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Epileptic encephalopathies and progressive neurodegeneration

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ABSTRACT

Developmental encephalopathies (DE), epileptic encephalopathies (EE) and developmental and epileptic encephalopathies (DEE) are overlapping neurodevelopmental disorders characterized by early-onset, often severe epileptic seizures, developmental delay, or regression and have multiple etiologies. Classical nosology in child neurology distinguished progressive and nonprogressive conditions. A progressive course with global cognitive worsening in DEE is usually attributed to severe seizures and electroencephalographic abnormalities whose deleterious effects interfere with developmental processes both in an apparently healthy brain and in an anatomically compromised one. Next generation sequencing and functional studies have helped identifying and characterizing clinical conditions, each with a broad spectrum of clinical and anatomic severity corresponding to a variable level of neurodegeneration, such that both a rapidly progressive course and considerably milder phenotypes with no obvious deterioration can be configured with mutations in the same gene. In this mini review, we present examples of genetic DEE that draw connections between neurodevelopmental and neurodegenerative disorders.

1. Introduction

Based on clinical and electroencephalography (EEG) features, etiologies, and comorbidities, different categories of epilepsy types and syndromes are recognized. Developmental encephalopathies (DEs) are severe disorders with early-onset developmental impairment associated with other neurological symptoms such as autonomic dysfunction, behavioral disorders, and motor impairment. Epileptic encephalopathies (EEs) comprise a heterogeneous group of severe epilepsy syndromes characterized by several seizure types, and epileptiform EEG activity, in which developmental delay or regression become apparent after epilepsy onset. Developmental and epileptic encephalopathies (DEEs) are characterized by early-onset, often severe epileptic seizures and EEG abnormalities on a background of developmental impairment that tends to worsen as a consequence of epilepsy [1]. The two categories of EE and DEE may not be clearly distinct as severe epilepsy may start before or after other signs of a progressive monogenic disorder appear,

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making it difficult to understand what is related to the underlying pathology and what is a consequence of epilepsy.

For instance, pathogenic variants affecting WDR45, a beta-propeller protein involved in a variety of functions, including transcription regulation, signal transduction, cell cycle control, autophagy, and apoptosis, have been associated with six different, albeit overlapping, disorders including early onset epileptic encephalopathies (EOEEs), DEEs, and neurodegeneration with brain iron accumulation-5 (NBIA5, OMIM 300894). NBIA5 is an X-linked neurodegenerative disorder accompanied by global developmental delay in early childhood that is essentially static, with delayed motor and cognitive gains until adolescence or early adulthood. In young adulthood, NBIA5 patients develop progressive dystonia, parkinsonism, extrapyramidal signs, and dementia, resulting in severe disability. Brain magnetic resonance imaging (MRI) shows iron accumulation in the globus pallidus and substantia nigra [2–4].

In this mini review, we present some examples of recently identified genetic DEEs whose phenotypic spectrum embraces DE, EE, and DEE with or without progressive course, featuring at times dramatically divergent long-term outcomes.

2. *SPTAN1* and DEE5

The spectrins, including nonerythrocytic alpha-spectrin-1 (SPTAN1), are a family of widely distributed filamentous cytoskeletal proteins with a highly conserved 106-amino acid repeat structure. Spectrins are heterodimers of a constant alpha-chain and variable tissue-specific beta-chains. Functions of these proteins include regulation of receptor binding and actin crosslinking [5].

Heterozygous *SPTAN1* pathogenic variants have been found in patients with variable phenotypes, most frequently mild-to-severe DEE (DEE5, OMIM 613477) and developmental delay (DD) and rarely with hereditary motor neuropathy; biallelic mutations cause autosomal recessive hereditary spastic paraplegia (HSP) with or without ataxia [6]. Initial descriptions of DEE5 reported global developmental delay and the onset of tonic seizures or infantile spasms in the first months of life, which are refractory to treatment and accompanied by hypsarrhythmia on the EEG, consistent with West syndrome. Affected children have severely impaired psychomotor development with lack of visual attention, poor head control, feeding difficulties, microcephaly, and spastic quadriplegia. Brain imaging shows cerebral atrophy and hypomyelination [7].

