



Incidence, prevalence and aetiology of seizures and epilepsy in children

Peter Camfield, Carol Camfield

Dalhousie University and IWK Health Centre, Department of Pediatrics, Halifax, Nova Scotia, Canada

Received September 25, 2014; Accepted February 08, 2015

ABSTRACT – *Aim.* To (1) summarize published, peer-reviewed literature about the incidence and prevalence of epilepsy in children from developed and developing countries around the world, and (2) discuss problems in defining aetiologies of epilepsy in children, and distinguish between seizures and epilepsy.

Methods. Review of selected literature with particular attention to systematic reviews.

Results. The incidence of epilepsy in children ranges from 41-187/100,000. Higher incidence is reported from underdeveloped countries, particularly from rural areas. The incidence is consistently reported to be highest in the first year of life and declines to adult levels by the end of the first decade. The prevalence of epilepsy in children is consistently higher than the incidence and ranges from 3.2-5.5/1,000 in developed countries and 3.6-44/1,000 in underdeveloped countries. Prevalence also seems highest in rural areas. The incidence and prevalence of specific seizure types and epilepsy syndromes is less well documented. In population-based studies, there is a slight, but consistent, predominance of focal seizures compared with generalized seizures. Only about one third of children with epilepsy can be assigned to a specific epilepsy syndrome, as defined by the most recently proposed system for organization of epilepsy syndromes.

Conclusions. The incidence and prevalence of epilepsy in children appears to be lower in developed countries and highest in rural areas of underdeveloped countries. The reasons for these trends are not well established. Although focal seizures predominate, the incidence and prevalence of specific epilepsy syndromes is not well documented.

Key words: incidence, prevalence, epilepsy, children

Correspondence:

Peter and Carol Camfield
IWK Health Centre,
PO Box 9700,
5850 University Ave,
Halifax,
Nova Scotia B3K 6R8, Canada
<camfield@dal.ca>

A variety of epidemiological studies of epilepsy have addressed the incidence and prevalence of epilepsy in children. Differing case ascertainment methods, definitions of epilepsy, age range of subjects, and inclusion of children

with febrile seizures makes comparison between studies a tremendous challenge (Cowan, 2002). In this article, we summarize the information, but do not provide all the details of all publications.

Some definitions are needed. *Incidence of epilepsy* is the number of new cases of epilepsy/year in a defined population and is typically presented as cases/100,000. Epilepsy is conceptualized as an “enduring” tendency to have seizures, but “enduring” is not easily defined (Fisher *et al.*, 2005). A recent report has refined this concept considerably (Fisher *et al.*, 2014), however, for practical reasons, epilepsy has usually been defined as ≥ 2 unprovoked seizures separated by at least 24 hours. This definition is based on the concept that the recurrence risk after two unprovoked seizures is about 80%, while the recurrence risk after a single unprovoked seizure is only about 50% (Camfield *et al.*, 1985; Hauser *et al.*, 1998; Shinnar *et al.*, 2000). The difference between 50% and 80% is considered substantial. There is some debate about the restriction that the two seizures need to be separated by 24 hours if there is return of full consciousness between seizures (Camfield and Camfield, 2000; Shinnar *et al.*, 2000; Wirrell *et al.*, 2011). The concept of epilepsy as two unprovoked seizures is most useful for patients who present with dramatic convulsive seizures. Almost all other epilepsies present only after multiple seizures; they easily fulfil the definition of epilepsy by the time they present for medical care with seizure types that include absence, akinetic, or even partial complex (dyscognitive).

The newborn period is complicated for epilepsy studies. Many newborns have seizures as the result of an acute encephalopathy. Separating these cases from those with “epilepsy” may be even more challenging, because the presence of brain disease may predispose the baby to hypoxic ischaemic encephalopathy. Many incidence/prevalence studies have excluded babies <1 month of age in order to get around this problem. Febrile seizures are not considered as epilepsy, however, this decision may be somewhat arbitrary. For example, documentation of fever is not always available, especially if the family does not seek medical care. Other children have a mixture of febrile and afebrile seizures. “Illness-related seizures” may also be difficult to interpret if there is no fever (Lee and Ong, 2004). The age limits for febrile seizures are said to be 6 months and 5 years, however, some older children will have a seizure with fever but not go on to develop epilepsy (Kim *et al.*, 2010).

