FULL-LENGTH ORIGINAL RESEARCH

Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort

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Summary

Objective: The study provides updated information about the distribution of seizures, epilepsies, and etiologies of epilepsy in the general child population, and compares the old and new classification systems from the International League Against Epilepsy (ILAE).

Methods: The study platform was the Norwegian Mother and Child Cohort Study. Cases of epilepsy were identified through registry linkages and sequential parental questionnaires. Epilepsy diagnoses were validated using a standardized protocol, and seizures, epilepsies, and etiologies were classified according to the old (ILAE 1981/1989) and new (ILAE 2017) classifications. Information was collected through medical record reviews and/or parental telephone interviews.

Results: The study population included 112,744 children aged 3–13 years at the end of follow-up on December 31, 2012. Of these, there were 606 children with epilepsy (CWE). Distribution of seizure types varied by age of onset. Multiple seizure types were common with early onset. Focal epilepsies were the most common, occurring in 317 per 100,000 children in the study population and in 59% of CWE. Generalized epilepsies were found in 190 per 100,000 (35% of CWE). CWE with onset during the first 2 years of life had an even distribution of focal and generalized epilepsies, whereas focal epilepsies became dominant at later ages of onset. A definite cause of epilepsy had been demonstrated in 33% of CWE. The ILAE 1989 classification allowed for a broad syndrome category in 93% of CWE and a defined epileptic syndrome in 37%. With the ILAE 2017 classification, 41% of CWE had a defined epileptic syndrome and 63% had either a defined syndrome or structural–metabolic etiology.

Significance: The distribution of seizures and epilepsies is strongly dependent on age of onset. Despite diagnostic advances, the causes of epilepsy are still unknown in two-thirds of CWE. The ILAE 2017 classifications allow for a higher precision of diagnoses, but at the expense of leaving more epilepsies classifiable only at the mode of onset level.

KEY WORDS: Childhood epilepsy, Classification, Epilepsies, Seizures, Etiology.

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Key Points

- The distribution of epileptic seizures depends on the age of onset of epilepsy. Multiple seizure types are common, particularly in early onset epilepsies
- There is an even distribution of focal and generalized epilepsies for CWE with onset before age 2 years, whereas focal epilepsies are most common at later onset
- A definite cause of epilepsy was demonstrated in 33% of CWE, most commonly structural and/or genetic causes
- The ILAE 2017 classifications increase the precision of diagnoses, but applying them to epidemiological and nonspecialist settings is challenging

Childhood epilepsy has a large spectrum of clinical manifestations and many different causes.[1–3] There is a variety of epileptic seizure types, and a number of electroclinical epilepsy syndromes have been defined.[4–13] However, specific syndromes may have considerable phenotypic variability, and the distribution of seizures and syndromes in the general child population is not well known.[1,2] Recent advances in diagnostic procedures have identified several new epilepsy syndromes and causes of epilepsy.

The previous classifications for seizures and epilepsies published by the International League Against Epilepsy (ILAE) in 1981 and 1989, respectively, have been widely used both in clinical practice and in research.[4,6] Subsequent revision proposals have sought to increase the precision of classification and incorporate newly identified syndromes and etiologies.[7–10] In 2010, Berg et al.[9] proposed a new organization of epilepsies that has been influential in the subsequent process of revising the classifications. This proposal used age of onset as a way of organizing epilepsies, highlighting the importance of age of onset in childhood epilepsy.[9] New classification systems for seizures, epilepsies, and etiologies, which will replace the classifications from 1981 and 1989, were published by the ILAE earlier this year.[11–13]

Classification of epilepsies is based on several factors: seizure type, age of onset, family history, electroencephalographic (EEG) findings, results of magnetic resonance imaging (MRI), and other medical investigations and clinical characteristics. The ILAE 1989 classification includes both specific electroclinical syndromes and broad syndromic categories based on seizure types and etiology. In the ILAE 2017 classification, epilepsies are classified on three levels, first by seizure type (focal, generalized, or unknown), then epilepsy type by mode of onset (focal, generalized, combined, or unknown), and then into specific epilepsy syndromes or constellations.[11] Etiology is incorporated at each stage.[11] ILAE 2017 does not include the broad syndromic categories from ILAE 1989.[10,11]

Given the advances in diagnostics and classification, there is a need for updated information about the distribution of epileptic seizures, epilepsies, and etiologies in the general child population, and for studies comparing the new classifications to the old. To provide this type of knowledge, we have investigated childhood epilepsies in the Norwegian Mother and Child Cohort Study (MoBa).[14] We specifically tested three hypotheses:

(1) Because childhood epilepsies are commonly age-related, we hypothesized that the distribution of seizures, epilepsies, and etiologies would vary by age of onset.

(2) Because of the increased precision of epilepsy diagnoses of ILAE 2017, and its lack of the broad syndromic categories used in ILAE 1989, we hypothesized that (1) a higher proportion of epilepsies would be unclassifiable at the syndrome level with ILAE 2017 and (2) that the distribution of epilepsies would be different at the mode of onset level (focal/generalized/unknown) because of the introduction of a separate category for combined focal and generalized onset in ILAE 2017.

(3) We hypothesized that the proportion of epilepsy cases with and without demonstrated causes would be equal across the classifications, that is, that the proportion with symptomatic epilepsies in ILAE 1989 would equal the combined proportion of structural, metabolic, known genetic, infectious, and/or immunological causes in ILAE 2017. Furthermore, we hypothesized that the combined proportion of idiopathic and cryptogenic epilepsies in ILAE 1989 would equal the combined proportion of presumed genetic and unknown causes in ILAE 2017.

