GRHTA
Glob Reg Health Technol Assess 2022; 9 (Suppl. 2): 4-9
ISSN 2283-5733 | DOI: 10.33393/grhta.2022.2418
REVIEW

Governance of the clinical pathway and management of the patient suffering from epilepsy and drug-resistant epilepsy

Angela La Neve, Giovanni Falcicchio

Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari - Italy

ABSTRACT

Epilepsy is a diffuse chronic neurological disease affecting around 50 million people worldwide. The diagnostic criteria by the International League against Epilepsy must be fulfilled to diagnose the disease, which is characterized by brief and transient episodes of abnormal neuronal activity involving one or both hemispheres, depending on the epilepsy type. The diagnosis of epilepsy should be properly and timely made because patients suffering from the disease are affected not only by seizure recurrence but also by epilepsy-related psychiatric and/or cognitive comorbidities that may have a huge impact with severe professional and social implications. It is of vital importance to define a specific governance model that has to be virtuously applied into the different phases of the clinical pathway of the patients with epilepsy in order to guarantee them the best model of care possible.

Keywords: Anti-seizure medicines, Drug-resistant epilepsy, Epilepsy, Epilepsy management, First seizure clinic, People with epilepsy

Premises

Disease characteristics

Epilepsy (E) is a chronic neurological disease diagnosed according to the criteria by the International League against Epilepsy (ILAE) if one of the following conditions occurs: (1) At least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) Diagnosis of an E syndrome (1).

An epileptic seizure is a brief and transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity (1). Epileptic seizures can be classified as *acute symptomatic seizures* when they have a strict temporal association with a transient and acute brain insult, which can be of metabolic, toxic, structural, infectious or inflammatory origin (2), and as *unprovoked seizures* when an enduring cerebral predisposition to generate epileptic seizures can be identified (1). Therefore, both types of epileptic seizures can be defined considering the reversibility of the underlying responsible cause and the temporal relationship with the acute brain insult (1,2). For example, a cortical dysplasia or a brain tumour may permanently alter specific neuronal networks, predisposing a particular area of the brain to develop seizures; so, in these circumstances, it is right to talk about unprovoked seizures.

The classification of a remote epileptic seizure, which is symptomatic of E, can be made according to the onset of the abnormal neuronal activity, which can be *generalized* – if the abnormal electric discharge involves simultaneously both cerebral hemispheres from the beginning – or *focal* – if the discharge originates within a specific neuronal network limited to one hemisphere and may (or may not) rapidly engage the contralateral hemisphere (3). The clinical presentation of seizures can be characterized by impaired or unimpaired awareness/consciousness and presence or absence of more or less diffuse motor phenomena (3).

E is a medical condition in which epileptic seizures can be the main but not the only symptom (4). In fact, along with seizures, other signs or symptoms (neurological, psychiatric or involving other organs and apparatus) can be identified (4), as in the case of epileptic encephalopathies or developmental encephalopathies, which can be defined as electro-clinical

Received: May 8, 2022
Accepted: May 30, 2022
Published online: June 28, 2022

Corresponding author:
Dr Giovanni Falcicchio
Department of Basic Medical Sciences,
Neurosciences and Sense Organs
University of Bari
Piazza Giulio Cesare, 11
70124 Bari - Italy
gio.fal@hotmail.it

syndromes with broad genetic spectrum in which E often combines with cognitive and behavioural alterations, electroencephalographic (EEG) abnormalities and other possible neurological or systemic manifestations (5).