All epilepsy incidence studies require an inclusive case-finding method (Kotsopoulos *et al.*, 2002). Accuracy of diagnosis is an issue for administrative databases, such as those based on billing claims. There is obviously bias in referred cases or patients presenting to emergency rooms, especially in countries without prepaid comprehensive health care. A fairly successful approach has been to search requests for EEG recordings in EEG laboratories, provided that they serve a regional population. This

approach is most successful if there is no cost barrier to this investigation (Cowan *et al.*, 1989; Camfield *et al.*, 1993). Incidence studies need to gather data prospectively and are, therefore, time-consuming and expensive. Not surprisingly, they are less common than prevalence studies.

Point prevalence is the number of people with epilepsy in a population at a certain point in time. An important issue is the definition of subjects who actually have epilepsy. If someone had a series of seizures years ago but is now seizure-free and no longer taking AEDs, do they have epilepsy? It is common to base prevalence studies on “active epilepsy” which is usually defined as having a diagnosis of epilepsy and at least one unprovoked seizure within the past five years. A person who continues to receive AEDs, but has been seizure-free for six years would be omitted from this definition of “active epilepsy”. A diagnosis of epilepsy and either ongoing AED treatment or an unprovoked seizure within the past five years may provide a compromise. Many children with epilepsy have a prompt remission from seizures and some studies have used two years rather than five to define “active epilepsy”. In this article, we use prevalence to indicate point prevalence. Lifetime prevalence is a less meaningful concept in paediatrics.

Door-to-door surveys may be the most effective way to establish prevalence, provided that the stigma of epilepsy is not too large, the interviewer is well trained in the manifestations of seizures, and the interviewee is knowledgeable about the health issues of those that he/she lives with. Administrative databases that combine drug prescriptions with clinical diagnosis may be reasonably accurate. Assessing prescriptions for AEDs alone is inadequate because many AEDs have psychiatric and other health-related indications. The prevalence of epilepsy is always higher than the incidence because epilepsy is often a chronic disorder; some incident cases promptly remit but others persist. At any point in time, the persistent cases will be added to the incidence cases to estimate prevalence. *Prevalence* is usually expressed as number of cases/1,000. The proportion of children in the population varies from country to country with the highest proportion found in developing countries. This makes comparison between countries difficult to interpret, although a few studies have used variable-adjusted calculations. Many studies indicate prevalence as cases in a given age range relative to 1,000 of the general population in the same age range.

Approximately 50% of seizures are considered to be provoked by a brain insult that is considered capable of causing seizures (Hauser, 1994). Febrile seizures are considered to be provoked even though fever itself is inadequate to provoke a seizure; febrile seizures appear to require a certain vulnerable age plus a

genetic susceptibility (Camfield and Camfield, 2005). They are not typically considered as epilepsy, but as noted above, some studies have included them in incidence and prevalence studies.

All of these considerations make comparison between studies difficult. Where possible, we refer the reader to studies in which meta-analyses were performed in order to try to overcome these methodological issues.

Incidence of epilepsy in children

Incidence of epilepsy studies in children have usually been restricted to new-onset epilepsy prior to 16 years of age. The reported incidence of epilepsy in children has quite a wide range, for example from 41/100,000 in all children in Nova Scotia to 187/100,000 in children 6-9 years of age in Kenya (Camfield *et al.*, 1996; Mung'ala-Odera *et al.*, 2008). The incidence of epilepsy in children in developed countries in population-based studies has ranged from 33.3 to 82 cases per 100,000 persons per year (Blom *et al.*, 1978; Cavazzuti, 1980; Doose and Sitepu, 1983; Hauser *et al.*, 1993; Camfield *et al.*, 1996; Freitag *et al.*, 2001; Larsson and Eeg-Olofsson, 2006; Christensen *et al.*, 2007; Adelow *et al.*, 2009).

