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ORIGINAL ARTICLE

Prevalence, risk factors and therapeutic aspects of injuries and accidents in women with epilepsy

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Abstract

Background Epilepsy-related injuries and accidents (ERIA) are a frequent cause of hospitalisation and represent a relevant burden for patients with epilepsy. In particular, osteoporosis and other gender-specific aspects may increase the risk of seizure-related fractures and injuries in women with epilepsy.

Aim and scope The aim of this analysis is to determine the prevalence and clinical nature of ERIA in a cohort of women with epilepsy, to identify possible determinants including osteoporosis and to give an overview of the current knowledge of clinically important prophylactic and therapeutic aspects.

Results In total, 167 women (mean age 39.0 years, range 18–67 years) with established diagnosis of epilepsy (mean disease duration 18.2 years, range 0–64) were analysed for the occurrence of ERIA. Overall, 22 patients (13.2%) reported at least one ERIA (mean number 3.4, ±3.1) during the last three months prior to enrollment. The most frequent types of ERIA were lacerations ($n=7/22$; 31.8%), abrasions, cuts, bruises or hematoma ($n=6/22$, 27.3%), burns ($n=3/22$, 13.6%), and fractures ($n=3/22$, 13.6%). Moreover, one seizure-related road traffic accident with consecutive trauma (4.5%) was reported. Ictal falls, periictal abnormalities of behaviour and missing seizure freedom were associated with ERIA. Furthermore, female patients with ERIA had a significantly reduced quality of life (QoL, $p=0.002$) and increased anxiety ($p=0.008$) compared to patients without ERIA. A review of the pertinent literature suggests decreased bone mineral density and use of enzyme-inducing AEDs to be risk factors for ERIA in women with epilepsy.

Conclusion ERIA represent relevant complications for women with epilepsy and are associated with a lower QoL and anxiety compared with non-affected controls. Improvement of anticonvulsive treatment and therapy for osteoporosis or osteomalacia may help to decrease ERIA and the associated burden.

Keywords Seizure · Female · Fracture · Burden · Quality of life · Osteoporosis

Introduction

Epilepsy is a common and chronic neurological disease with the clinical hallmark of recurrent seizures [1, 2]. Seizures are a frequent cause of trauma due to common features of seizure semiology such as loss of consciousness, ictal falls, or uncontrolled movements [3]. Based on recent publications, epilepsy-related injuries and accidents (ERIA) are reported by 14–18% of patients during study periods of up to 1 year, while the lifetime prevalence reaches up to 11% in population-based cohorts and up to 28% in patients with intractable epilepsy [3, 4]. However, the estimated number of unreported cases is much higher [3, 5, 6]. It has been shown that ERIA are associated with decreased quality of life (QoL), thereby representing a major burden for patients, their caregivers and society [3, 4,

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7–9]. Due to frequent injuries that require immediate medical care, e.g., fractures, burns or cuts, ERIA are a common reason for emergency medical care and often lead to diagnostic procedures and therapy in neurological or surgical emergency departments [3]. Therefore, both neurological and surgical personnel taking care of these patients should be aware of the most common types of injuries, specific risk factors and possible prevention strategies for ERIA. In addition, knowledge of osteomalacia and osteoporosis induced by different anti-epileptic drugs (AEDs) is crucial for a realistic risk assessment and individual counseling of people with epilepsy. Due to postmenopausal osteoporosis, oestrogen-related weakness of ligaments or other gender-specific aspects [10, 11], women with epilepsy seem to be at higher risk of epilepsy-related fractures or injuries.

The aim of this analysis is to retrospectively address the prevalence and clinical nature of ERIA in a cohort of women with epilepsy and to identify possible determinants for epilepsy-related injuries. Moreover, an overview of the current knowledge of clinically important causal, prophylactic and therapeutically aspects should help to improve knowledge of and care for women with ERIA.

Patients and methods

Study settings and design

The presented data on ERIA in adult females represent a subgroup analysis of a large cross-sectional, outpatient survey in people with epilepsy conducted in 2015 at multiple sites in the federal states of Hessen and Bavaria. Both states comprise large rural as well as metropolitan regions and offer a comprehensive health care system, which allows the comparison of this results with other German and European regions. The seizure and epilepsy syndrome classifications were adapted to the latest definitions of the International League Against Epilepsy [12, 13]. The study had the approval of the local ethics committee. STROBE guidelines for observational studies (Strengthening The Reporting of Observational Studies in Epidemiology) were followed [14]. Established questionnaires were used to assess sociodemographic and disease-specific characteristics, QoL (QOLIE-31) and anxiety [15, 16]. Statistical analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) using Kruskal–Wallis one-way analysis of variance. p values < 0.05 were considered to be significant.

