

SHORT RESEARCH ARTICLE

Epilepsy at different ages—Etiologies in a Norwegian population

Eline Dahl-Hansen¹ | Jeanette Koht^{1,2} | Marte Syvertsen^{1,2}

¹Department of Neurology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway

²Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence

Eline Dahl-Hansen, Department of Neurology, Drammen Hospital, Drammen, Norway.

Email: edahlhansen@yahoo.no

Summary

The causes of epilepsy are age related, but confirmative data from population-based studies are scarce. Our aim was to describe the typical causes of epilepsy in the different age groups of a defined population. The study was cross-sectional, based on a review of all medical files containing a diagnostic code for epilepsy at Drammen Hospital from 1999–2013. Drammen Hospital serves the population of Buskerud County, with 272 228 residents (as of January 1, 2014), including 1771 people with active epilepsy. This group of persons with active epilepsy was divided into different age groups with the causes of epilepsy mapped in each group. The proportion with unknown etiology ranged from 27% (age 5–9) to 41% (age 10–19). Structural-metabolic epilepsy and perinatal insults were the leading causes of epilepsy in the age group 5–9 (46%), whereas disturbances of brain development dominated in the youngest (23% in patients ≤4 years old). In the group comprising persons with epilepsy ≥60 years old, stroke was the most common cause of epilepsy (44%). Despite recent advances in research and technology, a large number of patients in all age groups (including the youngest) still have an unknown cause of epilepsy. We conclude that an effort must be made to improve the diagnostics for and understanding of the causes of epilepsy across all ages.

KEYWORDS

age, epidemiology, epilepsy, etiology

1 | INTRODUCTION

Epilepsy is one of the most common neurologic disorders,¹ affecting 0.65% of the population in our county in Norway.² The etiology of epilepsy is complex and usually multifactorial, often due to a combination of predisposing factors, development disorders, and external impact. Whatever alters the connections and signaling between the cerebral cortical cells may lead to epileptic seizures.³ In our county, 43% (767 patients) had a known structural-metabolic cause for their epilepsy and 20% (359 patients) had a genetic or presumed genetic cause, whereas 36% (645 patients) had an unknown cause.²

The etiology of epilepsy is age dependent, with stroke and neoplasia being the most important factors among the elderly.^{4,5} In younger men, traumatic brain injuries seem to dominate,⁶ as do cerebral palsy and malformations of cortical structures in the younger age groups.⁷ Yet, in several studies that mapped the etiologic factors of epilepsy, for large proportions of patients there is no explanation for the seizures.^{2,5,7–14} Most of these studies are old, however. Recent advances in research, that is, genetics and imaging technology, should help improve the diagnostics of epilepsy. Nevertheless, updated population-based data on the age-dependent causes of epilepsy are scarce.

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The aim of this study was to assess the typical causes of epilepsy in the different age groups of a defined population.

2 | METHODS

The study was cross-sectional and based on a review of all medical files (emergency, inpatient, and outpatient service records) containing an International Classification of Diseases, Tenth Revision (ICD-10) code for epilepsy (G40) at Drammen Hospital from 1999 to 2013. As of January 1, 2014, a total of 1771 people of 272 228 residents in Buskerud County had active epilepsy and were included.² Buskerud County has only one electroencephalography (EEG) laboratory, located at Drammen Hospital, and EEG is a part of the standard diagnostic workup for diagnosing epilepsy in Norway. Thus, we hypothesize that close to all subjects with a diagnosis of epilepsy in Buskerud County are registered in our database.²

The medical records of each identified subject were reviewed thoroughly by the last author (MS), who has several years of experience within the field of epileptology. Epilepsy was defined as 2 unprovoked seizures occurring at least 24 hours apart, and active epilepsy was defined as current treatment with antiepileptic medication, or at least one seizure within the last 5 years.² Patients who did not fulfill these criteria were excluded from the study, even if they were registered with an ICD-10 code of epilepsy.

