Natural course of treated epilepsy and medico-social outcomes. Turku studies. Part II

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SUMMARY

Introduction. Population-based data on the prognosis of childhood-onset epilepsy were almost non-existent in the 1960s. This prompted me to start an epidemiological prospective study on children with epilepsy.

Aim. To study the medical and social outcome of children with epilepsy.

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

Results and discussion. The natural course of treated epilepsy is remitting, uninterrupted by relapse (in 48%); a remitting-relapsing course (interrupted by relapses, in terminal remission) (19%); worsening course (early or late remission followed by drug-resistant epilepsy) (14%); and never in ≥5-year remission (drug resistance) (19%) The medical and social outcomes based on my unique, five decades followed cohort show that most subjects are in 10-year remission without medications, which is the definition of resolved epilepsy. Normal or subnormal IQ, non-symptomatic etiology, and low seizure frequency both in the first year of AED treatment and prior to medication appear to be clinical predictors of cure in childhood-onset epilepsy. Subjects with 1-year remission during the first five years form onset of treatment have more than 10-fold chance for entering 5-year terminal remission vs those who have no 1-year remission during the first five years. Even about one fourth of difficult-to-treat subjects become seizure free on medication and more than half of them enter one or more 5-year remissions. Epilepsy has a substantial impact on quality of life even in those who are seizure free off medication for many years and particularly those not in remission or in remission but still on medication.

Conclusions. The prognosis is excellent for medical and social outcome. The successful outcome is confirmed by several longitudinal studies from recent decades. Good response to early drug therapy does not necessarily guarantee a favorable seizure outcome, and even a late good response may still predict a successful prognosis. Our life-cycle study is being continued and targets to answer the question whether or not childhood-onset epilepsy is a risk factor for premature and/or increased incidence of mental impairment and dementia.

Key words: childhood-onset epilepsy • drug-resistant epilepsy • long-term outcome • natural course of epilepsy • population-based cohort

Review paper

INTRODUCTION

Outcome studies on epilepsy mostly include data on seizure outcome at the end of follow-up. My personal experiences on the seizure outcome of childhood-onset epilepsy were published as Part I in the issue no. 2/2015 of this journal (Sillanpää, 2015). Papers of that kind do not usually report on the course of epilepsy. Some reviews on the natural history of treated (and untreated) epilepsy have been published (Sander and Sillanpää 1997; Forsgren and Sillanpää, 2012). Similarly, comprehensive social outcome studies based on long-term follow-up are few.

AIM

The paper is aimed to present the medical and social course and outcome of children with epilepsy and the following items will be discussed: natural history, remissions, drug resistance, determinants of remission, risk of relapse, drug withdrawal, cure of epilepsy, predictors of drug response, comorbidities, learning disability, daily activities, quality of life, employment, driver's licence, reproductivity.

METHODS

The most crucial personal data on natural course of childhood epilepsy are reviewed and discussed with the relevant data of other studies. The search has been conducted to date using the PubMed, Scopus and Science Direct databases.

RESULTS AND DISCUSSION

Natural history of treated epilepsy

Based on the literature, the natural course of treated epilepsy is suggested "excellent" in 20–40%, "good" in 30–40", "uncertain" in 10–20% and "poor" in 20% (Sander and Sillanpää, 1997). In our study of 144 subject with incident cases were followed for the mean 37 years (SD 7.1, median 40, range 11–42) (Sillanpää and Schmidt, 2006a). The analysis of the course of epilepsy warranted the division of four groups a): remitting course of epilepsy uninterrupted by relapse (48%); b) remitting—relapsing course (≥5-year relapses interrupted by one or more relapses, but ending in terminal remission) (19%) c); worsening course (early or late remission followed by drug-resistant epilepsy) (14%); and d) never in ≥5-year remission (drug resistance) (19%) (Sillanpää and Schmidt, 2006a) (Figure 1). Worsening after surgery has been reported in 18.5% and explained been caused by extratemporal resections, incomplete resections, and multiple recorded ictal patterns (Sarkis et al., 2012). Postsurgical worsening of seizures might as well be explained by a worsening pattern of seizures irrespective of surgery (Schmidt and Sillanpää, 2013).

A good effect of early therapy did not reliably predict terminal remission or failure to achieve remission. In subjects with good early response, 61% achieved remission and in subjects who failed to respond to initial therapy, 42% entered remission. Our data are supported by Camfield et al. (1997) who found the response to the first AED only broadly predictive of outcome in 417 children with epilepsy. It is also worth note that 8 (18%)/45 subjects with initial good response finally failed to achieve terminal remission. Subjects in either early or late terminal remission, uninterrupted by relapse, were half (48%), and additional subjects in terminal remission interrupted by one or more relapses, that is, remitting-relapsing course were 20% of the follow-up cohort. An intermittent pattern with remissions and relapses found in the present study (14%) is well comparable with 12% obtained in the UK study (Goodridge and Shorvon, 1983). One fifth (19%) never entered ≥ 5-year remission. This is in keeping with previous studies that report drug resistance in up to 20% (Sander and Sillanpää, 1997).

Seizure remission (Sillanpää et al., 1998, 2014, 2015)

Five- to 10-year remission

There are numerous seizure outcome studies, but few are fixed population studies and based on tens of years of prospective follow-up. Our prospective, population-based fixed cohort, now entitled and later referred to as the TACOE (Turku Adult Childhood Onset Epilepsy) cohort was assessed for outcomes at 45 years in 2012 (Sillanpää et al., 2014; Sillanpää et al., 2015). Epilepsy syndromes, epilepsies, epileptic seizures, and etiology of seizures were defined according to the guidelines of the International League Against Epilepsy (ILAE) (Commission on revised classification of seizures, 1981; Commission on Classification and Terminology, 1989; Commission on Epidemiology and Prognosis, 1993; Central Statistical Office of Finland, 1989). Remission was defined in accordance with the newer definition as 10-year remission and off medication for ≥5 years (Fisher et al., 2014b). The design of the cohort including subjects and matched controls is described above in detail (Sillanpää, 1973; Sillanpää et al., 1998).

