

Diagnosis and Treatment of the First Epileptic Seizure: Guidelines of the Italian League Against Epilepsy

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Summary: The diagnosis and treatment of a first epileptic seizure are made by physicians with different types of expertise. Heterogeneous patterns of care are thus expected, which explain the need for shared patterns of care. These guidelines were developed by a group of experts from the Italian League against Epilepsy (LICE) in accordance with the requirements of evidence-based medicine. An accurate assessment of the seizure is required, with active questioning about circumstances of occurrence, clinical manifestations, and postictal symptoms. For seizures with loss of consciousness, the presence of cyanosis, hypersalivation, tongue biting, and postictal disorientation has a specific diagnostic value. Laboratory tests and toxicological screening should be performed only in the presence of circumstances suggesting a metabolic or toxic encephalopathy. Elevated prolactin levels 10–20 min. after the event help in differentiating generalized tonic-clonic or partial seizures from psychogenic nonepileptic seizures. Except for infants less than six months of age, CSF examination is recommended only when a cerebral

infection is suspected. An EEG should be performed within 24 h. after a seizure, particularly in children. If the EEG is normal during wakefulness, a sleep EEG is recommended. A CT scan is strictly indicated when a severe structural lesion is suspected or when the etiology is unknown. MRI may not be indicated in the emergency room, but it should be preferred to CT as part of the diagnostic assessment. The added value of other diagnostic tools (neuropsychological tests, ambulatory EEG, functional MRI, SPECT, and PET) is as yet unknown. These tests may be used on a case-by-case basis. In the presence of an acute symptomatic seizure, treatment of the cause is recommended. Symptomatic therapy is not justified unless the seizure has the characteristics of status epilepticus. Long-term treatment may be considered in patients with abnormal EEG and imaging data and after consideration of the social, emotional, and personal implications of seizure relapse. **Key Words:** First seizure—Diagnosis—Treatment—Guidelines—Italian League against Epilepsy.

In industrialized countries, the annual incidence rate of epilepsy (defined by the occurrence of two or more unprovoked seizures 24 or more hours apart) is 29–53 cases per 100,000 (Hauser et al., 1997). The rate rises to 73–86 cases when isolated unprovoked seizures are included, and to 93–116 cases by including acute symptomatic seizures (i.e., seizures occurring in close temporal relationship with an acute systemic, toxic, or metabolic injury of the central nervous system, CNS) (Annegers et al., 1995). On this basis, the annual number of cases expected in Italy (population of 57,000,000) is 17,000 to 30,000 for epilepsy, 20,000 to 25,000 for isolated unprovoked seizures, and 12,000 to 18,000 for acute symptomatic seizures. Given this high frequency, the diagnosis and treatment of epilepsy and epileptic seizures are made

by physicians working in primary, secondary, and tertiary centers, including neurologists, child neurologists, neurosurgeons, emergency room doctors, general practitioners, and pediatricians. The varying range of professionals involved may lead to heterogeneous patterns of care.

In this context, the problems posed by a patient with a first epileptic seizure are largely defined by the peculiarities of this condition:

- Epileptic seizures are episodic manifestations which tend to recur with similar characteristics in the same patient, to occur at any age, and to be unpredictable in the large majority of cases;
- Seizures expose the patient to environmental risks and limit his/her autonomy and socio-economic efficiency (with heavy personal and social consequences), even though they are rarely life-threatening;
- Seizures are caused by several different causes. Because they are sometimes the manifestation of an

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underlying clinical condition, they may disappear when the latter is removed;

- In many patients, seizures tend to persist over a prolonged period, sometimes for a lifetime, and require chronic treatment with drugs which are not always effective, cause significant adverse effects and, for most recent compounds, have a high cost;
- Seizures may interfere with several personal choices (school, professional activities, pregnancy, etc.);
- Occasionally, seizures represent a medical emergency, or at least they are perceived as such, and trigger emergency interventions involving many health care professionals;
- Seizures may occur in patients with comorbidities treated with drugs potentially interfering with antiepileptic medication.

In view of the importance of the correct management of patients presenting with a first seizure, the Italian League against Epilepsy (LICE) set up a working group to draft guidelines on diagnosis and treatment of these patients.

METHODS

Seizure types addressed in the guideline

Seizures addressed in this guideline include partial seizures (simple complex and secondarily generalized), and generalized tonic and/or clonic seizures. The guideline does not address *petit mal* absences, atonic and myoclonic seizures, which are more easily identified only after recurrence. The guideline also addresses acute symptomatic seizures. For the purposes of this guideline, two or more seizures occurring within 24 h. are considered as a single seizure.