All patients with active epilepsy were divided into 6 different age groups; 0-4, 5-9, 10-19, 20-39, 40-59, and ≥60 years of age. We chose narrower age intervals in the youngest age groups based on the knowledge that the incidence of epilepsy is higher in the first years of life.^{15,16} The age at entry was the age at the inclusion day, that is, January 1, 2014. The average life span in Buskerud county

is 79.7 years for men and 83.6 for women, corresponding to the general population of Norway (79.7/83.7). We chose to register age at the inclusion day as opposed to age at epilepsy onset, because the retrospective study design would make an approach to incidence data unreliable. Instead, we aimed to provide information about prevalence, that is, which causes of epilepsy are the most prevalent at a given age, irrespective of time of onset.

The causes of epilepsy were mapped in each group according to guidelines and terminology issued by the International League Against Epilepsy (ILAE).^{3,17} Our database was established before publication of the recent ILAE classification of the epilepsies,¹⁸ and as a consequence, the revised terminology for organization of seizures and epilepsies issued in 2010³ was used when classifying prevalent cases, in addition to the ILAE guidelines for epidemiologic studies of epilepsy.¹⁷ Subjects with a structural-metabolic etiology were subclassified into one of 12 different categories: stroke, perinatal insults, neoplasia, trauma, infections, malformations of cortical structures, degenerative diseases, metabolic or toxic insults, inborn errors of metabolism, mesial temporal sclerosis, neurocutaneous syndromes, and other.¹⁷

To approximate incidence data, all of the subjects who were diagnosed with epilepsy in 2013 were identified, and the causes of epilepsy were analyzed in this group separately.

Of the 21 municipalities of Buskerud County, 11 were considered rural (administrative center >50 km away from Drammen Hospital). The remaining were considered central.² Municipalities with average income <400 000 kroner per year were considered low-income (6 municipalities).

Descriptive demographic and clinical measures are shown as numbers and frequencies. All analyses were performed using the IBM SPSS Statistics 23 software. The chi-square test was used for comparison of categorical variables, and *P*-values <0.05 were considered statistically significant.

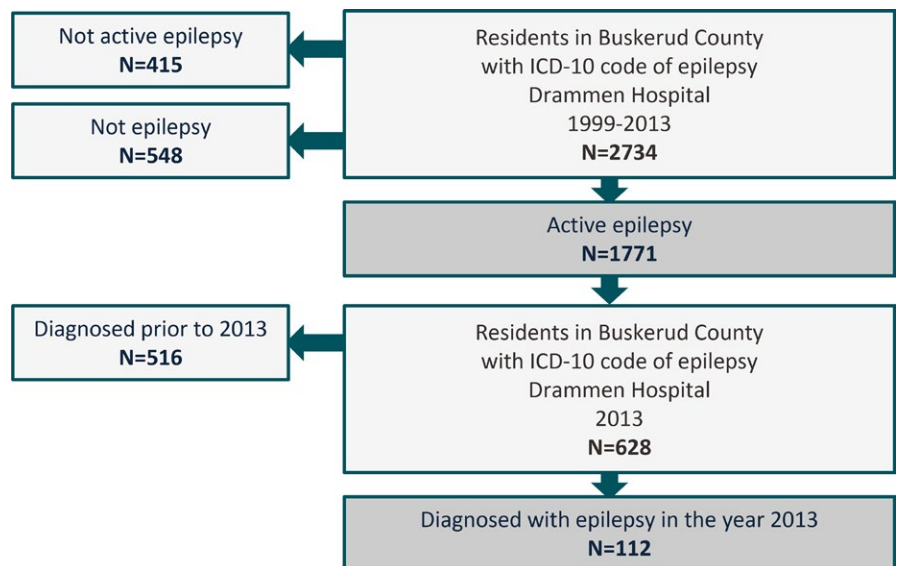


FIGURE 1 Flow chart of patient inclusion

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (ethical agreement no. 2013/1027).

3 | RESULTS

The number of medical records reviewed is illustrated in Figure 1. The age-dependent causes of epilepsy in Buskerud County are summarized in Figure 2. Genetic/presumed genetic causes dominated in youth and young adults (10-39 years), but a specific genetic diagnosis was found in only 10. No systematic use of newer genetic methods, such as next-generation sequencing, had been performed, but a phenotype-based single-gene approach had been done in some patients. In the remaining age groups, structural-metabolic etiology was the most prominent. For about one-third of the patients in all age groups etiology was unknown.

