Epilepsy and the elderly

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Summary:

As populations age globally there will be challenges and opportunities to deliver optimal healthcare to senior citizens. Epilepsy, a condition characterised by spontaneous recurrent seizures, is common in older adults and yet has received comparatively little attention in this age group. Here, we evaluate the underlying aetiologies of epilepsy in older people; explore difficulties in establishing a diagnosis of epilepsy in this group; discuss appropriate anti-seizure medications for the elderly and evaluate potential surgical treatment options. Cognitive, psychological and psychosocial comorbidities as well as the impact that epilepsy may have on an older person's broader social/care network in resource-rich and low to middle resource countries are considered. We emphasise the need for clinical trials to be more inclusive of older people with epilepsy to help inform therapeutic decision-making and discuss whether measures to improve vascular risk factors might be an important strategy to reduce the probability of developing epilepsy.

Introduction:

Epilepsy is the third most common neurological disorder in the elderly, after stroke and dementia – conditions which themselves increase the risk of seizures.[1] Given the shift in demographics towards an ageing population, the number of older adults who develop epilepsy is set to rise substantially across the world and in mature economies the incidence of epilepsy is already highest in those over 65.[2] People who developed epilepsy at a young age are also living longer. These factors imply that the prevalence of epilepsy among older people will escalate significantly in high, as well as in low and middle resource, countries.[3]

People with epilepsy have a high incidence of comorbidity,[4,5] which is even greater in the older population. New developments in Alzheimer's disease (AD) and late-onset epilepsy suggest there might be common pathological links mediated by vascular changes[6,7] or tau pathology[8–11], or both. There is also emerging evidence for common widespread brain network changes in epilepsy and dementia.[12–14] Might treatments for epilepsy therefore improve cognition in people with dementia. Would aggressive targeting of vascular risk factors, which impact on the integrity of brain networks, help prevent seizures or, potentially, cognitive decline in older people with epilepsy? Here, we seek to tackle these and other emerging areas of epilepsy and seizures in geriatric practice. We also provide suggestions for optimal care for older people with epilepsy that we hope will shape best practice for general physicians and specialists worldwide.

Epidemiology of epilepsy in the elderly

Those over the age of 65 years represent the fastest growing segment of the population in most regions of the world. It is estimated that the population of individuals over the age of 65 in the US alone will increase from 43.1 million in 2012 to 83.7 million by 2050[15] and similarly there will be increasing numbers of the very old (>age of 90 years). Despite this, there are currently no agreed definitions of 'epilepsy in the elderly', leading to the use of varied age thresholds between studies ranging anywhere from 50 to 70 years old. Machine learning, applied to a prospective cohort database to examine various attributes associated with elderly onset epilepsy, recently identified a threshold of 65-70 years as likely to be the most optimal to define elderly onset epilepsy[16], though further work is required to confirm these findings.

Incidence and prevalence of epilepsy in the elderly

Even though a standardised definition of epilepsy in the elderly is lacking, studies have consistently shown that the incidence of epilepsy is highest in the youngest and oldest age groups, increasing steadily after age 50 years,[17] with the greatest incidence occurring in persons aged ≥75 as shown in Figure 1.[17,18] This bimodal peak was also clearly shown in the 2016 Global Burden of Disease (GBD) report on epilepsy and figures, once age-standardised, show a similar picture in high and low resource countries[19]. In the Cardiovascular Health Study, the prevalence and incidence of epilepsy was measured in a cohort of almost 6,000, mostly white, older people.[20] An incidence rate of around 2.5 per 1,000 person-years was observed.[20] At the latest follow-up, the prevalence of epilepsy was 5.7/1,000, much higher than what is typically reported for the overall lifetime prevalence of active epilepsy of around 0.76/1,000 in all age groups.[20,21] Similarly, a prevalence of epilepsy of 5.4/1,000 in older populations was quoted in the GBD report. [19] As might be expected, the prevalence of epilepsy is even higher in nursing home residents, with a point prevalence of over 7.5% reported in some studies.[22] There have also been administrative database studies, for example, using Medicare data, reporting incidence by race, sex and age.[23,24] These confirm not only that the prevalence, but also the incidence of epilepsy, increases with age (Figure 2), and this is highest in African Americans and lower in Asians and Native Americans compared to whites. The reasons for these differences are uncertain. It is possible that the methodology applied led to some prevalent cases being misclassified as incident cases.[24]

Aetiology and risk factors associated with epilepsy and seizures in the elderly

As in younger people, there are numerous potential causes for new onset seizures in older adults.[25] Acute symptomatic seizures, defined as those presenting in close temporal association with a brain insult can occur, within one week of a stroke or in association with metabolic disturbance.[26] Such physiological disturbances are common in older people. For example, several medications commonly prescribed to older people are associated with hyponatraemia (e.g., anti-hypertensives; diuretics; anti-depressants) which increases the risk of seizures if sodium levels fall below 125mmol/l. Older individuals might also contract meningitis, use alcohol excessively, abuse recreational drugs and experience traumatic brain injury – which are all associated with acute symptomatic seizures and predispose to subsequent development of epilepsy. [25] Older adults are also more likely to develop epilepsy as result of brain tumours than younger adults. [27]

