Received: 6 April 2021 | Accepted: 25 August 2021

DOI: 10.1111/ene.15089

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Seizure prevalence in neurodegenerative diseases—a study of autopsy proven cases

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Funding information
Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology, Grant/Award Number: EXC 2145 SyNergy - ID 390857198

Abstract

Background and purpose: Knowledge about the seizure prevalence in the whole symptomatic course, from disease onset to death, in neurodegenerative diseases (ND) is lacking. Therefore, the aim was to investigate seizure prevalence and associated clinical implications in neuropathologically diagnosed ND.

Methods: Clinical records of cases from the Neurobiobank Munich, Germany, were analyzed. Neuropathological diagnoses of the assessed cases included Alzheimer disease (AD), corticobasal degeneration (CBD), frontotemporal lobar degeneration (FTLD), Lewy body disease (LBD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Seizure prevalence during the whole symptomatic disease phase was assessed and compared amongst ND. Associations between first clinical symptom and seizure prevalence and between seizures and disease duration were examined.

Results: In all, 454 patients with neuropathologically diagnosed ND and with available and meaningful clinical records were investigated (AD, $n = 144$; LBD, $n = 103$; PSP, $n = 93$; FTLD, $n = 53$; MSA, $n = 36$; CBD, $n = 25$). Seizure prevalence was 31.3% for AD, 20.0% for CBD, 12.6% for LBD, 11.3% for FTLD, 8.3% for MSA and 7.5% for PSP. Seizure prevalence was significantly higher in AD compared to FTLD ($p = 0.005$), LBD ($p = 0.001$), MSA ($p = 0.005$) and PSP ($p < 0.001$). No other significant differences regarding seizure prevalence were found between the studied ND. Cognitive first symptoms in ND were associated with an increased seizure prevalence (21.1% vs. 11.0% in patients without cognitive first symptoms) and motor first symptoms with a decreased seizure prevalence (10.3% vs. 20.5% in patients without motor first symptoms). Seizures were associated with a longer disease duration in MSA (12.3 vs. 7.0 years in patients without seizures; $p = 0.017$).

Conclusions: Seizures are a clinically relevant comorbidity in ND, particularly in AD. Knowledge of the first clinical symptom in ND may allow for estimation of seizure risk.

KEYWORDS
Alzheimer disease, epilepsy, neurodegenerative diseases, seizure prevalence, seizures

INTRODUCTION

Neurodegenerative diseases are estimated to be the second most common known cause of epilepsy in elderly people after stroke [1]. At nearly 50%, epilepsies with unknown cause represent by far the greatest proportion of epilepsies in elderly patients [1]. A substantial proportion of epilepsies with unknown cause in the elderly may be attributable to otherwise presymptomatic neurodegenerative diseases [2]. Therefore, neurodegenerative diseases could be one of the main causes of epilepsy in the age group at risk for neurodegenerative diseases.

Frequent neurodegenerative diseases in the elderly are Alzheimer's disease (AD), Lewy body disease (LBD) comprising the neuropathologically indiscernible dementia with Lewy bodies (DLB) and Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) [3–12]. Estimates for seizure prevalence in these diseases are inconsistent, scarce or absent in some conditions and very rarely based on neuropathologically proven diagnoses. Knowledge about potential predictors of seizure risk in the whole symptomatic course, from disease onset to death, and about associations between the presence of seizures and disease duration in neurodegenerative diseases, in particular in autopsy proven conditions, is lacking.

The goal of our clinical pathological correlation study was to assess the prevalence of seizures during the whole symptomatic phase in the common neurodegenerative diseases AD, LBD, FTLD, CBD, PSP and MSA. Neuropathological diagnoses should serve as the diagnostic gold standard. Further aims were to investigate the potential prognostic value of the first clinical symptom [13] regarding seizure risk and to study associations between seizures and disease duration in these common neurodegenerative conditions. Addressing these objectives may improve diagnosis and thereby may help to optimize treatment of seizures in neurodegenerative diseases.