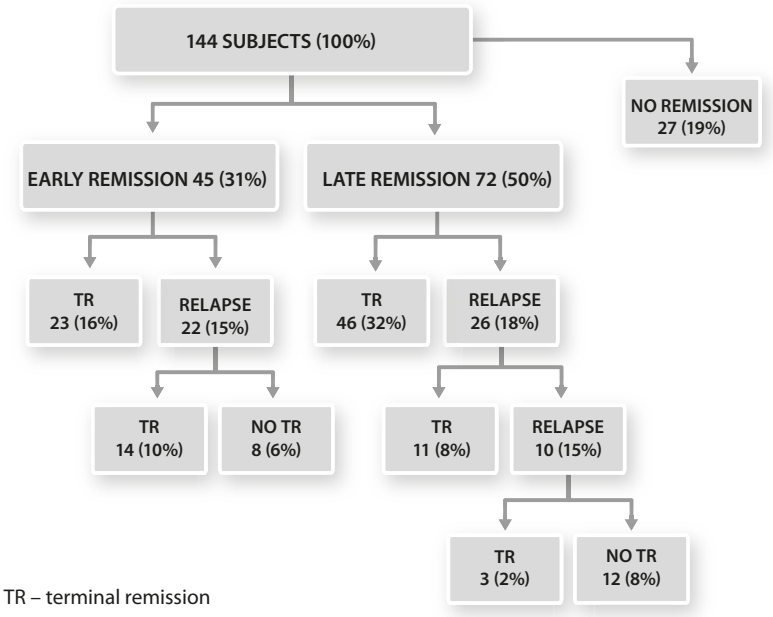


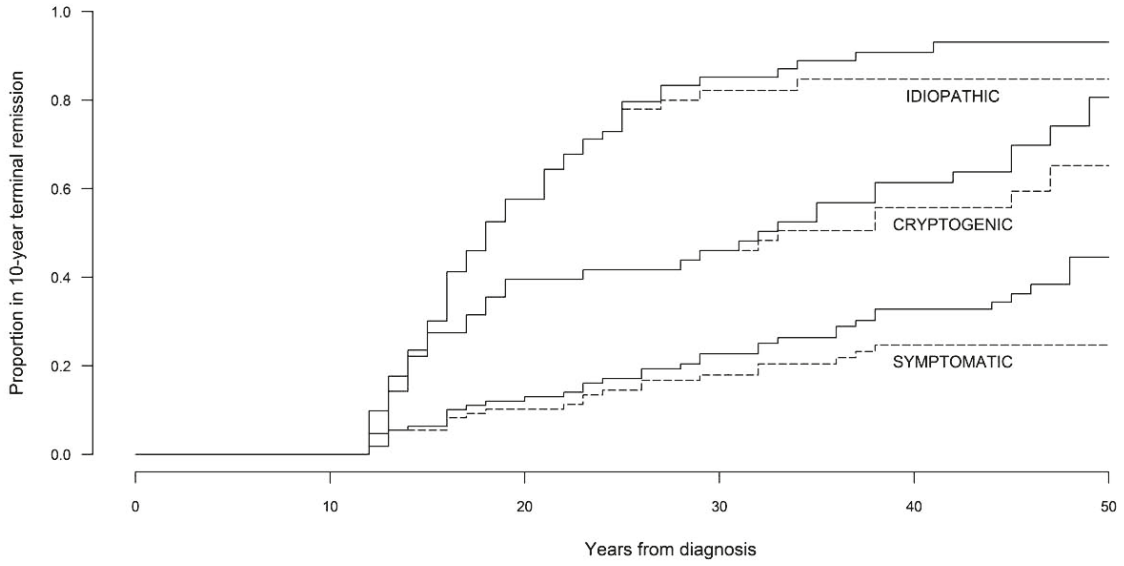
Figure 1. Subject disposition and outcome chart during 40-year follow-up of childhood onset epilepsy.

In 2012, outcomes were available on 81% or 199 of the original 245 subjects. Sixty-six subjects had died. Of the 179 surviving subjects, 133 (74%) were found and agreed to participate. The mean follow-up was 47.4 years (median 47.0, range 44–60) and mean age was 50.5 (median 51.0, range 43–60) years. At least one 10-year remission was entered by 99 (74%) of 133 subjects, 29% of whom had relapse following remission. At the end of follow-up 88 (89%) of 99 were in 10-year terminal remission and 67 (68%) of 99 were in 10-year terminal remission and off medication for ≥5 years. To maintain comparability to the previously reported remission rates of the present cohort, we also analyzed the cohort for 5-year terminal remission as seen in Figure 2. As seen in Figure 2, a steady rise in terminal remission rates continued past the 40 year mark, followed by a plateau, and then continued increase up to 50 years. The 5 and 10 year remission curves were approaching each other as the vast majority of subjects who achieve 5 year terminal remission also achieved 10 year terminal remission. Figure 2 also shows that, in the long run, cryptogenic etiology makes up the curve of its own and thus questions the justification of the synonym of "presumably symptomatic".

At 45 years, almost all (95%) of the idiopathic group and 72% of the cryptogenic group were in terminal remission on or off medication compared with only 47% of the remote symptomatic group ($p < 0.001$ log rank). The corresponding figures for terminal remission without medication were 81%, 63%, and 25% ($p < 0.001$ log rank). The sole independent predictors of terminal remission were idiopathic vs symptomatic etiology (2.0; 1.4–2.8) and cryptogenic vs symptomatic etiology (1.5; 1.01–2.3). A history of status epilepticus (Sillanpää and Shinnar, 2002) was not a significant factor.

