

Epilepsy in Elderly Population: A Comprehensive Review

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Abstract

Epilepsy is becoming recognized as a common disorder of the elderly. Within that population, it is the third most common neurological disease, after cerebrovascular disease and dementia. Clinical history and details of the event from carers or relatives is considered as the golden standard for diagnosis. Comorbidities and multiple risk factors are increasingly recognised as an important aetiological and prognostic markers. Older patients most often present with focal seizures, with less prominent auras and automatisms, and longer duration of postictal confusion. Status epilepticus is common and has a high mortality. In spite of advances in diagnosis, many cases are either misdiagnosed or undiagnosed. Care should be taken when prescribing anticonvulsants in this age group to minimize the drug side effects. The purpose of this review is to focus on epidemiology, aetiology, diagnosis and treatment of epilepsy in elderly population.

Keywords: *Elderly; Seizures; Epilepsy; Diagnosis; Anticonvulsant*

Abbreviations

MRI: Magnetic Resonance Imaging; EEG: Electroencephalogram; AED: Antiepileptic Drugs; NHS: National Health Service; eTNS: external Trigeminal Nerve Stimulation, ECoG: Electrocorticography; RNS: Responsive neurostimulation

Introduction

Epilepsy is one of the most common serious brain conditions, affecting over 70 million people worldwide. It has been thought of as a disease of the young, primarily affecting infants, children, and adolescents, however, it is becoming recognized as a common disorder of the elderly [1]. It has numerous neurobiological, cognitive, and psychosocial consequences [2]. Within the elderly population, it is the third most common neurological disease, after cerebrovascular disease and dementia. Although the phenomenon of population ageing is evident for high-income countries, approximately 80% of people with epilepsy live in low income and middle-income countries. It is believed over 75% of those with active epilepsy are untreated and this constitutes a major treatment gap, mostly concentrated in low- and middle-income countries (LAMICs) and will evolve into an increasingly important public health issue [3]. It should be considered as a global health priority, and as cost effective medicines are available worldwide which can considerably decrease disability, morbidity, and mortality [4,5].

Epidemiology

The prevalence of unprovoked seizures in those aged over 60 is at least 1%. This rate rises to 1.5% in those aged over 75, which is approximately twice that of younger adults [6,7]. Prevalence is even higher (3 - 9%) in populations such as nursing home residents [8-10].

Indeed, the incidence of epilepsy is greatest in those over the age of 65 [11-13]. Above 65 years, annual incidence in those aged 65 - 69 is 85.9 per 100,000 to more than 135 per 100,000 in those aged older than 80. This is compared to an overall incidence of 80.8 per 100,000 people across all age groups [14]. Patients with a first unprovoked seizure have an overall risk of recurrence beyond 2 years of 25 - 52% [15-18]. Similar to other age groups, this risk is increased in the presence of an abnormal electroencephalogram (EEG) and/or an identifiable epileptogenic substrate [16].

In 2017, the International League Against Epilepsy (ILAE) updated the classification and terminology of seizures [19,20] and epilepsy [21]. Status epilepticus becomes more common with age, with a 2- to 10-fold increase in incidence in those older than 60 relative to younger adults [22-24]. This increase is accompanied by a rise in mortality associated with status epilepticus, with a rate of 38% in those over 60 to nearly 50% in those over 80 [25,26]. Mortality in elderly patients with epilepsy is two to three times greater than that of the general population, likely due to their greater susceptibility to systemic illnesses, comorbidities and the underlying aetiology of their epilepsy [27]. The distinction between acute and remote symptomatic seizures is often not clear in the elderly. This is due to the inherent imprecision of the circumstances surrounding events, and the varying definitions for the acute period, from 48 hours to up to 3 months depending on the underlying aetiology [28].

Discussion

In the elderly, symptomatic seizures are most often precipitated by cerebrovascular disease (40 - 50%), which includes haemorrhagic, ischaemic, and embolic strokes, as well as subarachnoid haemorrhages [12,29-35]. Other causes include head trauma [36,37], CNS infections [30,31], drugs, toxins, alcohol, metabolic disturbances [38-41]. With regards to epilepsy, descriptions of its aetiology vary depending on the population studied, the definition of the elderly, and methodological factors [42-45]. In high-income countries, the most common identifiable causes include cerebrovascular disease, neurodegenerative disorders, intracerebral tumours, traumatic head injury, and CNS infections [46]. Population-based studies have shown that stroke increases the risk of a seizure by a factor of 23 and the risk of epilepsy in the first year after stroke by a factor of 17 [47]. The risk of epilepsy can be further stratified depending on the type of stroke, with the risk being greatest in those that are haemorrhagic, cortical, large, multiple and/or that present with acute symptomatic seizures [48].

