Epidemiology and long-term Turku outcome of childhood-onset epilepsy and mortality. Personal experiences. Part I*

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Summary

Introduction. Epidemiological studies on epilepsy were long based, with few exceptions, on hospital and institution patients with a subsequent bias toward more difficult cases and the reported prevalence and incidence rates were often obviously too low. Few data are available on the temporal changes in the incidence of epilepsy.

Aim. To study the prevalence and incidence in an unselected child population including all the children living either in the society or in the institution, temporal changes in the incidence and mortality through five decades.

Methods. The most important personal data were reviewed and compared with the relevant data of other investigators.

Results and discussion. The prevalence of epilepsy in our study was 3.2/1000, quite obviously true for the contemporary methodology and well comparable with 3.4–4.2/1000 of other relevant studies published about two decades later and using a more advanced methodology. Similarly, the incidence of 35/100 000, ascertained in two Finnish studies, was comparable with the relevant contemporary literature data. Another study of ours shows that, probably associated with the people "coming from the shadows" and an improved diagnostic methodology, the incidence of childhood epilepsy has increased and is now 60–70/100 000. However, the incidence of childhood epilepsy shows an obvious decreasing trend in the first two decades of the 2000s.

Conclusions. The incidence of childhood epilepsy, in all probability true for the contemporary methodology, was lower than it is now, but it now again shows a decreasing trend.

Keywords: childhood-onset epilepsy • incidence of childhood epilepsy • mortality in epilepsy • population-based study • prevalence of childhood epilepsy • temporal changes in the incidence

INTRODUCTION

Research into epilepsy and development of clinical practices had a kind of revival in the 1960s. The fourth series of Epilepsia, the Journal of International League Against Epilepsy (ILAE) began to appear in 1961 (Shorvon, 2007). An extensive, two-volume handbook on epilepsy and related disorders by William G. Lennox and his daughter was published in 1960 (Lennox and Lennox, 1960). The first international classification of epileptic seizures (Gastaut, 1970) and the classification of epilepsies (Merlis, 1970) were published in the revised form in 1969. A wave of new antiepileptic drugs (AEDs) began, when Tegretol (carbamazepine) was registered in 1959 and Depakine (sodium dipropyl-acetate, later called sodium valproate) in 1967.

My personal start within epileptology was in epidemiology and clinical neuropharmacology. We found the serum ratio of carbamazepine (CBZ) to be 25% in healthy volunteers (Pynnönen et al., 1977a). The percentage was in line with reported studies varying between 20–36% (Meinardi, 1972; Johannessen and Strandjord, 1973; Morselli et al., 1975; Monaco et al.,

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1979). Our study group was among the very first to report on the development of the blood concentration profile of CBZ and CBZ-epoxide (CBZ-E) under prolonged treatment including autoinduction and need for continuous follow-up of CBZ concentrations from the beginning of CBZ therapy (Pynnönen et al., 1980). The finding soon became generally accepted and autoinduction was later shown to be both CBZ dosage dependent and age dependent (Kudriakova et al., 1992; Sillanpää et al., 2009). We investigated placental transport, concentrations in children and fetus. Our group was the first to report on CBZ concentrations in mother's milk (Pynnönen and Sillanpää, 1975; Pynnönen et al., 1977b). We showed the ratio between milk and plasma to be 0.60. Later, a range between 0.25 and 0.80 has been reported (Terhaag et al., 1978; Meyer et al., 1985). We were first to show CBZ concentrations in breastfed newborn's blood and newborn's good capacity to metabolize CBZ (Pynnönen et al., 1977b). An extensive monography on the pharmacology and clinical uses was published in 1981 (Sillanpää, 1981).

New prospects for the drug treatment of epilepsy and consideration of the fact that onset of epilepsy is most common in childhood (Merlis, 1972) caused me to get interested in epileptology. My doctoral thesis on the epidemiology of childhood epilepsy and its outcome in children from the catchment area of the Turku University Hospital was entitled "Medico-social prognosis of children with epilepsy. Epidemiological study and analysis of 245 patients" (Sillanpää, 1973).