Material and Methods

Study population

MoBa is a nationwide, population-based cohort study that includes 114,427 children born from 1999 to 2009.[14] Within MoBa, we have established a nested case–cohort study of epilepsy, the Epilepsy in Young Children (EPYC) study.[15] Potential cases of epilepsy have been identified through linkages to the Norwegian Patient Register (all children recorded with International Classification of Diseases, 10th Edition codes G40.X) and by reports of epilepsy in the sequential parental questionnaires distributed to cohort participants.[15] The Norwegian Patient Registry collects data from all specialist health services in Norway. Reporting to the registry is mandated by law and linked to the governmental reimbursement system for health services. Details of the data collection, as well as the incidence and prevalence of epilepsy in the cohort, have been reported previously.[15]

We included all epilepsy cases meeting the new operational definition of epilepsy proposed by the ILAE in 2014,[16] that is, (1) children with two or more unprovoked

seizures occurring ≥24 h apart and (2) children with one unprovoked seizure who met the criteria for a defined epilepsy syndrome or had ≥60% risk of recurrent seizures. Children who only had febrile seizures or other provoked seizures were not included.

The children eligible for analyses were those who were liveborn and residing in Norway until death or the end of registry follow-up in December 2012. Age at end of follow-up was 3–13 years (median = 7 years), and all children were followed since pregnancy. Information about ethnicity was not available, but participation in MoBa requires parents to be fluent in Norwegian, and the vast majority of the cohort is of Norwegian or other European origin. We excluded 1,683 children who were stillborn, had emigrated, or were unavailable for follow-up due to missing personal identification numbers.

Classification

Epileptic seizures, epilepsy types, and etiologies were classified through medical record reviews and parental telephone interviews, using a standardized protocol for data collection.[15] All the available information was used for classification, including the reported results of EEGs, MRIs, and other clinical investigations. Results of some tests, like metabolic and genetic testing, might not be reported in medical records if results were negative. Classification was done by two child epileptologists (K.M.A., R.C.) according to the ILAE 1981/1989[4,6] and the ILAE 2017[11–13] classifications. Cases were reviewed independently, but complex and/or difficult cases (31% of total) were reviewed by both. Differences in opinion were resolved by consensus.

Statistical methods

Analyses were conducted using IBM SPSS Statistics version 22 and Stata/SE 14. We divided children with epilepsy (CWE) by categories of seizures, epilepsies, and etiologies, and calculated proportions of affected children in the study population as a whole, and as proportions within the CWE subpopulation. We also investigated differences determined by age of onset of epilepsy. The age of onset categories examined were <1 year (infancy), 1–4 years, and ≥5 years. It was not possible to cross-tabulate all syndromes by age of onset, but we have shown the distributions of the three main epilepsy categories (focal, generalized, and undetermined). We used Pearson chi-square tests, with two-sided p values, to compare age categories (hypothesis 1) and exact binomial probability tests to compare the old and new classifications (hypotheses 2 and 3).

Ethics

MoBa has a license from the Norwegian Data Protection Authority. Participation is based on informed consent, and this includes linkages to health registries and reviews of medical records. The EPYC study has approval from the Regional Committee for Medical and Health Research Ethics. Participation in the EPYC telephone interview was covered by additional informed consent. A number of epilepsy types/syndromes had been diagnosed in only a few children. To protect patient confidentiality, we inserted "<5" in all cells with less than five individuals in the table showing the distributions of epilepsy types and syndromes.

Results

The study population included 112,744 children. Of these, 606 children (0.54%) had a validated diagnosis of epilepsy, 162 with onset at <1 year of age, 273 with onset at age 1–4 years, and 169 with onset at age ≥ 5 years. Age of onset was defined as age at first unprovoked seizure,[17] and was unknown for two CWE. Medical records were available for 604 (99.7%), and 364 (60%) had parental interviews. All CWE had undergone EEG examinations, and 306 (50%) had undergone long-term EEG recordings (222 with video EEGs). Cerebral MRIs had been conducted in 532 (88%). Metabolic testing was reported for 118 (20%) and genetic testing for 160 (26%).

The general characteristics of the CWE are described in Table 1. There were considerable differences across age of onset categories. CWE with early onset were more likely to have a history of neonatal seizures ($p < 0.001$), febrile seizures ($p = 0.001$), more than one type of seizures ($p < 0.001$), abnormal findings on clinical neurological examinations ($p < 0.001$), and abnormal MRI findings ($p < 0.001$). There were no apparent differences across ages of onset with regard to sex distributions ($p = 0.67$) or family history of epilepsy ($p = 0.74$).

Epileptic seizures

The distribution of epileptic seizures, according to both the ILAE 1981[4] and ILAE 2017 seizure classifications,[12,13] is presented in Table 2 and Fig. 1A. In Table 2, the total numbers in each column add up to >606, because 56% of CWE had a history of more than one seizure type. The number of seizure types reported varied from one to seven, with a median of two. The seizure terminology has changed in ILAE 2017, and subcategories of seizures have been added, but the numbers of CWE in corresponding seizure categories were equal across the two classifications. Focal seizures were the most frequent seizure type in all age of onset categories, reported in 65% of CWE with onset age < 1 year, 69% with onset age 1–4 years, and 72% with onset age ≥ 5 years ($p = 0.76$). The majority of focal seizures were focal seizures with impaired awareness (referred to as complex partial seizures in ILAE 1981). Subcategories of focal motor and focal nonmotor seizures are not included, because the numbers were too small and there was often not information available to categorize on this level of detail. Generalized seizures were more frequent in CWE with earlier onset, reported in 55% of CWE with onset age < 1 year, 42% with onset age 1–4 years, and 32% with onset age ≥

