Key points

- Based on a large, unselected patient cohort we find that epilepsy and autoimmune disease frequently coexist. Epilepsy patients are more often prescribed medications used to treat type 1 diabetes mellitus, hypothyreosis, myasthenia gravis and multiple sclerosis, compared to the general population Autoimmunity as a factor for epilepsy or for the underlying brain dysfunction may have consequences for diagnostic procedures and treatment in some epilepsies. 1

INTRODUCTION

Epilepsy is one of the most common chronic brain disorders, and globally 50 million people areaffected (Legg til ref WHO 2014) (1). Epilepsy prevalence varies between 0.5 and 1 % (2). (3). (1). Common for all epileptic conditions are recurrent unprovoked seizures Epilepsy can have severe consequences for the patient, and treatment with antiepileptic drugs is strongly recommended for most patients. There is a wide range of antiepileptic drugs, and they can be used in combination as their mode of action varies. One third of the patients, however, does not become seizure free (4).

The etiology of epilepsy can be structural, infectious, genetic, metabolic or immune, or a combination of these. For more than half of the patients, the etiology is unknown (5, 6). Comorbidity can influence the risks of epilepsy and epileptic seizures and more knowledge about comorbidity in epilepsy should lead(7)to a better understanding of the pathophysiology of the disorder (8).

In the International League Against Epilepsy (ILAE)`s classification of epilepsies, an immune etiology has been included (6). This is due to the recent recognition of a range of rare immune epilepsies such as epilepsy caused by anti-NMDA receptor encephalitis and anti-LG1 encephalitis(9). A positive response to treatment with immunosuppressive drugs, and an association with some autoimmune diseases are topics discussed (2, 10). The risk of developing chronic epilepsy after antibody-associated encephalitis depends on the antigen (11). Further, brain autoantibodies can be detected in some patients with unexplained epilepsy suggesting an autoimmune pathogenesis of the underlying brain disorder, (12) and high serum GAD-A titers are associated with more severe epilepsy (13).

Comorbidity influences quality of life, treatment decisions and treatment response. Persons with epilepsy have high rates of comorbidity (14, 15). Early detection and treatment of comorbid conditions can decrease the severity of the epilepsy and increase quality of life (16). For optimal treatment, one should know the precise etiology and comorbidity of epilepsy (6, 16).

The primary aim of our study was to examine if, and to what degree, autoimmune disorders occur more frequently in patients with epilepsy. Mandatory national health registries represent important sources for information regarding comorbidity and risk factors (17). By using data from the

Norwegian Prescription Database (NorPD), we have examined a full national cohort of patients with active epilepsy treated with one or more antiepileptic drugs and recorded their use of drug treatments strongly associated with several autoimmune conditions. The treatment rates in epilepsy patients were compared to equivalent groups in the general population. Thus we have been able to define the comorbid disease load in the epilepsy population.

2 MATERIALS AND METHODS

2.1 The Norwegian Prescription Database (NorPD)

Most medications used in Norway, including all antiepileptic drugs, are strictly prescription controlled. Our study was based on NorPD, a health registry mandatory for registration of prescriptions dispensed at Norwegian pharmacies since January 2004. NorPD comprises a complete record of prescribed medications for the entire Norwegian population since 2004. This population counted 5.1 million people in 2014. Drugs dispensed during a hospital stay or in nursing homes are not recorded at an individual level in NorPD (18). The medicines are classified by the internationally accepted classification system, the Anatomical Therapeutic Chemical (ATC) Classification (19).

Nearly all medications used to treat chronic diseases in Norway are reimbursed, and the disease-specific reimbursement code is registered in NorPD. This also applies for antiepileptic drugs used to treat epilepsy. The clinical indication for the prescription of antiepileptic drugs has since March 2008 in addition been registered by a diagnostic code either from the International Classification of Diseases, 10th revision (ICD-10) or from the International Classification of Primary Care, 2nd edition (ICPC-2) (18). The reimbursement codes, and from 2008 also the diagnostic codes, have in this study been used as a proxy for the diagnosis of epilepsy(20).

