

Guidelines for Epidemiologic Studies on Epilepsy

Commission on Epidemiology and Prognosis, International League Against Epilepsy

Epidemiologic research on epilepsy has been developed relatively recently. Several studies have been performed in industrialized as well as in developing countries. The published results are often discordant, even in simple descriptive studies, because of lack of agreement regarding the most basic concepts. Definitions of epilepsy, seizures, and independent variables often are not elaborated. The classifications of seizures (Commission, 1981) and epileptic syndromes (Commission, 1989) proposed by the International League Against Epilepsy (ILAE) are either not used or are used incorrectly. Analysis of risk factors is also a source of confusion, and basic epidemiologic measures are frequently misstated.

For these reasons, The Commission of Epidemiology and Prognosis, created in 1990 by President H. Meinardi, decided to give priority to elaboration of a set of guidelines for future epidemiologic research. The Commission met three times: once in Rio de Janeiro, Brazil (September 1991) and, thanks to special grants from the Neuroepidemiology Branch, National Institutes of Health, twice in Bethesda, Maryland, U.S.A. (April and December 1992). The members of the Commission who participated were P. Jallon (Geneva, Switzerland), Chairman; A Hauser (New York, NY, U.S.A.); G. C. Roman (Bethesda, MD, U.S.A.); J.W.A.S. Sander (London, England); J. Manelis (Tel Aviv, Israel); M. Sillanpää (Turku, Finland); B. O. Osuntokun (Ibadan); and J. Overweg (Heemstede, The Netherlands). Consultants who contributed to the work of the Commission included P. Loiseau (Bordeaux, France); K. Nelson (Bethesda); J. Cereghino (Bethesda); R. Ottman (New York); S. Emery (Burlington, VT, U.S.A.); J. Sheller (Bethesda); S. Shinnar (New York).

The proposed guidelines represent a consensus between epileptologists and epidemiologists. These guidelines are presented in four parts: (a) Definition of seizures and epilepsy, (b) seizure type classification, (c) risk factors; and (d) recommended measurement indexes. Three appendices have been developed to help define the different situations and risk factors.

BASIC PRINCIPLES FOR EPIDEMIOLOGIC STUDIES OF EPILEPSY

Many neuroepidemiologic studies of epilepsy have been published worldwide, but lack of standardized definitions, differences in methods of case ascertainment, diagnostic accuracy, and seizure classification impede meaningful comparisons. Epidemiologic studies provide important information regarding the natural history and risk factors of epilepsy, but to be comparable studies should begin with use of standard definitions which could be reproduced in other geographic environments. We propose a set of basic definitions for epidemiologic studies. The first step in field studies is use of a screening instrument adapted to the population at risk. The specificity and sensitivity of the questionnaire must be tested and validated, and the methods used to validate the instruments should be clearly described.

Diagnosis of epilepsy is essentially clinical, based on a bonafide history of epileptic seizures. Diagnosis should be confirmed by a health professional with expertise in epilepsy, using available medical history, seizure description, and neurologic examination. Standardized study methods should be used to obtain information about the above three diagnostic elements, and standardized criteria should be used for their interpretation. If available, EEG records and other diagnostic tools should also be used, but lack of these instruments should not preclude the diagnosis of epilepsy. EEG contributes but does not always confirm a diagnosis of epilepsy: An abnormal EEG must not be considered as a requisite for inclusion since it could be normal (or indicate nonspecific abnormalities) in epileptic subjects. On the other hand, an abnormal EEG (with epileptiform abnormalities), after an isolated seizure, could suggest classification of the seizure as epilepsy.

Definitions

The importance of rigorous case definition in epidemiologic studies of seizure disorders and epilepsy cannot be overemphasized. The following definitions are proposed:

Epileptic seizure. A clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain. The clinical manifestation consists of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer.

Epilepsy. A condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-h period are considered a single event. An episode of status epilepticus is considered a single event. Individuals who have had only febrile seizures or only neonatal seizures as herein defined are excluded from this category.

Status epilepticus. A single epileptic seizure of >30-min duration or a series of epileptic seizures during which function is not regained between ictal events in a >30-min period.