Table 1. General characteristics of CWE

	All CWE, N = 606		CWE by age of onset[a]						
			<1 year, n = 162		1–4 years, n = 273		≥5 years, n = 169		
	n	%	n	%	n	%	n	%	p[b]
Male	327	54%	91	56%	149	55%	87	52%	0.67
Family history of epilepsy	151	25%	39	24%	66	24%	46	27%	0.74
History of neonatal seizures	74	12%	52	32%	18	7%	4	2%	<0.001
History of febrile seizures	117	19%	32	20%	68	25%	18	11%	0.001
Seizure precipitants reported	290	48%	74	46%	148	54%	68	40%	0.066
1 seizure type reported	265	44%	38	24%	122	45%	103	61%	<0.001[c]
2 seizure types reported	187	31%	46	28%	88	32%	53	31%	
≥3 seizure types reported	153	25%	77	48%	63	23%	13	8%	
Abnormal MRI findings	212	35%	80	49%	93	34%	38	23%	<0.001
Abnormal neurological exam	248	41%	109	67%	100	37%	38	23%	<0.001
Abnormal EEG findings (epileptic and nonepileptic)	522	86%	137	85%	225	82%	159	94%	0.002
Epileptiform EEG abnormalities	500	83%	132	82%	211	77%	156	92%	<0.001

CWE, children with epilepsy; EEG, electroencephalographic; MRI, magnetic resonance imaging.
[a]Age of onset of epilepsy is missing for two CWE.
[b]Probability values calculated with Pearson chi-square tests across age of onset groups.
[c]Probability value calculated with Pearson chi-square test across age of onset groups and number of seizure type categories.

5 years ($p < 0.001$). Typical absence seizures were the only generalized seizure type that was most common in those with a later onset of epilepsy. CWE with epilepsy onset in infancy (age < 1 year) had a high proportion (54%) of unclassifiable seizures ($p < 0.001$), most commonly unclassifiable neonatal seizures (15%) and epileptic spasms (35%).

As shown in Table 2, very few CWE had any of the new generalized seizure subtypes added in the ILAE 2017 seizure classification (myoclonic absence seizures and myoclonic–atonic seizures). For most cases of epileptic spasms, we lacked the information required to determine whether they had a focal or generalized onset, and we have categorized all spasms as unclassifiable or with unknown onset. Overall, there were 317 CWE (52%) with a history of tonic–clonic seizures, either primary generalized, secondary to focal seizures, or with uncertain mode of onset. A total of 111 CWE (18%) had reports of both focal and generalized seizures.

Epilepsies and syndromes

The distribution of epilepsy types and syndromes according to the ILAE 1989[6] and ILAE 2017[11] epilepsy classifications is shown in Table 3. Using the ILAE 1989 classification, focal (localization-related) epilepsies were the most common, occurring in 317 per 100,000 children in the study population and in 59% of CWE. Focal idiopathic epilepsies had a population proportion of 145 per 100,000 children (27% of CWE). Within this category, the most frequent specific syndromes were rolandic epilepsy, in 62 per 100,000 (12% of CWE), and childhood epilepsy with occipital paroxysms (including Panayiotopoulos syndrome), in 21 per 100,000 children (4% of CWE). Focal symptomatic epilepsies had been diagnosed in 135 per 100,000 (25% of CWE) and focal cryptogenic epilepsies in 36 per 100,000 (7% of CWE).

Generalized epilepsies were found in 190 per 100,000 children (35% of CWE). Under the ILAE 1989 classification, 96 per 100,000 children (18% of CWE) had generalized idiopathic epilepsies. The most frequent specific syndrome was childhood absence epilepsy, in 36 per 100,000 (7% of CWE). Generalized symptomatic and/or cryptogenic epilepsies occurred in 85 per 100,000 children (16% of CWE). Among these, the most frequent specific syndromes were West syndrome, in 42 per 100,000 (8% of CWE) and Lennox–Gastaut syndrome, in 11 per 100,000 (2% of CWE). Epilepsies that could not be determined as focal or generalized occurred in 50 per 100,000 (9% of CWE).

Overall, we were able to assign a broad syndrome category to 93% of CWE and a specific syndrome in 37% of CWE with ILAE 1989. Fig. 1B shows the distributions of the three main epilepsy categories (focal, generalized, and undetermined). Epilepsies with onset during the first 2 years of life have an even distribution between focal (49%) and generalized (47%) epilepsies ($p = 0.60$), but at later ages of onset, focal epilepsies become dominant and generalized epilepsies less frequent.

With the ILAE 2017 epilepsy classification (Table 3), we first classified epilepsy type according to mode of seizure onset as focal in 271 per 100,000 children (50% of CWE), generalized/bilateral in 130 per 100,000 (24% of CWE), both focal and generalized in 98 per 100,000 (18% of CWE), and unknown in 38 per 100,000 (7% of CWE). The introduction of a separate category for combined focal and generalized onset in ILAE 2017 reduced the proportion with

