Student thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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# Characteristics of Focal Epilepsies among Participants in HUNT 2 and 3

Student thesis in Medicine

Supervisor: Eylert Brodtkorb, Professor

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# Abstract

**Background**: The material collected in The Nord-Trøndelag Health Study (HUNT) provides an exclusive database of questionnaire data, clinical measurements and biological samples. Whole-genome association studies will be performed in subjects identified to have epilepsy as a part of the HUNT-MI study. In order for this to be meaningful, affirmation of the diagnoses and detailed classification of the epilepsies are obligatory.

**Purpose**: Our objective was to classify focal epilepsies according to the revised seizure and epilepsy classifications in relation to etiological groups, demographic features (age/sex), age of seizure onset, comorbidities and treatment response.

**Material and method:** The HUNT research coordinator identified all genotyped HUNT-2 and 3 participants with $\geq$ 2 appointments at neurological and/or pediatric clinics registered with epilepsy (ICD-10: G.40.x after 1999; ICD-9: 345.x prior to 1999) at hospitals in the county of Trøndelag. Validation of the diagnosis of epilepsy was carried out using medical record information according to current definitions presented by the International League Against Epilepsy (ILAE). Epilepsy characteristics were recorded in detail by using a Case Report Form (CRF). Data were analyzed using SPSS.

**Results**: In total 246 of 347 patients were identified with focal epilepsy (70.9%). There were 120 (48.8%) females and 126 males (51.2%). Structural etiology was identified in 145 (58.9%) patients, non-structural infectious etiology in 2 (0.8%), known/presumed genetic etiology in 2 (0.8%) and unknown etiology in 97 (39.4%) patients. The most common etiology was structural, with vascular events as the largest contributor. The age of seizure onset followed the general prevalence of cerebrovascular disorders with the largest proportion of patients $\geq$ 60 years. A total of 84 patients were seizure free for at least five years, and an additional 53 were seizure free the past year.

**Conclusion**: Epilepsy is a diverse condition. Focal epilepsies account for the vast majority, and most of them have a structural etiology. Although focal epilepsies long have been considered acquired, the knowledge concerning the genetic components is increasing. A large proportion of focal epilepsies have unknown etiologies based on currently available investigational methods in routine clinical practice. This study did not reveal obvious clinical differences between focal epilepsies with and without established cause, other than earlier onset in those without. Future clinical and translational research is needed to explore the etiologies of the large and important group of non-structural focal epilepsies.

# Sammendrag

**Bakgrunn**: Det innsamlede datamaterialet fra helseundersøkelsene i Nord-Trøndelag (HUNT) gir en enestående database med helseopplysninger, kliniske målinger og biologisk materiale tilgjengelig for forskning. Som en del av HUNT-MI studien, vil det bli gjennomført genom-assosiasjonsstudier på personer identifisert med epilepsi. For at dette arbeidet skal være meningsfylt er bekreftelse av diagnosen og detaljert klassifisering nødvendig.

**Mål**: Hensikten med studien var derfor å klassifisere pasientene med fokal epilepsi etter etiologi, demografi (alder/kjønn), alder ved anfallsstart, komorbiditet og behandlingsrespons.

**Materiale og metode**: Alle genotypede HUNT-2 og -3 deltagere med $\geq$ 2 kontakter ved nevrologiske og/eller pediatriske avdelinger registrert med en epilepsidiagnose (ICD-10: G.40.x etter 1999; ICD-9: 345.x før 1999) ved sykehusene i Trøndelag fylke ble inkludert i studien. Validering av diagnosen ble utført ved gjennomlesning av journaler og registrering av aktuell informasjon i henhold til den nyeste definisjonen presentert av "International League Against Epilepsy (ILAE)". Epilepsikarakteristika ble detaljert ført i vårt datainnsamlingsskjema. Dataene ble videre analysert i SPSS.

**Resultater**: Totalt var det 246 av 347 pasienter som hadde fokal epilepsi (70.9%). Av disse var 120 (48.8%) kvinner og 126 menn (51.2%). Strukturell etiologi ble identifisert hos 145 (58.9%) av pasientene, ikke-strukturell infeksiøs etiologi hos 2 (0.8%), kjent/antatt genetisk etiologi hos 2 (0.8%) og ukjent etiologi hos 97 (39.4%). Den vanligste etiologien var dermed strukturell, med vaskulære hendelser som den største bidragsyteren. Alder ved anfallsstart fulgte aldersfordelingen av cerebrovaskulære hendelser generelt i befolkningen. Følgelig var den største andelen av pasientene i denne gruppen $\geq$ 60 år ved første epileptiske anfall. Totalt var 84 pasienter anfallsfrie de siste fem årene. Ytterligere 53 hadde vært anfallsfrie det siste året.

**Konklusjon**: Epilepsi er en samlediagnose bestående av flere tilstander. Fokal epilepsi utgjør den største andelen av disse, og strukturell etiologi er vanligst. På tross av at fokal epilepsi lenge har vært betraktet som ervervet, er det nå stadig økende kunnskap om de genetiske komponentene. Etiologien forblir i mange tilfeller likevel ukjent basert på dagens undersøkelsesmetoder i klinisk praksis. Denne studien viste ingen åpenbare kliniske forskjeller mellom fokale epilepsier med og uten kjent årsak, bortsett fra tidligere anfallsstart hos de ukjente. Fremtidig klinisk og translasjonell forskning vil bli viktig i utforskningen av den store gruppen av ikke-strukturell fokal epilepsi.

# Table of contents

# List of figures



# List of tables

# Preface

This student thesis is part of the fifth year of Medical School at the Norwegian University of Science and Technology in Trondheim, Norway. Completing this thesis has been a valuable learning experience. We have obtained knowledge about collecting and analyzing statistical material. In addition, we have learned about cooperation, and the importance of good communication.

We were four students who worked on the same data material, the results were two separate student thesis projects. Therefore, we want to thank our two other collaborators, Bjørn Patrick Kolstad and Kristoffer Sandtrøen, for their cooperation in collecting data for the study.

Moreover, we want to thank our academic supervisor, Professor Eylert Brodtkorb, for thorough guidance throughout this process. He was always available and took his time of a busy schedule to give constructive feedback and advice. His commitment to this subject has inspired and encouraged our work.

We also want to thank friends and family for moral support, patience, and guidance. Finally, we would like to thank each other for good teamwork. Not only have we written and completed our first scientific work together, but this experience has also strengthened our friendship.

Marte Liang Aakvåg
Patricia Salcedo-Hokstad

# Introduction

Epilepsy is one of the most common serious chronic neurological conditions, affecting more than 50 million people worldwide (World Health Organization, 2019). It is a disorder of the brain characterized by an enduring predisposition to generate seizures and may occur at all ages. Clinical presentations, course and prognosis vary considerably from patient to patient. The disorder is defined by recurrent, unprovoked seizures, and by its neurobiological, cognitive, psychological and social consequences (Fisher et al., 2014). The prevalence in Norway is between 0.5–1% (Syvertsen et al., 2015).

The majority of people with epilepsy can achieve seizure control; nevertheless, drug therapy fails in about 30% (Kwan and Brodie, 2000) (Xue-Ping et al., 2019). The severe consequences of the disorder and the considerable fraction of people with drug refractory seizures render epilepsy as a huge global disease burden (Cianchetti et al., 2015).

Epilepsy is an extremely heterogeneous and complex disorder, and the classification of the various forms of epilepsy is challenging; hence, the classification criteria has been updated several times. The International League Against Epilepsy (ILAE) recently revised the framework for both epileptic seizures (Fisher et al., 2017) and seizure types (Fisher et al., 2017). Based on the initial clinical manifestations, epileptic seizures are currently classified into focal, generalized, and unknown onset seizures. The seizure classification forms the background for the classification of the epilepsies into focal, generalized, combined focal and generalized and unknown types. In some epilepsies, a specific syndromic diagnosis can be made: epilepsy syndromes or electroclinical syndromes.

The classification also incorporates etiological categorization into six subgroups: structural, genetic, infectious, metabolic, immune-mediated and unknown. However, the etiology is frequently multifactorial. Even in epilepsies caused by structural abnormalities, genetic variation may be underlying or may represent predisposing factors to developing epilepsy. In the so-called idiopathic or presumed genetic epilepsies, this influence is strong. A complex genetic/environmental interaction is thought to determine the clinical phenotype (Badawy et al., 2013). The new operational classification schemes have not yet been applied in epidemiological studies in adults.

