New-onset seizures in older people

Clinical features, course and outcomes

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Highlights

- 58% of first seizures were focal aware or impaired awareness seizures
- 40% of first seizures were attributed to vascular causes
- 64% of patients started on anti-seizure medication had no seizure recurrence
- Higher age or frailty did not predict seizure recurrence or medication side effects
- Severity of small vessel disease or atrophy did not predict seizure recurrence

Abstract

Objective: The incidence of epilepsy increases with age. With current demographic trends, this presents a healthcare challenge. We investigated the clinical spectrum of first seizures, evaluated neuroimaging and EEG findings, and determined clinical outcomes, including anti-seizure medication (ASM) response in older people. In addition, we sought to understand the relative effects of age and frailty on ASM response.

Methods: A retrospective single centre cohort study of 207 cases ≥60 years' old, 113 of whom were eventually diagnosed with a first seizure in a specialist epilepsy clinic.

Results: 65/113 (57.5%) presented with either focal aware or focal impaired awareness seizures. Stroke was the most common aetiological association (31.9%, 36/113), and likelihood of seizure recurrence did not significantly differ between aetiologies. 55/86 (64.0%) who started an ASM had no seizure recurrence. 14/48 (29.2%) who underwent EEG had epileptiform abnormalities, however EEG result directly affected management in only 4/48 (8.3%) The most common MRI findings were small vessel disease (37/93, 39.8%), stroke (27/93, 29.0%) and global atrophy (14/93, 15.1%). Increasing age and frailty did not affect the odds of seizure recurrence or of experiencing ASM side effects. Severity of small vessel disease or atrophy did not affect odds of seizure recurrence.

Conclusion: Our data inform the management of first seizures in older people and provisionally support the use of ASMs in patients with increasing age and frailty, despite concerns over polypharmacy and comorbidity. Our findings should be replicated in larger cohorts.

Keywords: epilepsy, seizure, older people, anti-seizure medication

[1]

[1] Abbreviations:
ASM = anti-seizure medication

1. Introduction

The incidence of epilepsy increases with age [1, 2, 3] and older people are more likely to be diagnosed with new-onset epilepsy than any other age group [4]. Despite the rising prevalence and disease burden of new-onset epilepsy in older people [5], aspects of aetiology, natural history and management require elucidation. Whilst there is a growing evidence base in this cohort [6, 7, 8, 9], further data are needed in patients with increasing frailty, comorbidity and polypharmacy [6, 10], in whom the initiation of anti-seizure medications (ASMs) may impair quality of life [11].

We undertook a retrospective cohort study of older people referred to a dedicated First Seizure service at The National Hospital for Neurology and Neurosurgery, Queen Square over a 12-year period. Our objectives were to investigate the spectrum of clinical features, evaluate neuroimaging and EEG findings, and determine clinical outcomes including response to ASMs. In addition, we sought to understand the relative effects of age, frailty and comorbidity on response to ASMs.

2. Methods

We conducted an observational retrospective cohort study of older people, defined as ≥60 years old, referred to first seizure clinic at the National Hospital for Neurology and Neurosurgery, London, UK between 2008 and 2019 following a suspected or reported first seizure. Consultations were carried out by epileptologists.

The following data were collected: sex, age, referral source, Rockwood frailty score [12], medical comorbidities, presence of a package of care, seizure type, aetiology, treatment received, prevalence of self-reported ASM side effects, treatment changes, clinical course. Frailty scores were calculated retrospectively according to the social history given in emergency department or internal medicine clerking proformas, general practice summary information, and clinic letters. Patients were only included where the acute event described as a seizure was: a) confirmed by a relative, friend or care staff; b) not associated with syncopal features, arrhythmia or cardiac event on electrocardiogram, metabolic disturbance, or psychogenic features; c) associated with confusion post-event. Patients were deemed seizure free if they experienced no further seizures during the follow-up period following clinic review (minimum of one year). Patients were excluded if they had a prior history of epilepsy.

EEG findings were classified as normal, epileptiform, and abnormal but non-epileptiform. Neuroimaging results (CT and/or MRI) were also collected. Severity of global atrophy or small vessel disease (SVD) was determined using MRI and graded in-house by neuroradiologists as mild, moderate, or severe according to standardised criteria [13, 14, 15].

Aetiology was marked as ‘undetermined’ if history, examination and investigations including EEG and/or neuroimaging did not determine the cause of the seizure. An aetiological association between SVD and first seizure was made where neuroimaging revealed moderate or severe SVD beyond that expected for age and no other cause for seizure was identified.