Benign childhood epilepsy

Benign childhood epilepsy with centrotemporal spikes or rolandic epilepsy (RE) was diagnosed in 24 (10%) of 245 children of the Turku study (Sillanpää, 1973). Similar proportions with the range of 6–1% have been reported (Heijbel et al., 1975; Berg et al., 1999; Camfield and Camfield, 2014). Seven were dropouts, two of whom had died (one committed suicide and another was met by sudden unexplained death), and five further patients declined. The remaining 17 were participants, who had a control group matched for age, sex and domicile and were included in the study (Sillanpää, 2010). The incidence was 3.5/100 000 person-years, keeping with 4.7/100 000 in Iceland (Astradsson et al., 1998). The mean age at onset was 2–12 years (SD 3.56, median 6.0), and the mean follow-up time was 42 years (range 38–



Solid lines – on or off medication; broken lines – off medication

Figure 2. Ten-year seizure outcome by etiology in subjects with childhood-onset epilepsy followed for 45 years.

53, median 40). According to the contemporary practice, almost all (88%) patients were treated with antiepileptic drugs, mostly for some weeks or months and all but three patients with phenobarbital. All the subjects were in terminal remission off medication. According to a meta-analysis (Bouma et al., 1997), at the age of 18 years, 99.8% of subjects with rolandic epilepsy were in remission. All the subjects were mentally normal, but 11 (65%) had various neurotic or psychoneurotic symptoms. All the patients entered five-year remission on the mean follow-up of 9.18 (SD 2.38, median 10, range 5–13) years. After five-year remission, five patients had one relapse during the following 7–13 years. At the end of the mean of 42-year follow-up, all the patients were in terminal remission, 16 (94%)/17 without medications on the mean of 32.65 years (SE 7.11, median 35, range 29–39 years, except for one patient who had a seven-year terminal remission) (Sillanpää, 2010).

No significant differences between subjects and controls existed I basic education, vocational education, employability, driver's licence, marital status, or having offspring except for the significantly lower number of children ($p = 0.0199$). No significant differences between subjects and controls were found on any of the eight subscales or in the total SF-36 scores. Conclusively, in agreement with a Canadian study (Camfield and Camfield, 2014), the seizure and social outcomes for subjects with benign rolandic epilepsy are remarkably better than for those with other major epilepsies and normal intelligence.

First one-year remission

At 40 years of follow-up (median 40.0, mean 37.6, SD 7.1, range 11–42), of the Turku population cohort of 150 children (<16 years) with onset of epilepsy in 1961–1964, was analyzed for predictors of long-term outcome in childhood-onset epilepsy (Sillanpää and Schmidt, 2009a). At 40 years, excluded were 6 (4%) were excluded due to less than 10-year follow-up, 41 for episodes of status epilepticus and 1 patient for self-induced photosensitive seizures. Thus, the remaining 102 subjects constituted the final population-based study cohort (Sillanpää and Schmidt, 2009a). At 40 years, 95 (93%) achieved 1-year remission (1YR). The remaining 7 never entered 1YR during the mean follow-up of 23.6 years (SD 12.4, median 24.0, range 11–41) and was categorized as drug-resistant. On univariate analysis, two factors were found that were associated with entering uninterrupted early 1YR in 20 patients versus the seven patients who never reached 1YR. These factors were seizure frequency less than weekly versus weekly during the first year of treatment ($p = 0.0002$) and idiopathic/cryptogenic versus symptomatic etiology ($p = 0.0317$). Multivariate analysis revealed seizure frequency less than weekly versus weekly during the first year of treatment significantly ($p = 0.0125$, hazard ratio 8.2 [1.6–43.0]) associ-

Table 1. Reported factors predicting good seizure outcome on multivariate analyses

Pre-seizure factors
Non-symptomatic etiology (Sillanpää et al., 1998; Ko and Holmes, 1999; Äikiä et al., 1999; Berg et al., 2004; Sillanpää and Schmidt, 2009a)
Normal intelligence (Brorson and Wranne, 1987; Camfield et al., 1993; Sillanpää et al., 1995; Äikiä et al., 1999)
Normal neurological status at examination (Brorson and Wranne, 1987)
Late childhood age at onset of epilepsy (Camfield et al., 1993; Sillanpää et al., 1995; Ko and Holmes, 1999)
No prior neonatal seizures (Camfield et al., 1993; Sillanpää et al., 1995)
Female sex (Arts et al., 2004)
Seizure-related factors
Low pre-treatment seizure frequency (Beghi and Tognoni, 1988; Camfield et al., 1993)
Low number of seizures during six months following onset of epilepsy (MacDonald et al., 2000)
No tonic or simple partial seizures (Ko and Holmes, 1999; Kwan and Brodie, 2000)
One seizure type (Brorson and Wranne, 1987)
Generalized vs focal epilepsy (Sillanpää and Schmidt, 2006a)
Extra-temporal lobe epilepsy vs others (Sillanpää and Schmidt, 2006a)
Generalized vs others (Sillanpää and Schmidt, 2006a)
Generalized idiopathic vs others (Sillanpää and Schmidt, 2006a)
Idiopathic with no febrile seizures (Arts et al., 2004)
Generalized cryptogenic/symptomatic vs others (Sillanpää and Schmidt, 2006a)
Absence of complex partial or atonic seizures (Sillanpää et al., 1998; Äikiä et al., 1999)
Absence of diffuse slowing in EEG (Ko and Holmes, 1999)
No focal spike and wave activity in EEG (Ko and Holmes, 1999; Äikiä et al., 1999)
No postictal signs (Arts et al., 2004)
Treatment-related factors
High seizure frequency during early treatment (Sillanpää et al., 1998; Arts et al., 1999; Sillanpää and Schmidt, 2009a)
Absence of early response to therapy (Sillanpää et al., 1998; Kwan and Brodie, 2000)
Delayed time to first remission (Sillanpää and Schmidt, 2009b)
Seizure clustering during drug treatment (Sillanpää and Schmidt, 2008)
Predictors of remission with or without AEDs
Entering 1-YR within first 5 years of treatment (Sillanpää and Schmidt, 2006a)
Likelihood for 5-YTR on/off AEDs (Sillanpää and Schmidt, 2009a)