All studies consistently find the incidence to be highest in the first year of life with a range of 81/100.00 in Rochester, Minnesota in 1945-54 (Hauser *et al.*, 1993), to 118/100,000 in Nova Scotia in 1977-1985 (Camfield *et al.*, 1996), to 130/100,000 in Iceland in 1995-1999 (Olafsson *et al.*, 2005). It is interesting that a more recent assessment in Rochester, Minnesota in 1980-2004 showed an incidence of 102/100,000 for children 1-12 months (Wirrell *et al.*, 2011).

From age 1 to about 12 years, the incidence does not show much variability. In Rochester, Minnesota in 1945-54, the incidence for children aged 1-9 years was 50-62/100,000 and decreased further to 39/100,000 in children aged 10-14 years (Hauser *et al.*, 1993). In Nova Scotia, the incidence for each year of age between 1 and 10 years was very constant (mean: $46 \pm 7/100,000$) (Camfield *et al.*, 1996). Between age 11 and 15, the incidence plateaued at about 21/100,000 which is very similar to most published rates in adults in developed countries. Again, in Rochester, Minnesota in 1980-2004, data showed the incidence for ages 13-17 to be 24.8/100,000 (Wirrell *et al.*, 2011).

Nearly all studies have found the incidence in boys and girls to be almost identical. A recent publication from Rochester suggested that the overall incidence of epilepsy has remained relatively stable over the past 25 years except that there appears to be trend for increasing incidence in boys (Wirrell *et al.*, 2011). The authors speculate that this might be the result of more boys being treated in neonatal intensive care units.

Incidence of seizure type and specific epilepsy syndromes in childhood

Most patients have a predominant seizure type at onset that can be defined (Commission on Classification and Terminology of the International League Against Epilepsy, 1981), however, only about a third of children with epilepsy can be assigned to a specific epilepsy syndrome using the most recent proposals for epilepsy syndromes (Wirrell *et al.*, 2011). Many of these syndromes are so rare that incidence data is meaningless; a change from one to two cases in a cohort would double the incidence.

The previous epilepsy classification system with which patients were assigned to broad groups of syndromes has been recently discredited (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Berg *et al.*, 2010). The broad groups of syndromes included idiopathic localization-related, idiopathic generalized, symptomatic generalized, and symptomatic localization-related groups, and it was possible to assign nearly all children to one of these categories (Lavados *et al.*, 1992). Because of these issues and the lack of "air-tight" definitions for syndromes, we only comment on the incidence of major syndromes and seizure types.

Table 1 shows the distribution of focal seizures, generalized seizures, spasms, and both focal and generalized seizures in five incidence studies where the information is fairly clear. These studies were carried out in Rochester, Minnesota (Wirrell *et al.*, 2011), Chile (Lavados *et al.*, 1992), Nova Scotia (Camfield *et al.*, 1996), Spain (Durá-Travé *et al.*, 2008) and Connecticut (Berg *et al.*, 1999). Across all studies, focal seizures are somewhat more common than generalized seizures. Spasms are uncommon and comprise only 2-5% of paediatric epilepsy (Trevathan *et al.*, 1999; Riikonen, 2001; Hino-Fukuyo 2009).

Prevalence of epilepsy in children

In Europe, the prevalence of epilepsy in children appears to lie between 3.2 and 5.1/1000, depending on the age range and country considered (Forsgren *et al.*, 2005). In the USA, a careful study in Oklahoma found the overall point prevalence in children 0-19 years of age to be 4.71/1,000 (Cowan *et al.*, 1989). A recent USA national paediatric survey found that the estimated lifetime prevalence of active epilepsy was 6.3/1,000 (95% CI: 4.9-7.8) (Russ *et al.*, 2012). In both of these USA studies, epilepsy was found to be more common in children from families with income below the US federal poverty level. In Canada, the prevalence of epilepsy in children in a national survey was

Table 1. Distribution of seizure types in incidence studies.

