OPINION

Pre-synaptic dysfunction in developmental and epileptic encephalopathies synaptopathies in developmental and epileptic encephalopathies

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ABSTRACT

The pre- and post-synaptic membranes, the synaptic cleft, and the surrounding glial cells and extracellular matrix all play a role in the correct connection between pre- and post-synaptic nerve cells. Synaptopathy is a change in the systems that control the physiological synergy between these synaptic components. Several neuropsychiatric illnesses are linked to mutations in genes producing proteins involved in neuronal transmission, but only a few are linked to Developmental and Epileptic Encephalopathies (DEEs). A diverse set of epileptic syndromes linked with cognitive disturbances/intellectual impairment, autistic traits, and movement abnormalities make up these ailments. This review focuses on processes influencing the neuronal pre-synaptic terminal and its function in the development of DEEs in order to better understand the aetiology of these diseases.

Key Words: *Encephalopathies; Neuronal transmission; Synapse; Neurotransmitters*

INTRODUCTION

The Synaptic transmission is a complicated and highly controlled mechanism that is essential for normal nervous system functioning. The increasing accuracy of the etiopathogenesis definition of nervous system diseases has been enabled by advances in neurobiology: from macroscopic involvement of anatomical structures and circuitry, the focus has shifted to microscopical elements of this system, including subcellular ones, such as transporting proteins, signalling superficial molecules, receptors, and neurotransmitters. The synapse, which is the nervous system's primary signal-transmitting unit, plays a crucial part in this information exchange. The release of neurotransmitters is dependent on the presence of synaptic vesicles, which fuse with the pre-synaptic membrane as soon as the action potential arrives. The recycling of synaptic vesicles occurs on a regular basis, and various proteins are involved in the process [1]. A synaptopathy is a change in the function of any component of the synapse, including the pre- and post-synaptic terminals, the synaptic cleft, and any surrounding components including glial cells and extracellular matrix. Although the term "synaptopathy" was first used in relation to Huntington Disease in 2003, pathogenic variants in genes encoding synaptic proteins have been shown to determine altered protein levels/function in a variety of neuropsychiatric diseases, including epilepsy, intellectual disability (ID), and autism spectrum disorder, in the last few decades. The phrase "epileptic encephalopathy" refers to a severe form of epilepsy that usually begins in infancy or early childhood and is characterised by epileptic activity that contributes significantly to severe Developmental Delay (DD) and behavioural abnormalities. The influence of epileptic activity produces a worsening of the developmental implications deriving directly from the genetic mutation in individuals with pre-existing DD, resulting in a clinical presentation known as "Developmental and Epileptic Encephalopathy" (DEE) [2]. Numerous genes have been linked to DEEs, and various synaptopathies have been found since the discovery of a genetic aetiology for epileptic encephalopathy. Because several proteins are involved in the processes underpinning the

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proper functioning of the synapse, these illnesses are usually researched by focusing on a single faulty gene. We concentrated our study on genes involved in the aetiology of DEEs that influence the pre-synaptic compartment, which includes the axon terminal and proteins involved in neurotransmitter release. Because these genes are often discovered in large groups of individuals who have undergone genetic testing, a clear description is not always provided, making it difficult to describe clinical symptoms and identify DEEs. As a result, all individuals with epilepsy and intellectual impairment were considered (ID).