AIM

The purpose of the present study was to review the epidemiology of childhood epilepsy and mortality from the last five decades based on our own data and similar papers in the literature.

METHODS

The most important data on the epidemiology and outcome of childhood epilepsy were reviewed including prevalence, incidence, trends in incidence and mortality including SUDEP.

RESULTS AND DISCUSSION

Epidemiology (Sillanpää, 1973)

The Turku population cohort included all children, who were 0–15 years of age, resided in the catchment area of the Turku University Hospital at the end of 1964, and had active epilepsy (Sillanpää, 1973). Epilepsy was defined as repeated, unprovoked seizures 24 hours apart at the age of 4 weeks to 15 years. Active epilepsy was defined as onset of epilepsy in 1961–1964 (incident cases) or at least one unprovoked seizure in a child who had been ascertained before 1961 as having epilepsy (prevalent cases). Children with epilepsy were identified by reviewing the files of three data sources: 1) inpatient and outpatient clinical and EEG records of hospitals and institutions for mentally retarded or cerebral palsy in the whole southern Finland; 2) private offices records; and 3) review of the National Health Service Registry of refundable antiepileptic drugs for epilepsy (but not for other indications). Thus, the enrolment of the subjects was not only based on hospital and institution records, but any public or private outpatient unit and, to be sure, on the review of all subjects in the study area who got 100% reimbursed antiepileptic drugs for the treatment of epilepsy, but not for the treatment of solely non-epileptic conditions. One and the same child neurologist (M.S.) reviewed all the records and clinically examined all the 245 children who were ascertained as children with epilepsy. In addition to the records data and clinical neurological examination, EEG and neuroimaging investigations were performed on clinical grounds, if needed. One hundred and fifty children were ascertained as incident cases, that is, they were first evaluated for epilepsy in 1961–1964. The remaining 95 patients were diagnosed as prevalent cases, whose diagnosis of epilepsy was made before 1961, but who had at least one unprovoked seizure during 1961–1964 (Sillanpää, 1973; Sillanpää et al., 1998).

The accuracy of the Turku study of the data collection method can be regarded as good, because ongoing surveillance has revealed only few subjects who fulfilled the inclusion criteria and should have been included in the study. Despite a very intensive case hunting, however, few inadvertent dropouts existed, and they could be considered in an epidemiological analysis. How much, if anything, the dropouts affected the outcomes cannot be estimated. Ninety per cent of my study subjects were identified from hospital and institution files. As a matter of fact, the percentage should have been 100%, because the rule was then that every child less than 16 years should be admitted to hospital (Sillanpää, 1973). The same rule is still followed in many parts of Finland (Rantala and Ingalsuo, 1999). However, non-hospitalized 10% of the study children were ascertained from all relevant sources outside hospitals

or institutions. Finally, it is to be noted that the Finnish National Health Service, effective in 1964 in Finland and a copy of the British National Health Service with slight national modifications made it possible to identify and ascertain any child with epilepsy and year of onset of epilepsy. Thus, a very dense network of public health centers and general practitioners are mostly the first to identify subjects with epilepsy. Since the 1960s, also board-certified pediatricians started to occupy posts in primary care. From the viewpoint of our study, an excellent system existed to check and reveal possible dropouts on ongoing surveillance.

