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Early onset epilepsy is associated with increased mortality: a population-based study

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SUMMARY

We examined mortality in early onset (age <12 months) epilepsy in a population-based group of children. Children with early onset epilepsy were significantly more likely to die (case fatality, CF 8/60 versus 8/407, $p < 0.001$; mortality rate, MR 14.5/1000 versus 2/1000 person years; standardized mortality ratio, SMR 22.25 versus 5.67). Mortality was greater in children with malignant neonatal (age <1 month) epilepsy (CF 4/12 versus 12/450, $p < 0.001$; MR 54/1000 person years versus 2.7/1000 person year; SMR 46.55 versus 7.22). Given that only 1/8 early onset epilepsy deaths was seizure-related, mortality appears to be more affected by underlying etiology.

Keywords

Pediatric epilepsy; mortality; early onset epilepsy; neonatal onset epilepsy

1.1 INTRODUCTION

Epilepsy that begins within the first year of life often portends increased morbidity. Although some epilepsy syndromes affecting children less than one of year of age can have favorable prognoses, others result in medically refractory seizures, developmental delay/intellectual disability, and other neurologic handicaps (Nunes, et al. 2008, Yamamoto, et al. 2011, van der Heide, et al. 2012). While the increased morbidity of early onset epilepsy is known, its mortality has not been robustly explored. We sought to determine the frequency of and risk factors for mortality in early onset epilepsy in a population-based group of children.

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2.1 METHODS

2.1.1 Case Identification

We identified all children aged birth through 17 years who were diagnosed with new onset epilepsy while residing in Olmsted County, MN between 1980 and 2009, using the complete diagnostic indexes of the Rochester Epidemiology Project (Melton 1996). All seizure and convulsion diagnosis codes were utilized to select charts for review.

Definitions—We defined epilepsy as a predisposition to unprovoked seizures. Most children had ≥ 2 unprovoked seizures. However, children with a single unprovoked seizure were included if they had evidence of an enduring alteration of the brain that increased the likelihood of further seizures and started antiepileptic drugs (AEDs) (Fisher, et al. 2005). Children with purely febrile seizures were excluded. Children with neonatal seizures (seizures prior to the age of one month) were included only if seizures continued beyond age 1 month.

We defined early onset epilepsy as epilepsy starting prior to the age of 12 months. Children with seizures prior to age 1 month which continued beyond the neonatal period were defined as having malignant neonatal epilepsy. Children with neonatal seizures that resolved but who developed epilepsy later in life were not classified as having malignant neonatal epilepsy.

2.1.2 Data Abstracted from Charts

The charts of all children with new onset epilepsy were reviewed by a pediatric epileptologist (ECW or KN). Each child's epilepsy was classified using the ILAE Commission on Classification and Terminology 2005–2009 report (Berg, et al. 2010). Information collected included gender, age at epilepsy diagnosis, neurologic examination abnormalities, neuroimaging abnormalities, and number of AEDs at last follow up/death. Developmental quotient (DQ, defined as the child's functional/developmental age divided by the chronological age × 100 based on developmental milestones recorded in the medical record) or IQ from formal neuropsychometric testing was recorded. Children were considered intellectually disabled if their DQ/IQ was <80. Mortality information was abstracted from charts and postmortem examinations when available.

2.1.3 Statistical Analysis

Data entry and statistical analysis were performed using IBM SPSS Statistics Version 19 (IBM, Armonk, NY, U.S.A.). We utilized chi-square analysis (Fisher's Exact Test, 2 sided) for categorical data and independent-samples Student's t-test (2 tailed, equal variances not assumed) for continuous data. Variables with significant correlation were subsequently entered into a linear regression model. P-values <0.05 were considered statistically significant. Case fatality (CF) was calculated by dividing the number of deaths by the number of subjects in the cohort. Mortality rate (MR) was calculated by dividing the number of deaths during the study period by the person-years at risk. Standardized mortality ratios (SMRs) were calculated by dividing the mortality rate observed in our group by the expected mortality rate observed in the Olmsted County population from 1980 to 2009. Olmsted County mortality rates are based on person-years methodology and age-, sex-, and calendar-year specific deaths. These population-based mortality rates were available as part of the Rochester Epidemiology Project infrastructure (St Sauver, et al. 2011).

3.1 RESULTS

3.1.1 Early onset epilepsy and mortality

A total of 467 children were diagnosed with new onset epilepsy in Olmsted County, MN between 1980 and 2009 and were followed beyond initial diagnosis. Sixty children (12.8%) were identified who developed epilepsy prior to the age of 12 months. Such children were more likely to have infantile spasms, a structural/metabolic etiology, developmental delay/intellectual disability, neurological examination abnormalities, and histories of status epilepticus than children with later onset epilepsy (see Table 1).