Table 2. Epileptic seizures in CWE

Seizure type	Population proportion per 100,000, N = 112,744	All CWE, N = 606[a]		CWE by age of onset[b]						p[c]
				<1 year, n = 162		1–4 years, n = 273		≥5 years, n = 169		
		n	%	n	%	n	%	n	%	
ILAE 1981 seizure classification										
Partial seizures	369	416	69%	105	65%	189	69%	121	72%	0.40
Simple partial seizures	60	68	11%	10	6%	33	12%	25	15%	0.04
Complex partial seizures	330	372	61%	100	62%	171	63%	100	59%	0.76
Partial seizures evolving to secondarily generalized seizures	167	188	31%	51	32%	85	31%	52	31%	0.99
Generalized seizures	229	258	43%	89	55%	114	42%	54	32%	<0.001
Absence	101	114	19%	21	13%	54	20%	38	23%	0.07
Tonic–clonic	99	112	19%	42	26%	59	22%	11	7%	<0.001
Myoclonic	75	84	14%	51	32%	28	10%	5	3%	<0.001
Clonic	0	—	—	—	—	—	—	—	—	—
Tonic	72	81	13%	51	32%	28	10%	2	1%	<0.001
Atonic	35	39	6%	18	11%	20	7%	1	0.6%	<0.001
Unclassified seizures	127	143	24%	88	54%	40	15%	15	9%	<0.001
Behavioral arrest	21	24	4%	7	4%	11	4%	6	4%	0.94
Tonic–clonic not classifiable	18	20	3%	4	2%	12	4%	4	2%	0.40
Epileptic spasms	53	60	10%	56	35%	4	2%	0	—	<0.001
Neonatal not classifiable	27	30	5%	24	15%	5	2%	1	0.6%	<0.001
Other nonclassifiable	14	16	3%	6	4%	7	3%	3	2%	0.55
ILAE 2017 seizure classification										
Focal onset seizures	369	416	69%	105	65%	189	69%	121	72%	0.40
Focal onset aware	60	68	11%	10	6%	33	12%	25	15%	0.04
Focal onset impaired awareness	330	372	61%	100	62%	171	63%	100	59%	0.76
Focal to bilateral tonic–clonic	167	188	31%	51	32%	85	31%	52	31%	0.99
Motor onset	266	300	50%	72	44%	144	53%	84	50%	0.25
Nonmotor onset	157	177	29%	42	26%	74	27%	60	36%	0.10
Generalized onset seizures	229	258	43%	89	55%	114	42%	54	32%	<0.001
Motor	176	198	33%	86	53%	91	33%	21	12%	<0.001
Tonic–clonic	99	112	19%	42	26%	59	22%	11	7%	<0.001
Clonic	0	—	—	—	—	—	—	—	—	—
Tonic	72	81	13%	51	32%	28	10%	2	1%	<0.001
Myoclonic	75	84	14%	51	32%	28	10%	5	3%	<0.001
Myoclonic–tonic–clonic	0	—	—	—	—	—	—	—	—	—
Myoclonic–atonic	4	5	1%	1	1%	4	2%	0	—	0.24
Atonic	35	39	6%	18	11%	20	7%	1	0.6%	<0.001
Epileptic spasms[d]	0	—	—	—	—	—	—	—	—	—
Nonmotor (absences)	101	114	19%	21	13%	54	20%	38	23%	0.07
Typical absences	55	62	10%	7	4%	24	9%	31	19%	<0.001
Atypical absences	17	19	3%	7	4%	9	3%	3	2%	0.41
Other absences (myoclonic, eyelid myoclonia, other)	32	36	6%	7	4%	23	8%	6	4%	0.06
Unknown onset	127	143	24%	88	54%	40	15%	15	9%	<0.001
Motor	76	86	14%	61	38%	19	7%	6	4%	<0.001
Tonic–clonic not classifiable[e]	18	20	3%	4	2%	12	4%	4	2%	0.40
Epileptic spasms[d]	53	60	10%	56	35%	4	2%	0	—	<0.001
Nonmotor (behavioral arrest)	21	24	4%	7	4%	11	4%	6	4%	0.94
Unclassified	31	35	6%	21	13%	10	4%	4	2%	<0.001

CWE, children with epilepsy; ILAE, International League Against Epilepsy.
[a]Column totals add up to >606, because 340 CWE had more than one seizure type.
[b]Age of onset refers to onset of epilepsy, not individual seizure types. Age of onset was missing for two CWE.
[c]Probability values calculated with Pearson chi-square tests across age of onset groups.
[d]All epileptic spasms were classified as having unknown onset due to lack of information about onset mode.
[e]Tonic–clonic seizure where mode of onset (focal or generalized) was unknown.

focal epilepsies from 59% to 50% ($p < 0.001$), and the proportion with generalized epilepsies from 35% to 24% ($p < 0.001$).

At the level of specific syndromes, constellations, and/or structural–metabolic etiologies, 37% of CWE were left unclassifiable in the ILAE 2017 epilepsy classification,

