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Epilepsy as a Network Disorder (2): What can we learn from other network disorders such as dementia and schizophrenia, and what are the implications for translational research?☆

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ABSTRACT

There is common agreement that many disorders of the central nervous system are 'complex', that is, there are many potential factors that influence the development of the disease, underlying mechanisms, and successful treatment. Most of these disorders, unfortunately, have no cure at the present time, and therapeutic strategies often have debilitating side effects. Interestingly, some of the 'complexities' of one disorder are found in another, and the similarities are often network defects. It seems likely that more discussions of these commonalities could advance our understanding and, therefore, have clinical implications or translational impact. With this in mind, the Fourth International Halifax Epilepsy Conference and Retreat was held as described in the prior paper, and this companion paper focuses on the second half of the meeting. Leaders in various subspecialties of epilepsy research were asked to address aging and dementia or psychosis in people with epilepsy (PWE). Commonalities between autism, depression, aging and dementia, psychosis, and epilepsy were the focus of the presentations and discussion. In the last session, additional experts commented on new conceptualization of translational epilepsy research efforts. Here, the presentations are reviewed, and salient points are highlighted.

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1. Introduction

After decades of focused research into complex disorders such as dementia, schizophrenia, and epilepsy, it has become clear that there are overlapping components. Often, this interrelationship is simplified by stating that seizures are a "comorbidity" of what is considered to be "another" disorder like Alzheimer's disease, or epilepsy is a "risk factor" for Alzheimer's disease. The implication is that "neurology" and "psychiatry" are less divided than one might think, and our approach to research and treatment should be adapted accordingly.

To reassess the relationships between neurological and psychiatric conditions in general, and specifically autism, depression, Alzheimer's disease, schizophrenia, and epilepsy, a recent meeting entitled "Epilepsy as a Network Disorder" brought together basic researchers and clinician scientists. This was the fourth in a biennial series of conferences, the "Fourth International Halifax Epilepsy Conference and Retreat".

The preceding publication by Kanner et al. (in this issue) describes the first presentations of the meeting, which summarized the current understanding of epidemiological data on all the medical conditions listed above in relation to their co-occurrence with epilepsy (Session "A" of the meeting program). The prior paper also discussed the second session of the program ("B"), which provided perspectives on the overlap and/or bidirectional relationship of autism and epilepsy. This was followed by a discussion of depression and epilepsy in the next session ("C"). Below, the second half of the program, sessions D–F, are summarized. First, an overview of session "D" is provided, which focused on the reasons and potential common pathophysiology underlying the comorbidity of aging and dementia. Session D was followed by different viewpoints about psychosis in people with epilepsy ("E"). The last session of the meeting ("F") included presentations of diverse researchers who tried to address a very difficult topic, the current conceptual thinking in translational research with respect to brain networks and abnormalities in neuronal circuitry in epilepsy.

2. Aging, dementia, and epilepsy (part "D" of the meeting program)

A very common complaint in patients with epilepsy is a change in memory and behavior [1,2]. In addition, it has been noted that patients have seizures when the primary diagnosis is dementia [3–6], the prototype being Alzheimer's disease. These clinical observations have led to a great deal of research to clarify the extent of these associations epidemiologically, and led to extensive efforts to develop and use animal models to understand potential mechanisms. In the past decade, the extent of the research has expanded greatly, making it timely to discuss the current state of knowledge. In addition, whether a new direction or set of directions in research should be taken is important to consider.

As pointed out by Nathalie Jette (University of Calgary) in manuscript 1 (Kanner et al., in this issue), epidemiological studies are very heterogeneous in their methods, so it is not clear whether any given comorbidity is common or rare. For example, self-report is not always accurate (and certainly poor in those with dementia), population-based data may include screening tools that are not validated, and underdiagnosis and underascertainment are further limitations. It is also problematic that 'dementia' is increasingly called 'neurocognitive disorder'. The extent of epilepsy (spontaneous recurrent seizures) in dementia is not as clear as the degree that single seizures occur with dementia. Regarding dementia itself, Erkinjuntti et al. [7] report estimates of dementia alone in the range of 3.1–29.1%, depending on diagnostic criteria. The pooled period prevalence of epilepsy in dementia is around 5%, while the period prevalence of dementia in epilepsy ranges from 8.1 to 17.5% (for review, see [8]).