Procedures for literature search

The scientific literature was examined by searching tertiary sources (guideline data banks), secondary sources (Cochrane Library), and primary sources (Medline). For the Medline search, original documents were traced using the following key words: *epilepsy, epileptic seizures, convulsions, first seizure, neuroimaging, electroencephalogram (EEG), meta-analysis, diagnosis, therapy*, in various combinations. For each publication, the abstract was first examined and, when it referred to the management of the first seizure, the entire publication was evaluated. Special consideration was given to *Commission Reports of the International League Against Epilepsy, the Scottish Intercollegiate Guidelines, and the Practice Parameters of the American Academy of Neurology*. Regional guidelines, formerly developed by the epilepsy centers of Lombardy and Tuscany, were also consulted. The structure of the latter guidelines provided the template for the development and finalization of this document.

Levels of evidence and strength of recommendations

This guideline was developed in accordance with the requirements of evidence-based medicine (CeVEAS, 2000). On this basis, diagnostic and therapeutic steps in a patient with a first epileptic seizure are defined in the light of the levels of published evidence, which justify the strength of the recommendations included in the guideline (Table 1).

Authors and development plan

The guidelines were prepared by the group of experts who authored this article. The group coordinator (EB) made a systematic review of the literature and drafted the document. The other members of the group helped in the search of key sources and contributed to the finalization of

TABLE 1. Levels of evidence and strength of recommendations (*)

Levels of evidence
Level 1. Evidence obtained from prospective cohort studies with adequate design; includes also evidence obtained from meta-analyses of randomized clinical trials and from at least one randomized clinical trial
Level 2. Evidence obtained from cohort studies with suboptimal design or from case-control studies; includes also evidence obtained from at least one controlled nonrandomized trial and evidence obtained from at least one other well-designed, quasi-experimental study
Level 3. Evidence obtained from other observational nonexperimental studies
Level 4. Evidence obtained from expert opinions (including commissions of experts and single authoritative experts). Indicates the absence of good quality studies

Strength of recommendations

Grade A. The intervention (whether diagnostic or therapeutic) is to be recommended because it is clearly effective, or to be discouraged because it is ineffective or harmful. The recommendation is based on evidence level 1.

Grade B. The intervention is probably effective, ineffective, or harmful. The intervention may be recommended to specific subgroups of patients. The recommendation is based on evidence levels 2 and 3.

Grade C. The intervention is possibly effective, ineffective, or harmful. The intervention deserves further evaluation before being recommended or discouraged. The recommendation is based on evidence level 4.

(*) The definitions of the levels of evidence and the strength of the recommendations used in this guideline are based on the scheme adopted by the U.S. Agency for Health Care and Policy Research. According to this scheme, each diagnostic and therapeutic intervention is recommended according to the level of scientific evidence. The efficacy of each diagnostic intervention (for example, the use of a laboratory test) is measured by its ability to modify the *a priori* diagnostic hypothesis. The efficacy of each therapeutic intervention is measured by its ability to modify the prognosis (i.e., the tendency of seizures to relapse). However, correlations between levels of evidence and strength of recommendations should be interpreted flexibly and within the context of the individual's clinical, social, emotional, and personal situation.

The levels of evidence and the strength of the recommendations are generally indicated at the beginning of each set of procedures being discussed; other indications requiring different diagnostic or therapeutic management are noted in parentheses within the text.

the document. The guideline was then submitted for final review and approval to the executive council of the Italian League Against Epilepsy (LICE).

This guideline illustrates the management of the first seizure by separating the acute phase (when the patient is seen at the time of the seizure) from the retrospective (or anamnestic) phase (when the patient is seen at a variable interval after the seizure), because of the different diagnostic and therapeutic implications and the need to separate emergency management from the planning of the diagnostic work-up and subsequent treatment. For each step, diagnostic and therapeutic procedures are considered together with the associated level of evidence and the strength of the recommendations (indicated in parentheses at the end of each heading).