Results

Sociodemographic and disease-specific characteristics

In total, 167 women with epilepsy with a mean age of 39.0 years (± 14.0, range 18–67 years) and mean disease duration of 18.2 years (± 13.0, range 0–64 years) were enrolled. Mean age at epilepsy onset was 22.0 years (± 16.4, range 0–66 years). Most patients ($n = 91$, 55.8%) reported epilepsy in remission; however, a relevant portion of the study population ($n = 76$, 44.2%) suffered from active epilepsy with ongoing seizures. Most patients reported the regular taking of AEDs ($n = 152$, 91.0%), and of that number, 47.3% ($n = 79$) took one and 43.7% ($n = 73$) took two or more AEDs. Mean AED number was 1.4 (± 0.8, range 0–5). Most common AEDs were levetiracetam ($n = 108$, 64.7%), lamotrigine ($n = 50$, 29.9%) and valproate ($n = 31$, 18.6%). In total, 43 patients (25.7%) were taking enzyme-inducing AEDs (EIAEDs). For further details on sociodemographic and disease-specific aspects please refer to Table 1.

Epilepsy-related injuries and accidents

A total number of 22 patients (13.2%) reported ERIA during the 3-month study period. Overall, 58 ERIA resulted in a mean number of 3.4 events (± 3.1, median 2.0, range 1–11) per affected subject. Most frequent injuries were lacerations ($n = 7/22$, 31.8%), abrasions, cuts, bruises or hematoma ($n = 6$, 27.3%), burns ($n = 3$, 13.6%), fractures ($n = 3$, 13.6%) or severe tongue bites ($n = 2$, 9.1%).

Table 1 Sociodemographic and disease-specific aspects of the cohort ($n = 167$)

Age, years	
Mean ± SD	39.0 ± 14.0
Median	38.0
Range	18–67
Disease duration, years	
Mean ± SD	18.2 ± 15.6
Median	13.0
Range	0–64
Age at epilepsy onset, years	
Mean ± SD	22.0 ± 16.4
Median	17.0
Range	0–66
Number of antiepileptic drugs	
Mean ± SD	1.4 ± 0.8
Median	1.0
Range	0–5
Seizure frequency, % (n)	
≤ 1 per day	8.0 (13)
≥ 1 per week	11.7 (19)
≥ 1 per month	12.3 (20)
≥ 1 per 6 months	9.2 (15)
≥ 1 per year	3.1 (5)
Seizure free ≥ 12 months	55.8 (91)

SD standard deviation

In addition, one seizure-related road traffic accident was reported (4.5%). For more details on the reported ERIA please refer to Table 2.

Quality of life in patients with epilepsy-related injuries and accidents

Patients reporting ERIA showed a significantly decreased QoL according to the QOLIE-31 score with a mean value of 36.5 (± 17.1, median 37.0, range 14.2–69.9, $p = 0.002$) compared to the remaining participants without ERIA (mean 55.6 ± 16.1, median 55.2, range 18.6–85.8, $p = 0.002$). Moreover, the presence of ERIA was associated with significantly increased anxiety, which was measured using an established worry scale (ERIA: mean 5.3 ± 1.1, median 6, range 3–6 vs. no ERIA: mean 4.3 ± 1.4, median 4.0, range 2–6, $p = 0.008$).

Table 2 Epilepsy-related injuries and accidents (ERIA) of the cohort ($n = 167$)

Occurrence of ERIA	
Total number of patients reporting ERIA, % (*n*)	13.2 (22)
Total number of reported ERIA	58
Mean ± SD	3.4 ± 3.1
Median	2.0
Range	1–11
Nature of ERIA, % (*n*)	
Laceration	31.8 (7)
Abrasion, cut, bruise, hematoma	27.3 (6)
Not specified	27.3 (6)
Burn	13.6 (3)
Fracture	13.6 (3)
Tongue bite	9.1 (2)
Road traffic accident	4.5 (1)

SD standard deviation

Possible determinants of epilepsy-related injuries and accidents

ERIA were significantly associated with active epilepsy ($p < 0.001$) as well as with certain semiological features of epileptic seizures, such as ictal falls ($p = 0.001$) and periictal abnormal behaviour ($p = 0.022$). In contrast, the presence of an epileptic aura, ictal loss of consciousness, nocturnal seizures, focal tonic or clonic seizures, generalised tonic–clonic seizures and focal unaware seizures were not associated with ERIA ($p \geq 0.05$). For further details on the analysed aspects please refer to Table 3.