(x-YTR – x-terminal seizure remission; AED – antiepileptic drug)

ated with entering uninterrupted early 1YR versus the seven who never reached 1YR and, on the other hand, never entering terminal 1YR (hazard ratio 2.7 [1.5–5.0], p = 0.0010). Having weekly seizures prior to treatment only slightly increased the risk to never enter terminal 1YR (hazard ratio 1.7 [1.04–2.9], p = 0.0350) (Sillanpää and Schmidt, 2009a). Table 1 shows factors suggested as predictors of seizure outcome.

Drug resistance (Sillanpää et al., 2012)

The above mentioned 102 subjects of the Turku population-based study were determined for 1-, 2- an 5-year remission and terminal 5-year remission, with special emphasis on remissions after incident or first ever occurrence of drug-resistant epilepsy (Sillanpää and Schmidt, 2012). In addition to the original inclusion criteria (Sillanpää, 1973), further criteria included focal or generalized epilepsy; well documented and adequate drug treatment; drug resistance of seizures, as defined by Kwan et al. (2010); and prospective follow-up of 10 year or more. At start, 98 of 102 subjects had focal seizures (68 symptomatic and 30 cryptogenic or idiopathic), one had generalized convulsive seizures and three had unclassified seizures. At the end of the mean follow-up of 36.2 years (SD 11.7; median 40.5, range 4–55), 84 (82%) of 102 patients with incident drug-resistant epilepsy eventually entered one or more one-year remissions, 81 (79%) one or more two-year remissions, 70 (69%) one or more five-year remissions and 52 (51%) of 102 five-year terminal remissions, while the remaining subjects in each category of remission did not enter remission, respectively. There are few data in the literature on the chances for remission with drug treatment for patients with apparently drug resistant epilepsy. Most of them have flaws including hospital-based retrospective study design, failure to assess relapse following remission, and lack of evidenced drug-resistance comparable with the ILAE definition of drug resistance (Selwa et al., 2003; Luciano and Shorvon, 2007). While epilepsy surgery is reportedly (Schmidt and Stavem, 2009) seven times as efficient as no surgery, our data show that 51–83% of subjects with apparent drug-resistance will

Table 2. Determinants of entering 5-year terminal remission on stepwise logistic regression analysis

	Single predictor models	Stepwise multipredictor models		
Determinant	**p**	**OR**	**95% CI**	**p**
Overall 5YTR (n = 144)				
Idiopathic/cryptogenic vs symptomatic etiology	<0.0001	6.1	2.5–14.8	<0.0001
Less than weekly vs weekly seizure frequency during treatment	<0.0001	5.5	2.3–13.3	0.0002
Less than weekly vs weekly pretreatment seizure frequency	0.0004	4.7	1.9–11.8	0.0009
Temporal lobe epilepsy	0.0398			0.4765
West syndrome/LGS	0.0006			0.8293
Rolandic epilepsy	0.0377			0.7671
Uninterrupted 5YTR (n = 76)				
Idiopathic/cryptogenic vs symptomatic etiology	<0.0001	12.5	3.1–50.4	0.0004
Less than weekly vs weekly seizure frequency during treatment	<0.0001	13.7	3.1–60.6	0.0005
Less than weekly vs weekly pretreatment seizure frequency	0.0050	7.8	1.8–33.4	0.0058
West syndrome/LGS	0.0222			0.9840
Uninterrupted 5YTR off meds (n = 70)				
Idiopathic/cryptogenic vs symptomatic etiology	<0.0001	20.0	4.2–95.9	0.0002
Less than weekly vs weekly seizure frequency during treatment	0.0002	8.3	1.8–38.3	0.0063
Less than weekly vs weekly pretreatment seizure frequency	0.0115	5.7	1.2–26.1	0.0245
Temporal lobe epilepsy	0.0372			0.4125
West syndrome/LGS	0.0120			0.4616
Rolandic epilepsy 0.2689	0.2689			

OR – odds ratio; 95% CI – 95% confidence interval; LGS – Lennox-Gastaut syndrome.

enter remission. On multivariate analysis, idiopathic or cryptogenic etiology of epilepsy was the only significant factor with a two-fold (hazard ratio 2.1, 95% CI 1.2–3.6, p = 0.0093) chance for five-year terminal remission compared with subjects with symptomatic epilepsy (Sillanpää and Schmidt, 2012). This is in keeping with previous data (Berg et al., 2001) that symptomatic etiology has a negative effect on the seizure outcome.

Determinants of remission

One-year remission as a predictor

The predictive value of the time to first 1YR for long-term antiepileptic drug response and entering 5-year terminal remission was studied in the Turku population cohort of 144 of 150 subjects with incident cases, who were prospectively followed up to the mean age of 48 years (Sillanpää and Schmidt, 2009b). Six of 150 subjects were excluded because of follow-up shorter than 10 years. At the end of the mean follow-up of 40 years (SD ± 8.8, range 11–47, median 44.0), patients who had their first one-year remission during the first 5 years of follow-up entered future 5YTR more often, compared with patients who had their first 1YR after more than 5 years (79% vs 25%, p = 0.0001). They had an 11-fold better chance of entering 5YTR (odds ratio [OR] = 11.4, 95% confidence interval [CI] = 2.9–45.3, p = 0.0005).