METHODS

Participants

Data from the Neurobiobank Munich (NBM) located at the Center for Neuropathology and Prion Research and from clinical files from the hospital of the Ludwig-Maximilians-Universität München and other hospitals in Germany were analyzed. All patients with adequate clinical data who were autopsied between 1985 and 2017 and who had a neuropathological diagnosis of AD, CBD (FTLD-tau CBD [14]), FTLD (FTLD-TDP [TAR DNA-binding protein 43], FTLD-UPS [ubiquitin proteosome system], FTLD-FUS [fused in sarcoma protein], FTLD-tau PiD [Pick's disease], FTLD-ni [no inclusions]), LBD, MSA or PSP (FTLD-tau PSP) were included. The Institutional Review Board of the Ludwig-Maximilians-Universität München, Germany, approved this study. All NBM cases were collected according to the guidelines of the local ethics committee.

Neuropathological processing

Brain banking was conducted using established procedures with a standardized protocol [15]. Neuropathologists experienced in neurodegenerative diseases made neuropathological diagnoses using current diagnostic criteria [14,16–24]. Two senior neuropathologists experienced in neurodegenerative diseases verified all neuropathological diagnoses in consensus. PS conveyed the neuropathological diagnosis, date of birth, date of death, age at death and gender to a standardized template.

Clinical data assessment

Paper and digital medical records were searched for seizure occurrence and time of onset of the first clinical symptom of the respective neurodegenerative disease. Only seizures that occurred in the symptomatic disease course of a neurodegenerative disease were considered. Analyses of seizure occurrence covered the whole symptomatic disease span, from onset of the first clinical symptom to death. Identification and definition of epileptic seizures was based on the judgment of the respective attending neurologists. Results were introduced in the standardized template by IK. Two senior neurologists (JV, JL) experienced in clinical care of neurodegenerative diseases discussed and validated the clinical data in consensus. JV and JL were blinded to the neuropathological diagnoses.

Data processing and statistical analyses

FileMaker Pro (Filemaker Inc., Santa Clara, CA, USA) was applied to produce the template for combining clinical and neuropathological data. Demographic and clinical characteristics of study participants were investigated and compared amongst subgroups with one-way analysis of variance for continuous variables and Pearson's chi-squared test for categorical variables. Seizure prevalence was compared between the neurodegenerative diseases using Pearson's chi-squared test. Thirty-seven distinct first clinical symptoms were identified in the study population. As these symptoms generally occurred in small numbers, patients were grouped into those with either cognitive first symptoms or motor first symptoms. Seizure prevalence was compared between patients with and without cognitive first symptoms and between patients with and without motor first symptoms using Pearson's chi-squared test. Within each neurodegenerative disease entity, patients with and without seizures were compared for disease duration using Student's t test or the Mann–Whitney U test, where appropriate. Disease duration was computed as the time interval between the date of onset of the first symptom and the date of death for each participant. p values below 0.05 were considered statistically significant. All tests were conducted two-sided. The Statistical Package for the Social Sciences (IBM SPSS Statistics, version 26) was used for statistical analyses.

RESULTS

Participants

In all, 978 cases were included at the NBM at the time of analysis, and 454 patients with neuropathologically proven AD ($n = 144$), CBD ($n = 25$), FTLD ($n = 53$), LBD ($n = 103$), MSA ($n = 36$) and PSP ($n = 93$) and sufficient clinical data were identified. As expected, the neurodegenerative diseases differed in mean disease duration and mean age at death. Study population characteristics are shown in Table 1.

Co-pathologies that are known to cause seizures included meningioma, infarcts, brain lesions after contusion, hemorrhages, brain tumors, lesions due to stimulation electrodes, encephalitis and cavernoma in the studied cases. Co-pathologies occurred in 16.1% of the studied patients. Seizure prevalence did not differ significantly between patients with and without these co-pathologies, neither when comparing within all cases (16.5% seizure prevalence in cases with co-pathologies vs. 16.0% in cases without; $p = 0.92$) nor when comparing seizure prevalences within single groups of neurodegenerative diseases.

Seizure prevalence in the whole symptomatic phase in neurodegenerative diseases

Seizure prevalence was 31.3% in AD, 20.0% in CBD, 12.6% in LBD, 11.3% in FTLD, 8.3% in MSA and 7.5% in PSP (Figure 1). For all diseases combined, seizure prevalence was 17.4%. Seizure prevalence differed statistically significantly between the neurodegenerative diseases ($p < 0.001$) and was higher in AD compared to FTLD ($p = 0.005$), LBD ($p = 0.001$), MSA ($p = 0.005$) and PSP ($p < 0.001$). The other disease entities did not differ statistically regarding seizure prevalence.