Of the 1771 people with active epilepsy, 767 had a structural-metabolic etiology. The structural-metabolic causes of epilepsy in different age groups are summarized in Table 1.

The gender distribution was equal for all causes of epilepsy, except for traumatic brain injury ($n = 99$, 75.8% male, $P \leq 0.001$), metabolic or toxic insults ($n = 20$, 85.0% male, $P = 0.003$), and mesial temporal sclerosis ($n = 13$, 77.0% female, $P = 0.037$). There were no statistically significant geographical or economic differences in the distribution of structural-metabolic causes of epilepsy (rural vs central municipalities and low-income vs the remaining municipalities). The proportion of patients with an unknown cause of epilepsy was higher in rural municipalities (35.4%) than in central ones (41.9%, $P = 0.036$), and it was higher in low-income municipalities (45.1%) compared to the remaining municipalities (35.6%, $P = 0.020$).

In the year 2013, a total of 112 subjects were diagnosed with epilepsy (56 female). The frequency of new cases of epilepsy per 100 000 inhabitants in the year 2013 was 41. The age distribution of new cases is shown in Figure 3. Twenty-five (22.3%) had a genetic or presumed genetic etiology, and 56 (50.0%) had a structural-metabolic cause of epilepsy. In 31 (27.7%), the etiology of epilepsy was unknown. The different subgroups of new cases of structural-metabolic epilepsy are presented in Table 1.

4 | DISCUSSION

The present study demonstrates the causes of epilepsy at different ages in a population-based material, stating that despite recent advances in imaging technology, genetic knowledge, and research, the proportion of patients with an unknown etiology remains large in all age groups. Identifying the cause of epilepsy is essential to offering the right treatment and follow-up and is timely underscored as an area of particular importance in the new ILAE classification of the epilepsies.¹⁸ However, it seems we still have a long way to go to fully understand this highly important aspect of epileptology.

When investigating the etiology of epilepsy, studies from the same geographic area should be explored, as we know that the causes of epilepsy are related to geographic and socioeconomic differences.¹⁹⁻²¹ Thus, such information from different parts of the world is of value. Within Norway, however, education, income, and ethnicity are fairly equally distributed. Consequently, the present data could be considered representative of the country as a whole. However, we did find a significantly higher proportions of patients with an unknown cause of epilepsy in rural and low-income municipalities. This is noteworthy and could reflect that even within the borders of a country with accessible and egalitarian public

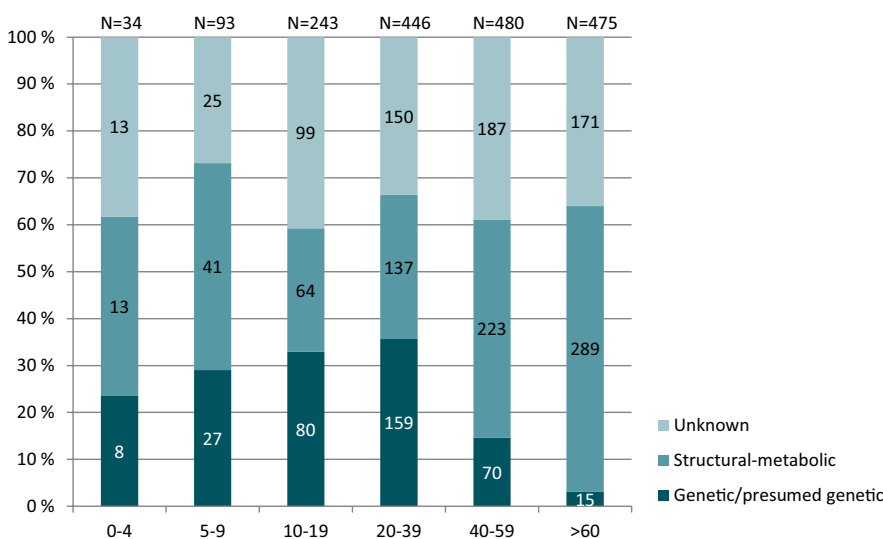


FIGURE 2 The etiology of epilepsy in different age groups at the prevalence day (January 1, 2014)

TABLE 1 Subclassification of structural-metabolic epilepsy in different age groups