STX1B

Syntaxin1 (Stx1) is a widely expressed protein in the nervous system that, along with Snap25 (encoded by SNAP25) and synaptobrevin-2 (encoded by VAMP2), forms a stable complex known as the soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) complex, which is involved in Ca2+-dependent synaptic vesicle exocytosis and neurotransmitter The vesicle membrane part of the SNARE neuronal complex (v-SNARE) is represented by Vamp2, whereas the plasma membrane of SNARE (t-SNARE) is represented by Stx1a and Snap25. Stx1 is a membrane protein with three functional domains: (1) the N-terminal peptide, (2) the Habc domain (an -helical domain), and (3) the SNARE and transmembrane motif in the C-terminal area. The "closed" and "open" Stx1 protein configurations are the two distinct protein configurations. A connection between the Habc domain and the N-peptide distinguishes the first. Switching from a closed to an open conformation is critical for controlling SNARE-mediated exocytosis, and Stx1 is involved in the start of synaptic exocytosis. The binding of Munc18 (encoded by STXBP1) and Stx1 in its closed state is the initial step that permits the SNARE complex to be assembled. Stx1 is divided into two isoforms: 1a and 1b. Stx1b is the primary mediator for spontaneous and induced rapid synaptic vesicle exocytosis, while sharing 84 percent of its amino acid sequence and basic function with neuronal t-SNAREs [3]. Stx1a is a gene on chromosome 7 that is one of the genes implicated in Williams-Beuren Syndrome (WBS), which is caused by a deletion of 7q11.23. In this way, the level of Stx1a expression in patients with WBS is linked to their intellect. It has also been discovered that certain STX1A variations are linked to an increased risk of migraines. Furthermore, evidence from research using Whole Exome Sequencing (WES) on numerous families show that STX1A might be a potential gene in the development of neurodevelopmental disorders. On the other hand, nothing is known regarding the role of pathogenic STX1A mutations in epilepsy development. However, Stx1a's effect on glutamate uptake and glutamatergic transmission might help to explain STX1A's participation in epileptogenesis. Stx1a appears to work by increasing the internalisation of the excitatory amino acid transporter 1 (EAAC1), which is responsible for glutamate re-uptake: increased internalisation and reduced expression on the cell surface result in a reduction in glutamate uptake. Furthermore, in animal models, a role for Stx1a in regulating voltage-gated K+ channels indicated by physical contact of this protein with ion channels has been established. In addition, single nucleotide polymorphisms (SNPs) in STX1A and VAMP2 have been linked to cryptogenic epilepsy [4].

The 1b isoform has received a lot of attention. The STX1B gene is found on chromosome 16, and investigations on mouse models have revealed that KO mice for STX1B die young and have abnormal neuromuscular junction function. The importance of Stx1b in normal nervous system signalling is highlighted by these findings. As a result, dysfunctions of this protein, whether due to mutations or deletions, are linked to the onset of a variety of nervous system illnesses, including ID, speech difficulties, and several types of epilepsy. STX1A-related DEEs have not been documented in the literature to our knowledge. As a result, we concentrated on the 1b isoform and found 20 individuals. Clinical data on the age at which symptoms began, the kind of seizures, the presence of Febrile Seizures (FS), electroencephalographic patterns, and the development of ID and/or movement problems was obtained. For some patients, not all clinical information could be found [5].

SNAP25

The synaptosomal-associated protein 25 kDa (Snap25) gene is found on chromosome 20 (20p12.2) and is highly expressed in nerve and neuroendocrine cells. Snap25 is a key component of the SNARE complex and, along with Stx1 and synaptobrevin-2, is involved in Ca2+-dependent synaptic vesicle exocytosis. Due to variable splicing of the SNAP25 gene in mammals, two distinct isoforms (Snap25a and Snap25b) are produced, with just nine amino acid differences. In humans and mice, however, they have varied expression and localization characteristics in different brain areas. Snap25b, which is largely expressed in central nervous system synapses and peripheral motor endplates and controls neurotransmitter exocytosis, is the most important isoform in synaptic transmission. De novo SNAP25 mutations have been linked to a variety of neurological illnesses, including epilepsy, movement problems, and psychiatric disorders, due to its critical involvement in nerve transmission [6].

