Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences

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Epilepsy in the county of Nord-Trøndelag

Diagnostic Difficulties and Focus on Generalized Epilepsy

Master's thesis in Medicine
Supervisor: Eylert Brodtkorb
July 2020

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Kunnskap for en bedre verden

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1. Abstract

Background: The Nord-Trøndelag Health Study (HUNT) is one of the largest epidemiological health studies ever performed. The study provides an exclusive database for questionnaire data, clinical measurements, and biological samples. Validation of the diagnoses and detailed classifications of the epilepsies with mapping of clinical characteristics are mandatory to perform meaningful genotype/phenotype association in future studies.

Aims: To validate the true G.40 diagnosis in the HUNT study cohort according to the revised classification of the epilepsies and explore misdiagnosis rate and patients with an uncertain epilepsy diagnosis, and to further focus on various aspects of generalized epilepsies in this population.

Methods: We identified subjects from the HUNT 2 and 3 study with two or more appointments at neurological and pediatric clinics recorded with epilepsy (ICD-9: 345.x prior to 1999 or ICD-10: G40.x after 1999) at Hospitals in the county of Trøndelag. We systematically reviewed the patients by reading the medical records. The diagnosis was validated and categorized according to the current classification schemes established by the International League Against Epilepsy (ILAE) by using a Care Report Form (CRF). The data was collected in EXCEL and further analyzed in SPSS.

Results: In total, 307 (88.5%) out of 347 patients had a valid epilepsy diagnosis. Focal epilepsy accounted for the majority (80.1%), followed by generalized (10.1%), unknown type (8.3%) and combined focal and generalized epilepsy (1.3%). Altogether 8,1% patients were incorrectly diagnosed with epilepsy and 3.5% had an uncertain epilepsy diagnosis.

Conclusion: The present study confirms that misdiagnosis is a common problem as many conditions resemble epilepsy, most commonly syncope and psychiatric conditions. Enhanced knowledge of the various imitators of epilepsy can contribute to lower misdiagnosis rates. We identified a small and heterogenous group of patients with an uncertain epilepsy validation. This patient group should be further acknowledged and investigated in other epidemiologic studies on epilepsy. A relatively high share of patients was identified with unknown type of epilepsy. This could be due to insufficient information in medical records and stricter classification criteria. A family history of epilepsy should be addressed. Enhanced knowledge on idiopathic generalized epilepsy, might be helpful to differentiate focal from adult onset generalized epilepsy.

2. Sammendrag

Bakgrunn: Folkehelseundersøkelsen i Nord-Trøndelag (HUNT) er en av de største epidemiologiske studiene som er blitt gjennomført. Studien gir en unik database med helseopplysninger, kliniske målinger og biologisk materiale. For å utføre fremtidige genom-assosiasjonsstudier er diagnosevalidering og kartlegging av kliniske karakteristika nødvendig.

Målsetting: Å finne andelen pasienter i HUNT-studien med verifisert epilepsi ved å bruke den nye epilepsiklassifikasjonen og se nærmere på feildiagnostisering og pasienter med en usikker epilepsidiagnose, og videre fokusere ytterligere på ulike aspekter ved generaliserte epilepsier i denne populasjonen.

Materiale og metode: Vi identifiserte personer fra HUNT 2- og 3 registrert med epilepsi (ICD-9: 345.x før 1999 eller ICD-10: G40.x etter 1999), med to eller flere opphold på nevrologiske og pediatriske klinikker ved sykehus i Trøndelag fylke. Vi har systematisk gjennomgått pasientene ved hjelp av medisinske journaler. Diagnosen ble validert og klassifisert i henhold til revidert klassifikasjon fra International League Against Epilepsy (2017) ved å bruke en Case Report Form (CRF). Dataene ble videre samlet i EXCEL og analysert i SPSS.

Resultater: Totalt var det 307 (88,5%) av 347 pasienter som hadde en verifisert epilepsidiagnose. Fokal epilepsi utgjorde størsteparten (80,1%), etterfulgt av generalisert (10,1%), ukjent type (8,3%) og kombinert fokal og generalisert epilepsi (1,3%). Til sammen var det 8.1% feildiagnostiserte pasienter, og 3,5% hadde en usikker epilepsidiagnose.

Konklusjon: Denne studien bekrefter at feildiagnostisering er et vanlig problem da flere tilstander ligner epilepsi, som oftest synkope og psykiatriske tilstander. Økt kunnskap om de vanligste imitatorene kan bidra til mindre feildiagnostisering. Vi identifiserte en liten og heterogen pasientgruppe hvor epilepsidiagnosen var ukjent. Denne gruppen bør det settes mer fokus på i fremtidige epidemiologiske studier. En relativt høy andel pasienter ble identifisert med epilepsi av ukjent type. Mulige årsaker kan være utilstrekkelig informasjon i legejournaler samt strengere krav i det nye klassifikasjonssystemet. Familieanamnesen bør få oppmerksomhet. Større kunnskap om idiopatisk generalisert epilepsi kan være nyttig i diagnostikken for å skille fokal fra generalisert epilepsi med sen debut.

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3. Acknowledgements

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Bjørn Patrick Kolstad

Kristoffer Sandtrøen

4. Introduction

Epilepsy is one of the oldest recognized diseases in the world. Recordings date back to over 5000 years (1). It is among the most common neurological conditions, and it is estimated that around 50 million people are affected worldwide (2). Living with a seizure disorder is often challenging, and many people with epilepsy experience prejudice and stigma that impact their quality of life (3). Epilepsy has been ranked to be the fifth most burdensome neurological condition regarding disability-adjusted life years by the 2015 Global Burden of Disease study (4), and it has been estimated that the total cost of the disease in Europe is about 15 billion Euro per year (5).

Being a complex and heterogenous disease, the clinical presentation, course, and prognosis of epilepsy vary considerably from patient to patient. Although most people with epilepsy manage to achieve an adequate seizure control with antiepileptic drugs. (AEDs), it is estimated that drug therapy fails in more than 30% of patients (6).

The definition of epilepsy has evolved over time. The core element is the occurrence of at least one epileptic seizure. In addition, the current definition encompasses psychological and social aspects, as well as the underlying biological mechanisms of the disease. In 2005, the International League Against Epilepsy (ILAE) conceptually defined epilepsy as a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizure and by the neurobiologic, cognitive, psychological, and social consequences of the condition." (7).

Moreover, in 2014, the ILAE developed a practical definition of epilepsy with the aim of being more applicable in a clinical setting (8). This definition characterizes epilepsy as

"a disease of the brain defined by any of the following conditions:

(1) at least two unprovoked (or reflex) seizures occurring > 24 h apart.

(2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years.

(3) diagnosis of an epilepsy syndrome".

The clinical manifestations of epilepsy are the epileptic seizures. A seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or

synchronous neuronal activity in the brain" (7). The symptoms reflect the function of the neurons that generate the seizures, and thus give rise to the wide clinical spectrum of epilepsy.

Classification of epilepsy is important in evaluating patients with seizures. Classification systems serve as a guide to assess the prognosis and the therapeutic approach, as well as providing valuable information to be used for research and epidemiologic studies (9). Due to the complex nature of the disease, the classification of epilepsy is challenging. Therefore, the classification criteria have been under debate and have been updated on several occasions. Scientific advances have enabled a better understanding of the underlying mechanisms of the disease. In parallel, revisions of the classification system have been needed alongside the emergence of new clinical and pathophysiological knowledge.

The prognosis and treatment choice are for a large part dependent on the type of epilepsy and its etiology (10). A genetic predisposition is thought to be present in most epilepsies, but it prevails in the generalized and genetic epilepsies (11). For most people with epilepsy, the principal therapy is still symptomatic in the form of pharmacological seizure treatment with AEDs, but etiological and mechanistic options targeting the underlying causes are now increasingly identified. In some seizure disorders, molecular genetic advances currently allow for specific treatments which directly influence the consequences of mutations. Examples are the genetic and structural epilepsy of tuberous sclerosis (mTOR inhibitors) (12), the genetic and metabolic disorders Glut 1 deficiency syndrome (ketogenic diet) (13), and pyridoxine-dependent epilepsy (vitamin B6 substitution) (14). Moreover, in several channelopathies the effect of mutations determines the optimal choice of specific AEDs based on their pharmacological actions, such as in SCN1A and SCN8A-related epilepsies (15) (16). In a number of people with epilepsy, these genetic abnormalities are not yet identified, so far leaving these patients without optimal treatment (17).

Current neurobiological research in epilepsy aims to identify further factors which may lead to discovery of underlying genetic dysfunctions which may be the target of mechanistic treatment (18). A prerequisite for success in this field, is a close collaboration between clinical epileptologists and basic neuroscientists to reveal detailed genotype-phenotype correlations in various seizure disorders. A more disease specific approach to the treatment of epilepsy in the context of personalized medicine will improve the quality of life for many patients with these disorders.

The Trøndelag Health Study (HUNT), the largest collection of health data from a defined population, has been conducted in three waves. The HUNT 2 survey (1995-1997) included 74,000 people in Nord-Trøndelag County in whom stored DNA for genotype studies are available in 65,000. In the HUNT 3 survey (2006-2008) 48,289 participants were included (19).

The purpose of this study was

1) to identify HUNT participants available for genotyping who had been registered with the diagnosis of epilepsy
2) to validate the true diagnosis of epilepsy in these patients
3) to further focus on misdiagnosis and various aspects of generalized epilepsies, including their differentiation from epilepsies with combined focal and generalized epilepsies and epilepsies of unknown type.

5. Study population and procedures

5.1 Study design

The study was descriptive and retrospective.

5.2 Study population

Genotyped subjects from HUNT 2 and 3 with more than two appointments at neurological and pediatric clinics in Trøndelag county recorded with epilepsy (ICD9, 345.- or ICD10, G40.-) in the period 1987-2019.

