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Conference Proceedings

Epilepsy as a Network Disorder (1): What can we learn from other network disorders such as autistic spectrum disorder and mood disorders?

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ABSTRACT

Epilepsy is a neurologic condition which often occurs with other neurologic and psychiatric disorders. The relation between epilepsy and these conditions is complex. Some population-based studies have identified a bidirectional relation, whereby not only patients with epilepsy are at increased risk of suffering from some of these neurologic and psychiatric disorders (migraine, stroke, dementia, autism, depression, anxiety disorders, Attention deficit hyperactivity disorder (ADHD), and psychosis), but also patients with these conditions are at increased risk of suffering from epilepsy. The existence of common pathogenic mechanisms has been postulated as a potential explanation of this phenomenon.

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

This manuscript summarizes the proceedings on potential relations between Epilepsy on the one hand and autism and depression on the other. A companion manuscript provides a summary of the proceedings about the relation between epilepsy and Alzheimer's disease and schizophrenia, closed by the role of translational research in clarifying these relationships. The review of the topics in these two manuscripts will provide a better understanding of the mechanisms operant in some of the common neurologic and psychiatric comorbidities of epilepsy.

1. Introduction

The evaluation of patients with epilepsy (PWE) is not limited to the characterization of the epileptic seizures and syndrome; it demands an early identification and management of common comorbid neurologic and psychiatric disorders that, in fact, tend to occur with a higher frequency in these patients than in the general population. These include stroke, migraine, dementia, and autistic spectrum disorder (ASD) [1] among the neurologic comorbidities, and mood, anxiety, attention-deficit hyperactivity, and psychotic disorders among the psychiatric comorbidities [2]. The need to include these comorbidities in the management of PWE stems from their negative impact at multiple levels, which may be worse than that of the actual seizures, and which can impact the actual course and response to treatment of the seizure disorder [3].

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The relation between epilepsy and these comorbidities can be complex and often bidirectional. That is, not only PWE are at greater risk of developing these comorbidities but also patients with these primary psychiatric and neurologic disorders are at greater risk of developing epilepsy [4]. This phenomenon does not imply necessarily causation, but could be explained by the existence of common pathogenic mechanisms operant in epilepsy and these comorbidities.

The Fourth International Halifax Epilepsy Conference and Retreat in September 2016 in Nova Scotia, Canada was devoted to the recognition of potential common pathogenic mechanisms operant in epilepsy, ASD, dementia, depression, and schizophrenia. The goal was to use these data as a way of understanding reasons behind the relatively high comorbid occurrence of these neurologic and psychiatric comorbidities in PWE and to develop new hypotheses on the pathophysiology of these comorbid conditions.

The first day of the meeting was devoted to the review of ASD and depression, and the highlights of these presentations are summarized in this initial manuscript. The second day focused on dementia, schizophrenia, and translational research, and these are summarized in the companion document.

2. The epidemiology of comorbidity in epilepsy: advantages and limitations (Nathalie Jette)

The meeting was introduced with a review of epidemiologic aspects of these psychiatric and neurologic comorbidities and the limitations of the available data. It is important to understand the epidemiology of epilepsy comorbidity, as these comorbid disorders can contribute to poorer outcomes. For example, depression in epilepsy is associated with poorer response to antiepileptic drugs (AEDs) [5–7], worse seizure outcome after epilepsy surgery [8], poor tolerance of AEDs [9], higher risk of premature mortality [10], and higher health resource utilization [11].

However, there are important methodological issues that must be considered when evaluating epidemiological studies of epilepsy comorbidity. First, the control group (if applicable) should be matched for age and sex and, ideally, also for psychosocial factors as these can influence the prevalence and/or incidence of comorbidity. Second, selection bias must be minimized. Comorbidity, for example, may be more prevalent in a tertiary care clinic where more severe and complex PWE are followed or may be more prevalent in uninsured individuals. The source of ascertainment and the validity of the case definitions used to ascertain epilepsy and its comorbidity must also be carefully considered. Self-report could be associated with under- or overascertainment and recall bias, while administrative data may underascertain psychiatric comorbidities. Most contemporary studies tend to consider many of the above issues, but these caveats must still be considered when interpreting the findings of a study examining the comorbidity of epilepsy.

