Prevalence and incidence of vertebral fractures

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Prevalence and incidence of vertebral fractures: a 7-year follow-up study in institutionalized adults with refractory epilepsy and intellectual disability

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ABSTRACT

Objective: The main objective of this cohort study is to determine the prevalence and incidence of morphometric vertebral fractures (VFs) over 7 years follow-up, in institutionalized adults with refractory epilepsy and intellectual disability (ID).

Methods: Dual-energy X-ray Absorptiometry (DXA) and Vertebral Fracture Assessment (VFA) were performed in 2009 and 2016. Vertebrae T4-L4 were assessed using quantitative morphometry. Severity of VFs was graded as 1 (mild; 20-25% reduction in height), 2 (moderate; 25-40% reduction) or 3 (severe; >40% reduction) according to the method described by Genant. Prevalent VFs were analyzed at baseline. VFs (grade 1, 2 or 3) present at follow-up, but not at baseline, were considered new VFs. Worsening VFs were defined as VFs with at least one grade deterioration at follow-up, compared to baseline (grade 1 to 2 or 3, or grade 2 to 3). Patients were treated with anti-osteoporosis treatment according to the Dutch guideline.

Results: Baseline and follow-up DXA and VFA could be obtained in 141 patients (87 male) aged between 18-79 years old (mean 44.8 ± 15.7). At baseline, 56 patients had at least one prevalent VF. Patients with a prevalent VF were significantly older than patients without (49.2 ± 13.7 vs 41.9 ± 16.4, $p < .01$). After 7 years follow-up, 38 new VFs occurred in 27 patients and 15 patients had a worsening VF, leading to an overall cumulative incidence of 27.0%. VF incidence was significantly higher in patients with at least one prevalent VF at baseline (48.2% vs 12.9%, respectively, $p < .01$) compared to no VF.

Significance: In adults with refractory epilepsy VFA is challenging, due to physical and behavioral aspects, resulting in a substantial proportion of unevaluable vertebrae and scans. Nevertheless, 40% of the patients had a VF at baseline and after 7 years follow-up, 27% had at least one new and/or worsening VF despite adequate anti-osteoporosis treatment.

1. Introduction

Worldwide, approximately 50 million people are affected by epilepsy. About 70% of those affected can be successfully treated with antiseizure drugs (WHO, 2018). Unfortunately, antiseizure drugs may have a negative impact on bone metabolism. The combination of bone mineral disorders (such as osteopenia and osteoporosis) and the use of antiseizure drugs has first been described around 1970 and focused on

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strong enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin and primidone (Dent et al., 1970; Hahn, 1976; Linde et al., 1971). In the intervening years, multiple studies have indicated the association between a decreased bone mineral density (BMD) and long-term use of antiseizure drugs (Beerhorst et al., 2013; Lee et al., 2010; Shen et al., 2014; Vestergaard, 2005), including antiseizure drugs with minimal to no enzyme-inducing effects (Diemar et al., 2019; Fan et al., 2016; Mitta et al., 2019). Besides the use of antiseizure drugs, patients with epilepsy are at a higher risk for fractures, due to seizures (Grzonka et al., 2019; Vestergaard, 2005) or (seizure-related) falls (Shiek Ahmad et al., 2012). In addition, neurological disorders and drug side effects can cause dizziness, incoordination, ataxia, clumsiness and weakness. In patients with epilepsy, fracture rates are found to be two to six times higher than in the general population (Lee et al., 2010; Shen et al., 2014; Vestergaard, 2005). The most frequently occurring osteoporotic fractures are vertebral fractures (VFs) (Cauley et al., 2008; Cummings and Melton, 2002; Melton et al., 1993) and those are often underdiagnosed, because only one third of patients with VFs present with an acute symptomatic episode (Cooper et al., 1992; Delmas et al., 2005; Fink et al., 2005). In patients with epilepsy, it has also been reported that VFs might occur with minor to no (seizure-related) trauma (Annegers et al., 1989; Vasconcelos, 1973). The presence, number and severity of VFs are strong predictors of future fracture risk, independent of age and BMD (Black et al., 1999; Gallagher et al., 2005) and VFs are associated with an increased mortality rate (Bliuc et al., 2009; Ioannidis et al., 2009; Kado et al., 1999).