However, those who achieved 1YR within the first 5 years vs later than 5 years of treatment had no significantly better chance of entering uninterrupted 5YTR (23% vs 17%; p = 0.7335, OR 1.5, 95% CI 0.3–7.3; p = 0.6020). More patients who had achieved first 1YR during the first 5 years of follow-up vs those with later onset of first 1YR were in future uninterrupted 5YTR without medications (45% vs 8%, p = 0.0140). Table 2 shows additional significant predictors of entering 5-year terminal remission.

The proportion of patients entering long-term seizure freedom was highly dependent on the length of time to first 1YR after onset of adequate treatment. A delayed entry into first remission gradually diminished the chances for long-term seizure freedom, whether on or off medication. However, failure to reach 1YR within 5 years after starting AEDs did not predict failure to achieve uninterrupted seizure freedom on med-

ication during the long follow-up. Additionally, prognostic factors were etiology and seizure frequency prior to and during the first year of treatment. Our data indicate that time to first remission allows predicting which children will become seizure free on medication and remain seizure free off medication as adults. Our study confirms the previous papers reporting pretreatment seizure frequency, etiology and seizure frequency during early treatment as significant predictors of outcome (Annegers et al., 1979; Kwan and Brodie, 2000; Arts et al., 2004).

Seizure clustering

The study included 120 of 150 children with epilepsy having started in 1961–1964 who had been followed since disease onset (average age 37.0 years, SD 7.1, median 40.0, range 11–42) were included (Sillanpää and Schmidt, 2008). Excluded were children with follow-up shorter than 10 years (6); with West or Lennox-Gastaut syndrome (15); with childhood or juvenile absence epilepsy or juvenile myoclonic epilepsy (8); or auto-induced photosensitive epilepsy (1). Seizure clustering was defined clinically as episodes of three or more afebrile seizures during a 24 h period (Randall, 1997; Haut et al., 1999). At the end of the follow-up period, 26 (22%) (11 of them boys) of the subjects had recorded clusters of seizures. Fourteen had recorded pre-treatment clusters, including 10 patients with clusters as first seizures; and in 12 subjects clusters occurred during treatment. In these 12 patients, first clustering began after 16 (range 0–35; median 15) years of treatment. Compared with the patients without clusters, those with clusters more often had at least one seizure per week at the initial stage (63% versus 32%, $p = 0.0178$) and during the follow-up period (p-value varied from 0.0464 to 0.0064). Patients having seizure clusters during drug therapy were more likely to have drug resistant epilepsy compared to those not experiencing seizure clusters (42% versus 13%; $p = 0.0102$) and had a lower rate of entering 5-year terminal remission ($p = 0.0039$) and 5-year remission ($p = 0.0230$) (Sillanpää and Schmidt, 2008). The cluster frequency of 22% in our study is lower than reported previously (Manford et al., 1996; Haut et al., 1999; Haut et al., 2002) probably due to different patient cohorts. Our study is the first population study on seizure clustering and first to present pretreatment cases of clustering. We may confirm the previous observation about poor seizure outcome associated with seizure clusters (Balish et al., 1991; Haut et al., 1999).

Risk of relapse (Sillanpää et al., 2012)

Although there are many studies on remission and drug-resistance of subjects with new-onset epilepsy, to the best of our knowledge, no studies have informed on the risks of relapse after preceding remission. Therefore, 115 subjects of the Turku population-based study (Sillanpää, 1973) who had prospectively been followed for 10 years or more from the onset of epilepsy and had experiences at least one 5-year terminal remission, were analyzed for relapses after five-year seizure remission (Sillanpää et al., 2012). The study subjects were a subgroup of initial 150 subjects with incident cases. Excluded were 6 for follow-up of less than 10 years; 3 for noncompliance; and 26 for not having entered any ≥ 5-year remission. The remaining 115 subjects had been followed for the mean of 42 years (SD 6.08; median 44, range 19–47). A majority, 69 (60%) of the 115 patients had no relapse. One or more relapses were seen in 46 (40%) and 14 (12%) never re-entered five-year remission. On multivariate analysis of clinical features, cognitive impairment predicted seizure relapse for those entering their first ≥ 5-year remission. Among the 115 patients, 33 (30%) were prematurely retired. The significant predictors of retirement were relapse, symptomatic etiology, and early onset of epilepsy (6 years or less). Thus, despite entering their first remission of 5 years or more, subjects with epilepsy still have clinically and socially important risks including relapse, failure to reenter remission following relapse, and premature retirement (Sillanpää et al., 2012).

AED withdrawal (Sillanpää and Schmidt, 2006)

Effects of antiepileptic drug withdrawal on the prognosis of epilepsy in 148 children of the Turku population-based study with onset of epilepsy in 1961–1964 and followed for the mean of 37.1 years (SD 7.1, median 40.0, range 11–42) (Sillanpää and Schmidt, 2006b). While 58 patients continued on medication, it was completely discontinued by 90 patients. AED medication was tapered with an interval of 6–9 months from reduction of dose to elimination of AED without randomization, after individual risk–benefit and compliance assessment 2 to 3 years after the last seizure in children aged <16 with generalized non-convulsive and convulsive epilepsies and 5 years after the last seizure in all other patients of different ages and with different types of epilepsy. Drug treatment was discontinued by 53% of the 90 patients within 2 years and by 73% within 5 years. After the first completed withdrawal,

the subjects were prospectively followed for 32 years (mean 32. SD 8.7, median 34.0, range 7–42). Strikingly, even about one fourth of difficult-to-treat subjects became seizure free on medication and more than half of them entered one or more 5-year remissions (Sillanpää and Schmidt, 2006b).

