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Neurodegeneration in epilepsy and the relationship between epilepsy and Alzheimer's disease

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Abstract

Alongside memory loss and cognitive impairment, seizures are reported in patients living with Alzheimer's disease, typically in the later stages. Similarly, epilepsy is not commonly referred to as a neurodegenerative disease despite repeated global and focal seizures having the potential to cause loss of function, sclerosis and neurodegeneration in patients. A diagnosis of epilepsy carries and increased risk of developing Alzheimer's disease and vice versa, a diagnosis of Alzheimer's disease makes the risk of seizure higher than the average population. The extent to which these diseases are related is under reported and not well understood. This review of the current research aims to identify the connections between Alzheimer's disease and epilepsy at the level of physical presentation, pathophysiology and the extent to which one may be responsible for the incidence of the other.

1 Introduction

Epilepsy is diagnosed based on the presence of more than one generalized, or focal seizure and can be present from childhood, or develop in later life. Seizures are defined by inappropriate synchronous activity of neurons due to an imbalance of inhibitor and excitatory activity (Staley, 2015), induced by heterogeneous cellular and molecular alterations (Pitkänen & Lukasiuk, 2009).

Epilepsy is not typically referred to as neurodegenerative. As a lifelong syndrome, cumulative seizures could feasibly cause neurodegeneration by consistent alteration of cellular mechanisms (Thom, 2014). Temporal lobe epilepsy (TLE) is the most common and widely studied epilepsy syndrome, predominantly characterized by hippocampal sclerosis (HS). Epileptic neurodegeneration is best described here, hence this essay will focus largely on TLE, exploring possible mechanisms for neurodegeneration such as seizures, protein aggregation and inflammation

Some of these mechanisms are shared with Alzheimer's Disease. This is unlikely a 33 coincidence. Increased risk of epilepsy within AD (and vice versa) has been known for some time. Seizures occur in AD patients up to 6-10 times more often than in healthy controls (Cretin et al., 2016), classically later in the disease course. However, this essay presents evidence for seizures occurring early or even preceding an AD diagnosis. Seizures in TLE originate in the temporal lobes, where AD pathology is highly prevalent, suggesting a disease spectrum may be present here.

Precisely how these diseases are associated remains to be elucidated. The relationship between AD and epilepsy is discussed with respect to potential interconnecting pathways, converging at the temporal lobes.

2 Methods

Articles were collected from PubMed, Medline and Google scholar. Search syntax included: epilepsy; atrophy; neurode-

generation; progressive; neuronal loss; Alzheimer's disease; mechanisms and seizures. Relevance was evaluated based on titles, abstracts and using the inclusion criteria: peer reviewed; published from 2007 onwards; clinical diagnosis if epilepsy, AD or MCI where appropriate; primary research data and reviews. Exclusion criteria included dissertations, abstracts, editorials and unpublished comment.

3 Results and Discussion

3.1 Epilepsy as a neurodegenerative disease

3.1.1 Evidence for neurodegeneration in epilepsy

Diagnostic criteria of HS in TLE is noteworthy in assessing neurodegeneration. Criteria requires neuronal loss in hippocampal pyramidal cells, principally in CA1, 3 and 4 (Pitkänen & Lukasiuk, 2009) (Thom, 2014), suggesting neuron reduction can indeed give 58 rise to an epileptic disease course. Additionally, kainic acid induced rat models of 59 epilepsy exhibit neuronal loss (Bertoglio et al., 2017). Conversely, the term 'neurodegeneration' implies ongoing loss, for which data is conflicting. Thom, 2014 report a general absence of necrotic or apoptotic neurons in surgically removed tissue in TLE treatment, suggesting lack of ongoing loss and indeed neurodegeneration is not necessary for epileptogenesis (Pitkänen & Lukasiuk, 2009).

Contrastingly, longitudinal analysis by Bernhardt et al., 2009 demonstrated progressive cortical atrophy in TLE using serial MRI, increasing with disease duration outside normal ageing. This study removed bias from post-surgery samples where patients have severe epilepsy, and shows the effects of focal seizures on the entire brain. It also provides high impact longitudinal MRI evidence, other studies largely using retrospective or post-surgery analysis. Exclusion criteria for randomized patient selection was absent, therefore comorbidities particularly in old age, where neurodegenerative disease is highly prevalent aren't accounted for.

