**EPILEPSY**

# Trends in new-onset epilepsy — the importance of comorbidities

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**A recent longitudinal study indicates that the incidence of new-onset epilepsy has remained stable in children and young adults but has increased in elderly individuals over the past 40 years. Rather than signalling a failure to prevent epilepsy, however, this phenomenon might be attributable to the comorbidities of epilepsy.**

Refers to Sillanpää, M., Gissler, M. & Schmidt, D. Efforts in epilepsy prevention in the last 40 years: lessons from a large nationwide study. *JAMA Neurol.*

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Current medical therapies for epilepsy are antiseizure rather than antiepilepsy medications; that is, they address the symptoms rather than the epileptogenic process. Numerous trials of treatments aiming to interrupt epileptogenesis — that is, the pathological process of epilepsy development — have been carried out among individuals with conditions such as traumatic brain injury, subarachnoid haemorrhage, stroke and neoplasms[1]. The limited success of these trials was mostly in the prevention of acute seizures, with no impact on the later development of epilepsy. The failure to demonstrate an effect on epileptogenesis was potentially attributable to failures in trial design, including timing and duration of the intervention and a lack of effective biomarkers of epileptogenesis[1,2]. Another important consideration is that most of the trialled agents were developed as antiseizure medications, and the mechanisms of epileptogenesis may be quite different from those underlying the generation of an individual epileptic seizure[2].

An indirect method to determine success in interrupting epileptogenesis, beyond animal models and clinical trials, is to examine temporal trends in the incidence of new-onset epilepsy. A number of such studies have been conducted, mostly reporting on regional populations, for example, in South East England, the Midwestern United States, and Northern Sweden[3]. Major efforts in Scandinavia have succeeded in longitudinally monitoring epilepsy incidence at the national level[4,5]. These studies examined changes in incidence over periods spanning from one to several decades, largely between the 1970s and early 2000s, and relied on various methods of study design and case ascertainment. The overall temporal trend, which could still be subject to systematic bias, was for a stable or mildly decreasing incidence of new-onset epilepsy over time, with some studies reporting a decrease in incidence among children that was balanced to varying degrees by an increase among older adults[3–5].

In an elegant study recently published in *JAMA Neurology*, Sillanpää and collaborators[6] reported on longitudinal patterns in the incidence of new-onset epilepsy, based on an administrative, nationwide Finnish cohort. The study used the Finnish Hospital Discharge Register, which monitored 5.04 million individuals between 1973 and 2013 — a remarkable 40-year follow-up period. The investigators identified 100,792 individuals with a first hospital admission for epilepsy, and reported an overall incidence of 50 cases per 100,000 person–years. The incidence was stable over the 40-year follow-up period among children and young adults, but increased fivefold among individuals aged ≥65 years. In addition, the incidence of generalized epilepsy was stable over time, whereas the incidence of focal epilepsy increased. The authors conclude that "no progress has been made in preventing new-onset epilepsy"[6].

Though admirable, this study has limitations. As the investigators readily concede, case ascertainment accuracy was not validated and, therefore, the degree of misidentification of

individuals with new-onset epilepsy, as well as focal versus generalized epilepsy, remains unknown. The investigators describe the Finnish practice of early referral to hospital for evaluation after a first seizure, and they acknowledge that the absence of primary care data could have as much as halved the recorded number of new-onset epilepsies. Moreover, at least some of the temporal trends observed might have been due to changes in referral patterns rather than changes in incidence at the general population level. The denominator of 5.04 million individuals used in the incidence estimation does not reflect the general Finnish population but, rather, those admitted to hospital during the study period, further emphasizing the potential difficulty in applying these findings to the general population.

The lack of inferential statistics (for example tests of significance with *P*-values, or 95% confidence intervals) further complicates our ability to understand which — if any — of the observed changes are important. Such statistics might also have helped us to understand the relevance of what may be U-shaped trend lines observed in a number of the subgroup analyses. It would have been interesting to control for age, changes in the distribution of which, as the investigators demonstrate, have important effects on the incidence of epilepsy.

We fully agree with Sillanpää and collaborators that the medical community continues to struggle to decrease the risk of new-onset epilepsy. As mentioned by the investigators, however, the increase in incidence among older individuals should not be interpreted simply as the result of our failure to prevent epileptogenesis — this phenomenon could also reflect both our success and failure to manage the comorbidities of epilepsy. The comorbidities of epilepsy encompass conditions that occur as a result of epilepsy and those that may act as the primary cause. The prevalence of several comorbidities has increased considerably over the past few decades[7], in particular, cerebrovascular and neurodegenerative disease, which are the most important risk

factors for epilepsy in elderly individuals[8]. The reported increase in focal epilepsy might reflect both a change in the prevalence of these comorbidities and increased survival of individuals with severe disease, who are invariably at higher risk of subsequently developing epilepsy. The decreased incidence in children could be a sign of our success in managing prenatal, perinatal and early childhood risk factors for epilepsy[9].

Important questions remain regarding temporal trends in epilepsy. Future efforts should be aimed at developing estimates that are representative of the general population, while minimizing the risk of misidentification of new-onset epilepsy. Ideally, in addition to examining the number of new cases, we should understand their character, including aetiology and severity. Care should be taken not to allow recent changes to the definition of epilepsy[10] to create artificial changes in the incidence of new cases. It is also important to remember that epilepsy is a heterogenic symptom complex rather than a disease on its own right, and the failure to take this fact into account contributes substantially to the misreading of epidemiological data. Findings such as those presented by Sillanpää and collaborators should not only inspire us to explore better ways to prevent epileptogenesis, but should also encourage us to double our efforts to prevent the comorbidities that are ultimately responsible for the development of many cases of epilepsy.

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