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Acute Seizures in Old Age and Cognitive Dysfunction

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Acute seizures in old age are associated with cognitive dysfunction. Neurodegeneration or age-related hippocampus changes and underlying vascular pathologies including white matter disease, silent infarction or microbleeding may contribute to the development of seizures in dementia. However, recent data suggested that high levels of amyloid β induces aberrant excitatory neuronal activity in Alzheimer disease and leads to an epileptiform activity, even at early stages of the disease process and in the absence of overt neuronal loss. Adequate early application of both anticonvulsants and neuroprotective treatments of acute seizures in old age with dementia is critical for preventing the extent of acute seizure activity-mediated cognitive dysfunction in the aged population. **J Neurocrit Care 2011;4:21-24**

KEY WORDS: Acute seizures · Old age · Cognitive dysfunction.

Introduction

The epilepsy increases in prevalence with age. The increased risk of newly diagnosed epilepsy in the elderly population (>65 years of age) has been confirmed.[1] As the elderly population continues to grow, this leads to increasing numbers of people who develop acute seizures with neurodegenerative disease.

The association of recurrent and unprovoked seizures in patients with dementia has been established. Patients with Alzheimer disease (AD) and other types of dementia are at 5-10 fold increased risk of epilepsy compared to age-matched controls.[2]

Previous studies have shown that eight to 22% of patients with AD have at least one unprovoked seizure.[3] However, Rao et al.[4] reported the frequency of epilepsy with dementia is lower than what has been reported previously. This may be due to multiple reasons including the fact that half of patients in this study were classified as having mild cognitive impairment. The milder degree of cognitive impairment and accompanying neuronal loss may be less epileptogenic.

While some studies have concluded that seizures occur in the more advanced stages of the illness, others did not detect an association between seizures and either disease duration or cognitive performance.[5] Lack of association between patient age at AD onset and seizures also has been noted in other studies.[6]

We reviewed the pathophysiologic processes of acute seizure activity in old age and closelinkage to cognitive decline.

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Pathophysiology: Closelinkage Epilepsy to Cognitive Decline

Several clinical and experimental data support a correlation between pathophysiological processes sustaining epilepsy and cognitive impairment of dementia. Ictal and postictal effects of the seizures themselves and the effects of the interictal epileptiform electroencephalography discharges may have an impact on cognition.[7,8]

There are several mechanisms that could link acute seizure activity in old age to cognitive dysfunction.

Neurogeneration and age-related factors

Seizure activity in AD has been widely interpreted as a secondary process resulting from advanced stages of neurodegeneration, perhaps in combinations with other age-related factors. The epileptogenic mechanism in patients with recurrent seizures and a progressive neurodegenerative disorder may relate to the findings of neuronal loss and gliosis in selected regions such as the medial temporal lobe. The pathological findings underlying the temporal lobe may be similar in patients with mesial temporal sclerosis associated with partial epilepsy and the clinical entity entitled "hippocampal sclerosis dementia".[9]

Aging and hippocampus

Aging induces numerous changes in the hippocampus. The changes in the aged hippocampus include decreased concentrations of vital neurotrophic factors that play neuroprotective roles, enhanced levels of glucocorticoids and molecules that induce oxidative stress, diminished concentration of endogenous antioxidants, decreased numbers of gamma-aminobutyric acid-ergic inhibitory interneurons that control the activity of excitatory principal neurons, the possible aberrant mossy fiber innervations of granule cell dendrites in the inner molecular layer enhancing the excitatory tone of the dentate gyrus, decreased frequency of spontaneous inhibitory postsynaptic potentials, and increased propensity for large amplitude prolonged excitatory postsynaptic potentials following disinhibition.[10,11] These above changes likely contribute to the perceived increases in the susceptibility of the aged population for developing acute seizure activity.

Previous studies in animal models have already suggested that aged animals exihibit increased seizure susceptibility and an enhanced injury after seizures.[11] This was mainly evidenced by the observation that much a lower dose of kainic acid is not only adequate for eliciting status epilepticus but also sufficient for maintaining a greater extent of overall acute seizure activity in aged rats.[12,13]

Hippocampal sclerosis is also frequently associated with frontotemporal lobar degeneration.[9,14] However, previous studies showed that the presence of hippocampal neuronal loss in patients with a progressive neurodegenerative disorder may not indicate an increased seizure tendency, and only one patient of eighteen with frontotemporal degeneration and hippocampal sclerosis had seizures.[15]

