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Long-term outcome of medically treated epilepsy

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ABSTRACT

Purpose: To review the long-term outcome of epilepsy in population-based studies.
Method: Analysis of population-based studies.
Results: About two of three patients with new-onset epilepsy will, in the long run, enter five-year terminal remission. Chances for remission are best for those with idiopathic or cryptogenic epilepsy. It is unclear whether the seizure outcome has improved over the last several decades. Social outcome, however, may have become better because of the improved level of knowledge on and public attitudes toward people with epilepsy, and possibly fewer prejudices at home, daycare, school, military and labor market.
Conclusion: While we still do not have a cure for epilepsy for all patients, relief of the medical and social consequences is available for many and hope is on the horizon for people with epilepsy.

1. Introduction

The first attempts, in a modern sense, to explore the medical and social outcome of patients with epilepsy were made in the 1950s [1] and 1960s [2] based on patients from hospitals and other institutions. According to those studies and the previous literature from 1901 to 1964 discussed by Rodin [2], the five-year terminal remission varied by etiology between 15 and 30%. Yet, studies based on unselected population cohorts are needed to get unbiased and valid data on this chronic disorder. The data are important for the treating doctor, but have usually have also many medical and social implications for the patients and society. The first population-based study, the Rochester Study [3], designed as a record linkage system and linking on one record clinical data derived 1935–1967 from inpatient, outpatient, emergency room contacts and home visits by health professionals at the Mayo Clinic. In long-term follow-up, 40% had entered terminal 5-year remission [3]. In more recent population studies, about two thirds were in 5-year terminal remission [4–7]. The improved prognosis can be ascribed, among other things, to advanced externally valid study populations, diagnostic methods and therapeutic armament [5,8–10]. Only a few long-term (more than 10 years), prospective unselected population-based cohort studies have been reported [4–6,8,11–13]. The review and discussion of the present paper is mainly, but not only, focused on the contribution of population-based reports.

2. Prospective cohort studies

2.1. Population-based long-term studies [11,12]

The recruitment of study subjects of Brorson [11] was from the Swedish province of Uppsala (total population of 0–19 years of age, n = 54,000) including general and epilepsy hospital inpatients and outpatients and clients from provincial medico-social board and special school registers, and the EEG laboratory of the university hospital of Uppsala. Excluded were patients with neonatal seizures during the three first days of life; provoked seizures; unprovoked non-convulsive epileptic attacks; and potential study subjects not medically treated for epilepsy. The baseline study sample included 195 children and adolescents aged 0–19 years who had had at least one provoked seizure in 1961–1964 and were thus considered as having active epilepsy. The study is apparently population-based. The baseline paper is a survey reported in Swedish by the national Social Board of Sweden in 1970 and not easily accessible. The prevalence was estimated as 3.5/1000 and the mean annual incidence 50/100,000. On 12-year follow-up [6], 124 (64%) were in 3-year terminal remission.

In the Turku study [12], recently re-named as the Turku Adult Childhood Onset Epilepsy (TACOE) study, the source population

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consisted of children aged 15 years or less who were living in the catchment area of Turku University Hospital at the end of 1964 (n = 108,019), and had unprovoked seizures [14]. Epilepsy was defined as repeated, unprovoked seizures 24 h apart at the age of 4 weeks to 15 years. Epileptic seizures and syndromes were later re-classified [15] to be in line with the update ILAE definitions [16–18]. Active epilepsy was defined as onset of epilepsy in 1961–1964 or one or more unprovoked seizures in a child with the diagnosis of epilepsy ascertained before 1961. Children with epilepsy were identified by reviewing the files from the following data sources: inpatient and outpatient clinical and EEG records of hospitals and institutions for mentally retarded or cerebral palsy in the catchment area of Turku University Hospital and any hospitals or institutions the whole southern Finland potentially treating or having treated children with epilepsy; special schools in the area; and community general practitioners' offices and private offices' records. Finally, the National Health Service Register data of refundable antiepileptic drugs for epilepsy (but not for other indications) could be reviewed by permission of the public authorities. That method of approach detected five cases not earlier identified, but then proven to fulfill the inclusion criteria. Thus, the enrolment of the subjects was not only based on hospital and institution records, but any public or private health units and, to be on the safe side, on the review of all subjects in the study area who got fully reimbursed antiepileptic drugs for the treatment of epilepsy. The special school and community and private office records did not virtually contribute to the data collection, because all the relevant cases had been identified by the hospital records. This was not unexpected, because there was and still is a rule in Finland that every child with an epileptic or suspected epileptic seizure should be referred to hospital with pediatric or child neurological expertise [5,19]. Access to board-certified pediatrician became possible all over the country since the 1950s to 1960s, when the countrywide network of tertiary care hospitals with pediatric departments was built and enabled specialist care for children despite the place of residence in Finland [20]. The registers of the national social security institution, based on the legislation largely copied form the British national health service, effective since 1964, has been proved to be a reliable source of data for research purposes in many reports [21–24].

