Short-term Seizure Outcomes in Childhood Epilepsy

Kari Modalsli Aaberg, MD,[a,b] Inger Johanne Bakken, PhD,[b] Morten I. Lossius, MD, PhD,[a,c] Camilla Lund Søraas, MD, PhD,[b] Kamath K. Tallur, FRCPCH, MD,[d] Camilla Stoltenberg, MD, PhD,[b,e] Richard Chin, MRCPCH, PhD,[d] Pål Surén, MD, MPH, PhD[a,b]

abstract

BACKGROUND AND OBJECTIVES: Seizure freedom is the optimal response to antiepileptic treatment. In previous studies, it has been shown that between 61% and 71% of children with epilepsy achieve seizure freedom, whereas 7% to 20% have drug-resistant epilepsy. The definition of drug resistance has not been consistent across studies, and there is a lack of contemporary population-based data. We used data from a large nationwide child cohort to provide such information, implementing the current standard definition of drug resistance.

METHODS: The study was based on the Norwegian Mother and Child Cohort Study. Potential epilepsy cases were identified through registry linkages and parental questionnaires. Medical record reviews and parental interviews were used to collect clinical information and to classify seizures, epilepsies, and etiologies.

RESULTS: The cohort included 112 745 eligible children aged 3 to 13 years (median age 7 years) at end of follow-up. Of these, 600 were epilepsy cases with at least 1 year of follow-up since epilepsy onset (median follow-up time: 5.8 years). There were 178 (30%) who had developed drug-resistant epilepsy, 353 (59%) who had been seizure free for ≥1 year, and 69 (12%) with intermediate seizure outcomes. Having an identified cause of epilepsy (genetic, structural, metabolic, or infectious) was associated with unsatisfactory seizure outcome (48% drug resistance) and influenced the relative risk associated with other prognostic factors. Sociodemographic characteristics were not associated with short-term seizure outcomes.

CONCLUSIONS: Drug resistance occurs in 3 out of 10 children with epilepsy, whereas 6 out of 10 become seizure free. Having an identified cause of epilepsy is associated with poor response to treatment.

[a]National Center for Epilepsy, Oslo University Hospital, Oslo, Norway; [b]Norwegian Institute of Public Health, Oslo, Norway; [c]Faculty of Medicine, University of Oslo, Oslo, Norway; [d]Muir Maxwell Epilepsy Centre, University of Edinburgh, Edinburgh, United Kingdom; and [e]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Drs Aaberg, Chin, and Surén contributed to the conception and design of the study, the collection of data, the analysis and interpretation of data, and the drafting of the manuscript; Drs Bakken, Lossius, Tallur, and Stoltenberg contributed to the analyses and interpretation of data and reviewed and revised the manuscript; Dr Lund Søraas contributed to the data collection and to the analyses and interpretation of data and reviewed and revised the manuscript; and all authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2017-4016

Accepted for publication Mar 26, 2018

Address correspondence to Kari Modalsli Aaberg, MD, National Center for Epilepsy, Oslo University Hospital, PO Box 4950, Nydalen, N-0403 Oslo, Norway. E-mail: kari.modalsli.aaberg@fhi.no

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

WHAT'S KNOWN ON THIS SUBJECT: Between 61% and 71% of children with epilepsy achieve remission, whereas 7% to 20% have drug-resistant epilepsy. Previous studies were conducted decades ago with divergent definitions of remission and drug resistance. It is unknown whether the findings are applicable to current pediatric practice.

WHAT THIS STUDY ADDS: In this population-based study of epilepsy, 30% of affected children had drug-resistant epilepsy, whereas 59% achieved ≥1 year of seizure freedom. Having an identified cause of epilepsy (genetic, structural, metabolic, or infectious) was associated with drug resistance.

To cite: Aaberg KM, Bakken IJ, Lossius MI, et al. Short-term Seizure Outcomes in Childhood Epilepsy. *Pediatrics.* 2018;141(6):e20174016

Freedom from seizures is the optimal response to antiepileptic treatment. In studies, it has been shown that between 61% and 71% of children with epilepsy (CWE) achieve permanent remission from seizures.[1–4] Childhood epilepsy often has a fluctuating course, and approximately one-third of CWE experience alternating periods of seizure freedom and seizure relapses.[5,6] Between 7% and 20% do not become seizure free, despite adequate treatment.[2–4,7]

Early onset of epilepsy is associated with worse outcomes. In a longitudinal study of CWE with onset before age 36 months, it was found that 35% did not become seizure free.[8] Early-onset epilepsies frequently have identified structural, metabolic, or genetic causes, and such epilepsies are more likely to have poorer treatment responses than epilepsies with nonidentified causes.[3,7,8] However, in a study of epilepsy with onset in infancy (age <1 year), it was found that 58% of affected children were in remission by age 24 months and that age of onset did not affect the outcome when etiology was accounted for.[9]

