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Long-term changes in the incidence of childhood epilepsy. A population study from Finland

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ABSTRACT

Background: The incidence of childhood epilepsy has changed during the past decades, but it is unclear whether it increased or decreased.
Methods: Changes in drug-treated childhood epilepsy between 1968 and 2012 were evaluated using the Finnish nationwide register of all children, aged ≤15 years, on antiepileptic drugs (AEDs) prescribed for the treatment of epilepsy. The first registered entitlement to full-refundable AEDs was used as a proxy for newly diagnosed epilepsy. Incidence densities were calculated as ratios of annual new cases per 100,000 person-years in each calendar year during 1968 to 2012.
Results: The annual incidence density of newly treated childhood epilepsy increased from 35 in the 1960s to 87 per 100,000 person-years in the 1990s and decreased thereafter to 61 per 100,000 person-years. Since 1996, the incidence density decreased 1–2% per year in children aged <1, 1–5, or 6–10 years (all 95% confidence intervals within 0.3%–3%), while no substantial change was seen in older children.
Conclusion: The incidence of drug-treated childhood epilepsy from the late 1960s to the early 1990s distinctly increased. The reasons for the increase are not fully understood but may include increasing ascertainment through improved diagnosis and a wider acceptance of AED treatment. Since the 1990s, a slight decline can be seen, probably reflecting the recent improvement in child health and safety.

1. Introduction

In the literature, the reported incidences and secular changes of the incidences in childhood epilepsy are influenced by various study designs, and the results controversially suggest a range from declining to increasing incidence. Even the few long-term studies show various methodological limitations and different definitions of epilepsy, study populations of small size and different age ranges, inconsistent enrollment criteria, or short observation periods [1–4]. Longitudinal population studies from western countries reported decreasing annual incidences ranging between 0.5 and 6% [4–6]. Conflicting with those data, the Minnesota study from the same decades showed an increase in the mean annual incidence, from 39 to 54 per 100,000 between the periods 1965–1974 and 1975–1984, respectively [5]. A Danish register study showed a plateau or a slight decline in 1977–1990 followed by a steep increase from 1990 to 1995 and then again a decrease from 1995 to 2002 [2].

The incidence rates reported in the few previous population-based incidence studies of childhood epilepsy in the 1960s are low, ranging from 35 to 41 per 100,000 person-years [5,7,8]. Recent cross-sectional studies from the 2000s show considerably higher incidences, ranging from 50 to 86 per 100,000 within the same age cohort [9–11].

Controversies in the literature between decreasing incidences in longitudinal studies and increasing incidences in cross-sectional studies prompted us to perform a nationwide long-term study on secular changes and their linearity in the incidence of childhood epilepsy. Based on cross-sectional studies showing a rising incidence from the 1960s to the 2000s and other studies suggesting a switch from an increase to a decrease of the incidence, we hypothesized that the incidence had risen from the 1960s but that the extent of the change varied considerably during the last decades.

Abbreviations: AEDs, antiepileptic drugs; CI, confidence interval; ICDs, International Classifications of Diseases; IDR, incidence density ratio; SII, the Social Insurance Institution.

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2. Study cohort and methods

2.1. Data source

The target population consisted of Finnish children aged <16 years during 1968–2012 (N = 952,010 in 2012). For data collection, three national registers were used including the Population Register, the Special Reimbursement Register, and the Drug Purchase Register.

The nationwide Population Register, maintained by Population Register Centre, covers the permanently resident population and includes data on sex, live births, deaths, immigration, and emigration. The Finnish population is very stable, with less than 6% of children born abroad in 2012.

The Special Reimbursement Register, effective since 1964 and maintained by the Social Insurance Institution (SII), lists subjects who have been granted 100% refund for drug expenses by SII. A statement of a clinical diagnosis of epilepsy given by a neurologist, child neurologist, or pediatrician based on contemporary International Classifications of Diseases (ICDs) is required in an application for the 100% reimbursement of AEDs. The procedure is similar for all noninstitutionalized patients (no more than 0.01% of 0–17-year-olds are institutionalized [12]) who purchase their prescribed medication from pharmacists, regardless of place of treatment. The SII refunds begin at the first documentation of the diagnosis of epilepsy. Thus, the date of first entitled AED reimbursement can be used as the date of the diagnosis of new-onset epilepsy. The Special Reimbursement Register, its structure, data collection principles, and the coverage of all Finnish citizens remained unchanged throughout the study period. The method of data collection is previously described in detail [6]. For the present study, the four first years were omitted, and the data collection was started from 1968 to minimize various enrollment biases.

The Drug Purchase Register, maintained by SII since 1994, includes all purchases of prescribed drugs refunded by SII. The SII routinely refunds 40%–50% of prescribed drugs for all Finnish residents [13]. Thus, the register includes AED purchases by all Finnish residents, with or without entitled 100% special reimbursement. The drug reimbursement regulations restrict the refunded drug supply period to a maximum of three months per purchase. Four or more consecutive AED purchases were considered to represent continuous AED use and a subsequent diagnosis of epilepsy.

