Epidemiology of Temporal Lobe Epilepsy

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ABSTRACT: To fulfill its task of informed clinical decision making and resource allocation, epidemiological studies in epilepsy must adhere to a series of methodological standards. These are reviewed. Because seizure and epilepsy classification systems may be viewed as extensions of the diagnosis, they have direct implications in the acquisition and interpretation of epidemiologic data. The International League Against Epilepsy (ILAE) classification systems are analyzed in this light. Finally, the lack of Canadian epidemiological studies is addressed, and the relevance and potential of Canadian epidemiological data in epilepsy is discussed.

RÉSUMÉ: Épidémiologie de l'épilepsie temporale. Les études épidémiologiques sur l'épilepsie doivent adhérer à des standards méthodologiques pour remplir leur rôle qui est d'éclairer le processus de décision clinique et d'allocation des ressources. Nous revoyons ces standards. Comme les systèmes de classification des crises et de l'épilepsie peuvent être considérés comme une extension du diagnostic, ils ont des implications directes sur l'acquisition et l'interprétation des données épidémiologiques. Nous analysons les systèmes de classification de la Ligue internationale contre l'épilepsie (LICÉ) sous cet éclairage. Finalement, nous commentons l'absence d'études épidémiologiques canadiennes et nous discutons de la pertinence et du potentiel de données épidémiologiques canadiennes sur l'épilepsie

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Epidemiology is concerned with the study of disease frequency, its determinants, natural history and burden of illness in populations. The importance of high quality epidemiological data is illustrated by their broad influence on health care and research. At the community level, these data inform on impact of illness, health care planning, resource allocation, and directions in population research. Epidemiology informs clinical researchers by identifying high risk populations and targeting aspects of the natural history or course of illness for diagnostic, prophylactic and therapeutic interventions. At the individual level, clinicians use epidemiological information to aid diagnoses (by considering demographic data) and determining etiology, treatment (by weighing risk factors and their modification), and prognosis (by knowing the natural history and course of illness).

MAKING SENSE OF EPIDEMIOLOGICAL DATA

What is meant by epilepsy?

Diagnostic certainty is paramount in epidemiology. Without it, few valid epidemiological inferences can be made.[1] This is especially important in epilepsy, which requires distinction between seizures, active and inactive epilepsy, febrile seizures and non-epileptic events, among others. If diagnostic categories are agreed upon, epidemiological studies can be interpreted and compared meaningfully.

The Commission on Epidemiology and Prognosis (CEP) of the International League Against Epilepsy (ILAE) defines Epilepsy as “a condition characterized by two or more recurrent epileptic seizures over a period longer than 24 hours, unprovoked by any immediate identified cause”.[2] In addition, the CEP defines diagnostic categories which aim at establishing common criteria for epidemiological studies performed in dissimilar settings.

While the CEP suggests using “standardized” methods to obtain clinical information, it is not explicit about them. Nor does it address the comparative validity of information sources, e.g., from patient, family, survey or medical records.[2] In this regard, Ottman et al found that when the proband and an immediate caregiver answered a broad screening question about the diagnosis of epilepsy or seizures, their agreement beyond

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chance (kappa) was 60%,[3] which is considered as substantially strong.[4] Agreement dropped to negligible levels when asked about the presence of isolated unprovoked seizures. More research in this area is needed.

Types of seizures and epilepsies

Classifying seizures and epilepsies may be viewed as an extension of diagnosis. The CEP recommends adhering to the ILAE clinical-electrographic classification of partial, generalized and unclassifiable seizures,[5] and provides an "etiological" classification.[2] Its criteria are based on medical history, seizure description and neurologic examination without electroencephalographic (EEG) data. Many aspects of current classifications remain unresolved. For example, their reliability, the impact of source of information on the ability to classify (e.g., retrospective review of seizure descriptions from medical records, patient interviews or questionnaire surveys), and the effect of time on individual patient classification.