The Nord-Trøndelag Health Study (HUNT) is one of the largest epidemiological health studies ever performed (Krokstad et al., 2013). It is a unique database of questionnaire data, clinical measurements, and biological samples in the geographical region of Nord-Trøndelag, Norway. It allows various association studies of various disorders and health issues. Data and samples were obtained in four waves of gathering: 1984–1986 (HUNT-1), 1995–1997 (HUNT-2), 2006–2008 (HUNT-3) and 2017–2019 (HUNT-4). The second HUNT survey (HUNT-2) was started in 1995 and ended in 1997. There were 93.898 people invited to participate and 65.237 participated. The participation rate was 69.5%. The third HUNT survey (HUNT-3) was started in 2006 and completed in 2008. 93.869 people were invited to participate and 50.807 participated. The participation rate was 54.1%. Biological material for genetic analysis has been provided from a large fraction of participating subjects. Whole-genome association studies will be performed in subjects identified to have epilepsy as a part of the HUNT-MI study.

To perform meaningful genotype/phenotype association studies, validation of the diagnoses and detailed classifications of the epilepsies with mapping of clinical characteristics are mandatory.

The main purpose of this student thesis was to classify focal epilepsies according to the revised epilepsy classification as well as in relation to etiological groups, demographic features (age/sex), age of seizure onset, comorbidities, and treatment response.

# Material and methods

## *Material*

Genotyped subjects from HUNT 2 and 3 with ≥ 2 appointments at neurological and/or pediatric clinics in Trøndelag county (St.Olav University Hospital, Namsos Hospital and Levanger Hospital) recorded with epilepsy (ICD9, 345.- or ICD10, G40.-) in the period 1987–2019.

## *Methods*

### Study design

Retrospective descriptive observational study.

### Ethics

This student project is part of the «HUNT-MI: Studiedel på epilepsi» were the objectives are to study how epilepsy is affected by genetic variation and to investigate the cause and effect of epilepsy and comorbid conditions.

The Regional Committee for Ethics in Research has evaluated the access to the patient records and the connection to health registers to be covered through the consent given in HUNT-3 (HUNT, 2006).

The committee also considered that the condition to give exception from consent to collect information from the hospital records are fulfilled for the participants in HUNT-2. The committee considers the HUNT-MI study to be beneficial and that welfare and integrity of the participants are ensured through the extensive measures to ensure data security. In addition, the information to be collected is of relatively low sensitivity. Moreover, the study population is large, and it will be difficult to collect consent from all participants.

Project modification to include medical students as collaborators has been approved.

Complying with good clinical practice regarding secure data protection, has received attention throughout the project.

## Subject collection

As part of the HUNT-MI study on epilepsy, the HUNT research coordinator identified all eligible subjects according to the inclusion criteria (see Material). The procedure was performed in cooperation with Helse Midt-Norge IT (HEMIT). A separate code list for personal identification was made.

## Classification using the Case Report Form (CRF)

Available medical information in the electronic medical records (EPJ/Doculive) from the years 2000 through January 2020 was systematically reviewed. For some subjects, background information from older paper medical records prior to 2000 was needed. Due to the outbreak of the corona virus disease (COVID)-19 pandemic, only paper journals that could be collected from the archive at St. Olav hospital were available. In total we were therefore able to complete 347 of 516 patient records (67.2%).

Careful ascertainment of the diagnosis of epilepsy was carried out using medical record information according to current definitions (Fisher et al., 2014). For those with a true diagnosis of epilepsy, seizure types were categorized according to the revised classification of the International League Against Epilepsy (ILAE) (Fisher et al., 2017). Seizure characteristics were recorded in detail as far as possible by using a Case Report Form (CRF) (Attachment 1) for collection of clinical details, including etiology, brain imaging findings, current treatment, seizure control as well as documented comorbidities.

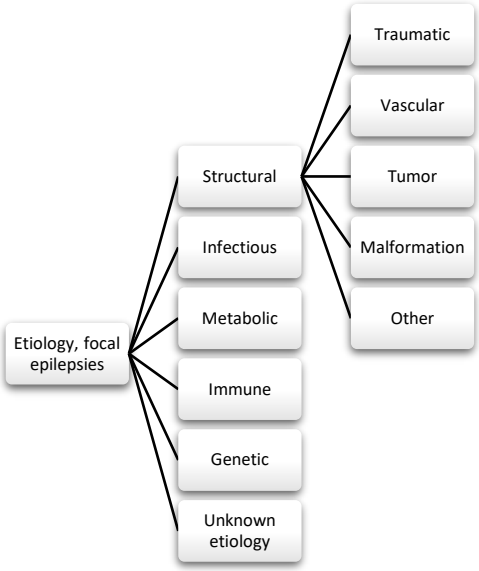


**Figure 1: Etiological groups and subgroups used in the classification**

## Plotting of data in Excel and SPSS

Data from the CRF was plotted in Excel adjusting for individual interpretations of the CRF. If a field was left blank in the CRF, plotting was recorded as unknown (=2). The correctness of the data was discussed among the investigators for consensus and subsequently exported to SPSS (Statistical Package for Social Sciences version 26 for Windows) for further analyses.

The final data set formed the foundation for two individual student thesis projects with separate objectives: one with focus on focal epilepsies and the other with focus on generalized epilepsies as well as combined focal and generalized epilepsies and those of unknown type. The present student thesis further presents the results of the focal epilepsies.

## Data security

Due to COVID-19 infection control considerations, we were not allowed admittance to the St. Olav hospital and NTNU campus facilities form March 12$^{th}$, 2020. We were thus assigned to work from home. Therefore, we tried to find secure solutions to keep our collaboration going without compromising patient sensitive information. The data protection advisor of St. Olav Hospital provided a method to encrypt and password protect files for secure e-mail communication. In this way, the files could be shared without compromising patient security.

## Analyses in SPSS

Focal epilepsies were studied in relation to etiological groups, demographic features, and age of onset with focus on frequencies among the patients. Comparisons were analyzed using Fisher's exact test and students t- test for independent variables.

# Results

## *Etiology*

Altogether 246 patients in the HUNT-2 and HUNT-3 study had focal epilepsy, making up 70.9% of the patients in our material. Figure 2 gives a detailed overview of the included patients and etiological groups and subgroups.

Of the 246 patients, there were 120 (48.8%) females and 126 males (51.2%) (Table 1). When analyzing gender according to each etiological group, there were no significant difference between the sexes (p=0.112). Structural etiology was identified in 145 (58.9%) participants, 66 were females and 79 were males. Unknown etiology was found in 97 (39.4%), 52 were females and 45 were males. Only two patients had a known or presumed genetic cause and two an infectious non-structural cause. None had known metabolic or isolated immunological etiologies.

**Table 1: Focal epilepsy according to etiology and gender**

| Etiology | All | Females | Males |
|---|---|---|---|
| Total | 246 (100.0%) | 120 (100.0%) | 126 (100.0%) |
| Structural | 145 (58.9%) | 66 (55.0%) | 79 (62.7%) |
| Infectious (non structural) | 2 (0.8%) | 0 (0.0%) | 2 (1.6%) |
| Genetic (non structural) * | 2 (0.8%) | 2 (1.7%) | 0 (0.0%) |
| Unknown etiology | 97 (39.4%) | 52 (43.3%) | 45 (35.7%) |

* Self-limited epilepsy with centrotemporal spikes; autosomal dominant sleep- related hypermotor epilepsy (ADSHE)