The current study compared the effects of 3 hours of acute seizure activity on the extent of hippocampal neurodegeneration between the young adult and aged rats.[10] The degeneration of neurons in the CA1 pyramidal cell layer showed a clear interaction between age and acute seizure activity (i.e. 56% in aged rats and 12% in young adult rats), suggesting that an advanced age makes the CA1 pyramidal neurons more susceptible to die with acute seizure activity. The precise reasons for an increased vulnerability of CA1 pyramidal neurons in the aged brain to acute seizure activitymediated death are unknown. This may be due to an increased level of intracellular calcium in CA1 pyramidal neurons of the aged brain. CA1 pyramidal neurons in the aged brain exhibit increased L-type voltage-sensitive calcium channels, elevated intracellular calcium levels, and an altered calcium homeostasis.[16] Thus, acute seizure activity in old age results in a greater loss of hippocampal CA1 pyramidal neurons, an increased tendency for developing chronic temporal lobe epilepsy, and a severe cognitive dysfunction.

Aging and acute seizure activity-mediated cognitive dysfunction

The effects of acute seizure activity on cognitive function are much severe in the old age than in the young adult age. This could be due to a greater loss of CA1 pyramidal neurons observed in the aged hippocampus after acute seizure activity and a decreased plasticity of the aged hippocampus to acute seizure activity. With regard to plasticity, it has been known that acute seizure activity or focal hippocampal injury in young adult rats increases the concentrations of multiple beneficial neurotrophic factors including the brain-derived neurotrophic factor.[10] However, this kind of neurotrophic response does not occur in aged rats.

Acute seizure activity in young adult rats greatly increases the extent of hippocampal neurogenesis,[17,18] and it is believed to be important for functions such as learning and memory. In contrast, enhancing hippocampal neurogenesis after acute seizure is failed in aged rats.

Finally acute seizure activity in the old age is highly detrimental for brain function. It leads to a much greater loss of hippocampal CA1 pyramidal neurons, enhances the intensity of spontaneous recurrent seizures, and induces a much greater impairment in the hippocampus-related cognitive function.

Underlying vascular pathology

The overall incidence of cerebrovascular related seizures is approximately 8.9%.[19] Stroke patients with epileptic seizures have an increased risk of new-onset dementia within 3 years after stroke.[20] Epileptic seizures are a marker of an underlying condition that is associated with an increased susceptibility to dementia. It may be due to pre-existing vascular pathologies such as white matter changes, silent infarcts or microbleeds.[20,21] Experimental studies in rats suggest that repeated seizure-like activity in the setting of cerebral ischemia increases infarct size and can impair functional recovery. Patients with white matter changes, who develop seizures, have a more severe decline of regional cerebral blood flow and regional cerebral metabolic rate for oxygen than those without seizures.[22] Subcortical white matter changes and lacunes account most for vascular cognitive impairment and vascular dementia.

It is not clear whether a single seizure may lead to a worse cognitive outcome. However, late-onset seizures after an ischemic stroke are considered to be harmful.[23] Treating adequately the first late-onset seizure episode after an ischemic stroke is needed to be considered to prevent cognitive impairment and its progression.

Although neurodegeneration/aging-related cofactors and preexisting vascular pathologies may contribute to the development of seizures in AD, recent data suggested that high

levels of Aβ are sufficient to elicit epileptiform activity and seizures, even at early stages of the disease process and in the absence of overt neuronal loss.[24]

Aβ-induced aberrant excitatory neuronal activity in Alzheimer disease

β-amyloid (Aβ) peptides may contribute to cognitive decline in AD by eliciting similar aberrant neuronal activity in humans.[4,25] Aβ-induced aberrant excitatory neuronal activity and cognitive decline in humans with AD raised the possibilities that epileptiform activity could represent a primary mechanism that may contribute to cognitive deficits.

High levels of Aβ cause epilepsy and cognitive deficits

Aβ causes depression of excitatory neurotransmitter at specific connections. High levels of Aβ are sufficient to elicit epileptiform activity in vivo in the absence of frank neurodegeneration. Therefore, aberrant network synchronization appears to be a primary effect of high Aβ levels rather than a secondary consequences of extensive neurodegeneration.

Recently Palop and Mucke reviewed the experimental data that high levels of Aβ in the brain can cause epileptiform activity and cognitive deficits in transgenic mouse models of AD.[25] Aβ-induced epileptic activity was associated with sprouting of inhibitory axonal terminals in the molecular layer of the dentate gyrus, enhancing synaptic inhibition, and alterations in several calcium- and activity-regulated proteins in granule cells including calbindin, Fos, and Arc (Fig. 1).[24] These alterations correlated tightly with each other and with deficits in learning and memory, suggesting that Aβ-induced aberrant neuronal activity and associated compensatory inhibitory responses may be causally linked to cognitive decline.