New onset genetic generalised epilepsy is much less common in the elderly although occasionally circumstances uncover a potentially lifelong tendency to generalised genetic epilepsy (see Case 1, supplementary materials). With increases in life expectancy, individuals with a history of a genetic generalised epilepsy, which may have long been in remission, may also present in old age with a relapse of their epilepsy. People who had severe, potentially genetically mediated epilepsy earlier in life, including

people with epileptic encephalopathies, are now more likely to live into older age. Epilepsy is also relatively common in people with dementia, including those with familial Alzheimer's disease[28,29], raising questions over what constitutes an 'epilepsy gene'. It may also occur in the context of tumors[30] or autoimmune diseases (see below).

The most common aetiology of seizures and epilepsy in senior citizens, however, is cerebrovascular disease, accounting for up to a third of cases[29–31] (Figure 3). A population-based US Veterans Administration study showed a clear association between epilepsy and stroke, as well as with dementia, brain tumour, traumatic brain injury and other central nervous system conditions.[32] Similarly a recent large population-based study reported that cerebrovascular diseases alone increased the risk of seizures during the initial year post stroke up to 23 times compared to the general population.[33] Factors associated with epilepsy in the older adults include older age; race (HR for blacks compared to white 4.04; 95% CI 1.99-8.17) and a history of stroke (HR = 3.49, 95% CI 1.37-8.88).[20] Intriguingly, in this context, statin prescription, older age (>85) and hypercholesterolemia were associated with lower odds of developing epilepsy.[32]

The possible associations between late-onset epilepsy and midlife risk factors were recently assessed in the Atherosclerosis Risk in Communities Study, in which over 10,000 participants were followed for more than a decade.[34] Overall, the incidence of new-onset epilepsy was 3.33 per 1,000 person-years, with those who were black having a higher occurrence compared to white participants.[34] Factors associated with late-onset epilepsy in the multivariable analysis included hypertension, diabetes, apoliprotein E ε4 genotype, incidence stroke and incidence dementia. Conversely, the risk of epilepsy was lower in those with higher levels of physical activity and moderate alcohol consumption (Figure 4).[34] This raises the interesting possibility that epileptogenesis itself could be modified through a holistic approach to reduce the impact of vascular risk factors.

Diagnosis of epilepsy in older people

While it is agreed that the incidence and prevalence of epilepsy is highest in senior citizens, these figures might still be an underestimate. As in younger people, the diagnosis of epilepsy is a clinical decision, but in older individuals it can be even more challenging to make.[35] Most epileptic seizures in this age group are focal in origin but often do not conform to the 'typical' presentation of focal seizures.[36] In younger people there is a preponderance of temporal lobe seizures, but in the elderly, the majority of seizures are of extra-temporal onset, tend to be very diverse in semiology and convulsive seizures are relatively rare. [35,36] The atypical presentation of seizures and lack of awareness that an unusual episodic event in an older individual might be ictal in origin might also play a role in missed or delayed diagnoses. Additionally, particularly in high resource

economies, many older people live alone, so eyewitness accounts are often lacking or unreliable which may further compound the problem.[37]

The most common differential diagnoses of a potential seizure in the older person include conditions which cause episodes of impairment of consciousness or alterations of mental state; unexplained falls and transient confusion.[35] Differentiating syncope, fluctuating cognitive impairment, migrainous events, delirium or impairment of cerebral circulation from seizures can be difficult. Paroxysmal confusion or episodes of behavioural arrest in an older adult, should, however, always lead to a suspicion of seizures. Likewise, non-convulsive status epilepticus, a condition that can associate with high morbidity and mortality in older adults, should be suspected in an those who present with confusion, fluctuating levels of awareness and behavioural changes. [38] In such cases an EEG recording could be diagnostic. Persistent headache or disorientation after an episode of impairment of consciousness is suggestive of a seizure as are events being stereotypical in characteristics. Recurrent focal seizures are often misdiagnosed as transient cerebral ischaemia particularly if the stereotypical nature of the epileptic symptoms is not recognised.

Multi-comorbidity [39] and polypharmacy [40] is the norm in this age group and these present further diagnostic challenges. Disorders which predispose to syncope, such as carotid sinus hypersensitivity micturition syncope, and postural hypotension, are common in the elderly. Focal jerking, termed limb shaking transient ischaemic attacks, may sometimes occur in severe carotid stenosis.[41,42] The aging brain may also be more sensitive to a number of insults. Cardiac arrhythmias can present with seizures in this age group and conversely seizures may present with autonomic disturbance and cardiac dysrhythmia. Similarly, epilepsia partialis continua may be confused with an involuntary movement disorder,[43] and the rare paroxysmal sensory epilepsy is often labelled as recurrent transient cerebral ischaemia.[44] Further complexity can arise owing to post-seizure phenomenon. Post-ictal states in the senior citizen may be prolonged. Post-ictal paresis (Todd's paresis) can persist for days and is often misinterpreted as a new stroke. [44] Similarly post-ictal confusion with disorientation, hyperactivity, wandering and incontinence may also continue for up to one week, occasionally longer.[44] It should also be recognised that dissociative seizures may similarly present de novo in later life, although 'non-epileptic' attacks are more likely to have a physiological than a psychological basis in older people. [45]