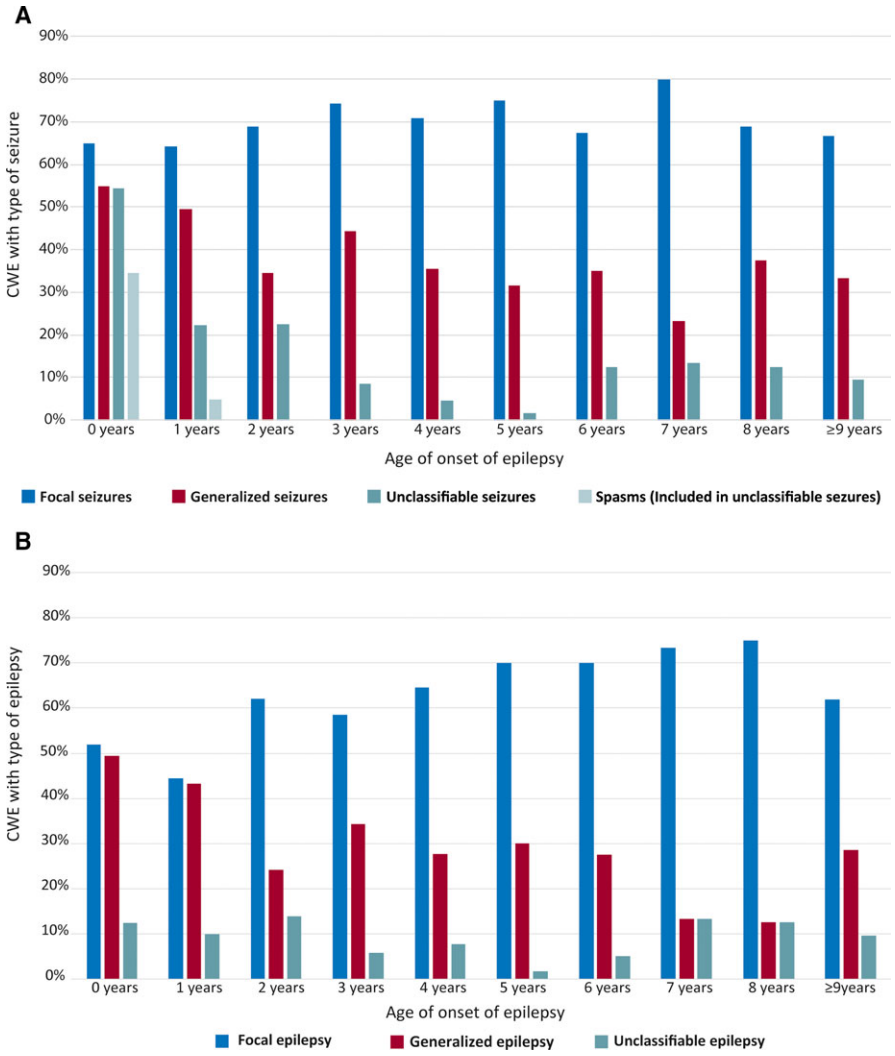

Figure 1.
Seizures **(A)** and epilepsies **(B)** by age of epilepsy onset (International League Against Epilepsy 1981/1989 classifications). CWE, children with epilepsy.
Epilepsia © ILAE

compared to the 6% who were unclassifiable in the broad syndromic/etiological groups of ILAE 1989 ($p < 0.001$). Numbers were equal across classifications for the specific syndromes included in both epilepsy classifications. ILAE 2017 includes several new syndromes that have been recognized since ILAE 1989 was published. The largest of these in our study was genetic epilepsy with febrile seizures plus, which occurred in 27 per 100,000 children (5% of CWE).

The ILAE 2017 epilepsy classification also introduces the term "developmental and epileptic encephalopathies," which includes West syndrome, Lennox–Gastaut syndrome, Landau–Kleffner syndrome, Dravet syndrome, and other early infantile epileptic encephalopathies. In total, such encephalopathies were found in 60 per 100,000 children (11% of CWE), with the highest proportion for those with epilepsy onset in infancy (32%). With ILAE 1989, the majority (78%) of these children were classified as having generalized cryptogenic or symptomatic epilepsies.

There were 45 CWE (7%) who met the criteria for more than one epileptic syndrome, because they transitioned from one age-related syndrome to another during follow-up. The most common transition was from West syndrome to other epilepsies. Of the 47 children who had West syndrome in infancy, 34 developed other types of epilepsy during follow-up: Lennox–Gastaut syndrome in nine, other generalized symptomatic epilepsies in eight, and multifocal epilepsies in 17 children.

Etiology

Table 4 and Figure 2 show the etiological classification of the epilepsies, by both the ILAE 1989[6] and the ILAE 2017[11] classifications. With ILAE 1989, the population proportion with idiopathic etiology was 242 per 100,000 children (45% of CWE), whereas 116 per 100,000 (22% of CWE) had cryptogenic etiology, and 179 per 100,000 (33% of CWE) had symptomatic etiology. These etiological categories were mutually exclusive. The distributions differed by age of onset, with symptomatic etiology being most frequent for epilepsies with infancy onset, whereas idiopathic etiology was most frequent at later ages of onset ($p < 0.001$).

Table 3. Distribution of epilepsy types and syndromes in CWE

ILAE 1989 epilepsy classification	Population proportion per 100,000, N = 112,744	All CWE, N = 606[a]		ILAE 2017 epilepsy classification	Population proportion per 100,000, N = 112,744	All CWE, N = 606[a]	
		n	%			n	%
1. Localization-related	317	357	59%	*Mode of seizure onset*			
1.1 Localization-related idiopathic	145	164	27%	Focal	271	305	50%
1.1.0 Localization-related idiopathic other/not further classified	62	70	12%	Generalized/bilateral	130	147	24%
1.1.1 Benign rolandic epilepsy (BCECTS)	62	70	12%	Combined generalized and focal	98	111	18%
1.1.2 Childhood epilepsy with occipital paroxysms	21	24	4%	Unknown	38	43	7%
1.2 Localization-related symptomatic	135	152	25%				
1.3 Localization-related cryptogenic	36	41	7%	*Epileptic syndromes by age of onset*			
				Neonatal syndromes (≤1 month)	4	4	1%
2. Generalized	190	214	35%	Benign familial neonatal epilepsy	<4	<5	<1%
2.1 Generalized idiopathic, age-related onset	96	108	18%	EME	0	0	—
2.1.1 Benign neonatal familial convulsions	<4	<5	<1%	Otahara syndrome	<4	<5	<1%
2.1.2 Benign neonatal convulsions	0	0	—	Other EIEE	<4	<5	<1%
2.1.3 Benign myoclonic epilepsy in infancy	<4	<5	<1%	Infant syndromes (1–11 months)	58	65	11%
2.1.4 Childhood absence epilepsy	36	41	7%	Epilepsy of infancy with migrating focal seizures	0	0	—
2.1.5 Juvenile absence epilepsy	0	0	—	West syndrome	42	47	8%
2.1.6 Juvenile myoclonic epilepsy	0	0	—	Myoclonic epilepsy in infancy	<4	<5	<1%
2.1.7 Epilepsy with GTCS on awakening	<4	<5	<1%	Benign infantile epilepsy	<4	<5	<1%
2.1.8 Other idiopathic generalized epilepsies	56	63	10%	Benign familial infantile epilepsy	6	7	1%
2.2 Generalized cryptogenic/ symptomatic	51	57	9%	Dravet syndrome	4	5	<1%
2.2.0 Generalized cryptogenic/ symptomatic not further classified	6	7	1%	Myoclonic encephalopathy in nonprogressive disorders	<4	<5	<1%
2.2.1 West syndrome	42	47	8%	Childhood syndromes (1–15) years	169	190	31%
2.2.2 Lennox–Gastaut syndrome	11	12	2%	FS+[b]	<4	<5	<1%
2.2.3 Doose syndrome	<4	<5	<1%	GEFS+[b]	27	30	5%
2.2.4 Epilepsy with myoclonic absences	0	0	—	Panayiotopoulos syndrome	21	24	4%
2.3 Generalized symptomatic	39	44	7%	Epilepsy with myoclonic atonic seizures	<4	<5	<1%

Continued

Table 3. Continued.