“Active” epilepsy. A prevalent case of active epilepsy is defined as a person with epilepsy who has had at least one epileptic seizure in the previous 5 years, regardless of antiepileptic drug (AED) treatment. A case under treatment is someone with the correct diagnosis of epilepsy receiving (or having received) AEDs on prevalence day.

Epilepsy in remission with treatment. A prevalent case of epilepsy with no seizures for ≥ 5 years and receiving AED at the time of ascertainment.

Epilepsy in remission without treatment. A prevalent case of epilepsy with no seizures for ≥ 5 years and not receiving AED at the time of ascertainment.

Single or isolated seizure. One or more epileptic seizures occurring in a 24-h period.

Febrile seizure. An epileptic seizure as herein defined, occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures.

Neonatal seizure. An epileptic seizure as herein defined occurring in the first 4 weeks of life.

Febrile seizure with neonatal seizure. One or more neonatal seizures in a child who has also experienced one or more febrile seizures as herein defined.

Nonepileptic events. Clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of a set of neurons of the brain, including: (a) disturbances in brain function (vertigo or dizziness, syncope, sleep and movement disorders, transient global amnesia, migraine, enuresis), and pseudoseizures (nonepileptic sudden behavioral epi-

sodes presumed to be of psychogenic origin; these may coexist with true epileptic seizures).

Seizure type classification

Current international classification of seizure disorders relies on use of clinical and EEG criteria, but in many field surveys of epilepsy, EEG is unavailable or impractical. Therefore, a classification based predominantly on clinical criteria is suggested. An effort should be made to classify seizure type based on the ILAE classification which separates seizures into generalized, partial, and unclassifiable (Commission, 1981). Furthermore, based on clinical criteria, an effort should be made to classify seizure subtypes further.

2.1. A seizure is considered generalized when clinical symptomatology provides no indication of an anatomic localization and no clinical evidence of focal onset. When possible, three main seizure subtypes may be categorized:

Generalized convulsive seizures with predominantly tonic, clonic, or tonicoclonic features

Generalized nonconvulsive seizures represented by absence seizures

Myoclonic seizures

In patients who have experienced several types of generalized seizure each seizure type must be categorized.

2.2. A seizure should be classified as partial when there is evidence of a clinical partial onset, regardless of whether the seizure is secondarily generalized. The first clinical signs of a seizure, designated for too long by the misleading term of “aura,” have a highly localizing value and result from the anatomic or functional neuronal activation of part of one hemisphere.

When alertness and ability to interact appropriately with the environment is maintained, the seizure is classified as a simple partial seizure.

When impairment of consciousness, amnesia, or confusion during or after a seizure is reported, the seizure is classified as a complex partial seizure.

When the distinction between simple and complex partial seizure cannot be made, from information provided by history or medical records, the seizure is classified as partial epileptic seizure of unknown type.

When a patient has several types of partial seizure, each should be separately categorized.

When a seizure becomes secondarily generalized, the seizure is classified as partial seizure, secondarily generalized (simple or complex).

2.3. Multiple seizure types

When both generalized and partial seizure are associated, each type must be described.

2.4. Unclassified seizures

The category of unclassified seizures should be used only when it is impossible to classify seizures owing to lack of adequate information.

Risk factors

Epileptic seizures and the epilepsies may be a manifestation of many cerebral or systemic diseases. The first step in categorization of seizures should be based on the presence or absence of a presumed acute precipitating insult, which will permit distinction into provoked and unprovoked seizures. Provoked seizures are therefore equivalent to acute symptomatic or situation-related seizures. Single or recurrent unprovoked seizures may belong to two possible categories: symptomatic seizures or epilepsies (of presumed remote cause) and seizures or epilepsy of unknown causes. Identification of the cause may depend on the degree of investigation, which also depends on availability of ancillary tests.

3.1. Symptomatic seizures or epilepsies are considered the consequence of a known or suspected cerebral dysfunction.

3.1.1. Provoked seizures (acute symptomatic seizures)

Seizure(s) occurring in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute CNS insult (infection, stroke, cranial trauma, intracerebral hemorrhage, or acute alcohol intoxication or withdrawal). They are often isolated epileptic events associated with acute conditions, but may also be recurrent seizures or even status epilepticus when the acute condition recurs, e.g., in alcohol withdrawal seizures. Some of the most common situations are listed in Appendix 1.