Of the 16 children who died, 8 (50%) had early onset epilepsy. Only one child's death was directly related to seizures; she died of aspiration during a seizure. The remaining deaths were related to the child's underlying neurodevelopmental disability (see Table 2). Children with early onset epilepsy were significantly more likely to die (CF 8/60, 13.3% versus 8/407, 2%, $p<0.001$; MR 14.5/1000 versus 2/1000 person years; SMR 22.25 [9.61–43.80] versus 5.67 [2.45–11.17]). Unknown etiology was associated with lower CF (0/8, 0% versus 21/52, 40.4% with genetic or structural/metabolic cause, $p=0.042$), while structural/metabolic causes tended to be associated with higher CF (7/8, 87.5% versus 25/52, 48.1%, $p=0.057$). Children with early onset epilepsy who died were significantly more likely to have developmental delay/intellectual disability (8/8, 100% versus 31/52, 59.6%, $p=0.042$), neurological examination abnormalities (8/8, 100% versus 30/52, 57.7%, $p=0.022$), and larger numbers of prescribed AEDs at final follow up/death (2.6 ± 0.5 versus 1.1 ± 1.2 , $p<0.001$). When entered into a linear regression model, unknown etiology (beta -0.14 , $p=0.41$), developmental delay/intellectual disability (beta -0.096 , $p=0.67$), and neurological examination abnormalities (beta -0.122 , $p=0.61$) were no longer independently predictive of mortality.

3.1.2 Malignant neonatal epilepsy and mortality

Of the 467 children in our cohort, 462 had available data regarding their neonatal development. Thirty five children (7.6%) had seizures during the first month of life. Children with any neonatal seizures were significantly more likely to die than those without (CF 6/35, 17.1% versus 10/427, 2.3%, $p=0.001$; MR 10.9/1000 person years versus 2.4/1000 person years; SMR 35.20 [12.91–76.56] versus 6.34 [3.04–11.67]).

Of the 35 children with neonatal seizures, 12 had malignant neonatal epilepsy (versus 23 with isolated neonatal seizures followed by childhood onset epilepsy). Children with malignant neonatal epilepsy were significantly more likely to die (CF 4/12, 33.3% versus 12/450, 2.7%, $p<0.001$; MR 54/1000 person years versus 2.7/1000 person year; SMR 46.55 [12.69–119.30] versus 7.22 [3.73–12.61]). This difference persisted when compared to children with epilepsy arising from ages 2–12 months (CF 4/12, 33.3% versus 4/48, 8.3%, $p=0.043$). Children with malignant neonatal epilepsy who died were prescribed significantly more AEDs at the time of last follow up/death than those who survived (2.8 ± 0.5 versus 1.4 ± 1.3 , $p=0.026$). Although children with malignant epilepsy who died tended to have a structural/metabolic etiology causing their seizures, this did not reach statistical significance (4/4, 100% versus 3/8, 37.5%, $p=0.081$).

4.1 CONCLUSIONS

Mortality in pediatric epilepsy is higher in children with early onset epilepsy. Children with epilepsy onset in the first year of life were over six times more likely to die than children with later onset epilepsy. This difference was even more dramatic for children with malignant neonatal epilepsy, who were over 12 times more likely to die than children with epilepsy onset at age 1 month. The MR of 14.5/1000 person years for children with early

onset epilepsy and 54/1000 person years for those with malignant neonatal epilepsy stand in stark contrast to those with later onset epilepsy. Previous studies examining mortality in all children with epilepsy have reported lower MRs ranging from 2.7 to 6.9/1000 patient years (Harvey, et al. 1993, Callenbach, et al. 2001, Berg, et al. 2004, Sillanpaa and Shinnar 2010, Nickels, et al. 2012). Such findings favor the acknowledgement of early onset epilepsy as a risk factor for death. Given that only 1/8 deaths in our cohort was seizure-related, mortality in early onset epilepsy appears to be more affected by the underlying etiology. This was supported by the fact that over 75% of deaths were secondary to respiratory complications arising from severe neurologic impairment.

Our finding that etiology affected mortality deserves notice. In our cohort, children with early onset epilepsy were almost twice as likely to die if their epilepsy etiology was structural/metabolic. Conversely, no children with early onset epilepsy and unknown etiologies died. Similar findings were recently reported in a study of childhood convulsive status epilepticus. Most deaths in the subsequent 8 years were not seizure related, but rather depended on preexisting neurological impairments (Pujar, et al. 2011). Our findings are also supported by studies utilizing the older system of classification, which found symptomatic etiology to be associated with a worse prognosis (Annegers, et al. 1979, Brorson and Wranne 1987, Callenbach, et al. 2001, Lhatoo, et al. 2001, Camfield, et al. 2002, Berg, et al. 2010, Geerts, et al. 2010, Sillanpaa and Shinnar 2010). Such results suggest there is value to utilizing the new ILAE Commission on Classification and Terminology 2005–2009 report beyond mere semantics. By assigning children to specific epilepsy etiologies and syndromes, it may be possible to identify children at greatest risk of death so protective measures can be taken.