The national administrative registers are well accepted by the Finnish population [14] and considered valid in Finland and other Scandinavian countries [14–17].

The study cohort consisted of all 29,567 children (15,526 [53%] of them boys) who fulfilled the inclusion criteria of being a Finnish resident; aged less than 16 years; with specialist-made diagnosis of epilepsy requiring drug treatment; and entitled for the first time to a 100% refund of AEDs for epilepsy during 1968 to 2012. The exclusion criteria included age of 16 years or more at onset of epilepsy, neonatal seizures only, temporary residence in Finland, institutionalization, or AEDs prescribed solely for indications other than epilepsy. The inclusion and exclusion criteria remained consistent throughout the study period.

The validity of the diagnosis of epilepsy, based on Special Reimbursement Register data, was ascertained using the Drug Purchase Register information of actual AED purchases (ATC code N03) during 1996–2012. First, all 11,142 study children who had 0–3 AED purchases were classified as cases of potential misdiagnosis and removed from sensitivity analyses. Second, a control group of 22,172 children with no 100% reimbursement for epilepsy was selected by the Population Register Centre (2:1 matching with the 11,142 study subjects by age, sex, and place of residence). Control children with ≥4 consecutive AED purchases were considered as potential undetected cases with childhood-onset epilepsy, unless they were granted reimbursement of AEDs for other indications.

2.2. Statistical analysis

Annual incidence densities for childhood epilepsy were calculated by dividing the number of newly-diagnosed cases by the number of person-years at risk [18]. The annual person-years within each dynamic risk cohort were calculated separately for boys and girls by averaging the number of children within each one-year age level at December 31st of the target year and the preceding year. Neonatal deaths were excluded from the risk population, as well as children with epilepsy after the diagnosis.

Mean annual incidence densities of childhood-onset epilepsy per 100,000 person-years in 5-year calendar time intervals are given for all children and separately within four age groups (<1 year, 1–5 years, 6–10 years, and 11–15 years). Poisson regression models were used to calculate the estimates with 95% confidence intervals (95% CI) for the incidence densities and incidence density ratios (IDRs). The deviance and residual plots were used for model diagnostics. Because of the nonlinearity of the annual incidence densities, the five-year intervals of the total 45-year observation period were used as a categorical predictor. Remaining overdispersion was controlled by using Generalized Estimating Equation estimation, clustering the data by sex, one-year age group and one-year calendar time. In the analyses of the latest 17-year period 1996–2012 with all diagnoses based on ICD-10, the slopes of temporal changes in the incidence densities were estimated from a Poisson regression model with year at diagnosis as a continuous predictor. The slopes were further evaluated with a sensitivity analysis, where only children with at least four AED purchases after the entitled reimbursement were accepted as newly diagnosed cases. As predictors, all models included age group at onset of epilepsy, sex, year at diagnosis, and their significant pairwise interactions. Confidence intervals in multiple comparisons were Bonferroni-corrected. The quality of the reimbursement data during 1996–2012, as a source of epilepsy diagnosis, was assessed by calculating the sensitivity, specificity, and positive and negative predictive values among the patients and controls with or without ≥4 AED purchases. Statistical analyses were done using SAS V9.4 software (SAS Institute, Cary, NC, USA).

2.3. Ethics

In accordance with Finnish legislation (Personal Data Act 523/1999), no approval by an ethical committee or informed consent by study individuals is required for studies based on encrypted register data. The data permissions were admitted by SII (Diary no. 26/522/2013).

3. Results

The nationwide incidence densities of childhood epilepsy on AED treatment from 1968 to 2012 in Finland increased during the first half and decreased during the second half of the observation period in all age groups (Fig. 1, Table 1). Adjusted for age and sex, the incidence was almost three-fold in the last vs. the first five-year period (Supplementary Table 1).

During the 45-year observation period from 1968 to 2012, the overall mean incidence density of epilepsy was 7% higher among boys than girls (IDR 1.07 [95% CI 1.03–1.10]) (Supplementary Table 1). The IDRs between the sexes remained similar through the follow-up ($p = 0.64$ for sex × time interaction, excluded from the model), but their direction and magnitude varied within the age groups ($p < 0.001$ for sex × age group) (Fig. 2; Supplementary Table 1).

Incidence densities of drug-treated epilepsy in infants were lowest of all age groups in the 1960s to the 1970s, comprising 1–3% of all childhood epilepsies. During the 1980s, the incidence densities of the infants equalled and exceeded those of the older children. The increase continued up to the mid-1990s and turned thereafter to a slow decrease yet remaining substantially above the incidences of the older children. During the 1990s to the 2010s, over 10% of all children with childhood