The most recent classification of E elaborated by the ILAE has included the classificatory axes into the aetiologies of E, identifying six groups: structural, genetic, metabolic, infectious, immune and unknown (4). An aetiology does not rule out another one; in fact, a patient suffering from tuberous sclerosis carrying characteristic brain lesions and presenting with seizures has both structural and genetic aetiologies. The category 'unknown aetiology' indicates that we are not able to identify the exact cause of the disease, but this gap will hopefully be filled in the future through the improvement of the available diagnostic tools or the discovery of new ones (6). The neurodegenerative aetiology has not been nosologically defined as another possible aetiology of E yet. However, considering the increasing scientific evidence about the existence of a bidirectional relationship between E and neurocognitive disorders in the elderly (i.e. Alzheimer's disease), the involvement of neurodegenerative processes into epileptogenesis should be further analysed and studied (7-9). There is an age-dependent variability of the aetiology of E (10). Once the diagnosis of seizure or E has been made, the second step for the clinician should be the identification of the underlying aetiology. Recognizing the responsible cause is fundamental because it allows diagnostic as well as prognostic accuracy, other than the identification of the best therapeutic approach possible for that specific patient.

Anti-seizure medicines (ASMs) are a milestone in the treatment of E. Nevertheless, even with a large number of therapeutic alternatives, about 30% of people with E continue to have uncontrolled seizures despite different and rational pharmacological associations, belonging to the pharmacoresistant portion of people with E (11). ILAE defined drug resistance as 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom' and considered this a testable, working hypothesis to be refined with time (12). It is known that after the failure of two appropriate and adequately chosen ASMs the possibility to have a clinically successful response with another ASM drastically decreases (13).

From a therapeutic point of view, a part of people with focal types of E could undergo surgical treatment. Aim of E surgery is to obtain complete seizure control in the absence of neurological complications, trying to eliminate the potential cognitive, psychological and socio-professional consequences caused by seizure persistence and/or chronic anti-seizure therapy (14). Before surgical treatment, the patient should be thoroughly studied and the evaluation should be directed to the identification of the so-called epileptogenic zone, the part of the brain from which the abnormal neuronal discharge originates, which should be possibly removed without consequences. Pre-surgical evaluation requires specific equipment and qualified medical staff. In the last decades, E surgery has become a more concrete therapeutic option, and a safer and less invasive surgical approach is now possible thanks to advances in structural and functional neuroimaging and video EEG monitoring, along with the simplification of invasive electrode implantation and the availability of new neurosurgical tools such as neuronavigation, intraoperative echography, endoscopic techniques and new resective surgical approaches (thermocoagulation, laser ablation, etc.) (15).

Currently, patients who may benefit from surgical treatment of E (as long as the resection of the epileptogenic zone is possible and without sequelae) should have the following prerequisites:

- Drug-resistant E;
- Patients with controlled seizures thanks to ASMs, but suffering from unbearable treatment-related adverse effects;
- Patients without drug-resistant E presenting with structural brain lesions, such as brain tumours, which should be further studied because of their high risk of determining pharmacoresistant E (15).

The 'ideal' candidate is a person with focal E, a clearly identifiable epileptogenic zone located outside eloquent cortical areas (15).

In case of drug-resistant patients who cannot undergo or refuse surgical treatment of E, there are other 'palliative' therapeutic options available, between them neuromodulation (vagus nerve stimulation, deep brain stimulation, etc.) (16).

Recent biotechnological progress and the rapid spread of information about the biological basis of some forms of E led to the so-called 'precision medicine', which is an innovative approach to discovering and developing therapies which can give better clinical outcomes to patients, by integrating clinical and molecular information to understand the biological basis of disease (17). In this field some goals have been achieved, even though there is a long way to go yet. For example, it has been elucidated that some epileptic and neurodevelopmental encephalopathies are caused by genetically determined deficits of some molecular transporters, as in GLUT-1 deficiency (18), or by altered enzymatic functions, as in pyridoxin-dependent encephalopathies (19). The earlier a specific substitutive therapy is started, the better could be the outcome for the patient.

Psychosocial impact

Many decades have passed since the famous epileptologist William Gordon Lennox (1884-1960) said that the person with E suffers more for its social consequences than for the disease itself and, in an editorial often cited in the *British Medical Journal*, the neurologist Rajendra Kale wrote, 'The history of epilepsy can be summarised as 4.000 years of ignorance, superstition, and stigma followed by 100 years of knowledge, superstition, and stigma' (20). Even though significant progress has been made in the last few years about the understanding of biological and molecular basis of E and despite the availability of multiple therapeutic options, people with E continue to be victims of discrimination and stigma (21). The origins of stigma are deep and resistant and, in our opinion, trying to understand why they exist could help in the management of E.