Among a cohort of 245 children collected from the catchment area of the Turku University Hospital, southwestern Finland, the median age at onset of epilepsy was 3 (range 0–14) years in 150 subjects with incident cases and 2 (range 0–12) years in subjects 95 with prevalent cases. At recruitment, 53% of 245 subjects had a symptomatic etiology of epilepsy (Sillanpää, 1973). A review of the etiologies based on modern neuroimaging methodology specified the percentage of remote symptomatic etiologies to be 50% and cryptogenic or idiopathic etiologies 50% (Sillanpää et al., 1999). Where to draw a line between symptomatic and cryptogenic (or presumably symptomatic) etiologies is often difficult with the classification differing, in particular, in the less-well-defined syndromes (Berg et al., 1999). One reason for the higher proportion of patients with remote symptomatic epilepsy than in other studies is the extensive analysis of patients which led to a reclassification of the cause and a move from the cryptogenic group to the symptomatic group (Sillanpää et al., 1998). However, the present percentage is largely the same as in similar population-based studies ranging from 42–46% (Brorson and Wranne, 1987; Sidenvall et al., 1996; Waaler et al., 2000).

Similar population studies on epilepsy have also their limitations. The Mayo Clinic Record Linkage Study was retrospective, virtually based on case ascertainments by one single institution, and covered the time period when EEG was not freely available (Shorvon and Goodridge, 2013). The Canadian study (Camfield et al., 1993) relied on the review of the electroencephalograms of one (and the only) EEG laboratory of the province. The EEGs were interpreted representative of virtually all the subjects with epilepsy in that area, but the method has not been validated.

The retrospective Tonbridge Study from the UK was based on the records of 6000 persons in a single general practice. The British National Health Service is described as an all-embracing in terms of an excellent case finding, because the general practitioners (GPs) work as "gate-keepers" and note all post-1948 hospital visits and visits to general practitioners during the patients' lifetime (Shorvon and Goodridge, 2013). Following our prospective population study, an extensive National General Practice Study of Epilepsy (NGPSE) study was conceived in 1983 (Shorvon and Goodridge, 2013). The NGBSE study, as other similar British studies, relied on GPs, who reported any seizures and, subsequently, any patients with occurring in the context of acute illness, febrile seizures, single seizures, and seizures with obvious precipitants (Hart et al., 1989). Their exclusion criteria were patients resided in institutions for epilepsy and patients who had seizures having started in the neonatal period and obviously also including those with continued seizures since the neonatal period. Given the well-known very high prevalence of epilepsy among institutionalized patients, it is unclear how many cases of epilepsy fulfilling the inclusion criteria were lost from the study due to institutionalization. Included were patients with any seizures, whether provoked or unprovoked, who were considered as having epilepsy, differently from and not comparably with the ILAE definition of epilepsy (Commission on Classification and Terminology, 1989; Commission on Epidemiology and Prognosis, 1993). The GP-based methodology includes some validity problems (Leach et al., 2005), among others misdiagnoses (Goodridge and Shorvon, 1983; Scheepers et al., 1998). A study from Glasgow, UK, found that 799 (69%) of 1156 adults with a diagnosis of epilepsy had never attended local epilepsy clinic and 55% of the population on antiepileptic medication had never received specialist advice (Leach et al., 2005). The problem concerns also children with epilepsy in the UK (Jeavons, 1975; Cross, 2009).

Prevalence of childhood epilepsy

The mean prevalence of childhood epilepsy was 3.2/1000 (Sillanpää, 1973). A Swedish study from the same years (1961–1964) and the same age group (0–15 years) gave the comparable prevalence of 3.5/1000 (Brorson, 1970), as did the more recent studies: 3.4/1000 in Estonia (Beilmann et al., 1999), 3.9/1000 in Finland (Eriksson and Koivikko, 1997) and 4.2/1000 in Sweden (Sidenvall et al., 1996). The mean prevalence of childhood and adolescence active prevalence, based mainly on the population studies from the UK and Nordic, Baltic and Med-

iterranean countries, is estimated to be 4.5–5.0/1000 (Forsgren et al., 2005a).

