When Epilepsy Grows Up…

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Neurocognition in Childhood Epilepsy: Impact on Mortality and Complete Seizure Remission 50 Years Later

Sillanpää M, Saarinen MM, Karrasch M, Schmidt D, Hermann BP. *Epilepsia*. 2019;60(1):131-138. doi:10.1111/epi.14606. Epub 2018 Nov 22.

Objective: To study associations of the severity of impairment in childhood neurocognition (NC) with long-term mortality and complete seizure remission. Methods: A population-based cohort of 245 subjects with childhood-onset epilepsy was followed up for 50 years (median = 45, range = 2-50). Childhood NC before age 18 years was assessed as a combination of formal intelligence quotient scores and functional criteria (school achievement, working history, and psychoneurological development). Impaired NC was categorized with respect to definitions of intellectual functioning in *International Classification of Diseases, Tenth Revision* (R41.83, F70-F73). The outcome variables, defined as all-cause mortality and 10-year terminal remission with the 5 past years off medication (10YTR), were analyzed with Cox regression models. Results: Of the 245 subjects, 119 (49%) had normal childhood NC, whereas 126 (51%) had various degrees of neurocognitive impairment. During the 50-year observation period, 71 (29%) of the subjects died, 13% of those with normal and 44% of those with impaired NC. The hazard of death increased gradually in line with more impaired cognition, reaching significance in moderate, severe, and profound impairment versus normal NC (hazard ratio [Bonferroni corrected 95% confidence interval] = 3.3 [1.2-9.2], 4.2 [1.2-14.2], and 5.5 [2.4-12.3], respectively). The chance for 10YTR was highest among subjects with normal NC (61%), whereas none of those with profound impairment reached 10YTR. In the intermediate categories, the chance was, however, not directly related to the increasing severity of impairment. Significance: The severity of neurocognitive impairment during childhood shows a parallel increase in the risk of death. In comparison with normal NC, subjects with lower childhood NC are less likely to enter seizure remission. However, normal NC does not guarantee complete remission or prevent premature death in some individuals with childhood-onset epilepsy.

Commentary

Clinicians working in pediatric epilepsy are often shielded from the later outcomes of this disease. Among our treatment goals, preserving developmental outcomes ranks high. We aim for optimal seizure control and support families in identifying early developmental delays in our young patients. In the middle childhood years, school services and social adjustment are discussed in clinic and referrals are made to assess and intervene. Transition to adulthood sneaks up on us at times. Considerations for guardianship are addressed for some, while others require accommodations at the college level. Access to mental health services in later adolescence and young adulthood factors into the treatment and transition planning for many of our patients. We are there to guide through the ups and downs of living with epilepsy. And then, often in the early 20s, our patients transition out of our care. At this stage of development, hopeful anticipation of a future with a career and independent living are on the horizon for many, while others need vocational training or continued support for daily living needs. What happens next? Sometimes we get updates, often we don't.

Sillanpaa et al provide a window into long-term outcomes with 50-year follow-up for 245 patients from Finland with childhood-onset epilepsy initially presenting for diagnosis and treatment between the years of 1961 and 1964. Patients were categorized based on level of neurocognition (NC) in childhood (based on test scores when available as well as need for services in the school setting), and long-term survival and seizure freedom were compared across groups. The choice to use cognitive development as a predictor of health-related variables rather than an outcome is novel and interesting. Their results document increasing levels of neurocognitive impairment associated with gradually increasing risk of death upon follow-up. Just under half of this in this large community sample of patients had normal cognition in childhood, and upon follow-up, 13% had died. The primary cause of death was sudden unexpected death in epilepsy (SUDEP). Incidence of

death upon follow-up were as follows for patients with neurocognitive impairment in childhood: borderline impairment (17%), mild impairment (29%), moderate impairment (41%), severe impairment (60%), and profound impairment (58%). Respiratory infection and cardiovascular disease were leading causes of death among patients with profound and severe neurocognitive impairment. Ten-year seizure remission was highest for patients with normal NC (61%) in contrast to none of the patients with profound impairment and up to a quarter of patients with intermediate of levels of neurocognitive impairment. Not surprisingly, earlier age of onset was associated with higher levels of neurocognitive impairment.

The authors acknowledge that since the 1960s when the patients in this sample were initially treated for epilepsy, substantial improvements in medical and surgical treatment have occurred. Advances in neuroimaging and neurosurgical intervention in pediatric epilepsy have revolutionized seizure control and contributed to the preservation of cognitive development. Of course, we would like to think that surgery makes a difference in seizure remission and survival over the long term.

There is paucity of truly long-term pediatric epilepsy surgery follow-up studies available to review. However, one such study offers parallel findings to those reported by Sillanpaa et al. Ten-year follow-up from epilepsy surgery for 85 Japanese patients[1] documented very good survival rate with only one death. Seizure remission in this sample was also highest for patients with normal cognitive development (81%) relative to patients with low cognitive development (47.4%). Most patients with full seizure remission underwent single lobe resection (80.3%). Seizure frequency at the time of surgery and age of seizure onset were found to be strong predictors of seizure remission following surgery. Social adjustment outcomes were best for patients with seizure freedom, in general.

How are clinicians in pediatric epilepsy to advise our young patients and their families? Early age of onset continues to be strongly associated with cognitive development and reduced likelihood of seizure remission. This association is likely related to the underlying causes of epilepsy with more systemic and globally impactful disease with onset in the early years of life. Patients with later onset and relatively preserved cognitive development are more likely to enjoy seizure remission, even without surgery. However, they may still be vulnerable to SUDEP, which is an important risk to factor into pediatric epilepsy surgery and counseling decision-making. Although patients with cognitive impairment and early onset of seizures may be less likely to experience complete seizure freedom from epilepsy surgery, they may still benefit from a reduction in seizure frequency, seizure severity, and antiepileptic drug usage. This may improve quality of life and is therefore a worthwhile option to consider.

The value of long-term follow-up research cannot be understated. Clinicians are asked to support the long-term development of their patients and predict outcomes. We need to understand hazards that lay ahead in later stages of development, long after our provision of care will come to an end.

By Katrina Boyer

Reference

1. Hosoyama H, Matsuda K, Mihara T, et al. Long-term outcomes of epilepsy surgery in 85 pediatric patients followed up for over 10 years: a retrospective survey. *J Neurosurg Pediatr*. 2017;19(5): 606-615.