Age in years	0-4 N = 13		5-9 N = 41		10-19 N = 64		20-39 N = 137		40-59 N = 223		≥60 N = 289		Total N = 767		New cases ^a N = 56	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Stroke	0	0	0	0	0	0	3	2	32	15	127	44	162	21	12
Perinatal insults	2	15	19	47	21	33	31	22	31	14	6	2	110	14	4	7
Neoplasia	2	15	3	8	3	5	12	9	43	19	38	13	101	13	20	36
Trauma	0	0	0	0	2	3	19	14	39	17	39	14	99	13	3	5
Infection	0	0	1	2	5	8	7	5	20	9	10	3	43	5	0	0
Malformations of cortex	3	23	5	12	9	14	10	7	4	2	0	0	31	4	1	2
Degenerative diseases	0	0	0	0	0	0	1	1	2	1	25	9	28	4	5	9
Metabolic or toxic insults	0	0	0	0	0	0	1	1	7	3	12	4	20	3	2	4
Inborn errors of metabolism	1	8	1	2	2	3	4	3	4	2	2	1	14	2	0	0
Mesial temporal sclerosis	0	0	0	0	0	0	4	3	5	2	4	1	13	2	1	2
Neurocutaneous syndromes	1	8	1	2	2	3	5	4	2	1	0	0	11	1	1	2
Other	4	31	11	27	20	31	40	29	34	15	26	9	135	18	7	12
Total	13	100	41	100	64	100	137	100	223	100	289	100	767	100	56	100

Age equals age at the inclusion day. As of January 1, 2014, a total of 1771 people were diagnosed with active epilepsy. For 20% there was a genetic or presumed genetic etiology, 36% had an unknown etiology, and 43% had a structural-metabolic etiology. Subjects with a structural-metabolic etiology (n = 767) were subclassified into one of 12 different categories.

^aNewly diagnosed structural metabolic epilepsy in 2013 for all age groups.

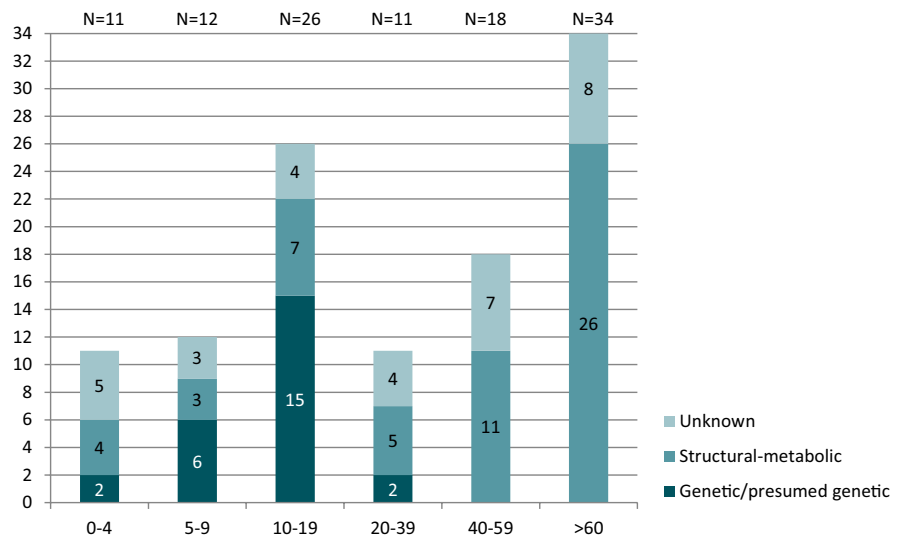


FIGURE 3 The different age groups and causes of newly diagnosed epilepsy in the year 2013

health care, there are differences in the diagnostic workup of epilepsy based on geography and income.

Regarding traumatic brain injuries and metabolic or toxic insults, we found a significantly higher prevalence in men,

which is not surprising. Traumatic brain injury is a leading cause of epilepsy in younger men,⁶ and abuse of alcohol and illicit recreational drugs is more common in men.^{22,23} Mesial temporal sclerosis, on the other hand, was more common in

women. To the best of our knowledge, such a gender difference has not been described previously. However, the total number of patients with identified mesial temporal sclerosis was low (13). Thus the finding must be interpreted with care.