Genotyped participants in HUNT 2 and HUNT 3 diagnosed with epilepsy form the basis of the data collection. As part of the HUNT-MI study on epilepsy (attachment 3), the HUNT research coordinator identified all genotyped HUNT 2 and HUNT 3 participants registered as in- or out-patients with epilepsy (ICD-10: G.x after 1999; ICD-9: 345.x prior to 1999) at hospitals in the county of Trøndelag. The procedure was performed in cooperation with Helse Midt-Norge IT (HEMIT).

5.3 Procedures

We systematically searched for patients with the epilepsy diagnosis by using the electronic coding system at St.Olavs Hospital, Namsos Hospital and Levanger Hospital. We identified patients with at least two outpatient appointments or hospitalizations with epilepsy as the main diagnosis. The search covered all ICD-10 codes for epilepsy (ICD9, 345.- or ICD10, G40.-) in the period 1987-2019. Clinical information recorded from the digital records available from 2000 until 2020 were reviewed. When needed, we collected background information from previous paper records prior to 2000.

We classified epilepsy and seizure types according to the current classification schemes (Attachments1 and 2). Seizure semiology, as well as clinical details, including etiology, brain imaging and EEG reports, other clinical characteristics, current treatment, and comorbidities, were recorded in detail as far as possible by using a Case Report Form (CRF) (Attachment 4). After the completion of the CRFs, the data was plotted in EXCEL and imported to SPSS for further analysis. Shapiro-Wilk test was used to ensure normal distribution of the data. Significant difference of means in age of onset was determined using student t-tests. Significance for all tests were set to 0.05.

In the present part of the study, we wished to validate the diagnoses and to focus on generalized epilepsies, combined focal and generalized epilepsies and epilepsies of unknown

type. We also wished to review electroclinical syndromes and non-syndromic generalized epilepsies, and to further categorize these seizure disorders in relation to demographic features, age of seizure onset, comorbidities, and treatment response. To further describe the group of unknown type of epilepsy, in relation to demographic features (age/sex), age of seizure onset, comorbidities, and treatment response.

5.4 Definitions and classification

Epilepsy was defined as two unprovoked seizures occurring at least 24 hours apart according to ILAE, one unprovoked seizure and at least 60% probability of further seizures the next 10 years, or the diagnosis of an epilepsy syndrome (8).

Misdiagnosed epilepsy was defined as conditions with paroxysmal events initially coded as epilepsy, but eventually identified as another disorder or perceived as non-epileptic.

Unclassified paroxysmal events (UPE) were conditions which remained uncertain whether epileptic or not.

In 2017, the ILAE revised the classifications for both epileptic seizures (20) (Attachment 1) and the epilepsies (9) (Attachment 2). This revision provided a system that incorporates seizure type, epilepsy type, epilepsy syndrome and etiology. Seizure types are now classified according to onset as focal, generalized, or unknown. The seizure classification forms the background for the classification of the epilepsy types.

Generalized seizures were divided into motor and non-motor (absence). Motor seizures were divided into groups of tonic-clonic, clonic, tonic, myoclonic and atonic. Patients with seizures of unknown onset were divided into motor, non-motor and unclassified. Consequently, the epilepsies are classified as focal, generalized, combined generalized and focal or of unknown type.

According to the 2017 ILAE classification, generalized epilepsy was defined by generalized seizure types along with generalized spike-wave discharges on EEG (9). Epilepsy with only GTCs and normal EEG findings were thus classified as unknown epilepsy type when no supportive evidence in the form of myoclonic jerks or a relevant family history were reported. Known electroclinical syndromes where identified when possible.

Seizure control was categorized as no seizures for at least five years or one year. Epilepsy resolved was defined as no seizures the last ten years, and no AED treatment during

the last 5 years (8). To identify epilepsy resolved we used the most recent neurological notes to explore the time since the last seizure.

Current AED treatment was defined as being treated with AEDs in 2019/2020.

Comorbidities were grouped into intellectual disability, psychiatric, motor, and other.

5.5 Ethics

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway.

6. Results

6.1 Epilepsy validation

***Table 1**. Epilepsy validation in patients alive or deceased with two or more ICD codes for epilepsy*

	All (100%)	Alive at study n (%)	Deceased n (%)
Epilepsy	307 (88.5%)	234 (76.2%)	73 (23.8%)
Misdiagnosed epilepsy	28 (8.1%)	21 (75%)	7 (25%)
Unclassified paroxysmal events	12 (3.5%)	11 (91.7%)	1 (8.3%)
Total	347	266 (76.7%)	81 (23.3%)

n, number.

A total of 307 (88.5%) out of 347 patients appeared to have a valid epilepsy diagnosis. The number of deceased patients in the cohort were 81 patients. Altogether 28 (8.1%) patients were considered to be incorrectly diagnosed with epilepsy and were later diagnosed with another condition causing episodic symptoms. In 12 (3.5%) patients, the diagnosis remained uncertain.

***Table 2**. Type of epilepsy in patients with confirmed epilepsy*

Epilepsy type	n (%)
Focal[1]	246 (80.1%)
Generalized[2]	31 (10.1%)
Combined focal and generalized[3]	4 (1.3%)
Unknown epilepsy type[4]	26 (8.5%)
Total	307

n, number. (1) (2) (3) (4) 62, 5, 2, and 4 patients, respectively, were deceased as of 01.01.2020

Of the patients with confirmed epilepsy, focal epilepsy accounted for 246 (80.1%), followed by generalized epilepsy (10.1%), unknown epilepsy type (8.5%), and combined focal and generalized epilepsy (1.3%).

6.2 Final diagnosis in initially misdiagnosed patients

Table 3. *Final diagnosis in misdiagnosed patients with non-epilepsy*

Alternative diagnosis	n (%)
Syncope[1]	7 (25%)
Psychogenic non epileptic seizures	3 (10.7%)
Acute symptomatic seizure[2]	3 (10.7%)
Alcohol withdrawal syndrome	2 (7.1%)
Eclampsia	2 (7.1%)
Hyperventilation syndrome	2 (7.1%)
Transient global amnesia	2 (7.1%)
Migraine	1 (3.6%)
Mononeuropathy[3]	1 (3.6%)
Multiple sclerosis	1 (3.6%)
Narcolepsia	1 (3.6%)
Unknown event perceived as definitely not epilepsy	3 (10.7%)
Total	28[4]

n, number. *(1) Convulsive (n=3), cardiogenic (n=1), reflex (n=1), and presyncope (n=2).* *(2) Seizures due to cerebral infarction (n=1), herpes encephalitis (n=1) and brain surgery (n=1).* *(3) Neuralgia caused by tumor compressing the trigeminal nerve.* *(4) Seven patients were deceased.*

Of the 347 patients diagnosed with epilepsy, 28 (8.1%) were misdiagnosed. The most frequent alternative diagnosis was syncope (25%), followed by psychogenic non epileptic seizure (PNES) (10.7%) and acute symptomatic seizure (10.7%).

6.3 Findings in patients with unclassified paroxysmal events

Table 4. *Demographics of patients with unclassified paroxysmal events according to age of symptom onset and gender*

	Female	Male	Total
Age group	n (%)	n (%)	n (%)
Under 10	2 (28.6%)	0 (0%)	2 (16.7%)
10 - 39	1 (14.3%)	0 (0%)	1 (8.3%)
40 - 59	1 (14.3%)	4 (80%)	5 (41.7%)
Over 60	2 (28.6%)	1 (20%)	3 (25%)
Unknown	1 (14.3%)	0 (0%)	1 (8.3%)
Total	7	5	12*

*n, number. *One patient was deceased as of 01.01.2020*

Altogether 12 (3.5%) of 347 patients had unclassified paroxysmal events. Of these, seven (54.5%) were female and five (45.5%) were male. Age of onset ranged from one to 72 years; more than 40% had onset between 40 to 60 years.

***Table 5**. AED treatment and unclassified paroxysmal events in patients with an uncertain epilepsy validation*

	Yes n (%)	No n (%)	Unknown n (%)
Current use of AEDs	3[1] (25%)	9[2] (75%)	0 (0%)
Events within last year	2 (16.7%)	6 (50%)	4 (33.3%)
Events within last 5 years	6 (50%)	3 (25%)	3 (25%)

n, number; AEDs, antiepileptic drugs. *(1) Despite given the option to discontinue AED treatment, two of these patients wanted to continue. (2) Seven of these patients had previously used AED.*

Three patients (25%) with an uncertain epilepsy diagnosis used AEDs. Despite given the option to discontinue AED therapy, two of these patients wanted to continue. Of the nine patients that did not use AEDs, seven had previously been treated with AEDs.

***Table 6.** Possible differential diagnosis in patients with unclassified paroxysmal events*

Differential diagnosis	n (%)
Alcohol related seizure	2 (16.7%)
Psychiatric disorder	1 (8.3%)
Syncope	1 (8.3%)
TIA/TGA*	1 (8.3%)
Undecided	7 (58.3%)
Total	12

*n, number. * Both conditions were possible differential diagnosis*

There was a possible differential diagnosis for five (41.7%) of the 12 patients with an uncertain epilepsy diagnosis. Two were suspected to have alcohol related seizures, but the majority remained undecided.

6.4 Findings in patients with generalized epilepsies

Table 7. *Demographics of generalized epilepsies according to gender and age of onset*

	Female n (%)	Male n (%)	Total n (%)
Age of onset			
Under 10	2 (11.1%)	3 (23.1%)	5 (16.1%)
10 – 19	10 (55.6%)	6 (46.2%)	16 (51.6%)
20 – 29	2 (11.1%)	2 (15.4%)	4 (12.9%)
30 – 44	2(11.1%)	0 (0%)	2 (6.5%)
Over 45	1 (5.6%)	1 (7.7%)	2 (6.5%)
Unknown	1 (5.6%)[1]	1 (7.7%)[2]	2 (6.5%)
Total	18	13	31[3]

n, number. (1) Childhood absence epilepsy. (2) Juvenile myoclonic epilepsy. (3)Five patients were deceased as of 01.01.2020.