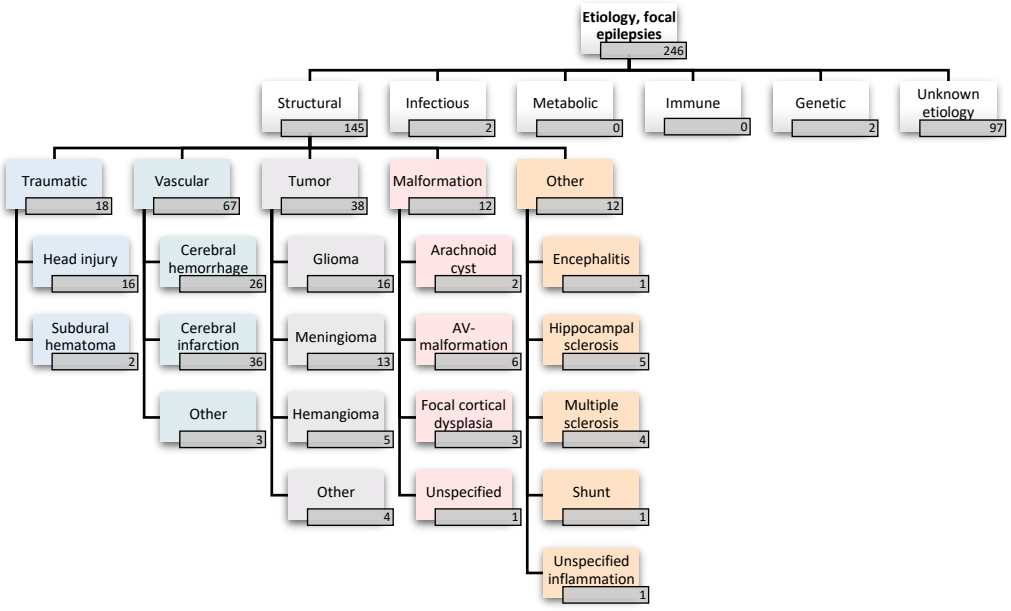


**Figure 2: Etiological groups and subgroups with number of patients**

Table 2 shows the etiology according to age of epilepsy onset. The patients were categorized into six age groups: unknown, 0–9, 10–19, 20–39, 40–59 and ≥ 60 years. Structural etiology increased with age and was most common in those ≥ 60. Unknown etiology was most prevalent in younger patients, particularly among patients with onset 10–19 years.

The two patients classified with genetic etiology had onset at ten and 12 years of age. Figure 3 provides a graphic representation of the distribution according to the etiology.

**Table 2: Focal epilepsy according to etiology and age of onset**

| Etiology | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 246 (100.0%) | 33 (100.0%) | 22 (100.0%) | 35 (100.0%) | 36 (100.0%) | 61 (100.0%) | 59 (100.0%) |
| Structural | 145 (58.9%) | 16 (48.5%) | 9 (40.9%) | 11 (31.4%) | 21 (58.3%) | 44 (72.1%) | 44 (74.6%) |
| Infectious (non structural) | 2 (0.8%) | 1 (3.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.7%) |
| Genetic (non structural) | 2 (0.8%) | 0 (0.0%) | 0 (0.0%) | 2 (5.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Unknown etiology | 97 (39.4%) | 16 (48.5%) | 13 (59.1%) | 22 (62.9%) | 15 (41.7%) | 17 (27.9%) | 14 (23.7%) |

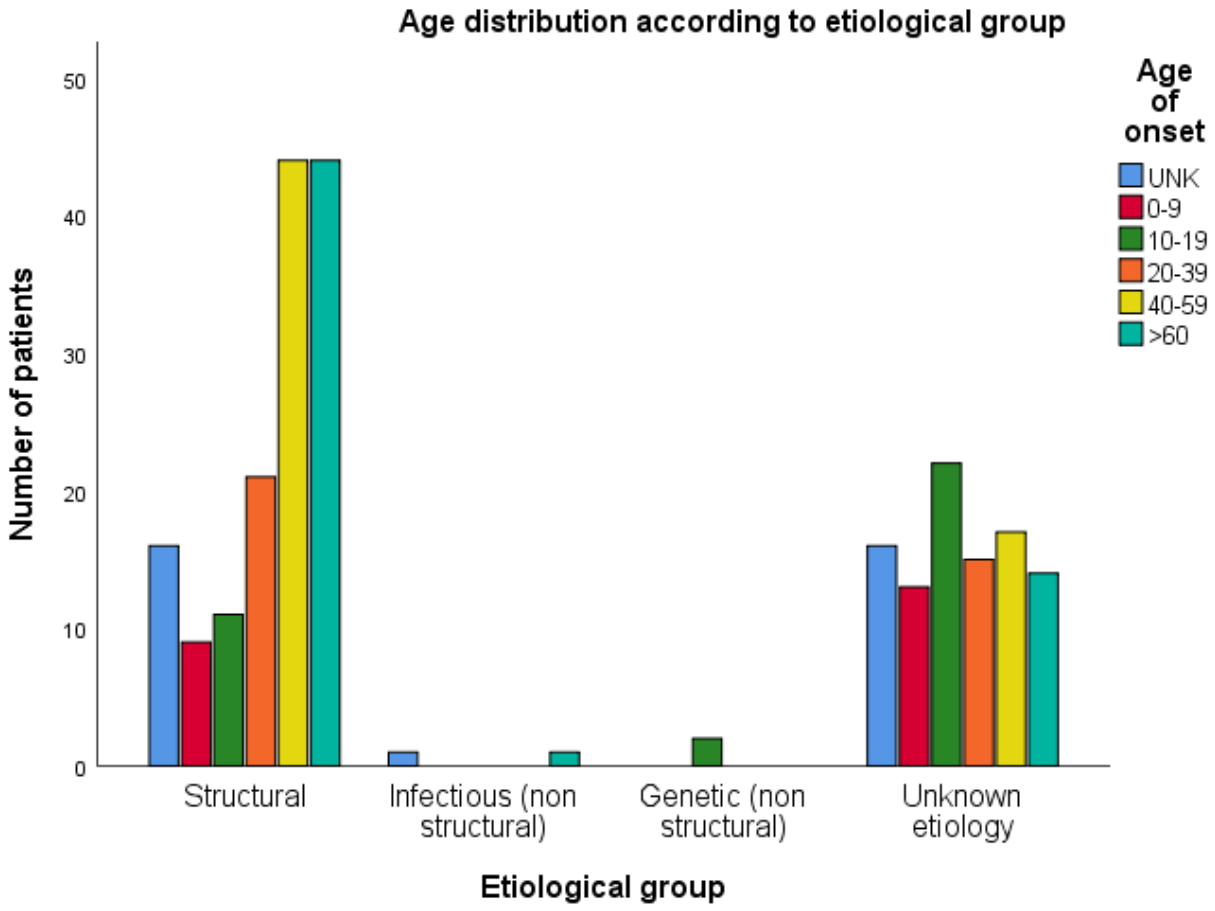


**Figure 3: Age of onset according to etiological group**

Table 3 and 4 describes the structural category in more detail. Structural etiology was divided into five subgroups: traumatic, vascular, tumor, malformation, and other abnormalities. Amongst these five subgroups 18 (12.4%) subjects had structural changes due to trauma, 65 (44.8%) had had a vascular event, 38 (26.2%) had tumors, 12 (8.3%) had various forms of malformations and 12 (8.3%) had other structural abnormalities. More patients had age of onset in older age due to the predominance of cerebrovascular disease in advanced age (Table 3), the same was seen with tumors, although to a lesser degree.

**Table 3: Structural type according to age of onset**

| Structural etiology | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 145 (100.0%) | 16 (100.0%) | 9 (100.0%) | 11 (100.0%) | 21 (100.0%) | 44 (100.0%) | 44 (100.0%) |
| Traumatic | 18 (12.4%) | 3 (18.8%) | 3 (33.3%) | 2 (18.2%) | 3 (14.3%) | 5 (11.4%) | 2 (4.5%) |
| Vascular | 65 (44.8%) | 9 (56.3%) | 0 (0.0%) | 3 (27.3%) | 5 (23.8%) | 19 (43.2%) | 29 (65.9%) |
| Tumor | 38 (26.2%) | 3 (18.8%) | 1 (11.1%) | 2 (18.2%) | 8 (38.1%) | 13 (29.5%) | 11 (25.0%) |
| Malformation | 12 (8.3%) | 0 (0.0%) | 3 (33.3%) | 2 (18.2%) | 3 (14.3%) | 4 (9.1%) | 0 (0.0%) |
| Other | 12 (8.3%) | 1 (6.3%) | 2 (22.2%) | 2 (18.2%) | 2 (9.5%) | 3 (6.8%) | 2 (4.5%) |

Regarding gender (Table 4), 66 patients were female (45.5%) and 79 were male (54.5%). In the two largest subgroups with structural etiology, 27 (40.9%) females had a vascular cause and 19 (28.8%) had tumors. Out of the 79 males, 38 (48.1%) had a vascular cause and 19 (24.1%) had a tumor.