3.2 Possible mechanisms of neurodegeneration

3.2.1 Seizures

Neurodegeneration often involves transient protein aggregation, associated with cellular dysfunction. Where this is absent in epilepsy, synchronous activity of seizures could induce neurodegeneration through cumulative excitotoxic insults. Lin et al., 2007 demonstrated through MRI, a reduction in cortical thickness ipsilateral to the site of seizure propagation in TLE (30 patients). One cannot definitively conclude seizures directly cause neurodegeneration from this, as patients were seizure free for 2 years. Alternatively, this could demonstrate long-term effects of seizures such as changes in cellular function and protein transcription via miRNA control (Thom, 2014). In support, pilocarpine-induced mouse models of TLE showed a negative correlation between seizure number and hippocampal neurons (Lopim et al., 2016). Here, seizure number peaked at 180 days of life before decreasing, whereas neuronal loss continued. Animal models enable the study of TLE where human post operation/post mortem samples are limited, although do not mimic human disease precisely; The effect of pilocarpine in this instance induced status epilepticus for 24 hours, unrepresentative of human epilepsy, although this may 'speed up' parallel events of human disease.

3.2.2 Inflammation

Inflammation could provide novel explanations for seizure induced neurodegeneration. Translocator protein (TPSO), is expressed on activation of glia and inflammation, and is upregulated in TLE. Amhaoul et al., 2015 demonstrated TPSO increase correlates with a decrease in hippocampal neuronal markers in kainic acid induced rat models of TLE, progressing with seizure number and time. This supports a progressive disease course.

However, measurements were only taken up to 3 months in a small number of rats, therefore applicability to lifelong human disease is modest.

3.2.3 Tauopathy

Hyperphosphorylated tau protein is implicated in several neurodegenerative diseases including AD and is now recognised in epilepsy. Tau may induce neurodegeneration via the 'protein aggregation' model. Cerebral tau deposition is measured using Braak stages 1-6. A study by Thom et al., 2011, evidenced a correlation between higher Braak stage and epilepsy duration, and higher Braak stages were associated with a younger age at death. Although there was no association between Braak stage and seizure number or type, suggesting tau may act independently from seizures. Analysis here was limited to Braak staging, hence tau present outside Braak areas will not be included.

The incidence of tau in epilepsy suggests a possible interconnecting mechanisms with. Tau, and other pathways have been explored, uncovering why a clinical relationship exists, at a molecular level.

3.3 Relationship between epilepsy and AD

3.3.1 Tauopathy

Tai et al., 2016, analysed the distribution of tau relative to that seen in AD using immunohistochemistry on surgically removed tissue from TLE patients. 10 of 24 cases showed 'Braak-like' distributions, although overall tau deposition did not correlate with AD distribution and markedly, most cases were categorized to lower Braak stages. Exact mechanisms of tau tangle formation may differ in epilepsy resulting in differential patterns through selective vulnerability depending seizure type (focal or general). Pooler et al., 2013 suggest tau is released by synaptic activity, clearly altered in epilepsy and differing seizure types.

Despite bias to severe disease through surgical samples, studying this raises an interesting hypothesis: If severe TLE is more likely to be associated with AD and hyperphosphorylated tau, could this represent a subcategory of TLE?

3.3.2 ApoE4

The ApoE4 allele is a well recognised risk factor for AD. Aboud et al., 2013 found ApoE4 carriers with either epilepsy or AD exhibited a reduction in neuron size, increase in caspase

3 levels, a reduction in S100 (neuron promoting cytokine) and an increase in oxidative stress. These differences were not observed in neurologically normal controls despite ApoE4 genotype. These mechanisms could link the 2 diseases and support the notion of epilepsy as neurodegenerative and the increase in oxidative stress could demonstrate an increase in inflammation, supporting its neurodegenerative role. The authors suggest a 'self-perpetuating' pathway whereby glutamate released in a seizure promotes ApoE4 expression, increasing APP, sAPP, IL-1, and subsequently glutamate.