Only 31 (10.1%) patients were diagnosed with generalized epilepsy. The majority (51.6%) of the patients with generalized epilepsy had an age of onset between 10 to 20 years. Altogether two thirds of patients had age of onset below 20 years of age. Two patients (6.5%) had an age of onset over 45 years.

Table 8*. Generalized epilepsy according to current treatment and seizure control*

	Yes n (%)	No n (%)	Unknown n (%)
Current use of AEDs	23 (74.2%)	8 (25,8.7%)	0 (0%)
Seizure within last year	8 (25.8%)	22 (71%)	1 (3.2%)
Seizure within last 5 years	16 (51.6%)	14 (45.2%)	1 (3.2%)
Epilepsy resolved	3 (9.7%)	27 (87.1%)	1 (3.2%)

*n, number; AEDs, antiepileptic drugs. *Seizure free for more than ten years and off AEDs for more than 5 years.*

Almost 75% of patients with generalized epilepsy used AEDs. Eight (25.8%) patients had a seizure within the last year, whilst 16 (51.6%) had a seizure within the last five years. Epilepsy was resolved in three patients.

***Table 9**. Comorbidity in patients with generalized epilepsies*

	Yes n (%)	No n (%)
Known comorbidity	22 (71%)	9 (29%)
Psychiatric disorders[1]	7 (22.6%)	24 (77.4%)
Intellectual disability[2]	3 (9.7%)	28 (90.3%)
Other[3, 4]	17 (54.8%)	14 (45.2%)

n, number. (1) Conditions recorded were anxiety (n=3), depression (n=2), and psychotic disorder (n=1). (2) All three patients had mild intellectual disability. (3) Cardiovascular disease (n=5), asthma (n=1), diabetes (n=1), migraine (n=1) and osteoporosis (n=1). (4) Substance abuse (n=1).

Psychiatric disorders were recorded for more than 20%, whereas intellectual disability was reported in 10%

***Table 10.** Overview of patients with electroclinical syndrome diagnosis*

	Female n (%)	Male n (%)	Total n (%)	Mean onset age (min – max age)
Electroclinical syndrome				
Juvenile Myoclonic Epilepsy*	6 (42.9%)	7 (63.3%)	13 (52%)	13.9 (5 - 21)
GTC Alone	4 (28.6%)	0 (0%)	4 (16%)	21.5 (11 - 49)
Juvenile Absence Epilepsy	3 (21.4%)	1 (9.1%)	4 (16%)	12.25 (7 - 15)
Childhood Absence Epilepsy	1 (7.1%)	0 (0%)	1 (4%)	Unknown
Jeavons syndrome	0 (0%)	1 (9.1%)	1 (4%)	13 (13)
Lennox-Gastaut Syndrome	0 (0%)	2 (18.2%)	2 (8%)	3 (2 - 4)
Total	14	11	25	

*n, number. * Juvenile absence epilepsy which later evolved into juvenile myoclonic epilepsy (n=1).*

Altogether 25 patients were identified with an electroclinical syndrome. Of these 14 were females and 11 were males. The most common electroclinical syndrome was juvenile myoclonic epilepsy (52%), followed by GTC alone (16%) and juvenile absence epilepsy (16%).

***Table 11**. Relatives with epilepsy in patients with Idiopathic generalized epilepsy*

Relatives with epilepsy	n (%)
Yes	9 (40.9%)
No	2 (9.1%)
No information	11 (50%)
Total	22

n, number.

A family history of epilepsy was identified in 41 % of patients with IGE, but it was only mentioned in half of the records; hence, in those with family history information, 82% confirmed relatives with epilepsy.

***Table 12**. AED treatment, seizure control and epilepsy resolved in patients with Juvenile myoclonic epilepsy*

	Yes n (%)	No n (%)	Unknown n (%)
Current use of AEDs	12 (92.3%)	1 (7.7%)	0 (0%)
Seizure within last year	4 (30.8%)	9 (69.2%)	0 (0%)
Seizure within last 5 years	7 (53.8%)	5 (38.5%)	1 (7,7%)
Epilepsy resolved*	1 (7.7%)	12 (92.3%)	0 (0%)

*n, number; AEDs, antiepileptic drugs. *Seizure free for more than ten years and off AEDs for more than 5 years.*

Of patients with JME, more than 90 % of patients used AEDs. More than 50% had suffered at least one seizure within the last 5 years.

6.5 Findings in patients with an unknown epilepsy type

***Table 13.** Demographics of patients with unknown epilepsy according to gender and age of onset*

	Female n (%)	Male n (%)	Total n (%)
Age of onset			
Under 10	0 (0.0%)	1 (5.3%)	1 (3.8%)
10 - 19	2 (28.6%)	3 (15.8%)	5 (19.2%)
20 - 29	0 (0.0%)	2 (10.5%)	2 (7.7%)
30 - 44	1 (14.3%)	2 (10.5%)	3 (11.5%)
Over 45	4 (57.1%)	8 (42.1%)	12 (46.2%)
Unknown	0 (0.0%)	3 (15.8%)	3 (11.5%)
Total	7	19	26

n, number.

A total of 26 patients in the present study were diagnosed with an unknown epilepsy type. The most frequent age of onset was over 45 years (46.2%). Only one patient (3.8%) had an age of onset under ten years.

Table 14. *AED treatment, seizure control and epilepsy resolved in patients with unknown epilepsy type*

	Yes n (%)	No n (%)	Unknown n (%)
Current use of AEDs	20 (76.9%)	6 (23.1%)	0 (0%)
Seizure within last year	3 (11.5%)	21 (80.8%)	2 (7.7%)
Seizure within last 5 years	11 (42.3%)	14 (53.8%)	1 (3.8%)
Epilepsy resolved*	2 (7.7%)	23 (88.5%)	1 (3.8%)

*n, number; AEDs, antiepileptic drugs. *Seizure free for more than ten years and off AEDs for more than 5 years.*

Approximately 75% of patients with unknown epilepsy type used AEDs. Three (11.5%) patients had a seizure within the last year, whilst 11 (42.3%) had a seizure within the last five years. Epilepsy was resolved in two patients.

Table 15. *Seizure type in patients with unknown epilepsy type*

Seizure type	n (%)
Motor	23 (88.5%)
Unclassified	3 (11.5%)

n, number.

The majority of patients with unknown epilepsy type had motor seizures (88.5%), whilst only a few had unclassified seizures (11,5%).

Table 16. *Comparison of mean onset age, AED treatment, seizure control and epilepsy resolved in patients with generalized and unknown epilepsy type*

	Generalized	Unknown epilepsy type
Mean onset age (years)[1]	18	42.9
Current use of AEDs	74.2%	76.9%
Seizure within last year	25.8%	11.5%
Seizure within last 5 years	51.6%	42.3%
Epilepsy resolved[2]	9.7%	7.7%

AEDs, antiepileptic drugs. [1]p-value<0.0001. [(2)] Seizure free for more than ten years and off AEDs for more than 5 years.

6.6 Findings in patients with combined focal and generalized epilepsy

Altogether four patients (1.3%) were identified with a combined generalized and focal epilepsy. Of these, three were male (75%) and one (25%) was female. For one patient the age of onset was unknown. For the remaining patients, all had an onset age under ten years,

ranging from two to eight. Three patients were identified with epileptic encephalopathy; Lennox-Gastaut syndrome (n=2) and Juvenile neuronal ceroid lipofuscinosis (Spielmeyer-Vogt disease) (n=1). Despite being treated with AEDs, seizure control was poor as all patients had seizures within the last year. Comorbidity recorded in this patient group was intellectual disability (n=3), motor disability (n=2), psychiatric disorders (n=1). Intellectual disability ranged from mild (n=1), severe (n=1), to profund (n=1).

7. Discussion

Hitherto, few studies have applied the new ILAE epilepsy classifications in larger series of patients. In this study, we reviewed 347 patients registered with two or more ICD codes for epilepsy. We found that 307 patients (88.5%) were correctly diagnosed, 28 were obviously misdiagnosed (8.1%), whereas in 12 (3.5%) the diagnosis remained obscure. Of the patients with a true diagnosis, focal epilepsy accounted for the majority (80.1%), followed by generalized (10.1%), unknown type (8.5%), and combined focal and generalized epilepsy (1.3%).

The study highlights some pitfalls which may take place in epidemiological studies of epilepsy regarding diagnosis, classification errors and uncertainty, including the differentiation between generalized epilepsies and epilepsies of unknown type. In the following, these issues are discussed in relation to our findings.

7.1 Misdiagnosis in epilepsy

In the present study, 8% of the patients had incorrectly been diagnosed with epilepsy. The majority of misdiagnoses were syncope (25%), psychogenic non-epileptic seizures (PNES) (10.7%) and acute symptomatic seizure (10.7%). These results are reflected in a systematic review from 2016 concluding that misdiagnosis is a common problem despite considerable heterogeneity across studies (21). Misdiagnosis rates from 2 – 71% were identified, indicating that false diagnoses of epilepsy span a wide range depending on the methodology and the included patient groups. Of the 27 studies analyzed in the review, seven had a misdiagnosis rate lower than 10%, while in 20 it was higher than 10%. Similar to the present study, syncope (52.4%) and PNES (34.7%) accounted for most of the alternative diagnoses.

An ICD-10-based epidemiological study performed in Buskerud County, Norway, concluded that 20% of patients were misdiagnosed with epilepsy. Paroxysmal symptoms not consistent with epilepsy (syncope and PNES) (44%) and solitary unprovoked seizure (23%) were the most common substitute diagnoses (22). A study from the tertiary epilepsy clinic at Montreal Neurological Institute, revealed that 26% of patients referred for epilepsy had a another condition (23). In the same study, syncope (33%), psychiatric symptoms (20%), migraine (10%) and PNES (9%) accounted for most of the alternative diagnoses. Taken

together, these studies show that misdiagnosis is high and that syncope and PNES represent most of the final diagnoses.