Statistical analysis was conducted using SPSS (SPSS, Inc.) and figures were produced with GraphPad Prism (GraphPad Software, Inc.). First, chi-square tests were used to compare

proportions. Then, we compared the likelihood of seizure recurrence amongst different aetiologies using binomial logistic regression. Finally, we ran binomial logistic regression models with severity of SVD or global atrophy, age or frailty score as independent variables and seizure recurrence or experiencing ASM side effects as dependent variables. Data did not violate assumptions of statistical methods used.

3. **Results**

3.1. Cohort characteristics including seizure types

207 patients who presented to the first seizure clinic were identified, of whom 94 were excluded from analysis as their events were due to seizure mimics (e.g., syncope). A frequency histogram of ages within our sample of the remaining 113 patients is displayed in Figure 1.

Clinical characteristics including seizure types are displayed in Table 1. Overall, focal seizures (65/113 [57.5%]) were more common than generalised seizures (48/113 [42.5%]).

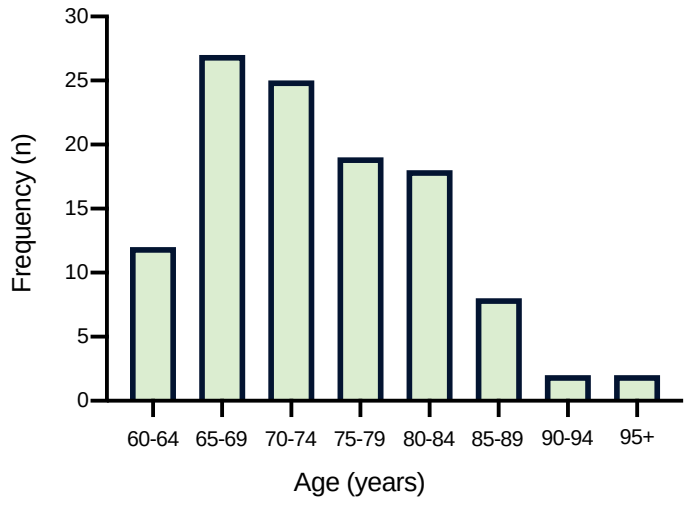

Figure 1 Frequency histogram of cohort age distribution

Characteristic	**Statistic**
Age, years (SD)	72.0 (8.1)
Female, n (%)	46 (40.7)
Follow-up period, median days (IQR)	517 (60-976)
Referral Source	**n (%)**
Emergency Department	21 (18.6)
General Practitioner	47 (41.6)
Internal (Hospital)	34 (30.1)
Other	11 (9.7)
Seizure type	**n (%)**
Focal aware motor	6 (5.3)
Focal impaired awareness non-motor	29 (25.7)
Focal impaired awareness motor	30 (26.5)
Bilateral tonic-clonic seizures*	43 (38.1)
Absence	5 (4.4)

Table 1 Clinical and demographic cohort characteristics (n = 113)

IQR = interquartile range, SD = standard deviation

*Presumed focal onset

Frailty scores and comorbidities are displayed in Table 2. The mean (SD) frailty score in our study was 4.8 (1.7), which represents being vulnerable to mildly frail on the Rockwood frailty scale [12]. Frailty scores ranged from 2 to 8. We included 39 patients who were moderately frail or above (score ≥6).

Characteristic	Statistic
Rockwood frailty score, mean (SD)	4.8 (1.7)
Regular formal carers, n (%)	19 (16.8)
Diabetes, n (%)	23 (20.4)
COPD, n (%)	14 (12.4)
Stroke, n (%)	37 (32.7)
Cancer, n (%)	22 (19.5)
Dementia, n (%)	19 (16.8)
Alzheimer's, n (%)	6 (5.3)
Vascular, n (%)	2 (1.8)
Mixed, n (%)	5 (4.4)
Not specified, n (%)	5 (4.4)
Frontotemporal, n (%)	1 (0.9)
IHD, n (%)	13 (11.5)
CKD, n (%)	56 (49.6)
Stage 2, n (%)	35 (31.0)
Stage 3, n (%)	18 (15.9)
Stage 4 or 5, n (%)	3 (2.7)
Hypertension, n (%)	59 (52.2)
Number of daily medications, mean (SD)	5.4 (4.3)

Table 2 Comorbidities and frailty scores

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, IHD = ischaemic heart disease, MCI = mild cognitive impairment, SD = standard deviation

3.2. Aetiological associations

The most common aetiological association with first seizure was stroke (36/113, 31.9%). An aetiological association was not ascertained in 25/113 (22.1%) of cases (Table 3).