Other characteristics associated with poor treatment responses are abnormal findings on neurological examinations, a history of febrile seizures, and pathologic findings in EEGs.[4,8] Children from families with low socioeconomic status have a higher baseline risk of epilepsy,[10] but socioeconomic factors do not appear to influence seizure outcomes in countries with universal access to health care.[2]

Different terms have been used to describe epilepsies in which seizure freedom is not obtained: drug-resistant, pharmacoresistant, intractable, or refractory. A consensus proposal from the International League Against Epilepsy (ILAE) recommends the term "drug-resistant epilepsy" (DRE) and defines this as failure to achieve sustained seizure freedom despite adequate trials of at least 2 antiepileptic drugs used in monotherapy or in combination.[11]

In most studies of childhood epilepsy, researchers include patients who were diagnosed decades ago, when the range of diagnostic procedures and antiepileptic treatments of today were not available. All previous studies have been based on the old classification systems for seizures and epilepsies, and definitions of drug resistance and seizure freedom have varied. Consequently, it is not known whether previous findings are applicable to current pediatric practice.

In this study, we have used information from a large population-based child cohort to provide contemporary data on short-term seizure outcomes in childhood epilepsy. We have used the revised classification systems published by the ILAE in 2017[12,13] and the current ILAE definition of DRE.[11] We investigated seizure outcomes across prognostic factors that are available and relevant to clinicians treating CWE: sociodemographic characteristics, epilepsy risk factors, clinical characteristics, investigation results, seizure types, epilepsy types, and etiological categories. We expected that the cause of epilepsy would be strongly associated with seizure outcomes and partly or fully account for associations observed for other prognostic factors.

METHODS

The study was based on the Norwegian Mother and Child Cohort Study (MoBa), a nationwide cohort study of children born from 1999 to 2009.[14] Within MoBa, we established a substudy of epilepsy, which was the Epilepsy in Young Children Study (EPYC).[15] CWE were identified through linkages to the Norwegian Patient Registry and parental report of epilepsy in sequential MoBa questionnaires. Clinical information was collected through medical record reviews and clinical telephone interviews with the parents. Seizures, epilepsies, and etiologies were classified by 2 child epileptologists (K.M.A. and R.C.). Details of the data collection have been described in previous publications.[15,16]

DRE was defined as seizures within the last year of follow-up despite adequate trials of at least 2 antiepileptic drugs, in concordance with the ILAE recommendation.[11] Seizure freedom was defined as being without seizures for ≥1 year at the end of follow-up (regardless of whether antiepileptic drugs were used). CWE with seizures within the last year of follow-up who had not completed trials of at least 2 drugs were defined as having intermediate seizure outcome. Children with <1 year of follow-up since epilepsy onset were not included in the case definition of epilepsy.

Statistical analyses were conducted by using IBM SPSS Statistics 22 (IBM Corp, Armonk, NY). We tested differences across seizure outcome categories by Pearson's χ^2 tests, with 2-sided *P* values. Log-binomial regression analyses were used to calculate relative risks (RRs) of DRE associated with each prognostic factor. Because of the large number of comparisons, we used an α of .01 for *P* values and 99% confidence intervals (CIs) for RR estimates.

MoBa holds a license from the Norwegian Data Protection Authority. Participation is based on informed consent by mothers and fathers. The consent includes permission to registry linkages and medical record reviews. The EPYC has approval from the Regional Committee for Medical and Health Research Ethics for Southeast Norway. Participation in the EPYC telephone interviews was based on an additional informed consent.

TABLE 1 Epilepsy Risk and Short-term Seizure Outcome by Sociodemographic Characteristics

	Noncases N = 112 145		All CWE[a] n = 600		P[b]	DRE[c] n = 178 (30%)		Intermediate Outcome[c] n = 69 (12%)		≥1 y Seizure Free n = 353 (59%)		P
	n	%	n	%		n	%	n	%	n	%	
Maternal education, y												
≤12	35 078	31	213	36	.08	64	36	29	42	120	34	.67
≥13	64 447	57	322	54		92	52	34	49	196	56	
Missing data	12 620	11	65	11		22	12	6	9	37	10	
Paternal education, y												
≤12	49 484	44	303	51	.004	87	49	34	49	182	52	.66
≥13	49 202	44	225	38		65	37	29	42	131	37	
Missing data	13 459	12	72	12		26	15	6	9	40	11	
Maternal living status												
Married or partner	97 761	87	513	86	.11	147	83	58	84	308	87	.65
Single	3390	3	27	5		10	6	4	6	13	4	
Missing data	10 994	10	60	10		21	12	7	10	32	9	
Pregnancy planning												
Planned	81 021	72	430	72	.85	121	68	46	67	263	75	.43
Unplanned	19 420	17	109	18		36	20	16	23	57	16	
Missing data	11 704	10	61	10		21	12	7	10	33	9	
Maternal age, y												
<25	13 058	12	84	14	.36	26	15	10	14	48	14	.92
25–34	79 261	71	412	69		126	71	46	67	240	68	
≥35	19 646	18	103	17		26	15	13	19	64	18	
Missing data	180	0.2	<5	<1	—	<5	<1	<5	<1	<5	<1	—
Paternal age, y												
<25	5801	5	31	5	.35	10	6	7	10	14	4	.15
25–39	94 462	84	512	85		155	87	51	74	306	87	
≥40	11 377	10	52	9		12	7	10	14	30	8	
Missing data	505	0.5	5	0.8	—	<5	<1	<5	<1	<5	<1	—

—, not applicable.

