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The Crossroads Between Alzheimer's Disease Pathophysiology and Epilepsy

Association of Plasma Aβ42/Aβ40 Ratio and Late-Onset Epilepsy: Results From the Atherosclerosis Risk in Communities Study

Johnson EL, Sullivan KJ, Schneider ALC, Simino J, Mosley TH, Kucharska-Newton A, Knopman DS, Gottesman RF. *Neurology*. 2023 Sep 26;101(13):e1319-e1327. doi:10.1212/WNL.0000000000207635. Epub 2023 Aug 4. PMID: 37541842

Background and Objectives: The objective of this study was to determine the relationship between plasma β-amyloid (Aβ), specifically the ratio of 2 Aβ peptides (the $A\beta_{42}/A\beta_{40}$ ratio, which correlates with increased accumulation of Aβ in the central nervous system [CNS]), and late-onset epilepsy (LOE). Methods: We used Medicare fee-for-service claims codes from 1991 to 2018 to identify cases of LOE among 1424 Black and White men and women enrolled in the Atherosclerosis Risk in Communities (ARIC) study cohort. The $A\beta_{42}/A\beta_{40}$ ratio was calculated from plasma samples collected from ARIC participants from 1993 to 1995 (age 50-71 years) and 2011 to 2013 (age 67-90 years). We used survival analysis accounting for the competing risk of death to determine the relationship between late-life plasma $A\beta_{42}/A\beta_{40}$, and its change from midlife to late life, and the subsequent development of epilepsy. We adjusted for demographics, the apolipoprotein e4 genotype, and comorbidities, including stroke, dementia, and head injury. A low plasma ratio of 2 Aβ peptides, the $A\beta_{42}/A\beta_{40}$ ratio, correlates with low CSF $A\beta_{42}/A\beta_{40}$ and with increased accumulation of Aβ in the CNS. Results: A decrease in plasma $A\beta_{42}/A\beta_{40}$ ratio from midlife to late life, but not an isolated measurement of $A\beta_{42}/A\beta_{40}$, was associated with the development of epilepsy in later life. For every 50% reduction in $A\beta_{42}/A\beta_{40}$, there was a 2-fold increase in the risk of epilepsy (adjusted subhazard ratio 2.30, 95% CI: 1.27-4.17). Discussion: A reduction in plasma $A\beta_{42}/A\beta_{40}$ is associated with an increased risk of subsequent epilepsy. Our observations provide a further validation of the link between Aβ, hyperexcitable states, and LOE.

Similar Brain Proteomic Signatures in Alzheimer's Disease and Epilepsy

Leitner D, Pires G, Kavanagh T, Kanshin E, Askenazi M, Ueberheide B, Devinsky O, Wisniewski T, Drummond E. *Acta Neuropathol*. 2024 Jan 30;147(1):27. doi:10.1007/s00401-024-02683-4. PMID: 38289539

The prevalence of epilepsy is increased among Alzheimer's disease (AD) patients and cognitive impairment is common among people with epilepsy. Epilepsy and AD are linked but the shared pathophysiological changes remain poorly defined. We aim to identify protein differences associated with epilepsy and AD using published proteomics datasets. We observed a highly significant overlap in protein differences in epilepsy and AD: 89% (689/777) of proteins altered in the hippocampus of epilepsy patients were significantly altered in advanced AD. Of the proteins altered in both epilepsy and AD, 340 were altered in the same direction, while 216 proteins were altered in the opposite direction. Synapse and mitochondrial proteins were markedly decreased in epilepsy and AD, suggesting common disease mechanisms. In contrast, ribosome proteins were increased in epilepsy but decreased in AD. Notably, many of the proteins altered in epilepsy interact with tau or are regulated by tau expression. This suggests that tau likely mediates common protein changes in epilepsy and AD. Immunohistochemistry for Aβ and multiple phosphorylated tau species (pTau396/404, pTau217, and pTau231) showed a trend for increased intraneuronal pTau217 and pTau231 but no phosphorylated tau aggregates or amyloid plaques in epilepsy hippocampal sections. Our results provide insights into common mechanisms in epilepsy and AD and highlight the potential role of tau in mediating common pathological protein changes in epilepsy and AD.