2.2 Study Design

The total number of prescriptions in NorPD during the study period, January 1st 2004 to June 30th 2014, was 76 002 263. We received all prescriptions for patients who were prescribed antiepileptic drugs during this period. Because confirmed epilepsy usually is treated over time the patient had to receive and collect prescriptions of an antiepileptic drug (ATC-code N03A) at at least two different time points. The prescriptions also needed to have the correct reimbursement code (§7, Epilepsy and other organic brain diseases) or diagnose code (ICD-10 G40 or ICPC N88) for epilepsy, or both. A total of 224 patients treated with gabapentin (N03AX12) and/or pregabalin (N03AX16) and no other antiepileptic drugs, were excluded regardless of diagnostic code, as these antiepileptic drugs mainly are used for non-epileptic conditions(21). Altogether 79 751 patients were defined to have epilepsy. This high number is explained by the ten-year inclusion period. For each year, we had between 33 0000 and 35 000 patients enrolled, which equivalents a prevalence of 0.64-0.76%, matching the estimated prevalence in the Nordic countries oft 0,6% ref 3. The antiepileptic drugs used in Norway during this period are listed in table 1.

Table 1. Antiepileptic drugs used in the studypopulation January 1st 2004 to June 30th2014	
ATC-number	**Generic name**
N03AB02	phenytoin
N03AB05	fosphenytoin
N03AD01	ethosuximide
N03AE01	clonazepam
N03AF01	carbamazepine
N03AF02	oxcarbazepine
N03AF03	rufinamide
N03AF04	eslicarbazepine
N03AG01	valproic acid
N03AG04	vigabatrin
N03AG06	tiagabine
N03AX03	sultiame
N03AX09	lamotrigine
N03AX10	felbamate
N03AX11	topiramate
N03AX12	gabapentin
N03AX14	levetiracetam
N03AX16	pregabalin
N03AX15	zonisamide
N03AX17	stripentol
N03AX18	lacosamide
N03AX21	retigabine
N03AX22	perampanel
N03AA02	phenobarbital
N03AA03	primidone

To examine autoimmune comorbidity in patients with epilepsy, we retrieved from NorPD medications typically used for autoimmune diseases, hereafter referred to as autoimmune drugs. We did not have the prescription codes for these drugs. The following medications were examined;

1) Insulin and insulin analogs (ATC code A10A), excluding patients who had been dispensed oral antidiabetics (A10B) in the same period, to increase specificity for type 1 diabetes mellitus. This according to the national guidelines in Norway recommending not to treat type 2 diabetes mellitus with insulin in monotherapy.
2) Thyroid hormone substitution, specific for hypothyreosis (H03AA01).

3) Antithyroid medications, specific for thyroid disease (H03B).

4) The cholinesterase inhibitor pyridostigmine, specific for myasthenia gravis (N07AA02).

5) Immunosuppressive drugs specific for treating multiple sclerosis (L03AB07-8, L03AB13, L03AX13, L04AA23, L04AA27, L04AA31, N07XX07, N07XX09).

6) Selective immunosuppressive drugs, semispecific for autoimmune disorders (L04A).

The epilepsy patients were grouped according to sex and age. Patients` age was defined by their age on January 1st 2004. The prescriptions of autoimmune drugs for the epilepsy patients were compared to the prescriptions of the same drugs in the same age- and sex groups in the general population. The comparison population consisted of the entire Norwegian population registered in NorPD in the study-period, apart from those with a diagnosis of epilepsy. Our study included 4 667 376 such controls [table 2].

Table 2 Demographic characteristics of the epilepsy patients and the population controls.

	Epilepsy patients (*n*= 79 751)	Population controls (*n*=4 667 376)
Sex (*n*, %)		
Men	39 489 (49.1)	2 098 584 (45.0)
Women	40 262 (50.9)	2 568 792 (55.0)
Age in years* (*n*, %)		
< 20	14 829 (18.6)	674 562 (14.5)
20-29	8 611 (10.8)	551 191 (11.8)
30-39	11 439 (14.3)	613 583 (13.1)
40-49	12 367 (15.5)	681 999 (14.6)
50-59	12 837 (16.1)	657 320(14.1)
60-69	9 066(11.4)	637 338(13.7)
70-79	6 974 (8.7)	618 035 (13.2)
80 +	3 628 (4.5)	233 348 (5.0)

* Age in January 1st 2004

2.3 Statistics

Standardized Incidence Ratios (SIR) were used to determine whether the occurrence of prescribed autoimmune medications in the epilepsy group was higher or lower than in the general population (20). To obtain standardized rates, we applied age- and sex-specific rates for the use of these drugs,

calculated from the total population without epilepsy. These rates were used to estimate the expected number of prescribed drugs in the epilepsy group, assuming this group had the same prescription rate as the general population. The SIR was obtained by dividing the observed number of prescriptions in the epilepsy group with this expected number. Significance was determined from a 95% confidence interval (CI) for SIR. All data processing and analyses were performed using IBM SPSS Statistics version 24.0 and Microsoft Excel 2016. The use of anonymous data retrieved from NorPD did not require approval from our regional ethics committee.