[a] CWE, according to the new definition (ILAE 2014) and ≥1 y of follow-up since onset.

[b] P values calculated with Pearson's χ^2 tests.

[c] DRE, defined as failure to achieve ≥1 y of seizure freedom at end of follow-up despite trial of ≥2 antiepileptic drugs in monotherapy or in combination. The intermediate category includes seizure outcomes in between DRE and ≥1 y of seizure freedom.

RESULTS

At the end of registry follow-up on December 31, 2012, MoBa included 112 745 children who were live born, had valid personal identification numbers, and were still residing in Norway. The age range at end of follow-up was 3 to 13 years with a median age of 7 years. There were 606 epilepsy cases in total, of which, 13 (2%) had died during follow-up. The median age of onset of epilepsy was 3 years. Among the cases, 600 had ≥1 year of follow-up since epilepsy onset (median: 6 years; range: 1–13 years). At the end of follow-up, 178 (30%) of these 600 CWE had DRE, 353 (59%) had been seizure free for ≥1 year, and 69 (12%) had intermediate seizure outcomes. The number of antiepileptic drugs tried out ranged from 0 to 16 per child, with a median of 2. A total of 91 CWE (15%) had never used antiepileptic drugs. Nonmedical treatment had been used by a total of 40 CWE (7%), with vagal nerve stimulator in 11 (2%), epilepsy surgery in 5 (1%), and ketogenic diet in 31 (5%). Of the 40 CWE who had tried nonmedical treatment, 34 (85%) had DRE at end of follow-up.

In Table 1, we compare the distributions of sociodemographic characteristics between CWE and noncases and across seizure outcome categories for CWE. In the comparison of CWE with noncases, the CWE had somewhat higher proportions of parents with <12 years of education, that is, parents who had not completed high school (P = .08 for maternal education and P = .004 for paternal education). There were no differences between CWE and noncases with regards to maternal living status, pregnancy planning, or maternal and paternal age. The comparisons across seizure outcome categories in CWE revealed that none of the sociodemographic characteristics were associated with seizure outcomes.

In Table 2, we have shown the distribution of short-term seizure outcomes across categories of epilepsy risk factors, seizure characteristics, and clinical and/or EEG characteristics, with crude RR estimates for DRE. CWE with a history of preterm birth and low Apgar scores had a somewhat increased risk of DRE, but testing across seizure outcome categories provided P values >.01. The child's sex, family history of epilepsy, and history of febrile seizures were not associated with DRE. The other characteristics (multiple seizure

types, status epilepticus, seizure precipitants, infancy onset, additional neurologic or developmental difficulties, abnormal neurologic examinations, and abnormal EEG findings) were all strongly associated with DRE, with *P* values ≤.001 for all comparisons across seizure outcome categories.

In Table 3, we show the distribution of seizure outcomes by the ILAE 2017 classifications of seizure type, epilepsy type, and epilepsy etiology. The crude RR of DRE was >1 for all seizure types except for typical absence seizures and unclassified seizures. It was particularly high for those with tonic seizures (RR = 3.0), myoclonic seizures (RR = 3.5), atonic seizures (RR = 2.4), and epileptic spasms (RR = 2.4). In the analyses of epilepsy types, we compared mode of onset categories, with focal onset as the reference category. CWE with generalized onset had similar seizure outcomes as those with focal onset (RR = 1.0), whereas those with combined focal and generalized onset had a substantially increased risk of DRE, with a crude RR of 2.9 compared with focal onset.

In the analyses by etiological category for Table 3, we started by examining individual etiological categories: structural, genetic, metabolic, infectious, and unknown causes. Among CWE with structural causes (*n* = 156), 47% had DRE, whereas among CWE with identified and presumed genetic causes (*n* = 204), 33% had DRE. Among the CWE with identified genetic causes (*n* = 56), the proportion with DRE was 56%, which was much higher than the proportion of 24% with DRE among CWE with presumed genetic causes (*n* = 147) (*P* < .001). The numbers of CWE with metabolic (*n* = 5) and infectious (*n* = 12) causes were too low to reliably calculate proportions of DRE. Immunologic causes had not been identified for any of the CWE, and few had reports of immunologic investigations. Among CWE with identified etiology, there were many who fit into more than 1 category. Given this etiological overlap, as well as the similar seizure outcomes across categories of identified causes, we merged all identified causes into 1 category in the analyses shown in Table 3. This category was compared with presumed genetic causes and unknown causes, with unknown causes as the reference category. Having an identified cause was positively associated with DRE (RR = 2.7). CWE with presumed genetic cause had a slightly higher risk of DRE than CWE with unknown cause (RR = 1.3), but the difference was not statistically significant.