Discussion

Injuries and accidents in women with epilepsy

Our survey highlights that ERIA are frequently occurring in women with epilepsy, thus representing a major burden for patients, their families and society [3, 4, 7–9, 17]. In line with other studies, women with ERIA showed a significantly decreased QoL and increased anxiety which particularly underlines especially the psychosocial aspects of ERIA [3, 5]. According to recent publications, the annual prevalence of ERIA ranges from 14 to 18% [3, 5, 6], which is compatible with the results of this retrospective analysis of female patients with epilepsy. Due to a high number of traumatic injuries, which were mistakenly not attributed to seizures or AED side effects, the estimated number of underreported cases has been shown to be even higher [18]. In line with other studies, missing seizure freedom as well as specific semiological features like ictal falls and periictal abnormal behaviour were significant determinants of ERIA [3, 5]. Loss of consciousness or generalised

Table 3 Factors associated with epilepsy-related injuries and accidents (ERIA, $n = 167$)

	With ERIA ($n = 22$)	Without ERIA ($n = 145$)	*p* value[a]
Seizure frequency			
Active epilepsy	95.5 (21)	37.9 (55)	< 0.001
Semiological features			
Aura	36.4 (8)	40.7 (59)	0.701
Loss of consciousness	59.1 (13)	45.5 (66)	0.085
Ictal falls	77.3 (17)	38.6 (56)	0.001
Periictal abnormalities of behaviour	36.4 (8)	15.9 (23)	0.022
Only nocturnal seizures	18.1 (4)	9.7 (14)	0.231
Predominant seizure type			
Focal tonic or clonic seizures	54.5 (12)	50.3 (73)	0.714
Generalised tonic–clonic seizures	36.4 (8)	34.5 (55)	0.888
Only automotor seizures	13.6 (3)	6.9 (10)	0.273

[a]Calculated using Kruskal–Wallis one-way analysis of variance

tonic–clonic seizures were not associated with ERIA in the present cohort, which is out of line with publications mentioned [3, 5]. Though male patients have been attributed with a slightly higher risk of ERIA in general, the nature of injuries sustained to be comparable between both genders [3]. The majority of ERIA can be classified as mild trauma such as lacerations, abrasions, cuts, bruises, burns or hematoma. In addition, sporadic severe traumas, such as fractures or high-speed trauma during road traffic accidents are reported [3, 5]. The occurrence of car accidents as a reason for ERIA supports the necessity of strict use of statutory driving restrictions amongst epilepsy patients to avoid seizure-related accidents [19, 20].

Fractures in women with epilepsy

The low prevalence of fractures in our study is in contrast with several publications highlighting increased fracture rates especially amongst older women, which were mainly attributed to osteoporosis or other gender-specific aspects, e.g., oestrogen-related weakness of ligaments and tendons [10, 11]. Here, the relatively young composition of our outpatient cohort represents a limitation in the present study. Moreover, regional features could have influenced the results of this study. However, the multicentre design and the high number of female patients within the original study population should reduce these biases to a minimum. In case of traumatic ERIA, fractures can be caused by seizures themselves, e.g., due to uncontrolled tonic movements during generalised tonic–clonic seizures, or by falls during or after seizures [21]. Common seizure-related severe injuries in a large population-based study were lacerations requiring sutures (30%), fractures (19%), broken teeth (14%), concussions (10%) and burns [22]. The latter is more common in non-industrial areas where open fire is used for heating and preparing food.

Case report for seizure-induced fracture

Figure 1 shows an illustrative case of a 65 year-old-woman undergoing presurgical evaluation [23] due to structural epilepsy. Neuroimaging (MRI) showed a cortical dysplasia of the left frontal lobe. As a comorbidity, postmenopausal osteoporosis was reported with a vertebral body fracture of unknown aetiology in the past. During an observed generalised tonic–clonic seizure without fall or additional external trauma, she suffered a fracture of the first lumbar vertebral body, which was conservatively treated. As a prophylactic approach for further seizure-related fractures, vitamin D and calcium supplements were started and bone mineral density measurements as well as a subsequent orthopedic treatment was recommended. Due to refractory epilepsy, the pre-existing polytherapy with three non-EIAEDs (lamotrigine, brivaracetam and zonisamide) was continued.