In a subsequent study on 20 patients harboring pathogenic *SPTAN1* variants [8], we found only 50% to exhibit the initially described EIEE5/DEE5 syndrome. The phenotypic spectrum included, at one extreme, a severe encephalopathy with rapidly progressive brain, brainstem, and cerebellar atrophy with severe hypomyelination (Fig. 1A), which was associated with mutations located in the spectrin heterodimer contact, whose functional consequences included aggregation and failure of heterodimerization of alpha and beta spectrins [8]. At the milder end of the spectrum were patients with focal epilepsy and mild cognitive impairment, who harbored missense mutations located in functionally more tolerant sites and showed no signs of clinical worsening.

3. *ATP6V1A* and DEE93

V-type proton (H^+) ATPase (v-ATPase) is a multi-subunit proton pump that regulates pH homeostasis in eukaryotic cells. The canonical functions of v-ATPase rely on its H^+-pumping ability in multiple vesicle organelles to regulate endocytic trafficking, protein processing and degradation, and coupled transport [9]. In neurons, v-ATPase plays additional and unique roles in synapse function, mediating the active loading of the amount of neurotransmitter needed to fully fill synaptic vesicles and increase their chance to be released [1].

v-ATPases are particularly important in lysosomes, the cellular organelles deputed to digest extracellular material from the endocytic pathway and intracellular material from the autophagic pathway. Altered v-ATPase activity and

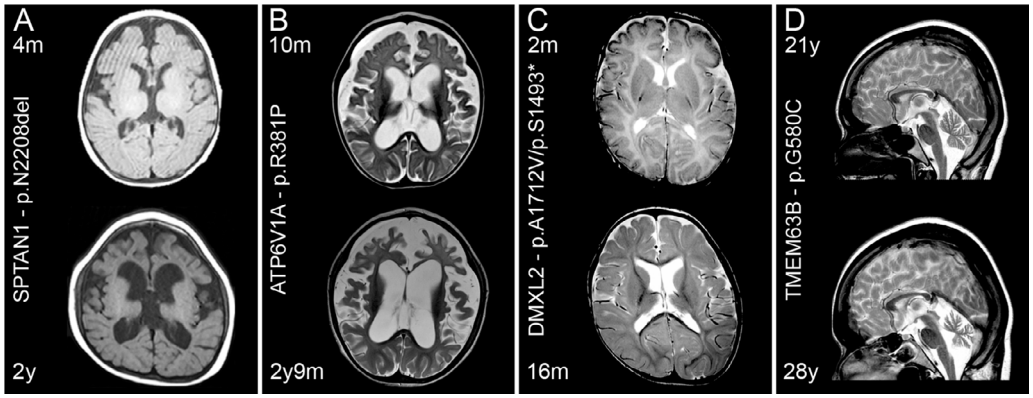

Fig. 1 – Progression of structural MRI abnormalities in DEE5, DEE93, DEE81, and *TMEM63B*-related DEE. Sets of brain MRI of patients carrying pathogenic variants in *SPTAN1* (A, images taken at 4 months and 2 years), *ATP6V1A* (B, images taken at 10 months and 2 years 9 months), *DMXL2* (C, images taken at 2 months and 16 months), and *TMEM63B* (D, images taken at 21 years and 28 years). For each patient, the pathogenic variant is indicated on the right side of the panel. Note the progressive dilatation of the ventricles and subarachnoid spaces in A, B, and C and the progressive cerebellar atrophy in D.

lysosomal pH dysregulation in lysosomes have been implicated in cellular aging, longevity, and adult-onset neurodegenerative diseases, including forms of Parkinson disease and Alzheimer disease [10]. Pathogenic variants in 16 of the 22 genes encoding for v-ATPase subunits have also been associated with a variety of congenital disorders with neurological impairment, including DEEs [1].

After the initial report associating de novo missense *ATP6V1A* pathogenic variants with a novel form of DEE (DEE93) in four patients [11], we established and characterized a cohort of 26 patients with pathogenic or likely pathogenic *ATP6V1A* variants [12]. In severely affected patients, phenotypic expression included DEE at time with early lethality and MRI scans exhibited progressive atrophic changes, whose severity paralleled progression of symptoms (Fig. 1B). Other patients had milder phenotypes with cognitive impairment, mild epilepsy and limited or no signs of clinical or anatomic progression. Fibroblasts of patients with DEE showed decreased LAMP1 expression and LysoTracker staining, and increased organelle pH, consistent with lysosomal impairment and loss of V-ATPase function, while those of patients with milder disease, with minor or no signs of progression exhibited increased LysoTracker staining, decreased organelle pH and no significant modification in LAMP1 expression. Electron microscopy of fibroblasts induced pluripotent stem cell-derived neurons showed electron-dense inclusions, lipid droplets, osmiophilic material and lamellated membrane structures resembling phospholipids. Quantitative assessment in induced pluripotent stem cell-derived neurons identified significantly smaller lysosomes. ATP6V1A-related encephalopathy is a combination of developmental brain abnormalities and neurodegenerative changes established during prenatal and early postanal development, whose severity is variably determined by specific pathogenic variants [12].