There was a significantly lower seizure prevalence in FTLD patients with FTLD-TDP ($n = 39$; 73.6% of all FTLD patients) compared to FTLD patients without FTLD-TDP ($n = 14$; 26.4% of all FTLD patients) (seizure prevalence 5.1% vs. 28.6%; $p = 0.036$; Fisher's exact test).

Hippocampal sclerosis was present in eight of the studied 454 cases (1.8%), in six cases with AD (4.2%) and in one case each with CBD and FTLD (4.0% and 1.9%). There was no significant difference in seizure prevalence between AD patients with and without hippocampal sclerosis (2.2% vs. 5.1%; $p = 0.67$). Neither of the CBD and FTLD patients with hippocampal sclerosis had seizures.

First clinical symptom and seizure risk in the whole symptomatic disease course

Cognitive first symptoms were associated with an increased seizure risk in the studied neurodegenerative diseases (22.1% in patients with cognitive first symptoms vs. 11% in patients without; $p = 0.012$). Patients with motor first symptoms had a lower seizure risk (10.3%) compared to patients without motor first symptoms (20.5%) ($p = 0.023$) (Figure 2).

Seizures and disease duration

The presence of seizures was associated with a longer disease duration in MSA (12.3 vs. 7.0 years in patients without seizures; $p = 0.017$) (Figure 3). No statistically significant differences were found between individuals with and without seizures in the other neurodegenerative diseases (AD, patients with seizures 10.0 vs. 11.3 years in patients without seizures; LBD, 11.3 vs. 13.9 years; PSP, 9.9 vs. 8.1 years; FTLD, 10.5 vs. 6.0 years; CBD, 4.3 vs. 7.3 years).

TABLE 1 Demographic, clinical and neuropathological characteristics of the study population

	AD ($n = 144$)	PSP ($n = 93$)	FTLD ($n = 53$)	LBD ($n = 103$)	MSA ($n = 36$)	CBD ($n = 25$)	Total ($n = 454$)	*p* value
Female sex, *n* (%)	76 (52.8)	44 (47.3)	18 (34.0)	42 (40.8)	19 (52.8)	12 (48.0)	211 (46.5)	0.36
Mean age at onset ± SD, years	63.0 (13.5)	63.8 (7.7)	59.4 (9.1)	64.1 (13.3)	58.5 (10.0)	59.8 (7.8)	62.3 (11.2)	0.10
Mean age at death (SD), years	74.9 (11.9)	73.2 (7.2)	63.4 (11.2)	76.7 (8.2)	67.2 (8.6)	67.2 (8.2)	72.6 (10.6)	*<0.001*
Mean disease duration (SD), years	10.9 (7.4)	8.2 (4.6)	6.0 (5.9)	13.6 (11.5)	7.5 (3.1)	6.6 (4.2)	9.4 (7.5)	*<0.001*

Note:: Pearson's chi-square test was applied to compare categorical variables and one-way analysis of variance to compare continuous variables between groups. *p* values below 0.05 were considered statistically significant and are shown italicized.

Abbreviations: AD, Alzheimer disease; CBD, corticobasal degeneration; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

DISCUSSION

In this clinical neuropathological correlation study light is shed on the prevalence of seizures throughout the whole disease span, from disease onset to death, in the frequent neurodegenerative diseases AD, CBD, FTLD, LBD, MSA and PSP. In the study population, nearly every fifth patient (17.4%) with a neurodegenerative disease experienced seizures in her or his disease course. A population-based study reported a lifetime risk for epilepsy of 4.2% through 97 years of age in the general population [25]. Seizure risk in the neurodegenerative diseases in this study is markedly higher, even though the aforementioned study accounted for epilepsy risk through the whole lifespan.

A comparison with previous literature of seizure prevalence in neurodegenerative diseases in general is challenging, as to our knowledge a systematic evaluation in one study has not been done to date. A recent study in clinically diagnosed AD, frontotemporal dementia (FTD) and DLB reported an average probability for developing seizures of 11.5% in these conditions [26]. This figure compares to a seizure prevalence of 21.3% for autopsy proven AD, FTLD and LBD of this study combined. The higher seizure frequency in the current study may be explained by the study design that covers the whole lifespan of patients with neurodegenerative conditions and not only a part of the disease time as it is possible in investigations based on clinical diagnoses during the lifetime of the patients.