Aetiological associations	n (%)
Small Vessel Disease	9 (8.0)
Post-stroke	36 (31.9)
Neurodegenerative	22 (19.5)
Other	9 (8.0)
Brain Tumour	9 (8.0)
Alcohol-related	7 (6.2)
Traumatic Brain Injury	7 (6.2)
Undetermined	25 (22.1)
Had MRI	16 (14.2)
Did not have MRI	8 (7.1)

Table 3 Aetiological associations of first seizures in older people

'Other' aetiologies included aneurysm, infection, anoxic seizure, non-traumatic haematoma, and dural calcification. Note some patients had more than one aetiological association, data are not mutually exclusive.

3.3. EEG and neuroimaging findings

48 patients underwent EEG, including routine EEG (duration <1 hour, n=35), ambulatory EEG (duration 24 hours, n=9), prolonged video EEG (duration 1-3 days, n=2), and portable EEG in intensive care (duration <1 hour, n=2). Among the 48/113 (42.5%) patients who had an EEG, 14 (29.2%) had epileptiform abnormalities, defined as sharp waves, spikes or spike-and-wave complexes. To understand the usefulness of requesting EEG in this population, we also collected data on how results affected management. Four patients (8.3%) had their management changed because of the EEG result (started ASM [n=1], changed ASM [n=2], referred for surgery [n=1]). 18 patients (37.5%) who were started on an ASM before EEG

continued their ASM following a normal result. Finally, there were 10 patients (20.8%) in whom the decision not to commence an ASM was supported by normal EEG.

CT scanning was performed in 41/113 (36.3%) and MRI scanning in 93/113 (82.3%) (Table 4). MRI scanning revealed SVD in 37/93 (39.8%) and global atrophy in 14/93 (15.1%). Logistic regression modelling showed that neither the severity of SVD or global atrophy predicted seizure recurrence (p = 0.529 and p = 0.711, respectively).

MRI finding	**n**	**Further seizure(s), n (%)**
Infarct	27	8 (29.6)
Small vessel disease	37	15 (36.6)
Mild	23	8 (34.8)
Moderate	13	4 (30.8)
Severe	1	0 (00.0)
White matter hyperintensities	4	1 (25.0)
Microhaemorrhage	2	2 (100.0)
Global atrophy	14	8 (57.1)
Mild	7	4 (57.1)
Moderate	6	3 (50.0)
Severe	1	1 (100.0)
Regional atrophy	9	4 (44.4)
Cystic changes	5	1 (20.0)
Tumour	10	2 (20.0)
Gliosis	4	2 (50.0)
Arteriovenous malformation	3	1 (33.3)
Other	5	2 (40.0)
Normal scan	5	2 (40.0)

Table 4 Association between MRI result and risk of further seizures

93 patients received MRI scans. 'Other' MRI findings included aneurysm (n=1), subdural haematoma (n=2), hippocampal sclerosis (n=1), calcification (n=1).

3.4. Seizure frequency outcomes

We sought to describe response rates to ASMs following first review in clinic. The median total follow-up time was 517 days (mean 917 days). Out of all patients reviewed in clinic, irrespective of whether they received treatment, 80/113 (70.8%) experienced no further seizures. Of those who commenced treatment, 55/86 (64.0%) had no seizure recurrence. We included patients who experienced more than one seizure whilst waiting for first review in clinic. We therefore ran a control analysis to investigate for differences in the pre-clinic seizure frequency between ASM responders and non-responders. A Mann-Whitney U test showed that this difference was significant (U = 594, p = 0.012), where patients who experienced further seizures had significantly more seizures before first clinic review.

3.5. Response by aetiological association

Aetiological association	Started ASM, n (%)	Seizure free, n (%)	Side effects, n (%)
Stroke	30/36 (83.3)	28/36 (77.8)	5/30 (16.7)
Neurodegenerative	19/22 (86.4)	15/22 (68.2)	3/19 (15.8)
Undetermined	14/25 (56.0)	17/25 (68.0)	3/14 (21.4)
Brain tumour	9/9 (100.0)	6/9 (66.7)	5/9 (55.6)
SVD	5/9 (55.6)	5/9 (55.6)	1/5 (20.0)
TBI	7/7 (100.0)	4/7 (57.1)	4/7 (57.1)
Alcohol	4/7 (57.1)	6/7 (85.7)	0/4 (00.0)

Table 5 Outcomes across different aetiological associations

ASM = antiseizure medication; SVD = small vessel disease; TBI = traumatic brain injury.