In addition to pathogenic variants in *ATP6V1A*, also those affecting genes encoding nine additional v-ATPase subunits (ATP6V0A1, ATP6V0A2, ATP6V0A3, ATP6V0A4, ATP6V0C, ATP6V0D2, ATP6V1B1, ATP6V1B2, and ATP6V1C2) or the accessory proteins ATP6AP1 and ATP6AP2 were associated with neurodegenerative traits in some patients [12]. These observations suggest that neurodegenerative alterations are relatively common in patients with impaired v-ATPase function.

4. *DMXL2* and DEE81

The synaptic protein encoded by *DMXL2*, rabconnectin-3a, mediates the assembly and incorporation of the v-ATPase into synaptic vesicles. Heterozygous copy number variations involving *DMXL2* and single nucleotide loss-of-function variants have been observed in individuals with different neurodevelopmental disorders, including autism spectrum disorders (ASD), intellectual disability, and attention-deficit hyperactivity disorder (ADHD), suggesting that *DMXL2* haploinsufficiency might act as a predisposing factor for these conditions [13].

Biallelic missense or truncating *DMXL2* variants cause a severe disorder with refractory seizures, with a suppression burst EEG pattern (Ohtahara syndrome) starting soon after birth or in the first months of life, and almost absence of any developmental progress (DEE81; OMIM 618663), associated with facial dysmorphisms, peripheral neuropathy and sensorineural hearing loss [14]. Early brain MRI investigations reveal thin corpus callosum and severe hypomyelination, followed by progressive brain shrinkage and leukoencephalopathy (Fig. 1C) [14]. Patients' fibroblasts and *Dmxl2* knockdown mouse hippocampal neurons exhibit lysosomal abnormalities, particularly decreased LAMP1 and pH within acidic organelles, impaired lysosomal degradative capacity, defective autophagy and a significant decrease in neurite complexity consistent with impaired synaptic connections. *DMXL2*-related DEE therefore has the characteristics of a developmental brain disorder that begins in the prenatal brain, prevents neural connections from reaching the expected stages at birth, and evolves with a progressive course [14].

5. *TMEM63B*-related DEE

TMEM63B, with its two paralogs *TMEM63A* and *TMEM63C*, belongs to a gene family initially identified as the closest homologs of the OSCA proteins, which represent the largest family of stretch-activated ion channels conserved across eukaryotes [15,16]. In mammals, members of the *TMEM63* family mediate cation currents in response to osmotic and mechanical stimuli affecting membrane tension [15,17]. This process is crucial for cell volume regulation and viability, as changes in osmolarity may cause water influx or efflux through the plasma membrane, resulting in cell swelling or shrinkage [18].

TMEM63B, which is ubiquitously expressed in humans, has multiple mRNA isoforms and post-translational modifications that are tissue specific. Although in the past the other members of the *TMEM63* family have been associated with monogenic disorders including transient infantile hypomyelinating leukodystrophy-19 (HLD19, OMIM 618688) and developmental delay of variable severity – *TMEM63A* – and autosomal recessive spastic paraplegia-87 (SPC-87, OMIM 619966) – *TMEM63C* –, *TMEM63B* has been identified as the disease-causing gene of a specific form of DEE only recently in 17 unrelated individuals with drug-resistant focal epilepsy, global developmental delay, moderate-to-profound intellectual disability and motor impairment, manifested in the most severely affected as spastic quadriparesis [19].

Brain MRI scans, performed between ages one week and 28 years revealed an association of multiregional or widespread white matter signal abnormalities, dysmorphic lateral ventricles, and thinning of the corpus callosum in all patients and atrophy of the cerebral cortex and/or of the cerebellum in 50%. In all individuals who were studied with two or more scans, comparison of images taken at different times revealed progressive brain damage that continued into adulthood (Fig. 1D) [19].