Incidence of childhood epilepsy

The mean annual incidence of epilepsy (two or more unprovoked seizures), initially erroneously reported to be 25/100 000 (Sillanpää, 1973), was 35/100 000 (95% confidence interval 24–49) (150 per 4 years per 108019 at risk) at enrolment (Sillanpää et al., 1998). The most recent data from virtually the same geographic area give the same annual incidence of 35/100 000 in 1968–1972 (Saarinen et al., submitted). The contemporary incidences are not much different from ours. Calculated from the Rochester study data (Hauser et al., 1993), in 1965–1974, the incidence was 46/100 000 children 0–14 years of age. Brorson and Wranne (1987) reported the incidence of 50/100 000 among Swedish 0–19-year-olds from years 1961–1964. Later Swedish investigations yield higher incidences (82–134/100 000), but they are not comparable because of the difference definition of epilepsy (one single or more unprovoked seizures) (Heijbel et al., 1975; Blom et al., 1978; Sidenvall et al., 1993). Recruitment at first single unprovoked seizure gives substantially higher incidences than repeated seizures (Sidenvall et al., 1993).

Temporal changes in the incidence of childhood epilepsy

One of our epidemiological studies was addressed temporal changes in the all-age incidence of epilepsy in Finland (Sillanpää et al., 2006). That study was prompted by two suggested trends in the literature: a declining trend in childhood epilepsy (Joensen, 1986; Hauser et al., 1993; Camfield et al., 1996) and increase in the elderly (Hauser and Kurland, 1975; Juul-Jensen and Ipsen, 1975; Keränen et al., 1989; Oun et al., 2003). A linkage study of the data on the nationwide full-refundable antiepileptic drug registry and the population registry, well-known as valid and reliable data resources among the nationwide Finnish registries (Gissler et al., 1995; Pietilä et al., 1997; Rapola et al., 1997) included all patients with epilepsy in 1986 through 2002. A declining trend could be seen by the five-year periods of onset of childhood epilepsy: 97/100 000 in 1986–1989; 82/100 000 in 1990–1994; 80/100 000 in 1995–1999; and 67/100 000 in 2001–2002. The decline over the study period was significant (risk ratio [RR] 0.77, CI95% 0.71–0.84, $p < 0.0001$) (Sillanpää et al., 2006).

There are certain differences in the genetics of the original Finnish population and subsequent differences in the incidence of some chronic conditions including, among others, cardiovascular diseases (Keys and Fidanza, 1958; Pyörälä et al., 1985) and recessive diseases, typical of the Finnish population (Norio, 2003). We divided Finland into three geographic areas: eastern Finland, middle Finland and western Finland and used the same registries as in our 2006 study (Sillanpää et al., 2011). During the years 1986 through 2008, the overall incidence of all-age epilepsy was significantly ($p < 0.0001$) higher in eastern Finland than in other regions of the country, and declined significantly ($p < 0.0001$) in all three regions. The annual decline in the incidence was 0.4% (0.94; 0.89–0.99, $p = 0.0243$) in western Finland; 1.7% (0.85; 0.80–0.91, $p < 0.0001$) in middle Finland; and 0.3% (0.93; 0.887–0.99, $p = 0.0207$) in eastern Finland. The risk for childhood epilepsy was significantly higher in eastern Finland than in western Finland, but fell from 1.21 (1.12–1.30, $p < 0.0001$) in 1986 to 1.12 (1.03–1.23, $p < 0.0001$) in 2008 (Sillanpää et al., 2011).

So far, there is only one longitudinal population study (Christensen et al., 2007) that includes children. Extracted from their picture, the incidence of epilepsy among children of different age groups appears to decline from 1977 and reach a plateau up to 1990, then increased up to 1995 only to decline again after that year down to the level of about 60–70/100 000 by age group. A general impression is that the incidence had slightly declined from 1977 to 2002.

In single short-term population studies from 1975–1990, the reported incidences of childhood epilepsy ranged from 39–60/100 000 (Hauser et al., 1993; Freitag et al., 2001). Studies from 1990–2010 report incidences of 40–63/100 000 (Beilmann et al., 1999; Larsson and Eeg-Olofsson, 2006; Durá-Travé et al., 2008; Casetta et al., 2012; Giussani et al., 2014). An exception is the recent retrospective observational analysis by Helmers et al. (2015) that showed the incidence of childhood epilepsy to be 86/100 000 in 2007–2011. Their study was, however, not population-based, but based on subjects of the health insurance system. Due to conflicts in the reported trends, further research is needed. An extensive trend study of ours over the four last decades is underway.