ILAE 1989 epilepsy classification	Population proportion per 100,000, N = 112,744	All CWE, N = 606[a] n	All CWE, N = 606[a] %	ILAE 2017 epilepsy classification	Population proportion per 100,000, N = 112,744	All CWE, N = 606[a] n	All CWE, N = 606[a] %
2.3.1 Generalized symptomatic, nonspecific etiology	20	22	4%	BCECTS	62	70	12%
2.3.2 Generalized symptomatic, specific etiology	20	22	4%	ADNFLE	<4	<5	<1%
3. Undetermined	50	56	9%	Late onset childhood occipital epilepsy	0	0	—
3.1 Epilepsies with focal and generalized features	20	22	4%	Epilepsy with myoclonic absences	0	0	—
3.1.0 Not further classified	7	8	<1%	Lennox–Gastaut syndrome	11	12	2%
3.1.2 Dravet syndrome	4	5	<1%	CSWS	6	7	1%
3.1.3 CSWS	6	7	1%	Landau–Kleffner syndrome	<4	<5	<1%
3.1.4 Landau–Kleffner syndrome	<4	<5	<1%	Childhood absence epilepsy	36	41	7%
3.2 Unclassifiable epilepsies	30	34	6%	*No specific age of onset*			
				Reflex epilepsy	<4	<5	<1%
				Distinctive constellations	<4	<5	<1%
				Mesial temporal lobe epilepsy with hippocampal sclerosis	<4	<5	<1%
				Hypothalamic hamartoma with gelastic seizures	<4	<5	<1%
				Epilepsy with hemiconvulsions and hemiplegia	0	0	—
				Rasmussen syndrome	0	0	—
				Epilepsies attributed to/ organized by structural–metabolic causes (see Table 4)	114	128	21%
				Unclassifiable epilepsies	200	225	37%

ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BCECTS, benign childhood epilepsy with centrotemporal spikes; CSWS, continuous spike-waves during slow sleep; CWE, children with epilepsy; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; FS+, febrile seizures plus; GEFS+, generalized epilepsy with febrile seizures plus; GTCS, generalized tonic–clonic seizures; ILAE, International League Against Epilepsy.

[a]Column totals add up to >606, because 45 CWE transitioned to another type of epilepsy during follow-up, thus meeting criteria for more than one type/syndrome.

[b]FS+ was defined as febrile seizures AND at least one unprovoked seizure. GEFS+ was defined as febrile seizures AND at least one unprovoked seizure AND first- or second-degree relatives with febrile seizures and/or epilepsy.

Under the ILAE 2017 classification, the major etiological categories were structural etiology (defined by abnormal structural MRI findings), occurring in 141 per 100,000 children (26% of CWE), and genetic etiology, in 183 per 100,000 (34% of CWE). Of the 206 CWE categorized as having genetic etiology, a specific genetic cause had been demonstrated in 58, whereas the other 148 were presumed genetic based on the specific epilepsy syndrome and/or a family history of epilepsy. Metabolic and infectious etiologies were rare. We did not detect any CWE with immunological causes of epilepsy, but a few CWE had undergone investigations for immunological causes. The etiology of epilepsy was classified as unknown in 229 per 100,000 children (43% of CWE).

The ILAE 2017 classification allows for the use of more than one etiological category in the same patient. There were 21 CWE who had both structural and genetic abnormalities, and all 12 CWE with infectious etiologies also had structural findings. Both structural and known genetic etiologies were associated with early onset of epilepsy ($p < 0.001$ for both), whereas epilepsies with onset age ≥ 5 years had a higher proportion with unknown etiology

Table 4. Etiologic classification in CWE

Etiology	Population proportion per 100,000, N = 112,744	All CWE, N = 606		CWE by age of onset[a] <1 year, n = 162		1–4 years, n = 273		≥5 years, n = 169		p[b]
		n	%	n	%	n	%	n	%	
ILAE 1989 epilepsy classification										
Idiopathic	242	273	45%	28	17%	134	49%	111	66%	<0.001[c]
Cryptogenic	116	131	22%	44	27%	59	22%	27	16%	
Symptomatic	179	202	33%	90	56%	80	29%	31	18%	
ILAE 2017 epilepsy classification[d]										
Structural	141	159	26%	66	41%	63	23%	29	17%	<0.001
Perinatal event[e]	71	80	13%	31	19%	35	13%	13	8%	0.008
Congenital CNS malformation	27	31	5%	11	7%	17	6%	3	2%	0.064
Malformation of cortical development	29	33	5%	20	12%	10	4%	3	2%	<0.001
Other structural[f]	16	18	3%	8	5%	7	3%	3	2%	0.21
Metabolic	4	5	1%	4	3%	1	0.4%	0	—	0.024
Genetic	183	206	34%	69	43%	92	34%	45	27%	0.009
Genetic cause found	51	58	10%	30	19%	26	10%	2	1%	<0.001
Presumed genetic cause	131	148	24%	39	24%	66	24%	43	25%	0.95
Infectious	11	12	2%	5	3%	2	0.7%	5	3%	0.13
Immunological	0	0	—	0	—	0	—	0	—	—
Unknown	229	258	43%	35	22%	126	46%	96	57%	<0.001

CNS, central nervous system; CWE, children with epilepsy; ILAE, International League Against Epilepsy.
[a]Age of onset was missing for two CWE.
[b]Probability values calculated with Pearson chi-square tests across age of onset groups.
[c]Probability value calculated with Pearson chi-square test across age of onset groups and etiological categories.
[d]Column totals add up to >606 because some CWE fit into more than one etiological category in ILAE 2017.
[e]Hemorrhage, infarction, hypoxic–ischemic events, leukomalacia, other.
[f]Tumors, neurocutaneous disorders, other.