Our study was not without limitations. It is possible we failed to identify all children with epilepsy in our cohort. However, we screened the complete Medical Diagnostic Index of the Rochester Epidemiology Project for children diagnosed at any time with seizure or convulsion. We were unable to directly interview and examine all children in our cohort, relying instead on the observations of other physicians to determine epilepsy etiology. Therefore, it is possible some children's etiologies would have changed if all children were seen by a pediatric epileptologist. However, complete medical records, including neuroimaging, laboratory results, and electroencephalograms, were available for each child and reviewed by a pediatric epileptologist, minimizing the possibility that information was missed. We relied on DQ as a measure of neurocognitive ability rather than formal neuropsychological testing. Although formal testing would have yielded more robust cognitive measures for some children, we deemed that such testing in our early onset epilepsy group would have either not been possible or yielded unreliable results. This is particularly true given that the majority of children in the early onset group who died did so prior to their second birthday, with many remaining nonverbal and nonambulatory their entire lives. Given the small number of children in our cohort with malignant neonatal epilepsy, it was impossible to make many significant inferences regarding risk factors for mortality. Larger population based studies are needed to determine prognostic factors in this population so that risk can be appropriately stratified and, if possible, preventive measures initiated.

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Table 1

Differences between children with early onset epilepsy and later onset epilepsy.

Variable examined	Early onset epilepsy (n=60)	Later onset epilepsy (n=407)	P value
Gender	29/60 male (48.3%)	217/407 male (53.3%)	0.49
Duration of epilepsy at last follow up (months)	110.1+/-93.3	120.1+/-89.1	0.44
Focal mode of onset	42/60 (70%)	275/407 (67.6%)	0.77
Generalized mode of onset	5/60 (8.3%)	108/407 (26.5%)	0.001
Focal and generalized mode of onset	0/60 (0%)	4/407 (1%)	1
Spasms mode of onset	10/60 (16.7%)	4/407 (1%)	<0.001
Unknown mode of onset	3/60 (5%)	16/407 (3.9%)	0.72
Structural/metabolic etiology	32/60 (53.3%)	92/407 (22.6%)	<0.001
Genetic etiology	6/60 (10%)	103/407 (25.3%)	0.008
Structural/metabolic and genetic etiology	1/60 (1.7%)	1/407 (0.2%)	0.24
Unknown etiology	21/60 (35%)	211/407 (51.8%)	0.018
AEDs prescribed at last follow up	1.3+/-1.2	0.8+/-0.8	0.002
AEDs that failed secondary to LOE	1.4+/-2	0.6+/-1.4	0.008
Developmental delay/intellectual disability	39/60 (65%)	153/407 (37.6%)	<0.001
Neurological examination abnormalities	38/60 (63.3%)	81/407 (19.9%)	<0.001
History of status epilepticus	23/60 (38.3%)	71/407 (17.4%)	<0.001

Key: AED=antiepileptic drug; LOE=lack of efficacy

Mortality in early onset epilepsy (n=8).

Table 2

ID	Sex	Age at epi dx (years)	Duration f/u (months)	Mode onset	Etiology	Syndrome	Prenatal problems	Perinatal problems	Cognitive status	Neuro exam	MRI	AEDs at last f/u	AEDs failed LOE	Status	Cause of death
A	M	Birth	18	Foc	St	N	N	>7	Sev	Ab	IIG	2	0	Y	Respiratory failure 2/2 severe neuro impairment
B	F	0.8	84	Foc	St	N	Y	>7	Bor	Ab	CC	2	2	Y	Seizure-related aspiration
C	M	0.1	47	Gen	St	N	N	N	Sev	Ab	MCD	3	0	Y	Respiratory illness 2/2 severe neuro impairment
D	F	0.7	78	Foc	G	N	N	>7	Sev	Ab	NP2	2	0	Y	Respiratory (tracheostomy dislodgment)
E	F	0.2	63	Gen	St	N	N	>7	Sev	Ab	MCD	3	5	N	Pneumonia 2/2 severe neuro impairment
F	M	Birth	2	Foc	St	N	Y	>7	Sev	Ab	NP	3	0	N	Cardiovascular compromise (large VSD)
G	F	0.3	17	S	St	West syndrome	Y	7	Sev	Ab	MCD	3	1	N	Respiratory illness 2/2 severe neuro impairment
H	F	Birth	9	Foc	St	N	Y	>7	Sev	Ab	MCD	3	0	Y	Acute respiratory distress syndrome 2/2 severe neuro impairment

Key: 7=neonatal ICU but home by 7 days; >7=neonatal ICU and home after 7 days; 2/2=secondary to; Ab=abnormal; AEDs=anti-epileptic drugs; Bor=borderline (DQ between 50–80); CC=partial agenesis of corpus callosum; dx=diagnosis; epi=epilepsy; F=female; Foc=focal; f/u=follow up; G=genetic; Gen=generalized and focal; IIG=ischemia/infarction/gliosis; LOE=lack of efficacy; M=male; MCD=malformation of cortical development; N=no; NP=not performed (but CT done and abnormal); NP2=not performed (but CT done and normal); S=spasms; Sev=severe impairment (DQ<50); St=structural/metabolic; Y=yes