Apolipoprotein E4 is associated with subclinical epileptiform activity in carriers without dementia

Apolipoprotein is the most important known genetic risk factor for sporadic AD.[26] ApoE4 also exacerbates epilepsy and promotes memory impairment in patients with long-standing intractable temporal lobe epilepsy.[3] Major genetic risk factors for developing AD are associated with increased network excitability in individuals without dementia, suggesting that this type of network dysfunction might play an early role in the establishment of pathogenic cascades leading to AD.

Limitations of Diagnostic Approach for Elderly Epilepsy Patients with Dementia

There are several limitations for immediate notifying partial seizures, especially in elderly. Partial seizures without convulsive components or with subtle alterations in alertness may have been underrecorded. Thus seizure diagnosis may underestimate the rates of seizure occurrence. Furthermore description of epileptic semiology may be less reliable in individuals with dementia. These factors may lead to seizure underestimated.[23] In contrast, fluctuations in alertness and attention and presence of tremor may lead to seizure overestimation.

Conclusion

The most striking finding in epilepsy patients with elderly

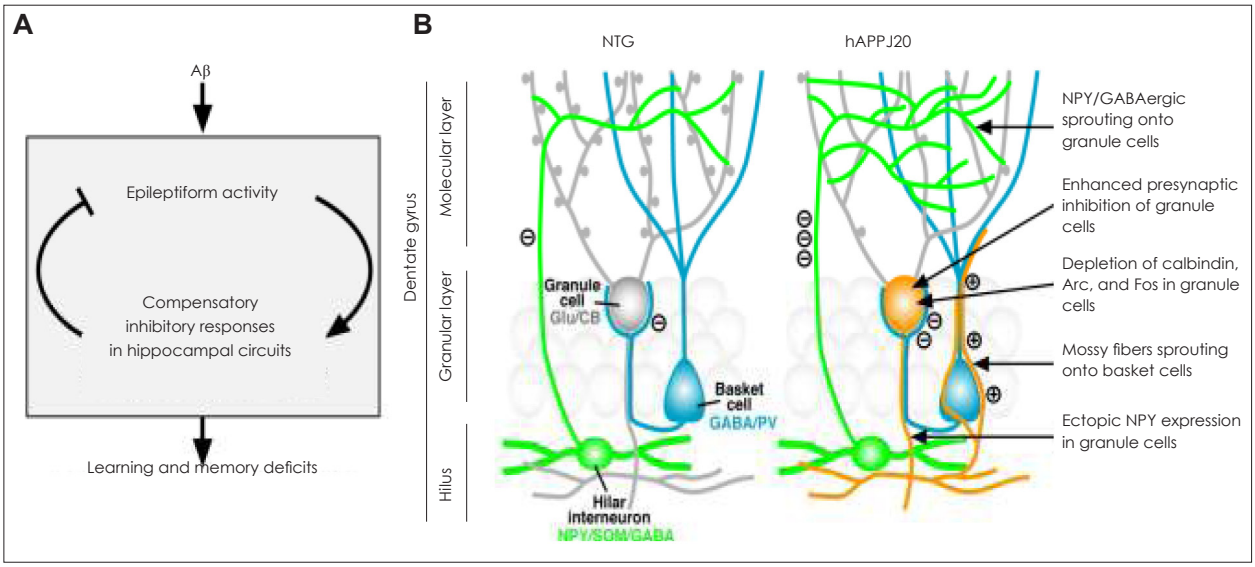

FIGURE 1. β-amyloid (Aβ) cascade hypothesis and hippocampal remodeling. A: High levels of Aβ induce epileptiform activity, which triggers compensatory inhibitory response to overexcretion. B: Aβ-dependent circuit remodeling in the dentate gyrus of human amyloid precursor protein transgenic mice (hAPPJ20). NTG: nontransgenic mice, CB: calbidin, Glu: glutamate, GABA: gamma-aminobutyric acid, PV: parvalbumin, NPY: ectopic neuropeptide Y, SOM: somatostatin. Adapted from Neuron.[25]

is the excellent treatment outcome. Although the long-term effect of seizure activity on the neurodegenerative disorder is unknown, one could speculate that treating the epilepsy is beneficial to the patient. Early application of both anticonvulsant and neuroprotective treatments after the onset of acute seizure activity is critical for preventing or decreasing the extent of acute seizure activity-mediated cognitive dysfunction in the aged population.

