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Survey of management of first-ever seizures in a hospital based community

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Summary

Background: Epidemiological studies focusing on first-ever seizures have been carried out mainly on community based populations. However, since hospital populations may display varying clinical features, we prospectively analysed patients with first-ever seizure in a hospital based community to evaluate prognosis and the role of complementary investigations in the decision to administer antiepileptic drugs (AED).

Methods: Over one year, we recruited 177 consecutive adult patients with a first seizure acutely evaluated in our hospital. During six months' follow-up data relating to AED treatment, recurrence of seizures and death were collected for each patient.

Results: Neurological examination was abnormal in 72.3%, neuroimaging in 54.8% and biochemical tests in 57.1%. Electroencephalogram (EEG) showed epileptiform features in 33.9%. Toxicity represented the most common aetiology. AED was prescribed in 51% of patients. Seizure recurrence at six months involved 31.6% of patients completing the follow-up; mortality was 17.8%. Statistical analysis showed that brain CT, EEG and neurological examination are independent predictive factors for AED administration, but only CT scan is associated with outcome.

Conclusions: Patients evaluated acutely for first-ever seizure in a hospital setting have severe underlying clinical conditions apparently related to their relatively poor prognosis. Neuroimaging represents the most important paraclinical test in predicting both treatment administration and outcome.

Key words: first-ever seizure; aetiology; prognosis; recurrence; AED; hospital cohort

Introduction

Epilepsy, defined as a condition typified by seizure recurrence, is a common neurological disorder with a prevalence of 0.4–1% in the general population [1] and has a major social and economic impact. The risk of experiencing a single seizure during one's lifetime is estimated at 5–10% [2, 3]. The annual incidence of seizures in adults ranges from 40–84 per 100 000 persons in developed countries [1, 4].

Several prospective studies have investigated the incidence of first-ever seizure in adult life and related aetiologies [5–10], chiefly in community based cohorts [6–10]. Others have considered only outpatients referred to the emergency unit or outpatient clinic [5, 11, 12]. Data on recurrence after the initial incident are of great importance in defining the population at risk of developing epilepsy. They are contradictory, ranging from 23–71% in the literature [13–24]. When to initiate treatment with antiepileptic drugs (AED) remains a major unresolved issue. Some authors suggest that prompt treatment of the first seizure with AED leads to a significant reduction in seizure recurrence [21, 22], but this assumption has been questioned by others [20]. Moreover, there is still a lack of consensus concerning the necessary diagnostic workup of first seizure in an emergency setting.

As far as we are aware there are no studies specifically focusing on a hospital-based cohort including outpatients referred to the emergency department and inpatients. We postulated that clinical features and prognosis of patients evaluated acutely for first seizure in a hospital setting would differ from those in community based cohorts. The aim of this survey was to prospectively analyse patients with a first-ever seizure in a hospital based population, to evaluate prognosis and the role of complementary investigations (i.e. neurological examination, EEG, laboratory investigations, neuroimaging).

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Methods

Our study was conducted at the University Hospital of Lausanne, Switzerland, a tertiary reference centre serving a population area of 1'000'000, and a primary reference centre for the city (urban population approx. 200'000). Over one year, from 1 June 2002 to 31 May 2003, we prospectively collected patients diagnosed with a recent seizure event. Patients were included in the study only if this was their first-ever seizure episode, they were over the age of 16 and the acute evaluation occurred in our hospital (i.e., emergency department, intensive care departments, other inpatient departments including neurology). Subjects with anoxic encephalopathy and patients referred to our outpatient clinic after evaluation for first seizure elsewhere were excluded from the study.

Each patient was given a standard medical and neurological examination, haematological and biochemical screening tests (including serum electrolytes, liver and kidney function tests, glucose, creatinine kinase and C-reactive protein), and 21-lead waking EEG according to the international 10–20 system. Patients underwent brain CT or MRI scan, unless relatively contraindicated (i.e., if idiopathic generalized epilepsy in a young patient was very likely according to history and EEG). All tests were performed within 12 hours of clinical evaluation. Diagnosis of seizure type was according to the ILAE classification [29] taking into account history, clinical features and ancillary tests.