VAMP2

Vamp2 is encoded by the VAMP2 gene, which is found on chromosome 17. As previously stated, the Vamp2 protein is a component of the v-SNARE and is essential for promoting synaptic transmission, which is also influenced by Ca2+ ions and other proteins. Neurodevelopmental problems such as visual impairment, hyperkinetic movements, autism spectrum disorder, and epilepsy are linked to pathogenic variations of the VAMP2 gene. Individuals with nonsynonymous VAMP2 mutations have more severe neurological symptoms. A new research examining the crucial function of VAMP2 and DLG4 in the advancement of epilepsy and behavioural disorders, particularly ADHD, has underlined the relevance of a right method of neuronal trafficking mediated by Vamp2. The expression of Dlg4 and Vamp2 is downregulated in these situations, resulting in aberrant neurotransmission, which is thought to be the aetiology of the disease. Only three individuals with pathogenic VAMP2 mutations linked to DEE have been documented thus far described five individuals (aged 2 months to 14 years) who had de novo heterozygous VAMP2 gene mutations and had a variety of neurodevelopmental abnormalities, including epilepsy, hypotonia, ID, and autistic characteristics. Two of these individuals did not have epileptic symptoms, although they did have abnormal EEGs (such as high-voltage delta activity, sharp-and-slow-wave complexes or only a

disorganised EEG). Three individuals, on the other hand, had seizures during the first few months of life: one had focal seizures, another had generalised tonic-clonic seizures and focal seizures, and the third had infantile spasms. Disorganized activity, widespread and/or multifocal abnormalities, sharp wave-slow wave complexes, and various localised paroxysms were also seen on EEGs. All of the patients had autistic traits and variable motor stereotypies equivalent to Rett syndrome (RTT) (3/3), and their language was always poor (1/3) or nonexistent (2/3), and they all had autistic symptoms and variable motor stereotypies comparable to Rett syndrome (RTT). The patients had drug-resistant epilepsy and had tried a variety of AEDs, including VPA, vigabatrin, and lamotrigine. VPA was shown to be the most effective in two people; one of them, in particular, has been seizure-free since the age of 12 years, and his follow-up EEGs were normal.

DISCUSSION

DEEs are a diverse collection of illnesses that begin in infancy or early childhood and result in considerable epileptic activity interfering with development, resulting in severe DD/ID and other neuropsychiatric disorders. A change in the synapse, the nervous system's primary unit of signal transmission, might be the cause of many disorders. Many genes are involved in the correct functioning of synaptic transmission, and changes to this complicated system can lead to synaptopathy. We investigated the clinical aspects of 119 individuals who had a clinical presentation that resembled a DEE and studied the literature, concentrating on those genes implicated in the normal operation of the pre-synaptic terminal. It's challenging to draw a reliable genotype-phenotype association, especially in studies with only a few individuals with DEEs. On the other hand, a clear association is difficult to acquire when several patients with pathogenic variations of the same gene appear with varied symptoms; this is especially true when the same mutation is linked to many clinical presentations. This phenotypic variability has long been researched, and it is linked to a number of variables that intervene during development, including epigenetic factors, physiological gene expression timing and location, and modifier genes. Nonetheless, several important aspects of DEE clinical symptoms connected to the genes we investigated may be highlighted, leading the physician to a genetic candidate. Patients with VAMP2 pathogenic mutations, for example, had ID, central visual impairment, movement difficulties, epilepsy or electroencephalographic abnormalities, autistic characteristics, and lack of intentional hand motions, which resembled Rett syndrome. Almost all individuals with a pathogenic variation of TBC1D24 have their first seizure during the first three months of life, with severe development typically leading to death within the first decade. Despite the fact that EIMFS has been described as a characteristic epileptic phenotype linked to TBC1D24, we were able to identify 5/30 (16%) individuals who acquired this kind of DEE throughout our analysis.

In terms of therapeutic techniques, an individually customised treatment is preferable in order to intervene directly on the changed mechanism defining the DEE, hence enhancing seizure control and developmental result. However, in the majority of severe epilepsies, there is no gene-specific therapy available, and the only therapeutic choices are the standard AEDs, which do not target the underlying causal mechanism. Despite several treatment combinations, most patients had a poor prognosis with extremely drug-resistant seizures, according to our literature assessment of DEEs associated to genes implicated in pre-synaptic processes.

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