**Table 4: Structural type according to gender**

| Structural etiology | All | Females | Males |
|---|---|---|---|
| Total | 145 (100.0%) | 66 (100.0%) | 79 (100.0%) |
| Traumatic | 18 (12.4%) | 6 (9.1%) | 12 (15.2%) |
| Vascular | 65 (44.8%) | 27 (40.9%) | 38 (48.1%) |
| Tumor | 38 (26.2%) | 19 (28.8%) | 19 (24.1%) |
| Malformation | 12 (8.3%) | 4 (6.1%) | 8 (10.1%) |
| Other | 12 (8.3%) | 10 (15.2%) | 2 (2.5%) |

The following paragraphs describe the age of onset distribution amongst the structural subgroups in more detail.

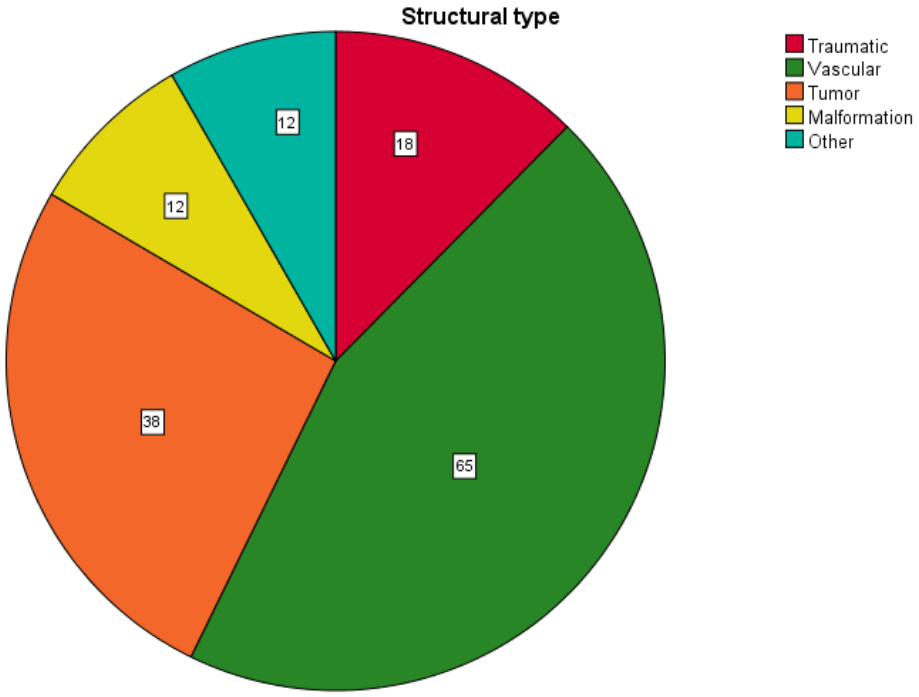


Figure 4: Structural subcategories, number of patients

**Types of traumatic etiology according to age of onset (Table 5)**

A total of 18 patients had suffered a head trauma causing their epilepsy, of these 16 (88.9%) had parenchymal brain changes, whereas two (11.1%) had a subdural hematoma. Epilepsy onset due to trauma was marginally more common in patients with onset <40 years.

Table 5: Types of traumatic etiology according to age of onset

| Trauma | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 18 (100.0%) | 3 (100.0%) | 3 (100.0%) | 2 (100.0%) | 3 (100.0%) | 5 (100.0%) | 2 (100.0%) |
| Parenchymal brain changes | 16 (88.9%) | 3 (100.0%) | 2 (66.7%) | 2 (100.0%) | 3 (100.0%) | 5 (100.0%) | 1 (50.0%) |
| Subdural hematoma | 2 (11.1%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) |

**Types of vascular etiology according to age of onset (Table 6)**

A total of 65 participants had a vascular etiology, representing the largest group of the structural patients. Vascular etiology was divided into three subgroups: hemorrhage, infarction and other; 26 (40.0%) had a cerebral hemorrhage, 36 (55.4%) had a cerebral infarction and three (4.6%) patients formed the category "other".

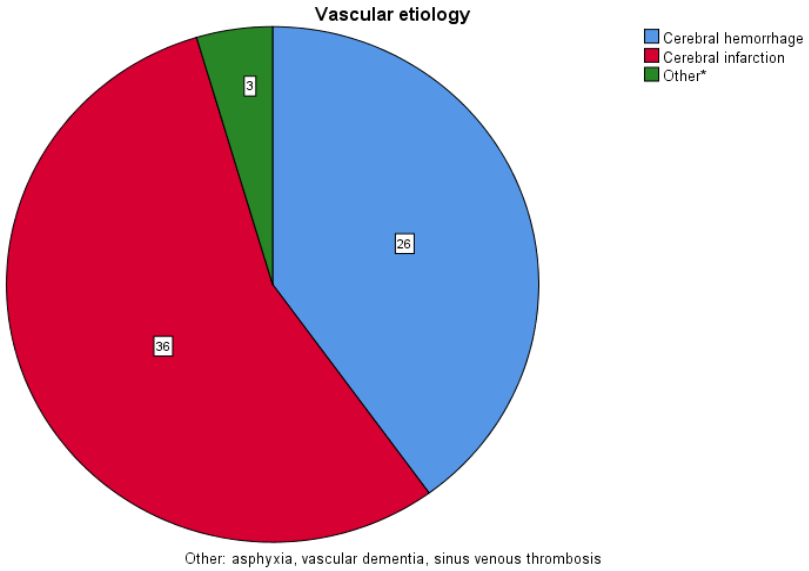


**Figure 5: Types of vascular etiology**

Vascular etiology was not found in children with onset below the age of ten, but the number increased with age. In the age group with onset 40–59, 19 had vascular etiology, eight of them (42.1%) had suffered a hemorrhage and 11 (57.9%) had had an infarction. Of the 29 patients with onset ≥ 60 years, nine of them (31.0%) had hemorrhagic and 20 (69.0%) had ischemic etiology.

**Table 6: Types of vascular etiology according to age of onset**

| Vascular | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 65 (100.0%) | 9 (100.0%) | 0 (0.0%) | 3 (100.0%) | 5 (100.0%) | 19 (100.0%) | 29 (100.0%) |
| Hemorrhage | 26 (40.0%) | 4 (44.4%) | 0 (0.0%) | 2 (66.7%) | 3 (60.0%) | 8 (42.1%) | 9 (31.0%) |
| Infarction | 36 (55.4%) | 4 (44.4%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 11 (57.9%) | 20 (69.0%) |
| Other * | 3 (4.6%) | 1 (11.1%) | 0 (0.0%) | 0 (0.0%) | 2 (40.0%) | 0 (0.0%) | 0 (0.0%) |

* asphyxia 1; vascular dementia 1; sinus venous thrombosis 1

**Types of tumors according to age of onset (Table 7)**

Brain neoplasms caused epilepsy in 38 patients. According to the *WHO classification of tumors of the central nervous system (Louis et al., 2016, chapter 23, page 520-521)* we subdivided the tumors into four groups: gliomas, meningiomas, hemangiomas (mesenchymal tumors) and other. In total 16 (42.1%) subjects had a glioma, five (13.2%) had a hemangioma, 13 (34.2%) had a meningioma and four (10.5%) were classified as other tumors. The two largest groups were the gliomas and the meningiomas. Out of the 16 gliomas, five patients had an astrocytoma, four had a glioblastoma and one had an oligodendroglioma. The last six were not further specified.