Compared to most current literature, our study has a lower reported rate of misdiagnosis. Possible explanations for these discrepancies are the inclusion criteria used in our study and an older cohort of patients eliminating commonly misdiagnosed paroxysmal events in children. In the present study, only patients who had two or more epilepsy contacts at the hospital were included. First-time referrals and patients with less than two G.40 codes were not included in the dataset to avoid patients with yet incomplete assessments. Additionally, this excludes occasional erratic epilepsy diagnoses; hence, our results are not fully comparable to those presented by Syvertsen et al. (22) and Pana et al. (23). Our methodology excluded a potentially large patient group that in other studies received a correct alternative diagnosis during the second hospital visit, which may have contributed to the relatively low misdiagnosis rate. In the study by Pana et al. (23), one visit to a specialist was sufficient to diagnose 62% of referred patients without epilepsy, while a second hospital visit was needed for 30% of the cases. This emphasizes that many patients are initially recognized with another diagnosis than epilepsy during the second hospital contact.

The patients in the present study were at least 13 years of age when they were included in the HUNT study. Consequently, we dealt with a different age group compared to many other studies also including younger children. A Danish study found that 39% of all patients admitted to a tertiary epilepsy centre did not have epilepsy. The final diagnoses were staring episodes, PNES, syncope, parasomnias, hyperventilation and breath holding spells (24), of which some typically occur in the youngest age group. This may have contributed to a lower rate of misdiagnosis in the present study.

Many conditions have overlapping clinical features with epilepsy and thus pose a diagnostic challenge for the clinicians. Several studies, including the present one, confirm that syncope is the most common imitator of epilepsy. Though often hard to distinguish on clinical grounds, there are a range of clinical factors that differentiates the two conditions, such as facial color, triggers, type and duration of motor symptoms, postictal phase, and the fact that loss of consciousness occurs prior to jerks in convulsive syncope. Enhanced knowledge and focus on the most common imitators are crucial for preventing misdiagnosis (25).

Epilepsy is primarily a clinical diagnosis requiring a detailed patient history and reinforced by paraclinical investigations, such as brain imaging and EEG. However, the most

important diagnostic method is still a complete description of the progression of the event which should include the following elements in detail: precipitating factors/situation, the patient's own narrative, observations by eye witnesses, duration of the attack and the postictal state. A comprehensive patient history can help exclude many differential diagnoses during evaluation and should therefore be conducted in a systematic manner (25). However, in some cases, it is difficult, and occasionally impossible, to get a satisfactory anamnesis due to factors such as cognitive alterations, absence of eyewitnesses, and atypical presentations. Thus, diagnostic uncertainty is occasionally inevitable in the clinical reality.

Misdiagnosis leading to the mismanagement of patients with AED treatment may have serious consequences. Additionally, the diagnosis of epilepsy implies significant psychosocial impact on the patient's life such as restrictions on driving, employment, and leisure activities. Enhanced knowledge on the imitators can contribute to fewer cases with misdiagnosis. However, diagnostic uncertainty is inevitable, and acknowledging this may reduce misdiagnosis rates.

7.2 Uncertain epilepsy diagnosis

In some cases, despite a thorough examination, diagnostic uncertainty reflects clinical realities and not poor clinical judgement. Chowdhury et al. (26) proposed that this should be documented and monitored. Acknowledging ambiguous diagnoses has the potential to prevent rushed and often incorrect evaluations of paroxysmal events (27). Utilizing terminology such as "unclassified paroxysmal event" suggested by Beach and Reading (27), can help reduce these misdiagnosis rates and avoid incorrect treatment. In the present study, 11 (3.2%) of 247 patients fit this category.

Diagnostic uncertainty is not a widely studied aspect of epilepsy research. After an exhaustive literature search, two studies were found that reported cases with an uncertain epilepsy diagnosis. A case review study performed in Norfolk and Norwich University Hospital, England, aimed to acknowledge diagnostic uncertainty in a cohort of children presenting with paroxysmal events. They found that the diagnosis remained ambiguous in 29 (4.2%) of 684 patients (27), displaying results similar to those in the present study. In a study performed in Montreal, a final diagnosis remained unknown for 11 (2.7%) out of 404 patients, although the epileptologists that reviewed these cases felt that epilepsy had been ruled out (23).

The findings of the present study support the literature stating that cases with an uncertain diagnosis are common in clinical practice, but underrepresented in epidemiologic studies (26, 27). This could be due to a tendency for paroxysmal events to be classified as either epileptic or non-epileptic. This dichotomy forces cases with a questionable diagnosis to fall into one of the two categories instead of encouraging continued investigation. Another contributing element for underrepresentation in the literature could be the use of medical coding systems. This is particularly relevant for epidemiologic studies based merely on coded data. As there is no precise code for patients with an uncertain epilepsy diagnosis, they are either coded with epilepsy or with a code closest to what the condition resembles. Taken together, these factors facilitate the underrepresentation of patients with an uncertain diagnosis in epidemiological studies.

Our study revealed that most patients with an uncertain diagnosis (83.3%) were at one point treated with AEDs. Of these patients, three still used AEDs, whilst six had discontinued their medication under supervision of a clinician or at their own initiative. For those who still used AEDs, two wanted to continue their medication despite being given the choice by a clinician to discontinue. Many clinicians perceive missing a diagnosis of epilepsy and not treating seizures as a higher risk than acknowledging uncertainty and waiting to administer AEDs (28), as uncontrolled epilepsy is associated with increased morbidity and mortality (29). Seizure-related sudden unexpected death (SUDEP) is currently receiving increased attention (30). Thus, there are significant consequences associated with leaving epilepsy untreated. However, AED medication may come with many harmful side effects of central nervous as well as systemic types. Therefore, deciding whether to initiate AED treatment requires weighing the benefits up with potential adverse reactions. These factors demonstrate the challenges clinicians are faced with when managing patients with clinical uncertainty. Oto (28) suggests that when faced with uncertainty, clinicians should adopt a practice where diagnoses are regularly questioned and reviewed. Acknowledging uncertainty has clinical utility and may reduce misdiagnosis by alleviating the pressure to make a hasty but unfounded diagnosis of epilepsy (27). Our findings, taken together with current literature, indicate that a prudent attitude to AED treatment could be favourable for the patient in situations of clinical uncertainty.

The patients identified with an uncertain diagnosis represented a heterogenous group. However, alcohol related seizures accounted for 18.2% of the differential diagnoses. For all these patients, alcohol use preceded at least one of their documented seizures. There is a well-

known association between alcohol and seizures; however, ambiguity exists between withdrawal seizures and actual epilepsy. When a pharmacological action is the sole mechanism of a seizure, epilepsy is, by definition, not present (31). Classical alcohol withdrawal seizures are characterized by a temporary reduction of the seizure threshold and typically occurs 6 to 48 hours after the last drink (32). Other withdrawal symptoms may be inconspicuous or underreported. In some cases, it is difficult to determine whether a seizure is provoked by a pharmacological action alone, or if they are precipitated in the context of an underlying epilepsy. Moreover, as chronic alcohol use has been suggested to have an epileptogenic effect (33) clinical uncertainty is inevitable in some patients with alcohol misuse. These factors, along with the results of the present study, suggest that alcohol misuse characterize a portion of patients with an uncertain epilepsy diagnosis (31).

The seizure inducing effects of alcohol often go unrecognized in clinical practice due to improper reporting of alcohol consumption (34). As alcohol habits are not defined based on a standardized measurement system, they reflect the patient's or doctor's personal frame of reference leading to inaccurate reporting (35). Additionally, some patients also underestimate their alcohol consumption or are simply not willing or able to give an exact estimation (35). Moreover, alcohol consumption is often poorly recorded at hospital admissions making it probable that there are more patients with alcohol misuse than recognized in our study and similar epidemiological surveys. Consequently, if abuse is unidentified, recurrent seizures precipitated by alcohol use are liable to be perceived as epilepsy (31). Bråthen et al. (35) suggests that a standardized questionnaire, such as the Alcohol Use Disorders Identification Test (AUDIT), supported by biomarkers, may be useful to recognize patients with excessive drinking habits and may assist in reducing rates of misdiagnosis.

The effort to identify cases with an uncertain epilepsy diagnosis enabled our study to more accurately reflect clinical realities and challenges associated with diagnosing and treating epilepsy. The patient group labeled with unclassified paroxysmal events is a clinical challenge. Further research is needed to determine if common features exist within this group apart from excessive alcohol intake. Increased focus on this patient group can improve epilepsy care and contribute with knowledge on how to manage these patients.

7.3 Generalized vs unknown type of epilepsy

The current epilepsy classification contains a category of epilepsy of unknown type with seizures of unknown onset. This is sometimes a temporary diagnosis which is given at the outset of epilepsy when thorough and detailed EEG and imaging studies are not yet finalized. However, some patients remain with epilepsy of unknown type. Focal epilepsies manifesting with focal onset seizures with rapid evolvement to bilateral tonic-clonic seizures (FTC), particularly with frontal lobe origin, may be difficult to differentiate from generalized epilepsy with GTC alone. This is referred to in the authoritative classification article (9): "Caution needs to be exercised for patients with generalized tonic-clonic seizures and a normal EEG. In this case, supportive evidence would need to be present to make a diagnosis of generalized epilepsy, such as myoclonic jerks or a relevant family history". Hence, a relatively large proportion of epilepsies were presently classified as belonging to the recently more clearly delineated group of unknown type of epilepsy.

In our study, a total of 26 patients were diagnosed with epilepsy of unknown type. This category accounted for 8.5% of all patients with epilepsy in the present study. In Syvertsen et al. (22), the seizure types could not be determined in 4% due to lack of information in the medical record. In another 0.8% of the cases, the seizure type could not be classified as focal or generalized, including some patients with West Syndrome. Thus, altogether 4.8% of epilepsies appeared to be of unknown type in that study. Wang et al., 2018 (36), reviewed patients with epilepsy in rural China and classified only 2.8% as "unknown type" of epilepsy according to the new ILAE classification (20), which was an increase from 1.2% based on the 1981 classification (37).