In absolute terms, the risk of DRE was 48% in CWE with an identified cause and 21% in CWE with a nonidentified cause. These differences between CWE with and without identified causes confirmed our a priori expectation that the cause of epilepsy would be strongly associated with short-term seizure outcomes. We also found that the RR estimates for other prognostic factors often differed between the 2 main etiological categories. Because of these differences, we chose to stratify regression analyses by CWE with identified cause and CWE without identified cause. The results of regression analyses are shown in Tables 4 and 5.

In Table 4, we divided the examined characteristics into 3 groups: epilepsy risk factors, seizure and/or epilepsy characteristics, and clinical and/or EEG characteristics. We calculated crude RRs for DRE and then fitted models with mutual adjustments for all prognostic factors within each group. For preterm birth and low Apgar scores, the associations with DRE that were observed for CWE overall became weaker or disappeared in the adjusted regression models. Male sex was associated with a lower risk of DRE in CWE without an identified cause (adjusted RR = 0.6) but not in CWE with an identified cause (adjusted RR = 0.9).

As shown in Table 4, a history of ≥3 seizure types was always strongly associated with DRE, regardless of etiology and other seizure and/or epilepsy characteristics. For status epilepticus, seizure precipitants, and combined focal and generalized onset, the associations with DRE became weaker or disappeared after stratification and adjustment. This was also the case for infancy onset of epilepsy. Additional neurologic and developmental difficulties were associated with DRE in CWE without identified cause (adjusted RR = 2.0), whereas abnormal findings on neurologic examinations were associated with DRE in CWE with identified cause (RR = 2.3). Findings of epileptic activity in EEGs was associated with DRE across the CWE subgroups, but the association between nonepileptic EEG pathology and DRE was substantially weakened after stratification by etiology and adjustment for other clinical and/or EEG characteristics.

In Table 5, we have shown RR estimates for associations between DRE and the different seizure types, stratified by main etiological category. In the adjusted models, the RR estimates were adjusted for the total number of seizure types (1–2 vs ≥3) because having multiple seizure types was so strongly associated with DRE. All the associations between individual seizure types and DRE were attenuated after adjustment, and most were not statistically significant.

DISCUSSION

In this study, we provide contemporary population-based data on the short-term outcomes of childhood epilepsy. At end of follow-up, 59% of CWE had achieved seizure freedom lasting 1 year or more, whereas 30% had DRE. The

TABLE 2 Short-term Seizure Outcome by Risk Factors, Clinical Characteristics, and EEG Findings

	All CWE[a] *n* = 600		DRE[b] *n* = 178 (30%)			Intermediate Outcome[b] *n* = 69 (12%)		≥1 y Seizure Free *n* = 353 (59%)		*P*[c]
	n	%	*n*	%	RR for DRE (99% CI)	*n*	%	*n*	%	
Epilepsy risk factors										
Preterm birth (gestational age <37 wk)										
Yes	76	13	31	17	1.5 (1.0–2.2)	10	14	35	10	.04
No	520	87	146	82	1 (reference)	58	84	316	90	
Missing	4	1	—	—	—	—	—	—	—	—
5-min Apgar score <7										
Yes	34	6	16	9	1.6 (1.0–2.7)	2	3	16	5	.07
No	564	94	162	91	1 (reference)	67	97	335	95	
Missing	2	∼0	—	—	—	—	—	—	—	—
Sex										
Male	324	54	85	48	0.8 (0.6–1.1)	40	58	199	56	.13
Female	276	46	93	52	1 (reference)	29	42	154	44	
Family history of epilepsy										
Yes	154	26	38	21	0.8 (0.5–1.2)	24	35	92	26	.09
No	446	74	140	79	1 (reference)	45	65	261	74	
History of febrile seizures										
Yes	118	20	30	17	0.8 (0.5–1.3)	16	23	72	20	.46
No	482	80	148	83	1 (reference)	53	77	281	80	
Seizure characteristics										
No. seizure types										
≥3	152	25	106	60	7.6 (4.5–12.8)	14	20	32	9	<.001
2	187	31	48	27	2.8 (1.5–5.1)	26	38	113	32	
1	261	44	24	13	1 (reference)	29	42	208	59	
History of status epilepticus										
Yes	140	23	68	38	2.0 (1.5–2.8)	14	20	58	16	<.001
No	460	77	110	62	1 (reference)	55	80	295	84	
History of seizure precipitants										
Yes	289	48	104	58	1.5 (1.1–2.1)	39	57	146	41	<.001
No	311	52	74	42	1 (reference)	30	43	207	59	
Clinical and/or EEG characteristics										
Age of epilepsy onset, y										
<1	161	27	68	38	1.8 (1.2–2.9)	15	22	78	22	.001
1–4	272	45	72	40	1.2 (0.7–1.8)	30	43	170	48	
≥5	166	28	38	21	1 (reference)	24	35	104	29	
Missing	1	∼0	—	—	—	—	—	—	—	—
Additional neurologic or developmental difficulties[d]										
Yes	321	54	142	80	3.4 (2.2–5.3)	36	52	143	41	<.001
No	279	47	36	20	1 (reference)	33	48	210	59	
Neurologic examination										
Abnormal	242	40	120	67	3.1 (2.2–4.4)	29	42	93	26	<.001
Normal	358	60	58	33	1 (reference)	40	58	260	74	
EEG: epileptic activity										
Yes	495	83	169	95	4.0 (1.7–9.2)	51	74	275	78	<.001
No	105	18	9	5	1 (reference)	18	26	78	22	
EEG: nonepileptic pathology										
Yes	197	33	99	56	2.6 (1.7–3.5)	19	28	79	22	<.001
No	403	67	79	44	1 (reference)	50	72	274	78	