Intuitively, the impairment of awareness/consciousness happening during an epileptic seizure can increase the risk of traumas, fractures, accidents, burns and drowning for the patient, and this could happen everywhere, at home, at school, in the street or in the workplace (22). The risk of these E-related risks has a burden on patients and caregivers, especially parents of children with E, leading to a progressive inactivity (i.e. physical inactivity), dependence and social isolation (23). When seizures are characterized by impaired awareness/consciousness but do not provoke violent falls to the ground, there is surely a lower risk of physical injuries for the person, but even so the patient does not have control of him/herself in relation to the environment, compromising educational, professional and social activities, such as driving. Limitations on driving can influence employment, social interactions and personal independence, representing one of the biggest issues for patients with E (24). That being said, the global situation of a patient with E includes not only seizure recurrence but also higher risk of anxiety, depression, suicide, cognitive impairment and systemic diseases, such as obesity (25). This complex clinical scenario leads to psychological consequences (impairment of self-esteem) and psychosocial implications (lower possibility of having a partner, low-grade educational goals, unemployment or unqualified jobs, low income and stigma) (25).

On the other hand, motor phenomena that often accompany seizures scare witnesses of these events, especially those not familiar with the disease, worsening the burden of the stigma over people with E.

E is a burdensome disease because of seizure recurrence, chronic anti-seizure treatment and E-related somatic and psychological consequences (26). Compared with other neurological disorders, in men and women, E has both the highest rates of standardized disability-adjusted life years (DALYs) – the measure combining the time lost for premature death and the time lived in suboptimal conditions or in a condition of disability related to a specific disease – followed by migraine and Alzheimer's disease. E accounts for >13 million DALYs (27).

Based on these considerations, in November 2020, the 73rd World Health Assembly (WHA) adopted a resolution to develop an intersectoral global action plan on E and other neurological diseases. The action plan aims to reduce and eliminate preventable deaths caused by E and other neurological disorders, to improve access to promotion, prevention, management and care services, decreasing stigma and discrimination and protecting the human rights of people with neurological disorders. This action plan promotes physical and mental health, prevention, early diagnosis, assistance, treatment and rehabilitation, along with social, economic and educational needs and necessity of inclusion for people with E or different neurological diseases and their family (28).

Epidemiology

E is one of the most frequent chronic diseases, affecting around 50 million people worldwide (29). Its prevalence in high-income countries accounts for 4-8/1,000 individuals (the highest values being the most reliable) and the annual incidence is about 50,000 cases per 100,000 individuals (30). The rate increases to 73-86 cases considering isolated seizures and 93-116 cases if provoked and acute symptomatic seizures are included (30). So, 500,000 people with active E are present in Italy and 36,000 new cases of E are expected every year. Incidence seems to be higher in the first year of life, decreases during adolescence, remains low in adulthood and increases again after 75 years (31). It has to be considered that the age-dependent distribution of E in the general population has significantly changed over the past century with a five-fold increase in the incidence of E in individuals ≥60 years in the last 40 years (32).

The patients' journey and unmet needs: governance hypothesis

If we consider the journey of a person suffering from E, some 'key' moments can be identified:

T0: when the first seizure occurs or the person recognizes seizure recurrence;
T1: when the patient becomes drug-resistant;
T2: the medical or surgical management of drug-resistant E.

T0: the diagnosis

Epileptic seizures are brief and transient episodes characterized by recurrence of signs/symptoms often resembling other paroxysmal events, so that the differential diagnosis can be challenging. The risk of misdiagnosis is still very high if we consider that about 20% of patients presenting to centres specialized in E surgery have an erroneous diagnosis or suffer from seizure recurrence due to wrong therapeutic management (33). This initial diagnostic mistake is the starting point of a diagnostic and therapeutic odyssey with increasing healthcare costs for the national sanitary system (34), other than E-related psychological and psychosocial consequences (26). This scenario is quite common because the initial diagnosis of E is often made by a clinician without specific education in E.