The Dutch guideline on osteoporosis and fracture prevention recommends systematic evaluation of VFs in high risk patients with osteopenia and osteoporosis (CBO, 2011).

There is a lack of knowledge concerning the prevalence and incidence of VFs in institutionalized adult patients with refractory epilepsy and studies using standardized protocols for identifying VFs in this specific group are scarce. Therefore, the main objective of this study is to determine the prevalence and incidence of VFs in adults with refractory epilepsy and intellectual disability (ID), residing at a long-stay care facility between 2009 and 2016.

2. Material and Methods

2.1. Study population and design

This prospective cohort study included adult patients from Epilepsy Center Kempenhaeghe, a long-stay care facility for people with epilepsy and ID in the Netherlands. All patients have a diagnosis of epilepsy, caused by a variety of factors (i.e. structural, genetic, infectious, metabolic, immune or unknown) and almost all patients (99%) have some degree of intellectual disability, ranging from mild to profound.

In 2009, all patients aged 18 years or older (n = 261), were invited for a fracture risk assessment, including dual-energy X-ray absorptiometry (DXA) measurements and a vertebral fracture assessment (VFA). Of these, 205 patients (or their legal representatives) agreed to participate (78.5%). In 2016, DXA and VFA were repeated. Patients with a missing VFA at baseline and/or follow-up, were excluded from analyses.

Patient characteristics (age, sex, length, weight, ID, Barthel scale, ambulatory status, use of cigars/cigarettes and alcohol, number and types of seizures) and medication use (antiseizure drugs, calcium, vitamin D, bisphosphonates) were collected through the medical records of the patients. In general, patients were recommended oral bisphosphonates according to the Dutch guidelines. At the care facility, all prescribed medications (including bisphosphonates and supplementation of vitamin D and calcium) are administered by nurses and/or taken under direct supervision.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local medical ethical committee of Epilepsy Center Kempenhaeghe, Heeze (NL26095.068.09). In 2009, informed consent was obtained from all individual participants and/or their legal representatives. During DXA and VFA procedures, all patients were accompanied by a familiar nurse and/or family member. Measurements were stopped when a patient refused to cooperate or showed significant signs of resistance.

2.2. DXA and VFA

Initial DXA and VFA measurements were performed between August 31st and September 29th 2009, and follow-up measurements between October 5th and November 30th 2016, using a Hologic densitometer (Discovery W and A, respectively).

BMD of lumbar spine (L1-L4), femoral neck and total hip was expressed as the amount of mineral (g) divided by the area scanned (cm^2) and in T-scores. T-scores compare data with sex-matched peak bone mass, which is attained at the age of 20-30 years. The criteria of the World Health Organization (WHO) were used to classify bone mineral disorders, based on the lowest reported T-score. A T-score of -1.0 and above was considered as normal bone mass, a T-score between -1.0 and -2.5 as osteopenia and a T-score of -2.5 and below as osteoporosis (Kanis, 1994).

For VFA, all scans of 2009 and 2016 were evaluated in a random order by one trained staff member, who was blinded for previous VF and DXA outcomes. First, the evaluable vertebrae were determined for each individual, starting with the identification of L4. Vertebrae with deformities were excluded from the vertebral fracture analyses. In case of doubt, images were discussed with two experienced researchers to reach consensus. Subsequently, vertebral height at the anterior, middle and posterior part of the vertebral body was measured and the percent reduction in height was used to grade VFs as grade 0 (<20% reduction in height), 1 (mild; 20-25% reduction in height), 2 (moderate; 25-40% reduction) or 3 (severe; >40% reduction) according to the method described by Genant et al. (1993).

Incident VFs were defined as new or worsening VFs. A new VF was defined as a VF (grade 1, 2 or 3) that was present at the follow-up scan, but not at baseline (grade 0). A worsening VF was defined as a VF with at least one grade deterioration at follow-up, compared to baseline (i.e. from grade 1 to 2 or 3, or from grade 2 to 3).

2.3. Statistical analysis

The primary outcome of this study is VF incidence after 7 years follow-up. Data are presented as means (±SD) or as percentages. Cumulative incidences were calculated as the number of patients with incident VFs divided by the total number of patients. Differences between groups were compared using Student's *t*-test for continuous variables and Pearson's Chi-Square or Fisher's exact test for categorical variables. All outcomes were analyzed using SPSS version 25 (IBM Corporation, UK). Statistical tests were two-tailed with a level of significance of .05.