—, not applicable.

[a] CWE, according to the new definition (ILAE 2014) and ≥1 y of follow-up since onset.

[b] DRE, defined as failure to achieve ≥1 y of seizure freedom at end of follow-up despite trial of ≥2 antiepileptic drugs in monotherapy or in combination. The intermediate category includes seizure outcomes in between DRE and ≥1 y of seizure freedom.

[c] *P* values calculated with Pearson's χ^2 tests.

[d] Diagnosed neurologic and developmental disorders or reported neurologic and developmental problems.

TABLE 3 Short-term Seizure Outcomes by ILAE 2017 Classification of Seizures, Epilepsies, and Etiologies

	All CWE[a] $n = 600$		DRE[b] $n = 178$ (30%)			Intermediate Outcome[b] $n = 69$ (12%)		≥1 y Seizure Free $n = 353$ (59%)		P[c]
	n	%	*n*	%	RR for DRE (99% CI)	*n*	%	*n*	%	
Seizure classification										
Focal seizures, any type[d]										
Yes	413	69	143	80	1.8 (1.2–2.8)	51	74	219	62	<.001
No	187	31	35	20	1 (reference)	18	26	134	38	
Generalized seizures[e]										
Tonic-clonic seizures										
Yes	111	19	46	26	1.5 (1.1–2.2)	9	13	56	16	.009
No	489	82	132	74	1 (reference)	60	87	297	84	
Tonic seizures										
Yes	80	13	56	31	3.0 (2.3–3.9)	4	6	20	6	<.001
No	520	87	122	69	1 (reference)	65	94	333	94	
Myoclonic seizures										
Yes	82	14	64	36	3.5 (2.7–4.6)	5	7	13	4	<.001
No	518	86	114	64	1 (reference)	64	93	340	96	
Atonic seizures										
Yes	39	7	25	14	2.4 (1.6–3.4)	3	4	11	3	<.001
No	561	94	153	86	1 (reference)	66	96	342	97	
Typical absence seizures										
Yes	62	10	20	11	1.1 (0.7–1.8)	4	6	38	11	.42
No	538	90	158	89	1 (reference)	65	94	315	89	
Atypical or other absence seizures										
Yes	54	9	25	14	1.7 (1.1–2.5)	4	6	25	7	.02
No	546	91	153	86	1 (reference)	65	94	328	93	
Unclassifiable seizures										
Epileptic spasms										
Yes	60	10	38	21	2.4 (1.8–3.3)	5	7	17	5	<.001
No	540	90	140	79	1 (reference)	64	93	336	95	
Other unclassifiable seizures										
Yes	87	15	26	15	1.0 (0.6–1.6)	11	16	50	14	.93
No	513	86	152	85	1 (reference)	58	84	303	86	
Epilepsy mode of onset										
Focal	304	51	70	39	1 (reference)	46	67	188	53	<.001
Generalized	144	24	34	19	1.0 (0.6–1.6)	11	16	99	28	
Combined generalized and focal	110	18	73	41	2.9 (2.1–4.0)	5	7	32	9	
Unclassifiable	42	7	1	1	0.1 (0.0–1.3)	7	10	34	9	
Epilepsy etiology										
Identified cause[f]	196	33	95	53	2.7 (1.8–3.9)	22	32	79	22	<.001
Presumed genetic cause	147	25	36	20	1.3 (0.8–2.2)	9	13	102	29	
Unknown cause	257	43	47	26	1 (reference)	38	55	172	49	

