CURRENT LITERATURE

EPIDEMIOLOGY IN EPILEPSY

Newly Diagnosed Unprovoked Epileptic Seizures: Presentation at Diagnosis in CAROLE Study.

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PURPOSE: We describe first unprovoked seizures and newly diagnosed epilepsies at initial presentation, with a special emphasis on epilepsy syndromes, in a large cohort recruited in the mid-1990s in France.

METHODS: The French Foundation for Research on Epilepsy set up a network to conduct a prospective study of patients with newly diagnosed unprovoked seizures. Information was provided by 243 child or adult neurologists. Four neurologists classified each case according to the International League Against Epilepsy (ILAE) criteria. First-seizure patients and patients with previously undiagnosed seizures were compared.

RESULTS: Between May 1, 1995, and June 30, 1996, 1,942 patients aged from 1 month to 95 years were identified: 926 (47.7%) with a single seizure and 1,016 (52.3%) with newly diagnosed epilepsy. All but 17 patients had EEGs. In the first-seizure and newly-diagnosed-epilepsy groups, neuroimaging studies were performed in 78.2 and 68.3% of patients, and medication prescribed in 54.1 and 89.6%, respectively. There were significant differences between the two groups with respect to age at onset and diagnosis, sex, etiology, several specific syndromes, as well as the type and presentation of initial seizure. In patients for whom the first seizure was convulsive, only sex, multiple seizures in a day or status epilepticus, and cryptogenic localization-related syndrome differed between the two groups.

CONCLUSIONS: Approximately half of patients who first came to attention for an unprovoked seizure already met epidemiologic criteria for epilepsy. There were significant differences between the types of patients with a first seizure and those with newly diagnosed epilepsy. One or several seizures at diagnosis did not influence the diagnostic assessment of the patients but had a strong influence on the initiation of treatment.

COMMENTARY

Ideally, identification of an epilepsy syndrome should help direct evaluation and treatment as well as provide some information about likely prognosis. The usefulness of the ILAE classification of the epilepsies (1) depends, in part, on whether it can be applied early in the course of the disorder in typical community practice.

There are many cross-sectional studies from tertiary referral centers that have examined the distribution of syndromes in what are often poorly characterized samples of patients. There are now a handful of studies that have prospectively identified patients at initial presentation, either with a first seizure or with newly diagnosed epilepsy (2+ seizures) (2–5) on a population or community basis. The recent study by Jallon et al. represents the largest and most comprehensive of these efforts. The investigators were able to assign specific syndromes in 52% of first seizure patients and in 82% of epilepsy patients. Indispensable to the successful classification of such a high proportion of cases is the near universal access to health care in France and the relatively routine use of neurologists for diagnosing, evaluating and treating epilepsy: 99% of patients in the cohort had an EEG and ~80% had neuroimaging. Such a result might not be attainable in countries where healthcare is not as widely available or where specialists do not routinely make the initial diagnosis.

Although someone with a single seizure technically does not (yet) meet the criteria for "epilepsy" [2 or more seizures (6)], the authors correctly point out that this does not preclude assigning an individual to a specific syndrome if the electrographic and other criteria are met. This is key to fully understanding the natural progression of specific syndromes from the very outset. Because they have included both first seizures and epilepsy, they are in a unique position to study this issue and to provide a bridge between the first seizure and epilepsy literature. This topic is further explored in a separate article from this group (7).

The continued follow-up of this superbly assembled and elegantly described cohort will teach us much regarding the prognostic significance of syndromes as identified at onset in the population as well as about the stability of the classification system over time.

by Anne T. Berg, Ph.D.

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Mortality Risk in Children with Epilepsy: The Dutch Study of Epilepsy in Childhood

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Objective. Long-term follow-up studies of patients with epilepsy have revealed an increased mortality risk compared with the general population. Mortality of children who have epilepsy in modern times is as yet unknown. Therefore, the objective of this study was to determine mortality of children who have epilepsy in comparison with the general population.

Methods. Between August 1988 and August 1992, 472 children, aged 1 month to 16 years, who presented in one of the participating hospitals with two or more newly diagnosed unprovoked seizures or at least one status epilepticus were enrolled in the study. All children were followed for five years or until death. The number of deaths observed during follow up was compared with the expected number of deaths in the same age group in the general population in the Netherlands.

Results. Nine children died during follow up, amounting to a mortality rate of 3.8/1000 person-years, which is sevenfold higher than expected (95% confidence interval = 2.4–11.5). No deaths were observed among the 328 children who had epilepsy of nonsymptomatic cause. All deceased children had epilepsy that was caused by a static or progressive neurologic disorder (mortality risk = 22.9; 95% confidence interval = 7.9–37.9). None of them died from sudden unexpected and unexplained death of epilepsy.

