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Epilepsy and Neurodevelopmental Disorders: A Biological Perspective

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Abstract

Childhood epilepsy represents a complex group of seizure disorders with neuropsychological deficits and diverse outcomes during developmental stages and later in life. Epilepsy can lead to neurodevelopmental disorders, such as attention-deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). This study based on review of literature, the association of etiologically diagnosed childhood epilepsy with the subsequent risks of neurodevelopmental disorders. Papers for this review were selected from established databases like PubMed, Proquest, and ScienceDirect among many. It has shown high comorbidity between epilepsy and intellectual deficits. However, it merely hints at common neurological mechanisms and does not adequately imply causation. Medications for treating epilepsy in children are also implicated in the development of neurodevelopmental disorders later in life. These claims are also explored in the review. There may be common mechanisms between epilepsy and neurodevelopmental disorders, which has to be further explored to develop causal factors. There is not much literature on the neurodevelopmental effects of antiepileptic drugs in the postnatal phase.

Keywords: ADHD & autism, Antiepileptics, Epilepsy, Neurodevelopmental disorders, Seizures

Introduction

Neurodevelopmental disorders is a group of disorders that typically occurs in children before they start their schooling. These are characterized by impairments in brain developments that impact brain functions like learning, emotion, memory, language and motor control. These are largely biological in etiology and often result in delays in developmental milestones. These could either be limited to specific learning deficits or amount to more widespread problems in social and intellectual functioning. These are also co-morbid with intellectual deficiency. Some prototypical disorders of this group are autism spectrum disorder, Attention-deficit/hyperactivity disorder (ADHD), Tourette's syndrome and various specific learning disorders (American Psychiatric Association, 2013). There existed little consensus or clarity on the differentiation between seizures and epilepsy. The International League against Epilepsy (ILAE) and the International Bureau for Epilepsy released definitions for the same to dispel any ambiguities. An epileptic seizure "is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). The use of the word epileptic is to demarcate this from any other physical or psychological events that may resemble the

epileptic seizures. Epilepsy "is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure" (Fisher et al., 2005). Epilepsy is not a single disease but encompasses a wide variety of disorders that are characterized by brain dysfunction that could occur due to many causes. According to Amudhan, Gururaj, & Satishchandra (2015), there is an incidence rate of 0.2-0.6 per 1,000 population per year, which highlights the need to understand the disorder as much as possible. Epilepsy also shares a high level of comorbidity with neurodevelopmental disorders like autism spectrum disorders and intellectual deficits, which demands further exploration of any underlying mechanisms (Brooks-Kayal, 2010). This also provides a strong basis to explore causality between the two highly co-occurring disorders.

Objectives

The main objectives of this review article are to review papers on epilepsy and its neuro developmental effects, along with papers on the common mechanisms between epilepsy and neurodevelopmental disorder, and to identify possible causal factors. It also looks at how these biological factors contribute to the subsequent risk of neurodevelopmental disorders. Lastly, papers on the pharmacological treatment of epilepsy and how they could affect neurodevelopment would be reviewed.

Methods

A traditional literature review was done using keywords such as, epilepsy, neurodevelop mental disorders, autism spectrum disorder, antiepileptics and anticonvulsants, which were used for the review. Papers, as a result of this search, were reviewed from Pubmed, Wiley Library, ScienceDirect, etc. and included journals like Epilepsia, Brain and Development, Annals of Indian Academy of Neurology, Neuropsychology Review and Epilepsy & Behaviour, among others.

Results

Results revealed some underlying neural -mechanisms such as, epileptogenesis, altered neurotransmitter circuitry and genetic correlation, that are similar for epilepsy and neurodevelopmental disorders, along with how treating epilepsy also leads to neurodevelop mental deficits.