Several previous studies have divided seizures into provoked and unprovoked [29], the former supposedly involving a lesser likelihood of recurrence [7, 9, 10, 24]. In our view, however, this classification may cause confusion when facing first-ever seizures: a first seizure elicited by an as yet undiagnosed tumour, for example, may be classified as provoked [29]; it would nevertheless be hazardous not to administer AED, at least for some weeks. Similar considerations apply to some extent to first seizures related to severe head trauma, CNS infections and possibly stroke, but not to transient metabolic dysfunction, withdrawal or intoxication. In fact, in a previous study mortality did not differ between patients with provoked or unprovoked seizures, and one-third of seizure relapses occurred after unprovoked seizures [24]. To investigate this concern, we classified seizure aetiologies in a descriptive manner and compared this classification with the "classical" one.

One of the participating neurologists initiated AED treatment when the likelihood of seizure recurrence was felt to be important. If the risk of recurrence was considered to be low, patients received no treatment or transitory benzodiazepine therapy.

Data on demographics (age, sex), seizure type, suspected aetiology, biochemical tests, emergency EEG, neurological exam, neuroimaging results and treatment prescribed were collected for each patient. Six months after enrolment, through the records of our outpatient clinic and structured questionnaires addressed to general practitioners or neurologists working outside the hospital, we assessed AED treatment and incidence of recurrent seizures as primary endpoints, and death as secondary endpoint. Treatment at the end of the follow-up period was compared with treatment strategy decided acutely.

Statistical analysis was performed by means of univariate analysis (χ^2 test with Yates continuity correction; unpaired t-test) for the association of complementary investigations with outcome and the relationship of aetiological classification and outcome; and multivariate analysis (logistic regression) for the association between complementary investigations and the decision to treat. Cutoff for significance was set at $P < 0.05$.

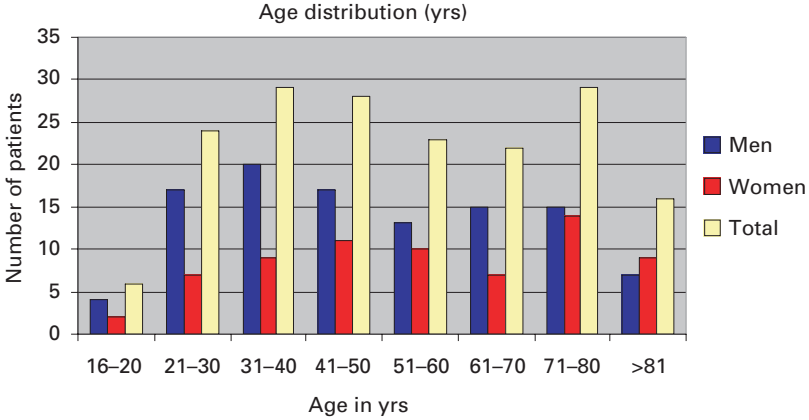
Results

Of 179 patients diagnosed with a first-ever seizure evaluated at our hospital, two with anoxic encephalopathy were excluded from the study. Of the remaining 177, 108 (61%) were males and 69 (39%) females. The mean age was 52.92 ± 17.76 (range 16–100 yrs). Age distribution is shown in figure 1.

Seizure types were found as follows: 106 (60%) generalised, 29 (16%) complex partial, 14 (8%) simple partial, 26 (15%) partial secondarily generalised and 2 (1%) generalised status epilepticus. Figure 2 represents the occurrence of first seizures along the period of our study, showing a peak incidence at the end of the year both for episodes related to toxicity and other aetiologies.

Figure 1

Age distribution for occurrence of first seizure.



The neurological examination was abnormal in 128 patients (72.3%). An electroencephalogram (EEG) was performed in all patients and found to be abnormal in 137 (77.4%). 60 (corresponding to 33.9% of the total) showed epileptiform discharges, whereas 77 (43.5% of the total) showed only unspecific changes chiefly consisting of generalised or focal slowing.