($p < 0.001$). A definite cause had been demonstrated in 33% of CWE overall, and in 53% of CWE with infancy onset epilepsies.

The percentage of CWE classified as having a demonstrated cause with ILAE 2017 (structural, metabolic, known genetic, infectious, and/or immunological) was 33%, which was equal to the 33% with symptomatic epilepsies with ILAE 1989 ($p = 0.90$). Similarly, the proportion with unknown or presumed genetic causes with ILAE 2017 (67%) was equal to the proportion with cryptogenic or idiopathic etiology with ILAE 1989 (67%; $p = 0.90$).

Discussion

The study provides updated information about the distribution of seizures, epilepsies, and etiologies in a general child population, and explores the differences between the old and new classification systems. In the following, we will discuss our main findings and describe advantages and disadvantages of the different classifications.

Distribution of epileptic seizures

Despite differences in age distributions, our findings are similar to those of previous studies of childhood epilepsy, in that focal seizures are most frequent at all ages of epilepsy onset, and become relatively more predominant with later onset of epilepsy.[1,3,18–22] The MoBa cohort is still relatively young, and the CWE had a median age of 3 years at epilepsy onset and 9 years at end of follow-up. It is likely that we captured most epilepsies with an onset before 5 years of age, but there is incomplete ascertainment of epilepsies starting at age 5 years or older, because the age range of the study population was 3–13 years at the end of follow-up. Consequently, the subpopulation with epilepsy is skewed toward the younger ages of onset, and that could explain why the proportion of CWE with infancy onset (27%) is higher than in previous studies, where the range is from 12% to 18%.[18,19,21–25] It would also explain why we found higher proportions with epileptic spasms (10% of CWE) and the seizure types associated with early onset, that is, atonic, tonic, and myoclonic seizures (23% overall for CWE). Studies of older children have reported proportions of 1–8% for epileptic spasms.[20,22,23,26,27] The young median age is probably also why we have high proportions of CWE with multiple seizure types (25% with ≥3 seizure types) and histories of both focal and generalized seizures (18%). The proportion with ≥3 seizure types is much higher than what has been reported in children with newly diagnosed epilepsy (0.5%),[19] but lower than that of a previous Norwegian study of children with active epilepsy (36%).[22] The high proportion with multiple seizure types may also result from our attempt to record and classify all seizure types. Most previous studies have reported either the predominant[22,27] or initial/presenting[19,23,24,28] seizure type.

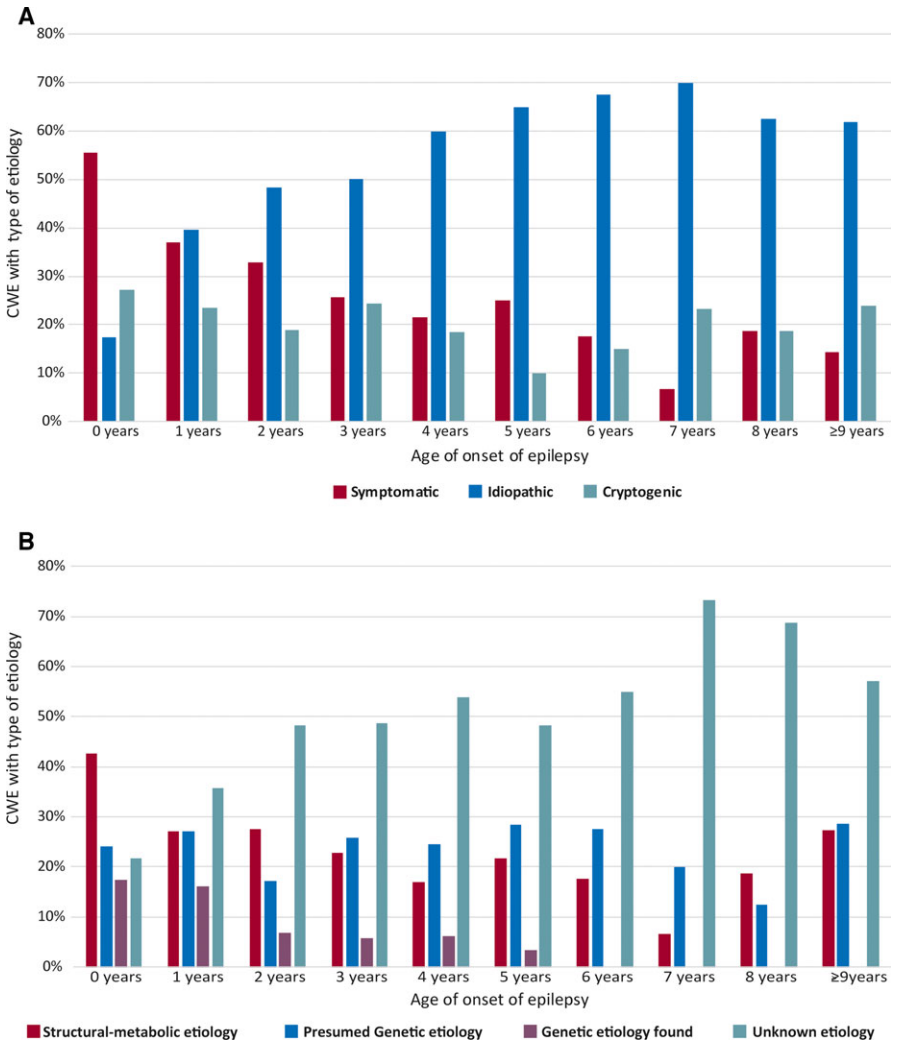

Figure 2.
Type of etiology by age of epilepsy onset, with International League Against Epilepsy (ILAE) 1989 **(A)** and ILAE 2017 **(B)** classifications. CWE, children with epilepsy.
Epilepsia © ILAE