2.1. Epilepsy and autism

The prevalence of epilepsy in ASD and vice versa can range from about 1% (similar to the general population) to more than 40% depending on the source population. This variation can be explained by a multitude of factors such as methodological variables (e.g., different ascertainment methods), misdiagnosis in those with intellectual disabilities, and more recently, changes in diagnostic criteria. Autism spectrum disorder according to DSM-5 now includes not only autism, but also pervasive developmental disorders not otherwise specified and Asperger's syndrome [12]. A recent systematic review confirmed that the prevalence of epilepsy in females with autism is consistently higher than that noted in males (e.g., 34.5% vs. 18.5% respectively) [13]. In addition, the prevalence of epilepsy in autism tends to be higher in those with lower intelligence quotient (IQ). Finally, in general, the prevalence of epilepsy in children with autism tends to increase with age [14].

2.2. Epilepsy and depression

Depression in epilepsy is common, affecting 24% of those with epilepsy in the general population according to a systematic review. Indeed, those with epilepsy have close to three times the odds of having active depression compared with those without epilepsy in population-based studies [15]. There is excellent evidence to support the bidirectional association between epilepsy and depression [16] (see also below).

2.3. Epilepsy and psychosis

The association between epilepsy and psychosis has been extensively studied relative to other psychiatric comorbidities. A recent systematic review with high level of heterogeneity reported a pooled estimate prevalence of psychosis in epilepsy of 5.6%, psychosis in temporal lobe epilepsy of 7%, interictal psychosis of 5.2%, and postictal psychosis of 2% [17]. Overall, those with epilepsy had an almost 8-fold increase risk of psychosis compared with those without epilepsy. There is also evidence to support the bidirectional association between epilepsy and psychosis [17].

2.4. Epilepsy and dementia

Although epilepsy and dementia are considered common neurological conditions, studies examining their association are scant. In addition, many diagnostic criteria have been proposed for dementia over the years, with one study showing that estimates of dementia ranged from 3.1% to 29.1% depending on the diagnostic criteria applied to the same population [18]. Keeping this in mind and the limited studies on the topic, 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% [18]. Recent studies, however, suggest that the prevalence might be higher especially when considering, for example, focal hippocampal nonconvulsive seizures [19].

3. Autistic spectrum disorder

The session on ASD and epilepsy was introduced with a review of ASD in adult patients with newly diagnosed epilepsy; it was followed by a discussion of clinical and therapeutic aspects of ASD in children with epilepsy. The potential pathogenic mechanisms reviewed included (i) the genetic aspects of ASD, (ii) the theory of an imbalance between excitation and inhibition in children with ASD, such that neural circuits exhibit abnormally high excitation to inhibition ratios, and (iii) the theory of an abnormal connectivity in the brain of these patients, highlighted in the last presentation.

3.1. Autism as comorbidity in new-onset epilepsy: the perspective from an adult first seizure clinic (Bernd Pohlmann-Eden and Karen Legg)

Autism spectrum disorder and epilepsies are both considered brain network disorders (BND) which may cooccur as mutual comorbidities in complex brain diseases. Childhood data suggest that every 20th child with epilepsy develops ASD, and up to 2 out of 5 children with ASD develop epilepsy [13,20], while data from controlled studies in adults are lacking. It is uncertain, which distinct shared causal mechanisms play a role and how to disentangle contributing factors. The topic is further complicated by the fact that there are currently no biological or specific golds standard diagnostic tests for ASD, while seizures and epilepsy become increasingly well defined as functional and/or structural entities with variable roles of genetic determinants. As indicated by Dr. Jette above, low IQ is a well-established risk factor for ASD in children with epilepsy [13] and vice versa, but there is no consensus on how to conceptualize ASD (without epilepsy) with and without intellectual disability (ID).

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