Epilepsy and its neuropsychiatric complications in older adults

Introduction

When we think about epilepsy we think of children and young adults. However, older age (>65 years) is one of the commonest times of life to have epilepsy. The incidence and prevalence of epilepsy in the elderly is about twice that in younger adults (Leppik, 2006). Mortality rates are higher in older patients and they present with status epilepticus more often (Sung and Chu, 1989; Hesdorffer et al, 1998).

Is epilepsy the same in older people?

About 70% of new seizures in old age are focal in onset (Hauser, 1992) and epilepsy often has an atypical presentation with non-specific symptoms such as episodes of confusion or inattention, syncope or pseudodementia. Focal seizures can go undiagnosed for some time. Diagnosis is more challenging as a result of co-morbid conditions, such as stroke and dementia, or disabilities such as auditory or visual impairment. Electroencephalographs may be less helpful in old age because of increasing rates of non-specific abnormalities or abnormalities relating to medications and co-morbid conditions. However, electroencephalography can help detect rare presentations of non-convulsive status presenting with psychiatric symptoms.

Understanding the aetiology of seizures in this age group changes one's index of suspicion when faced with a patient having 'funny turns' and also clarifies why a magnetic resonance imaging scan of the brain at the time of diagnosis may be more important than in younger patients.

New-onset epilepsy in old age is unlikely to be idiopathic or related to an underlying genetic abnormality. Instead, it is likely to be symptomatic, cryptogenic or iatrogenic. The commonest symptomatic causes are stroke (haemorrhagic or ischaemic, acute or old) (Lühdorf et al, 1986), metabolic (abnormal glucose, abnormal sodium, low calcium, uraemia, liver disease), brain trauma (head injury is twice as likely to result in epilepsy in old age), infection (lung, urinary tract, CNS), alcohol withdrawal (alcohol dependence should be explicitly asked about), or a space-occupying lesion. Iatrogenic causes might include antipsychotics, antidepressants, ginkgo biloba (Leistner and Drewke, 2010), antibiotics, theophylline, levodopa or thiazide diuretics.

Patients with Alzheimer's disease also have more than five times the risk of developing epilepsy, especially those with early onset (Romanelli et al, 1990) and those who have had Alzheimer's disease for more than 6 years (Mendez et al, 1994).

How does treatment differ in this age group?

According to the Department of Health (2001) guidelines, anyone with a recent onset suspected seizure should be seen urgently by a specialist regardless of their age. Initiation of antiepileptic drug treatment should be considered after a first seizure if there is a neurological deficit or if the risk of having a further seizure is unacceptably high (Poza, 2007). However, the authors would argue that specialist input in initiating antiepileptic drug therapy is particularly important as older patients have altered pharmacokinetics and pharmacodynamics, and are more likely to experience side effects and idiosyncratic reactions to drugs.

There are further specific considerations in this age group. Restrictions on driving may cause more practical difficulties in patients with thinner social networks. Falls may occur during seizures or as a result of antiepileptic drug side effects. In older patients, injuries take longer to repair and full functional recovery is less likely. These issues may influence decisions such as whether to treat after an isolated seizure and which antiepileptic drug is chosen.

Once a patient is established on medication he/she should have a regular structured review, at least yearly, with either a specialist or a generalist (Department of Health, 2001). If the epilepsy is not well controlled or there are complicating factors a specialist is more appropriate.

What are the common neuropsychiatric complications of epilepsy?

The neuropsychiatric complications of epilepsy are important to address as they may have more impact on health-related quality of life than seizure-related variables such as seizure frequency (Boylan et al, 2004; Cramer et al, 2004). They may also have an adverse effect on mortality rates and health-care costs. However, they are not always easy to diagnose, they do not always fit neatly into diagnostic categories, risk factors may differ from the general population and screening tools need to be used in conjunction with sound clinical judgement. Electroencephalography may be particularly important when a patient with epilepsy also presents with a mental health problem, especially psychosis, as the symptoms rarely may be a manifestation of non-convulsive status for which treatment would be different.

In any patient presenting with neuropsychiatric symptoms, the neuropsychiatric complications of the underlying disorder need to be considered as well as those of epilepsy. For example, in a patient with underlying cerebrovascular disease one would be more vigilant in looking for secondary depression or increased emotionality, while in Alzheimer's dementia one might look for personality change, visual hallucinations, behavioural disturbances, depression and anxiety.

Once a diagnosis is made treatment requires careful consideration because of the altered pharmacokinetics, interactions between antiepileptic drugs and psychotropics, and the tendency for some psychotropics to lower seizure threshold.