The higher share of epilepsies of unknown type (8.5%) in the present study compared to several other studies may be due to insufficient available information in the medical records. The ILAE Task Force recommends classifying it as a focal or generalized type only when there is a high degree of confidence involved (20). Otherwise, the seizure should remain as unclassified (20).

The majority (57.7%) of patients with unknown type of epilepsy had an onset age above 40 years. The mean onset age was 42.9 years compared to 18 in the category of generalized onset ($p<0.0001$). The predominance of onset in adult and older age, might point towards a direction of unrecognized focal epilepsy in some of these patients, particularly those occurring during sleep. Most of these patients had tonic clonic seizures of unknown

type; 88.5% was classified with a motor seizure, and 11.5% as unclassified. Seizures are often unwitnessed, particularly during the night (20). Tonic-clonic seizures of unknown onset with debut in younger age, particularly occurring during wakefulness and with morning predominance, suggest underlying generalized epilepsy, even in the absence of detectable interictal EEG correlates.

7.4 Generalized epilepsy

7.4.1. Epilepsy syndromes

In our study, 80.6%, of all generalized epilepsies, could be categorized as known epilepsy syndromes. An epilepsy syndrome is defined as "a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder." (38) An epilepsy syndrome in the form of an electroclinical entity is a specific epilepsy type based on EEG characteristics, age of onset, types of seizure and other features (39). The different syndromes have different treatment and prognosis.

Most of the generalized epilepsies (71.0%) were categorized as idiopathic generalized epilepsy (IGE) in this study. Within IGE, there are subgroups like Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), General tonic clonic seizures alone (GTC Alone) and other less common IGEs (40) (41).

In our study, generalized epilepsies could not be further classified in 19.4% of the cases. Of all epilepsy syndromes, 88.0% were categorized as IGE, while two cases (8.0%) were diagnosed with Lennox Gastaut syndrome (an epileptic encephalopathy) and one with Jeavons syndrome (Eyelid myoclonia with absences). The seizure disorders of the patients with Lennox-Gastaut syndrome belonged to the category of "combined focal and generalized epilepsy."

7.4.2. Idiopathic generalized epilepsy

Approximately one fifth of all epilepsies are IGE (42). Typical clinical features are GTCs, absences and myoclonic jerks, which may occur alone or in combination (41). Common clinical characteristics are a genetic predisposition and typical age of onset in childhood or adolescence, as well as a good response to appropriate AEDs, and a generally lifelong duration, apart from CAE (41). The EEG shows bilateral synchronous spike and wave discharges and is a sensitive tool in diagnosing IGE (41).

In the present selected cohort, IGEs constituted 7.2% of all epilepsy diagnosis, lower than in most epidemiological studies. In a comprehensive review of IGEs, the general frequency of IGEs were estimated to be around 15-20 % (42).

There was a slight predominance of women with IGE. In a total of 22 patients with IGE, 63.6% were women, and 36.4% were men. A female preponderance has also been found in other studies (43) (44) (45) (46), in contrast to a somewhat higher proportion of males in epilepsy in general (45).

IGE usually starts in childhood and adolescence, but different age of onset is characteristic for each of these syndromes (41) (40). In this study, 85.0% of patients had an onset before 20 year. The mean age of onset was 15.1, range 5-49 years, which is similar to other studies (47) (43). Approximately one sixth (15%) of the patients, had an onset age beyond 20 years. In Michelucci et al. (48), adult onset IGE was defined as onset beyond the age of 20. The proportion of adult onset was 38% and 28% in the studies of Sinha et al. (47) and Marini et al. (49). Hence, adult onset of IGE is not unusual. This might have important implications. Onset of GTCs in adults may be wrongly interpreted as epilepsy of unknown onset or even FTCs, which could challenge correct management.

As to the hereditary aspect, in 50% of the medical records of patients with IGE we were unable to find any information about relatives with epilepsy. When this was addressed, a family history was reported in 82%, whereas in 18% it was denied. A high proportion of patients lacking information about family history was also found in an Irish study (44). The family history should be explored in the assessment of patients with epilepsy, as it may enhance the suspicion of IGE.

7.4.2.1 Childhood Absence Epilepsy

Patients with CAE have absences with a high frequency (40). The number of absences may vary from tens to hundreds each day, and each absence usually lasts from 4 to 30 seconds (40). Absences cause a severe impairment of consciousness (41). Typically, they occur in children with an age between 4 and 7 year (40). There is a strong genetic predisposition and most children have intellectual development within normal limits (41). The frequency of CAE is higher in girls than in boys (41). When suspected, this is an easy syndrome to recognize with several daily absences and typical 3/second spike-wave discharges provoked by hyperventilation (41). Monotherapy with valproate or ethosuximide controls absences in 80% of patients. CAE has an overall good prognosis with remission before age of 12 in most patients (41).

In this study, the frequency of CAE was 4.5% of the IGEs, which is lower compared to 11% in other studies (44) (43), conceivably due to the age selection of this material.

7.4.2.2. Juvenile Absence Epilepsy

In JAE, absences occur with a lower frequency than in CAE, ranging from about one to ten absences each day (41). They often last for more than 4 seconds and may be associated with mild automatisms (40, 41). Additionally, the majority have GTCs and some also have myoclonic jerks (40). The age of onset is around puberty, with 70% of the patients between 9-13 years (41). The syndrome equally affects girls and boys and there is also a genetic predisposition (41). The prevalence in adults older than 20 years is about 2-3% for all epilepsies and 8-10% for IGE (41).

JAE can be controlled in 70-80% of the cases, but the syndrome is generally a life-long disorder with a tendency of becoming less severe later in life (41). Valproate is the drug of choice (41). Sleep deprivation, fatigue, alcohol, excitement, and flickering lights are precipitating factors for GTCs (41).

JAE represented 18.2% of IGEs in our study, which is in line with other studies. A comprehensive review (36) concluded that JAE represents approximately 20% of the IGEs.

7.4.2.3 Juvenile Myoclonic Epilepsy

The hallmark of JME is the myoclonic seizure (40) (50). JME commonly occurs between the ages of 8 to 26 (40), usually in adolescence. Most patients also have GTCs (roughly 90%), whereas absences occur in approximately one third (50). GTCs often take place in the morning (50). JME appears equally in both boys and girls (41). Social problems related to impulsivity, disturbed sleep/wake rhythm, poor decision-making and risk-taking behaviour may occur in a subset of these patients (51) (52). Some people with JME exhibit non-compliance concerning both drug adherence and seizure provoking factors, as well as to missing out on outpatient appointments (52). Neuropsychological testing has suggested that these personality traits are associated with signs of frontal lobe impairment (52). Important precipitating factors are sleep deprivation, fatigue, stress, and alcohol (40) (50). The genetic predisposition is pronounced, and in 50-60% of the cases there are seizures in first- or second-degree relatives (41). JME is regarded as a lifelong syndrome, but the seizures are controlled with valproate in up to 80% of the cases (50). Valproate is the drug of choice in most cases,

but not in fertile women (50). Important factors are long-term adherence to AED treatment and lifestyle with avoidance of alcohol and sleep deprivation (50).

In our study, the percentage of JME was almost 60% of the IGEs. In Syvertsen et al., 2015 (53), JME represented 32.5% of all the electroclinical syndromes. In our study, this percentage was 52%.

7.4.2.4 GTC Alone

GTCs typically occur one to two hours after awakening (40). Age of onset varies from 6-47 years, with a peak at 16 or 17 years (41). Women and men are almost equally affected (41). A high incidence of epilepsy has been reported in families (41). As in other IGEs, fatigue, sleep deprivation and alcohol consumption are seizure precipitants (40). Epilepsy with GTCs Alone is also considered a life-long disease, with a high relapse of seizures when withdrawn from AEDs (41). Controlling seizure precipitants is important and the drug of choice is the same as in other IGEs with GTCs (41).

GTC Alone represented 18.2% of all the IGEs in this study, at the lower end of findings in epidemiological studies (44) (43).

7.4.3 Considerations on seizure control in IGE

The seizure type of epilepsy guides the choice of AEDs, whereas the epilepsy syndrome suggests the duration of seizure control before discontinuation of treatment can be considered (41). Hence, an important mission of the seizure and epilepsy classifications is to aid the clinician in providing suitable treatment; “It is hoped that this new Classification of the Epilepsies will serve the epilepsy community well, leading to improved diagnosis, understanding of etiology, and targeted therapies to the patient’s disease” (9). However, IGEs are still diverse and overlapping, but they are classically thought of as pharmacoresponsive conditions. In JME, the most common form of idiopathic generalized epilepsy, 20-30% of patients remain refractory to treatment (54). JME accounted for more than 40 % of patients with generalized epilepsy in this study; hence we discuss this condition in more detail.

By reviewing the prescription database at the time of the present study, we found that a total of 92.3% of JME patients still was treated with AEDs, while 7.7% were off treatment. In Landmark et al, 2019 (55), 91% of the patients were treated with AED. Seizure control during the last year was reported in 69.2% of the patients in our study, while nearly one third

(30.8%) had at least one seizure. In contrast, in patients from Drammen Hospital only one third was considered completely seizure free during the last year (55).

The difference between our study and the patients from Drammen (55), could be due to several reasons. One reason might be the low number of patients in our study. Another reason might be different criteria for seizure control in the present patients who were evaluated by different physicians. From medical records, it was sometimes impossible to ascertain whether isolated myoclonic jerks were viewed as overt seizures. Some patients might not report myoclonic jerks as full-blown seizures, occasionally due to fear of driving restrictions. They may accept myoclonic jerks if GTCS do not occur (56), sometimes to avoid further dose increase which may cause adverse effects in the short and long term (56). Moreover, the higher tendency to social problems and poor decision-making, as previous stated (20) (51), might play a role for inaccurate reporting of seizure frequency.