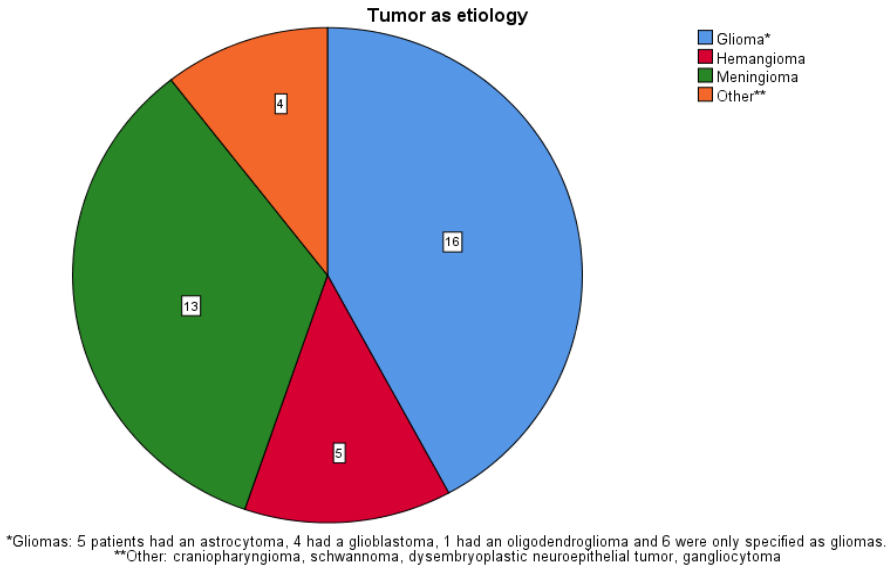


**Figure 6: Types of tumors, etiology**

There were no patients with epilepsy onset due to meningiomas under the age of 20. The majority of patients with tumor etiology were found in the age group 40–59 with 13 patients in total. Seven of these (53.8%) were meningiomas. Amongst the gliomas the number of patients increased after 20 years of age, consisting of 4–5 patients in each age group.

**Table 7: Types of tumors according to age of onset**

| Tumors | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 38 (100.0%) | 3 (100.0%) | 1 (100.0%) | 2 (100.0%) | 8 (100.0%) | 13 (100.0%) | 11 (100.0%) |
| Glioma * | 16 (42.1%) | 1 (33.3%) | 0 (0.0%) | 1 (50.0%) | 5 (62.5%) | 4 (30.8%) | 5 (45.5%) |
| Hemangioma | 5 (13.2%) | 1 (33.3%) | 1 (100.0%) | 0 (0.0%) | 1 (12.5%) | 1 (7.7%) | 1 (9.1%) |
| Meningioma | 13 (34.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (12.5%) | 7 (53.8%) | 5 (45.5%) |
| Other ** | 4 (10.5%) | 1 (33.3%) | 0 (0.0%) | 1 (50.0%) | 1 (12.5%) | 1 (7.7%) | 0 (0.0%) |

*astrocytoma 5; glioblastoma 4, oligodendroglioma 1; unspecified 6
** schwannoma 1; craniopharyngioma 1; dysembryoplastic neuroepithelial tumor 1; gangliocytoma 1

**Types of malformations according to age of onset (Table 8)**

A total of 12 participants had a structural malformation as their etiology. In two (16.7%) subjects an arachnoid cyst was considered causative, six (50.0%) had an AV-malformation, three (25.0%) had malformation of cortical development and one (8.3%) had an unspecified malformation. The largest number of patients were found < 40 years of age. Five of these patients were <20 years and three patients were between 20–39. In the group from 40–59 there were four patients, and no patients presented with epilepsy after the age of 60 years due to malformations.

Most patients had an AVM, and the mean age of these patients were 37.2 years. The malformations of cortical development were two with focal cortical dysplasia (FCD) and one with tuberous sclerosis. One of the patients with FCD had changes suggestive of Taylors dysplasia (FCDT). The age of onset for these patients were one year for the FCD (not further specified), 44 years (Taylors dysplasia) and four years (tuberous sclerosis).

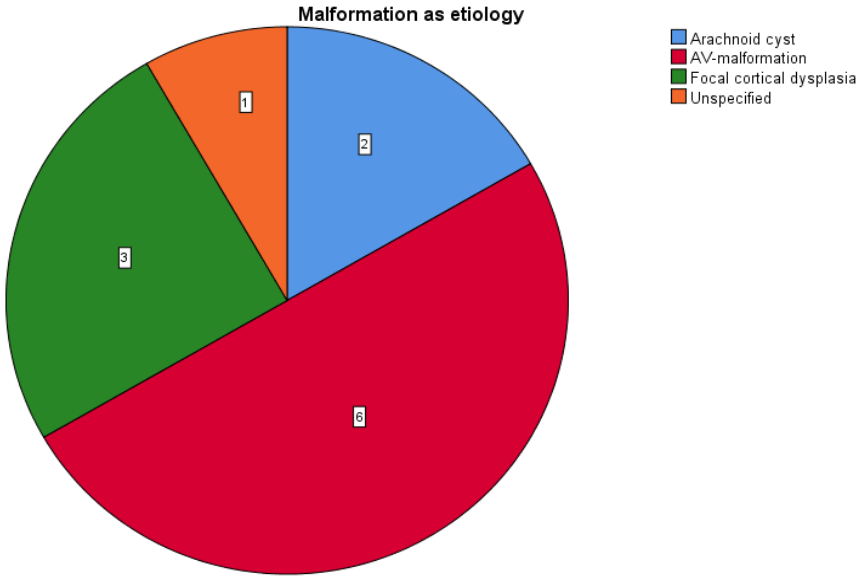


**Figure 7: Types of malformations, etiology**

**Table 8: Types of malformations according to age of onset**

| Malformations | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 12 (100.0%) | 0 (0.0%) | 3 (100.0%) | 2 (100.0%) | 3 (100.0%) | 4 (100.0%) | 0 (0.0%) |
| Arachnoid cyst | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (66.7%) | 0 (0.0%) | 0 (0.0%) |
| AV-malformation | 6 (50.0%) | 0 (0.0%) | 1 (50.0%) | 1 (50.0%) | 1 (33.3%) | 3 (75.0%) | 0 (0.0%) |
| Malformation of cortical development | 3 (25.0%) | 0 (0.0%) | 2 (66.7%) | 0 (0.0%) | 0 (0.0%) | 1 (25.0%) | 0 (0.0%) |
| Unspecified | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

**Other structural etiologies according to age of onset (Table 9)**

Out of the 12 patients with other structural changes, one (8.3%) had encephalitis, five (41.7%) hippocampal sclerosis, four (33.3%) multiple sclerosis, one (8.3%) had a hydrocephalus (shunted) and one (8.3%) had an unspecified inflammation.

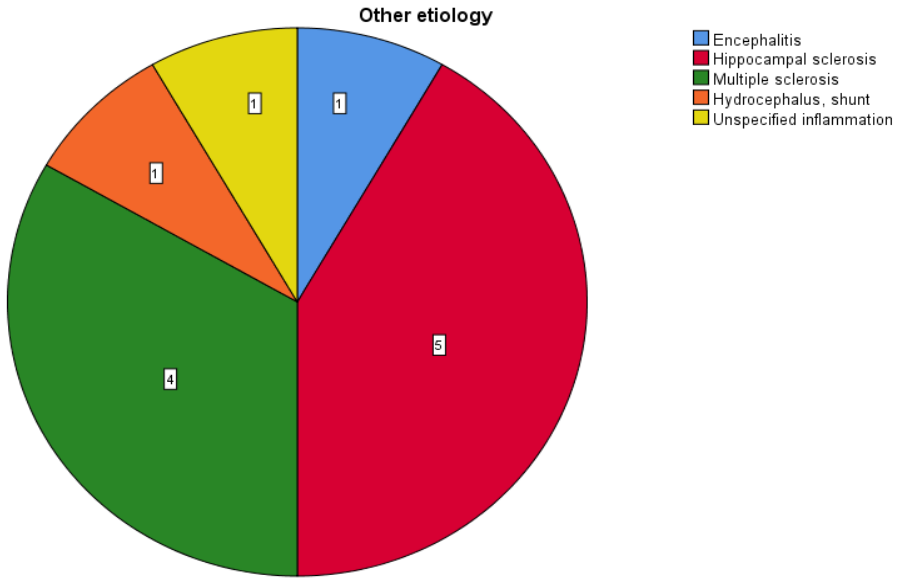


**Figure 8: Types of other structural etiologies**

**Table 9: Other structural etiologies according to age of onset**

| Other structural etiologies | All | Unknown | 0-9 | 10-19 | 20-39 | 40-59 | ≥60 |
|---|---|---|---|---|---|---|---|
| Total | 12 (100.0%) | 1 (100.0%) | 2 (100.0%) | 2 (100.0%) | 2 (100.0%) | 3 (100.0%) | 2 (100.0%) |
| Encephalitis | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) |
| Hippocampal sclerosis | 5 (41.7%) | 1 (100.0%) | 1 (50.0%) | 2 (100.0%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) |
| Multiple sclerosis | 4 (33.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) | 2 (66.8%) | 1 (50.0%) |
| Hydrocephalus. shunt | 1 (8.3%) | 0 (0.0%) | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Unspecified inflammation | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (50.0%) |

### *Treatment response*

The last neurological record was used as reference point to calculate if the patient had a seizure during the past year or within the last five years. Epilepsy was resolved if the patient had been seizure free >10 years and off medications >5 years.

