enrolled patients. LBW = Low Birth Weight; VLBW = Very Low Birth Weight.

GENERAL DATA	Frequency (% or range)
Males (%)	82 (57.34)
Medium age in months at admission (range)	78.26 (4–218)
Neurodevelopment delay reported (%)	78 (65)
Medium age in months at epilepsy onset (range)	12 (0–180)
Aura reported (%)	29 (20.28)
Patients already under treatment (%)	77 (53.85)
PERINATAL RISK FACTORS	
None	69 (48.25)
Birth Asphyxia	48 (33.57)
Convulsions	12 (8.39)
Jaundice	12 (8.39)
Sepsis	7 (4.9)
LBW/VLBW	7 (4.9)
Pre-eclampsia	4 (2.8)
Infections during pregnancy	4 (2.8)
Bleeding during pregnancy	1 (0.7)
Others	5 (3.5)
LIFETIME RISK FACTORS	
None	95 (66.43)
Severe infection	29 (20.28)
Febrile convulsions	16 (11.19)
Familiality	11 (7.69)
Malnutrition	3 (2.1)
No vaccinations	2 (1.4)
Head trauma	1 (0.7)

epilepsies were largely predominant (57 patients) (Fig. 2B). Generalized epilepsies were diagnosed in 24 patients, whereas six patients received the diagnosis of epilepsy with an unknown onset (Fig. 2 B). Etiology remained unknown for most cases (51.72%) because of the lack of neuroimaging, metabolic, immune, and genetic laboratory tests. Thirty-four patients were considered to have epilepsy due to hypoxic-ischemic encephalopathy (HIE) because their perinatal history, neurological examination, and seizure types were clinically consistent with this condition. Etiology was considered post-meningeal in three patients because unprovoked seizures seemed after the resolution of meningitis. The other three cases diagnosed with childhood absence epilepsy were considered to have a genetic predisposition [10].

International System 21-channel EEG recordings were performed on 48 patients. Twenty-three children (47.91%) underwent a wakefulness EEG, five patients (10.42%) had a sleep EEG, and in the remaining 25 cases (52.08%), both wakefulness and sleep EEG were recorded. Intermittent Photic Stimulation (IPS) was performed in 26 patients according to the methodology suggested by Kasteleijn-Nolst Trenité et al. [11], whereas 21 patients could complete hyperventilation (HP) procedures lasting four minutes.

EEG was reported as normal in nine patients (18.75%). Background activity abnormalities were found in 27 patients and interictal abnormalities in 34 children. EEG abnormalities (either ictal or interictal) were focal in 19 children (39.58%), multifocal in 9 (18.75%), and diffuse in 7 (14.58%). Seizures occurred during the EEG recording of eight patients. In five of them, focal ictal abnormalities were detected, whereas diffuse abnormalities were observed in three children. EEG led to changes in diagnosis in 14 patients (29.16%) and treatment changes in 15 patients (31.25%). Specific epileptiform patterns were assessed in six cases: three of them presented with 3 Hz generalized spike-waves complexes associated with an abrupt onset and offset of altered awareness; two showed burst-suppression switching to hypsarrhythmia; and newly onset hypsarrhythmia was reported in one patient.

3.3. Treatment and follow-up

Tables 2 and 3 compare seizure frequency and response to treatment between baseline and follow-up visits. About half of the enrolled patients (77 patients, 53.85% of the cases) were already under treatment at the first evaluation, with the list of commonly prescribed ASMs being restricted to phenobarbital (PB) (43.36%), carbamazepine (CBZ) (16.08%), valproic acid (VPA) (11.19%), phenytoin (PHE) (2.8%) and lamotrigine (LTG) (1.4%) (Table 3). Notably, CBZ had always been prescribed at 200 mg once daily, regardless of body weight. Fig. 3 illustrates the efficacy of the past treatment as perceived by caregivers. A positive effect (seizure control or improvement) was perceived by caregivers of patients who had used VPA and CBZ (respectively, 15 out of 16 cases for VPA and 14 out of 23 for CBZ). PB, on the other hand, was ineffective in more than half of the patients (34 out of 61). At admission, the pharmacological treatment was modified in 89 patients