[a] CWE, according to the new definition (ILAE 2014) and ≥1 y of follow-up since onset.
[b] DRE, defined as failure to achieve ≥1 y of seizure freedom at end of follow-up despite trial of ≥2 antiepileptic drugs in monotherapy or in combination. The intermediate category includes seizure outcomes in between DRE and ≥1 y of seizure freedom.
[c] P values were calculated with Pearson's χ^2 tests.
[d] Analyzed as 1 category because there were no differences in seizure outcomes between subcategories of focal seizures.
[e] There were 5 CWE with myoclonic-atonic seizures and none with clonic and myoclonic-tonic-clonic seizures. These seizure categories are not included in the table.
[f] Includes structural, genetic, metabolic, and infectious causes. There were large degrees of overlap between these categories. No CWE had immunologic etiology.

remaining 12% had intermediate seizure outcomes.

The proportion with DRE in this study was higher than that of other studies.[2–4,7] One reason is our relatively young study sample, with a median age of 3 years at epilepsy onset for CWE. Our proportion of DRE (30%) is comparable to that of the previously mentioned study of epilepsy with onset before 36 months of age, in which researchers found intractable seizures in 35%.[8] The CWE in our study sample had a higher proportion with identified causes (33%) than previous studies. Having epilepsy with an identified cause (previously referred to as symptomatic epilepsy) is predictive of a higher risk of DRE.[3,7,8] Mean follow-up time was also shorter in our study. Finally, our definition of DRE[11] is likely to capture more CWE than the definitions used in previous studies.[17]

TABLE 4 RR for DRE by Risk Factors, Clinical Characteristics, and EEG Findings

	CWE[a] With Identified Cause[b] (n = 196) Overall Proportion of DRE: 48%		CWE Without Identified Cause (n = 404) Overall Proportion of DRE: 21%	
	Crude RR for DRE[c] (99% CI)	Adjusted[d] RR for DRE (99% CI)	Crude RR for DRE[c] (99% CI)	Adjusted[d] RR for DRE (99% CI)
Epilepsy risk factors				
Preterm birth (gestational age <37 wk)				
Yes	1.2 (0.8–1.9)	1.2 (0.8–1.8)	1.0 (0.4–2.5)	1.0 (0.4–2.4)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
5-min apgar score <7				
Yes	1.3 (0.8–2.0)	1.4 (0.9–2.2)	Not estimated[e]	Not estimated[e]
No	1 (reference)	1 (reference)	—	—
Sex				
Male	1.0 (0.7–1.4)	0.9 (0.7–1.4)	0.6 (0.3–1.0)	0.6 (0.4–1.0)
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Family history of epilepsy				
Yes	0.7 (0.4–1.3)	0.7 (0.4–1.3)	1.0 (0.6–1.8)	1.0 (0.6–1.7)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
History of febrile seizures				
Yes	1.1 (0.7–1.7)	1.3 (0.8–2.0)	0.6 (0.2–1.2)	0.6 (0.3–1.3)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Crude RR for DRE[c] (99% CI)	Adjusted[f] RR for DRE (99% CI)	Crude RR for DRE[c] (99% CI)	Adjusted[f] RR for DRE (99% CI)
Seizure and/or epilepsy characteristics				
No. of seizure types				
≥3	3.6 (2.2–6.0)	2.9 (1.6–5.2)	4.0 (2.5–6.2)	3.5 (2.1–5.9)
1–2	1 (reference)	1 (reference)	1 (reference)	1 (reference)
History of status epilepticus				
Yes	1.5 (1.0–2 1)	1.1 (0.9–1.5)	2.0 (1.2–3.3)	1.2 (0.7–1.9)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
History of seizure precipitants				
Yes	1.2 (0.8–1.8)	1.0 (0.8–1.2)	1.9 (1.1–3.1)	1.7 (1.0–2.7)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Mode of seizure onset				
Combined generalized and focal	2.5 (1.7–3.6)	1.4 (1.0–1.9)	2.6 (1.5–4.3)	1.0 (0.6–1.8)
Focal or generalized or unclassifiable	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Crude RR for DRE[c] (99% CI)	Adjusted[g] RR for DRE (99% CI)	Crude RR for DRE[c] (99% CI)	Adjusted[g] RR for DRE (99% CI)
Clinical and/or EEG characteristics				
Age of epilepsy onset, y				
<1	1.4 (1.0–2.0)	1.2 (0.8–1.6)	1.2 (0.7–2.3)	1.0 (0.5–1.8)
≥1	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Additional neurologic or developmental difficulties[h]				
Yes	2.9 (0.7–11.4)	1.2 (0.2–6.1)	2.8 (1.7–4.7)	2.0 (1.1–3.8)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Neurologic examination				
Abnormal	2.9 (1.2–6.6)	2.3 (0.8–6.5)	2.4 (1.5–3.9)	1.3 (0.7–2.4)
Normal	1 (reference)	1 (reference)	1 (reference)	1 (reference)
EEG: epileptic activity				
Yes	4.7 (1.1–19.2)	3.9 (1.0–15.8)	3.1 (1.1–8.9)	2.5 (0.9–7.0)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
EEG: nonepileptic pathology				
Yes	1.9 (1.1–3.0)	1.4 (0.9–2.3)	2.2 (1.3–3.6)	1.4 (0.8–2.4)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)

—, not applicable.