Epilepsy and its neurodevelopmental effects

Tracing epilepsy along the lifespan, we find that it does indeed seem to affect neurodevelopment. Psychiatric and neuro develop mental disorders were more likely in children with epilepsy, as compared to their peers. This was especially true for children with complicated seizures (presence of brain lesions or low IQ). However, there was also a methodological flaw, where the determination of complicated seizures due to low IQ, leads to significant overlap with neurodevelopmental disorders. This was not the case with uncomplicated seizures, where externalizing disorders like ADHD had a strong association with neurodevelopmental disorders as well. This also involves deficits in attention and executive functioning. Also of note, was the fact that there was no particular form of epilepsy associated with neurodevelopmental disorders, which shows that it is the overall general effect of being afflicted with epilepsy itself (Berg, Caplan, & Hesdorffer, 2011). Epilepsy is a chronic condition and its incidence seems to heighten among children and the ageing population. This indicates that a lifespan perspective is more likely to guarantee a better view of epilepsy and its associated neurobehavioral comorbidities. There has been an increase in cognitive and social comorbidities in children with epilepsy that does not seem to differ between uncomplicated and complicated seizures (Lin, Mula, & Hermann, 2012). A look into possible mediators for these comorbidities includes epilepsy syndromes, as well as any brain abnormalities, along with psychosocial factors. Epilepsy syndromes are associated with the locations of the brain and,

as such, would implicate dysfunction in those areas. The most commonly occurring focal seizure, which is the temporal lobe epilepsy, affects the hippocampus and impairs memory, while similarly, frontal lobe epilepsy impairs executive functioning and absence epilepsy affects the thalamocortical network leading to deficits in attention. These also share problems with other neurodevelopmental disorders like ADHD, conduct disorders, as well as psychiatric comorbidities like depression. Furthermore, a bidirectional relationship is also implicated. The age of epilepsy onset, years of epilepsy and prescribed medications are major factors (Sarhan, Ayouty, Elsharkawy & Elmagid, 2015; Lin et al., 2012). In relation to pediatric epilepsy, there are many cognitive comorbidities which have led to an increase in the call for cognitive screening with most cases of epilepsy. There have been claims of seizures being the cause for autism spectrum disorder (ASD), where an EEG showed epileptic form activities in about 61% of children with ASD. However, this might not be the case for a majority of the cases. Epileptic encephalopathies, such as West Syndrome, are more likely to be comorbid with ASD. ADHD holds a similar level of comorbidity with epilepsy. In cases where there is a treatment for epilepsy, the associated comorbidity often goes undiagnosed and untreated which may also lead to dysfunction in academic, occupation and social settings (Nickels, Zaccariello, Hamiwka, & Wirrell, 2016). With such high levels of comorbidity, it would be useful to try and understand the mechanisms that underlie these two types of disorders.

Shared mechanisms

Brooks-Kayal (2010) sought to ascertain whether there were any common developmental mechanismsfor epilepsy and autism spectrum disorder. The theory of synaptic plasticity results in excitation and inhibition in the brain and is the mechanism for both epilepsy and ASD. Epileptogenesis results in maladaptive synaptic plasticity that contributes to abnormalities, due to alterations in receptors and signalling molecules. These alterations occur after early-onset epilepsy and lead to genetic conditions that are associated with ASD as well. During the neurogenesis and gliosis phase, there is an increased likelihood of spontaneous seizures occurring. These would either perpetuate or strengthen the progression of epilepsy. The effect of this is seen on GABA-A receptors which are the primary inhibitory neurotransmitters. Animal models suggest that this could lead to learning and behavioural deficits. Research on postmortem human samples also shows an altered GABAergic neuron circuitry for both ASD and epilepsy. This is to an extent where epilepsy in ASD is now being declared a spectrum disorder in and of itself. This is further emphasized by fragile X syndrome (FXS), Rett syndrome, and tuberous sclerosis complex (TSC) as well (Sgadò, Dunleavy, Genovesi, Provenzano, & Bozzi, 2011). Another disorder that is related to the aforementioned is Attention Deficit and Hyperactivity Disorder (ADHD). TSC and FXS seem to hold the key and indicate a common genetic basis which could lead to the development of biology-based treatment plans (Lo-Castro & Curatolo, 2014). Epilepsy in autism is greatly characterized by intellectual disability and female sex. Even in the absence of seizures, most patients with autism do show epileptic anomaly on EEG. Epilepsy may also induce the development of autistic features, especially if located in the temporofrontal regions of the brain (Amiet et al., 2008).

A recent review by Tuchman and Cuccaro (2011) explored the neurodevelopmental perspective between epilepsy and autism. It reiterated the fact that early-onset epilepsy puts children at a higher risk of developing autism, but the causality is still uncertain. However, a number of causal genes have been identified for epilepsy, autism and intellectual disability. The copy number variants (CNV) in the genome is the latest in identifying a common genetic link, as they lead to a rise in various phenotypes linked to epilepsy and autism. These common mechanisms and pathways hold the key to identifying the causal mechanisms.