Table 10 shows the treatment response in the form of seizure control according to etiology. In total 68 patients had a seizure the last year, 53 had been seizure free >1 year, but <5 years and 84 had been seizure free >5 years.

In ten out of the 53 being seizure free >1 year, but <5 years, we did not have information about all five years in their records. Hence, it is possible that these patients had been seizure free for five years, and not only the last. Furthermore, in 41 patients we could not determine one or both intervals for assessing seizure freedom due to lack of information in the records. Of these, 14 patients had at least one seizure within last five years, but unknown during the past year. Finally, there were 27 patients without information for the past five years, including the last.

Excluding the 41 with insufficient information, 40.9% were seizure free >5 years, and an additional 25.9% were seizure free for >1 year, but <5 years. Therefore, a total of 66.8% were seizure free for at least one year.

Only 19 patients had resolved epilepsy; nine had structural, one had presumed genetic (self-limited), one infectious and eight unknown etiology. Fourteen remained unknown due to lack of information while 213 had not resolved epilepsy.

**Table 10: Treatment response according to etiology**

| Etiology | Seizure(s) last year | Seizure free >1 year, but <5 years | Seizure free >5 years | Unknown | Epilepsy resolved |
|---|---|---|---|---|---|
| Total | 68 (100.0%) | 53 (100.0%) | 84 (100.0%) | 41 (100.0%) | 19 (100.0%) |
| Structural | 44 (64.7%) | 31 (58.5%) | 45 (53.6%) | 25 (61.0%) | 9 (47.4%) |
| Infectious (non structural) | 0 (0.0%) | 1 (1.9%) | 1 (1.2%) | 1 (1.2%) | 1 (5.3%) |
| Genetic (non structural) | 0 (0.0%) | 1 (1.9%) | 1 (1.2%) | 1 (1.2%) | 1 (5.3%) |
| Unknown etiology | 24 (35.3%) | 20 (37.7%) | 37 (44.0%) | 37 (44.0%) | 8 (42.1%) |

Two subcategories in the structural group were of particular interest as they often are associated with drug resistant epilepsy. Firstly, within the malformations, we find the subcategory “malformations of cortical dysplasia (MCD)” with three patients. Of these only one were seizure free for five years, while the other two had seizures within the last five years. All were currently using antiepileptic drugs (AEDs).

Of five patients with hippocampal sclerosis, four had been seizure free the last year, whereas two had been definitely seizure free all five years. All patients were currently using AEDs and two had undergone surgery.

Another interesting factor is the impact of seizure semiology (Table 11). Of 68 patients having a seizure the last year, 50 (73.5%) of the patients were those with a history of FTC. In contrast only 17 (25,0%) of those without FTCs experienced the same. Even so, there was no statistical significance (p=0.093) between the groups. Looking at the 53 patients who had been seizure free >1 year, but <5 years, the difference was smaller with 29 (54.7%) FTC patients and 20 (37.7%) non-FTC patients. The same numbers for the 84 patients who had been seizure free for at least five years; 53 (63.1%) FTC patients and 22 (26.2%) non-FTC. Of the 19 resolved patients, 13 (68.4%) had experienced FTC-seizures.

**Table 11: Treatment response according to seizure type**

| Seizure semiology | Seizure(s) last year | Seizure free >1 year, but <5 years | Seizure free >5 years | Unknown | Epilepsy resolved |
|---|---|---|---|---|---|
| Total | 68 (100.0%) | 53 (100.0%) | 84 (100.0%) | 41 (100.0%) | 19 (100.0%) |
| Not FTC * | 17 (25.0%) | 20 (37.7%) | 22 (26.2%) | 10 (24.4%) | 5 (26.3%) |
| FTC * | 50 (73.5%) | 29 (54.7%) | 53 (63.1%) | 26 (63.4%) | 13 (68.4%) |
| Unknown if FTC * | 1 (1.5%) | 4 (7.5%) | 9 (10.7%) | 5 (12.2%) | 1 (5.3%) |

*, statistically insignificant

## *Structural vs. unknown etiology*

Table 12 compares some clinical characteristics between the patients with structural and unknown etiology.

The first, and most notable difference, is the mean age of onset. For the structural patients, mean age is 43 years in contrast to 27 years in the unknown group ($p<0.001$).

Secondly, recorded relatives with epilepsy differed (Table 13). In total six (4.1%) of the structural and 11 (11.3%) of the unknown patients had recorded relatives with epilepsy. This was also statistically significant with a $p=0.032$.

Considering seizure control, a slightly larger proportion of the unknown patients were seizure free after five years, likewise a somewhat larger proportion had epilepsy resolved. None of these numbers reached statistical significance.

**Table 12: Comparison of clinical characteristics between patients with structural and unknown etiology**

| Clinical characteristics | Structural | Unknown |
|---|---|---|
| Total | 145 (100.0%) | 97 (100.0%) |
| Mean onset age (years) * | 43 | 27 |
| Males | 79 (54.4%) | 45 (46.4%) |
| FTC** | 90 (62.1%) | 65 (67.0%) |
| Intellectual disability | 4 (2.8%) | 2 (2.1%) |
| Seizures last year | 44 (30.3%) | 24 (24.7%) |
| Seizure free >5 years | 45 (31.0%) | 37 (38.1%) |
| Epilepsy resolved | 9 (6.2%) | 8 (8.2%) |

*, $p<0.001$
**, data available for 223 patients

## *Recorded relatives with epilepsy*

**Table 13: Etiology according to relatives with epilepsy**

| Etiology | All | Yes | Unknown/No |
|---|---|---|---|
| Total | 246 (100,0%) | 18 (100,0%) | 228 (100,0%) |
| Structural* | 145 (58,9%) | 6 (33,3%) | 139 (61,0%) |
| Infectious (non structural) | 2 (0,8%) | 0 (0,0%) | 2 (0,9%) |
| Genetic (non structural) | 2 (0,8%) | 1 (5,6%) | 1 (0,4%) |
| Unknown* | 97 (39,4%) | 11 (61,1%) | 86 (37,7%) |

*p=0,032

# Discussion

The majority of focal epilepsies in this study had structural etiology, whereas nearly 40% were MRI-negative with unknown etiology. In the following, the various main etiological groups are discussed in relation to our findings.

## *Etiology*

### Vascular

Amongst our vascular patients the most common age of epilepsy onset was >40 years (Table 6). In the study *The Global Burden of Disease from 2013*, the incidence and prevalence rates of ischemic and hemorrhagic stroke were estimated. These rates showed an exponential growth with age, respectively after the age of 39 and 49 (Feigin et al., 2015). Considering that our results only include age at epilepsy onset and not age at stroke, the data cannot be directly compared. It is however well known that seizures and epilepsy can develop after a stroke, in fact as many as 3-30% develop post stroke epilepsy (PSE) (Pitkänen et al., 2016). There have been several studies on the topic trying to map epidemiology and clinical course. In an observational study by Roivainen et. al, it was described that the annual event risk of seizures after the first-ever ischemic stroke was 6.3% after first year, 2.4% after two years, 1.3% after three years and 0.3% thereafter (Roivainen et al., 2013). Based on these observations, it seems clear that the increased risk of epilepsy in older age, is related to the natural increase in cerebrovascular events.

### Tumor

The second most common cause of structural epilepsy was a tumor of the central nervous system (CNS). The Norwegian cancer registry shows that the median age for a tumor with primary cite in the CNS was between 58–60 years of age during the years 1984–2018 (Cancer Registry of Norway, 2019, table 5.2, p. 19). For both men and women there is an increase in the age-specific incidence rates with advancing age (Cancer Registry of Norway, 2019, table 5.11 and 5.12, p. 36-39). Hence, the increase in tumor-related epilepsy follows the statistics from the cancer registry (Table 7).