Relapses

Relapses were experienced by 33 (37%) subjects, within the first year by 36%, within the first two years by 46%, and within the first three years by 67%. Our relapse rate of 37% is in line with 36–37% rates obtained from shorter follow-up periods (Todt, 1984; Shinnar et al., 1994). The duration of the treatment was significantly shorter in subject with relapse than in those without (median 4.0 vs 8.0, $p = 0.0284$). The last documented relapse was 28 years after drug discontinuation. At relapse, 25 (76%) of all 33 subjects with relapse preferred to remain off medication. Two of the remaining 8 subjects who wanted to restart drug therapy reached 5-year terminal remission, which six (18%) never did that (Sillanpää and Schmidt, 2006b). This rate of drug resistance well compares with the mean of 19% drug-resistant cases reported in the review of 14 observational studies (Schmidt and Löscher, 2005).

Cure of epilepsy (Sillanpää et al., 2014)

An intensive object of discussion is how to which is "cure of epilepsy" and how to make a difference between remitted epilepsy and cured epilepsy. In our population cohort study, 133 of 150 subjects with new-onset epilepsy in 1961–1964 were followed for 45 years (mean = 39.8, median 44, range 11–47). The reasons for the exclusion of 17 subjects included too short follow-up (< 10 years); non-compliance; and 5-year remission on medication making it difficult to ascertain cure. Cure was defined in accordance with the literature as entering at least 5-year terminal remission following withdrawal of all AEDs during sustained remission (Schmidt and Löscher, 2003; Fisher et al., 2014). Eighty-one (61%) of the 133 patients had entered at least 5-year remission off AEDs, meeting our definition of cure. The 81 patients were seizure-free off AEDs for a mean of 34.4 (median 38, range 6–46) years and 59 (73%) of the 81 patients following the first standard medication until the end of follow-up (mean 36.5, median 39, range 14–46 years) (Sillanpää et al., 2014).

Independent factors associated with cure compared with having seizures while on AEDs included seizure frequency less than weekly during the first 12 months of AED treatment ($p = 0.002$), pretreatment seizure frequency less than weekly ($p = 0.002$), higher IQ (>70, $p = 0.021$), and idiopathic or cryptogenic vs symptomatic etiology ($p = 0.042$). Patients with seizure frequency of less than once a week during early treatment and idiopathic etiology had a 9-fold chance of being cured since the onset of the first adequate antiepileptic therapy until the end of follow-up compared with patients who a symptomatic etiology had at least weekly seizures while on AEDs (RR = 8.7, 95% CI 2.0–37.0; $p < 0.001$). In conclusion, normal to subnormal IQ, non-symptomatic etiology, and low seizure frequencies both in the first year of AED treatment and prior to medication appear to be clinical predictors of cure in childhood-onset epilepsy (Sillanpää et al., 2014).

One limitation in the present long-term prospectively followed population study is that the subjects were not initially treated with the presently available new-generation AEDs. This anachronistic issue concerns any longitudinal study with follow-up of a cohort for many decades. It is to be noted, however, that there is so far no objective evidence of the superiority of the new AEDs to older ones in terms of therapeutic efficacy (Perucca, 2002; Snead and Donner, 2007; Gauffin et al., 2009; Schmidt, 2011; Abraham and Shaju, 2013; Löscher et al., 2013).

Predicting antiepileptic drug response (Sillanpää and Schmidt, 2011)

Numerous studies have been published on determinants of seizure outcome. Many of them are bivariate associations overlapping each other and disappearing on multivariate analyses. Consequently, multivariate analyses are preferable and more helpful in clinical practice.

Sustained seizure remission can be expected in over 90% of idiopathic epilepsies in children, who are neurologically normal; have infrequent seizures; and show early remission after starting treatment with AEDs. Even in the presence of symptomatic etiology of epilepsy with focal seizures and syndromes; high seizure frequency prior to or during treatment; seizure clustering; and poor or delayed response to first adequate drug therapy, up to 60% of children with treated epilepsy are able to enter long-term remission. However, remission can be expected in only 30% or less of those with catastrophic epilepsies of childhood (Sillanpää and Schmidt, 2011).

Chronic Comorbidity (Jalava et al., 1996)

Somatic comorbidity

Comorbidity is common in epilepsy. In our study, based on clinical examination (69%) and/or questionnaire (31%), in 220 (90%) of 245 original children with active epilepsy in 1961–1964 (Sillanpää, 1973), one or more concurrent somatic disorders whatsoever were found at 35 years of age (mean 35.6, median 35, range 28–45) (Jalava and Sillanpää, 1996). Comorbidity was significantly ($p < 0.05$) higher in subjects than general population sample controls (69%) (Table 3). Allergic manifestations were significantly ($p = 0.0211$) more common in subject with multiple AED treatment vs monotherapy. We also compared 99 random controls to 94 subjects with uncomplicated epilepsy, that is, epilepsy with no initial major neurological handicap. Psychological disorders were significantly associated with psychiatric disorders; connective tissue symptoms; and insomnia, all irrespective of whether on medication or not. Subjects with uncomplicated epilepsy did not use non-AEDs significantly more than their matched controls (Jalava and Sillanpää, 1996).

Psychiatric and psychosomatic comorbidity

Psychiatric and psychosomatic symptoms, both separately and combined, were diagnosed, not unexpectedly, significantly more often in subjects than controls ($p < 0.01$) (Table 4). Subjects suffered from insomnia significantly more frequently than controls ($p < 0.05$). Somatic comorbidity was significantly associated with both psychiatric ($p = 0.001$) and psychosomatic ($p < 0.01$) comorbidity (Jalava and Sillanpää, 1996).