3. Results

From a total of 205 patients who gave informed consent, a DXA including VFA was obtained in 184 patients at baseline (Fig. 1). At follow-up (mean follow-up duration of 7.1 ± 0.04 years), DXA and VFA could be obtained in 141 patients. In total, 64 patients (31.2%) were lost to follow-up or had a missing VFA in 2016. Patients without follow-up measurements were older (51.2 ± 17.7 vs 44.8 ± 15.7 years, $p = .011$), scored worse on the Barthel scale (8.9±7.3 vs 12.8±5.9, $p < .01$) and were less often able to walk (57.8% vs 78.0%, $p < .01$) than patients with complete follow-up.

Baseline characteristics of the 141 fully evaluable patients (87 male, 61.7%) aged between 18-79 years (mean 44.8 ± 15.7) are summarized in Table 1. The average number of prescribed antiseizure drugs at baseline was 2.5 (SD ± 1.0). Most prescribed were carbamazepine (61.0%), valproic acid (44.7%) and lamotrigine (36.9%). A total of 76

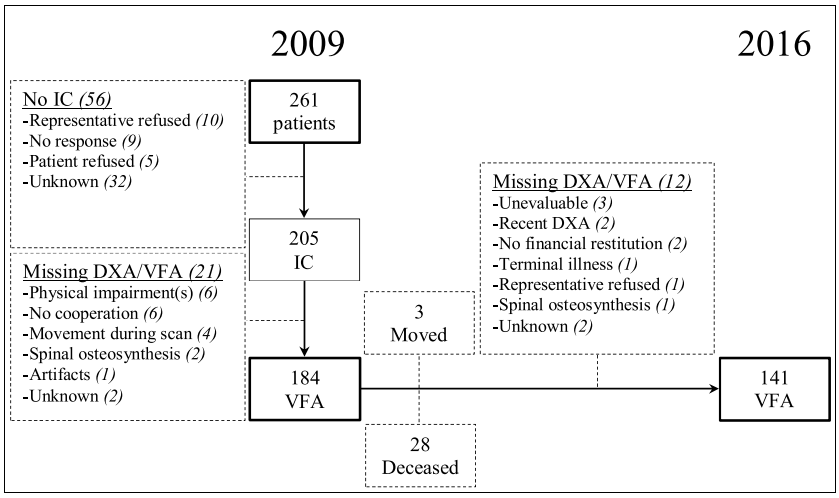

Fig. 1. Flowchart of included and evaluable patients.
DXA = Dual-Energy X-Ray Absorptiometry, IC = Informed consent, VFA = Vertebral Fracture Assessment.

patients (53.9%) had no changes in types of antiseizure drugs that were prescribed during follow-up. Forty-eight patients (34.0%) stopped at least one antiseizure drug and 51 patients (36.2%) started at least one other antiseizure drug. Between baseline and follow-up, a total of 117,510 seizures were reported (Table 2). The median number of seizures per patient was 344 (IQR 64-1193) over 7 years. Twelve patients (8.5%) were reported to be seizure-free. Half of the patients (49.6%) had more than one seizure a week. Of all seizures, a focal onset was reported in 36.6% and a generalized onset in 18.5%. The onset of the remaining seizures (45.0%) was unknown.

At baseline, 32 patients (22.7%) were classified as having a normal BMD, 70 (49.6%) as having osteopenia and 39 (27.7%) as having osteoporosis. At follow-up, 26 patients (18.4%) had a normal BMD, 64 (45.4%) had osteopenia and 50 (35.5%) osteoporosis. In 1 patient (0.7%) the BMD result was missing. At baseline, 24 patients (17.0%) were prescribed calcium and 19 (13.5%) vitamin D.

3.1. VFA

Vertebrae were excluded for VFA because of projection of arms or hands (29), intestinal gas (25), movement errors (18), the presence of osteosynthetic material (12) and projection of jewelry or clothing (2). Within the range of T4 to L4, 80.1% of the vertebrae were considered evaluable at baseline versus 76.1% at follow-up. Consequently, a total of 23 prevalent VFs (in 19 patients) were not evaluable at follow-up, and 5 fractured vertebrae (in 4 patients) at follow-up were not evaluable at baseline.