During the last four decades, from 1973 to 2013, the incidence of childhood epilepsy (<16 years of age) remained rather constantly on the level of 60–70/100 000 person-years (Saarinen et al., submitted).

Temporal changes in the incidence of adult epilepsy

Our nationwide study on the incidence of adult epilepsy showed that the all-age incidence of epilepsy was significantly (risk ratio 0.83 [95% confidence interval 0.81–0.84], $p < 0.0001$) declining from 1986 to 2008 in Finland (Sillanpää, et al., 2011). The mean annual decline was 0.6%. The incidence remained, throughout the observation period significantly higher in men than in women. In addition to children, the incidence significantly declined in the middle-aged (16–64 years of age) with annual decline of 0.8%. In contrast, there was a significant increase in the epilepsy of the elderly (risk ratio 1.25, 95% confidence interval 1.18–1.33, $p < 0.0001$). The mean annual increase was 3.5% (Sillanpää, et al., 2011). The increasing trend in the incidence of epilepsy in the elderly is now widely reported (Hauser et al., 1993; Keränen et al., 1989; Oun et al., 2003) in support of our findings.

The increase of epilepsy in the elderly is not clear. In line with other industrialized countries including Finland, the mean age after the 65th birthday steadily increasing and associated with increasing risk factors for epilepsy, such as stroke and dementia. Further research is needed to elucidate this issue.

The Turku mortality study (Sillanpää et al., 1998, 2008; Sillanpää and Shinnar, 2010, 2013)

The study included 245 subjects, 150 with incident cases and 95 with prevalent cases. The median follow-up period was 40 years. Death data were continuously collected from different clinical sources and from the Finnish National Death Registry. Until the end of 2002, 60 subjects had died. At the time of last follow-up contact or death, after the mean follow-up period of 40 years, 45% of 245 subjects were in 5-year terminal remission without medication, 11% were in 5-year terminal remission on medication and 44% were not in terminal remission. The overall case fatality rate was 24% or 6.9/1000 person-years (Sillanpää and Shinnar, 2010). The rate is slightly higher than 6.2/1000 person-years obtained on 35-year follow-up (Sillanpää et al., 1998). The rates of death, adjusted for sex and age, 7.2/1000 person-years, with standard mortality ratios (SMR) of 5.5 (95% confidence interval [CI] 4.6–6.6) in incident cases and 6.4 (5.9–7.0) in the overall cohort (Sillanpää and Shinnar, 2010). The risk for death was not higher than expected in subjects with idiopathic epilepsy.

Subjects with childhood-onset epilepsy from the Turku study were analyzed for SUDEP (Nashef and Shorvon, 1997) and other causes of death after the prospective median follow-up of 40.0 (range 1–53) years (Sillanpää and Shinnar, 2013). The median follow-up for subjects with incidence cases was 39.5 years with a range of 1–42 years. Of the 60 deaths, 33 (55%) were related to epilepsy (Sillanpää and Shinnar, 2010), one could argue whether two cases of suicide could be included in the epilepsy-related causes. Deaths were in the younger age group associated with a remote symptomatic etiology and due to the underlying disease. Epilepsy-related causes of death are more common in adolescence and adulthood. SUDEP was the most common single cause of death (30%), but worth note is that no cases of SUDEP were found among children of less than 13 years of age in the cryptogenic or idiopathic group (Sillanpää and Shinnar, 2013).