Antiepileptics and Neurodevelopmental Disorders

The primary focus in this area is on the effects of exposure to antiepileptics in utero and its neurodevelopmental and cognitive effects. Antiepileptic drugs (AEDs) are often required for women with epilepsy throughout their pregnancies. AEDs are compounds that reduce seizure activity, through biochemical changes. There is now increasing evidence that these also lead to neurodevelopmental deficits, depending on when these are exposed. In particular, if during critical periods of development, it may lead to long term effects on the cognition and behavioural areas. Valproate may lead to cognitive deficits, however these are more likely to be dose dependent (Kellogg & Meador, 2017; Meador & Loring, 2016). These are classified as teratogens and have been associated with developmental delays among children who were exposed to it prenatally. There is an increased risk of major congenital malformations in children exposed to sodium valproate in utero leading to poor cognitive development, when compared to control children and children exposed to other AEDs. They were also at a higher risk for ASD. AEDs negatively impact early neuronal development and put children at a higher risk of developmental delays, cognitive impairment in terms of processing speed and memory, along with a higher risk for neurodevelopmental disorders such as ASD (Bromley, Leeman, Baker, & Meador, 2011). This was further supported by mounting evidence of prenatal exposure to sodium valproate that led to an increased prevalence of ASD in children whose mothers were undergoing treatment for epilepsy. This was particularly noted when the children turned six years old. This, however, is not noted in exposure to other AEDs, which means that sufficient guidelines must be prescribed when using sodium valproate. In addition to the treatment itelf, the type used is also an indication of teratogenicity and development of neurodevelopmental deficits. Polytherapy is more likely to cause deficits than monotherapy, especially if valproate is involved as well (Velez-Ruiz & Meador, 2015; Wood et al., 2015; Bromley et al., 2013).

Much of the studies on the neurodevelop mental effects of AEDs come from in utero exposure or animal studies, while a few of them have ventured into childhood exposure as well. While there is greater support for the negative effects of exposure to valproate, there is limited literature to document postnatal exposure to AEDs. Hence, it would be difficult to study the long-term effects of chronic exposure to AEDs in children. The incorporation of regular neurobehavioral testing might aid in this process moving forward. There is a need for more prospective and retrospective studies with better cohorts to isolate the effect of AEDs (Kellog & Meador, 2017). Older AEDs like phenobarbital and their use in childhood was associated with cognitive slowing, and these also led to memory impairment. However, these results are mixed. There has been little research done on new AEDs in this regard, and their cognitive side effects are yet to be explored (Palac & Meador, 2011). Teratogenicity of AEDs has been an area of research interest for a while now, nearly since the 1960s, to be precise. While there have been instances of malformations, especially associated with valproate and phenobarbital, the same cannot be said for the newer AEDs. There is much scope for future research in this field (Verrotti, Mencaroni, Castagnino & Zaccara, 2015).

Discussion

From the articles reviewed, it is clear that epilepsy does not function as a standalone disorder but has larger implications for the pathophysiology of many other disorders as well. While these are more clearly explored in cases of psychiatric disorders like depression, the link is somewhat lost with neurodevelopmental disorders. There are many deficits that can be explored when it comes to epilepsy syndromes, however, these are a tentative link to the development of full-blown disorders. The famous axiom “Correlation does not imply causation” continues to hold in this case as well. There is a

high level of comorbidity between ASD, epilepsy and ID, which seems to suggest that they might have similar mechanisms governing their etiology, but current research has just stopped short of definitive proof of causality. The common mechanisms did seem to enjoy good research backing, especially in the theory of synaptic plasticity and spontaneous seizures that are more likely to occur during the proliferation and migration period. There were also factors, such as the age of onset, chronicity of epilepsy and the use of AEDs, that provided both causal and protective factors. The abnormal activity that governed both types of disorders was further exacerbated due to the dysfunction of GABAergic circuitry which is the primary inhibitory neurotransmitter in the brain. A genetic link was found in the form of CNVs, and other disorders such as FXS and TCS, which cause all future directions to take a deep plunge into the depths of genome mapping and the like. These are the few biological markers that preceded the development of neurodevelop mental deficits in childhood epilepsy. However, more research would be required to completely ascertain their role and their impact on neurocognitive functionining. There was not a lot of research to support the neurodevelopmental side-effects of AEDs. While there was a lot of evidence against older AEDs, like sodium valproate and Phenobarbitals, these were in utero. There is not much research on newer AEDs. This leaves much to be researched on the new AEDs, and to contribute immensely to treatment guidelines for women of reproductive age.