3.1.1. Prevalent VFs at baseline

At baseline, 56 of 141 patients (39.7%) had at least one prevalent VF (Table 3) of whom 40 patients (28.4%) had ≥1 mild VF, 34 (24.1%) had ≥1 moderate VF and 3 patients (2.1%) had a severe VF. Twenty of these patients (14.2%) had multiple VFs with different grades. About half of the prevalent VFs (52.5%) were located in the thoracolumbar region (T11-L1). When comparing patients with and without a prevalent VF, those with a VF were significantly older (49.2 ± 13.7 vs 41.9 ± 16.4, $p <$ .01). No significant differences were found regarding Barthel score ($p =$ .294) and ambulatory status ($p =$ .264). The proportion of men and women with at least one VF was not different (46.0% vs 29.6%, $p =$ .054).

3.1.2. Incident VFs after 7 years follow-up

After 7 years follow-up, 38 new VFs occurred in 27 patients (19.1%) and 15 patients (10.6%) had a worsening VF (Table 3). Four patients (2.8%) had both new and worsening VFs, leading to an overall cumulative incidence of 27.0% over 7 years. Of all patients with a new morphometric VF, only two (7.4%) were diagnosed as having a clinical (symptomatic) VF.

The cumulative VF incidence was significantly higher in patients with at least one prevalent VF at baseline (48.2% vs 12.9%, respectively, $p <$ .01) compared to no VF at baseline (Fig. 2). No significant differences regarding age ($p =$ .125), sex ($p =$ .544), Barthel scale ($p =$ .752), ambulatory status ($p =$ .451), number of seizures (p=.561) and severity of prevalent VFs at baseline ($p =$ .534) were found between patients with and without an incident VF. No significant differences in VF incidence were found between patients who were seizure-free (25.0%) and those who were not (27.1%, $p >$ .999).

In patients with osteoporosis at baseline, VF incidence was significantly higher (41.0%) than in patients with a normal BMD (18.8%, $p =$ .043) or osteopenia (22.9%, $p =$ .046).

3.2. Bisphosphonates use

A total of 82 patients (58.2%) had never used bisphosphonates at the end of follow-up. Thirty-one patients (22.0%) started treatment with bisphosphonates during the follow-up period, for a duration of at least 1 year. Of those, 23 (16.3%) started within 1 year after baseline. In this particular group, the incidence of VFs was 39.1%, compared to 19.5% (p = .051) in the group of patients who have never used bisphosphonates.

4. Discussion

The prevalence (39.7%) and 7-year cumulative incidence (27.0%) of morphometric VFs in institutionalized adult patients with refractory epilepsy is found to be high, even though the study population is relatively young (mean age 44.8 ± 15.7 years) with a predominance of male patients. In a population-based study in the Netherlands, the prevalence of VFs in men and women aged 55 and over, was found to be 6.9% and 7.6%, respectively (van der Klift et al., 2002). Studies reporting on VFs in patients with epilepsy are scarce. To our knowledge, our study is among the first in this population to address VFs longitudinally and in a systematic way.

VF prevalence at baseline in our study is higher (39.7% overall, 46.0% in males) than reported by Lazzari et al. (2013) in male veterans with epilepsy and chronic use of antiseizure drugs (30%). Noteworthy, they attributed the high prevalence to the use of tobacco (71%) and alcohol (35%) in their study participants. In our study population, though, only 18 patients (12.8%) smoked at baseline and 31 patients

Table 1
Baseline (2009) and follow-up (2016) characteristics of 141 patients with refractory epilepsy and intellectual disability.