Investigation of suspected seizures in older people

Thorough investigation of potential seizures in the elderly is often required, particularly if witness descriptions are lacking. Basic blood work (full blood count, urea, creatinine, electrolytes, liver function tests, glucose) is perhaps more indicated than in the healthy young person. At the time of acute presentation, consideration should be given to CT brain imaging (alternatively MRI brain if available) and cerebrospinal

fluid analysis in appropriate cases (for example those in whom an infective, haemorrhagic, malignant or inflammatory cause is suspected). [46] Older people with 'explosive' onset epilepsy (sudden emergence of very frequent seizures, up to several times per day, with no background history of a seizure disorder), particularly if associated with significant cognitive and psychological comorbidity, should be screened for auto-antibodies, particularly leucine-rich glioma inactivated 1 (LGI1); contactin associated protein like 2 (CASPR2); and paraneoplastic antibodies, in serum and cerebrospinal fluid.

In the outpatient setting, MRI brain is important to further exclude tumours and other lesional pathology. In resource limited settings, CT brain imaging with contrast offers a pragmatic alternative. To determine if paroxysmal events may or may not be seizures, prolonged EEG and ECG recording in the hope of capturing an episode can be diagnostic and, in addition to clinical acumen, is perhaps the most helpful tool to securing a diagnosis.[35] For a multitude of reasons, though, EEG, and especially prolonged monitoring, may be difficult to conduct. Reviewing video clips of events may also be helpful. Carers, partners, family member or others directly involved with the person, should, within the limits of safety, attempt to record events. Such an approach is increasingly applicable in low income societies where mobile phone usage is high[47] and smart-phones are becoming increasingly commonplace. Diagnostic uncertainty may, though, persist in a considerable proportion of senior citizens despite multiple and repeated investigations.[48]

Management of seizures in the older population

The mainstay of management for older people with epilepsy remains medication and a list of commonly available anti-seizure medications (ASMs) is listed in Table 1, highlighting specific considerations as applied to the older population. [25,49,50] Overall, older people are more likely to benefit from ASMs in term of seizures freedom as they are less likely to have drug resistant epilepsy than younger people. [27] For all medications, it is recommended that the initial dose and titration rate in the older population be half that used in younger adults to minimise potential side effects. The treatment dose required may also be half that for those under the age of 65 years.

It has been argued that even a single unprovoked seizure in people over the age of 65 might warrant initiation of an ASM owing to the enduring propensity of the likely underlying pathology (stroke, dementia) to generate further seizures.[35] This would seem reasonable, particularly as the potential risk from seizures in the elderly can be greater. For example, older people may be more prone to fractures or to bruising and haemorrhage, especially if anticoagulated. The relative social isolation often occurring in older life means that seizures may be unwitnessed and thereby associate with a higher possibility of sudden unexpected death in epilepsy (SUDEP; see below). The choice of an appropriate ASM in the elderly is, however, much more limited than for younger people predominantly owing to potential side effects and interactions with concomitantly taken

medication. For example, older ASMs such as carbamazepine and phenytoin, should be avoided owing to their more severe impact on bone health, lipid metabolism and balance as well as their propensity to enzyme induction (Table 1).

ASMs can adversely impact the cognitive profile of older people with epilepsy. It has been reported that older people taking ASM polytherapy had, on average, more cognitive deficits than those on monotherapy; while those on monotherapy performed similarly to people with mild cognitive impairment (a likely precursor of dementia).[51] Multiple regression analyses have also shown that polytherapy contributed significantly to cognitive impairment; whereas age, education, duration of epilepsy, age at epilepsy onset, seizure frequency and aetiology did not.[52] ASM polytherapy might exacerbate cognitive deficits, but, to date, it is not clearly delineated whether this is due to ASMs themselves or the epilepsy. People with more resistant epilepsy are those most likely to be taking more medications to control seizures and older people may also be more susceptible to the neurotoxicity of certain drugs.[53]

A recent systematic review and meta-analysis was published evaluating the medical treatment of epilepsy in older adults (Lezaic et al, 2019). Eighteen studies were included, evaluating 12 ASMs. Lamotrigine was reported to be better tolerated than carbamazepine. Lamotrigine has a favourable cognitive profile in older individuals suffering from age-associated memory impairment and offers a possible mood-stabilising effect.[57,64] On the other hand the systematic review found that lamotrigine was associated with a lower probability of seizure freedom compared to levetiracetam and with similar tolerability. Levetiracetam and carbamazepine were equally efficacious and tolerated (Lezaic et al, 2019). Levetiracetam seems to be a favourable drug given its pharmacological profile with rapid and complete oral absorption, linear pharmacokinetics and low potential for clinically significant drug interactions.[62] However, levetiracetam can be associated with difficulty concentrating, drowsiness, depression and altered behaviour such as agitation and irritability.[61,63] Single studies demonstrated that brivaracetam, gabapentin, lacosamide, perampanel and topiramate may be efficacious and/or tolerated. More recent data also suggest that eslicarbazepine and zonisamide may be of value in the older person with epilepsy. [49,50])