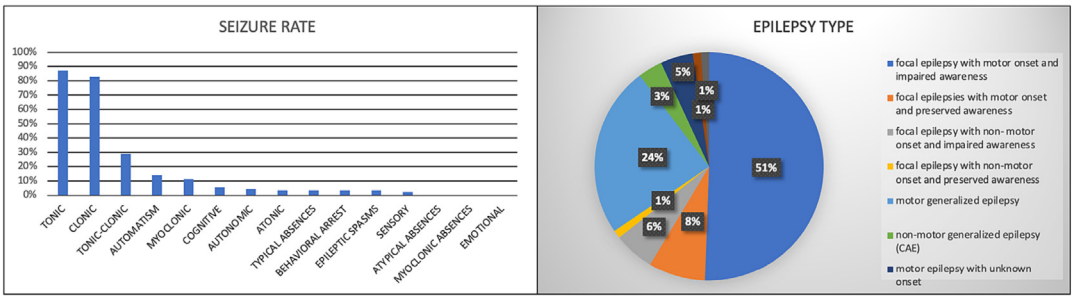

Fig. 2. A) Seizure types and their frequency in patients with confirmed epilepsy; B) Distribution of different epilepsy types among patients with confirmed epilepsy (CAE = Childhood Absence Epilepsy).

Table 2
Condition trend of the patients with confirmed epilepsy across four follow-up consultations compared with the baseline visit. LEGEND: 1st FU = first follow-up; 2nd FU = second follow-up; 3rd FU = third follow-up; 4th FU = fourth follow-up.

	BASELINE VISIT	1st FU	2nd FU	3rd FU	4th FU
Total number of patients with confirmed diagnosis of epilepsy	87	60	48	35	25
Total number of patients with generalized seizures	24	18	9	8	6
Total number of patients with focal seizures	57	36	33	21	13
Mean number of seizures per month	3.15 ± 3.66	1.5 ± 1.87	1.26 ± 1.58	1.07 ± 1.23	0.88 ± 1.03
Number of patients with seizure control	13	35	29	22	19
Number of patients with reduced frequency of seizures after treatment	32	15	11	11	5
Number of patients with unchanged frequency of seizures after treatment	33	9	3	2	0
Number of patients with increased frequency of seizures after treatment	1	1	5	0	1

Table 3
Response to different ASMs in patients with confirmed epilepsy across four follow-up visits. LEGEND: 1st FU = first follow-up; 2nd FU = second follow-up; 3rd FU = third follow-up; 4th FU = fourth follow-up; ASM = Antiseizure medication; FU = follow-up; VPA = Sodium Valproate; CBZ = Carbamazepine; PDN = Prednisone.

ASM	Number of patients prescribed with the ASM	Condition of the patients	Number of patients – 1st FU	Number of patients – 2nd FU	Number of patients – 3rd FU	Number of patients – 4th FU
VPA	40	Control	17	14	8	5
		Improvement	9	6	6	3
		No difference	7	2	0	0
		Worsening	1	1	0	0
CBZ	35	Control	12	11	9	7
		Improvement	4	2	1	0
		No difference	0	0	1	0
		Worsening	0	1	0	1
PDN	4	Control	0	0	0	0
		Improvement	2	1	2	2
		No difference	0	0	0	0
		Worsening	0	1	0	0

(62.24% of the cases) because of incorrect diagnosis, poor seizure control, or side effects. The previously prescribed treatment was confirmed in a few cases (six patients, 4.2%), whereas ASMs were discontinued in epileptic patients with documented seizure freedom in the last two years (six patients, 4.2%). PB was discontinued in most patients; it had been previously prescribed (61 patients out of 62). VPA was prescribed in 46 patients (32.16%), CBZ in 42 patients (29.37%), LTG in one patient, and Prednisone in four patients (2.79%).

Up to November 2022, seven patients achieved a seizure-free period of 4 months, 11 obtained a seizure-free period of 3 months, and 18 were seizure-free for 2 months. At the fourth follow-up, 76% of the patients with confirmed epilepsy (19 out of 25) experienced complete seizure control (CGI-I = 1), 20% (5 out of 25) experienced a clinical improvement (CGI-I = 2), and 4% (1 out of 25) experienced a worsening of seizures (CGI-I = 6) (Table 2).

Among patients with confirmed epilepsy, the introduction of valproate resulted in seizure control in 50% of the cases at the first follow-up visit and in 62.5% of the cases at the fourth follow-up visit, whereas the introduction of CBZ resulted in complete seizure control in 75% of the cases at the first follow-up visit and in 87.5% of the cases at the last ones.

4. Discussion

In November 2020, WHO launched a resolution for "global actions on epilepsy and other neurological disorders" [12]. The resolution encouraged the Member States to provide an "*integrated (multisectoral) response to epilepsy and other neurological disorders*" [12,13].

