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Review

Challenges in the pharmacological management of epilepsy and its causes in the elderly

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ABSTRACT

Epilepsy represents the third most common neurological disorders in the elderly after cerebrovascular disorders and dementias. The incidence of new-onset epilepsy peaks in this age group. The most peculiar aetiologies of late-onset epilepsy are stroke, dementia, and brain tumours. However, aetiology remains unknown in about half of the patients. Diagnosis of epilepsy may be challenging due to the frequent absence of ocular witnesses and the high prevalence of seizure-mimics (i.e. transient ischemic attacks, syncope, transient global amnesia or vertigo) in the elderly. The diagnostic difficulties are even greater when patients have cognitive impairment or cardiac diseases. The management of late-onset epilepsy deserves special considerations. The elderly can reach seizure control with low antiepileptic drugs (AEDs) doses, and seizure-freedom is possible in the vast majority of patients. Pharmacological management should take into account pharmacokinetics and pharmacodynamics of AEDs and the frequent occurrence of comorbidities and polytherapy in this age group. Evidences from double-blind and open-label studies indicate lamotrigine, levetiracetam and controlled-release carbamazepine as first line treatment in late-onset epilepsy.

Contents

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1. Introduction

Elderly is commonly defined as a chronological age ≥ 65 years [1]. Epilepsy represents the third most common neurological condition after dementia and stroke in this age group [2]. The incidence of treated epilepsy rises from 63.2 per 100,000 people at 5–9 years, to 85.9 at 65–69 years, 82.8 at 70–74 years, 114.5 at 75–79 years, 159 at 80–84 years and 135.4 > 85 years [3]. As the world's population rises and ages, the number of elderly people with epilepsy will increase [4]. Of note, elderly epilepsy subjects show a 2–3 fold greater risk of mortality than the younger age groups [5]. The aetiologies of new onset epilepsy in the elderly differ from those of other age groups. Diagnosis of epilepsy may be challenging in elderly due to the frequent absence of ocular witnesses and the high prevalence of comorbid disorders (transient ischemic attacks, syncope, transient global amnesia, vertigo, etc.) which can imitate seizures. The diagnostic difficulties are even greater when patients have cognitive impairment or cardiac problems [6]. Epilepsy management in elderly is often challenging. Indeed, physiological aging affects both the pharmacokinetics and pharmacodynamics of antiepileptic drugs (AEDs). Furthermore, the frequent concomitant intake of therapies for comorbidities exposes the patients to drug interactions.

In this review we will focus on new onset epilepsy in the elderly, detailing its peculiar aetiologies, diagnostic issues and therapeutic management.

2. Review of the literature

Medical publications concerning epilepsies in elderly were reviewed. References were identified by searches of PubMed and Google Scholar until December 2015 with the terms "epilepsy" or "seizures" in various combination with "old", "elderly", "antiepileptic drugs", "tumours", "cancer", "neoplasms", "dementia", "neurodegenerative disorders", "stroke", "cerebrovascular diseases". Articles were also identified through searches of the authors' own files. Selection criteria were novelty, importance, originality, quality and relevance to the scope of this review.

3. Peculiar aetiologies of epilepsy in elderly

3.1. General considerations

The prevalence of specific causes of epilepsy in elderly varies in the literature, depending on the study populations, definitions and investigation strategies [7]. The most peculiar aetiologies are stroke, neurodegenerative diseases and brain tumours, although many others causes, including brain trauma, encephalitis, cortical dysplasia may be observed [8]. Despite the use of advanced neuroimaging techniques, the cause of a late-onset epilepsy still remains unknown in ~50% of patients [9].