More trials are needed to compared newer ASMs to older ones. Future trials should aim to include, rather than actively exclude, people over the age of 65. Similarly, the magnitude of risk of a second event in an older person who has had a seizure needs clarification. For example, what burden of small vessel disease on MRI or what degree of focal slowing on an EEG might indicate that an ASM is warranted? Notably, in all people with epilepsy in whom vascular changes are detected on brain imaging, modification of vascular risk factors should be advocated.[66]

Epilepsy surgery in the elderly

It is now recognised that epilepsy surgery is better than medical management in appropriately selected people with drug resistant epilepsy – defined as people whose seizures have not been controlled with adequate trials of two or more ASMs.[67–69] In optimal candidates, surgery not only improves seizure outcomes, but is also associated with a decrease in healthcare costs.[70] Older people with drug-resistant epilepsy are less likely to undergo surgery which may reflect individual choice, physician choice or both.[71]

Data relating to epilepsy surgery in the older population are limited. Only a few studies have focused on those aged 60 years or older, or stratified the results such that outcomes could be examined in older age groups.[72–76] The results and conclusions appear dichotomous. For example, in earlier studies, surgery in older people was associated with reduced likelihood of seizure freedom and increased rate of complications.[77,78] Other centres have, however, reported similar rates of post-operative seizure control and complications in people over 50 versus their younger counterparts[79], with one study reporting good results in people over 70 years who underwent anterior temporal lobectomy albeit in small numbers.[75] Notwithstanding that there might be bias towards publication of positive results, overall, studies demonstrate that resective epilepsy surgery can be effective and usually safe in carefully selected older individuals with rates of seizure freedom ranging between 57% to 80%.[72–76]

As in younger people, potential post-operative risks to cognition also exist. In one study, when older people aged 50-69 (*N*=55) were compared to individuals aged less than 50, seizure freedom rates at one year were reported to be similar.[80] However, the rate of post-operative cognitive impairment was substantially higher in the older group, particularly those undergoing left temporal lobectomy.[80] Older people undergoing epilepsy surgery had lower pre-operative memory performance than younger surgical candidates. Any reduction in cognitive function in individuals with poor cognitive reserve could precipitate significant difficulties in daily life. By contrast, other centres reported no differences in post-operative cognitive outcomes, specifically memory decline[77,81] and it may be that the underlying pathology is important. For example, when people with hippocampal sclerosis were examined at a single centre, operated on by the same surgeon utilising the same operative technique, no difference in post-resection outcome in terms of either seizure control or cognitive impairment was found between people older than 50 (*N*=21) compared to those under 50 (*N*=109).[82]

A single study analysed seizure outcome after vagal nerve stimulation (VNS) in older adults and found that the outcomes were similar to those in younger people[83] while another recent publication assessed the benefits of laser interstitial therapy compared to anterior mesial temporal resection, finding it to be equally effective and without higher complication rates in those 50 years and older.[84] Laser hippocampectomy may offer further promise in older cohorts owing to the lower morbidity in the immediate post-operative period

and the shorter post-operative hospital stay.[85] Similarly, neuromodulation approaches (e.g. responsive neurostimulation, deep brain stimulation) should also likely be better tolerated than resective surgery in older populations. It is apparent that more high-quality studies are needed to understand epilepsy surgery outcomes in the elderly and to inform appropriate referrals for epilepsy surgery in this group. As the population ages, distinctions will need to be made between biological and chronological age when determining appropriateness for, and evaluating the risk of, epilepsy surgical interventions.

Specific epilepsy syndromes in the elderly

It is now recognized that some epilepsy syndromes are more frequent in older individuals.

1. Dementia-associated epilepsy

Dementia of all types, but especially Alzheimer's disease (AD), is a common cause of seizures in older age.[86] The period prevalence of epilepsy in persons with dementia is ~5% while the prevalence of dementia in epilepsy ranges from 8.1 to 17.5%.[87] People with familial early onset AD may have an 87 fold increase in the risk of seizures compared to age matched controls[28]. Cognitively asymptomatic individuals who harbour pathogenic autosomal dominant AD mutations[88] are also more likely to have seizures. In people over 65, those with AD are up to ten times more likely to have seizures than those without dementia.[89,90] In fronto-temporal dementia, 2.2% of patients are reported to have seizures[91] while people with vascular dementia might have similar risk to AD.[92] Recent work using prolonged or invasive monitoring reveals that people with dementia are also likely having subclinical or even clinical seizures that are not being detected.[93–95]