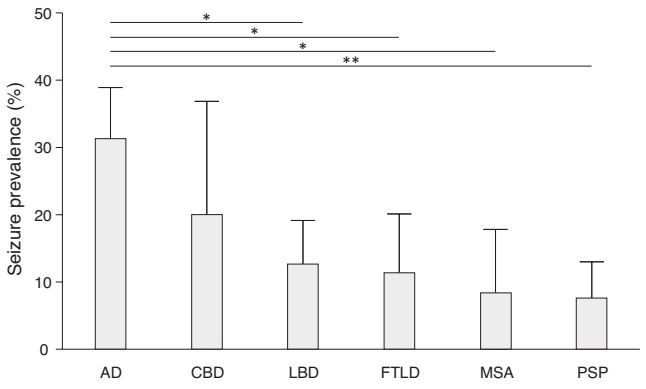

FIGURE 1 Comparison of seizure prevalence during the whole symptomatic disease phase of autopsy proven neurodegenerative diseases in this study. Prevalence was compared amongst conditions using Pearson's chi-squared test. *p value <0.01, **p value <0.001. Error bars represent 95% confidence intervals. AD, Alzheimer disease; CBD, corticobasal degeneration; LBD, Lewy body disease including the clinical syndromes dementia with Lewy bodies and Parkinson disease; FTLD, frontotemporal lobar degeneration; MSA, multiple system atrophy; PSP, progressive supranuclear palsy

In this study, approximately every third AD patient experienced seizures. This compares to a seizure frequency of 17.3% in a previous investigation of seizures in neuropathologically confirmed AD [27]. Taken together, both studies show a high seizure prevalence in patients with autopsy proven AD.

Second to AD, seizures were most common in CBD in this study. Every fifth patient had seizures in the course of CBD. This clinically relevant finding is unique as, besides one report of a single case, no studies are available reporting seizures in CBD/corticobasal syndrome [28,29].

In LBD, which includes the clinical disease entities PD and DLB, a seizure prevalence of about 13% was found. An investigation based on autopsy proven DLB from the observational study of the National Alzheimer's Coordinating Center (NACC) reported a seizure frequency of 3.8% [30]. The difference in frequencies may be explained by the different assessment methods of the NACC study and our investigation. Whilst in the current study medical records were examined, the NACC study used a single item question for seizure assessment. The higher seizure prevalence in this study is remarkable, as the neuropathological condition LBD includes PD besides DLB. PD was reported to feature a very low seizure prevalence of 1.2% in a longitudinal study on seizure occurrence based on clinical diagnoses [31].

In FTLD, seizure prevalence was approximately 11%. No study with pathologically confirmed diagnoses was found for comparison. Studies with clinical FTD diagnoses reported seizure frequencies of 2%–3% [26,32]. Differences in numbers may be explained by the type of diagnosis (neuropathological vs. clinical). Furthermore, the time span covered as determined by study design could account for differences in seizure prevalence (whole disease course vs. fraction of disease course).

Seizure prevalence was approximately 8% in MSA. To date and to our knowledge, this represents the first available published information about seizure prevalence in MSA not only regarding autopsy proven but also for clinically diagnosed MSA [29].

In all, 7.5% PSP patients suffered from seizures during their disease course. A study in clinically diagnosed PSP came to a slightly higher number of 11.3% seizure frequency. No clinical pathological correlation studies were found for comparison. Interestingly, although the lowest seizure prevalence amongst the investigated

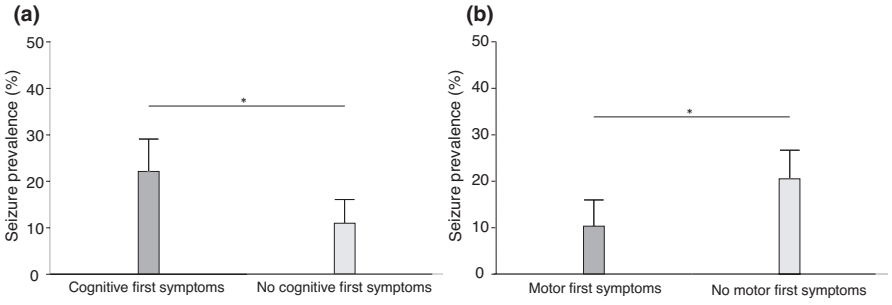

FIGURE 2 Comparisons of seizure prevalence between patients with neurodegenerative diseases with and without cognitive first symptoms (a) and with and without motor first symptoms (b). For comparison of prevalence, Pearson's chi-square test was used. *p value <0.05. Error bars represent 95% confidence intervals