Outcomes by aetiological association are described in Table 5. To understand whether outcomes significantly differed across aetiologies, we ran binomial logistic regressions using aetiological association as an independent variable and seizure freedom or suffering side effects as a dependent outcome variable. Aetiological association did not predict seizure freedom (χ^2_{df} =6.569$_7$, p = 0.475). Similarly, aetiological association did not predict whether a

patient suffered side effects from treatment (χ^2_{df} =11.346$_7$, p = 0.124). These remained non-significant when only the three most common aetiological associations were studied (stroke, neurodegenerative and undetermined).

3.6. Response to anti-seizure medications

86 out of 113 (76.1%) patients were started on an ASM. We identified the relative effectiveness of levetiracetam (mode total daily dose 1000mg) and lamotrigine (mode total daily dose 150mg), which were the two most commonly prescribed ASMs (Table 5). Levetiracetam was associated with greater seizure freedom rate than lamotrigine (35/44 [79.6%] vs 14/25 [56%]). We compared this difference using a chi-square test and it was statistically significant (χ^2_{df} = 4.294$_1$, p = 0.038). After defining the absolute percentage of patients who experienced side effects at initial or increased ASM dose, we ran a chi-squared test to compare side effect prevalence of levetiracetam vs lamotrigine. This difference was not significant (χ^2_{df} = 3.013$_1$, p = 0.083).

Drug	**Seizure freedom**	**Further seizure(s)**	**Side effects at start dose**	**Side effects at higher dose**
Levetiracetam (n = 44)	35 (79.5)	9 (20.5)	8 (18.2)	3 (6.8)
Lamotrigine (n = 25)	14 (56.0)	11 (44.0)	1 (4.0)	1 (4.0)

Table 6 Response to anti-seizure medications, n (%)
In addition to levetiracetam and lamotrigine, smaller numbers of patients were prescribed valproate (n=9), carbamazepine (n=4), phenytoin (n=2), lacosamide (n=1), and topiramate (n=1).

3.7. Age, frailty and outcomes

Next, we wanted to test the hypothesis that increasing age affects the odds of suffering side effects or experiencing seizure freedom. We therefore ran two binomial logistic regression models using age as an independent continuous variable and seizure freedom or medication side effects as dependent variables. These did not show a significant effect of age on the

likelihood of having further seizures (p = 0.515) or experiencing medication side effects (p = 0.987).

Finally, we repeated this analysis with frailty score as an independent variable. Increasing frailty did not affect likelihood of seizure recurrence (p = 0.176) or experiencing side effects from treatment (p = 0.135).

4. Discussion

4.1. Seizure presentation

The preponderance of focal seizures is consistent with previous reports [9, 16], and reflects the increased incidence of structural injury arising generally from vascular and neurodegenerative changes in the older demographic. However, 38% of patients presented with bilateral tonic-clonic seizures, of presumed focal onset. This figure is higher than expected and is likely due to sampling bias, since older people who have bilateral tonic-clonic seizures are more likely to present to healthcare professionals than those with focal seizures. Moreover, focal seizures are often unrecognised in older people due to atypical manifestations [17, 18], and may only be identified retrospectively following the advent of a first generalised motor seizure. In keeping with this suggestion, a recent survey of reported first seizures showed that a history of previous seizures was established in almost half of cases [19].

4.2. Seizure aetiology

In accordance with previous observations [8, 16] the commonest association with seizures was cerebrovascular disease. This highlights the need for identification and optimal treatment of vascular risk factors during middle and late life in order to potentially reduce the prevalence of epilepsy in older people. Targeting vascular risk factors is also likely to reduce the incidence of neurodegenerative conditions including dementia [20], which was a common identified seizure aetiology in our study. Alcohol was associated with almost 5% of new-onset seizures, comparable with previous descriptions [21, 22]. In our sample, these were related to

excessive alcohol intake as well as alcohol withdrawal (50% attributed to each). There is a well-established relationship between alcohol intake and seizure risk [23], as well as research suggesting that older patients are more likely to experience severe alcohol withdrawal symptoms than younger patients [24]. Our findings suggest that alcohol use should be accurately ascertained and mitigated in older people in order to decrease the prevalence of epilepsy.