172 patients underwent cerebral CT scan or (exceptionally) MRI; neuroimaging was abnormal in 99 (54.8%). The CT scan was not performed in five subjects: one died shortly after the seizure, one was diagnosed with idiopathic generalised epilepsy after the EEG (thus not fulfilling the criteria for CT), one left hospital before having the CT, and in the case of the last two there was a protocol violation during the weekend.

In 101 patients (57.1%) laboratory tests showed at least one abnormality potentially related to the seizure aetiology or resulting from seizures

Figure 2

Occurrence of first seizures during the period of study.

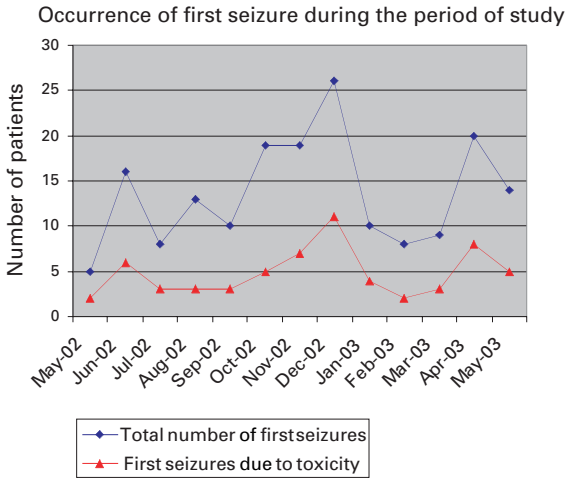


Figure 3

Aetiologies of first seizure.

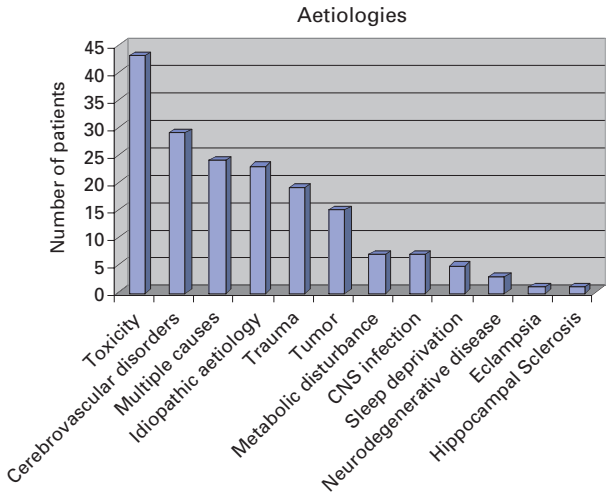


Table 1

Risk of seizures following ischaemic and haemorrhagic stroke and following head trauma (as single aetiology).

	Immediate/early seizures (<1 week)		Late seizures (>1 week)	
Total stroke (20)	7/20 (35%)		13/20 (65%)	
	Recurrence	Death	Recurrence	Death
	2/7 (29%)	4/7 (57%)	5/13 (38%)	3/13 (23%)
Total head trauma (19)	13/19 (68.4%)		6/19 (31.6%)	
	Recurrence	Death	Recurrence	Death
	4/13 (30.8%)	1/13 (7.7%)	2/6 (33.3%)	1/6 (16.7%)

Table 2

2 most common aetiologies as per relative importance and in relation to patient age (absolute number in parenthesis).

	1st most common aetiology	2nd most common aetiology
<20 yrs (6)	Trauma (3)	Idiopathic (2)
21–30 yrs (24)	Toxicity (7)	Idiopathic (5)
31–40 yrs (29)	Toxicity (9)	Multiple (6)
41–50 yrs (28)	Toxicity (10)	Cerebrovascular (5)
51–60 yrs (23)	Cerebrovascular (7)	Toxicity (7)
61–70 yrs (22)	Multiple (4)	Toxicity (4)
71–80 yrs (29)	Cerebrovascular (7)	Trauma (6)
>81 yrs (16)	Cerebrovascular (5)	Multiple (3)

(electrolyte abnormality, hypo- or severe nonketotic hyperglycaemia, significant urinary or hepatic enzyme disturbance).