3 RESULTS

Table 3 Total number of epilepsy patients treated with autoimmune drugs, and the standardized incidence ratios (SIR) when compared to the general population. Women and men were also examined separately.

	Total		Women		Men	
Drugs (ATC group)	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
Insulin and insulin analogs (A10A)	1237	1,8 (1.7-1.9)	524	1.7 (1.6-1.9)	713	1.8 (1.7-2,0)
Thyroid hormone substitution (H03AA01)	8370	1.7 (1.7-1.8)	6148	1.6 (1.6-1.6)	2222	2.2 (2.1-2.3)
Antithyroid medications (H03B)	387	1.0 (0.9-1.1)	306	1.0 (0.9-1.1)	81	1.0 (0.8-1.3)
Cholinesterase inhibitor (N07AA02)	37	1.5 (1.1-2.1)	28	2.1 (1.4-3.0)	9	0.9 (0,4-1.6)
MS drugs (L03AB07-08;L03AB13; L03AX13;L04AA23;L04AA27;L04AA31;N07XX07; N07XX09)	609	4,9 (4,6-5,3)	414	4,8 (4,4-5,3)	195	5,2 (4,5-5,9)
Immunosuppresive drugs (ATC L04A)	1944	1.2 (1.1-1.2)	1144	1.2 (1.2-1.3)	800	1.1 (1.0-1.2)

A total of 79 751 individuals fulfilled the inclusion criteria and were defined as epilepsy patients. 29% of these were below 30 years, and 46% were between 30 and 60 years old [table 2]. The epilepsy patients more often received medications for most autoimmune diseases examined, independent of age and sex [table 3].

3.1 Insulin and Insulin analogs

The epilepsy group was more often treated with insulin and insulin analogs compared to the controls, SIR 1.8 (95% CI 1.7-1.9). This was observed for men, SIR 1.8 (95% CI 1.7-2.0) and women, SIR 1.7 (95% CI 1.6-1.9), and in all age groups from 20 to 79 years, SIR varying from 1.2 to 2.1 [table 3 and 4]. Adults aged 20 to 30 years, had SIR 1.9 (95% CI 1.6-2.2). For the age group 40-49 years, SIR was 2.3 (95% CI 2.0 - 2.6) and for the group 50-59 years, SIR was 2.4 (95% CI 2.1-2.7)

figure 1

3.2 Thyroid hormones

Epilepsy patients were more often treated with thyroid hormone substitution, SIR 1.7 (95% CI 1.7-1.7). SIR was 2.2 (95% CI 2.1-2.3) for men and 1.6 (95% CI 1.6-1.6) for women [table 3]. Epilepsy patients < 20 years had the highest ratio, SIR 2.9 (95% CI 2.6-3.2) [table 4]. For men < 20 years, the SIR was 5.1 (95% CI 4.4-5.9) [figure 2B].

3.3 Antithyroid drugs

Epilepsy patients were not prescribed more antithyroid drugs when compared to the controls, SIR 1.0 (95% CI 0.9-1.1) [table 3 and 4]. This was true for both men, SIR 1.0 (95% CI 0.8-1.3) and women, SIR 1.0 (95% CI 0.9-1.1) [figure 3].

3.4 Cholinesterase inhibitors

Epilepsy patients were treated more often with pyridostigmine, SIR 1.5 (95% CI 1.1-2.1) [table 3 and figure 4]. Altogether, 37 patients in the epilepsy group received prescriptions of pyridostigmine. Eight of these were women aged 60-69 years.

3.5 Multiple sclerosis (MS) drugs

Epilepsy patients < 70 years were prescribed more medications for multiple sclerosis than the comparable controls, with SIR varying between 1.9 and 9.0 in the different age groups [table 4]. The ratios were highest for patients older than 40 years with SIR 6.0 - 9.0, but also the younger age groups 20 - 39 years were more often treated with MS drugs, SIR 2.7 - 3.9 [figure 5]. This was true for both men and women.

3.6 Selective immunosuppressive drugs

The epilepsy group was more often treated with selective immunosuppressive drugs than the controls, SIR 1.2 (95% CI 1.1-1.2) [table3]. Female patients younger than 50 years, and male patients 40 to 49 years were the subgroups with a significant difference [table 3,figure 6].