With regard to source of information, the usefulness of an interviewer-administered standardized questionnaire to classify seizures according to the ILAE[5] was assessed by Reutens et al.[6] The non-chance agreement with a neurologist's classification was very strong for the broad categories of generalized and focal seizures (K= 0.87), but less so for simple and complex partial seizures (K= 0.5 and 0.63, respectively). As expected, agreement was lowest when the patient alone answered the questionnaire and highest when assisted by a caregiver. Ottman et al. obtained similar results using a semistructured telephone interview administered by non-medical, trained personnel.[7] The inter-rater reliability of the ILAE seizure classification[5] has been highly variable among studies (Kappa ranged from 0.11-0.9).[8]

Loiseau et al,[9] in a practice-based survey found that for epidemiological purposes, the ILAE syndromic classification was more suitable (fewer unclassifiable cases) than seizure classification, and that diagnosis was time-dependent, i.e., 9.2% of patients were reclassified over one year as more seizures occurred and new diagnoses emerged. Most commonly, patients were changed from idiopathic unprovoked and acute symptomatic seizures to symptomatic partial and undetermined epilepsies.[9] In the CAROLE practice-based study,[10] patients were classified according to the ILAE seizure,[5] epilepsy[11] and etiologic[2] classifications. Investigators found the latter two to be complementary and least ambiguous. On the other hand, Manford et al[12] have pointed out many of the syndromic classification's pitfalls. For example, its limited usefulness in a general clinical setting, difficulties allocating subtypes of localization related epilepsies (widely contrasting EEG and imaging findings), missing categories (e.g., cryptogenic generalized epilepsy), the rarity of many of the ILAE syndromes in clinical practice (e.g., idiopathic localization related and undetermined epilepsies), and the lack of emphasis on imaging studies. Furthermore, although 97% of patients could be classified, 66% fell into non-specific, uninformative categories, i.e., they remain indeterminate. Thus, although tertiary care studies find the classification useful,[13] it may create a false sense of diagnostic precision in primary care settings. Despite its many caveats and ongoing modifications, the ILAE classifications remain the most widely used means of information exchange about seizures and epilepsy.

What do the measures mean?

Clinically relevant frequency measures consist of a numerator (the number of cases) and a denominator (the number of people who could become cases), and are often referred to as "rates." The ILAE[2] endorses the following measurement indexes: *Point prevalence:* proportion of patients with epilepsy in a given population at a specified point in time. *Period prevalence:* proportion of patients with epilepsy in a given population during a defined time interval. *Lifetime prevalence:* proportion of patients with a history of epilepsy, regardless of treatment or recent seizure activity. *Incidence:* number of new cases of epilepsy occurring during a given time interval. *Incidence rate:* ratio of new cases of epilepsy to population at risk. *Incidence density:* ratio of new cases to a dynamic population at risk (denominator expressed as persons/year). *Cumulative incidence:* the individual's risk of developing epilepsy by a certain time or age.

Finding people with epilepsy

In epilepsy, the precision of incidence and prevalence estimates depends on the methods used to find cases. It is accepted that under-ascertainment is pervasive and that no single method will identify all cases in a population. However, some methods are more precise than others, and a combination of strategies may be desirable. The CEP makes no specific recommendations in this regard.[2] Hauser and Hesdorffer[14] provide an informative analysis of the strategies used in epilepsy. They underscore that methodologic accuracy depends on the population (e.g., demographic setting, health care accessibility, socioeconomic status, age, sex, ethnicity), on the depth of the investigations, and on the duration of the ascertainment period (i.e., longer periods provide more accurate estimates).

Studies in Norway[15] and North America[16] independently demonstrate that specialist practice-based methods may fail to account for up to 80% of cases unless this is the only source of health care and the latter is readily available.[17,18] On the other hand, use of all available medical records may miss from 7% (North America)[19] to 27% (Poland)[14] of incident and prevalent cases found by door to door surveys.[19]

In Australia, Beran et al[20] found that a survey of their population underestimated previously documented prevalent cases by 23%. It is important for other studies to assess this high rate of survey under-reporting, whose possible explanations include cohort characteristics and questionnaire validity, among others.