The association between epilepsy and stroke and vice versa is not always obvious and seizures may be only the first presentation of previously unrecognized cerebrovascular disease. A large study of patients with new-onset seizures over 60 years, none of whom had any known history of trauma, tumor, dementia, cerebrovascular disease, or alcohol abuse, the 5-year risk of stroke was 2.89 times higher than that of control subjects without seizures [49]. Hypertension itself has been identified as a risk factor for seizures, likely because of its association with progressive arterial changes [50]. Such seizures may reflect the presence of subclinical cortical lesions in patients with predisposing vascular risk factors like hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease. The second most common antecedent of epilepsy in the elderly is neurodegenerative disease, which is associated with a 5- to 10-fold increase in epilepsy relative to the general population [51,52]. Patients with Alzheimer disease dementia, the incidence of epilepsy is approximately 8 - 20% [53,54]. Although seizure control does not appear to be more difficult as the disease progresses, the long-term effect of epilepsy on cognition and subsequent neurodegeneration is unknown [55].

In some studies, head trauma, usually secondary to falls, can account for up to 20% of epilepsy in the elderly [56]. The severity of the injury can predict the risk of subsequent epilepsy, with a loss of consciousness increasing the risk of subsequent epilepsy threefold [29]. Similar to other age-groups, other risk factors include sustaining a brain contusion with subdural haematoma, skull fracture, and loss of consciousness or amnesia for more than 1 day [57]. Of the remaining causes of epilepsy in the elderly, tumours account for between 10 - 30% of seizures, and are typically meningiomas, gliomas, or brain metastases [58]. Epilepsy is more common with primary relative to secondary tumours and with low-grade tumours rather than high grade [59]. Finally, CNS infections carry a threefold increase in risk of developing epilepsy [58].

Epilepsy in the elderly is almost always focal, and indeed complex partial seizures are the most common seizure type [59]. In the Veterans Administration cooperative study of new onset epilepsy in a community-dwelling cohort, 27% of patients with epilepsy had been initially misdiagnosed [42]. Some elderly patients with epilepsy may remain undiagnosed altogether [60]. Commonest reasons for difficulties in diagnosing epilepsy in the elderly are a) under-reporting of events [61], b) lack of auras and recognized automatisms [62] c) mimickers of epilepsy i.e. not true epileptic event [63]. The diagnosis of epilepsy in an elderly patient is most difficult when witnesses are unavailable or unreliable [64]. Computed tomography is useful only as an initial screening study (or when MRI is unavailable) for intracerebral haemorrhage, tumours and encephalomalacia, and should be followed by a MRI if any obvious pathology is not detected in a patient with definite epilepsy [65]. EEG has an important role in activity and localization of the epilepsy, may aid in prognostication - for example, patients who experience focal spikes or periodic lateralized epileptiform discharges (PLEDs) after a stroke are at greater risk for developing seizures in the future [66]. It is suitable in patients who present with prolonged confusional states or unexplained coma due to non-convulsive status epilepticus [67-70]. Video telemetry is useful in uncertain cases, in which patients present with recurrent and frequent atypical events and to distinguish epileptic seizures from sleep disorders [71]. Awareness that the interictal EEG is of relatively less utility in the elderly due to the high occurrence of non-specific abnormalities. In one study, video-EEG monitoring detected interictal epileptiform discharges in 26% of those with non-epileptic events and in 75% of those with epilepsy [72].

Main goal of treatment of epilepsy in elderly is to improve overall quality of life, with good seizure control, while minimizing adverse pharmacological side effects. However, treatment is complicated by three main issues 1) dysbalanced homeostatic and in milieu physiological mechanism making elderly patients more susceptible to worst side effects, 2) polypharmacy and drug-drug interactions 3) comorbid medical conditions like hypertension, diabetes, dyslipidemia etc [108]. Basic principles which treating physicians, epileptologists and neurologist should focus during treatment a) document previous drug reactions - idiosyncratic skin reactions and cross-reactivity [73], b) to use single, non-enzyme inducing, anticonvulsant drugs [74], c) surgical work-up and intervention if seizures remain refractory and the underlying pathological substrate is known [75], d) screen for and manage the underlying aetiological disorder (e.g. cerebrovascular risk factors, neurodegenerative disorders).