[a] CWE, according to the new definition (ILAE 2014) and at least 1 y of follow-up since onset.

[b] Includes structural, genetic, metabolic, and infectious causes. There were large degrees of overlap between these categories. No CWE had immunologic etiology.

[c] DRE, defined as failure to achieve ≥1 y of seizure freedom at end of follow-up despite trial of ≥2 antiepileptic drugs in monotherapy or in combination. The intermediate category includes seizure outcomes in between DRE and ≥1 y of seizure freedom.

[d] Adjusted for all other epilepsy risk factors.

[e] Not estimated because no CWE without identified cause had a 5-min Apgar score <7.

[f] Adjusted for all other seizure and/or epilepsy characteristics.

[g] Adjusted for all other clinical and/or EEG characteristics.

[h] Diagnosed neurologic and/or developmental disorders or reported neurologic and/or developmental problems.

TABLE 5 RR for DRE by ILAE 2017 Seizure Classification

	CWE[a] With Identified Cause[b] (n = 196) Overall Proportion of DRE: 48%		CWE Without Identified Cause (n = 404) Overall Proportion of DRE: 21%	
	Crude RR for DRE[c] (99% CI)	Adjusted[d] RR for DRE (99% CI)	Crude RR for DRE[c] (99% CI)	Adjusted[d] RR for DRE (99% CI)
Seizure classification				
Focal seizures, any type				
Yes	2.0 (1.0–4.1)	1.0 (0.6–1.9)	1.4 (0.8–2.4)	1.1 (0.7–1.9)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Generalized seizures[d]				
Tonic-clonic seizures				
Yes	1.6 (1.1–2.3)	1.2 (0.9–1.5)	1.1 (0.6–2.1)	0.8 (0.4–1.5)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tonic seizures				
Yes	2.2 (1.6–3.1)	1.3 (1.0–1.7)	2.9 (1.7–4.9)	1.6 (1.0–2.7)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Myoclonic seizures				
Yes	2.5 (1.8–3.5)	1.5 (1.1–2.0)	3.7 (2.3–5.9)	1.5 (0.8–2.7)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Atonic seizures				
Yes	1.7 (1.2–2.5)	1.2 (0.9–1.6)	1.9 (0.8–4.9)	1.0 (0.4–2.3)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Typical absence seizures				
Yes	Not estimated	Not estimated	1.2 (0.6–2.4)	1.4 (0.8–2.4)
No	—	—	1 (reference)	1 (reference)
Atypical or other absence seizures				
Yes	1.2 (0.7–2.0)	1.1 (0.7–1.6)	2.2 (1.2–4.0)	1.4 (0.8–2.3)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Unclassifiable seizures				
Epileptic spasms				
Yes	1.5 (1.0–2.2)	1.0 (0.8–1.4)	3.1 (1.8–5.4)	1.8 (1.2–2.8)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other unclassifiable seizures				
Yes	1.2 (0.8–1.9)	0.9 (0.7–1.3)	0.5 (0.2–1.5)	0.5 (0.2–1.2)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)

—, not applicable.

[a] CWE, according to the new definition (ILAE 2014) and at least 1 y of follow-up since onset.

[b] Includes structural, genetic, metabolic, and infectious causes. There were large degrees of overlap between these categories. No CWE had immunologic etiology.

[c] DRE, defined as failure to achieve ≥1 y of seizure freedom at end of follow-up despite trial of ≥2 antiepileptic drugs in monotherapy or in combination. The intermediate category includes seizure outcomes in between DRE and ≥1 y of seizure freedom.

[d] Adjusted for number of seizure types (1–2 vs ≥3).

Our study was conducted in a high-income country with universal health service coverage where all CWE have access to modern diagnostic procedures and antiepileptic treatments. From a global perspective, these children have grown up under optimal circumstances. It was somewhat disappointing to find that 3 out of 10 CWE had not obtained seizure control despite adequate diagnostics and treatment. This suggests that recent diagnostic and therapeutic advances have not yet led to significant improvements in short-term seizure outcomes for CWE and confirms the need for increased understanding and more effective treatments of early-onset epilepsy.