ACUTE DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF A PATIENT PRESENTING WITH A FIRST SEIZURE

When the first seizure is ongoing at the time of the medical observation, assessment of its duration is imperative. If the seizure lasts more than 20 min., a diagnosis of status epilepticus should be considered. The management of status epilepticus is addressed elsewhere in this supplement (Minicucci et al., 2006). In all other cases, the physician must collect past and recent history (by direct interview of the witness, where available) to ascertain the epileptic origin of the seizure and to determine whether the event was isolated or not. Nonepileptic events, whether neurological, psychiatric, or systemic, must be adequately excluded.

An accurate description of the clinical features of the seizure and the results of neurological examination as well as electrophysiological, laboratory, and neuroimaging tests, as outlined below, contribute to the definition of the origin and etiology of the seizure. With reference to the interval between an underlying predisposing or provoking clinical condition, the seizure is defined as unprovoked (i.e., occurring in the absence of precipitating factors) or provoked or acute symptomatic (i.e., occurring in close temporal relationship with an acute systemic, metabolic or toxic CNS insult) (Commission, 1993). Unprovoked seizures may also occur in the presence of a non-progressing CNS spontaneous or traumatic injury (remote symptomatic seizures) (Commission, 1993). The separation between unprovoked and provoked seizures has relevant implications with reference to the decision to start antiepileptic treatment and to the type and duration of the treatment.

Patient's history (level of evidence 3, strength of recommendation B)

- Clinical characteristics of the seizure
- Sleep/wake cycle
- Concurrent symptoms/conditions: fever, infection, trauma, dehydration, hypertension

- Provoking factors: sleep deprivation, toxic compounds, photic stimulation, other environmental stimuli
- Comorbidity (previous or current)
- Family history of epilepsy/seizures

Clinical examination (level of evidence 3, strength of recommendation B)

- General examination
- Neurological examination

Levels of evidence

Except for some symptoms accompanying or following the seizure, there are no adequately controlled studies supporting the value of the history or the clinical examination. Good indicators of the epileptic nature of a convulsive seizure include cyanosis and, to a lesser extent, hypersalivation (accompanying symptoms) and tongue biting and disorientation (symptoms following the seizure) (Hoefnagels et al., 1991) (level of evidence 3).

Recommendations

The lack of evidence from controlled studies does not exclude the need to perform an accurate clinical assessment (including history taking, general, and neurological examination) in all individuals with a first seizure. Active questioning is required for cyanosis, hypersalivation, tongue biting, and post-ictal disorientation.

Biochemical/hematological assays (level of evidence 2, strength of recommendation B)

- Complete blood cell count
- Glucose
- Urea
- Electrolytes
- Calcium
- Creatinine
- ALT, AST
- Creatine kinase/prolactin
- Urine analysis
- Toxicological tests (where needed)

Levels of evidence

Except for infants aged less than six months, in whom hyponatremia (<125 mM/L) is frequently associated with epileptic seizures (Farrar et al., 1995), metabolic disorders (hyperglycemia or hypoglycemia, electrolyte disturbances, etc.) are rarely found in children and adults undergoing biochemical/hematological screening after a seizure (Turnbull et al., 1990) (levels of evidence 1 and 2). For the differentiation between epileptic seizures and psychogenic nonepileptic seizures, an elevated serum prolactin (twice the baseline level or > 36 ng/mL) is highly suggestive of either generalized tonic-clonic or complex partial seizures (Chen et al., 2005) (levels of evidence 1 and 2). Prolactin elevations can be observed after tilt-test induced syncope (Chen et al., 2005) (level of evidence

2). There is no evidence that creatine kinase helps in differentiating epileptic from nonepileptic seizures (level of evidence 3). Toxicological tests may be helpful only after excessive intake or abuse of drugs or other epileptogenic agents (level of evidence 4).

Recommendations

Laboratory tests should be performed only in the presence of circumstances suggesting a metabolic encephalopathy, particularly in patients with persisting impairment of consciousness during the examination. Toxicological screening is indicated only when exposure to drugs or other toxic substances is suspected. An elevated serum prolactin level, when detected at 10–20 min. after a suspected event, helps in differentiating between a generalized tonic-clonic or a complex partial seizure and a psychogenic nonepileptic seizure. Serum prolactin does not distinguish an epileptic seizure from a syncope. Creatine kinase is noninformative in the differential diagnosis between epileptic and nonepileptic seizures.

Electroencephalogram (EEG) (level of evidence 3, strength of recommendation B)

Levels of evidence

An EEG done in the first 24 h. after the seizure has a greater probability of detecting epileptiform abnormalities than an EEG done in the subsequent days (King et al., 1998) (level of evidence 3). By contrast, slowing of the EEG background activity at 24–48 h. after the seizure may be transient and should be interpreted with caution.