Until around 10 years ago, it was perhaps thought that seizures were likely epiphenomena, simply a consequence of neuronal loss in degenerating hippocampi. It now seems, however, that epilepsy itself might contribute to the pathogenesis of dementia itself.[13,96] The exact mechanisms through which this occurs remain uncertain, but several molecular commonalities exist between the cascades that are important in synaptic function and those implicated in neurodegeneration.[9,97–99] This bidirectional link between AD and epilepsy is of increasing interest as it offers exciting new therapeutic opportunities. Reduction of tau in an animal model of Dravet syndrome (a severe epileptic encephalopathy) ameliorates seizures[100] while, perhaps more immediately applicable to clinical practice, treatment of transgenic murine models of AD with the ASM levetiracetam helps restore cognitive function.[99] Open questions remain: namely how aggressively to investigate the possible presence of subclinical seizures and interictal epileptiform discharges in older people, and how to assess the long-term impact of increasing ASM dose on cognition if such phenomena are identified. Similarly, studies are now recruiting people with AD that have not experienced seizures to determine if ASMs might actually improve cognition and, possibly, prevent the development of epilepsy (for

example: the Investigation of Levetiracetam in Alzheimer's Disease (ILiAD study; clincaltrials.gov identifier NCT03489044) and Levetiracetam for Alzheimer's disease associated network hyperexcitability (LEV-AD; clinicaltrials.gov identifier NTC02002819)).

2. Transient epileptic amnesia

Transient epileptic amnesia is an episode of amnesia, associated with a seizure that frequently lasts less than an hour. It appears to have specific characteristics including events being more frequent on awakening, repetitive questioning and a residual incomplete amnesia of the event itself ("able to remember not being able to remember").[101] Around 40% of people with transient epileptic amnesia have olfactory hallucinations. The condition is most easily distinguished from transient global amnesia owing to the recurrent nature of stereotypical events. Transient epileptic amnesia is predominantly observed in people, men more than women, over the age of 65. Overt seizures in this condition are often responsive to medication, being controlled by low doses of first line ASMs. As well as the ictal amnesia, however, individuals are also affected by interictal memory difficulties, notably loss of autobiographical memory and accelerated long term forgetting.[102] Long term follow up does not, though, indicate a risk of supervening dementia.[102]

3. Antibody-mediated epilepsy

Autoimmune conditions, such as systemic lupus erythematosus are known to associate with epilepsy but the concept of antibodies contributing directly to seizure generation is recent.[103] It has now been accepted that specific antibodies, particularly neuronal surface antibodies, may be causal to seizures.[104] The main antibodies implicated are against the neuronal surface antigens leucine-rich glioma inactivated 1 (LGI1); contactin associated protein like 2 (CASPR2); N-methyl-D-Aspartate receptors (NMDAr), alpha-amino-3-hydroxy-5-methly-4-isoxazolepropioninic receptors (AMPAr); gamma aminobutyric A/B receptors (GABA-A/Br); glycine receptors as well as antibodies against intracellular glutamic acid decarboxylase.[105,106] Of these, anti-GABA-Br, anti AMPAr and especially anti LGI1/CASPR 2 antibodies tend to be seen in middle aged to older adults.[106]

The clinical manifestations associated with antibody-mediated disease are becoming progressively more pleomorphic, although people with autoimmune epilepsy tend to present with a combination of seizures coupled with cognitive and behavioural change.[105] Certain well-defined phenotypic features have also emerged. Anti-LGI1 antibodies can associate with characteristic facio-brachio-dystonic seizures (FBDS; see video for example of seizure type; supplementary material)[107] while delayed onset dyskinesias are seen in anti-NMDAr syndromes[108] and myoclonus in anti-glycine receptor antibody disease.[109] People who develop, for example, anti-LGI1/CASPR2 antibodies tend to have a specific underlying HLA type[110] and an 'initial precipitating injury' may then trigger a cascade leading to an autoimmune encephalitis. These neuronal

surface antibody conditions do not always associate with malignancy, but, especially in older people, detailed investigation to determine if there is a neoplasm is mandatory.

One of the reasons that autoimmune epilepsies have attracted such attention is that they are poorly responsive to conventional ASMs and instead should be treated with immunosuppression.[105] The earlier the immunosuppressive agents are administered, the better the likely outcome. For example, if FBDS are recognised early then immunosuppression can prevent development of the autoimmune encephalitis and subsequent cognitive decline that typically associates with anti-LGI1 autoimmune epilepsy.[107,111] Treatment should also include removal and appropriate adjunctive therapy of any associated tumour.