In 2015, we performed a review of all publications regarding the prevalence and incidence of epilepsy in the Nordic countries during the last 60 years.²⁴ We could not identify any previous Nordic study that systematically explored the etiology of epilepsy in all different age groups. However, Aaberg and colleagues recently mapped the causes of epilepsy in Norwegian children younger than 13 years of age.²⁵ The results are not directly comparable to ours, as the different groups were based on age at onset as opposed to age at inclusion. However, like us, they found that for a large proportion of Norwegian children with epilepsy, there is no explanation for their seizures. Of 606 children with epilepsy who are younger than 13 years of age, 43% had an unknown cause of epilepsy, excluding those with a presumed genetic cause, that is, the group with idiopathic generalized epilepsy (IGE). If one accepts that IGE in fact also has no known cause, up to 67% of the children had epilepsy of unknown etiology.²⁵ In the present study, 53.4% of the children younger than age 10 had epilepsy of unknown etiology, including those with a presumed genetic cause (ie, IGE).

A study from Estonia, including 560 patients aged 0-19 years, also looked into the structural-metabolic causes of epilepsy. Like the present study, the authors found that perinatal factors were the most frequent cause of structural-metabolic epilepsy in children. However, they identified a neurodegenerative cause of epilepsy in up to 12% of their pediatric cases,⁷ as opposed to 0 (<19 years of age) in the present study. This discrepancy could be explained by different definitions of neurodegenerative causes, as pediatric neurodegenerative disorders were classified as metabolic or presumed genetic in the present study.

Overall, and not surprisingly, we found that vascular diseases/cerebral circulation disturbances were the most common reasons for developing epilepsy. Stroke was responsible for up to 44% of the patients 60 years of age or older. Perinatal insult was a common cause of structural-metabolic epilepsy across several age groups, showing that even in a country with efficient childbirth care, perinatal insults can remain an important cause of epilepsy. However, this reveals one of the limitations of the study: exploring prevalent as opposed to incident cases. Consequently, the factors causing epilepsy at an early age follow along into the older age groups, because health care services are well established and accessible in Norway and survival is generally good. Thus, incidence studies are preferred when investigating the causes of epilepsy.²⁶ It should be noted, however, that prospective incidence studies require substantial resources and may be unreliable in large clinics if they depend on clinicians remembering to report new cases

in a busy setting. Furthermore, we think that a prevalence study has an important practical utility, showing the clinician which cause for epilepsy a patient at a given age is most likely to have.

To shed light on the incident causes of epilepsy, an analysis of subjects registered with a diagnosis of epilepsy was performed in 2013. Our numbers of newly diagnosed epilepsy in 2013 do not represent the true incidence, however, as time of diagnosis does not necessarily equal time of the first seizure. Consequently, these results must be interpreted with care. Diagnosis of epilepsy may sometimes be delayed, especially if the initial symptoms were subtle. Nevertheless, our finding of 44 new cases per 100 000 person-years is in line with comparable studies of epilepsy incidence from other Nordic countries.²⁴ It is noteworthy that when analyzing new cases as opposed to prevalent cases, neoplasia was the leading cause of structural metabolic epilepsy. Neoplasia is a condition with high mortality, thus it will be underestimated in a cross-sectional study of point prevalence.

Another limitation is that we have most likely missed patients in the older age groups, reflected by an unexpected drop in the epilepsy prevalence of persons >80-years-old.² We think that some cases of epilepsy go undiagnosed in the oldest patients due to focal seizures with somewhat subtle symptoms and/or different comorbidities of a more serious nature. Furthermore, we think that a visit to the hospital and an EEG examination would not always be undertaken when diagnosing epilepsy if the burden of comorbidity is substantial, as would often be the case, for instance, in retirement homes. Thus, cases of epilepsy caused by stroke or degenerative diseases are probably underrepresented in the present study.

All in all, we conclude that the proportion of patients with an unknown cause of epilepsy remains large in all age groups. An effort must be made to better understand and identify the reasons that some people develop a susceptibility to seizures.

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DISCLOSURE OF CONFLICTS OF INTEREST

Dr. Syvertsen is a member of the steering committee of Eisai's Epilepsy Experts educational program. The remaining authors have no potential conflicts of interest to declare. 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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