3.3.3 Amyloid beta (a)

In the same study, ApoE4 carriers with epilepsy showed an increase in a plaque, associated with AD, compared with ApoE2/3 carriers. a accumulation could be explained by the self-propagating mechanism previously described. The study does not compare epileptic ApoE4 carriers against control ApoE4 carriers, which would show whether an epilepsy diagnosis amplifies ApoE4 effects and increases AD risk with respect to the population. However, the notion that ApoE4 can cause plaques to mature rapidly, as the authors demonstrate in a patient 10 years old, could highlight an early onset AD predisposition in epilepsy patients.

In support, in animal models, a plaque triggers epileptogenesis (Cretin, Di Bitonto, Blanc, & Magnin, 2015).a could be responsible for network synchronization and increased seizure risk in AD patients (Palop & Mucke, 2009).

3.3.4 Seizures

Seizures are often reported at late stage AD. Conflictingly, Cretin et al., (2015), Cretin et al., (2016) and Vossel et al., (2013) showed seizures preceded amnesic mild cognitive impairment (aMCI) by up to 7 years and was correlated with cognitive decline. In case control studies by Cretin et al., 2016, patients had existing aMCI and were retrospectively studied for comorbid epilepsy. Retrospective detail was given by patients/carers. Unresponsive/non-convulsive spells (now known to be common in early AD (Vossel et al., 2013), may be forgotten or missed, underestimating seizure frequency.

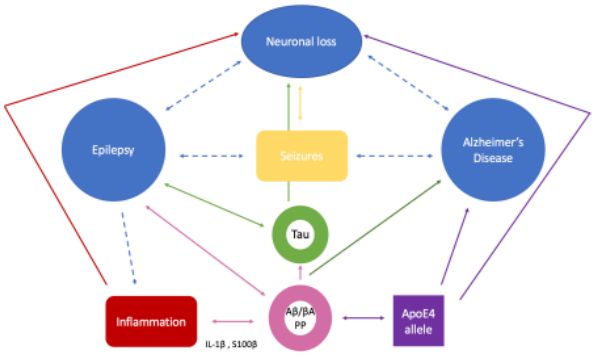
AD patients experiencing seizure disorders have greater cognitive impairment than AD alone, and clinical symptoms correlate with location of seizure onset. Vossel et al., (2013) found patients who developed epilepsy had a quicker onset to AD from MCI than those who did not by 6.8 years. Epileptiform activity was also largely apparent in the temporal lobes, consistent with AD pathology. This evidence shows epilepsy not only predisposes patients to AD, but also perpetuates symptoms.

4 Conclusions

Although evidence for epilepsy as a neurodegenerative disease is conflicting, strong evidence is given by serial MRI in humans correlating with disease duration. Global seizures are widely understudied and could represent another mechanism of neuronal loss separate from TLE. The data suggests rather than being a disease mechanism, neuronal loss could manifest as a result of epilepsy over time. Future studies should consider biomarkers for inflammation/plaque accumulation supporting current studies for mechanisms of neuronal loss.

Results demonstrate a huge potential connection between seizures, a and tau deposition summarized in Figure 1. Particularly at the level of tau tangle formation and implications for AD risk. Further studies should indicate at what level tau is correlated with a in epilepsy and by comparison with AD. From the presently discussed data, it seems feasible there could be a spectrum of the two diseases or even, an epileptic variant of AD.

Figure 1.



Summary of possible interconnecting mechanisms between Alzheimer's disease and TLE and modes of neurodegeneration discussed. The figure demonstrates how complex this interaction could be with many factors being implicated. Potentially the most important connection highlighted here could be the correlation between seizures and neuronal loss, leading to cognitive dysfunction seen at MCI, and secondly, the implication of tau and amyloid in epilepsy, which could give rise to a direct link to AD.

Author statements

Conflicts of interest statement

No conflicts of interest have been declared by any authors.

Authorship statement

All authors fulfill ICMJE authorship criteria, which can be accessed at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. All authors have read and approved the final version, and accept responsibility for information published.

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identity and institution.

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