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Depression

Depression is thought the most common neuropsychiatric complication of epilepsy with rates varying between 7.5% and 55% depending on study setting or assessment tools. It is important to recognize and treat because of the potential benefits in terms of quality of life and the increased risk of suicide when epilepsy is associated with depression (Christensen et al, 2007). Untreated depression may make seizures worse.

Depression in epilepsy can be pre-ictal, ictal, post-ictal or inter-ictal. These probably have differing underlying pathophysiology and should be managed differently.

Pre-ictal depression occurs in the hours or few days preceding a seizure and usually resolves after it. Patients may present as more irritable than depressed. Ictal depression may be a symptom of the seizure and usually starts suddenly along with other manifestations of seizure. Common symptoms are feelings of guilt, anhedonia and suicidal ideation. It is self-terminating. Post-ictal depression, like pre-ictal depression, is usually self-limiting. In pre-ictal, ictal and post-ictal depression the main treatment is optimization of seizure control. In severe and prolonged post-ictal depression a low dose antidepressant may be appropriate (Blumer, 1992).

Inter-ictal depression – depression that is not temporally related to seizure activity – has been well studied. It is thought to be caused by a combination of environmental, psychological and seizure-related factors. Its diagnosis is challenging as standard criteria for depression may not apply. The effect of epilepsy, underlying aetiology and antiepileptic drugs could either mask or mimic biological features of depression (insomnia, hypersomnia, increased or decreased appetite, impaired cognition). There may be atypical presentations of depression with prominent symptoms of irritability, anhedonia, hopelessness, fear and anxiety (Gillham, 1990) or with inter-ictal dysphoria. Features more likely to present in inter-ictal depression are agitation, psychotic features and impulsive self-harm (Harden et al, 1999).

Treating inter-ictal depression

First possible medical causes of depression such as drug-induced, endocrine or metabolic (e.g. low folate) should be ruled out, as one would in non-epileptic patients.

Ideally the choice of antiepileptic drug would take into account a patient's mood. Topiramate or tiagabine lower mood in people with epilepsy (Harden, 2002), so a drug which also acts as a mood stabilizer is preferred, e.g. sodium valproate, carbamazepine or lamotrigine. However, this may not be possible. Newer and less sedative antiepileptic drugs generally have better pharmacokinetic and side-effect profiles.

Doctors are often reluctant to prescribe antidepressants because they fear lowering the seizure threshold and provoking seizures. This may be true for some tricyclic antidepressants but a number of selective serotonin-reuptake inhibitors are effective and safe. Kanner et al (2000) showed that sertraline caused no significant increase in seizure rate and severity and psychiatric symptoms completely resolved in 54% of patients. They proposed a starting dose between 25 and 50 mg increasing to a maximum of 200 mg per day.

Kühn et al (2003) found no difference in efficacy between mirtazepine, citalopram and reboxetine, with no patients having an increase in seizures. Venlafaxine may have slightly higher potential to lower seizure threshold. Moclobemide is not thought to increase risk of seizure but dietary restrictions and potential for drug interactions make it unlikely to be the first choice of medication in older patients. Clomipramine, maprotiline, bupropion, amitriptyline and dothiepin should be used with caution because of the increased risk of seizures.

Many of the older antiepileptic drugs are metabolized by cytochrome P450 isoenzymes and some antidepressants affect their activity. Antiepileptic drug level monitoring may be advisable when starting treatment. Antidepressants which inhibit P450 isoenzymes are fluoxetine, luoxamine, nefazodone, paroxetine and sertraline (dose-related) and they may lead to raised levels of phenytoin, phenobarbital and carbemazepine (Levy, 1995). Conversely, primidone, phenytoin, carbamazepine and phenobarbital induce P450 enzymes which may lead to reduced levels of clomipramine and imipramine (Joint Formulary Committee, 2010).

Side effects of antidepressants may compound those of antiepileptic drugs and should be actively looked for and closely monitored, in particular sedation and cognitive impairment. Older people are more sensitive to side effects and other medication may compound this problem further.

Anxiety

Symptoms of anxiety are found in between 10 and 25% of community samples of epilepsy patients, although rates may be as high as 30% in inpatients (Jones et al, 2005) or 40% in patients with refractory epilepsy (López-Gómez et al, 2008). Anxiety is more frequent among patients with focal epilepsy (Gureje, 1991) and in those with depression (López-Gómez et al, 2008). The aetiology is likely to have both a neurobiological and a psychosocial component. Symptoms of anxiety in epilepsy impact on quality of life and higher anxiety levels in epilepsy are associated with increased rates of attempted suicide (Batzel and Dodrill, 1986).