Hypothesis of virtuous governance (First Seizure Clinic)

When a suspected epileptic seizure occurs, people should seek medical attention according to the two principal following scenarios:

1. The person with the paroxysmal event/events is addressed by the general practitioner (GP) to a qualified E centre with an urgent request for a deferable neurological/epileptological consultation (within 7 days);
2. In the second case, the interested person is sent by the GP or voluntarily goes to the emergency services of the nearer hospital, where the physicians usually execute urgent blood tests (including haemachrome, hepatic and renal functions, electrolytes and coagulation tests) and a computed tomography scan of the brain in order to exclude acute metabolic disorders. After excluding acute conditions, the physician sends the patient to a specialized E centre with a request of deferable neurological/epileptological consultation within 7 days.

At the moment of the first epileptological consultation, if the suspect of seizure is confirmed by a highly trained epileptologist, an EEG with and without sleep deprivation and a magnetic resonance imaging (MRI) of the brain should be suggested according to the ILAE recommended protocol (HARNESS-MRI protocol) (35). This protocol, involving 3-Tesla-MRIs, would allow to identify even small cortical dysplasias or otherwise undetectable epileptogenic lesions. It is important to use this protocol to identify a potential epileptogenic structural alteration of the brain from the start to avoid useless future MRIs and to allow the best therapeutic approach for the patient who can also be properly informed about his/her prognosis (1).

If the suspect of seizure is not confirmed, other diagnostic options should be provided to the patient.

An approach like this would guarantee to the person the inalienable right of having a correct diagnosis in the least possible time, obtaining the best treatment possible as well.

T1: the diagnosis of pharmacoresistance

After the failure of the second appropriately chosen and adequately used ASM, according to ILAE guidelines, the patient is considered drug-resistant (12), even though this is a dynamic condition that can change over time even for the same person. As mentioned earlier, the chances of achieving seizure freedom drastically diminish with subsequent therapeutic approaches (13), so in this exact moment it is mandatory to revise the clinical history of the patient, taking into account the possibility of a surgical approach. E surgery, when possible, can give optimal outcomes with benefit for the patient and the healthcare system.

E surgery should be immediately considered in front of a patient with focal seizures, in the absence of cognitive or behavioural disabilities and with an epileptogenic zone located outside eloquent cortical regions (15).

In this way, the right to have the best therapeutic approach in the least time possible would be guaranteed to the patient, avoiding the psychological and social consequences of drug-resistant E (26).

Hypothesis of virtuous governance: to verify in the less time possible if the patient could be a candidate to surgical treatment of E.

T2a: the surgical management of drug-resistant E

Once the criteria for the inclusion of the patient in the pre-surgical evaluation are fulfilled, in the majority of cases, a video EEG is required. So, the presence of specific equipment and specialized medical and paramedical staff completely dedicated to the 'long-term monitoring' of EEG is essential for the structure where the patient has been sent.

In the case of positive outcomes after 'long-term' registration, the patient will be guided to hyper-specialized centres dedicated to E surgery.

The possibility of 'long-term monitoring' of EEG – and the subsequent E surgery as well – should be guaranteed to the patient, even though this is not an ubiquitous and homogeneous condition in Italy.

Hypothesis of virtuous governance: early access to E surgery increases the number of centres completely dedicated to increasing surgical treatment of E.

T2b: the medical management of drug-resistant E

This is the case of people with drug-resistant E who refuse or cannot/did not benefit from E surgery.

People with drug-resistant E and rare and complex epilepsies are burdened not only by seizure recurrence but also by different and multiple comorbidities, which require specific interventions and a multidisciplinary approach with the involvement of various medical figures as geneticists, psychologists, psychiatrists, gynaecologists and physiatrists. Moreover, chronic diseases and E in particular affect not only the single individual but also caregivers. Intellectual disability and behavioural alterations associated with E add an additional burden on caregivers' shoulders in terms of costs, responsibility of care, centralization of the family's attention and social isolation (36).

