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INCIDENCE OF FRACTURE IN EPILEPTICS

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In 87 epileptics on diphenylhydantoin, the occurrence of non-seizure-related fractures, over a period of 7 years, was six times greater than that found in the normal population. The significant increase in fracture incidence was found to lie within the 45–64 age group indicating that epileptics are not only more prone to fractures but also have an earlier fracture début.

Key words: diphenylhydantoin; epilepsy; fracture; osteomalacia

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A great number of studies in recent years have shown that 25 per cent of all patients undergoing antiepileptic treatment develop osteomalacia. This finding is based on blood chemistry tests and on X-ray examinations (Dent et al. 1970, Hunter et al. 1971, Borgstedt et al. 1972, Christiansen et al. 1972, Kraft et al. 1974, Livingstone & Pauli 1974, Kruse 1975). A high incidence of fracture in epileptic patients can be expected because of the nature of the illness (Vasconcelos 1973), but no investigation of this subject can be found in the literature. The aim of the present study, which is part of a larger survey, has been to compare the incidence of fractures not related to seizures in 87 epileptics, over a period of 7 years, with the expected incidence in a normal population.

MATERIAL AND METHODS

Proband material

The material comprises 87 epileptics, 49 women and 38 men. The mean age for the women was 56 ± 12 years and for the men 55 ± 12 years. Most of the epileptics have suffered from the disease since childhood, and all have been on anticonvulsant therapy for more than 10 years, in most cases on diphenylhydantoin (200–500 mg, average dose 350 mg) and Phenemal (100 mg). More recently Mylepsin has been prescribed for a few patients. Serum concentration determination of diphenylhydantoin has not been carried out routinely. Most of the epileptics are debilitated to a minor degree but have had steady employment and lived in their own apartments in a home for epileptics (Fogdarödshemmet). None of them have been on general steroid therapy. Two have diabetes mellitus and one has rheumatoid arthritis, but these three are not included in the fracture group.

In cases of serious skeletal damage, examinations have been carried out in one of three X-ray units. We have gone through the archives in all three units for the period January 1969 through December 1975. During this time all of the patients in the present study lived in the above-mentioned home. This has made it possible for us to register the majority of the more serious fractures. At the same time, with the help of the personnel at the home and by studying the referrals for X-ray examination, we have been able to differentiate the fractures which have occurred in connection with epileptic seizures.

Control material

Studies of fracture incidence in a normal population have been carried out earlier in the city of Malmö (210,000 inhabitants), and have included fractures of the forearm (radius) (Alffram & Bauer 1962), cervical and trochanteric fractures of the femur (Alffram 1964), ankle fractures (Nilsson 1969) and fractures of the upper end of the humerus (Horac & Nilsson 1975). In this investigation we have compared the observed (registered) number of non-seizure-related fractures in the bones named above in epileptics with the expected incidence of fracture in these bones in a normal population.

*Statistical methods**

Using the hypothesis that the group of patients under study are exposed to fractures at no higher than the normal rates, the expected number of fractures of each type in each age and sex group during the period of study can be computed as the product of the normal group rate by the number of patients in the group by the number of years under study. A significantly higher number of observed fractures in any group indicates that this group is exposed to fractures at a higher rate than the normal group.

To determine what should be meant by a significantly higher number of observed fractures, the instances of fracture are considered as occurring randomly in time and independently of each other. This somewhat idealized model immediately leads to the consequence that the number of observed fractures in any one group is Poisson-distributed, with the mean equal to the expected number of fractures in that group, and that the number of fractures in different groups are independent. Within that model, the numerical levels of significance can readily be computed. Also, because of the additive property of Poisson variables (i.e. the sum of independent Poisson variables is itself Poisson-distributed, with the mean equal to the sum of the means of the variables), both the expected and the observed numbers in any set of subgroups can be added to form a larger group, and the same type of test can then be used for this new group.

The large number of single tests allowed by this material (in the order of 100) makes it necessary to consider the problem of spurious significance. A series of 100 independent tests, each performed on the 5 per cent level, will contain on the average five spurious significances, and so forth. To keep down the risk of spurious significances, a much lower level has to be used in each test. To make the risk of one spurious significance 1 per cent, each test has to be performed on the 0.01 per cent level of significance.

RESULTS

Fifty-three epileptics had no fractures during the 7-year period. Thirty-four had 70 fractures. Of these, 26 were with certainty related to epileptic seizures and 44 probably not related to seizure. Table 1 shows the type of fracture.

Of the fractures, 35 in number, for which we have incidence totals from the Malmö surveys, 22 in 17 epileptics were probably not related to seizures (Table 1). These we have studied further. The mean age for the 17 epileptics was 61 ± 8 years.

In Tables 2–6 a comparison is made between the expected number of frac-

Table 1. Seventy fractures in 34 epileptic patients.