Figure 3 shows aetiologies established in the acute phase. The most common causes were toxicity in 43 patients (24.3%) (illicit drug or benzodiazepines (BDZ) withdrawal; alcohol withdrawal or intoxication or both: 17 of these were exclusively BDZ abusers, the others were abusing more than one substance); cerebrovascular disorders in 29 patients (16.4%): ischaemic stroke (16), subdural haematoma (5), haemorrhagic stroke (4), arteriovenous malformation (3), subarachnoid haematoma (1): multiple causes (2 or more aetiologies) in 24 (13.6%); idiopathic/cryptogenic in 23 (13%); head trauma in 19 (10.7%). Within the most common aetiology (toxicity), 69.8% of patients were males and the type of seizure was generalised in 77%, complex partial in 16% and partial secondarily generalised in 7%.

The risk of immediate/early seizures and late seizures after stroke and head trauma is shown in table 1.

Table 2 summarises the two most common agerelated aetiologies.

The drug management protocol assessed at the end of the first hospitalisation was as follows: 86 patients (49%) were not given AED (but in many cases received transient BDZ), 69 (39%) received AED monotherapy and 22 (12%) AED polytherapy.

Assessment at six months was possible in 152 patients (85.9%) and 25 (14.1%) were lost to follow-up. Seizure recurred in 48/152 subjects (31.6% of patients evaluated). The commonest aetiologies associated with recurrence were cerebrovascular disorders in 9 (18.8%), multiple causes in 8 (16.6%), neoplasia in 7 (14.6%), trauma in 6 (12.5%), and CNS infection in 6 (12.5%). At six months, 70.8% of the 48 patients were under AED therapy. 27 patients died, ten having experienced at least one recurrence, and 19 on AED therapy (70.4%). The commonest seizure aetiologies associated with death were cerebrovascular disorders in 8 (29.6%), multiple causes in 5 (18.5%) and neoplasia in 3 (11.1%). Table 3 shows the treatment at 6 months and illustrates the fact that at 6 months most of our subjects were treated as at the beginning of the study, except for polytherapy which tended to be less frequent at follow-up. This shows that there is a tendency to simplify treatment over time whenever possible.

Frequency of seizure recurrence at six months was 16.3% in patients who received no treatment acutely (86), 36.2% in patients who received AED monotherapy, and 40.9% in those on an AED polytherapy regimen. Subjects on AED were likely to have a recurrence or die; conversely, they were less likely to be lost to follow-up (figure 4).

Table 4 shows the rate of normal complementary examinations depending on the final outcome (patients who died after a seizure recurrence, considered a primary outcome, are included in the

first column). Table 5 presents the relationship between normal complementary examinations and the decision to administer AED treatment at study enrolment. Table 6 shows the distribution of aetiologies according to the international definition [29], with its relationship to recurrence and death, for the 152 patients who completed the follow-up.

Discussion

This series differs from previous studies for two principal reasons. First, in contrast to previous epidemiological studies it focused on a hospital based cohort, excluding outpatients referred after the acute diagnostic work-up. Second, the follow-up period is shorter than in other series due to the relatively high mortality and drop-out rate.

Our survey confirms that males are more likely to come to medical attention for seizures, as previously shown in several epidemiological studies [1, 5, 9, 10]. This is probably related to males' higher rate of seizure related to drug (69.8%) or alcohol intoxication (83.7%), especially in the 31–40 age group. The age distribution does not show a clear maximum, unlike community cohorts [9], a fact which probably reflects patient selection in our population. The minima corresponding to the 16–20 and over-80 age groups are probably related to the prevalence of those subpopulations in our hospital.

Incidence fluctuation during the year is not solely related to toxic-metabolic aetiologies, since seizures related to other causes also exhibit marked variability paralleling theirs. We postulate that other variables, such as psychological, infectious, or possibly meteorological, may account for the peak in midwinter.