In the Turku population-based study, at baseline, neurotic symptoms occurred in 57%, psychoneurotic in 37%, and psychotic in 5% (Sillanpää, unpublished data). The rates are in consonance with epidemiological studies from different countries in Europe, Scandinavia and the USA which have confirmed rates of psychiatric disorders in children with epilepsy typically ranging around 30 to 50%. In children with additional impairment, particularly those with intellectual disability, the rates are even higher, over 50% (Sillanpää et al., In press).

On 50-year follow-up of the subjects of the original Turku study (Sillanpää, 1973), 51 subjects at a mean age of 56.1 and 52 matched controls with a mean age of 56.0 were re-examined (Sillanpää et al., 2015). The most striking finding was high number of markers of cerebrovascular diseases among subject with uncomplicated epilepsy compared with controls (30% vs 12%) obtained from 3T magnetic resonance imaging and meaning a 2.5-fold (Risk ratio 2.5; 95% confidence interval 1.04–6.9) higher risk in the subjects. The importance of the finding needs further research that is underway. Determinants of school performance can be divided into epilepsy and associated neurologic deficits; treatments with AEDs; and psychosocial factors. Early age at onset of epilepsy in in correlation with neuropsychological disorders and with high seizure frequency, two most important predictors of underachievement in school (Sander and Sillanpää, 1997).

Table 3. Somatic comorbidity in 220 young adults with childhood-onset epilepsy at age 35 years

Disorder	Patients n = 220 %	Random controls n = 99 %
No	11	31
Yes	89	69
Neurological	53	2
- low intelligence	49	
- visual defect	9	
- other	7	
Respiratory	12	15
- Cardiovascular	18	21
- high blood pressure	11	13
- organic heart disease	4	2
- other vascular	3	9
Dermatological	17	20
- nonallergic dermatitis	13	5
- allergic dermatitis	6	15
Endocrinological	5	4
- diabetes mellitus	2	4
- thyroid	2	
- other	1	
Alimentary tract	30	27
- stomatological	24	
- alimentary obesity	8	11
- gastritis	5	
- other	6	16
Connective tissue	17	21
- arthralgia	12	14
- rheumatic diseases	1	
- other	6	7
Other somatic	15	12
- gynecological	5	1
- anemia	6	
- other	6	11

Table 4. Psychiatric and psychosomatic comorbidity in 220 young adults with childhood-onset epilepsy at age 35 years

Disorder	Patients, n = 220 %	Random controls, n = 99 %
No	89	93
Yes	**11**	**7**
- psychosis	2	7
- neurosis	9	
Psychosomatic symptoms	**46**	**42**
Functional neurological	**29**	**38**
- migraine	14	15
- non-migraine headache	16	25
Connective tissue	**27**	**12**
- neck pain	15	7
- back pain	18	6
Insomnia	**7**	**1**
Other	**23**	
- chronic fatigue	16	
- hyperhidrosis	9	
- burnout	4	
- restless legs	5	
Both psychiatric and psychosomatic symptoms	8	5

Social outcome (Sillanpää, 1983; Sillanpää et al., 2009)

Learning disability and school performance

In the Turku population-based study, 37% had an IQ less than 70. Of 204 subjects with childhood epilepsy living in the community or in institutions, 28% had an incomplete basic education or were educated in classes for children with learning disabilities (Sillanpää, 1983). Similar proportions have been presented in previous reports (Rodin et al., 1977; Seidenberg, 1989). Any learning disability was found in 76% of 242 subjects, of whom 28% were mentally normal, 10% near normal and 62% were mentally retarded (Sillanpää, 2004).

Quite obviously, some people with chronic epilepsy will deteriorate cognitively (Besag, 1988; Sander and Sillanpää, 1997). The association is shown with West and Lennox-Gastaut syndromes and status epilepticus (Besag, 1988). A very interesting question is, whether or not cognitive impairment will develop in the future for subjects who have childhood-onset epilepsy. Such an ongoing study of ours is underway.

Activities of daily living

In the review of Sillanpää and Cross (Sillanpää and Cross, 2009), based on the Turku population-based study of childhood epilepsy (Sillanpää, 1973) and the PISALA study (Sillanpää, 1983; Sillanpää and Upronen, 1984), even slight cognitive, learning and behavior disorders were all significantly more common and activities of daily living were more of a problem in subjects with complicated epilepsy compared with those who had uncomplicated epilepsy. A near normal IQ (71–85) already constituted a 1.4-fold (95% CI 1.1–1.8) risk for learning disorder vs normal IQ, mainly due to reading and writing difficulties. Behavioral hyperkinetic disorders occurred in 17% (in 25% of boys and 8% of girls, $p = 0.0090$) of the Turku study and in 16% of the PISALA study. As measured by the WHO classification (World Health Organization., 1980), epilepsy was a significant risk factor for behavioral disorders. While virtually all (98%) could clear daily activities, two thirds of subjects with uncomplicated epilepsy and four fifths of those with complicated epilepsy had significantly more problems vs controls in taking care of personal hygiene, making one's bed and similar daily activities. With regard to social integration, subjects with epilepsy had significantly more problems in getting and having mutual friends, and having overall leisure activities.

Impact of childhood epilepsy, as found in our studies, compares with the data in previous studies (Camfield et al., 2003; Baker et al., 2005). Learning and behavior are significantly affected by epilepsy (Camfield et al., 2003; Beghi and Cornaggia, 2006). Social isolation may be contributed to by several factors (Baker et al., 2005).