Anxiety in epilepsy can also be sub-categorized into pre-ictal, ictal, post-ictal and inter-ictal, which may take the form of phobic anxiety.

Anxiety can be more difficult to identify in epilepsy but some differentiating symptoms include anxious or depressed mood, tension, insomnia, cardiovascular symptoms, genitourinary symptoms, impaired intellectual function and anxious behaviour (López-Gómez et al, 2008). Inter-ictal fear has also been associated with increased incidence of post-ictal fear (Kanner, 2004).

Panic attacks may be particularly common in epilepsy with reported rates from 5.3 to 21% (Pariente et al, 1991). Panic attacks can be particularly difficult to differentiate from ictal fear. Useful features of the history to probe are duration (ictal fear usually lasts less than 30 seconds, episodes of panic may be up to 20 minutes long), and the presence or otherwise of transient confusion and subtle automatisms (suggestive of ictal fear) or autonomic symptoms such as shortness of breath, palpitations or sweating (suggestive of panic disorder).

It is not uncommon for patients to experience phobic anxiety inter-ictally. This could be fear of injury occurring during an attack, fear of a place where an attack has occurred or fear of having an attack in public. This can seriously affect a patient's ability to function between attacks.

Treating anxiety symptoms in epilepsy

Ictal and post-ictal fear or anxiety are part of the aura of a focal seizure and should be treated by improving seizure control.

Inter-ictal anxiety is managed as it would be in a non-epileptic patient although benzodiazepines should be avoided because of the risk of dependence and withdrawal seizures. An antidepressant should be chosen which is licensed for anxiety disorders. Choosing an antiepileptic medication such as pregabalin which is licensed to treat generalized anxiety may help. One might be more inclined to refer for non-pharmacological treatment such as anxiety management and cognitive behavioural therapy, especially in panic disorder and phobic anxiety.

Psychosis

Accurate recognition and early treatment of psychosis in epilepsy helps improve patients' quality of life, reduce the burden on family members and improve compliance with antiepileptic medication. Psychotic symptoms in elderly patients could be caused by underlying pathology and may be more likely to be associated with confusion and cognitive impairment.

Ictal psychosis may take the form of hallucinations or delusions (in particular grandiose or paranoid). Usually its short duration makes it easy to differentiate from a more chronic psychotic illness such as schizophrenia. Features suggestive of ictal psychosis are concomitant confusion, absence of a delusional system and relatively prominent olfactory, visual or gustatory hallucination. Treatment involves optimizing seizure control.

Post-ictal psychosis is the most common form of epilepsy-related psychosis, seen in 6–10% of epilepsy patients (Kanner et al, 1996). There is classically a lucid period of hours between the end of the seizure and onset of psychosis and episodes tend to be relatively short (hours–days). Mood abnormalities tend to predominate and negative symptoms and first rank symptoms of schizophrenia are less common (Logsdail and Toone, 1988). Treatment involves prompt introduction of low dose antipsychotics which should be discontinued once symptoms resolve. Affective components may require antidepressants or mood stabilizers.

By contrast with post-ictal psychosis, the presentation of inter-ictal psychosis may more closely resemble schizophrenia as affective symptoms are less prominent. However, thought disorder and delusions of passivity are uncommon. Negative symptoms and decline in functioning may be a particular problem in elderly patients with more severe illness.

Psychosis may sometimes occur or worsen following normalization of the electroencephalograph and suppression of seizures, known as forced normalization or alternative psychosis. It is unclear whether this truly relates to normalization of the electroencephalograph or if it is a side effect of antiepileptic medication, but it is a relatively infrequent cause of psychosis in patients with epilepsy (Krishnamoorthy et al, 2002).

Use of antipsychotics in patients with epilepsy

Many doctors have concerns about antipsychotics lowering the seizure threshold and because some antiepileptic drugs affect cytochrome P450 enzymes, ensuring adequate antipsychotic treatment is more challenging. When psychosis complicates epilepsy in an older patient specialist advice should be sought.

Haloperidol is thought to have low proconvulsive effects but is not a first-line option in elderly patients. Newer antipsychotics such as risperidone, quetiapine and amisulpiride are probably safe. Olanzapine, chlorpromazine and zotepine should be avoided. Given the vascular risk factors in the elderly, quetiapine or amisulpiride are first-line treatment. Depot antipsychotics are not thought to increase the risk of seizures but the difficulty of withdrawing them if seizures occur means they are best avoided. Clozapine should be avoided as it can cause dose-dependent epileptiform activity (Freudenreich et al, 1997).