3.1.2. Unprovoked seizures

Seizures may occur in relation to a well-demonstrated antecedent condition, substantially increasing the risk for epileptic seizures. Two major subgroups may be categorized:

Remote symptomatic unprovoked seizures owing to conditions resulting in a static encephalopathy. Such cases are individuals with epilepsy subsequent to an insult to the CNS, such as infection, cerebral trauma, or cerebrovascular disease, which are generally presumed to result in a static lesion (Appendix 2).

Symptomatic unprovoked seizures owing to progressive CNS disorders (Appendix 3)

3.2. Unprovoked seizures of unknown etiology

Cases of unprovoked seizures for which no clear antecedent etiology can be detected. If possible,

these cases can be further classified into the following subheadings:

3.2.1. Idiopathic epilepsies

The term idiopathic is used here as defined by the ILAE (Commission, 1989) and must be reserved for certain partial or generalized epileptic syndromes with particular clinical characteristics and with specific EEG findings, and should not be used as generally used to refer to epilepsy or seizures without obvious cause.

3.2.2. Cryptogenic epilepsies

The term cryptogenic is used to include partial or generalized unprovoked seizures or epilepsies in which no factor associated with increased risk of seizures has been identified. This group includes patients who do not conform to the criteria for the symptomatic or idiopathic categories. Whenever possible, the Commission on Epidemiology and Prognosis encourages use of the most recent ILAE Classification of Epilepsies and Epileptic Syndromes. Appropriate categorization of individual cases may require use of state of the art technologies and procedures. In many settings in which epidemiologic studies are conducted, however in particular in field situations, all information frequently required for proper classification of epileptic syndromes cannot be obtained.

Recommended measurements indexes

Several measures have been used to describe the frequency of epilepsy, but often these indexes are inappropriately used or are used without definition. All these measures require a numerator which should reflect complete case ascertainment, as well as a clearly defined denominator. The methods used for case ascertainment and for population enumeration should be clearly described. The following indexes are recommended:

4.1. Point prevalence. The proportion of patients with epilepsy in a given population at a specified time (usually a specific day, the prevalence day). Inclusion criteria should be specified (i.e., active epilepsy, epilepsy in remission with treatment, and epilepsy in remission without treatment).

4.2. Period prevalence. The proportion of patients with epilepsy in a given population during a defined time interval (e.g., 1 year). Inclusion criteria should be specified (i.e., active epilepsy, epilepsy in remission with treatment, and epilepsy in remission without treatment).

4.3. Lifetime prevalence. The proportion of patients with a history of epilepsy, regardless of treatment or recent seizure activity (includes patients with active epilepsy or epilepsy in remission; they repre-

sent all individuals identified with a history of epilepsy at any time). Prevalences, which represent the ratios of identified cases to the total population, are usually expressed as cases per 1,000 persons.

4.4. Incidence (or incident number). The number of new cases of epilepsy occurring during a given time interval, usually 1 year, in a specified population.

4.5. Incidence rate. The ratio of new cases to population at risk, usually expressed as cases per 100,000 persons/year. Criteria for defining an incident case must be clearly stated, including specification of whether it is based on date of diagnosis or date of onset.

4.6. Incidence density. The ratio of new cases to a dynamic cohort at risk, usually expressed as cases per 100,000 persons/year.

4.7. Cumulative incidence. The individual's risk of developing epilepsy by a certain time, e.g., the time a specified age is reached. Comparison of frequency indexes among different populations requires adjustment of the values to a well-defined population [usually the World Health Organization (WHO) standard population or the official U.S. Census population for a specific year such as 1970 or 1980]. Optimally, age-specific and gender-specific rates should be provided whenever possible. If summary measurements (frequency indexes) are used, adjustment to a well-defined and readily accessible specified population should be made to facilitate comparisons across studies.

4.8. Standardized mortality ratio. The ratio of observed number of deaths in a population with epilepsy to that expected based on the age- and sex-specific mortality rates in a reference population.