In 22% of patients the cause of seizures was not determined, which is comparable to previous studies [8, 9, 25]. The absence of an aetiology has an impact on predicting seizure recurrence and its corollary, the decision to start treatment. It is possible that a proportion of the 'imaging-negative, undetermined aetiology' cohort may have undetectable SVD and/or early neurodegenerative change. However, in the appropriate clinical context, 'rarer' causes should also be considered including, paraneoplastic, autoimmune and 'systemic' aetiologies [8] as co-morbidities are common in this age group. Indeed, there is an emerging view of epilepsy as a systemic disorder with a preponderance of neurological features as opposed to a pure brain disorder. Within this conceptual framework, one may have to consider the role of broader age-related mechanisms, both neuronal and systemic, which may also be contributory.

We observed that 29.2% of patients who underwent EEG had epileptiform changes. This figure is similar to a previous study of 70 patients with new onset epilepsy after 60 years of age [26]. However, results directly changed management in only a small subset of patients who had EEG (8.3%). The use of EEG in this population should therefore be weighed up against its time and cost burden, particularly in more resource-poor settings. MR imaging is the gold standard for investigating the cause of seizures, particularly to delineate subtle abnormalities and evaluate vascular burden. However, in our study, the severity of SVD or atrophy did not predict likelihood of having further seizures and may therefore not help differentiate which patients would benefit from an ASM.

4.3. Response to treatment

In keeping with previous descriptions, this study suggests that levetiracetam is effective in older people [8, 9, 27]. We did not observe that aetiological association predicted seizure freedom rates, which may reflect our relatively small sample size. 78% of patients with post-stroke seizure remained seizure free. Seizure recurrence post-stroke varies by stroke subtype [28]. Accordingly, this low rate of post-stroke seizure recurrence may reflect the preponderance of ischaemic versus haemorrhagic stroke in our cohort.

We also observed that increasing age and frailty did not significantly predict the prevalence of side effects across an older population. This suggests that newer ASMs such as lamotrigine and levetiracetam may be well tolerated even in very old, frail patients. This is an important finding, since many older people with epilepsy suffer impaired quality of life due to concerns about the implications of taking ASMs [11]. We did not find any significant differences in tolerability between ASMs. This is in keeping with a previous meta-analysis of randomized clinical trials which did not show a significant difference in the likelihood of discontinuing lamotrigine compared with levetiracetam [6].

4.4. Prognosis

Knowledge of long-term outcomes following a first seizure in older people is vital for counselling patients on future ideas, concerns and expectations about new-onset epilepsy. We found that prognosis was favourable in the vast majority of patients during the follow-up period, with 71% of patients having no further seizures in our follow-up period. This figure is similar to a previous study which described 81% of patients experiencing a reduction in seizures by two years follow-up [22]. This may reflect use of newer ASMs with better tolerability and therefore improved compliance, but also raises the possibility that older people are more responsive to treatment. This underscores the importance of early diagnosis and treatment initiation in appropriate cases.

4.5. Limitations

This study is strengthened by combining clinical characteristics, including objective measures of frailty and comorbidity, detailed neuroimaging results, and response to ASMs in a single

cohort. Calculation of frailty scores was limited by being determined retrospectively from electronic records. Whilst relevant information was available for most patients, such as mobility status and the presence of formal care, documenting frailty score at the time of assessment in first seizure clinic would have been more robust. We did not collect information about self-reported quality of life, which would help guide choice of ASM. In addition, this study is observational and was not powered to directly compare different ASMs as has previously been achieved in randomized controlled settings [29]. The minimum follow-up time was one year; a longer period of study would have strengthened observations on clinical course and response to treatment and should be the focus of future research. We also assigned 8% of first seizures to SVD. However, ascribing a seizure to SVD can be difficult due to its non-specific presenting features and high neuroimaging prevalence in late onset epilepsy cohorts. Finally, 7% of cases did not have MRI due to patient contraindication, logistical reasons, and clinical judgement. MRI remains the gold standard for ascertaining aetiology.

5. Conclusion

Our data suggest that increasing age and frailty do not affect response to ASMs in older people. Future studies should focus on elucidating seizure aetiology in the 'cryptogenic' cohort of older people, which continue to represent a substantial minority across studies [8, 9]. Finally, the interface of ageing and epilepsy is emerging as an important area of research [10, 30], especially at the intersection of vascular and neurodegenerative disease. A deeper understanding of the mechanisms could inform the development of more specific prevention and treatment of epilepsy in older people. From a clinical perspective, we hope our data will allow for more patient-centred and evidence-based care for older people with new-onset seizures, a demographic which presents both unique and complex clinical questions.

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