Overall, 60% of our seizures were generalised, 24% partial (simple and complex), 15% partial secondarily generalised and 1% status epilepticus. Retrospectively, 48% of the patients with generalised seizures had a focal lesion. The high proportion of generalised seizures may be explicable by the lack of precision in the description of the seizure, resulting in overestimate of generalised seizures [1, 30]. This is illustrated in the divergent rates found in previous studies (generalised seizures ranging between 39% and 68%) [5, 6, 9], and shows that even when carefully and prospectively assessed, as in our case, the exact history may

Table 3

Treatment and follow-up at 6 months in relation to chosen treatment at study enrolment.

		Treatment at 6 months				
		Without drugs / BDZ alone	**Monotherapy**	**Polytherapy**	**Death**	**Drop-out**
Treatment at enrolment	Without drugs/BDZ alone (86)	50	10	0	8	18
	Monotherapy (69)	6	40	4	14	5
	Polytherapy (22)	2	12	1	5	2

Table 4

Rate of normal complementary examinations at D0 (day of the first seizure) divided by recurrence, death and absence of recurrence at six months' follow-up. The table includes only patients who completed follow-up. Note: the 5 CT not performed were considered normal CT scans.

	A. Recurrence (48) at 6 months	**B. Death (17) at 6 months (without recurrence)**	**C. Patients alive without recurrence (87) at 6 months**	**Univariate analysis (A+B vs. C)**
CT	14/48	3/17	47/87	P = 0.001, χ^2 = 10.738*
EEG	32/48	10/17	57/87	P = 0.908, χ^2 = 0.013
Neurostatus	8/48	1/17	23/87	P = 0.092, χ^2 = 2.831
Laboratory	21/48	5/17	41/87	P = 0.477, χ^2 = 0.504

* significant

Table 5

Relationship between normal complementary examinations and treatment decision at enrolment. The 5 CT not performed were considered normal CT scans. OR = odds ratio (95% confidence Interval).

	A. No therapy (86)	**B. Monotherapy (69)**	**C. Polytherapy (22)**	**Univariate analysis (A vs. B+C)**	**Multivariate analysis**
CT	62/86	13/69	5/22	P = 0.0001, χ^2 = 46.761*	P = 0.00001; OR = 12.03 (3.93–36.86)*
EEG	70/86	40/69	7/22	P = 0.0001, χ^2 = 16.158 *	P = 0.001; OR = 8.08 (2.23–28.45)*
Neurostatus	35/86	11/69	3/22	P = 0.0003, χ^2 = 12.915 *	P = 0.0001; OR = 3.78 (1.13–12.65)*
Laboratory	32/86	36/69	8/22	P = 0.1780, χ^2 = 1.809	P = 0.97; OR = 0.98 (0.35–2.74)

* significant

Table 6

Relationship between aetiologies according to international definition [29] and recurrence and death, for the 152 patients who completed follow-up.

	A. Provoked (94)	B. Unprovoked nonprogressive (26)	C. Unprovoked progressive (13)	D. Idiopathic/ cryptogenic (19)	A vs. B+C	D vs. B+C
Recurrence (48 patients)	32/94 = 34%	8/26 = 31%	6/13 = 46%	2/19 = 11%	0.839	0.043*
Death (27 patients)	16/94 = 17%	5/26 = 19%	4/13 = 31%	2/19 = 11%	0.420	0.260

Unpaired t-test (* = significant)

be difficult to obtain. On the other hand, one may postulate that patients experiencing simple partial seizures are less likely to come to medical attention acutely, thus possibly resulting in a referral bias.

The aetiology could be established acutely in 87% of our patients. The low rate of idiopathic seizures (13%) differs from data from other studies [5, 8, 9, 12] ranging from 23.9–40%, and can be explained by the extensive work-up and prospective design of our series. Toxicity, especially alcohol-related, is the most common cause, and cerebrovascular disorders are the second most important aetiology, especially in older subjects. These trends are similar to previous reports [4–6, 31–34].