4 DISCUSSION

Our study shows increased prescription of medications used to treat autoimmune diseases for both male and female epilepsy patients, indicating a high frequency of type 1 diabetes mellitus, hypothyreosis, myasthenia gravis and multiple sclerosis compared to the general population. This was evident also for medications used to treat autoimmune diseases that never give any structural brain lesions or brain dyfunctions, such as myasthenia gravis, indicating that the findings not only are explained by confounders, but may represent a comorbidity partly based on common pathogenetic factors.

Our study has several strengths, determining comorbidity in a nationwide cohort with a large, unselected group of epilepsy patients. The prescriptions of antiepileptic drugs are strictly regulated by national laws and the drugs are state-funded. By using the NorPD, we ensured inclusion of all drug treated epilepsy patients in Norway, minimizing selection bias. The diagnostic and reimbursement codes secured that the patients had epilepsy. To further increase specificity, we only included patients with at least two prescriptions of one or more antiepileptic drugs, since patients with a confirmed epilepsy usually are treated over time. Prescriptions for epilepsy can be renewed regardless of consulting physician, reducing surveillance bias. For diseases with low prevalence, like myasthenia gravis, large population cohorts are needed to study comorbidity.

The epilepsy patients were more often treated with insulin and insulin analogs compared to the general population The Norwegian Directorate of Health did not recommend to treat type 2 diabetes mellitus with insulin/insulin analogs in monotherapy during the entire study period(ref). Thus, by excluding all patients who received oral antidiabetics, and only including patients who recieved insulin or insulin analogs in monotherapy the dominating part of our study group should have type1 diabetes mellitus (T1DM). Our findings are true for men and women and in nearly all age groups further strengthening a true association between epilepsy and the autoimmune disease T1DM. Our result is supported by other studies showing that patients with T1DM have an increased risk of

developing epilepsy (22). A population-based open-cohort study found that patients with T1DM had a three-times increased risk of developing epilepsy (23). Both metabolic, structural and autoimmune causes of this co-occurrence have been suggested (7, 22). Patients with T1DM have a higher risk of cardiovascular disease (24) and thereby a higher risk of post-stroke epilepsy. Post-stroke epilepsy isa likely confounder.. However, we found that epilepsy patients below 40 years who rarely have epilepsy due to cerebrovascular disease (ref 25)also were more often treated with insulin and insulin analogs (25). T1DM is proven as an autoimmune disease (26) and it has been suggested that autoimmunity is implicated in epilepsy as patients with T1DM have a high prevalence of epilepsy with unknown etiology (8). ?

The epilepsy group had more prescriptions of thyroid hormones than the general population.. This was true for both men and women and in all age groups, but most pronounced in the younger patients. Epilepsy patients < 20 years had a near three times increase in thyroid substitution, compared to the general population. Awareness of hypothyreosis in epilepsy patients is important, especially because symptoms of hypothyreosis can mimic both side effects of antiepileptic drugs and effects of repeated epileptic seizures. Based on the high ratio of hypothyreosis in epilepsy all epilepsy patients should be screened for hypothyreosis. Our findings are supported by previous studies showing that hypothyreosis is a frequent comorbid disease in epilepsy patients (27). Surveillance bias may be a contributing factor as patients with epilepsy are examined thoroughly at the time of diagnosis and with regular follow-ups, often also with blood tests. Some antiepileptic drugs can induce hypothyreosis and carbamazepine, topiramate, levetiracetam and valproate are associated with low fT4(28, 29). Another study found that enzyme-inducing antiepileptic drugs can reduce thyroid hormone concentrations, but that patients remain clinically euthyroid (30). Still such patients could have been treated with thyroid hormones. Residual confounding, for instance brain tumors causing both secondary hypothyreosis and epilepsy may explain a minor part of the

findings. Nevertheless, the markedly increased use of thyroid substitution in the epilepsy group, and especially in the younger patients, is of interest regarding autoimmunity. Hypothyroidism has an autoimmune etiology in 50% of the cases (31), and anti-thyroid antibodies are elevated in patients with severe NMDA encephalitis and epileptic seizures (32, 33). The severity of neuromyelitis optica spectrum disease, another autoimmune disease that can lead to epileptic seizures, is related to anti-thyroid antibody abnormalities (34). We did not find that epilepsy patients were more often treated with antithyroid drugs, used mainly for autoimmune Graves` disease (35).