Conclusions Acknowledgements

While there is high comorbidity between epilepsy and neurodevelopmental disorders, there is not much research that can adequately support a causal relationship. Future research areas would involve genes and genome alteration during prenatal development. These can help present a much clearer picture, along with also exploring possible environmental factors and studying their interaction with biological factors. There also needs to be better treatment guidelines to handle epilepsy in ASD, as this presents a different entity than the two disorders being comorbid. There also needs to be more research into AEDs and their neurodevelopmental effects. The current scenario has been found lagging in this regard and the newer AEDs would benefit from the evidence-based research.

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References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®).* American Psychiatric Pub.

Amiet, C., Gourfinkel-An, I., Bouzamondo, A., Tordjman, S., Baulac, M., Lechat, P., ... Cohen, D. (2008). Epilepsy in Autism is Associated with Intellectual Disability and Gender: Evidence from a Meta-Analysis. *Biological Psychiatry, 64*(7), 577-582.

Amudhan, S., Gururaj, G., & Satishchandra, P. (2015). Epilepsy in India I: Epidemiology and public health. *Annals of Indian Academy of Neurology, 18*(3), 263.

Berg, A. T., Caplan, R., & Hesdorffer, D. C. (2011). Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. *Epilepsy & Behavior, 20*(3), 550-555.

Bromley, R. L., Leeman, B. A., Baker, G. A., & Meador, K. J. (2011). Cognitive and neuro developmental effects of antiepileptic drugs. *Epilepsy & behavior: E&B, 22*(1), 9–16.

Bromley, R. L., Mawer, G. E., Briggs, M., Cheyne, C., Clayton-Smith, J., García-Fiñana, M., ... & Liverpool and Manchester Neuro development Group. (2013). The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry, 84*(6), 637-643.

Brooks-Kayal, A. (2010). Epilepsy and autism spectrum disorders: are there common developmental mechanisms?. *Brain and Development, 32*(9), 731-738.

Fisher, R. S., Boas, W. V. E., Blume, W., Elger, C., Genton, P., Lee, P., & Engel Jr, J. (2005). Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia, 46*(4), 470-472.

Kellogg, M., & Meador, K. J. (2017). Neuro developmental effects of antiepileptic drugs. *Neurochemical research, 42*(7), 2065-2070.

Lin, J. J., Mula, M., & Hermann, B. P. (2012). Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *The Lancet, 380*(9848), 1180-1192.

Lo-Castro, A., & Curatolo, P. (2014). Epilepsy associated with autism and attention deficit hyperactivity disorder: is there a genetic link?. *Brain and Development, 36*(3), 185-193.

Meador, K. J., & Loring, D. W. (2016). Develop mental effects of antiepileptic drugs and the need for improved regulations. *Neurology, 86*(3), 297–306.

Nickels, K. C., Zaccariello, M. J., Hamiwka, L. D., & Wirrell, E. C. (2016). Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. *Nature Reviews. Neurology, 12*(8), 465-476.

Palac, S., & Meador, K. J. (2011). Antiepileptic drugs and neurodevelopment: an update. *Current neurology and neuroscience reports, 11*(4), 423-427.

Sgadò, P., Dunleavy, M., Genovesi, S., Provenzano, G., & Bozzi, Y. (2011). The role of GABAergic system in neurode velopmental disorders: a focus on autism and epilepsy. *International journal of physiology, pathophysiology and pharmacology, 3*(3), 223–235.

Sarhan, A. A., Ayouty, M. M., Elsharkawy, A. A., & Elmagid, D. S. A. (2015). Neurodevelop mental and neurobehavioral aspects of childhood epilepsy. *Benha Medical Journal, 32*(1), 13.

Velez-Ruiz, N. J., & Meador, K. J. (2015). Neurodevelopmental effects of fetal antiepileptic drug exposure. *Drug safety, 38*(3), 271–278.

Verrotti, A., Mencaroni, E., Castagnino, M., & Zaccara, G. (2015). Foetal safety of old and new antiepileptic drugs. *Expert opinion on drug safety, 14*(10), 1563-1571.

Wood, A. G., Nadebaum, C., Anderson, V., Reutens, D., Barton, S., O'Brien, T. J., & Vajda, F. (2015). Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia, 56*(7), 1047-1055.