Seizure outcomes were similar across sociodemographic categories, which are in line with previous findings from Canada.[2] The overall risk of epilepsy was somewhat higher among children of parents with low levels of education, but the differences were not large. There were no associations between epilepsy risk and other sociodemographic characteristics. In our data, it was indicated that sociodemographic factors have little influence on epilepsy risk in Norwegian children. Some caution is warranted because socially disadvantaged groups such as immigrants and single mothers are underrepresented in the MoBa cohort.[18] In nationwide survey data from the United States, it has been shown that childhood epilepsy is more common in low-income families.[10] In our study, we may not have fully captured the potential risk associated with social disadvantage. The findings are likely to be generalizable to other high-income countries with universal access to health care but may not be representative of more diverse populations where health care is not easily accessible to all children.

A number of characteristics were associated with increased risk of DRE for CWE overall: preterm birth, low

Apgar scores, multiple (≥3) seizure types, history of status epilepticus, history of seizure precipitants, combined generalized and focal mode of onset, infancy onset of epilepsy, additional neurologic and developmental difficulties, abnormal findings on neurologic examinations, and abnormal EEG findings. This is in line with findings from previous studies.[4,8] Most of the associations were attenuated or disappeared after stratification by etiology and adjustment for related prognostic factors, indicating that they are partially or fully explained by the underlying cause of epilepsy.

Some prognostic factors were associated with DRE regardless of etiology and other prognostic factors. CWE with multiple (≥3) seizure types had a large increase in risk compared with those with 1 to 2 seizure types. The associations observed between individual seizure types and DRE were largely driven by epilepsies with multiple seizure types. This also applied to the seizure types associated with a particularly high risk of DRE, that is, tonic seizures, myoclonic seizures, atonic seizures, and epileptic spasms. Approximately two-thirds of the CWE with 1 or more of these seizure types had a history of ≥3 seizure types. Epileptic activity in EEGs was also strongly associated with DRE across subgroups, but the majority of CWE had such findings, and it is more correct to say that the absence of such findings was predictive of sustained seizure freedom.

We found that additional neurologic or developmental difficulties were associated with DRE in CWE without identified cause, whereas abnormal findings on neurologic examinations were associated with DRE in CWE with identified cause. These characteristics were often overlapping in CWE, regardless of the underlying cause. The differences in adjusted RR estimates between the 2 main etiological categories may just be artifacts of the statistical modeling. We believe that clinicians should always be aware of an increased risk of DRE whenever CWE have any of these characteristics.

The genetic etiological category of the ILAE 2017 classification includes both epilepsies with identified genetic causes and presumed genetic causes. The identified genetic causes often represent de novo mutations that lead to severe epilepsy syndromes, whereas the presumed genetic causes pertain to genetic generalized or familial epilepsies. Consequently, using 1 single category for genetic epilepsies may not always be clinically meaningful in children. This was confirmed by the large difference in risk of DRE between CWE with identified genetic causes and CWE with presumed genetic causes. On the other hand, CWE with poor treatment responses may have been more likely to undergo genetic testing, and such reverse causation could have contributed to the association found between identified genetic causes and DRE.

The proportion of CWE who had died was 2%. In a previous study with the same mean duration of follow-up (5 years), it was also found that 2% of CWE had died,[19] whereas mortality was 3.5% in studies with follow-up until adulthood.[20] Thus, the mortality of CWE in our study appears to be similar to that of previous studies.

The main limitation of this study was that we were only able to investigate short-term seizure outcomes. However, these are of interest regardless of the final outcome because repeated seizures and long-term antiepileptic treatment are likely to have independent negative effects on the developing brain. The main strength of the study was the population-based and prospective cohort design with follow-up from pregnancy and onwards. This design enabled us to capture the complete spectrum of epilepsies occurring in the general child population. The combination of questionnaire data, registry data, medical record reviews, and parental interviews provided opportunities to explore a wide range of prognostic factors, including sociodemographic risk factors. We have added to previous knowledge by showing how the prognostic value of individual prognostic factors is often determined by the cause of epilepsy.

CONCLUSIONS

In this population-based study of childhood epilepsy, 30% of CWE had DRE, 59% had achieved ≥1 year of seizure freedom, and the remaining 12% had intermediate seizure outcomes. Having an identified cause of epilepsy (structural, genetic, metabolic, or infectious) was associated with DRE, and the cause modified the associations observed for most other prognostic factors.

ACKNOWLEDGMENTS

We are grateful to all the participants in MoBa and the parents who participated in telephone interviews in the EPYC. We would also like to thank our network of pediatricians, neurologists, neurophysiologists, and radiologists at the hospitals providing data and Therese Wardenær Bakke and Kaja Schau Knatten for their efforts in facilitating the data collection.

ABBREVIATIONS

CI: confidence interval
CWE: children with epilepsy
DRE: drug-resistant epilepsy
EPYC: Epilepsy in Young Children Study
ILAE: International League Against Epilepsy
MoBa: Norwegian Mother and Child Cohort Study
RR: relative risk

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by grants from the Research Council of Norway (grant 213699) and the Regional Health Authority of South-East Norway (grant 2014057).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2018;141;
DOI: 10.1542/peds.2017-4016 originally published online May 22, 2018;

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