Osteoporosis and osteomalacia in patients with epilepsy and intake of anticonvulsants

The impact of postmenopausal osteoporosis and osteomalacia on ERIA has been controversially discussed over recent decades. A large European meta-analysis revealed that the overall relative risk of fractures in patients with epilepsy compared with healthy controls was increased (OR 2.2), with particularly high risks of hip, forearm and spine fractures. In patients with seizure-related fractures, bone mineral density levels (BMD, *Z* score) were significantly decreased [24]. Another monocenter study on postmenopausal women (mean age 54 years) reported ERIA in 40% of the enrolled patients [25]. Both studies underline the increased risk of epilepsy-related trauma in older women [10, 11]. Many authors hypothesise that osteoporosis solely is not sufficient to explain the increased rate of fractures in postmenopausal females with epilepsy [24, 25]. In this context, the impact of AEDs on bone metabolism has been proposed as an additional risk factor.

Both enzyme-inducing AEDs (EIAEDs), such as phenytoin (PHT), carbamazepine (CBZ) and phenobarbital (PB), and non-EIAEDs, e.g., lamotrigine or valproate (VPA), have been shown to generally influence endocrine functions. Consecutively, plasma levels of bioactive sex hormones are decreased leading to a dysregulation of bone metabolism that might lead to impaired bone mass and structure [26]. Secondarily, an AED-induced acceleration of vitamin D and vitamin K turnover has been revealed which additionally promotes long-term bone degradation [27–29]. For several EIAEDs such as PHT, PB, and CBZ as well as for VPA, a direct interaction with bone cells resulting osteomalacia has been shown [27, 30, 31]. Additionally, newer, non-EIAEDs like oxcarbazepine [32], perampanel [33], zonisamide and topiramate [34] have been associated with altered bone metabolism in humans and animal models. In spite of contrasting findings, the commonly used AED levetiracetam seems to have no clinically relevant impact on bone metabolism and fracture risk [35–38]. To date, there are no studies available that analyse the role of the structural-related brivaracetam on BMD or pathologic fractures [39, 40]. In our cohort, the use of EIAEDs was quite low which is in line with recommendations in German epilepsy guidelines. Since 2008, the guidelines urge clinicians to avoid EIAEDs and that guideline has been well-adopted among German neurologists [41, 42].