Of the patients presenting with tumors, 42.1% were gliomas. It is known that tumor type and location are factors that determine the risk of developing epilepsy. High-grade gliomas, which are rapidly growing tumors situated in deeper structures, are prone to present with other

symptoms than seizures. The low-grade gliomas, on the other hand, grow slowly and seizures are a more frequent symptom (Lee et al., 2010). In our material there was insufficient information to determine the WHO grade of all tumors. Nevertheless, only four of the 16 patients *had* a glioblastoma (high-grade glioma). Even though the data do not provide sufficient information to support Lee et al. in their findings, our definite high-grade patients are a minority.

The second largest group was the meningiomas accounting for 34.2% of the tumors. These are the most frequent benign intracranial tumors, associated with epilepsy and seizures. Possible explanations found in the literature are cortical affection, tumor invasion, ischemic changes and compression of surrounding cortex (van Breemen et al., 2007).

**Malformations**

A group with presumed younger patients is malformations of the brain. Such abnormalities were identified in only 8% of the structural patients in this study. Of these patients most had arteriovenous malformations (AVM).

AVMs are vascular anomalies that cause shunting of blood from arteries to veins in a high-flow and high- pressure system (Frösen and Joutel, 2018). Changes of the structure lead to risk of rupture and thereby the number one presenting symptom is intracerebral hemorrhage (Friedlander, 2007). Interestingly, even without bleeding, the AV- malformations frequently cause seizure activity (Brown et al., 1996) (von der Brelie et al., 2015). In fact, in a study by Ding et al. seizure activity was the most common presenting symptom of an unruptured AVM, and the second most common in AVMs overall (Ding et al., 2015).

Age of epilepsy onset in AVM-related epilepsy ranged from 9–50 years with a mean of 37.2 (Table 8). In the study performed by Ding et al. (Ding et al., 2015), the mean age of an AVM presenting with seizures were 35.2 ±14.4 years. Similar numbers are found in a study not distinguishing between seizures as a consequence or presenting symptom (von der Brelie et al., 2015). In our material we have classified ruptured and unruptured AVMs within the same category considering all our patients had seizures. However, to our knowledge only one patient experienced a rupture prior to seizure onset. Therefore, we consider the studies to be comparable and the age of seizure onset in our material resembles the age of larger studies.

In only three patients, malformations of cortical development (MCD) were identified. Of these, two had focal cortical dysplasia (FCD) and one had tuberous sclerosis (structural and genetic epilepsy). One FCD was suggestive of Taylors dysplasia (FCDT). Conceivably, some small or bottom sulcus FCDs had not been detected with only standard and low Tesla MRI techniques (Hofman et al., 2011). The collective term MCD describes conditions in which cells during embryogenesis form disorganized lesions of the cortex. Based on timing in the process the type of MCD are determined (Spreafico and Tassi, 2012, chapter 32, p. 535). Over the years several classification systems trying to include all aspects of the many diagnoses within the term have been proposed (Najm et al., 2014). One of these are from the group of Barkovich (BC) which was last reviewed in 2012 (Kuzniecky and Barkovich, 2001) (Barkovich et al., 2012). This classification divides the diagnoses in three main groups based on the earliest disruption of development.

Of our patients two appeared to belong to group 1 (Taylors dysplasia and tuberous sclerosis), and the last could be either 1 or 3 (FCD, not further specified) according to the BC classification. Age of seizure onset was 44, four and one years old, respectively. In a study performed on patients in Western- China they found that the mean age at seizure onset in BC-group 1 was 16.9 with a standard deviation of 2.6. In BC-group 3, the same number was 18.9 ± 2.8 (Liu et al., 2015). Two of our patients were young at age of onset in accordance with the literature.

The patient with age of onset at 44 had FCD, most likely of FCDT-type. This is a histological subgroup of FCDs classified as more severe. The Cleveland Clinic foundation (Widdess-Walsh et al., 2005) reviewed age of seizure onset in accordance with FCD subgroup and found that the degree of abnormality influenced the result. For the milder types of dysplasia, age of onset was later than in those with more severe dysplasia. Age of onset in our patient with FCDT is unusual. However, in a study by Siegel et al. (Siegel et al., 2005), age of onset in 213 patients with confirmed FCDT was >18 years of age in 10% with a range up to 55 years. In addition, they found that the older aged patients had better outcome after surgery. Interestingly, even without surgery our oldest patient had no seizures during the last five years, as opposed to the younger patients who both had seizures in the last five years.

**Other structural etiologies**

Twelve patients had various other structural abnormalities. Of these multiple sclerosis and hippocampal sclerosis are of particular interest.

Multiple sclerosis (MS) is an immune-mediated inflammatory condition with white matter lesions. The four patients in our material all had structural changes visible on MRI thought to cause their epileptic seizures. They can thus be classified as structural and immunological. In a study from Nordland county in Norway, data from 14 patients with MS and active epilepsy (seizures last five year or AED at prevalence point) were analyzed. The results point towards focal brain pathology affecting cortical structures as the main cause for comorbid epilepsy (Benjaminsen et al., 2017). Furthermore, they found the prevalence of epilepsy to be 4–5 times higher amongst MS-patients than in the general population.

Table 9 shows that all four patients with MS were female, and >20 years old at epilepsy onset. As with other autoimmune diseases, the majority of diagnosed patients are women. In the Nordland study, the female predominance was also pronounced with 11/14 being women. As MS are mostly diagnosed between 20-40 years of age, logically both our patients and the patients in Nordland were >20 years at epilepsy-onset.

Five subjects had hippocampal sclerosis visible on MRI. It is a common condition in surgical resections from medial temporal lobe epilepsy, with typical findings of neuronal loss and gliosis (Johns, 2014). The etiology of hippocampal sclerosis is however unknown, but an association with febrile seizures and CNS-infection is seen in between 40–45% of cases (Perry and Brat, 2010, chapter 23, p. 520, Woermann and Vézina, 2013, chapter 77, p. 754). In our material, two patients had CNS-infection ahead of epilepsy onset. A third patient had several febrile seizures as a child. These three patients were all <20 years at age of onset, and there were <10 years from the initial events to onset of epilepsy.

Studies suggest that 65% of intractable focal epilepsy is caused by hippocampal sclerosis, and that many patients require surgery to accomplish seizure control (Perry and Brat, 2010, chapter 23, page 520-522). Even so, four out of five patients were seizure free over the last year. Two of these had undergone surgery, and all five are currently using AEDs.

### *Treatment response*

Regardless of etiology, recurrent epileptic seizures impact everyday life of the patients. Hence, the number one treatment goal is seizure freedom. In 2000, Kwan et. al found that up to 70% achieve this goal, while more than 30% are drug resistant (DRE) (Kwan and Brodie, 2000). However, until 2009 there was no consensus as to the definition of DRE. Therefore, the ILAE proposed the following core definition: *"DRE is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (monotherapy or combined) to achieve sustained seizure freedom."(Kwan et al., 2010).* Regarding the definition of seizure freedom, ILAE proposed 12 months as a minimum, or seizure freedom three times the inter-seizure interval pre-medication (if longer than 12 months).

In the present data collection, several factors made it difficult to obtain appropriate information in order to apply the ILAE definition, first and foremost, the lack of precise records regarding the treatment regimen. Evaluating appropriateness and adequateness proves difficult without thorough recording of type of antiepileptic drug (AED), duration of use, dosage and the degree of treatment adherence. Hence, we have focused on the interval of seizure freedom as an expression of treatment response. For practical reasons, we tried to record whether the patient had been seizure free for the last year and last five years.

If we exclude the 41 patients with unknown time since last seizure (Table 10), a total of 205 patients had sufficient details in their records to analyze seizure freedom. Of these, 66.8% had been seizure free for at least one year. Although these data on seizure control are not based on current ILAE definitions, they compare to studies done before a consensus- definition was reached (Kalilani et al., 2018).

In a recent meta-analysis by Xue- Ping et. al, prevalence and risk factors of DRE was reviewed (Xue-Ping et al., 2019). It showed that even ten years after the proposed ILAE-definition of DRE, they struggled with heterogeneity among their included studies. The pooled prevalence was 25%, whilst the same number when only including those with two AEDs or more, was 27%. Likewise, a meta- analysis on the consistency between definitions prior to and after the introduction of the ILAE-definition, concluded that there was no association between their ILAE-concordance score and the prevalence estimates of the included studies (Kalilani et al., 2018).