In our opinion, the most appropriate form of management in these cases is represented by the so-called 'complex and coordinated ambulatorial programmes', which are a group of medical services finalized to specific diagnostic and therapeutic goals, tailored to the patient and included in the regional list of ambulatorial specialties. These programmes take place in the morning, requiring about half a day, avoiding economic expenses to patient and caregivers and hospitalization, guaranteeing a better quality of life and a reduction of healthcare costs.

Also in these cases, only highly specialized centres with specific equipment and trained medical and paramedical personnel can adopt this kind of multidisciplinary programmes, where the cooperation between different specialists is a fundamental requirement.

The multidisciplinary approach in a selected setting dedicated to E and its comorbidities can improve the quality of care (i.e. with the access to new treatments in compassionate programmes or the simplification of complex and often useless polytherapies) and the quality of life for the patient and his/her family, reducing the number of hospitalizations or accesses to emergency settings.

In patients with drug-resistant E, 'palliative' and non-pharmacological approaches can be adopted, such as vagus nerve stimulation, which can reduce seizure frequency and intensity, improving the quality of life (16).

Hypothesis of virtuous governance: create highly specialized centres where trained and expert personnel could guarantee to the patient and his/her family a multidisciplinary approach, especially in case of rare and complex epilepsies.

Conclusions

The management of E should be given to clinicians with a certified and high competence in E working in specific settings considering the number of patients, the required personnel and the organizational complexity.

In the Italian territory, specific centres with highly qualified staff defined according to the regional needs and

numerosity of people should be accessible to every person with E. In order to avoid discrepancies in the care of people with E and to overcome the 'regionalization of the sanitary system', the central government should guarantee a homogeneous and equal presence of centres completely dedicated to E with uniformity in medical personnel and specific equipment.