Between 1989 and 2015, thirty-one international programs were implemented in 18 low- and middle-income countries (LMIC), and the effectiveness of the correlated interventions was measured by the efficacy of ASMs in 25 of these programs [14]. PB was the most common medication used in most cases, and a mean compliance of 79.3% was assessed (range 21.6–100.0%) [14]. ETG may vary between 25% and 100% in LMICs with differ-

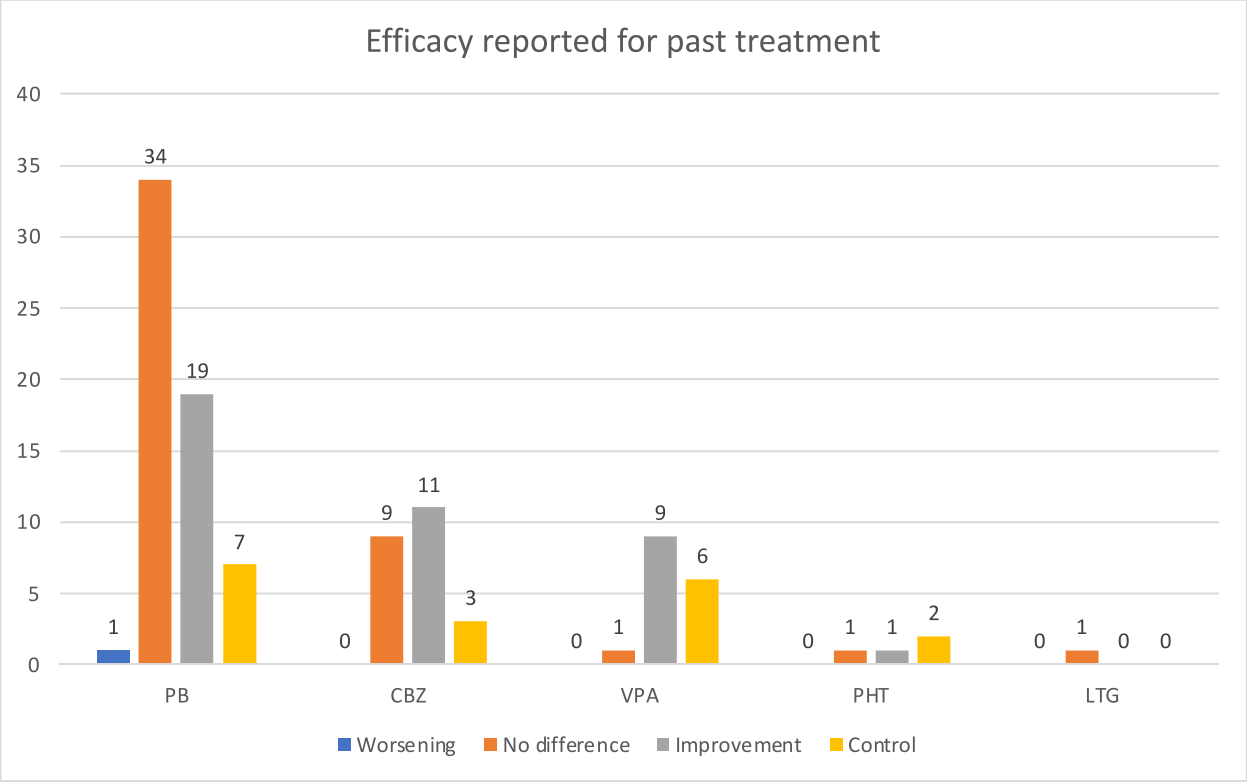

Fig. 3. Efficacy of past treatments perceived by caregivers. PB = phenobarbital, CBZ = carbamazepine, VPA = valproic acid, PHT = phenytoin, LTG = lamotrigine.

ences due to socioeconomic contexts and peaks of 90% of African patients without access to treatment compared with only 10% in industrialized countries [14]. The present study suggested that the organization of well-structured pediatric epilepsy centers may substantially improve specialistic diagnostic pathways based on adequate characterization of clinical and EEG epilepsy phenotypes and therapeutic management in LMIC with subsequent positive impacts toward reducing ETG.

The clinical scenario in the newly established center highlighted the predominance of focal epilepsy with motor onset and impaired awareness. This predominance is commonly reported in high-income countries (HIC), whereas the few previously published data about SSA depicted a higher frequency of motor generalized epilepsies, mainly including the ones presenting with generalized tonic-clonic seizures [15–18]. The probable under-ascertainment of other seizure types, including non-motor seizures (e.g., absence seizures) and seizures with less easily recognizable features (infantile spasms, myoclonic seizures, and focal seizures), reflects the higher social alarm elicited by motor seizures but also the lack of specialized expertise in pediatric epileptology and the limited access to electroencephalography (EEG) and other diagnostic tools [16].