Site of fracture	Men	Women
Humerus-neck	2 (1)	2 (2)
Radius	4 (1)	3 (1)
Femur-neck	1	5
Femur-trochanter	4 (3)	4
Ankle (mall. ped.)	5 (2)	5 (3)
Clavicle	3 (3)	1
Humerus-supracondyle	0	1 (1)
Olecranon	0	1
Hand	2 (2)	3 (1)
Vertebrae	0	2 (1)
Pelvis	1 (1)	3
Femur-supracondyle	0	4
Tibia-condyle	0	6 (1)
Tibia and fibula	1	1
Foot	1 (1)	5 (2)
Total	24 (14)	46 (12)
Total	70 (26)	

The numbers within parentheses indicate fractures which have occurred during epileptic seizures.

* Statistical calculations were performed by Per Överbeck, Department of Mathematical Statistics, University of Lund.

Table 2. Observed frequency of fractures of the upper end of the humerus (Fract. colli humeri) in epileptic patients as compared with expected frequency in the normal population.

Age		25–44 years	45–54 years	55–64 years	65–74 years	75–79 years	Total
Men	Obs. freq.	0	1	0	0	0	1
							$P > 0.05^{-1}$
	Exp. freq.	0.0147	0.0189	0.0770	0.0910	0	0.2016
Women	Obs. freq.	0	0	0	0	0	0
							$P > 0.05^{-1}$
	Exp. freq.	0.0210	0.0406	0.2016	0.1848	0.0392	0.4872
Total	Obs. freq.	0	1	0	0	0	1
							$P > 0.05^{-1}$
	Exp. freq.	0.0357	0.0595	0.2786	0.2758	0.0392	0.6888

Table 3. Observed frequency of forearm fractures (Fract. radii) in epileptic patients as compared with expected frequency in the normal population.

Age		25–44 years	45–54 years	55–64 years	65–74 years	75–79 years	Total
Men	Obs. freq.	0	2	0	1	0	3
							$P < 0.001^{**}$
	Exp. freq.	0.0266	0.0112	0.0567	0.0385	0	0.1330
Women	Obs. freq.	0	0	2	0	0	2
							$P > 0.05^{-1}$
	Exp. freq.	0.0385	0.1120	0.6930	0.5103	0.0798	1.4336
Total	Obs. freq.	0	2	2	1	0	5
							$P > 0.05^{-1}$
	Exp. freq.	0.0651	0.1232	0.7497	0.5488	0.0789	1.5666

Table 4. Observed frequency of cervical fractures of the femur (Fract. colli fem.) in epileptic patients as compared with expected frequency in the normal population.

Age		25–44 years	45–54 years	55–64 years	65–74 years	75–79 years	Total
Men	Obs. freq.	1	0	0	0	0	1
							$P > 0.05^{-1}$
	Exp. freq.	0.0032	0.0039	0.0356	0.0658	0	0.1085
Women	Obs. freq.	0	1	3	1	0	5
							$P < 0.0001^{***}$
	Exp. freq.	0.0028	0.0125	0.1058	0.1959	0.0701	0.3871
Total	Obs. freq.	1	1	3	1	0	6
							$P < 0.0001^{***}$
	Exp. freq.	0.0060	0.0164	0.1414	0.2617	0.0701	0.4956

Table 5. Observed frequency of trochanteric fractures of the femur (Fract. troch. fem.) in epileptic patients as compared with expected frequency in the normal population.

Age		25–44 years	45–54 years	55–64 years	65–74 years	75–79 years	Total
Men	Obs. freq.	0	0	0	1	0	1
							$P > 0.05^{-1}$
	Exp. freq.	0.0019	0.0037	0.0178	0.0606	0	0.0840
Women	Obs. freq.	0	0	3	1	0	4
							$P < 0.0001^{***}$
	Exp. freq.	0.0007	0.0049	0.0391	0.0899	0.0461	0.1807
Total	Obs. freq.	0	0	3	2	0	5
							$P < 0.0001^{***}$
	Exp. freq.	0.0026	0.0086	0.0569	0.1505	0.0461	0.2647

Table 6. Observed frequency of ankle fractures (Fract. mall. pedis.) in epileptic patients as compared with expected frequency in the normal population.

Age		25–44 years	45–54 years	55–64 years	65–74 years	75–79 years	Total
Men	Obs. freq.	0	1	1	1	0	3
							$P < 0.01^{*}$
	Exp. freq.	0.0707	0.0420	0.1001	0.0651	0	0.2779
Women	Obs. freq.	0	0	1	0	1	2
							$P > 0.05^{-1}$
	Exp. freq.	0.0413	0.0391	0.1764	0.1134	0.0056	0.3758
Total	Obs. freq.	0	1	2	1	1	5
							$P < 0.001^{**}$
	Exp. freq.	0.1120	0.0811	0.2765	0.1785	0.0056	0.6537

tures in 87 persons over a period of 7 years and the observed number in the epileptic group. The fractures are classified according to type. This comparison is also shown for the totals graphically in Figure 1.