Conclusions. In our cohort, we found no indication that children who have nonsymptomatic epilepsy have an increased mortality risk compared with the general population, whereas children who have symptomatic epilepsy have a 20-fold increased mortality risk. These data provide guidance for counseling parents of children who have epilepsy.

COMMENTARY

Mortality is increased over population-based levels in people who have epilepsy. The relative increase in risk appears to be greatest in young people (1). The risk and risk factors of mortality in individuals with epilepsy have been the focus of tremendous research efforts recently. It is clear that symptomatic etiology and poor seizure control are consistently two of the strongest predictors of mortality. In addition, the risk appears to be highest relatively early in the course of the disorder and to diminish over time. The recent article by Callenbach et al. from the well-documented Dutch Study of Epilepsy in Childhood is a welcome addition to the current literature.

In their cohort of 472 children, only nine deaths occurred during the first five years of follow up. While this is a small proportion of the cohort, it in fact represents a seven-fold increase in mortality relative to the population. Three of the deaths were in association with progressive disorders and none occurred in children with nonsymptomatic epilepsy. The careful analysis and presentation of mortality by etiology and syndromic grouping further helps to explain the increased risk of mortality in childhood onset epilepsy.

The results of the Dutch study are highly comparable to an entirely independent population-based study from Nova Scotia (2) which found a very low overall risk of mortality mostly confined to symptomatic epilepsy. Both studies also demonstrate that the risk of sudden unexplained death in epilepsy (SUDEP) in pediatric epilepsy is very low. There were no

cases in the Dutch study and only one in the study from Nova Scotia. Another recent study from the Province of Ontario estimated the incidence rate for SUDEP in children with epilepsy to be 2/10,000 person-years (3).

Well-done carefully reported epidemiological studies such these as have greatly added to our understanding of this rare but serious outcome of epilepsy.

by Ann T. Berg, Ph.D.

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Early Development of Intractable Epilepsy in Children: A Prospective Study.

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BACKGROUND: Little is known about early prediction of intractable epilepsy (IE) in children. Such information could help guide the early use of new therapies in selected patients. METHODS: Children with newly diagnosed epilepsy (n = 613) were prospectively identified from child neurology practices in Connecticut (1993–1997) and followed up for the occurrence of IE (failure of >2 drugs, >1 seizure/month, over 18 months). Etiology and epilepsy syndromes were classified per International League Against Epilepsy (ILAE) guidelines.
RESULTS: The median follow up is 4.8 years, and 599 (97.7%) have been followed for more than 18 months. Sixty children (10.0%) have met the criteria for IE, including 34.6% with cryptogenic/symptomatic generalized, 2.7% with idiopathic, 10.7% with other localization-related, and 8.2% with unclassified epilepsy ($p < 0.0001$). After multivariable adjustment for epilepsy syndrome, initial seizure frequency ($p < 0.0001$), focal EEG slowing ($p = 0.02$), and acute symptomatic or neonatal status epilepticus ($p = 0.001$) were associated with an increased risk of IE, and age at onset between 5 and 9 years was associated with a lowered risk ($p = 0.03$). The absolute number of seizures and unprovoked or febrile status epilepticus were not associated substantially with IE.
CONCLUSIONS: Approximately 10% of children meet criteria for IE early in the course of their epilepsy. Cryptogenic/symptomatic generalized syndromes carry the highest risk and idiopathic syndromes the lowest. Half of IE occurs in children with nonidiopathic localization-related syndromes. Initial seizure frequency is highly predictive of IE. By contrast, absolute number of seizures and unprovoked or febrile status epilepticus are not.

COMMENTARY

This important study demonstrates that a significant subgroup—perhaps 10%—of children with newly diagnosed epilepsy will be found to have intractable seizures. The authors found that prognosis often could be determined relatively soon after initial diagnosis.

Patients were to have had at least one unprovoked seizure between the first month and 15th year of life, to have had at least two unprovoked seizures on separate days, and to be newly diagnosed by a study physician. Intractability was defined as lack of seizure control despite use of maximized doses of two first-line anticonvulsants, and the presence of more than one seizure per month for an 18 month period.

Patients with cryptogenic/symptomatic epilepsy showed the highest risk for long term intractability. The study also found that initial seizure frequency, but not overall seizure frequency, was highly predictive of long-term outcome. Importantly, neither unprovoked nor febrile status epilepticus predicted intractability.

As the authors note, these findings suggest that there is a definable subgroup of patients who will have intractable epilepsy. The patients in this subgroup can be identified early in the course of their disease. They are not likely to respond to conservative treatments and should be considered early for more aggressive treatments, such as surgery.

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