	Rochester n=359 (7)	Chile n=314 (30)	Nova Scotia n=693 (15)	Connecticut n=631(29)	Spain n=191(31)
Generalized seizures	84 (23%) includes 28 with absence	127 (40%)	280 (40%) includes 97 with absence	277 (40%) includes 89 with absence	82 (43%) includes 20 with absence
Focal seizures	244 (68%)	170 (54%)	369 (53%)	284 (55%)	105 (55%)
Unknown	19 (5.3%)	17 (5.4%)	12 (1.7%)	25 (4%)	4 (2%)
Spasms	10 (2.8%)	Not specified	32 (4.6%)	24 (3%)	10 (5%)
Both focal and generalized seizures	2 (0.5%)	Not specified	Not specified	5 (1%)	4 (2%)

5.26/1,000 (Prasad *et al.*, 2011) and in the Province of British Columbia 5.5/1,000 (Schiariti *et al.*, 2009).

Prevalence studies in underdeveloped countries are more numerous than incidence studies, and in general, the prevalence is higher than in developed countries (Ngugi *et al.*, 2010). It is suggested that the higher incidence/prevalence relates to more acquired brain disease through high rates of meningitis, encephalitis, cystercrosis, head injury, etc. This is a very reasonable hypothesis but, in our opinion, remains unproven.

In Arab countries, the estimated prevalence of epilepsy in children ranges from 3.6 to 10.5/1,000, depending on the age brackets studied (Benamer and Grosset, 2009). In Latin America, the estimated prevalence in children ranges from 7.5 to 44.3 (Burneo *et al.*, 2005). One small, but carefully performed, study of children from a geographic area of Chile estimated the prevalence at 17.8/1,000 for children 0-17 years of age (Lavados *et al.*, 1992). In a systematic review of epilepsy in Latin America, Burneo *et al.* noted that the overall prevalence of epilepsy (birth to death) was fairly consistent across almost all studies and ranged from about 8-19/1,000 with one outlier (Burneo *et al.*, 2005). A similar review for Asian countries found an overall prevalence of 6/1,000, but again with considerable variability between studies (Mac *et al.*, 2007). It was not easy to summarize the paediatric data from these large reviews.

There are some important exceptions to the concept that developing countries have a high prevalence of epilepsy, for example a systematic review of prevalence in Asian countries reported low prevalence (Mac *et al.*, 2007). Studies from Africa and Latin America suggest a high incidence (Senanayake and Román, 1993; Burneo *et al.*, 2005; Mung'ala-Odera *et al.*, 2008; Winkler *et al.*, 2009; Sampaio *et al.*, 2010; Lekoubou *et al.*, 2012). The prevalence of epilepsy amongst children in Cuba in an

urban study was low, a finding that the authors speculated might be related to the efficient nature of Cuban public health (Garofalo *et al.*, 2012).

In developing countries, when overall prevalence is considered, there is a fairly consistent trend towards a higher prevalence in rural areas, compared with urban areas (Ngugi *et al.*, 2010). Several studies have found the prevalence in urban areas of underdeveloped countries to be similar to that in developed countries.