APPENDIX 1

Acute Symptomatic Seizures or Situation-Related Seizures

1. Head injury
Seizures occurring within 7 days of a traumatic brain injury.
2. Cerebrovascular accident
Seizures occurring within 7 days of any cerebrovascular accident.
3. CNS infection
Seizures occurring in the course of active CNS infection.
4. CNS tumor
Seizures occurring as the presenting symptom of a CNS tumor.
5. Postintracranial surgery
Seizures occurring in the immediate postoperative period of an intracranial neurosurgical intervention.

6. Toxic
Seizures occurring during the time of exposure to recreational drugs (e.g., cocaine), prescription drugs (e.g., aminophylline, imipramine), drug overdose, environmental exposure (carbon monoxide, lead, camphor, organophosphates), and alcohol (acute alcohol intoxication).
7. Withdrawal
Seizures occurring in association with elimination of alcohol and drugs (e.g., barbiturates, benzodiazepines).
8. Metabolic
Seizures related to systemic disturbances, e.g., electrolyte imbalance, hypoglycemia, uremia, cerebral anoxia, and eclampsia.
9. Fever
Seizures occurring with fever in the absence of CNS infection in children.
10. Multiple causes
Seizures occurring with several concomitant conditions.
11. Undefined
Seizures occurring in the context of any acute not otherwise definable condition.

APPENDIX 2

Remote Symptomatic Seizures or Epilepsies (Static Conditions)

Seizure or epilepsy in relation to:

1. Head injury
Seizures occurring more than a week after head injury must meet one or more of the following criteria:
 - open head injury including brain surgery
 - closed head injury with intracranial hematoma, hemorrhagic contusion, or focal neurologic deficit
 - depressed skull fracture or unconsciousness or posttraumatic amnesia for >30 min.
 Epidemiologic studies have failed to demonstrate an increased risk for epilepsy in individuals with loss of consciousness or amnesia for <30 min in the absence of other brain pathology. Individuals with injury who have only brief or no loss of consciousness should not currently be considered to be at increased risk for epilepsy and should not be assigned to this category.
2. Cerebrovascular disease
Seizures occurring >1 week after clinically identified cerebral infarction or intracerebral hemorrhage or subarachnoid hemorrhage.
3. CNS infection or infestation
Seizures occurring as a sequela of CNS infec-

tions or parasitic infestations (meningitis, encephalitis, abscess), including those of the pre- and perinatal period

4. Pre- and perinatal risk factors

Seizures occurring with:

- developmental malformations of brain
- severe neonatal encephalopathy with residual motor disorder
- mental retardation and/or motor disorder in persons without other defined etiology.

5. Alcohol related

Seizures occurring in a person with a history of chronic alcohol abuse, with no evidence of acute withdrawal or intoxication and no criteria for other remote symptomatic seizures or epilepsy.

6. Post encephalopathic states

Seizures in persons with a history of toxic or metabolic encephalopathy.

7. More than one of the above.

8. Other

Seizures observed in static conditions not listed above, clearly associated with increased risk for epilepsy. Coding in this category should be accompanied by strict definitions for inclusion.

in evolution. In this situation, it is unclear whether seizures occur in relation to abnormalities associated with existing damage, thus being akin to the concept invoked for remote symptomatic seizures or to the evolving pathologic process, thus being akin to acute symptomatic seizures.

Seizures occurring in persons with progressive neurologic diseases, e.g.:

- Neoplasms. Incompletely or unsuccessfully treated CNS tumors
- Infections. Slow virus infections such as Creutzfeldt-Jacob or SSPE; incompletely or unsuccessfully treated bacterial, fungal or viral infections including human immunodeficiency virus
- Autoimmune. Diseases affecting the CNS and presumed to be of autoimmune mechanism, such as lupus or multiple sclerosis.
- Metabolic. Diseases affecting the nervous system and associated with identified metabolic errors, such as ceroid lipofuscinosis, mitochondrial encephalopathies, and phenylketonuria.
- Degenerative. Neurodegenerative diseases such as Alzheimer disease or Baltic myoclonus.

APPENDIX 3

Epilepsy or Unprovoked Seizures Associated with Progressive Neurologic Conditions

Individuals in the category of epilepsy or unprovoked seizures with progressive neurologic conditions experience recurrent seizures, but the condition is characterized by a pathophysiology which is

REFERENCES

- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389-99.
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