3.2. Stroke

Strokes account for 15–40% of all epilepsy aetiologies in the elderly [9–11]. Evidences from both animal and human studies suggest that enhanced cortical excitability, possibly related to impaired GABAergic or increased glutamatergic intracortical activities in the perilesional areas, may contribute to the development of post-stroke epilepsy (PSE) [12]. Cortical involvement and presence haemorrhage seems to be the main risk factors for epilepsy, although studies are hard to compare due to different study design, population and time-span distinguishing early from late seizures. Seizures are usually focal motor, reflecting the higher incidence of strokes involving the middle cerebral artery territory [13]. Secondary generalization can be observed in half cases [14,15]. Status epilepticus (SE) may occur in 3.6–17.6% of stroke patients, in both early and late periods after cerebrovascular insult [15,16]. SE is associated with a higher risk (44.8%) of long-term mortality, regardless on the time of its onset after the vascular injury [17]. Of note, seizures may aggravate the neurological status or the post-stroke recovery [18,19]. Brain MRI frequently shows white matter rarefaction (leukoaraiosis) in adult patients with otherwise unexplained new-onset epilepsy. However, the epileptogenic role of leukoaraiosis is still matter of debate [13] and the two phenomena (epilepsy and leukoaraiosis) may be accidentally associated, since leukoaraiosis is a common finding in the advanced adulthood. The relationship between epilepsy and stroke seems to be bidirectional. In a population-based study, Cleary et al., found a higher risk for stroke (hazard ratio 2.89; 95% CI 2.45–3.41) in elderly patients with new onset epilepsy without previous diagnosis of acquired brain injury, as compared to non-epileptic controls [20]. Chang et al., found that stroke incidence in epilepsy patients was 3-fold higher as compared to non-epileptic subjects [21]. In a prospective study by Sillanpää et al., adult patients with childhood-onset epilepsy had a significantly higher rate (RR 2.5; 1.04–5.9) of cerebrovascular lesions as compared to non-epileptic controls [22]. Hamed et al., found a significantly higher rate of increased intima-media thickness in 225 epilepsy patients (85 not receiving AED) as compared to controls [23]. Overall, these studies suggest that epilepsy represents a risk factor for stroke although the role played by different variables (underlying aetiology, seizure frequency and treatment) remains to be fully elucidated.

3.3. Neurodegenerative disorders with dementia

Neurodegenerative disorders account for ~10–20% of the aetiologies of epilepsy in the elderly [24–26]. Alzheimer disease (AD) represents the most frequently and studied dementia associated with epilepsy. Hauser et al., found a 10-fold risk increase for recurrent seizures among patients with autopsy-proven AD than expected in a reference population [27]. Hesdorffer et al., reported a 6-fold increased risk for unprovoked seizures among patients with AD or other forms of dementia as compared to controls [28]. In the prospective study by Scarmeas et al., 2% of 453 AD patients developed unprovoked seizures at 5-year follow-up, corresponding to a 8-fold increased risk as compared to the general population [29]. However, the enhanced risk of epilepsy is not restricted to AD, but may include vascular dementia, mixed AD with vascular dementia, dementia with Lewy bodies, and fronto-temporal dementia [30].

Seizures may occur at any stage of the disease. Although seizures have long been related to dementia severity [31], they are frequently observed in mild to moderate AD patients [32]. Hesdorffer et al., described an average seizure onset between 0.4–9.3 years after AD onset [25]. Moreover, in the observational study by Lozsadi and Larner cognitive decline and seizures occurred approximately at the same time in 3.4% of cases [33]. Finally, some studies report that seizures may even occur one or more years prior to any clinically evident cognitive decline [30,34]. Seizures can be either focal or "apparently" generalized (mainly tonic-clonic) [25,31] and respond to AED in up to 88% of cases [30]. Myoclonus may occur in about 10% of AD patients, prevails at upper limbs and appears more frequently in severely demented subjects [27].

The role played by genetic factors in pathophysiology of epilepsy in dementia has been recently studied. Patients with familial AD, especially those with mutations of Presenilin 1 and Presenilin 2 or those with mutations or duplication of Amyloid Precursor Protein genes, are at higher risk for developing epilepsy as compared to subjects with sporadic form of AD [35]. In a prospective study by Amatniek et al., patients with early-onset familial AD had a 87-fold increased risk for developing epilepsy compared to the general