Finally it is worth considering whether the antiepileptic drug is the cause as psychosis has been reported with ethosuximide, topiramate, levetiracetam, pregabalin, vigabatrin, zonisamide and tiagabine.

Suicide

The rate of suicide is increased in patients with epilepsy (5% compared with 1.4% in the general population; Jackson and Turkington, 2005). This increases further in patients with epilepsy and a mental disorder, especially depression (up to 32 times higher risk) (Christensen et al, 2007) and psychosis (up to 12 times higher risk). Rates of suicide increase with age beyond middle age in both sexes, and between 15 and 20% of completed suicides in those over 60 years of age had evidence of both cognitive impairment and cerebrovascular changes at post mortem (Batchelor and Napier, 1953).

Suicidality should be actively screened for and managed in at-risk patients, and a review of the antiepileptic considered if this could be contributing to low mood.

Personality disorder

A personality syndrome specific to epileptic patients has been hypothesized since at least the late 19th century. Kraeplin noted traits of slowing, meticulousness of mental processes, circumstantiality, preoccupation with religious ideas and irritability in more than half his patients. People with epilepsy may manifest viscosity, hypergraphia, religiosity, hyposexuality and inter-ictal aggression or hostility (Blumer, 1995), described as Gastaut–Geschwind syndrome. People may present with just one or two manifestations of this syndrome.

It is often thought that personality disorders are less common in old age, but this is not true. Elderly people with epilepsy may be more prone to personality change and behavioural problems because of additional effects of underlying brain lesions such as in stroke and dementia.

Functional non-epileptic attacks

These are also known as pseudoseizures or psychogenic non-epileptic seizures, and are classified as dissociative or conversion disorders. Onset is thought to be preceded by trauma, stress or conflict and the patient is not consciously producing the symptoms. Presentation in the elderly may be different to that in younger patients with trembling attacks (rather than violent thrashing) and variable loss of responsiveness. Precipitating trauma is more likely to be health related.

Cognitive impairment

Impaired memory in older patients with epilepsy affects between 20 and 50% of patients irrespective of the type of epilepsy or seizures. It may be caused by the underlying disease; seizure variables such as frequency and severity; antiepileptic drug therapy (which may also cause impaired language and psychomotor retardation; Brodie et al, 1987); or neuropsychiatric complications (depressive pseudodementia, anxiety, psychosis).

In addition to memory, speed of mental processing and attention may be impaired although in some instances this is related to

inter-ictal discharges on electroencephalograph or epileptiform discharges at night, so may be transient (Weglage et al, 1997).

Other cognitive impairments may relate to the seizure focus, e.g. left hemisphere focus may cause impaired verbal functions while right hemisphere focus may cause visuoperceptual, visual memory and constructional disabilities (Lezak et al, 2004). Temporal lobe focus is particularly associated with memory impairment (Elger et al, 2004) and consolidation of memories. In one subtype of temporal lobe epilepsy, transient epileptic amnesia, memory impairment is part of the seizure. Frontal lobe epilepsy may affect executive function.

Treatment of cognitive impairment in epilepsy involves treating any underlying cerebral pathology, optimizing epilepsy treatment (monotherapy is preferable (Brodie, 1992), consider vagus nerve stimulation), treating any psychiatric comorbidity and possibly memory rehabilitation which involves psychoeducation and support to develop personal coping strategies.

An open-label pilot study of donepezil in 18 patients with partial epilepsy showed improved word recall but worsening seizures in two patients (Fisher et al, 2001). There has been no randomized controlled trial.

Antiepileptic drugs such as phenobarbitone and topiramate are more likely to impair cognitive function (Aldenkamp and Bodde, 2005); lamotrigine and levetiracetam may have better cognitive effect profiles.

Conclusions

Epilepsy is common in this age group and may be difficult to identify and treat. Older patients are more susceptible to neuropsychiatric complications as a high proportion have an underlying condition associated with increased psychiatric morbidity in its own right. This makes identifying and disentangling these problems more difficult.

Treatment is more challenging because of age-related changes in the body's handling of medication and the likelihood of comorbidity and polypharmacy. Yet this group of patients is at risk of a shortfall in healthcare provision compared with their need. When a recent onset seizure is suspected, the patient should be seen urgently by a specialist. Neuropsychiatric complications should be looked for actively in these patients and, if recognized or suspected, patients should be referred for specialist input. **BJHM**

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KEY POINTS

- Epilepsy is a common neurological condition in old age.
- Neuropsychiatric comorbidities of epilepsy are common in old age.
- If neuropsychiatric comorbidities with epilepsy are suspected, specialist opinion should be sought.