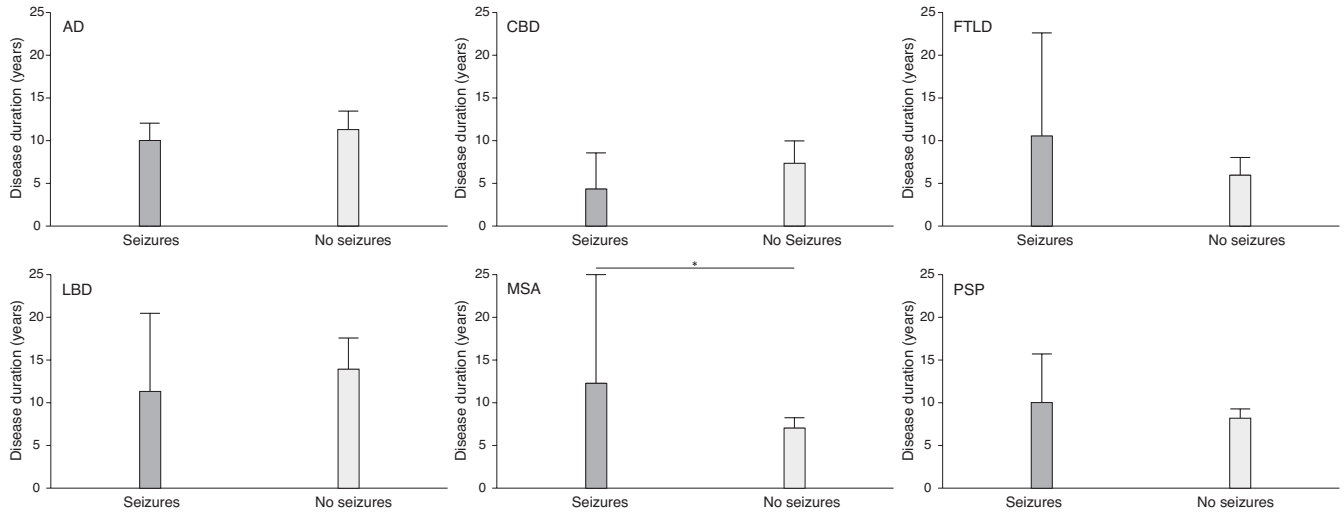

FIGURE 3 Comparisons of disease duration between patients with and without seizures in the investigated neurodegenerative diseases. To compare groups Student's *t* test or the Mann–Whitney *U* test were used, where appropriate. **p* value <0.05. Error bars represent 95% confidence intervals. AD, Alzheimer disease; CBD, corticobasal degeneration; FTLD, frontotemporal lobar degeneration; LBD, Lewy body disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy

neurodegenerative diseases was found in PSP and seizures are not widely recognized as a major clinical problem in this condition, three of the eight PSP patients described in the classic PSP case series from Steele et al. suffered from seizures [33].

In the current study, cognitive first symptoms were associated with an increased and motor first symptoms with a decreased seizure risk in neurodegenerative diseases. This may be attributable to the widely accepted concepts that cognitive symptoms may rather be caused by cortical pathology and motor symptoms by subcortical pathology, and cortical pathological processes are more epileptogenic than subcortical pathologies [34]. In AD, an earlier age of onset and worse cognitive performance are associated with an increased risk of seizures [35]. Beyond that, knowledge about clinical parameters or even non-clinical parameters that facilitate estimation of seizure risk in neurodegenerative diseases is lacking. In this regard, the findings of the current study may be auxiliary.

In MSA the presence of seizures was associated with a longer disease duration, which may be a consequence of advanced neurodegeneration. In AD, no association between the occurrence of seizures and survival was found. Seizures have been associated with a limited survival in patients with Down syndrome and dementia ($n = 11$) [36]. A population-based study of patients with clinical diagnoses of probable early-onset AD ($n = 198$) showed no association between seizures and reduced survival [37]. Beyond these two older reports, no relevant studies regarding associations of seizures and survival in AD were found. To our knowledge, the current study is the largest study in neuropathologically diagnosed AD that includes an analysis of association between seizure occurrence and survival. The lack of association between seizures and reduced survival in this study could be explained either through (1) the absence of an effect of seizures on mortality or (2) the known higher risk for seizures in later stages of AD [38]. The limitations of this work are that data cannot be provided regarding time of seizure onset during the course of the diseases, semiology, number of attacks, and whether seizures were provoked or unprovoked, and the therapeutic regimes are not known.