4. Status epilepticus and SUDEP in the elderly

In the Greater Richmond Metropolitan Area study, people older than 60 years had an incidence of status epilepticus (SE) of 86/100,000, higher than in any other age groups, except for those <1 year old. [112] The higher incidence of SE in the elderly compared to younger adults has been confirmed in several studies including in prospective studies in Italy, Germany and in the US with estimates being up to 5 times higher in the elderly compared to young adults.[112,113] Not only is the incidence of SE high in the elderly, associated mortality increases with age, with the highest mortality occurring in those 85 years and older.[112,114] In one study, age was the only independent predictor of death after adjustment.[29] SUDEP is another important cause of mortality in those with epilepsy, and was recently found to have been underestimated in the elderly, regardless of sex.[115] This would support ensuring that older people with epilepsy are informed about the potential risks of epilepsy including SUDEP and underscores that epilepsy in the elderly cannot be considered benign.

Comorbidities in older persons with epilepsy

There is a complex interplay between comorbidities in older people with epilepsy owing to the underlying substrate for the epilepsy, polypharmacy and social situation. Cognitive and psychological difficulties that can associate with epilepsy across the lifespan also play a role (Figure 4)

Cognitive function in older people with epilepsy

People with epilepsy are prone to cognitive and psychological comorbidity as well as psychosocial difficulties. All three of these aspects are exacerbated in older individuals with epilepsy. Remarkably, though, there is only one detailed report on cognitive function in people who first develop epilepsy aged >65.[116] This study examined over 250 older people (mean age: 71.5 years) with new-onset focal epilepsy *before* initiation of an

ASM. Cognition was assessed using measures of only executive function.[117] Just over a third of cases had suffered a cerebral infarct while another third had cerebrovascular disease. More than 80% had focal seizures with impaired awareness and just over half suffered bilateral tonic-clonic seizures. A key finding was that almost half had markedly impaired executive function, even before initiation of ASMs.[116] A possible mechanistic explanation comes from data that showed people with late onset epilepsy without a clear cause were more likely to have abnormal $A\beta_{1-42}$ in their cerebrospinal fluid and progression to AD dementia compared with healthy controls.[118] These results underline the importance of cognitive screening at baseline so that any subsequent assessments can be evaluated in context to determine whether there has been any true decline in cognitive function, or whether ASM treatment has made any impact (Case 2).

There are some investigations that have examined cognitive function in older people with epilepsy who first developed seizures when they were younger than 65.[51,52,119–121] Most of these reports are cross-sectional in nature, with small sample sizes (details in [66]). Taken together, however, these studies show impairments across cognitive domains in this population compared to healthy older people, particularly with respect to attention, visual and verbal short and long-term memory, executive functions and processing speed (reviewed in [66]). Several investigations also report that there can be *progression* of cognitive deficits over time in epilepsy but, again, most of these studies are in people younger than 65 (reviewed in [122,123]). One study followed older individuals (mean age: 64 years) for 2-3 years.[120] Overall cognitive deficits did not worsen over this period in this small sample, but performance remained below that of matched healthy older adults. Two areas of cognitive function, however, did show significant decline: memory and executive function.

Whether any progression of cognitive deficits in people with epilepsy, regardless of age, represents *accelerated aging* over time [122,124] has been the subject of considerable debate.[125,126] Some argue that this might occur because of chronic accrual of pathology leading to epilepsy (e.g., vascular), the effects of epilepsy itself (overt seizures or, sub-clinical, abnormal cortical activity) or both.[122] Others propose instead that an initial insult to the brain, e.g. stroke or traumatic brain injury, leads to cognitive function simply running below and parallel to the expected normal trajectory of cognitive change with aging.[127] As these individuals start from a lower point, they reach thresholds for significant cognitive and functional impairment – dementia – far earlier than those without seizures. Still others have argued that while an initial insult such as a stroke might be a 'first hit', subsequent development of epilepsy is effectively a 'second hit', leading to even further deviation from normal cognitive decline with aging (Figure 5).[125]

Overall, therefore, people with epilepsy aged 50-75 appear to have a higher risk of being diagnosed with dementia over the subsequent 8 years.[128] Conversely, those with AD and vascular dementia are also more

likely to develop epilepsy as has been demonstrated in UK and Chinese populations.[82,129–131] These findings suggest bidirectional relationship between epilepsy and dementia, such that epilepsy and associated risk factors increase the risk of dementia, and dementia concurrently increases the risk of epilepsy.[121] As such it can be argued that epilepsy might best be considered a symptom rather than a condition[121]. In other words, epilepsy is simply one manifestation of the underlying pathological process that might contribute to seizures, cognitive decline, psychological problems, systemic illness and, perhaps indirectly, psychosocial difficulties.[4,122]

Two important candidate pathologies in older individuals with epilepsy have been implicated in dementia: small vessel cerebrovascular disease and tau or amyloid deposition, both of which impact on large-scale brain networks that subserve cognition (reviewed in [66]). Several sets of findings point to potential convergence of mechanisms such that these pathologies increase the risk of epilepsy, and, in turn, epilepsy itself increases the risk of developing these pathologies. For example, some investigators have reported that cognitive decline may start several years earlier in people with MCI and AD who develop seizures compared to those who do not.[83,123,124] At post mortem, there is a higher incidence of cerebrovascular disease in older individuals with chronic epilepsy, with a significant correlation between cerebrovascular disease and prevalence of AD pathology[125] while immunohistochemical analysis of tissue from older people with epilepsy secondary to focal cortical dysplasia has demonstrated aggregation of tau, similar to that in AD.[9] It remains to be established, however, whether these effects are due simply to epilepsy and dementia sharing common predispositions (e.g. cardiovascular) or whether there is a true bidirectional relationship between them and, in either event, whether the processes underpinning epileptogenesis can be modified through of vascular risk factors.