Recommendations

An EEG should be performed within 24 h. after a seizure, particularly in children.

Brain computerized tomography (CT) scan/magnetic resonance imaging (MRI) (level of evidence 2, strength of recommendation B)

Levels of evidence

Although abnormalities may be found in up to one-half of adults (Russo and Goldstein, 1983) and in up to one-third of children (Hirtz et al., 2000), the contribution of neuroimaging is limited even in patients with documented epileptogenic brain injuries and/or partial seizures (levels of evidence 1 and 2). There is no evidence that MRI is superior to CT scan in an emergency setting, at least in children (Ferry, 1992).

Recommendations

The use of brain CT scan or MRI in the emergency room is indicated when specific interventions may be needed. A CT scan is strictly indicated when a structural lesion is suspected or when the etiology of the seizure cannot be easily identified. Structural lesions include, among others, post-traumatic complications, cerebral hemorrhage, brain edema, and space-occupying lesions, which may be

suggested by post-ictal deficits and/or persisting impairment of consciousness. In the emergency room, MRI is not indicated, except for very selected circumstances, to be evaluated on an individual basis.

Examination of cerebrospinal fluid (CSF) (level of evidence 2, strength of recommendation B)

Levels of evidence

For its high sensitivity and specificity, examination of the CSF is generally performed in the presence of a febrile seizure associated with meningeal signs, to exclude a cerebral infection (Anonymous, 1993). In infants under six months of age with impaired consciousness and delay in the recovery of alertness, the CSF may be abnormal even in the absence of signs of meningeal irritation. By contrast, the value of CSF examination in patients with a first afebrile seizure is as yet unproven (levels of evidence 2 and 3).

Recommendations

Except for infants less than six months of age, examination of the CSF is recommended in children and adults only when cerebral infection is suspected (Hirtz et al., 2000). Examination of the CSF is generally contraindicated in the absence of fever.

Therapy (level of evidence 3, strength of recommendation B)

Levels of evidence

Etiological treatment of acute symptomatic seizures has strong biological plausibility, although there is no evidence from adequately controlled studies that treating the etiology of a first acute symptomatic seizure is followed by a lower risk of relapse. In one randomized (evidence level 2) study (Solari et al., 1997), treatment with benzodiazepines of a first unprovoked generalized tonic-clonic seizure was followed by a significant decrease in the risk of relapse.

Recommendations

In the presence of a first acute symptomatic seizure (metabolic encephalopathy, acute CNS injury in patients with an underlying treatable condition), treatment of the cause is recommended. Symptomatic therapy of a first unprovoked seizure is not justified unless the seizure has the characteristics of status epilepticus. For guidelines on the management of status epilepticus, refer to Minicucci et al. (2006) in this supplement.

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF A PATIENT WITH A HISTORY OF A FIRST SEIZURE

When a first seizure is reported during an outpatient or a hospital medical consultation and the post-ictal phase has elapsed, there is still a need for differential diagnosis

between epileptic and nonepileptic seizures and, in the case of an epileptic seizure, between acute symptomatic and unprovoked seizures. In the latter case, a search must also be made for the putative etiology of the seizure. An accurate history, as well as a general and neurological examination, is needed to identify symptoms and signs predictive of an epileptic seizure. The results of laboratory, electrophysiological, and imaging tests must also be obtained as appropriate, looking for the etiology of the seizure, in order to make a decision about the need to start antiepileptic treatment and the choice and duration of treatment.

Patient's history (level of evidence 3, strength of recommendation B)

- Clinical characteristics of the seizure
- Sleep/wake cycle
- Concurrent symptoms/conditions: fever, infection, trauma, dehydration, hypertension
- Provoking factors: sleep deprivation, toxic compounds, photic stimulation, other environmental stimuli
- Comorbidity (previous or current)
- Family history of epilepsy/seizures

Clinical examination (level of evidence 3, strength of recommendation B)

- General examination
- Neurological examination

Levels of evidence

The value of the history and clinical examination is supported by level 3 evidence, with reference to symptoms and signs accompanying or following the ictal event (see above). Cyanosis and hypersalivation (among accompanying symptoms and signs) and tongue biting and disorientation (among symptoms and signs documented after the seizure) are good predictors of the epileptic nature of a seizure (Hoefnagels et al., 1991).