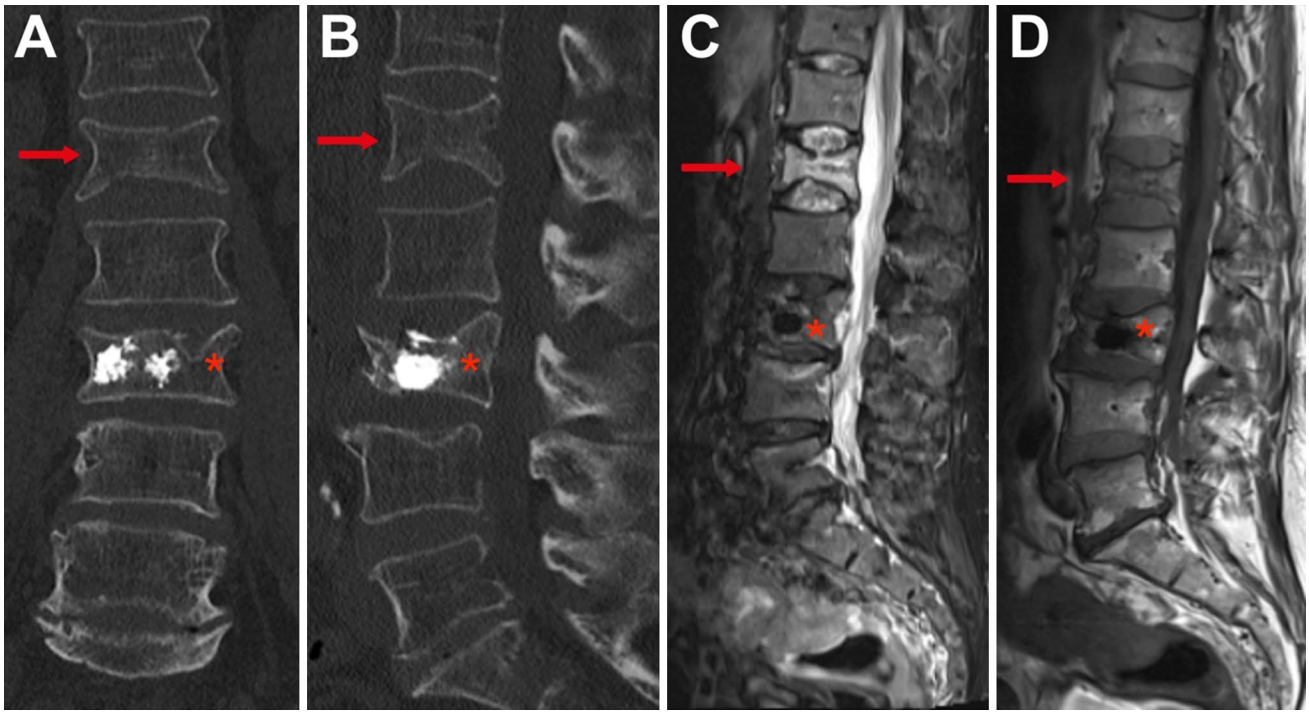

Fig. 1 CT and MRI of lumbar spine depict recent compression fractur of lumbar vertebra 1 (LV). The CT scan shows a height reduction and fracture line of LV1 in frontal (**a**) and sagittal plane (**b**) marked with a red arrow. MRI shows traumatic edema of LV1 with hyperintense signal in T2-weighted fat suppressed (**c**) and hypointense signal T1-weighted sagittal images (**d**). Artefacts of LV3 in CT and MRI scans originate from bone cement that was injected in to stabilize an old fracture of unknown cause (asterisis)

Role of vitamin D in epilepsy patients

Vitamin D deficiency has been shown in up to 45% of epilepsy patients. The risk of decreased vitamin D plasma levels does not significantly differ between patients with focal or generalised epilepsies and is associated with the intake of EIAEDs. Current knowledge suggests that EIAEDs lead to a faster degradation and metabolisation of the active compound 25-hydroxy-vitamin-D to lower or non-active metabolites [43]. To avoid AED-induced or enhanced BMD loss prophylactic therapy with vitamin D (1000–2000 IE/day) and calcium (600–1000 mg/day) has been proposed [31, 44]. In addition, a prospective study analysed the additional benefit of bisphosphonate on a supplementation with calcium and vitamin D resulting in a significant increase in BMD and decrease in fracture rates [45]. The use of hormone replacement therapy (HRT) has to be individually discussed, as this might result in an associated benefit for prevention of osteoporosis in postmenopausal women [46], but also a frequent increase in seizure frequency has been shown with HRT [47]. In addition, the consequent use of hip protectors may help to decrease the risk of ERIA or seizure-related fractures [3, 48].

Conclusion

Compared to mixed study populations, female patients with epilepsy show a comparable prevalence incidence and nature of ERIA. The multitude of ERIA can be classified as mild trauma; however, severe injuries like fractures are also frequently reported. Due to the risk of postmenopausal osteoporosis and possible AED-induced or enhanced changes in bone metabolism, especially postmenopausal women in particular seem to have an increased risk of severe ERIA. To avoid seizure-related fractures, a prophylactic therapy with vitamin D and calcium seems feasible in elderly women. In the presence of a diagnosed osteoporosis or determinates for ERIA an interdisciplinary therapy concept with optimisation of AEDs and extended anti-osteoporosis therapy seem to be advisable.

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Author contributions RDV and LMW developed the idea for this project and performed the statistical analysis. RDV, NS, IM, SK, EP, FR, AS and LMW wrote the paper. Each author contributed important content-related aspects.

Compliance with ethical standards

Conflict of interest R. D. Verboket, E. Paule, N. Söhling, L. M. Willems report no conflicts of interest. I. Marzi reports personal fees and grants from AO-foundation and Deutsche Forschungsgemeinschaft. S. Knake reports honoraria for speaking engagements from Desitin and UCB as well as educational grants from AD Tech, Desitin Arzneimittel, Eisai, GW, Medtronic, Novartis, Siemens and UCB. F. Rosenow reports personal fees from Eisai, UCB, Desitin Arzneimittel, Novartis, Medtronic, Cerbomed, Sandoz, GW-Pharma, BayerVital and Shire, grants from the European Union, Deutsche Forschungsgemeinschaft and the Detlev-Wrobel-Fonds for Epilepsy research. A. Strzelczyk reports personal fees and grants from Desitin Arzneimittel, Eisai, LivaNova, Sage Therapeutics, UCB Pharma and Zogenix.

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