One factor to be considered, is that young and usually well-controlled patients with JME still might get a seizure after a party with alcohol and sleep deprivation. Comprehensive management in the form of repeated information about common seizure precipitants is crucial in patients with this seizure disorder.

8. Limitations and strengths

This study only covers a selected part of the population with epilepsy in Nord-Trøndelag. Only those who actively agreed to take part in HUNT 2 and 3 with additional consent to participate in the genome association study, were included.

The study is based on ICD coding. The medical records of all patients twice receiving an epilepsy diagnosis code during the study period were scrutinized in detail for correct diagnosis and classification by using the recently revised epilepsy definition and classification system compiled by the ILAE. For patients referred with suspected epilepsy, the initial contacts are sometimes first coded with a G.40 diagnosis, which may be reconsidered on further evaluation. Hence, we only included patients with more than two contacts with the diagnosis of epilepsy in general

We formed a group of student investigators with little background experience within the field of clinical epileptology. Our knowledge on epilepsy increased considerably during the study, and the interpretation improved as knowledge was gained. The classification of seizures and epilepsy was based on medical records written by different physicians with variable experience in epilepsy. Hence, the reported medical histories and seizure descriptions varied considerably regarding clinical details. Diagnostic and classification difficulties were discussed with our supervisor.

The number of subjects with generalized epilepsy was surprisingly low and may not reflect the true epidemiological situation in Nord-Trøndelag. However, one reason for the limited number may be that generalized epilepsy is now more strictly defined in the current ILAE classification (20) (9). Patients with tonic-clonic seizures without focal semiological features and normal imaging and EEG findings are now classified among epilepsies of unknown type in contrast to in previous studies. Another reason for the low fraction of generalized epilepsies may be the relatively high age of the present patient sample. Moreover, we speculate whether IGE as a whole may share some of the personality traits sometimes seen in JME (51) (52). It has been shown that people with IGE in average have lower abilities in various executive functions (57). This cognitive profile might possibly render these people less disposed to partake in voluntary undertakings like the HUNT-study, which require planning, organizing, attendance and compliance.

All digital medical records dating back to 2000 were reviewed, including older paper-based records form St. Olav Hospital. A significant number of the patients had paper records at the hospitals of Levanger and Namsos. We planned to collect these records by visiting the

hospital archives in Namsos and Levanger, but because of the restrictions due to the corona virus outbreak we were denied access to these hospitals.

A minor weakness, but worth noting, is that a few subjects had partly been followed up by private neurologists.

9. Concluding remarks

This study comprises a large number of patients with epilepsy in the county of Nord-Trøndelag. However, it is not a general epidemiological survey, as the patient material was limited to subjects who had actively taken part in the HUNT studies. This may explain that some of the results are at variance with overall epidemiological studies which include larger parts of the epilepsy populations in the target areas.

9.1 Validation and classification issues

Epilepsy is a complex and heterogenous disease, which for most cases can be classified into focal or generalized types. However, some seizure disorders are difficult to diagnose and classify. As this study demonstrates, a number of patients presents with obscure clinical characteristics and unspecific paraclinical findings, consequently making the diagnosis challenging. The validation of epilepsy based on medical records from routine clinical practice is often difficult and will remain incomplete. This study highlights some important pitfalls which may occur in epidemiological studies.

Misdiagnosis remains as a common problem in patients with symptoms suggestive of epilepsy. Approximately 8% of patients were misdiagnosed, and the most common imitators were syncope and psychiatric conditions. In some cases, diagnostic uncertainty is inevitable. Despite a thorough review, the epilepsy diagnosis remained uncertain in 3.2% of the patients. They were labeled as unclassified paroxysmal events. Moreover, in the present study, the new ILAE classification from 2017 was applied. A stricter definition of generalized epilepsy is now suggested, which left a relatively large proportion of patients in the group of epilepsy of unknown type (8.5%). A narrower definition along with insufficient available information in the medical records, was identified as potential reasons.

Patients misdiagnosed and those with unclassified paroxysmal events, as well as patients considered to have epilepsy of unknown type, may together form a complex group of patients with normal or unspecific EEG and imaging findings. These conditions may sometimes overlap and be difficult to differentiate. This problem should receive more clinical and scientific attention.

9.2 Generalized epilepsy

Within the generalized epilepsies, the majority (80.6%) was classified as known epilepsy syndromes and 71.0% as IGE, with JME as the most common. One sixth had onset age beyond the age of 20, supporting other studies viewing adult onset of IGE as not that unusual. This might have important implications regarding correct management. More than 90% of the patients was still treated with AEDs and almost 70% had no seizures within the last year.

The etiology of epilepsy is multifactorial. In some seizure disorders, especially in the generalized epilepsies, genetic factors appear to predominate. In half of the present cases with generalized epilepsy, no information was available in the medical records about relatives with epilepsy, supporting the view of the importance of a detailed medical record to identify disorders with strong genetic etiological components.

9.3. Precision medicine

In epilepsy, the genetic influence is usually polygenetic and yet largely unidentified on a molecular basis, such as thought to prevail in the large group of IGE. However, in some specific syndromes, underlying monogenetic molecular mechanisms have been discovered that allow for specific treatments which directly influence the consequences of genetic mutations. Precision medicine strategies such as specific diets (e.g. in Glut-1-deficiency and phenylketonuria), vitamins (e.g pyridoxin-dependent epilepsy) and enzyme replacement in deficiency syndromes, as well as channel blockers in gain of function channelopathies, can be strikingly successful (58). Intense neurobiological research in epilepsy currently aims to identify factors which may lead to the discovery of more underlying genetic dysfunctions which may be the target of mechanistic treatment. Improved clinical phenotyping is an essential part of these efforts. By validating and classifying the seizure disorders in this cohort, we have identified a unique data set that can be genotyped and used in future research.

10. References

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11. Attachments

Attachment 1

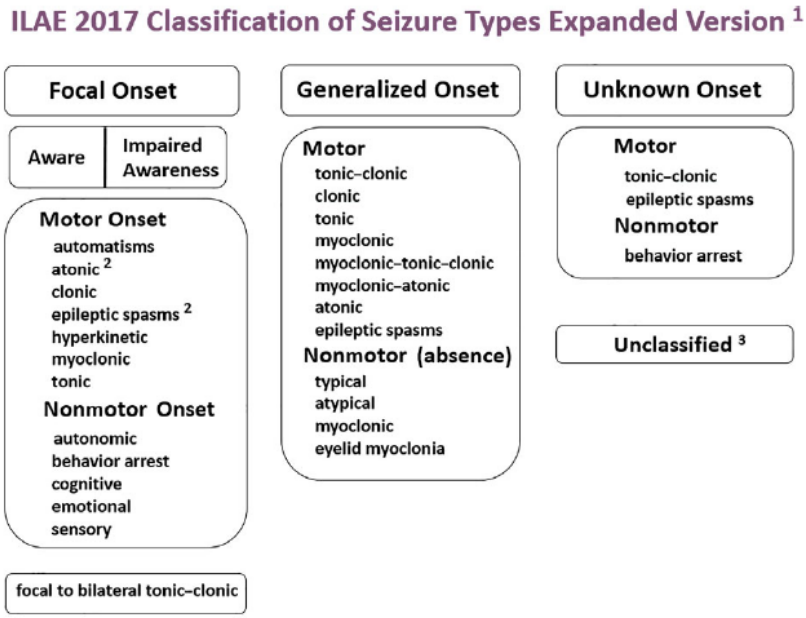

Figure 2.
The expanded ILAE 2017 operational classification of seizure types. The following clarifications should guide the choice of seizure type. For focal seizures, specification of level of awareness is optional. Retained awareness means the person is aware of self and environment during the seizure, even if immobile. A focal aware seizure corresponds to the prior term simple partial seizure. A focal impaired awareness seizure corresponds to the prior term complex partial seizure, and impaired awareness during any part of the seizure renders it a focal impaired awareness seizure. Focal aware or impaired awareness seizures optionally may further be characterized by one of the motor-onset or nonmotor-onset symptoms below, reflecting the first prominent sign or symptom in the seizure. Seizures should be classified by the earliest prominent feature, except that a focal behavior arrest seizure is one for which cessation of activity is the dominant feature throughout the seizure. A focal seizure name also can omit mention of awareness when awareness is not applicable or unknown and thereby classify the seizure directly by motor onset or nonmotor-onset characteristics. Atonic seizures and epileptic spasms would usually not have specified awareness. Cognitive seizures imply impaired language or other cognitive domains or positive features such as déjà vu, hallucinations, illusions, or perceptual distortions. Emotional seizures involve anxiety, fear, joy, other emotions, or appearance of affect without subjective emotions. An absence is atypical because of slow onset or termination or significant changes in tone supported by atypical, slow, generalized spike and wave on the EEG. A seizure may be unclassified due to inadequate information or inability to place the type in other categories. [1]Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms. [2]Degree of awareness usually is not specified. [3]Due to inadequate information or inability to place in other categories.
Epilepsia © ILAE