Epilepsy patients were more often treated with pyridostigmine than the general population. Pyridostigmine is the drug of choice for myasthenia gravis, and is not prescribed regularly on other indications (20). Only in exceptional cases it is used to treat rare diseases such as Lambert-Eaton myasthenic syndrome and congenital myasthenia. It is therefore a reliable surrogate marker for active myasthenia gravis. Prevalence of myasthenia gravis varies between 150 and 180 per million (36), in Norway beiing 131 per million (37). In our study, we found 37 patients treated with pyridostigmine among 79 751 with epilepsy, significantly more than expected. This is supported by a population-based study from the United States that found a myasthenia gravis prevalence of 0.4% in epilepsy patients (2). Myasthenia gravis is an autoimmune disease that does not affect the brain and therefore does not cause epilepsy secondary to structural brain lesions

We found that epilepsy patients more often were treated with medications specific for multiple sclerosis (MS). The results were significant for both men and women and in all adult age groups. Several strengths in our study make this result reliable. The criteria and diagnostic procedures for MS have been clearly defined in the period from 2004 (38, 39). Treatment of MS is now aggressive, and the drugs used are MS specific. Our results show that the association between epilepsy and MS is definite, in line with previous studies (40, 41). Patients with primary progressive MS do not

receive immunosuppressive drugs and are therefore not included, unless using fampridin (ATC N07XX07). Untreated MS patients werenot identified in our study. We found that the frequency of treatment with MS specific medications in the epilepsy group increased with age, indicating that MS progression is associated with an increase in epilepsy risk. Focal MS brain pathology with cortical lesions probably explains the majority of the epilepsy comorbidity in MS and such pathology increases with age (41). (42) However epileptic seizures in MS patients are often generalized (sett inn ref,42). Therefore we speculate that a shared autoimmunity could explain some of the epileptic seizures in MS, despite their focal brain lesions,

Selective immunosuppressive drugs were more often used by female epilepsy patients under 50 years. This group of medications is mainly used to treat diseases like rheumatoid arthritis, lupus and psoriasis. However, they are not specific for autoimmune disorders and are used also after transplantations and for some cancers. The frequent use of selective immunosuppressive drugs in young and middle aged female epilepsy patients still supports a high autoimmune disease load in our epilepsy patients.

Our findings indicate that epilepsy and autoimmune diseases frequently coexist (12, 43). Young patients have more epilepsy of unknown etiology (25), but this is true also for one half of adult onset focal epilepsy (44). Some of these epilepsies have a positive effect of immune therapy (45-48). About two thirds of premature deaths in epilepsy patients can be attributed to comorbidity (49). Guidelines for detection of epilepsy comorbidity is a pressing gap in epilepsy care (7). Our findings increase the knowledge of comorbidity in epilepsy, and point to potential screening strategies. Optimal treatment of comorbidity leads to better epilepsy control and increased quality of life (6).

Our study has some limitations. Misuse of codes might lead to a small overestimation of epilepsy patients, perhaps relevant for some diabetes-and MS patients receiving treatment for neuropathic pain (50). To reduce this risk we excluded patients that had gabapentin and/or pregabalin as their only antiepileptic treatment. The great majority of patients with confirmed epilepsy and autoimmune disorders receive drug treatment. Such treatment was a prerequisite for detection in our study. Drugs dispensed in institutions are not registered in NorPD, this mainly concerning the elderly patients. The great majority of patients receiving epilepsy and autoimmune medications in these institutions have also received such drugs either before or after being at the institution, and have thus been included in our study. Our data does not answer whether the patient got antiepileptic drugs or autoimmune treatment first, nor do we know type of epilepsy or seizure activity. We did not have reimbursement or diagnostic codes for the autoimmune medications.

5 CONCLUSION

Our study shows that epilepsy patients more often are prescribed medications used to treat several autoimmune diseases,compared to the general population. This was true for both men and women, and in most age-groups, and also for autoimmune diseases that do not give structural brain lesions or brain dysfunction. Autoimmunity as a factor for epilepsy or for the underlying brain dysfunction may have consequences for diagnostic procedures and treatment in some epilepsies.

DISCLOSURE

Nils Erik Gilhus has received speaker`s or consulting honoraria from Octapharma, Alexion, Argenx and Ra Pharma. Anna Wie Børsheim and Anders Engeland have no conflicts of interest to report. We confirm that we have read the Journal`s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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