Some studies have found that CT is essential in the evaluation of first seizure, since structural lesions are found in 26–37% of patients [5, 35, 36]. Others concluded that CT, although useful in selected patients, should not be used indiscriminately as a part of a standard evaluation [11, 32, 37], or does not predict outcome [24]. In our series, neuroimaging was abnormal in 54.8% of cases, a fact which in our opinion highlights the importance of this investigation. The incidence of abnormality is higher than previously reported, probably owing to our patients' underlying general condition. CT scan was the only test related to both the outcome and the decision to treat, being statistically significant in uni- or multivariate analysis.

Many previous studies point to the fact that the EEG is an important aid to evaluation of seizure patients [4, 5, 38, 39], showing epileptiform activity in 21–32.9% [5, 38]. Moreover, some studies have shown that the EEG is an important predictive factor for seizure recurrence [4, 20, 24, 37, 40, E. Beghi, personal communication]. For other authors the EEG is unnecessary and has no influence on the management of epileptic patients [11, 31, 41]. Since in the UK there is a long waiting list for EEG in most units, physicians are obliged to manage acute seizures without an EEG [31]. In our study, 77.4% of patients had an abnormal EEG, including 33.9% with epileptiform discharges, a figure in line with the published literature. In statistical analysis, a normal EEG was associated with the decision not to treat, but not with outcome.

Neurological examinations were, surprisingly, found to be abnormal in the majority of our patients. This contrasts with previously published data [5, 12]. The discrepancy is probably related to two factors: first, we scored the neurological examination as "abnormal" in cases where both focal and nonfocal signs occurred. Second, as discussed before, our subjects may reflect a relatively morbid, hospital-based population. Normal neurological examination was statistically associated with the decision not to treat, but not with outcome.

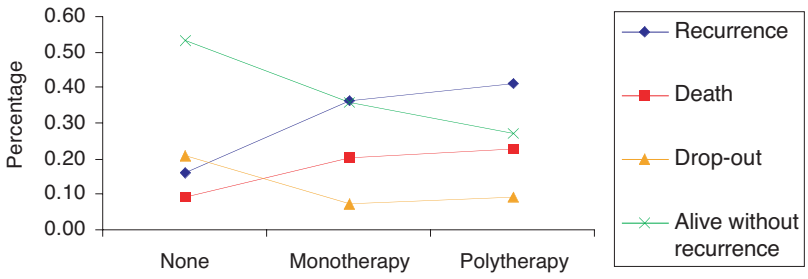
Previous studies suggest that haematological and biochemical screening tests are of minimal or no value in the evaluation of patients with seizures [5, 11, 12, 35, 37]. Our results confirm that laboratory tests are not predictive of outcome or of the decision to administer AED. However, in our series biochemical abnormalities potentially related to seizure aetiology were detected in 57.1%. As these are potentially treatable, we suggest that biochemical screening should be part of the standard work-up. Moreover, the high incidence in our series compared to the data reported in other studies (4.9% [12]) again underlines our patients' pre-existent morbidity.

Mortality has been shown to be higher in newly diagnosed patients than in the standard population, especially during the first 2 years after diagnosis, and to be related to the underlying pathology [13, 25–28], as shown in our study (especially pneumonia, neoplasia and stroke). Mortality at one year has been found to be 14–18.4% [13, 26] and at ten years 36.4% [25]. Another study reported mortality of 26% in patients aged under 20 for a cohort of 1355 patients with a mean follow-up of 28 years [28]. Within our six months' follow-up period, 17.8% of the patients died, a figure apparently higher than previous data. This again is probably related to our patients' underlying clinical condition.

Published studies report big differences in prognosis after first seizures [13–23]. The variation found in recurrence rates appears to be due to methodological differences or to study populations' characteristics (retrospective versus prospective design, selection of patients, length of time before study entry and of follow-up). The risk of relapse has been reported to vary between 46% at six months [14], 23–71% at two years [E. Beghi, personal communication; 22], and 29–78% of patients at three years [11, 14, 18, 20, 23, 35]. More than 50% of patients who have a recurrence will

Figure 4

Percentage of patients with recurrence, death or drop-out at six months in relation to AED treatment. prescribed acutely.