Disclosures

Conflicts of interest: GF has received consultancy fees from Angelini Pharma. ALN has received speaker's or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW, Arvelle Therapeutics, Angelini Pharma and UCB Pharma.
Financial support: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Payment of publication fees was supported by Angelini Pharma S.p.A.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4): 475-482. CrossRef PubMed
2. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010;51(4): 671-675. CrossRef PubMed
3. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-530. CrossRef PubMed
4. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521. CrossRef PubMed
5. Musante L, Costa P, Zanus C, et al. The genetic diagnosis of ultrarare DEEs: an ongoing challenge. Genes (Basel). 2022;13(3):500. CrossRef PubMed
6. Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county – a population based study. Epilepsia. 2015;56(5):699-706. CrossRef PubMed
7. Stefanidou M, Beiser AS, Himali JJ, et al. Bi-directional association between epilepsy and dementia: The Framingham Heart Study. Neurology. 2020;95(24):e3241-e3247. CrossRef PubMed
8. Yu T, Liu X, Wu J, Wang Q. Electrophysiological biomarkers of epileptogenicity in Alzheimer's disease. Front Hum Neurosci. 2021;15:747077. CrossRef PubMed
9. Balestrini S, Arzimanoglou A, Blümcke I, et al. The aetiologies of epilepsy. Epileptic Disord. 2021;23(1):1-16. CrossRef PubMed
10. Dahl-Hansen E, Koht J, Syvertsen M. Epilepsy at different ages – etiologies in a Norwegian population. Epilepsia Open. 2018; 4(1):176-181. CrossRef PubMed
11. Löscher W, Potschka H, Sisodiya SM, Vezzani A. Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev. 2020;72(3): 606-638. CrossRef PubMed
12. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-1077. CrossRef PubMed
13. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-319. CrossRef PubMed
14. Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. Lancet Neurol. 2008;7(6):514-524. CrossRef PubMed
15. Consales A, Casciato S, Asioli S, et al. The surgical treatment of epilepsy. Neurol Sci. 2021;42(6):2249-2260. CrossRef PubMed
16. Mao H, Chen Y, Ge Q, Ye L, Cheng H. Short- and long-term response of vagus nerve stimulation therapy in drug-resistant epilepsy: a systematic review and meta-analysis. Neuromodulation. 2022;25(3):327-342. CrossRef PubMed
17. Dolsten M, Søgaard M. Precision medicine: an approach to R&D for delivering superior medicines to patients. Clin Transl Med. 2012;1(1):7. CrossRef PubMed
18. Daci A, Bozalija A, Jashari F, Krasniqi S. Individualizing treatment approaches for epileptic patients with Glucose Transporter Type1 (GLUT-1) deficiency. Int J Mol Sci. 2018;19(1):122. CrossRef PubMed
19. van Karnebeek CD, Tiebout SA, Niermeijer J, et al. Pyridoxine-dependent epilepsy: an expanding clinical spectrum. Pediatr Neurol. 2016 Jun;59:6-12. CrossRef PubMed
20. Kale R. Bringing epilepsy out of the shadows. BMJ. 1997; 315(7099):2-3. CrossRef PubMed
21. Kwon CS, Jacoby A, Ali A, et al. Systematic review of frequency of felt and enacted stigma in epilepsy and determining factors and attitudes toward persons living with epilepsy – report from the International League Against Epilepsy Task Force on Stigma in Epilepsy. Epilepsia. 2022;63(3):573-597. CrossRef PubMed
22. Beghi E, Cornaggia C; RESt-1 Group. Morbidity and accidents in patients with epilepsy: results of a European cohort study. Epilepsia. 2002;43(9):1076-1083. CrossRef PubMed
23. Beghi E. Accidents and injuries in patients with epilepsy. Expert Rev Neurother. 2009 Feb;9(2):291-298. CrossRef PubMed
24. Noe K. Counseling and management of the risks of living with epilepsy. Continuum (Minneap Minn). 2019;25(2):477-491. CrossRef PubMed
25. Shorvon S, Perucca E, Engel J. The treatment of epilepsy. 4th ed. Oxford (UK): Wiley-Blackwell; 2015.
26. Beghi E, Giussani G, Nichols E, et al; GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(4):357-375. CrossRef PubMed
27. Beghi E. Addressing the burden of epilepsy: many unmet needs. Pharmacol Res. 2016;107:79-84. CrossRef PubMed
28. Kanmounye US, Abu-Bonsrah N, Shlobin NA, Djoutsop OM. Letter: The World Health Organization's Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders 2022-2031. Neurosurgery. 2022 Jun 1;90(6):e201-e203. CrossRef PubMed
29. World Health Organization. Epilepsy: a public health imperative. 2019. Online (Accessed June 2022).
30. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017 Jan 17;88(3):296-303. CrossRef PubMed
31. Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe – a systematic review. Eur J Neurol. 2005;12(4):245-253. CrossRef PubMed
32. Stefan H. Epilepsy in the elderly: facts and challenges. Acta Neurol Scand. 2011;124(4):223-237. CrossRef PubMed
33. Kanemoto K, LaFrance WC Jr, Duncan R, et al. PNES around the world: where we are now and how we can close the diagnosis and treatment gaps – an ILAE PNES Task Force report. Epilepsia Open. 2017;2(3):307-316. CrossRef PubMed

34. Ricci L, Boscarino M, Assenza G, et al; Epilepsy Study Group of the Italian Neurological Society. Clinical utility of home videos for diagnosing epileptic seizures: a systematic review and practical recommendations for optimal and safe recording. Neurol Sci. 2021;42(4):1301-1309. CrossRef PubMed
35. Larivière S, Federico P, Chinvarun Y, et al. ILAE Neuroimaging Task Force Highlight: harnessing optimized imaging protocols for drug-resistant childhood epilepsy. Epileptic Disord. 2021;23(5):675-681. CrossRef PubMed
36. Oliveira MC, Lima EM, de Paiva MLN, Valente KDR. Factors associated with caregiver burden of adults with epilepsy in a middle-income country. Seizure. 2022;98:1-7. CrossRef PubMed