Finally, incidence and prevalence vary among different segments of the population whose omission may bias the estimates, e.g., they are higher in prison inmates,[21] and among the institutionalized and the mentally retarded.[22]

EPIDEMIOLOGY OF TEMPORAL LOBE EPILEPSY

What is temporal lobe epilepsy (TLE)?

Because standardized diagnoses are pivotal to epidemiological research, we will consider TLE as defined by the ILAE classification of epileptic syndromes.[11] The ILAE groups TLE within the broad category of "localization-related symptomatic epilepsies characterized by seizures with specific modes of precipitation",[11] and offers a tentative description based on strongly suggestive clinical features plus ictal and interictal EEG

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findings. It allows two subcategories of TLE, i.e., amygdalo-hippocampal and lateral temporal. As pointed out by Manford et al,[12] the classification does not address the role of MRI and other imaging in the diagnosis and treatment of TLE. Furthermore, the ILAE etiological classification[2] fails to include mesial temporal sclerosis, the commonest pathological substrate of TLE. Because accurate classification depends on depth of investigation and follow-up, it is remarkable that ILAE classifications make no allowance for rating diagnostic certainty, e.g., definite, probable, possible. Neither is there explicit (nor implicit) weighting of diagnostic features, e.g., major and minor criteria. As Oka et al[23] point out, attempts at classifying seizure disorders without further qualification are fraught with ambiguity.

How common is TLE?

Population studies show that partial seizures account for up to 50% and 60% of incident and prevalent epilepsy cases, respectively, and that complex partial seizures (CPS) are the most frequent single seizure class.[24] A worldwide census of 107 epilepsy surgery centres confirmed that, in surgical centres, TLE is by far the commonest type of localization-related epilepsy. Of 8,234 operations performed between 1985 and 1990, 66% involved the temporal lobe.[25] Unfortunately, series from specialty units (the source of available TLE frequency estimates) are biased toward patients who are surgical candidates, have more severe epilepsy and are more intensely investigated.[26,27] Consequently, although clinicians feel that TLE may be the most frequent cause of CPS, the true frequency of TLE in the population is unknown. Because of insufficient information, general practice- or population-based studies may result in uncertain localization at best[12] and in no localization at worst.[23] For example, of 255 patients with partial seizure onset in the British national general practice study, 36% were unlocalized, 43% overlapped ILAE regions (19% involving the temporal lobe) and 20% localized to a single ILAE region (only 1% to the temporal lobe).[12] Similarly, previously used epidemiological methods suffer from moderate to fatal biases. Clinical series of newly diagnosed cases are less biased but lack diagnostic precision (localization is tentative) and sufficient follow-up.[28,29] Cases in population-based prevalence studies are more representative, but definitive diagnosis of localization-related symptomatic epilepsies has not been possible, and authors have resorted to seizure classification.[30] The Rochester, Minnesota retrospective, longitudinal incidence and prevalence studies provide some of the best currently available epidemiological data.[31,32,33] In these studies a neurologist classified seizures and etiology by ILAE criteria,[2,5] using seizure description and clinical – but not EEG – information obtained from medical records. Unfortunately, syndromic categories are not provided.[11] This precludes making inferences about epidemiology of TLE or any of the localization related symptomatic epilepsies. Thus, longitudinal, population-based incidence cohorts with syndromic classifications are necessary to determine the frequency of TLE.

Are Canadian epidemiological studies of epilepsy necessary?