Psychiatric comorbidity in the elderly with epilepsy

Studies of psychiatric comorbidities in the elderly are scarce. A US-wide population-based study reported that pre-existing psychiatric conditions, including substance abuse, psychosis, bipolar disorder, schizophrenia and depression, associate with new-onset epilepsy. [137] Likewise, the Treatment in Geriatric Epilepsy Research (TIGER) study of over 800,000 veterans over age 66 reported a three-fold increase in odds of psychiatric admissions in those with new-onset epilepsy. Alcohol dependence was the strongest factor associated with psychiatric admissions in the first year after epilepsy onset. [138] Furthermore, while only 1% of Veterans without epilepsy had a psychiatric hospitalization during the study period, 6% of those with epilepsy required admission. [138] In the prospective longitudinal Einstein Aging Study, 18% of elderly with epilepsy had depression compared to none of the controls. [139] Anxiety scores were also higher. [139] More recently, a prospective Brazilian study of older people admitted with new seizures found that psychiatric disorders,

sepsis and cardiac arrhythmias were associated with higher odds of early seizure recurrence. [140] Perhaps most intriguingly, however, a Canadian case-control study showed that older people with epilepsy had 2.9 times the odds of having a psychiatric comorbidity compared to younger counterparts. [27] These reports demonstrate that psychiatric comorbidity is common in older people with epilepsy and can associate with poor outcomes. As such psychological aspects warrant specific attention in this population, in terms of evaluation and treatment.

Systemic comorbidity in the older person with epilepsy

People with epilepsy are more likely to have additional systemic comorbidities[4] and this is exaggerated in older people who, whether they have seizures or not, are more prone to multi-modal health difficulties.[39] As illustrated not only might these comorbidities predispose to epilepsy, they also compound treatment options. In particular older enzyme inducing medications (for example carbamazepine and phenytoin) can prove problematic owing to drug-drug interactions, a propensity to affect sodium and lipid metabolism[126] and their effect on balance (Table 1). Drug-induced balance difficulties can increase falls which, especially in the elderly, may associate with fractures and hospital admission. Most ASMs can have an adverse impact on bone health (see Table 1). It has been proposed that all people with epilepsy should be maintained on vitamin D supplementation[127]; this is perhaps even more indicated in older people with epilepsy who may additionally benefit from regular bone densitometry scans.

Psychosocial impact of epilepsy in the elderly

Studies on the psychosocial impact of epilepsy in the elderly are again limited and have focused mostly on quality-of-life (QOL) and stigma. Existing epilepsy-related QOL measures were, however, exclusively developed or validated in those younger than 65, which is, again, a major gap in research. Nonetheless, one of the first studies on QOL in the elderly compared outcomes in women older than 60 and men older than 65 years with younger subjects, stratifying by whether the epilepsy was diagnosed before or after the above respective age cut-off. In general, the older and younger age groups did not appear to differ significantly with respect to QOL, but the younger age group reported more stigmatisation.[128] Other reports have provided different perspectives. One multicentre study compared older people with late onset epilepsy to older people whose epilepsy had started earlier in life and to younger people with epilepsy. The results showed that younger people had better QOL while older people who had chronic epilepsy were most likely to fear stigmatisation.[129] New onset epilepsy in the elderly has also been shown to associate with poorer physical and mental health in the past year.[130]

To explore stigmatisation in older people further, one study interviewed over 50 elderly with epilepsy and found that more than 70% of them had felt some form of stigma, less commonly enacted stigma (8.7%).[131] The findings were concerning, with participants describing that their family members were distancing themselves from them due to their epilepsy; that they were no longer accepted by their family or that they were refused admission into, for example, a public gym facility due to their history of epilepsy[131]. By corollary, the impact of epilepsy in older people can also be profound on families and caregivers. A UK-based study that evaluated the impact of epilepsy on heterosexual marriage in a predominantly older, Caucasian population, reported that onset of epilepsy within marriage correlated to increased perceived stigmatisation and low mood.[147] There were also significant differences in the approach to the person with epilepsy depending on whether the spouse was male or female.[147]

In exploring the causes of adverse psychosocial outcome, an early investigation of older people with epilepsy found that not being able to drive was the most frequently cited concern (affecting 64% of the sample) and the greatest concern for over a third of respondents. [148] A similar adverse impact of not being able to drive, was also shown in a recent study with the impact on males being significantly greater than on females. [147] Driving remains the main means of transport for the elderly and 68% of UK households with one person over the age of 70 have a car. [149] Not being able to drive can therefore be very limiting, potentially compounded by frailty and difficulties in using, or inaccessibility of, public transport.