Incidence of seizures as opposed to epilepsy

An accurate estimate of all "seizures" in childhood is not available. It has been estimated that the lifetime risk of a seizure of any kind is about 8% (Hauser *et al.*, 1993; Hauser, 1994). The lifetime risk of epilepsy is about 1%. An additional ~1% of the population will have a single unprovoked seizure that does not recur. This suggests that there is a 6% lifetime risk of a provoked seizure ("acute symptomatic seizure"). About 3-4% of all children will have a febrile seizure (a provoked seizure) but it is unclear how much of the remaining 2% lifetime risk of a seizure is encountered in childhood. With the exception of febrile seizures, provoked seizures appear to have little risk of recurrence once the provoking factor has resolved. The sequence of a provoked seizure followed later by epilepsy is usually uncommon, depending on the cause and severity of the provocation. For example, if a seizure is provoked by a closed head injury and there is no evidence of cerebral haemorrhage or other brain injury, the risk of unprovoked seizures is no greater than that in the normal population. If there has been a traumatic cerebral haemorrhage or penetrating head

injury, the risk increases markedly to as much as 50% (Lowenstein, 2009).

Febrile seizures may be considered a specific example of provoked seizure. They are provoked by a combination of factors: a particular stage of brain maturation, genetic susceptibility, and fever. Although about 3-4% of children will have at least one febrile seizure, the overall risk of later epilepsy is only about 2-3% (Camfield and Camfield, 2005).

Aetiologies of epilepsy in children

The causes of epilepsy in children are legion, however, for at least 50% of childhood epilepsy the cause is unknown. In the past, attempts have been made to organize causes into four categories: idiopathic, symptomatic, cryptogenic, and unknown (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). These categories are difficult to defend (Berg *et al.*, 2010).

Idiopathic in the epilepsy world does not mean "cause unknown", as it does in all other areas of medicine. Rather, idiopathic is applied to a group of epilepsy syndromes where the patient is otherwise fairly normal, the interictal EEG shows a normal background and a specific focal or generalized spike discharge pattern, brain imaging is normal, and no other cause has been found. The idiopathic epilepsies were proposed to have a genetic cause. The evidence for a genetic aetiology is fairly convincing for the generalized idiopathic epilepsies (Berkovic *et al.*, 1998), especially from twin studies. The evidence for a genetic aetiology for the focal idiopathic epilepsies is very sketchy (Vadlamudi *et al.*, 2006).

Symptomatic epilepsies were said to have an identifiable, pre-existing or underlying cause prior to the onset of the epilepsy. In cryptogenic cases, there was no identified cause but a "suspicion" that there might be one! It is unclear if a child develops epilepsy and has pre-existing intellectual disability if the epilepsy is symptomatic or cryptogenic. The number of cases in the cryptogenic category is clearly related to the sophistication of brain imaging and genetic studies. It is also clear that a given cause can result in different types of epilepsy. For example, a child with a congenital hemiplegia from a prenatal stroke might develop West syndrome with infantile spasms or focal motor seizures, or both.

The unsatisfactory nature of this classification has made it very challenging to make any general statements about causes of epilepsy in children. A recent proposal has suggested that cause be divided into three categories: unknown, genetic, and structural/metabolic (Berg *et al.*, 2010). To date, the only population-based study to attempt this classification

of cause in childhood epilepsy was from Rochester, MN (1980-2004) in which it was reported that "approximately half of children had an unknown aetiology for their epilepsy, and of the remainder, 79 (22%) were genetic and 100 (28%) were structural/metabolic" (Wirrell *et al.*, 2011).

In developed countries, the large majority of cases are not currently preventable (Camfield and Camfield, 2007). Preventable causes are primarily traumatic, perinatal and infectious. It is likely that these many specific causes in each of these categories are more prevalent in less developed countries with lower rates of immunization, fewer preventative strategies for head injuries, and lack of access to optimal medical care (Senanayake and Román, 1993; Singhi, 2011; Lekoubou *et al.*, 2012). □

Disclosures.

The authors have no conflicts of interest to disclose.

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TEST YOURSELF



- (1) What is the definition of incidence and prevalence?
- (2) Why is the prevalence of epilepsy in children higher than the incidence?
- (3) Is there a difference in the incidence of epilepsy in boys and girls?
- (4) Why might the prevalence of epilepsy in children be higher in rural underdeveloped and developed countries?
- (5) How has the ILAE 2010 proposed organization of epilepsy syndromes changed the way we think about incidence and prevalence?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".