2.1. The neurovascular unit in aging and epilepsy

Alon Friedman

The "neurovascular unit" includes the vasculature and its functional interactions with the adjacent brain neuropil, including pericytes and adjacent extracellular matrix, neurons, and glia. Current animal research demonstrated in several models the role of compromised blood–brain barrier (BBB) in seizures and epileptogenesis, cognitive decline, and neurodegeneration.

Injury to a brain blood vessel not only results in activation of clotting mechanisms but also is followed by a progressive, often long-lasting increase in endothelial permeability [9]. Blood–brain barrier dysfunction following insults to the brain may last months and even years after injury [10,11]. It triggers the activation of astrocytes and neuroinflammation [12,13] that, depending on the brain region involved and age of the animal, will result in epileptogenesis and seizures [14,15]. One reported mechanism is the leak of serum proteins from the blood into the brain neuropil. Albumin, for example, has been shown to leak and activate transforming growth factor tumor growth factor beta (TGFβ) receptors and activate a proinflammatory signaling system. Mediated by phosphorylation of the Smad2/3 pathways, changes in gene expression underlie glial transformation [12] with altered extracellular homeostasis, neuroinflammatory response with rapid increase in IL-6 release as well as other proinflammatory cytokines [13,16], changes in extracellular matrix with reduced Gamma amino-butyric acid (GABAergic) transmission [17], and excitatory synaptogenesis with pathological plasticity [18]. The presence of serum albumin within the hippocampus will lead to further aberrant adult neurogenesis in the dentate gyrus, which has been suggested to alter the threshold for seizures [19–21]. Recent development of imaging methods allow quantitative imaging of BBB dysfunction after injuries to the cerebral cortex and white matter tracts (e.g., in American football players [22]).

Importantly, endothelial dysfunction triggers not only a neuroinflammatory response and epileptogenesis, but also prolonged seizures and status epilepticus — well-known inducers of the epileptogenesis process associated with vascular pathology [23,24] and leaky BBB [25]. In epileptic animals, vascular pathology was also reported to reflect angiogenesis [26] probably because of increased vascular endothelial growth factor (VEGF), which is important because VEGF can have anti-seizure effects [23,24,27]. Changes in BBB integrity are also observed with aging and were recently associated with cognitive decline [28]. The increased occurrence of BBB dysfunction in the aging brain may also explain the well-known increase in the incidence of epilepsy with age. Together with the development of novel imaging methods for the detection of BBB pathology, it has been suggested that a leaky BBB may become a method for the identification of injury- or age-related brain regions with hypersynchronous activity, or undergoing epileptogenesis, thus allowing the prediction of epilepsy [29] and related cognitive dysfunction. Overall, this presentation emphasized the close association of BBB leakages resulting from nonspecific injuries and age-related factors with seizure threshold reduction [22].

2.2. Network abnormalities and interneuron dysfunction in Alzheimer's disease

Jorge Palop

There is increasing evidence of commonalities between epilepsy and Alzheimer's disease in experimental findings in mice that overexpress a mutated form of amyloid precursor protein (APP), so that amyloid Aβ is increased. The original research demonstrated hyperexcitability in several animal models that simulate Alzheimer's disease neuropathology (for review see [30]).

These laboratory findings have been replicated, especially with models using the mice with APP overexpression and mutation [31–35]. Several clinical studies have found sporadic seizures in people with Alzheimer's disease. In one study [36], seizures were found particularly in patients with an onset of Alzheimer's disease that was relatively young (e.g., 50–70). In a recent paper by Zarea et al. [6], 132 patients of dominantly inherited Alzheimer's disease had seizures. However, these studies of familial Alzheimer's disease reflect the minority of patients because the vast majority are sporadic.

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