Few Canadian data exist on the epidemiology of epilepsy. Perhaps the perception that it suffices to extrapolate readily available United States data has contributed to a lack of Canadian research. However, strong arguments exist against the validity of unqualified extrapolation. First, it is difficult to interpret and apply data from non-Canadian studies because of methodological issues such as variability in case definition and ascertainment, presence of confounders, study design, (e.g., prospective or historical cohorts, case control studies), study size, and overall methodological quality. Second, accessibility to health care may determine case finding, intensity of investigation and treatment, completeness of follow-up and prognosis.[34,35] Third, general health variation is likely to play a role in the different frequency and etiology of epilepsy found among various populations.[31,36] Fourth, genetic makeup, exposure to, definition and impact of risk factors for epilepsy differ across social and ethnic groups,[37] resulting in conflicting results.[38] Finally, societal attitudes toward illnesses may influence health care seeking behaviour, burden of illness and response to surveys.[35,39] For example, the Camfields' team in Nova Scotia found that the incidence of epilepsy in Canadian children was lower than in most other studies.[36,40] Their childhood cohort studies use an EEG laboratory case finding method in a confined population where nearly all children with epilepsy obtain an EEG. It is uncertain whether their findings are due to study methods, universal Canadian health care coverage resulting in decreased risk factors, or other cohort peculiarities. Therefore, the frequency, risk factors, prognosis, and burden of epilepsy in the Canadian population can accurately be estimated only from studies performed in Canada.

Directions for research in Canada

If one agrees that a major goal of epidemiological research in epilepsy is to inform decisions about interventions aimed at risk factor and burden of illness modification, and that the dearth of epidemiological research in epilepsy in Canada is significant and out of keeping with epilepsy research in other areas, a call for a nation-wide, concerted effort is in order. This would require carefully planned, multi-stage, population-based, prospective, incidence cohort studies, with standardized and prolonged follow-up. Furthermore, if inferences about particular forms of epilepsy and comparisons with other studies are to be made, widely accepted classification systems (e.g., ILAE 1981 and 1989) must be applied and reviewed longitudinally as clinical information accrues. Ideally, regional cohort studies should be complemented by data from studies performed at a national level.

Conceivably, the main stages of a Canadian epidemiological epilepsy research programme would comprise:

1) defining optimum sampling strategies to establish representative inception cohorts;
2) gathering comprehensive data prospectively, in a standardized fashion and over a sufficiently long period of time;
3) evaluating burden of illness to patients (health status, quality of life, preferenced-based utilities and costs), their family or care-giver (quality of life, costs) and society (attitudes, costs);
4) devising strategies aimed at impacting on burden of illness and evaluating the effectiveness of these strategies.

The following prerequisites are integral to a successful research programme of this nature:

1) Assembling a comprehensive review of Canadian data from

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all available sources. These include clinical series, epilepsy registries such as the Canadian Epilepsy Database and Registry (CEDaR),[41] population-based studies, and data from national surveys and administrative databases.[42]

2) Informing the public, the medical community and granting agencies about the important epidemiological research gap in Canadian epilepsy.
3) Launching large scale fund-seeking efforts.
4) Maintaining close collaboration among researchers from various disciplines throughout all stages of the programme.

These aims may be a tall order, but they are not out of keeping with the strong tradition of epilepsy research in Canada.

Participants' discussion

Participants discussed issues of classification systems used for research versus those applicable to clinical data of a less differentiated nature. Mention was made of the possibility of furthering research by using large databases that rely on less controversial and sophisticated classifications. It was emphasized that standardization of definitions and operative procedures would facilitate outcome analyses and make them more applicable.

It was suggested that despite difficulties in assessing the true frequency of TLE, surgical treatment is underutilized in Canada. The question was raised as to whether this was simply a misperception of the true frequency of TLE (e.g., that it is less frequent than suspected), or whether patients with surgically remediable TLE are not referred for evaluation and surgery. Dr. Wiebe felt that the estimates were reasonably accurate and that deficiencies in knowledge dissemination and treating physicians' understanding of the role of epilepsy surgery accounted for the perceived underutilization of surgery.

The importance of establishing a linkage among epilepsy clinics across Canada for clinical and research purposes was emphasized by a number of discussants.

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