Attachment 2

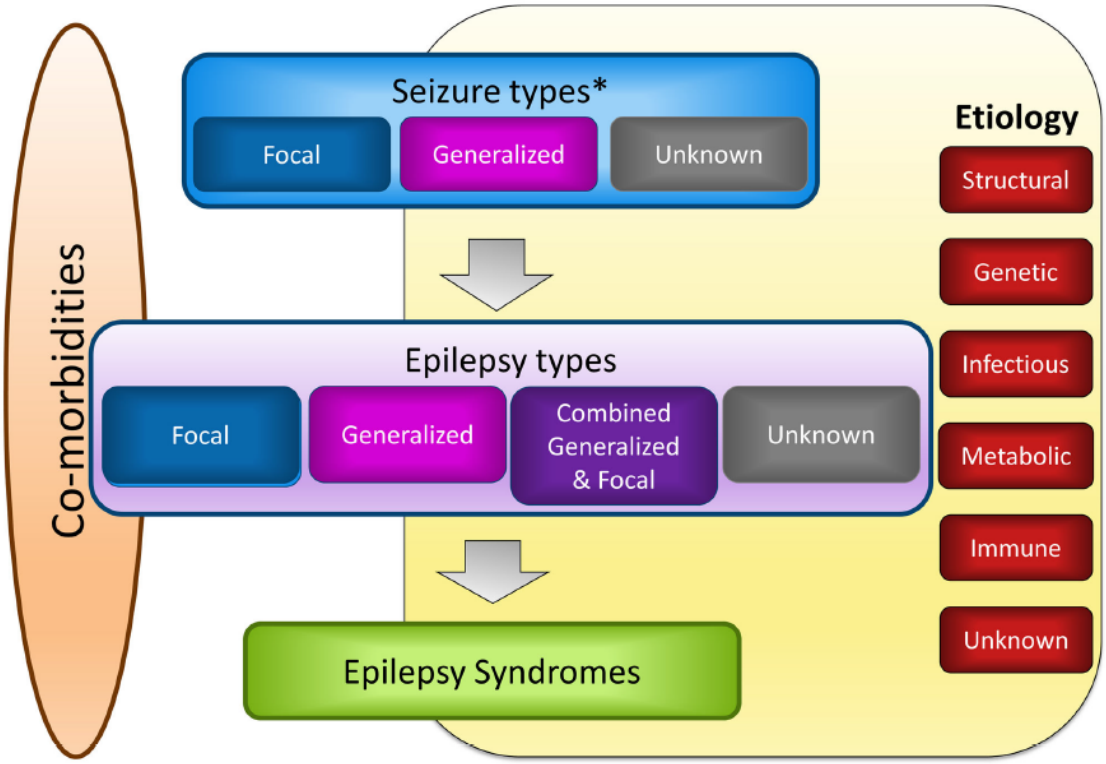

Figure.
Framework for Classification of the Epilepsies. * Denotes onset of seizure

Attachment 3

HUNT-MI: Studiedel på epilepsi

Dette dokumentet beskriver bakgrunnen og de spesifikke problemstillingene knyttet til HUNT-MIs studiedel om epilepsi. Generell informasjonen om prosjektet finnes i hoveddokumentet "HUNT-MI - økt forståelse av helse og sykdom gjennom studier av genetiske faktorer på befolkningsnivå" (REK#2014/144).

Medarbeidere

I tillegg til personer listet i hovedsøknaden, vil følgende forskere ha tilgang til data beskrevet i denne studiedelen:

Delprosjektledere (PI)	**John-Anker Zwart, MD, PhD, FORMI/UIO** **Kristian Hveem, MD, PhD, ISM/NTNU**
Delprosjektledere analyse	**Bendik Winsvold, MD, FORMI/UIO**
Medarbeidere	**Eylert Brodtkorb**, MD, PhD, INB/NTNU **Kaja Kristine Selmer**, MD, PhD OUS **Roar Fjær**, **Marianne Bakke Johnsen**, PhD, FORMI/UIO **Sigrid Børte**, MD, FORMI/OUS **Amy Elise Mitchell**, MSc, FORMI/OUS **Maiken E. Gabrielsen**, PhD, ISM/NTNU **Anne Heidi Skogholt**, ISM/NTNU

Generelt om epilepsi

Forekomst og sykdomsgrupper. Epilepsi er en av de hyppigste nevrologiske lidelsene med en prevalens på i underkant av 1%. (1) Sykdommen er svært heterogen og kan oppstå i alle faser av livet, med stor variasjon i klinisk presentasjon og forløp. Den kjennetegnes av gjentagende, uprovoserte epileptiske anfall, og av de alvorlige psykologiske, kognitive og sosiale konsekvenser som følger med tilstanden. Hyppigst behandles pasientene med anfallsreduserende medisiner, men så mange som 1/3 av pasientene oppnår ikke tilfredsstillende effekt av disse. (2, 3) Kombinasjonen av de alvorlige konsekvensene av sykdommen og hyppigheten av mangelfull effekt av behandling gjør at epilepsi utgjør en stor sykdomsbyrde: både for den enkelte pasient, for dens pårørende og for samfunnet generelt.(4) Verdens Helseorganisasjon har beregnet at epilepsi utgjør 1% av global sykdomsbyrde, beregnet i leveår med nedsatt helse eller uførhet. (4,5)

Fordi epilepsi er så heterogen har klassifikasjon av de ulike epilepsiformene vært utfordrende, og klassifikasjonskriteriene stadig blitt oppdatert. Den internasjonale organisasjonen International League Against Epilepsy (ILAE) publiserte i 2017 de nyeste klassifikasjonskriteriene (6), der etiologi deles inn i strukturell, genetisk, infeksiøs, metabolsk, immun-relatert eller ukjent årsak. I mange tilfeller er det imidlertid vanskelig å vite årsak, eller epilepsien er forårsaket av flere faktorer fra de ulike kategoriene.

Arvelig tilstand. Genetikk spiller en viktig rolle for utvikling av epilepsi, noe som gjenspeiles i de høye arvbarhetsestimater som er vist i flere populasjonsstudier (7-9). Nærmere hundre former for monogene epilepsier, dvs. epilepsier der én genvariant (eller mutasjon) i ett gen alene er nok til å forårsake epilepsi, er de siste tiårene blitt kartlagt.(10) Særlig har det vist seg at alvorlige epileptiske encefalopatier hos barn ofte skyldes en nyoppstått mutasjon i ett gen.(10) Likevel antas de aller fleste epilepsiformene å være multifaktorielle, det vil si at de er forårsaket av både genetiske varianter og miljøfaktorer, og samspillet dem i mellom.(11) Til tross for anerkjennelsen av genetiske faktorer i

epilepsi har man til dags dato svært få funn fra helgenoms assosiasjonsstudier (også kalt GWAS – genome-wide association studies). Den seneste publiserte meta-analysen av GWAS'er kunne ved hjelp av >8000 pasienter og >26 000 kontroller kun finne assosiasjon til fire genomiske områder (12) – noe som er svært lite sammenlignet med GWAS-resultater fra andre genetisk komplekse sykdommer med lignende arvbarhetsestimater. Man antar at årsakene til at man har gjort så få funn i disse studiene bl.a. skyldes heterogene pasientgrupper. Identifisering av genetiske risikofaktorer for de multifaktorielle epilepsiene vil kunne bidra til en bedre forståelse av de underliggende patologiske prosessene ved disse tilstandene og gi håp om ny behandling.

Spesielt om epilepsi i HUNT og Tromsøundersøkelsen

Spørreskjemaene i HUNT og Tromsøundersøkelsen er ikke utfyllende i forhold til epilepsi, men inneholdt enkeltstående spørsmål om hvorvidt deltakeren har, eller har hatt epilepsi.. HUNT Databank og Tromsøundersøkelsen inneholder for øvrig viktig informasjon om risikofaktorer (slik som hjerneslag) og komorbide tilstander (slik som kognitive vansker) som kan være av betydning ved epilepsi.

Tilgjengelige datakilder

HUNT og Tromsøundersøkelsen. Vi ønsker å koble den genetiske dataressursen mot spørsmål i HUNT og Tromsøundersøkelsen omkring epilepsi, samt demografiske variabler (som alder, kjønn og utdanning, utflytting og død), risikofaktorer og komorbide tilstander, slik som kognitive vansker, alkoholbruk, angst, depresjon og hjerte-/karsykdom. En andel av deltakerne som gav DNA i HUNT-3 deltok også i Ung-HUNT-undersøkelsene, og for disse vil vi også benytte informasjon samlet inn gjennom disse undersøkelsene.

Opplysninger om diagnoser. Den genetiske dataressursen vil kobles mot ICD-9 og ICD-10 diagnoser for HUNT-deltakere registrert med epilepsidiagnoser ved Sykehus i Helse Midt-Norge og mot KUHR for diagnoser satt i primær og spesialisthelsetjenesten. Som del av dette prosjektet ønsker vi også å validere disse diagnosene ved gjennomgang av sykehusjournal.

Nasjonalt reseptbasert legemiddelregister (Reseptregisteret). Vi ønsker å kunne koble den genetiske ressursen mot Reseptregisteret for informasjon om bruk av sykdomsspesifikke medikamenter. Denne koblingen vil benyttes til å definere medikamentrespons (indikert ut fra gjentatt uthenting av samme medikament), og til å validere diagnoser. I henhold til reseptregisterets forskrifter vil det også søkes datatilsynet om kobling.

UK Biobank. Vi ønsker å benytte dataene fra UK Biobank til meta-analyser og replikasjon av eventuelle funn i HUNT (og Tromsø der dette er relevant). Dataene som inngår i UK Biobank er sammenlignbare med de som inngår i HUNT og inkluderer demografiske variabler (som kjønn og fødselsår), livsstilsrelaterte variabler (som røyking, alkohol og fysisk aktivitet), selvrapportert helse fra spørreskjema, kliniske undersøkelser (som BMI og blodtrykk) og blodprøver (som kolesterol). Genetiske data som genotyper (og sekvenseringsdata fra 2019) og data fra elektronisk pasientjournal er også tilgjengelige for alle deltakerne.

Forskningsspørsmål

Ny genetisk variasjon. Vi ønsker å studere sammenhengen mellom epilepsi og genetisk variasjon i HUNT-populasjonen. Ved bruk av analysemetoder som er beskrevet i hovedprotokollen, vil vi teste for assosiasjon mot vanlige og sjeldne genvarianter for forekomst og behandlingsrespons for disse tilstandene. Prosjektet har også som målsetning å delta med oppsummeringsdata i internasjonale forskningsprosjekter og konsortier knyttet til epilepsi.

Årsakssammenhenger. Vi ønsker også å undersøke årsak- og virkningsspørsmål mellom epilepsi og observerte samsykdommer (komorbiditeter). Dette gjøres ved å undersøke i hvilken grad epilepsi-relatert genvariasjon også disponerer for komorbiditetene og vice versa (toveis mendelisk randomisering og andre analyser av genetisk pleiotropi).