Patients taking antidepressants, antipsychotics, certain antibiotics for specific illness can decrease the seizure threshold [76]. Sodium valproate is notable in that it lacks the side effects of sedation and motor slowing, and does not induce hepatic enzymes, and can be a useful first treatment option when used in low dose (400 - 800 mg/day) in the elderly while monitoring the side effects. However newer-generation AEDs are less sedating and offer more favourable side effect profiles particularly drug-drug interactions. Recent guidelines published efficacy and safety in elderly population [77]. Lamotrigine is as effective as carbamazepine, but better tolerated, with a lower incidence of rash and somnolence [78]. A second study with an identical design actually showed no difference between lamotrigine and carbamazepine if a controlled-release formulation of carbamazepine was used, with a target dose of 400 mg daily [79]. Veterans Administration Study compared lamotrigine, gabapentin and carbamazepine (standard release) in a randomized double-blind design [80]. Levetiracetam has been suggested as an alternative first-line agent for several reasons apart from other drugs [81-84]. Data from open label studies in support of oxcarbazepine [85] and topiramate [86].

The elderly are more sensitive to the central and systemic side effects of AEDs [87]. Elderly patients showed that both good seizure control and minimal side effects could be achieved with serum concentrations of valproate or carbamazepine that were at, or well below, the 'therapeutic range' [88]. In general, halving the target dose of most AEDs and titrating these drugs at dosage increments half that for younger adults, and over intervals twice as long is a standard practice considering old age of the patients [89]. Apart from the standard known side effects of AED, several other things should be kept in mind like decreased bone mass [104,105], osteoporosis [106] leading to falls and fracture. Vitamin D, proper sunlight exposure, calcium supplements, liver and kidney function monitoring, nutrition, exercise and mobility [112] becomes a very important issue to address in elderly population. Vitamin B1 and C should also be followed up in elderly patients receiving AEDs [113]. Hyponatremia is a common side effect of AED like oxcarbazepine and carbamazepine when used along

with thiazide diuretics [95,96]. Epilepsy surgery, especially temporal lobectomy, is performed in older patients with intractable epilepsy yielding good results [97-103,127,128]. Lin., *et al.* recently reported significant improvement in social functioning in people with epilepsy after surgery as quality of life (QoL), but it took more time to exhibit improvement as it was dependent on years of education. They also think more early the intervention of rehabilitation programs after epilepsy surgery better improvement in social functioning can be expected [107].

Hernandez., *et al.* demonstrated subregion-specific alterations in synaptic signaling with age and the potential for a ketogenic diet to alter these processes in dissociable ways across different brain structures [114] and also studied in NHS UK [115]. Neurostimulatory techniques are palliative options when surgery is not possible or if surgery failed with doubt efficacy [116-118,122,129-131]. Effectivity of eTNS is similar to some of the new treatments available, with a retention rate of 52% in the first year and 285% at 4 years with excellent tolerability [119]. Chronic ECoG may provide a more accurate estimate of seizure frequency and provide additional insight into the true efficacy of the RNS system and response to antiepileptic drugs in patients already treated with responsive stimulation [120,121]. Novel developments like wearable, non-EEG based, automatic seizure detection devices are under study currently [123-126], because of underreporting and undetection [132].

Things to be kept in mind is late-onset seizures, a predictor of subsequent stroke, those who have their first unprovoked seizure above age 60 should have their vascular risk assessed, and their risk factors managed appropriately [90]. In the two-thirds of patient in whom no aetiology is found, it is prudent to remain vigilant and monitor for the possibility of seizures as the sentinel event of an emerging neurodegenerative disorder. Patients who have had a severe traumatic brain injury [91], brain neoplasm [92], metastasis to brain from different sites [93], no fine evidence for long-term seizure prophylaxis with anticonvulsant therapy exists.

The effect of epilepsy and treatment with medication itself can cause enormous trouble with quality of life and independence of the elderly patient. Falls, confusion, amnesia, driving restrictions that are imposed following a seizure can cause social isolation. Higher prevalence of depression, anxiety, and poor sleep is seen as compared to age-matched controls [94]. Status epilepticus is common and has a high mortality in elderly population so special management plan is needed in hospital settings [109-111].

Conclusion

Care of the elderly patient with epilepsy poses tremendous challenges to the modern neurologist and clinicians. Epilepsy symptom complex and status epilepticus are common in elderly population however presentation may be atypical. A detailed clinical history in addition to blood and imaging to rule out other causes remains the golden standard for diagnosis. However, this must always be balanced against the alternative likelihood of seizure 'mimickers'. Cerebrovascular risk factors and cognitive impairment should be evaluated on regular basis in this subset of patients to decrease overall morbidity and mortality. Close attention should be given to AEDs impact on patient's physical well-being, other comorbidities, and concomitant medications taken to avoid polypharmacy and drug-drug interaction. Antiseizure medications suppress seizures in up to two-thirds but do not alter long-term prognosis. Future studies should focus on neurocognitive status, lifestyle factors, multidisciplinary approach in treating old age population with diagnosed epilepsy.

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