The review of all the above mentioned records including EEG statements was made by one child neurologist (M.S.) who also clinically examined all the 245 children who were ascertained as children with epilepsy. 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 one or more unprovoked seizure during 1961–1964 [5,12]. In addition to the reviewed records, EEG and clinical neurological examination data, additional EEG and neuroimaging investigations were performed on clinical grounds, if needed. Ongoing surveillance after the baseline study detected only very few children who fulfilled the inclusion criteria and should have been considered in an epidemiological analysis. On 35-year follow-up, 67% were in five-year remission [5,25].

2.2. Community based study [10]

The British national general practice study of epilepsy (NGPSE), with the study subjects followed for 25 years [26], was based on a surveillance process with 275 general practitioners (GPs) recruiting al patients of different ages who had any definite or possible new-onset epileptic seizures during 1984–1987. The method of recruiting patients only covered those living in the community. Subsequently, patients who resided in institutions (institutions for mentally retarded, nursing homes or prisons) were excluded. However, institutions for patients who have epilepsy do exist in the UK [27,28], and it is well-known that institutionalized patients, and those with mental comorbidity in particular, are at markedly higher risk of epilepsy than those living in the community; percentages between 25 and 40% [29–32] have been reported. The enrolment method per se then excludes institutionalized patients, because they are virtually invisible to GPs. An obvious weakness in GP-based inclusion method is external and internal validity [33], among other things, over-diagnoses and under-diagnoses [34,35]. 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 [33]. The problem concerns also children with epilepsy in the UK [36,37]. The study comprised 302 patients with a single unprovoked seizure at presentation and 354 patients with epilepsy (two or more unprovoked seizures) at presentation. In 318 patients, 73% were in 5-year terminal remission at the end of follow-up and 80% in those who could be followed up to the last contact. The 73% is probably calculated up to the last contact or death, whichever came first, and the comparable with the previous studies.

Overall, approximately two thirds are in terminal remission (Table 1).

2.3. Hospital-based studies

Hospital-based studies are, mainly due to their easier feasibility, much more common than population studies. Typically, the hospital studies rely on inpatient and outpatients of one tertiary care hospital. Even in case of multi-institutional recruitment of study subjects, they are approximations of the real prevalence and incidence, because those studies are subject to selection bias and, subsequently, a weak external validity. The risk of a selection bias is still higher, if the study population is based on one laboratory clients. In such a study, no more than 86% of regional physicians indicated they use to order an EEG after a first seizure [38]. A potential gap between intention and practice was not tested. Among 127 children referred as patients of "first seizure" to a tertiary care First Seizure Clinic, the diagnosis was epileptic in 74%, among patients referred by family physicians only 65% and an EEG done in all 127 children was abnormal in 41% [39]. Without

Table 1
Five-year terminal remission (5-YTR) reported from population-based and institution-based long-term studies. I = incident cases; P = prevalent cases.

Study design	Duration of follow-up (years)	5-YTR (%) on or off medication	Author(s) and year
Population-based, prospective studies			
I&P (n = 227)	10	56	Sillanpää, 1983
I&P (n = 178)	20	58	Sillanpää, 1990
I&P (n = 220)	30	64	Sillanpää et al., 1998
I%P (n = 220)	40	61	Sillanpää et al., 1998
I (n = 144)	40	67	Sillanpää et al., 2006
Surviving I&P (n = 133)	45	70	Sillanpää et al., 2015
Cases with one or more, probably unprovoked seizures (n = 228)	22	68	Cockerell et al., 1997
Population-based, retrospective studies			
I (n = 475)	10	65	Annegers et al., 1979
I (n = 141)	20	70	Annegers et al., 1979
Hospital-based cohort studies			
I (n = 730)	10	79	Oka et al., 1989
I&P (n = 141)	10	52	Wakamoto et al., 2000
I&P (n = 75)	20	56	Wakamoto et al., 2000
I (n = 413)	15	71	Geerts et al., 2010
I (n = 516)	21	60	Berg and Rychlik, 2015

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