Characteristics	2009 n	2009 Mean ± SD	2009 %	2016 n	2016 Mean ± SD	2016 %
Age (years)	141	44.8 ± 15.7		141	52.0 ± 15.7	
Sex						
Male	87		61.7			
Female	54		38.3			
Body Mass Index (in kg/m^2)	141	25.4 ± 4.0		141	25.5 ± 3.8	
Underweight (<18.5)	2		1.4	1		0.7
Normal weight (18.5-25)	67		47.5	69		48.9
Overweight (25-30)	52		36.9	49		34.8
Obese (≥30)	20		14.2	22		15.6
Intellectual disability (IQ score)						
None (≥70)	2		1.4			
Mild (55-70)	43		30.5			
Moderate (40-55)	52		36.9			
Severe (25-40)	38		27.0			
Profound (<25)	6		4.3			
Barthel scale (0-20)	141	12.8 ± 5.9		141	11.8 ± 6.3	
Ambulatory status						
Immobile	16		11.3	21		14.9
Independent in wheelchair	15		10.6	19		13.5
Walk with aid	11		7.8	21		14.9
Walk without aid	99		70.2	80		56.7
Smoking (cigars/cigarettes a day)						
None	123		87.2			
1-5	5		3.5			
6-10	1		0.7			
11-15	3		2.1			
16-20	5		3.5			
>20	4		2.8			
Alcohol (units a week)						
None	110		78.0			
1-2	16		11.3			
3-5	8		5.7			
6-10	6		4.3			
>10	1		0.7			
Number of antiseizure drugs	141	2.5 ± 1.0		141	2.6 ± 1.1	
None	5		3.5	4		2,8
1	14		9.9	14		9.9
2	47		33.3	51		36.2
3	53		37.6	48		34.0
4	19		13.5	18		12.8
5	3		2.1	6		4.3
≥1 Enzyme-inducing drug*	120		85.1	117		83.0
Carbamazepine	86		61.0	79		56.0
Phenobarbital	15		10.6	13		9.2
Strong Phenytoin	32		22.7	26		18.4
Primidone	-		-	1		0.7
Oxcarbazepine	21		14.9	19		13.5
Weak Topiramate	22		15.6	22		15.6
≥1 Non-enzyme-inducing drug*	108		76.6	110		78.0
Acetazolamide	1		0.7	3		2.1
Clonazepam	24		17.0	23		16.3
Ethosuximide	3		2.1	3		2.1
Felbamate	1		0.7	1		0.7
Gabapentin	6		4.3	3		2.1
Lacosamide	1		0.7	11		7.8
Lamotrigine	52		36.9	51		36.2
Levetiracetam	22		15.6	22		15.6
Perampanel	-		-	3		2.1
Pregabalin	6		4.3	7		5.0
Valproic acid	63		44.7	69		48.9
Vigabatrin	1		0.7	1		0.7
Zonisamide	2		1.4	5		3.5
≥1 enzyme-inducing and ≥1 non-enzyme-inducing drug	92		65.2	90		63.8

IQ = Intelligence quotient, SD = Standard deviation.
* Due to polytherapy and/or the use of both enzyme- and non-enzyme-inducing antiseizure drugs, total numbers add up to more than 100%.

(22.0%) occasionally drank alcohol. The difference might be explained by the inclusion of study participants, as Lazzari et al. (2013) included ambulatory outpatients who were not osteoporotic at baseline. In addition, only 10% of their study participants was on polytherapy (Lazzari et al., 2013), vs 86.5% of our patients.

The incidence of VFs in patients without a prevalent VF in our study was twice as high (7-year incidence of 12.9%) compared to the annual VF incidence of 0.9% reported by Nevitt et al. (2005) in postmenopausal women, aged 65 or older, without a prevalent VF. The risk of (vertebral and non-vertebral) fractures is shown to be higher as the number and severity of VFs is greater (Delmas et al., 2003; Lindsay et al., 2001; Melton et al., 1999; Siris et al., 2007). We observed that the incidence of VFs increased with the presence, but not with the number or severity of prevalent VFs.

Annegers et al. (1989) assessed the incidence of clinical fractures (both vertebral as non-vertebral) among patients with unprovoked seizures without using a standardized protocol for detection of VFs. As a result, only symptomatic VFs were analyzed, probably leading to an underestimation of the total number of VFs. Based on their findings, Annegers et al. (1989) concluded that the incidence of VFs in patients with epilepsy decreased with duration of epilepsy (11.1/1000 p-y at the first years of follow-up to 4.4/1000 p-y at ≥10 years after diagnosis) and with duration of treatment with antiseizure drugs (10.6/1000 p-y during the first 5 years to 6.1/1000 p-y at ≥10 years of treatment with antiseizure drugs). Similarly, Vasconcelos (1973) concluded that in his study, many VFs occurred during the first, second or third seizure the patient had ever experienced. As for all fractures, Vestergaard et al. (1999) found an increased risk within the first year after diagnosis of epilepsy. They provided two possible explanations: 1) fractures may be the first presentation of epilepsy, or 2) seizure control has not been achieved in the initial period following diagnosis (Vestergaard et al., 1999). The first possibility is not likely to explain the high incidence of VFs in our study group, since most of the patients have been diagnosed in childhood. The second explanation might be more relevant for our study group. In most of our patients seizure control remains difficult, as shown by the high seizure frequency and the number of patients (46.1%) who had changes in types of prescribed antiseizure drugs during the study.