Not all older people with epilepsy feel stigmatised. Some describe positive outcomes as a result of their new epilepsy diagnosis and, unsurprisingly, psychosocial outcomes and lived experiences can vary substantially between elders with epilepsy. [146] More studies are needed to help us understand factors associated with psychosocial outcomes in this growing population of individuals with epilepsy and what the best interventions are to improve these outcomes. They will need to be specifically tailored, be different for those who have recently been diagnosed with epilepsy compared to people with chronic seizures and will need to be gender and culturally appropriate. In resource-poor settings where stigmatisation of epilepsy can be marked, thoughtful handling of older people who develop epilepsy may help to disentangle epilepsy for entire communities since, in these societies, it is often elders who have most influence.

Strategic healthcare implications

With the incidence of epilepsy being highest in the elderly and the global population aging, older people with epilepsy will present a significant burden on all healthcare and social care systems due to admission to hospitals with seizures or resulting injuries; need for long-term medication(s); limitations on driving and the

stigma associated with the condition. These factors, and others, may have an adverse impact on older people with epilepsy, as might comorbidities[4,126] and cognitive impairment. It is therefore essential that healthcare providers prioritise epilepsy in the elderly and view the condition holistically. Early diagnosis with prompt, appropriate individual management may prevent unnecessary hospitalisation and reduce the impact of co-morbidities while closer integration between primary and secondary care would afford improvements in the care of older people with epilepsy. A possible pathway for older people with seizures is provided in Figure 7. Formal practice guidelines to optimise care for older people with epilepsy would be of great benefit in resource rich and resource poor nations. Culturally appropriate online tools to help in the management and empowerment of senior citizens with epilepsy and those who care for them who also be helpful.

At a broader, more strategic, level, modifications of shared risk factors for stroke and dementia[133] – hypertension, diabetes, alcohol consumption, smoking and low exercise[4,134] – appear to also represent a clear global health opportunity to reduce the risk of developing seizures in later life. Importantly, many of these modifications can be made at an individual level with minimal cost (or potentially being cost saving, for example stopping smoking) or at a population level using established drugs many of which are affordable and widely available across the world.

Conclusions and future directions

Even though epilepsy in older adults is a common condition and can have enormous impact on the person affected and their family/care partners, it is a relatively under-appreciated and under-researched area of medicine. We have explored several aspects including appropriate treatment options – ASMs and surgical options; specific epilepsy syndromes observed in the elderly and relevant co-morbidities. The links between dementia, cerebrovascular disease and epilepsy have been highlighted, emphasising that modifiable vascular risk factors may have a positive impact on reducing the future risk of developing epilepsy. We have also highlighted how there is a lack of research in older people with epilepsy compared to younger populations. Drug trials, the role of epilepsy surgery, psychosocial evaluations and assessment of relevant comorbidities all require much deeper assessment in people with epilepsy over 65 years so that there are informed choices of how to optimise the care of this group, the largest cohort of people with epilepsy in resource rich and, increasingly, resource poor societies.

Contributions:

The concept of the manuscript was devised by AS who also performed the overall literature searches with NJ and created initial drafts of figures. Sections on epidemiology, epilepsy surgery, psychological/psychiatric aspects, SUDEP and status epilepticus were initially drafted by NJ. Cognitive difficulties in older people was initially written by MH. JWS wrote sections on diagnosis, investigation and

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medical management. All authors reviewed and extensively revised the manuscript prior to approving the final version of the work

Search Strategy and selection criteria:

Several PubMed searches were run on 1 September 2019 using the search terms “epilepsy or seizure or status epilepticus or sudep” AND “elderly or older”. These were then combined with search terms related to, for example, (1) epilepsy surgery or (2) incidence or prevalence or epidemiology or mortality or (3) psychosocial or quality of life or stigma. Separate searches were run to include studies that, for example, explored cognitive difficulties in people with epilepsy. Reference lists of identified articles were hand searched to retrieve additional studies. Publications were selected mainly from the past five years. By necessity, preference was given to the most major and relevant works although we were also keen to illustrate the breadth of the topic hence selecting some more minor publications that highlighted particular areas of interest. Review articles were selected and are highlighted in the text to direct potential readers to source materials. We are conscious that there are many publications on epilepsy and the elderly now emerging, but hope that we have provided a comprehensive review of the topic and a platform from which to seed further research.

Declarations of Interest

AS has received speaker honoraria/ travel expenses or research monies from Bial, Eisai Limited, GW Pharma, Livanova, UCB Pharma. NJ receives grant funding paid to her institution for grants unrelated to this work from NINDS (NIH U24NS107201, NIH IU54NS100064) and PCORI. She also receives an honorarium for her work as an Associate Editor of Epilepsia. She is a member of the editorial board of Neurology and JAMA Neurology. JWS has been consulted by and received research grants and fees for lectures from Eisai, UCB, Zogenix and GW Phama, outside the submitted work. MH has been on an advisory board for Otsuka Phamaceuticals and received speaker honorarium from Lilly.

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