Distribution of epilepsy types and syndromes

The distribution of epilepsy types and syndromes is also comparable to other studies from high-income countries, with focal epilepsies being the most common.[1,19,22,25,26,29,30] Our proportion of focal (localization-related) idiopathic epilepsies (27%) is higher than in previous hospital-based studies (7–17%),[22,27,31,32] but comparable to an Italian population-based study (24%),[33] suggesting that some cases of focal idiopathic epilepsies are not captured in hospital-based study samples. Our proportion of focal cryptogenic epilepsies (7%) is lower than in older studies (11–19%),[18,19,27,32] possibly because recent advances in diagnostics have identified a specific cause in more cases.

With the ILAE 1989 epilepsy classification, 94% of the CWE were classifiable into the broad syndromic groups, which is in the same range as previous population-based studies (90–99%).[19,20,22,27] Our proportion with a specific epileptic syndrome (41%) was somewhat lower than in studies where all CWE were diagnosed by neurologists (49–99%).[19,20,28,29] This is not surprising, because specialist health services for Norwegian children are often provided by small pediatric departments, and most of the CWE in this study had been initially diagnosed by general pediatricians and not by child neurologists. Conversely, we identified a higher proportion of CWE with specific syndromes than other population-based studies (12–28% with specified syndromes),[23,34,35] probably because of our comprehensive set of data from medical records (99.7% of CWE) and parental telephone interviews (60% of CWE). Our results are similar to a recent comparable population-based study of infants with epilepsy, which found that a specific syndrome was reported in 42%.[36]

The ILAE 2017 epilepsy classification allowed for a specific epilepsy diagnosis in 63% of CWE, either as a defined syndrome or with a structural–metabolic etiology, whereas 94% of CWE fit into a broad syndromic category with ILAE 1989. In other words, the increased diagnostic precision of ILAE 2017 comes at the expense of leaving more cases classifiable only at the mode of onset level. Our

findings indicate that the need for detailed information can make the new classification challenging to use in population-based studies and clinical settings where CWE are not diagnosed by child neurologists.

Distribution of causes of epilepsy

A specific cause of epilepsy had been demonstrated in 33% of all CWE. This was somewhat higher than in previous population-based studies of children, in which 18–26% had a known cause.[18,19,28] However, given that those studies were conducted nearly 2 decades ago, it is disappointing that the proportion without a demonstrable cause is still so high. Our proportions with infectious (2%) and traumatic (<1%) causes were lower than in older studies, where infectious causes have been found in 2–4% and traumatic causes in 1–9%.[1,27,37,38] This may indicate a decline in epilepsies with currently preventable causes.

With the ILAE 1989 etiological classification, 67% of CWE were defined as having an unknown cause of epilepsy (idiopathic or cryptogenic etiology), whereas this proportion declined to 43% with unknown etiology in the ILAE 2017 etiological classification. This decline may seem like an improvement at first sight, but the difference was explained by including "presumed genetic cause" under genetic etiology in ILAE 2017 (these were idiopathic according to ILAE 1989). The proportion with unknown and presumed genetic causes combined in ILAE 2017 was equal to the proportion of idiopathic and cryptogenic etiologies combined in ILAE 1989 (67%).

Strengths and limitations

The main strength of our study is the size and the population-based cohort design, with nationwide recruitment and prospective follow-up of all children. The combination of registry linkages and questionnaire follow-up ensured that most cases of epilepsy were identified. Our ability to collect data from multiple sources, using both medical records and parental interviews, ensured that most epilepsy cases could be classified at some level.

The main limitation is that some data were collected several years after the onset of epilepsy. This did not affect the quality of information from the medical records, which was recorded prospectively, but we might have obtained more detailed seizure descriptions from the parents if we had been able to conduct interviews closer to the time of onset. Another limitation is that we had to rely on investigations carried out as part of routine clinical practice. If more CWE had undergone genetic, metabolic, and immunologic investigations, a higher proportion of them might have had specific syndrome diagnoses and specific causes of epilepsy demonstrated.

Our study sample is derived from a cohort study. Previous comparisons of the cohort to the general Norwegian population have shown that the MoBa parents have somewhat higher levels of education and healthier lifestyles than other Norwegians of similar ages, and that the cohort includes very few immigrants and people of non-Caucasian origin.[39] Single mothers are also underrepresented.[39] However, this skewness in selection does not appear to affect the incidence of childhood epilepsy, and MoBa is similar to the general population in this respect.[40] Therefore, we believe that the distributions of epilepsies shown here are representative for Norway and similar countries, that is, high-income countries with universal access to health care.

Conclusion

The distribution of childhood epilepsies is highly dependent on age of onset. Focal seizures are the most frequent seizure type at all ages, but early onset epilepsies, particularly those with infancy onset, are characterized by higher proportions of generalized seizures and epileptic spasms. There is also often a history of multiple seizure types in these children. Early onset epilepsies are more likely to have a demonstrable cause, with structural and genetic causes being the most common. This shows the importance of including neuroimaging and genetic investigations in clinical care, especially for early onset epilepsies. For epilepsies with onset after age 5 years, focal seizures are the dominant seizure type, and the underlying causes are unknown in most cases. The ILAE 2017 classifications allow for increased precision, but require advanced diagnostic skills and are challenging to use in epidemiological studies and clinical settings where diagnoses are not assigned by neurologists.

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Disclosure

The authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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