In adding together the totals for the various types (Tables 2–6), we find that the significant increase in the occurrence of fractures appears in the 45–54 and 55–64 age groups (Figure 1). The ex-

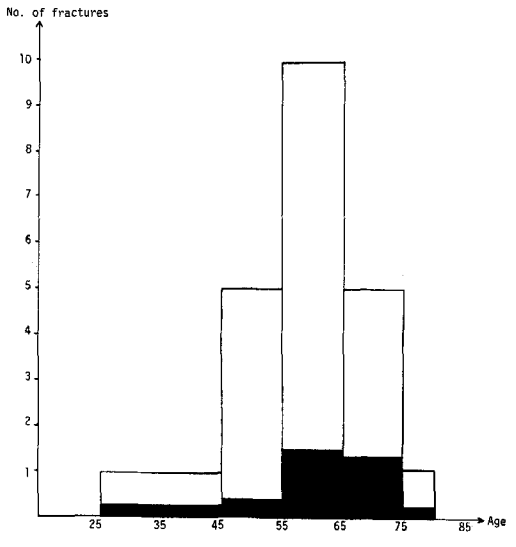

Figure 1. Observed frequency of fractures not related to seizures in 87 epileptics (open columns) as compared with frequency in the normal population (filled columns) over a 7-year period.

pected incidence for the age group 45–54 years is 0.3 fractures, whereas the observed incidence is 5.0 ($P < 0.0001^{***}$); the expected incidence for the age group 55–64 years is 1.5 and the observed is 10.0 ($P < 0.0001^{***}$).

The expected fracture incidence for men, for the five fracture types, is 0.8 and the observed incidence is 9.0 ($P < 0.0001^{***}$). The expected incidence for women is 2.9 fractures, while the observed incidence is 13 ($P < 0.0001^{***}$). The consolidated totals show an expected incidence of 3.7 fractures and an observed incidence of 22 ($P < 0.0001^{***}$).

DISCUSSION

Several reports on osteomalacia in epileptic patients have appeared in the literature in recent years and it has been suggested that antiepileptic therapy, especially diphenylhydantoin, is the cause of the skeletal changes and that osteomalacia in epileptics is probably related to a relative deficiency of vitamin D or of its metabolites. Epileptics with osteomalacia have a low urine-calcium value, a high level of alkaline phosphates, and, in 10–20 per cent of cases, a low serum-calcium value. The low serum-calcium rate can in turn possibly cause cramp attacks and antiepileptic therapy can mask this effect (Gharib & Munoz 1974).

Vitamin D_3 (cholecalciferol) can be produced in the skin through the effect of ultra-violet light, or it can be absorbed from the intestinal canal. A first step in the hydroxylation process occurs in the liver, producing 25-hydroxycholecalciferol. This metabolite is probably not active but circulates in the blood. The next hydroxylation process occurs in the kidneys, producing the active metabolite 1.25-dihydroxycholecalciferol. This metabolite affects the mucous membranes of the small intestine, the kidney tubuli and the bone tissue, principally by increasing the organism's absorption-reabsorption of calcium and phosphorus and also regulates the mineralization of bone tissue. The hydroxylation process is probably affected by diphenylhydantoin, but it is not yet clear if this occurs in the liver or in the kidneys (Boyle 1974, Schaefer 1974, Apold 1976).

Fracture incidence in epileptics is high, as expected, because of the nature of the disease (Table 1), but it is possible that antiepileptic therapy with diphenylhydantoin and the resultant osteomalacia cause an increase in frequency. Several reports on material comprising smaller numbers of patients have indicated that treatment with vitamin D can have a beneficial effect on osteomalacia in epileptic patients on diphenylhydantoin (Christiansen et al. 1973 a, b, Christiansen & Rödbo 1974, Latorre & Kenny 1974, Christiansen et al. 1975 a, b).

In 87 patients on diphenylhydantoin, we found a significant increase in the incidence of non-seizure-related fractures, in particular cervical and trochanteric fractures of the femur (Tables 4 and 5), and ankle fractures (Table 6), as compared with the expected incidence in a normal population. In the 7-year period the frequency of occurrence of non-seizure-related fractures in the 87 epileptics was six times that in the normal population (nine times for the men and four times for the women) (Tables 2–6).

When the epileptics are grouped according to age, the significant increase in fracture incidence is found within the 45–64 age group (Figure 1). This indicates that epileptics are not only more prone to fractures, but also have an earlier fracture début.

Our present study represents part of a larger survey undertaken to relate fracture-proneness to the morphology and blood chemistry of epileptics in an effort to establish a basis for preventive treatment.

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