In our study, a total of 117,510 seizures were reported, including many seizures with a generalized and/or motor onset. In a systematic review of Grzonka et al. (2019) thoracic and lumbar vertebral compression fractures were found to be among the most frequently reported fractures (14 of 48 in detail described fractures) as a direct consequence of generalized convulsive seizures and/or status epilepticus. Since we performed a systematic assessment of morphometric VFs, independent of the moment of seizures or trauma, no conclusions can be drawn regarding preceding factors, like seizures or (seizure-related) falls. However, of the twelve patients who were seizure-free, three (25.%) patients had incident VFs, eliminating seizures as a cause in those cases. Desai et al. (1996) and Vestergaard et al. (1999) suggested that anti-seizure treatment contributes to the increased fracture risk, independent of the influence of seizures.

Retrospectively, of the patients who were diagnosed with a new morphometric VF, only two (7.4%) presented themselves at the hospital

Table 2
Seizure frequency and types of seizures between baseline (2009) and follow-up (2016) of 141 patients with refractory epilepsy and intellectual disability.

Seizure frequency			N of patients	%		
None			12	8.5		
Less than 1 a year			9	6.4		
1 a month to 1 a year			21	14.9		
1 a week to 1 a month			29	20.6		
1 a day to 1 a week			60	42.6		
More than 1 a day			10	7.1		
Type of seizure			**N of patients**	**%**	**N of seizures**	**%**
Focal onset	Motor	Automatisms	62	66.0	13,205	11.2
		Atonic	11		2,887	2.5
		Clonic	22		1,599	1.4
		Hyperkinetic	15		5,202	4.4
		Myoclonic	5		2,300	2.0
		Tonic	20		10,251	8.7
	Non-motor	Autonomic	9	32.6	1,196	1.0
		Behavior arrest	27		4,276	3.6
		Sensory	12		1,537	1.3
	Focal to bilateral tonic clonic		5	3.5	505	0.4
Generalized onset	Motor	Atonic	6	29.1	203	0.2
		Clonic	6		210	0.2
		Myoclonic	8		1,113	0.9
		Tonic	37		20,168	17.2
	Non-motor	Atypical	1	1.4	2	0.0
		Typical	1		6	0.0
Unknown onset	Motor	Myoclonic	23	71.6	3,109	2.6
		Tonic	40		17,757	15.1
		Tonic Clonic*	86		13,806	11.7
	Non-motor	Behavior arrest	2	1.4	104	0.1
	Unclassified		122	86.5	18,074	15.4
Total					**117,510**	**100.0**

* Incomplete information to differentiate between 'generalized tonic clonic 'and 'focal to bilateral tonic-clonic' seizures.

Table 3
Prevalence and cumulative incidence of VFs, stratified by presence and severity of VFs at baseline (n = 141).

	N patients (prevalence %)		N patients (cumulative incidence %)		
	Baseline*	Follow-up*	New VFs	Worsening VFs	Incident VFs
No VF	85 (60.3)	80 (56.7)	11 (12.9)	-	11 (12.9)
VF	56 (39.7)	61 (43.3)	16 (28.6)	15 (26.8)	27** (48.2)
Grade 1	21 (14.9)	17 (12.1)	5 (23.8)	7 (33.3)	9** (42.9)
Grade 2	32 (22.7)	37 (26.2)	10 (31.2)	6 (18.8)	15** (46.9)
Grade 3	3 (2.1)	7 (5.0)	1 (33.3)	2 (66.7)	3 (100.0)
Total			27 (19.1)	15 (10.6)	38* (27.0)

VFs = Vertebral fractures.
* In 19 patients prevalent VFs were not evaluable at follow-up and in 4 patients VFs at follow-up were not evaluable at baseline.
** Four patients had both new and worsening VFs.