Håndtering og deling av data

Som beskrevet i hovedprotokollen.

Etiske utfordringer tilknyttet studien

Som beskrevet i hovedprotokollen.

Denne studiedelen omfatter helseinformasjon fra Tromsøundersøkelsen. Genetisk informasjon benyttes kun fra individer som, i tillegg til Tromsø 4, har deltatt i en eller flere av de etterfølgnede Tromsøundersøkelsene, Tromsø 5, 6 og 7. Samtykkeeklæring og informasjon fra Tromsø 5 og 6 er vedlagt i søknaden.

Referanser

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Attachment 4

Case Report Form

NUMBER: _____ DATE:_____

PATIENT INITIALS: _____ Filled in by (initials):_____

Gender 1 Male, 2 Female ☐

Date of birth: ☐☐☐☐☐☐

Codes: 1 yes, 0 no, 2 unknown

Epilepsy validation: ☐ If no, other diagnosis (explain): ----------

Mors ☐ When (if recorded)_____

SEIZURE CLASSIFICATION (Fisher et al.-17) **EPILEPSY TYPE** (Scheffer et al.-17)

1. Focal onset ☐

Aware ☐

Motor ☐

Automatisms ☐

1. Focal ☐

2. Generalized ☐

3. Combined Gen. & Focal ☐

4. Unknown ☐

Other motor ☐ Describe_____

Non motor ☐ Describe_____

(behavioral arrest, autonomic, cognitive, emotional, sensory):

Impaired awareness ☐

Motor ☐

Automatisms ☐

Other motor ☐ Describe_____

Non motor ☐ Describe_____

(behavioral arrest, autonomic, cognitive, emotional, sensory):

Focal to bilateral tonic-clonic ☐

2. Generalized onset ☐

Motor ☐

Tonic-clonic ☐

Clonic ☐

Tonic ☐

Myoclonic ☐

Atonic ☐

Other ☐ Describe_____

Non-motor (Absence) ☐

Typical ☐

Atypical ☐

Myoclonic absence ☐ Describe (eyelid?) _____

3. Unknown onset ☐

Motor ☐

Nonmotor ☐

Unclassified ☐

KNOWN ELECTROCLINICAL SYNDROME ☐ (Berg et al.-10)

Self-limited Focal Epilepsy ☐ Describe_____

Childhood Absence Epilepsy ☐

Juvenile Absence Epilepsy ☐

Juvenile Myoklonic Epilepsy ☐

GTC Alone ☐

Epileptic encephalopathy ☐ Describe_____

Other ☐ Describe_____

EPILEPSY ONSET AGE ☐☐ years; unknown ☐

ETIOLOGY

MRI available ☐: Year: _____Finding:_____

a) Acquired: ☐

Structural ☐ Traumatic ☐ Vascular ☐, Tumor ☐, Malformation ☐, Other

Describe_____

Infectious ☐ Describe_____

Metabolic ☐ Describe_____

Immune ☐ Describe_____

b) Non-acquired

Genetic ☐ Unknown mutation ☐ Specific mut. ☐: Describe:_____

Unknown ☐

c) Undetermined due to lack of information ☐

KNOWN COMORBIDITY ☐

Intellectual Disability ☐ Grade: Mild ☐, Severe ☐, Profound ☐, Unk.☐

Psychatric ☐ Describe_____

Motor: ☐ Describe_____

Other ☐ Describe_____

AED Treatment ☐

Treatment Specifications:

Treatment response:

Sz within last year? ☐

Active epi (szs within last 5 years)? ☐

Epilepsy Resolved ☐

(Seizure free >10 years, off medication>5 years)

Recorded relatives with epilepsy ☐ Specify:

Collect more info from old records:

Dora ☐,

Levanger ☐ Namsos ☐ **Ferdig**: ☐

Classification Aid for CRF

1. Seizures

Epileptic seizures are currently classified into focal onset, generalized onset and unknown onset seizures.

1.1 Focal onset seizures

In focal onset seizures awareness is used as a classifier. Focal onset seizures are further classified into motor onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic myoclonic, tonic) as well as non motor onset ((autonomic, behavior arrest, cognitive, emotional, sensory). They are further characterized by their spreading pattern to bilateral tonic-clonic seizures (Fisher et al., 2017).

1.2 Generalized onset seizures

Generalized onset seizures are classified into motor (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms) and non motor or absence seizures (typical, atypical, myoclonic, eyelid myoclonic).

1.3 Unknown onset seizures

Available data do not allow for determination of seizure onset mode. Seizures can be classified as motor or non-motor.

2. Epilepsy types

The seizure classification forms the background for the classification of the epilepsies into 1) focal, 2) generalized and 3) combined generalized and focal, as well as 4) epilepsy of unknown type. In some epilepsies a specific syndromic diagnosis can be made: epilepsy syndromes or electroclinical syndromes.

The classification also incorporates etiological classification into six subgroups (structural, genetic, infectious, metabolic, immune-mediated and unknown.

Classification Aid for CRF

3. Seizures

Epileptic seizures are currently classified into focal onset, generalized onset and unknown onset seizures.

1.1 Focal onset seizures

In focal onset seizures awareness is used as a classifier. Focal onset seizures are further classified into motor onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic myoclonic, tonic) as well as non motor onset ((autonomic, behavior arrest, cognitive, emotional, sensory). They are further characterized by their spreading pattern to bilateral tonic-clonic seizures (Fisher et al., 2017).

1.3 Generalized onset seizures

Generalized onset seizures are classified into motor (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms) and non motor or absence seizures (typical, atypical, myoclonic, eyelid myoclonic).

1.3 Unknown onset seizures

Available data do not allow for determination of seizure onset mode. Seizures can be classified as motor or non-motor.

4. Epilepsy types

The seizure classification forms the background for the classification of the epilepsies into 1) focal, 2) generalized and 3) combined generalized and focal, as well as 4) epilepsy of unknown type. In some epilepsies a specific syndromic diagnosis can be made: epilepsy syndromes or electroclinical syndromes.

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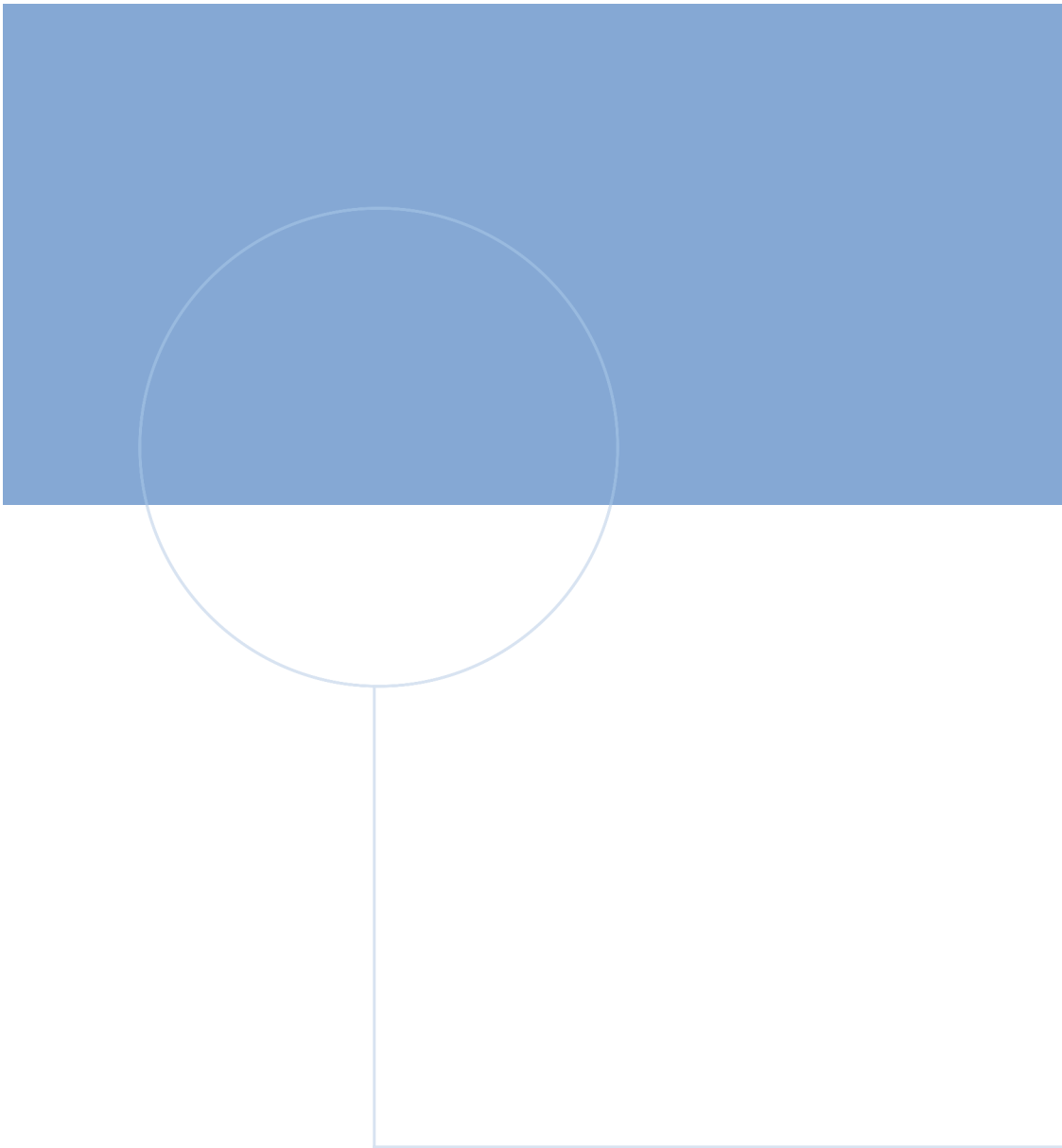

NTNU

Kunnskap for en bedre verden