Recommendations

Despite lack of evidence from good quality studies, history and a general and neurological examination are needed for a correct assessment. When interviewing witnesses of the seizure, special attention must be given to the possible occurrence of cyanosis, hypersalivation, tongue biting, and post-ictal disorientation, which are useful indicators of an epileptic origin of the seizure.

Biochemical/hematological assays (level of evidence 2, strength of recommendation B)

Please refer to acute diagnostic and therapeutic management.

Examination of CSF (level of evidence 2, strength of recommendation B)

Please refer to acute diagnostic and therapeutic management.

EEG (level of evidence 1, strength of recommendation A)

- If a standard EEG during wakefulness is not informative, a sleep EEG is recommended (level of evidence 2, strength of recommendation B)

Levels of evidence

In children with a first epileptic seizure, the presence of focal slowing or epileptiform abnormalities in the EEG is followed by a greater risk of relapse (Hirtz et al., 2000) (level of evidence 1). In children, in the presence of a cryptogenic seizure, an abnormal EEG doubles the risk of relapse (Shinnar et al., 1994) (level of evidence 1). In adults, the predictive value of the EEG is less certain. With a sleep EEG, the probability of detecting abnormalities in the tracing is increased (King et al., 1998; Schreiner and Pohlman-Eden, 2003). There are no data on the value of an ambulatory EEG in patients with a first seizure.

Recommendations

EEG is part of the diagnostic screening of epileptic seizures both in children and in adults. If the EEG during wakefulness is normal, sleep EEG is recommended. An ambulatory EEG is not justified in patients with a first seizure of suspected epileptic origin.

Brain CT scan/MRI (level of evidence 1, strength of recommendation A)

Levels of evidence

In the literature, there are consistent findings on the greater sensitivity of MRI compared to CT for the diagnosis of epileptogenic conditions (Hirtz et al., 2000) (levels of evidence 1 and 2). By contrast, MRI is mandatory for the detection of structural brain abnormalities, to assess the risk of relapse, and to guide therapeutic management in patients with cryptogenic and remote symptomatic epilepsies. The role of MRI is less defined in the diagnostic work-up and prognostic assessment of patients with idiopathic partial epilepsy.

Recommendations

MRI is an integral part of the diagnostic assessment of a patient with a suspected first cryptogenic or remote symptomatic seizure. MRI should be preferred to CT, but it is not necessary in the presence of a diagnosis of idiopathic partial epilepsy. CT is an alternative tool in patients in whom MRI is contraindicated or cannot be performed.

Other diagnostic tools (level of evidence 4, strength of recommendation C)

Levels of evidence

There is no sound evidence in the literature that neuropsychological tests, functional MRI, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) are of value in the differential diagnosis of a first epileptic seizure.

Recommendations

Neuropsychological tests, functional MRI, SPECT, and PET are not generally recommended in a patient with a first epileptic seizure, but they may be used on a case-by-case basis.

Therapy (level of evidence 1, strength of recommendation A)

Levels of evidence

The decision to treat a first seizure with antiepileptic drugs (AEDs) is largely determined by the risk of relapse. Even if this risk may vary from case to case, the highest rates of recurrence are found in patients with an abnormal EEG and a documented brain lesion (Berg and Shinnar, 1991) (level of evidence 1). In general, the risk of recurrence is highest in the first 12 months and is almost reduced to zero two years after the seizure (Beghi, 2003). Evidence level 1 and 2 studies have consistently shown that treatment of a first unprovoked seizure decreases the risk of relapse in the following two years, but it does not affect the probability of long-term remission both in children and in adults (Musicco et al., 1997; Hirtz et al., 2003; Marson et al., 2005).

Recommendations

Indiscriminate treatment of the first unprovoked seizure with AEDs is not recommended. Treatment may be considered in patients in whom electrophysiological and imaging data indicate an increased risk of relapse (as indicated, most notably, by the presence of structural CNS abnormalities and/or EEG abnormalities) and/or in those in whom the risks and the benefits of treatment are in favor of the latter, after consideration of the social, emotional, and personal implications of seizure relapse and of treatment itself. There are situations which may indicate deferral of treatment (e.g., pregnancy) while others, for example patients performing potentially dangerous activities, may favor initiation of treatment. In either case, the patient should be involved in the decision process. Treatment modalities (choice of drug, drug dosages, and duration of treatment) are the same as for the treatment of patients who had recurrent seizures and their discussion is beyond the scope of the present guideline.

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