The interventions on therapeutic schedules in the reported cohort resulted in a positive trend in seizure frequency, including a switch from almost half of the patients reporting seizures more than once per month to 76% obtaining one full month of complete seizure control. This result is consistent with the target of 70% of patients with epilepsy living seizure-free that the World Health Organization (WHO) indicates as the target that could be achieved if all the adequate diagnostic and therapeutic tools are used [19].

Even if 2017 Tanzanian guidelines no longer suggested PB as the first line ASM, our study reported that the prescription of this drug by local physicians is still very common (PB was taken by 80.51% of patients at the first evaluation in the herein-reported cohort), probably because of its broad spectrum and its easy availability at a low cost [20,21]. The replacement of PB with VPA, which has become diffusely routinary in HIC, and the use of adequate dosages of CBZ resulted in better seizure control in more than 70% of the cases, suggesting two specific aims for LMIC-tailored global action programs on epilepsy by international institutions:

- the cut in costs to ensure the availability of VPA beyond health insurance networks that are not affordable for most treated patients [22–25],
- promoting education programs focused on treating epilepsy in pediatric ages to avoid diffuse underdosages of available ASMs [25].

Although VPA is included in the WHO essential list of ASMs, a strong limitation for its diffusion in LMIC is given by logistic disorganization and inadequate storage [24,25]. A recent survey distributed by the ILAE Task Force on Access to Treatment in 101 countries evidenced a large variability in the availability of the different VPA formulations among income classes, with limited access to tablets being reported in up to 25% of LMIC, to granules in about 60% of LMIC, and to liquid formulations in more than 90% of LMIC [25]. A recent cross-sectional study in Gabon, Kenya, and Madagascar evidenced an acceptable quality of formulations available in these areas only in about one-third of the cases [24]. Another limitation may be represented by the warning activated towards females with childbearing potential, as in developed countries, with the same implications about the risk or benefit ratio to consider [26].

Adequate education, including practical clinical management and EEG recording training, of all health professional figures involved in the management of children with epilepsy is crucial for the reduction of ETG [27]. Pilot educational intervention programs oriented towards primary care health providers resulted in

increased diagnostic and therapeutic performances in Brazil, China, and other LMIC [27]. A decline in epilepsy knowledge over 9 months had been reported in primary care providers involved in some of these projects, highlighting the risk of failure after the block of occasional funding or the attenuation of individual interest [27]. Adequate support of "train the trainers" programs, the promotion of extensive projects to increase the number of specialists working in the pediatrics and the efficiency of local political and social health care networks might avoid these negative evolutions [27]. These strategies might result in a diffuse improvement of therapeutic responses and, subsequently, in reinforcing adherence to treatment and depowering mechanisms behind the social stigma, especially in the poorest strata of LMIC society [27].

Access to EEG is commonly restricted in LMIC because of the lack of materials and suitable locations for recordings [28] (e.g., in the herein-reported experience, its realization was possible only in about half of the patients with diagnosed epilepsy). In a survey on neurodiagnostic facilities in 37 countries in 2014, EEG testing was available in 63% of low-income, 71% of lower-middle income, and 92% of upper-middle-income countries, with no specialization for pediatric age in almost all the LMIC [28]. In the same study, no linear associations between country income level and EEG access time were reported, with faster access to EEG in private settings than in public ones in most LMICs, exactly as in HIC [28]. Online-based programs of tutoring for EEG reports and the use of a smartphone-based EEG application (e.g., Smartphone Brain Scanner-2-SBS2) for patients living far from recording laboratories were tested in some countries, with interesting potential impacts in other geographical realities in terms of time to access [29].

The main limitations of our study included its small temporal duration and, consequently, the restricted number of recruited patients with the correlated reduced amount of data about prognosis, adherence to therapy, and EEG data. The progressively decreasing adherence to follow-up visits and the lack of objectively measurable parameters for measuring the effects of therapeutic choices might also have influenced the relevance of the reported results. The small number of recruited patients and the limited temporal duration of the study did not allow adequate validation of the diagnostic and therapeutic algorithm summarized in Fig. 1 and the definition of long-term outcome predictors in the studied cohort. These aspects might be interesting topics for future studies.

5. Conclusions

Extensive data collection on prevalence estimates of epilepsy and epileptic seizures is necessary to obtain adequate national planning and allocation of funds, especially for children and young people, whose prognosis can change significantly through targeted treatment and follow-up [13]. Adopting specific measures suggested by the ILAE Task Force on Access to Treatment might represent a valid starting point to promote the reduction of ETG during the next decade through sustainable intervention in pediatric healthcare networks and international institutions [25]. These measures included interventions on the distribution and availability of essential ASMs on the WHO list, educational programs for local specialists and primary care providers, and socio-economic and political projects to ensure the sustainable care of children with epilepsy [25].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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