To our knowledge, with nearly 500 cases the current work is the largest epilepsy study in neuropathologically proven neurodegenerative diseases to date. A further strength is the study design that allows for determination of seizure prevalences in the whole symptomatic disease phase, from symptom onset to death, for each disease cohort in the Munich brain bank.

According to the current guidelines of the International League Against Epilepsy, a diagnosis of epilepsy can be made if at least two unprovoked seizures occur more than 24 h apart or there is a recurrence risk of at least 60% in 10 years after a single unprovoked seizure [39]. An epilepsy diagnosis may implicate drug treatment of seizures. AD was reported to feature a high seizure recurrence risk of over 70% within 7.5 months [35]. Therefore, starting a seizure drug treatment after a single seizure can be considered in AD, as considered by many practitioners in the case of a single seizure after stroke, also a constellation with a suggested seizure risk of over 70% [40–42]. However, for the other neurodegenerative diseases studied here, data on seizure recurrence risk is lacking. Assuming that neurodegenerative conditions share similar disease mechanisms and neurodegeneration may be considered as an enduring predisposition for seizures, a deduction of treatment concepts may be permissible.

In summary, the current clinical neuropathological correlation study reveals a high seizure risk during the symptomatic course of six common neurodegenerative diseases that ranges from just below 10% to over 30%. Additionally, the study shows that the clinical first symptom may facilitate estimation of risk for seizures. The study findings may expedite clinical awareness for seizures and thus may contribute to an optimized treatment of epilepsy in neurodegenerative diseases.

ACKNOWLEDGEMENTS

This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198). The altruism of the study participants and their relatives is gratefully acknowledged. Open Access funding enabled and organized by Projekt DEAL. WOA Institution: LUDWIG-MAXIMILIANS-UNIVERSITAET MUNCHEN Blended DEAL: Projekt DEAL

CONFLICT OF INTEREST

Jonathan Vöglein reports no disclosures. Irena Kostova reports no disclosures. Thomas Arzberger reports no disclosures. Soheyl Noachtar reports no dislosures. Marianne Dieterich reports no disclosures. Jochen Herms reports no disclosures. Peer Schmitz reports no disclosures. Viktoria Ruf reports no disclosures. Otto Windl reports no disclosures. Sigrun Roeber reports no disclosures. Mikael Simons reports no disclosures. Günter U. Höglinger has ongoing research collaborations with Prothena; served/serves as a scientific advisor for Abbvie, Alzprotect, Asceneuron, Biogen, Biohaven, Lundbeck, Novartis, Roche, Sanofi, UCB. Adrian Danek reports no disclosures. Armin Giese reports no disclosures. Johannes Levin reports personal fees from Aesku, personal fees from Bayer Vital, personal fees from Willi Gross Foundation, personal fees from Axon Neuroscience, personal fees from Ionis Pharmaceuticals, personal fees from Roche, non-financial support from Abbvie, compensation from MODAG GmbH for work as CMO outside the submitted work.

AUTHOR CONTRIBUTIONS

Jonathan Vöglein: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (equal); resources (lead); software (lead); supervision (equal); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). Irena Kostova: Data curation (equal); resources (equal); writing—review and editing (equal). Thomas Arzberger: Resources (equal); writing—review and editing (equal). Soheyl Noachtar: Writing—review and editing (equal). Marianne Dieterich: Resources (equal); writing—review and editing (equal). Jochen Herms: Resources (equal); writing—review and editing (equal). Peer Schmitz: Data curation (equal); software (equal); writing—review and editing (equal). Viktoria Ruf: Writing—review and editing (equal). Otto Windl: Writing—review and editing (equal). Sigrun Roeber: Resources (equal); writing—review and editing (equal). Mikael Simons: Writing—review and editing (equal). GU Höglinger: Writing—review and editing (equal). Adrian Danek: Writing—review and editing (equal). Armin Giese: Conceptualization (equal); resources (equal); writing—review and editing (equal). Johannes Levin: Conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); supervision (lead); validation (lead); visualization (lead); writing—review and editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Vöglein J, Kostova I, Arzberger T, et al. Seizure prevalence in neurodegenerative diseases—a study of autopsy proven cases. *Eur J Neurol*. 2022;29:12–18. https://doi.org/10.1111/ene.15089

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