Causes of death were related to seizures in 15% of our subjects and in 11–15% of the Dutch and Connecticut cohorts. The causes of seizure-related death were sudden, unexplained death (SUDEP) in 18, witnessed seizure in 6, inadvertent drowning in 6, status epilepticus in 6 and probable seizure in 3 subjects (Sillanpää and Shinnar, 2010). The most common seizure-unrelated causes were pneumonia and cardiovascular disease. Risk for death was significantly ($p < 0.0001$) higher in symptomatic cases than in non-symptomatic cases. On multivariate analysis, absence of 5-year terminal remission was a significant risk factor with hazard ratios of 4.7–5.0 in all deaths, epilepsy related deaths, and SUDEPs. Worth note is that the autopsy rate was exceptionally high (70% for the overall cohort and 80% for the incident cohort) enabling the determination of definite cases of death (Sillanpää and Shinnar, 2010). Remote symptomatic etiology or neurological disorder was the significant risk factor in the Canadian study (Camfield et al., 2002) and epileptic encephalopathy in the Connecticut study (Berg et al., 2004). SUDEP was the cause of death in 30% of our subjects. It is a marked cause of death in various age groups, as shown in the Chalfont study. A retrospective study of 235 cases of death (122 post-mortem examined) showed SUDEP as the cause of death in 18% (Novy et al., 2013).

While absence of ≥5-year terminal remission, a remote symptomatic etiology and a history of status epilepticus were significant risk factors for death and separately for SUDEP (Sillanpää and Shinnar, 2010; Sillanpää and Shinnar, 2013), on multivariate analysis, failure to enter ≥5-year terminal remission remained the only significant risk factor.

One more risk factor for premature death is seizure clustering. Seizure clusters during drug therapy compared with those who had not experienced any clustering (42% versus 14%; p = 0.0299, two-sided Fisher). The risk ratio for patients with clusters was 3.49 (95% CI 1.25–9.78) in the Turku population-based study of 120 subjects with childhood epilepsy (Sillanpää and Schmidt, 2008).

Due to our very long-term follow-up, at first glance, the case fatality rate (24.5%) was substantially higher than 2.1–3.8% reported in comparable studies with a substantially shorter follow-up (Callenbach et al., 2001; Camfield et al., 2002; Berg et al., 2004; Geerts et al., 2010). After standardization, however, the SMR was higher in all other cohorts than ours, 9.7 (5.7–15.3) in the Dutch cohort (Callenbach et al., 2001; Geerts et al., 2010), 7.5 in the Connecticut cohort (Berg et al., 2004) and 5.3 (2.3–8.3) and 8.8 (4.2.–13.4) depending on whether a reference population was from the 1980s or 1990s, respectively, in the Canadian study (Camfield et al., 2002).

A closer examination and comparison between the three cohorts with childhood-onset epilepsy (Callenbach et al., 2001; Camfield et al., 2002; Berg et al., 2004; Geerts et al., 2010) and our cohort shows that the age structure of our cohort is different from the three ones because of our much longer follow-up of 40 years than 14.8 years in the Dutch cohort, 13.9 years in the Canadian cohort and 7.9 years in the Connecticut cohort. Consequently, our study cohort was substantially longer followed-up and older than the three others with a different spectrum of causes of death in adulthood than in childhood. In addition to age-related effects, a cohort effect may be involved (Keyes et al., 2010). Population-based mortality in the fourth and fifth decades of life is much higher than in the first two decades with a resultant higher mortality per 1000 person-years even though the SMRs are not necessarily very different. The SMRIs start to increase since 20 or more years since diagnosis of epilepsy (Forsgren et al., 2005b). Furthermore, the SUDEP rate has its peak incidence in the third and fourth decades of life (Ficker et al., 1998; Devinsky, 2011). When one adds the two last mentioned facts to our cohort, the difference to the three cohorts is well understandable (Sillanpää and Shinnar, 2013).

CONCLUSION

Incidence, prevalence of and mortality in epilepsy in Finland are not dissimilar to the studies from other studies. Temporal changes in the incidence show a declining trend in childhood epilepsy and an increase in the incidence among the elderly. Further research is needed to understand the causes of the changes.

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CONFLICT OF INTERESTS

Nothing to declare.

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