Commentary

Incidence of epilepsy diagnosis peaks at lifetime opposites, at the first decade and after age 60, with a higher incidence at age 70 than during childhood years. Focal seizures are the most frequent presentation in late-onset epilepsy (LOE), with an underlying cause identified in most patients including cerebrovascular insult, tumors, dementia, and paraneoplastic syndromes.

One of the most important evolving questions in aging populations is the relationship between Alzheimer's disease (AD) pathophysiology and epilepsy, and more so LOE of unknown etiology.[1] AD is a neurodegenerative disease characterized by the accumulation of amyloid β (Aβ) and microtubule-associated protein tau in the brain, starting with extracellular deposition and spread of Aβ plaques prior to the onset of clinical symptoms, down streaming with intraneuronal cytoplasmic hyperphosphorylated tau (p-tau). These neuropathological changes result in synaptic toxicity, neuronal dysfunction, accumulation of neurofibrillary tangles, neurodegeneration, and cognitive impairment. Epilepsy occurs 2 to 3 times more frequently in people with AD than in the general population, and the risk of seizures increases with disease duration and progression.

When seizures arise early in the disease course, however, it might enhance the rate of progression of cognitive decline. Data from experimental models support an epileptogenic role of Aβ pathology, including observation of neuronal hyperexcitability, epileptiform discharges, unprovoked seizures, findings which are associated with cognitive decline.[2] In support of this framework, human data suggest that focal seizures presenting with subtle and nonconvulsive features can go undiagnosed, be an inaugural clinical manifestation, and even present with pharmacoresistance, before dementia is diagnosed. Electroencephalography utilizing foramen ovale electrodes in AD patients can identify subclinical seizures and frequent epileptiform discharges not depicted by scalp recordings.[3]

For long, AD diagnosis required confirmation of Aβ and tau pathology in post-mortem brains. AD can now be diagnosed in vivo through cutting-edge biomarkers, including affordable and noninvasive measurements, some of which are now clinically approved diagnostic tools. Quantification of Aβ and tau biomarkers in cerebrospinal fluid (CSF), through positron emission tomography, and more recently in plasma, bring AD patients the possibility of early diagnosis and candidacy for disease-modifying therapies. There is now a unique unfolding opportunity based on new biomarkers for in vivo diagnosis and multiomics research advances to further clarify clinical and basic science evidence linking AD and epilepsy.[4]

The Aβ peptide has been previously identified as a key player between AD and seizures. Aβ1-40 ($A\beta_{40}$) and 1–42 ($A\beta_{42}$) peptides mediate synaptic and cognitive dysfunction in AD, and decreased CSF levels of $A\beta_{42}$ in patients with LOE of unknown etiology suggest brain accumulation of this peptide as a possible link between the 2 diseases. $A\beta_{42}/A\beta_{40}$ ratio is a validated AD biomarker in CSF, but limitations in blood measurements make it yet not suitable for routine clinical testing. In the Arizona Study of Aging and Neurodegenerative Disorders cohort, which included antemortem plasma samples and a postmortem neuropathological exam of 105 individuals, the $A\beta_{42}/A\beta_{40}$ ratio, likewise p-tau231, was associated with Aβ plaques but not with neurofibrillary tangles.[5] Experimental mesial temporal lobe epilepsy (MTLE) models have demonstrated tau hyperphosphorylation during epileptogenesis as well as during the chronic stage when spontaneous seizures occur, with an increase in hyperexcitability mediated through increased presynaptic glutamate release. A large Swedish study on CSF biomarker results from 17 901 AD patients, including 851 who also had epilepsy, found that concentrations of total tau and p-tau were higher in patients with epilepsy than those without, and that $A\beta_{42}$ levels were significantly lower in patients with epilepsy.[6]

In brief, the study by Johnson et al[7] explored the association of plasma $A\beta_{42}/A\beta_{40}$ ratio, as an indirect index for Aβ brain pathology, and the development of LOE. The article by Leitner et al[8] reported protein change differences and similarities between epilepsy and AD post-mortem brain analyses.