Quality of life

Our health-related quality of life study (Sillanpää et al., 2004) compared 91 subjects who had an childhood un-

complicated epilepsy with 91 matched controls using the 36-item SF-36 (Jenkinson et al., 1993) and the Impact of Epilepsy Scale developed by Jacoby et al. (Camfield et al., 1993; Jacoby et al., 1993). Of the subjects, 67% were in remission off medications, 14% in remission on medications and 19% were not in remission. Subjects on medication, whether in remission or not had worse scores on both general measures of QOL and epilepsy specific measures than either controls or subjects in remission off medications. They also had significantly ($p < 0.001$) higher rates of unemployment and lower socioeconomic status. These differences did not depend on differences in education or seizure frequency. Subjects in remission off medication had rates of employment and socioeconomic status similar to controls. All subjects regardless of remission status had significantly ($p < 0.001$) lower rates of marriage and of having children than controls. Our unique study investigated long-term (over 30 years) consequences of epilepsy and its impact on the quality of life, not only in subjects with active epilepsy as usually reported (Jacoby et al., 1993; Sillanpää et al., 1998; Suurmeijer et al., 2001) but also among those in remission. There major findings include a substantial impact of childhood-onset epilepsy even in those who are seizure free off medication for many years. The most affected are those not in remission or in remission but still on medication; and little difference in this population between those not in remission and those in remission but still on medication. Thus, even in patients with uncomplicated epilepsy, seizures per se may not be the dominant reason why patients with epilepsy have difficulty finding employment.

Employment

In our 1998 study (Sillanpää et al., 1998), we showed that, compared with the unemployment rate of 8% in controls on 35 years of follow-up, the same rate was more than 3-fold (relative risk [RR] 3.76, 95% confidence interval [CI] 1.82–7.76) in all subjects with uncomplicated epilepsy; more than 2-fold (2.36, 1.04–5.38) in among subjects in remission off medication; more 2-fold (2.44, 1.05–5.70) in subjects with incident cases off medication; and virtually equal to controls in subjects with idiopathic epilepsy in remission off medication.

Surviving subjects with incident cases who had been followed for longer than 10 years ($n = 141$) were compared with a matched control group with regard to the employment status at the mean age of 23 (range 18–35) years and 48 (range 43–59) years (Sillanpää and Schmidt, 2010). At age 18, 71% of 119 subjects living in the community were employed. Best employed were those who had normal intelligence, vocational education, and more than six years of age at onset of epilepsy. At age 48, 59% of 76 subjects living in the community were employed in comparison to 78% of 81 controls ($p = 0.01$). Predictors of employment were normal intelligence; having offspring; uninterrupted ≥ 5-year terminal remission from age 23 to age 48; and no history of status epilepticus.

Our results of a lower employment rate in subjects vs controls are consistent with previous data (Ounsted et al., 1987; Callaghan et al., 1992). While remission and absence of history of status epilepticus were significant predictors in our study, medical features of childhood epilepsy such as seizure remission are reportedly of less relevance for the social outcome in adulthood (Camfield et al., 1993; Kokkonen et al., 1997; Camfield and Camfield, 2007). Many earlier reports also cover prevalent cases and complicated epilepsy that makes comparisons to our present study difficult. Consistently with previous reports our study showed that 60% of adults with childhood-onset epilepsy will be employed (Sillanpää, 1977; Camfield and Camfield, 2013).

Driver's license

While no more than 11% of controls were not owners of a driver's license, the risk for not being granted it was 3.5-fold (3.55, 1.93–6.51) for patients with childhood-onset uncomplicated epilepsy (Sillanpää et al., 1998). Later (Sillanpää and Shinnar, 2005), at 45-year follow-up of 81 subjects with childhood-onset uncomplicated epilepsy had entered ≥ 2-year terminal remission and were eligible to a noncommercial driver's license according to the contemporary legislation. Of them, 64% vs 90% of matched controls had been licensed ($p < 0.0001$). On multivariate analysis, significant factors for not being licensed were female gender (RR 2.4, 95% CI 1–5.5); non-idiopathic etiology (2.0, 1.1–3.8); and presence of learning difficulties. Relapse was experienced by 37% of 81 theoretically eligible, but only 25% of 52 who actually obtained the license ($p = 0.003$). Shortening of the requirement of 2-year terminal remission to one year would not significantly have altered the relapse rate. Learning disabilities occurred in 21% of the subjects who were normal by intelligence, could read and write and had completed at least elementary school education. Subjects with a driver's license were more likely to be employed than those without the license (85% vs 44%; RR 1.9, 1.2–2.9).

Reproductive activity

Our 35-year follow-up study showed that living in marriage or other constant partnership is significantly—about three-fold—less common among adults with childhood-onset uncomplicated epilepsy irrespective of current seizure status, medication status or etiology of epilepsy (Sillanpää et al., 1998). Continued AED treatment significantly increased the risk of low reproduction (Jalava and Sillanpää, 1997). Their number of offspring, if any, is also significantly lower than in controls. The lower reproductive activity of our study is consistent with reported data (Wallace et al., 1998; Artama et al., 2004; Artama et al., 2006). In a nationwide population-based cohort study from Finland, Artama et al. (Artama et al., 2004; Artama et al., 2006) showed a lower than expected fertility and its association with AEDs and then confirmed our results in a of about 14 000 subjects and almost 30 000 controls (Jalava and Sillanpää, 1997).

CONCLUSION

There was a traditional conception that epilepsy, and childhood-onset epilepsy in particular, is a lifelong disorder with poor prognosis. Our long-term, prospective population study of childhood epilepsy, started as a historically prospective cohort and then prospectively followed for a total of five decades, indisputably shows that the prognosis is excellent for medical and social outcome. The successful outcome is confirmed by several longitudinal studies from recent decades. Our life-cycle study is continued and targets to answer the question whether or not childhood-onset epilepsy is a risk factor for premature and/or increased incidence of mental impairment and dementia.

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CONFLICT OF INTEREST DISCLOSURE

Nothing to declare

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