The same meta- analysis from 2018, stated that due to different definitions, the etiology and risk factors of DRE were hard to evaluate. In our study, two different main factors were analyzed to look for possible influence: epileptic etiology (Table 10), and seizure semiology in the form of FTC (Table 11). A marginal difference in seizure control in favor of those with unknown compared to structural etiology was found. Moreover, a higher percentage of patients having had FTC experienced seizures during the last year compared to those without, but the difference was not significant. More studies on the possible influence of FTCs should be conducted.

### *Structural vs. unknown etiology*

It is well known that structural changes of the brain have epileptic potential. Focal epilepsies in general were therefore previously thought to be acquired conditions. However, with the introduction of genomic studies, there is emerging evidence for a genetic contribution to focal epilepsies, both with structural etiology, such as e.g. tuberous sclerosis, and those without (Thomas and Berkovic, 2014). The first focal epilepsy identified with a pure monogenetic etiology was autosomal dominant sleep-related epilepsy (ADSHE) (Steinlein et al., 2000), which was identified in one of the present patients. Another monogenetic focal epilepsy has also been reported from Norway, autosomal dominant lateral temporal lobe epilepsy (ADTLE) (Gu et al., 2002).

We have found it of interest to compare certain factors of the patients with unknown etiology to those presenting with structural changes (Tables 12 and 13). Recorded relatives with epilepsy were significantly more common in those with unknown etiology ($p=0.032$). Recorded epilepsy in the family do influence etiology. However, these data are scarce and may be biased by the likelihood of clinicians addressing heritability to a greater extent in epilepsy of unknown etiology compared to epilepsy with established cause. The difference concerning age of epilepsy onset was highly significant; it was lower in those with unknown etiology. Considering the difference in MRI- findings of these patient groups, we assumed seizure semiology might differ. However, we found no statistical difference in the frequency of FTC.

## *Limitations*

The investigators were students collecting medical information from hospital records. Consequently, the interpretation of medical notes improved during the period of data collection. In addition, there is a potential weakness that our classification is based on information provided by different physicians with variable experience regarding epilepsy. Thus, the seizure descriptions and additional history varied widely in level of detail in this retrospective study. To minimize the possible errors, most patients were discussed with the supervisor. Hence, we consider these problems to be of relatively small impact on the results. However, as already mentioned, the data on epilepsy in relatives are scanty and weak and should be interpreted with caution.

As discussed in the section "Analyses in SPSS" we controlled our data and re-read some patient journals. As a result, some patients kept their initial classification while others were reclassified. There were no predefined criteria for reviewing a record a second time. Therefore, it is possible that some additional changes could have been made if all records were re-read. However, the selection of records was based on the clinical eye of our supervisor, and we believe reading these journals a second time strengthened our material.

Moreover, it is obvious that this study covers only 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. This selection may explain the very low number of included people with intellectual disability.

Another limitation is that the various MRI techniques and magnetic field strengths (Tesla) could not be recorded for many patients in this study. MRIs were performed at different hospitals with variable neuroradiological expertise. Small and inconspicuous lesions, such as e.g. subtle FCDs, may not have been detected in all patients.

## Concluding remarks

Epilepsy is an extremely heterogenous condition. Focal epilepsies account for the vast majority of seizure disorders, and most of them have a structural etiology. Although focal epilepsies long have been considered acquired, the acknowledgement of the genetic influence on the enduring predisposition to generate seizures are emerging. A large proportion of focal epilepsies remain with an unknown etiology based on currently available investigational methods in routine clinical practice.

This study did not reveal obvious clinical differences between focal epilepsies with and without established cause, apart from an earlier onset in those without, and possibly a marginally more favorable prognosis regarding seizure control. The exploration of the underlying etiologies of the large and important group of non-structural focal epilepsies is a challenge for future clinical and translational research. Although the retrospective data on recorded relatives with epilepsy are incomplete and unsystematic in this study, they may suggest a more common genetic impact in focal epilepsies of unknown compared to structural etiology. This hypothesis should be further investigated.

Hopefully, combined collaborative efforts between clinicians, geneticists and molecular biologists will bring new discoveries regarding focal epileptogenesis, which may lead to improved treatment and even mechanistic and personalized options. This may particularly apply to uncontrolled seizure disorders with yet obscure etiology, as well as the prevention of the development of epilepsy after acquired insults to the brain.

# Attachments

## *Attachment 1*

## 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** ☐

**1. Focal** ☐
**2. Generalized** ☐
**3. Combined Gen. & Focal** ☐
**4. Unknown** ☐

Aware ☐
Motor ☐
Automatisms ☐
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 ☐ **Completed**: ☐

***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.

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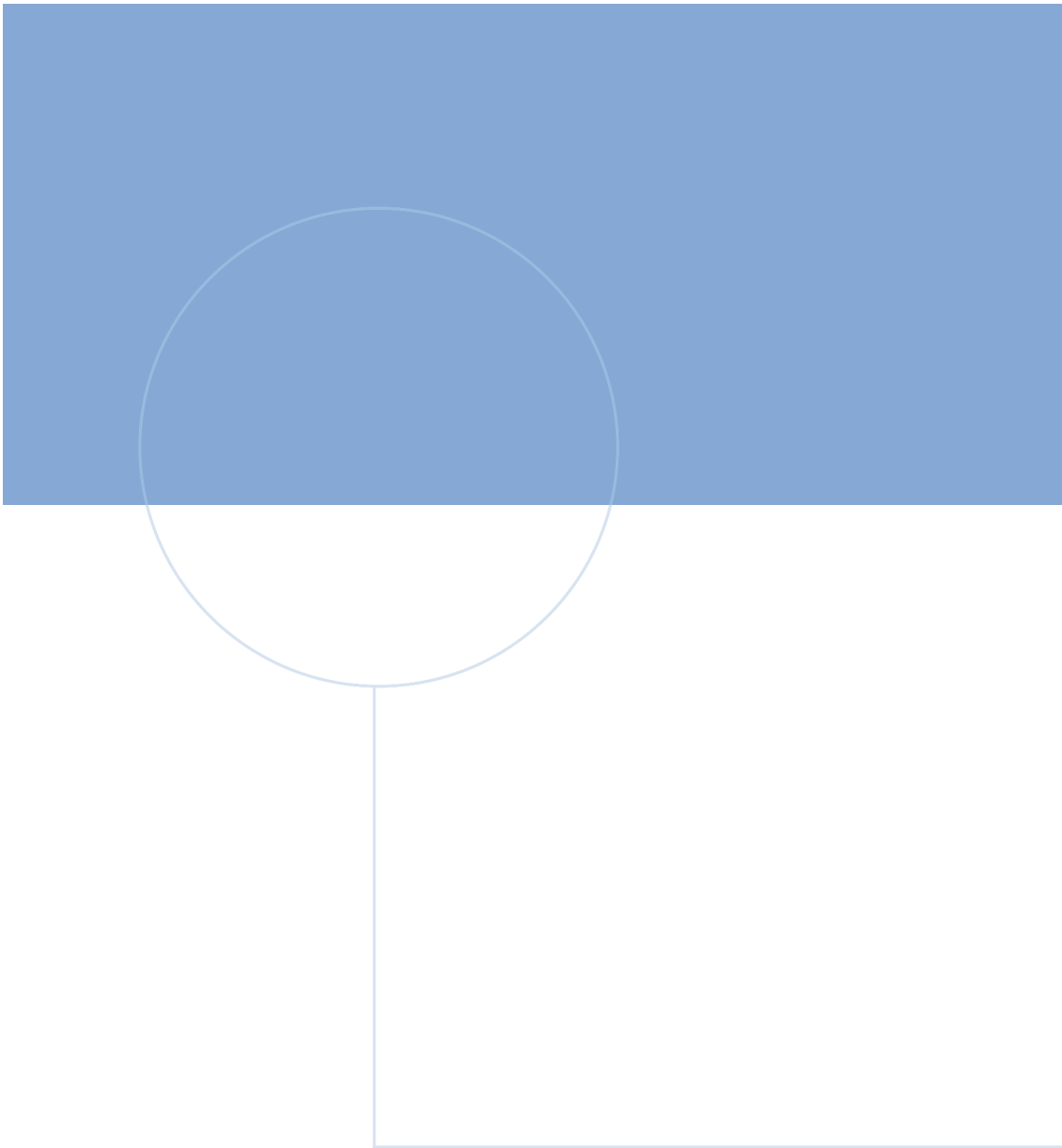

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