do so within 6 months [11], which corresponds to our follow-up period. The most important predictors of seizure recurrence are apparently related to the underlying aetiology and the result of the EEG [37], as well as to the number of seizures in the first six months [13]. In our survey, seizure recurred in 48 patients (31.6% of patients completing the follow-up), which is in line with published data. Previously described causative factors associated with recurrence are the presence of brain lesions, neuropsychiatric handicaps, poor compliance, stroke, head trauma and alcohol consumption [15, 18, 22]. The last mentioned 3 aetiologies alone resulted in 40% recurrence within 12 months [18]. In our study, relapse was due mainly to cerebrovascular disorders, neoplasia, trauma and CNS infection. It is noteworthy that toxicity – representing our most frequent aetiology – was not associated with a major risk of recurrence. It is generally accepted that seizure recurrence in the setting of symptomatic epilepsy is more likely to occur after late seizures than after early ones. However, our results show that this tendency was only seen after stroke, but not after brain trauma (table 1).

A classification focusing on provoked/unprovoked/idiopathic-cryptogenic aetiologies seems to have little practical significance in this setting (apart from the latter group, which statistically has a marginally better prognosis for recurrence). This is probably related to the concerns described in the Methods section, and especially to the fact that in our survey aetiologies were determined at enrolment, since previous studies show not inconsiderable reclassification in some instances [24].

Some papers have supported a beneficial role for early treatment with AED in reducing the risk of relapse [15, 19, 21, E. Beghi, personal communication; 42]. Conversely, evidence against starting AED treatment after a first seizure is provided by non-randomised studies [11, 14, 20]. Other authors argue that treatment appears to reduce short-term relapse but is apparently ineffective in regard to the chance of long-term remission [E. Beghi, personal communication; 24, 43]. We observed a greater likelihood of death and seizure recurrence associated with AED treatment (figure 4), probably reflecting the severity of the underlying pathology. Conversely, the major drop-out rate of patients without treatment is probably related to their good outcome.

In conclusion, our study shows that patients evaluated on admission for an first seizure in a hospital setting have different clinical characteristics from community based cohorts. The high ratios of abnormal neurological findings, neuroradiological imaging and laboratory tests, associated with the high mortality rate, underscore the fact that these patients tend to have serious underlying conditions. Hence, in our view, an extensive clinical work-up appears to be reasonable for patients in this setting. Statistical analysis shows that brain imaging, EEG and neurological examination represent an independent predictive factor for AED treatment, whereas only neuroimaging is associated with outcome in univariate analysis. Laboratory investigations were found to be significantly linked to neither treatment administration nor outcome. Treatment administration appears to be associated with the risk of a bad outcome (seizure recurrence or death): the design of this observational study precludes analysis of treatment efficacy, but it is likely that in many patients the decision to administer AED reflects the gravity of their underlying clinical condition.

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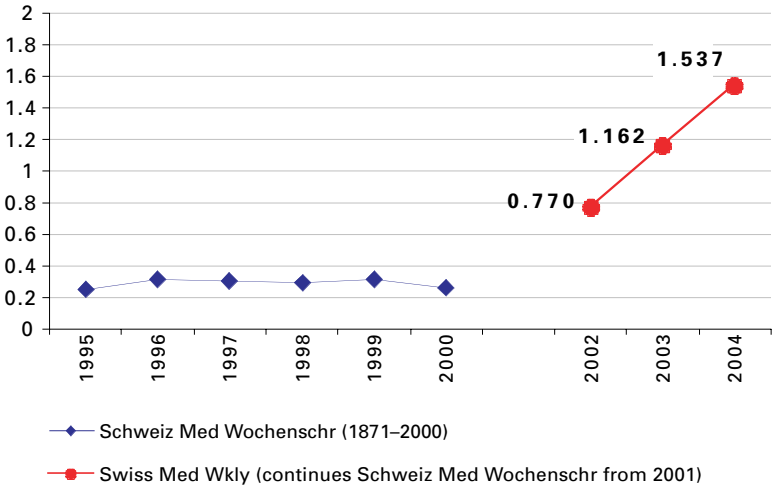

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