REFERENCES

1. de la Court A, Breteler MM, Meinardi H, Hauser WA, Hofman A. Prevalence of epilepsy in the elderly: the Rotterdam Study. *Epilepsia* 1996;37:141-7.
2. Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. *Drugs Aging* 2003;20:791-803.
3. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* 2006;47:867-72.
4. Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. *Epilepsy Behav* 2009;14:118-20.
5. Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, et al. Seizures in Alzheimer disease: who, when, and how common? *Arch Neurol* 2009;66:992-7.
6. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch Neurol* 1990; 47:847-50.
7. Bottaro FJ, Martinez OA, Pardal MM, Bruetman JE, Reisin RC. Nonconvulsive status epilepticus in the elderly: a case-control study. *Epilepsia* 2007;48:966-72.
8. Aldenkamp AP, Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of "transient cognitive impairment" still valid? *Epilepsy Behav* 2004;5 Suppl 1:S25-34.
9. Velez-Pardo C, Arellano JI, Cardona-Gomez P, Jimenez Del Rio M, Lopera F, De Felipe J. CA1 hippocampal neuronal loss in familial Alzheimer's disease presenilin-1 E280A mutation is related to epilepsy. *Epilepsia* 2004;45:751-6.
10. Hattiangady B, Kuruba R, Shetty AK. Acute Seizures in Old Age Leads to a Greater Loss of CA1 Pyramidal Neurons, an Increased Propensity for Developing Chronic TLE and a Severe Cognitive Dysfunction. *Aging Dis* 2011;2:1-17.
11. Patrylo PR, Tyagi I, Willingham AL, Lee S, Williamson A. Dentate filter function is altered in a proepileptic fashion during aging. *Epilepsia* 2007;48:1964-78.
12. Darbin O, Naritoku D, Patrylo PR. Aging alters electroencephalographic and clinical manifestations of kainate-induced status epilepticus. *Epilepsia* 2004;45:1219-27.
13. Liang LP, Beaudoin ME, Fritz MJ, Fulton R, Patel M. Kainate-induced seizures, oxidative stress and neuronal loss in aging rats. *Neuroscience* 2007;147:1114-8.
14. Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, et al. Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia. *Neurology* 2004;63:538-42.
15. Josephs KA, Whitwell JL, Jack CR, Parisi JE, Dickson DW. Frontotemporal lobar degeneration without lobar atrophy. *Arch Neurol* 2006;63:1632-8.
16. Raza M, Deshpande LS, Blair RE, Carter DS, Sombati S, DeLorenzo RJ. Aging is associated with elevated intracellular calcium levels and altered calcium homeostatic mechanisms in hippocampal neurons. *Neurosci Lett* 2007;418:77-81.
17. Rao MS, Hattiangady B, Shetty AK. Status epilepticus during old age is not associated with enhanced hippocampal neurogenesis. *Hippocampus* 2008;18:931-44.
18. Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely declined dentate neurogenesis in the adult hippocampus. *Neurobiol Dis* 2004;17:473-90.
19. Reith J, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. *Stroke* 1997;28:1585-9.
20. Cordonnier C, Hénon H, Derambure P, Pasquier F, Leys D. Early epileptic seizures after stroke are associated with increased risk of new-onset dementia. *J Neurol Neurosurg Psychiatry* 2007;78:514-6.
21. Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Post-stroke dementia: incidence and relationship to prestroke cognitive decline. *Neurology* 2001;57:1216-22.
22. De Reuck J, Decoo D, Boon P, Strijckmans K, Goethals P, Lemahieu I. Late-onset epileptic seizures in patients with leukoaraiosis: a positron emission tomographic study. *Eur Neurol* 1996;36:20-4.
23. De Reuck J, De Clerck M, Van Maele G. Vascular cognitive impairment in patients with late-onset seizures after an ischemic stroke. *Clin Neurol Neurosurg* 2006;108:632-7.
24. Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* 2007;55:697-711.
25. Palop JJ, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. *Arch Neurol* 2009;66:435-40.
26. Busch RM, Lineweaver TT, Naugle RI, Kim KH, Gong Y, Tilelli CQ, et al. ApoE-epsilon4 is associated with reduced memory in long-standing intractable temporal lobe epilepsy. *Neurology* 2007;68:409-14.