Johnson et al[9] assessed the cohort from the Atherosclerosis Risk in Communities (ARIC) study, which is a prospective multicenter cohort study initiated in 1985, to identify risk factors for subclinical atherosclerosis. ARIC included 15 792 participants from African American and Caucasian ethnicities, between the ages of 45 and 65, from 4 USA communities, with follow-up over 35 years. In an earlier secondary analysis of the ARIC cohort, LOE (defined in the study as ≥ 2 seizure-related diagnostic Medicare claims codes at age 67 or older) occurred in 596/10 420 participants studied. Hypertension, diabetes, smoking, incident stroke and dementia, and the apolipoprotein (APOE) ϵ4 genotype, were positively associated with the risk of developing LOE. In the current study, the authors observed that for a 50% decrease in plasma $A\beta_{42}/A\beta_{40}$ ratio (corrected for the previously identified factors) from a first sampling at midlife, to a second sampling approximately 18 years later, there was a 2-fold increase in the risk of LOE.

These interesting observations provide background rationale for future prospective studies combining imaging and fluid biomarkers. Keeping in mind that Aβ pathology correlates with age, age-related reduction in $A\beta_{42}/A\beta_{40}$ ratio measured at 2 timepoints 18 years apart might be co-occurring with other mechanistic factors underlying increased Aβ pathology, independently of the occurrence of LOE. The authors clearly recognize the limitations of a small number of included participants and the oversampling of cognitively impaired participants (half of whom were diagnosed with cognitive impairment at the time of the second sampling), which impact the findings and their possible relevance. It is also important to note that as blood biomarkers are validated in well-characterized cohorts, their performance and applicability to the clinical practice still require validation in real-world scenarios for demonstration of robustness. In cognitively unimpaired individuals, plasma $A\beta_{42}/A\beta_{40}$ ratio has been shown to be significantly lower in comorbid diabetes, and arterial hypertension, and it is influenced by glomerular filtration rate. More studies are necessary to determine the extent to which confounders such as these

can have an impact on peripheral biomarkers such as $A\beta_{42}/A\beta_{40}$ ratio, before establishing an association with LOE.

Proteomics encompasses the comprehensive study of the whole set of proteins produced by a living organism, including their structure and functions.[10] The study by Leitner et al evaluated protein differences in post-mortem brain tissue from younger (9-64yo at death) epilepsy patients and controls from autopsy, using published proteomics datasets for epilepsy and AD.

The proteomic epilepsy dataset was obtained from the authors' previous study on the North American sudden unexpected death in epilepsy (SUDEP) Registry, from a subset of patients who died from other causes than SUDEP, at 1 to 49.5 years from disease onset. Types of seizures were not determined in 10/14 patients and were described as focal in 4. The dataset used in the recent study consisted of 777 proteins significantly altered in microdissected CA1-3 hippocampal regions in epilepsy versus controls (134 of which showed similar directional changes in the other brain regions analyzed, ie, the dentate gyrus and the superior frontal gyrus). The proteomic AD profile was derived from NeuroPro (https://neuropro.biomedical.hosting), which is a combined analysis of 38 published proteomic studies and includes 5311 proteins altered in human AD brain tissue, from multiple brain regions.

Interestingly, there was a significant overlap in protein differences in epilepsy and AD, with 89% (689/777) of proteins altered in the hippocampus of epilepsy patients being also significantly altered in advanced AD, many of which were tau-regulated proteins. Synaptic and mitochondrial proteins were markedly decreased in epilepsy and AD, suggesting common disease mechanisms. Presynaptic and postsynaptic proteins, as well as proteins associated with synaptic vesicles, were decreased in both epilepsy and AD. In contrast, ribosome proteins were increased in epilepsy but decreased in AD, a finding that might indicate translation as a main drive in the establishment of an aberrant hyperexcitable network in epilepsy. The finding of many altered tau-regulated proteins in epilepsy hippocampal sections in the absence of increased total tau levels, p-tau aggregates, or amyloid plaque deposition, could suggest a potential downstream effect of tau in the maintenance of epileptogenicity. However, post-mortem findings cannot resolve the sequence of events leading to recurrent seizures and epilepsy. These proteins and their related pathways/networks could be altered as a consequence of epileptogenicity, or be a co-existing phenomenon.

With the advent of disease-modifying therapies for AD and the possibility of monitoring the effect of these therapies with fluid and CSF biomarkers, research on AD pathophysiology as possible drivers (or bystanders) in epileptogenesis should continue to be a high priority.

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