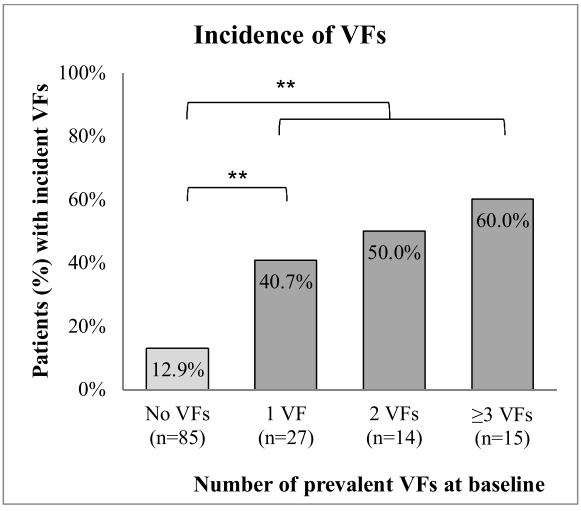

Fig. 2. Incidence of VFs after 7 years follow-up, stratified by the presence and number of prevalent VFs at baseline.
** $p < .01$.

for back pain. The rest of the patients either experienced no pain, or more likely, they were not able to express it. Increased awareness among professionals for the presence of subclinical VFs in these patients is therefore essential.

Early reports about bone mineral disorders and antiseizure drugs focused on strong enzyme-inducing drugs which induce the liver's cytochrome P450 enzyme-system., resulting in an increased vitamin D metabolism and bone loss. However, antiseizure drugs with minimal to no enzyme-inducing effects are shown to decrease BMD as well, even though the multiple pathophysiological mechanisms are far from clear (Diemar et al., 2019; Fan et al., 2016; Mitta et al., 2019), In our study, 65.2% of the patients used both enzyme- and non-enzyme-inducing antiseizure drugs at baseline. As for enzyme-inducers, oxcarbazepine and topiramate are weaker inducers than carbamazepine, phenobarbital, phenytoin and primidone. The majority (82.5%; 99 of 120) of the patients on enzyme-inducers were prescribed strong inducing antiseizure drugs at baseline. Six patients went from using enzyme-inducing drugs to using no enzyme-inducing drugs during the study. Due to the many changes in prescriptions and the use of multiple types of antiseizure drugs, no conclusions can be drawn regarding the effects of (strong) enzyme- versus non-enzyme-inducing drugs.

This study has limitations. Follow-up results could only be obtained in half (54.0%) of all invited patients (n = 261). Our results, may therefore represent the better part of our total group of institutionalized patients with refractory epilepsy and ID. Of the patients who had a VFA at baseline, 15.2% (n = 28) died during follow-up, highlighting the frailty of the participants. In this specific study population, VFA appeared to be complicated. Both physical and behavioral issues led to challenges and failed scans in multiple patients. In addition, image

artifacts and disrupting factors were frequently present, resulting in a substantial number of baseline vertebrae with and without prevalent VFs not evaluable at follow-up, and in vertebrae with VFs at follow-up which could not be evaluated at baseline. All images were analyzed by the same researcher and discussed with two other researchers for consensus in case of doubt. However, some technical issues may have led to an underestimation of the total number of VFs and the proportion of patients diagnosed with VFs.

Also, the exact timing of incident VFs is unknown, since we only had one follow-up moment seven years after baseline assessment. In our study population all patients suffered from epilepsy since childhood, so no conclusions can be drawn regarding the influence of duration of epilepsy or antiseizure treatment on VF incidence.

We followed a large group of patients over seven years and started treatment with bisphosphonates according to the Dutch guidelines. In patients who started treatment after baseline, the incidence of VFs was found to be higher than in patients who had never used bisphosphonates. This confirms that patients who are osteoporotic and in need of therapy have a higher risk of VFs than those who have a normal BMD. This study was not designed as an intervention study and it was ethically not justified to define a control group within our cohort. Hence, no conclusions can be drawn regarding the effects of bisphosphonate therapy in our study group.

5. Conclusion

In adults with refractory epilepsy VFA is challenging, due to physical and behavioral aspects, resulting in a substantial proportion of unevaluable vertebrae and scans. Nevertheless, 40% of the evaluable patients had a VF at baseline and after 7 years follow-up, 27% had at least one new and/or worsening VF despite anti-osteoporosis treatment according to the Dutch guidelines. This high prevalence and incidence of VFs emphasizes the importance of routine screening with DXA and VFA in institutionalized adult patients with refractory epilepsy. Early recognition may improve prevention and treatment of VFs.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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