In this study, modeled *TMEM63B* variants led to inward leak currents resulting in a gain in conductance even in the absence of the hypo-osmotic stimulus gating the channel, without altering the maximal channel conductance. In addition, calcium imaging experiments demonstrated a selective reduction of the relative permeability to Ca^{2+} [19].

Globally, these data indicate that *TMEM63B* variants cause a gain in conductance with impaired Ca^{2+} homeostasis and are associated with neurodegenerative changes affecting the cerebral white and gray matter and the cerebellum that start during prenatal brain development and slowly progress during postnatal development and adulthood [19].

6. Conclusions

Neurodevelopmental disorders affect the process that starts early in embryonic life, continues during adolescence, is completed in young adulthood, and implies a series of coordinated processes that regulate the proper development of all cell types that populate the brain and the establishment and maintenance of neuronal connections that will remain functional for the lifetime. Neurodegenerative disorders imply the progressive dysfunction and loss of neurons in specific brain regions that lead to alterations in brain connectivity and cognitive decline. Based on this distinction, classical neuropediatric nosology distinguishes between neurodevelopmental disorders, that are the expression of 'fixed' encephalopathies, from progressive disorders with neurodegeneration, mainly related to neurometabolic causes.

However, this distinction seems now inadequate to seize the pathophysiological background of a growing number of genetically determined disorders as it fails to recognize two main aspects. The first aspect is related to the demonstration that different variants in the same gene may associate to either a non-progressive (neurodevelopmental) or a progressive (neurodegenerative) course. The second aspect is that some seemingly fixed neurodevelopmental disorders are originating from neurodegenerative changes that are initiated during intra-uterine life. The examples of the DEEs we reviewed here represent prototypic examples of epileptogenic conditions in which both neurodevelopmental and progressive alterations coexist and strengthen the assumption that some DEEs may be the expression of early neurodegenerative disorders.

DDE81 and DEE93 are caused by pathogenic variants in genes encoding proteins (ATP6V1A and DMXL2) involved in the autophagy/lysosomal degradative pathway [20]. For such proteins, a 'dual' phenotype including neurodevelopmental anomalies and signs of neurodegeneration is somewhat expected. Disorders of autophagy have been initially divided into severe neurodevelopmental and neurological disorders with onset early in life, often referred to as ''congenital disorders of autophagy'', and neurodegenerative diseases presenting late in adulthood, often after a long symptom-free or subclinical interval [21]. However, this distinction is somewhat artificial as there is emerging evidence for a lifetime continuum of autophagy-associated disorders, both on the level of the individual patient and specific conditions [21].

In addition to DEE5, *SPTAN1* variants have been implicated in psychiatric and neurodegenerative conditions. This latter association has been substantiated by studies in animal models that demonstrated how specific *SPTAN1* variants cause progressive ataxia with widespread neurodegenerative changes [22]. The finding that progressive atrophy of the cerebellum and brainstem are present only in patients with a severe form of *SPTAN1*-related encephalopathy [8] suggests that only the most deleterious variants affecting this gene can cause degenerative hallmarks already visible in childhood.

TMEM63B has been identified as a DEE-causing gene recently [19], and this initial description suggests that progressive brain damage could be a prominent feature of *TMEM63B*-related DEE.

The natural history of many DEEs is still poorly understood, especially with respect to the evolution of phenotypic traits beyond early childhood [23]. This limited knowledge is mainly related to the recent identification and rarity of these disorders. However, natural history studies, ideally based on international disease registries collecting sufficiently large cohorts, would appear to constitute an attainable goal capable of delineating the entire clinical spectrum associated with these complex encephalopathies in the long term.

Here, we discussed only selected examples of DEEs with neurodegenerative traits we described. However, the spectrum of neurodegenerative pathologies with epilepsy is broad. Other examples include the hyperphosphorylated tau protein-related pathology, in which mixed characteristics of both Alzheimer's disease and chronic traumatic encephalophaty (CTE) cooccur in neuropathology specimens of patients operated for temporal lobe epilepsy [24], and the recently described severe DEE with massive reduction of white matter, hypo/aplasia of the corpus callosum, neurodevelopmental arrest, and early death associated with biallelic *SNF8* variants [25]. Biallelic variants in *SNF8*are associated with defective autophagy with accumulation of autolysosomes and abnormal lysosomes in fibroblasts [25], which strengthens the hypothesis that this pivotal cellular process may play a primary role in DEEs neurodegeneration.

The complex interplay between inflammation, epilepsy, and neurodegeneration should also be considered here. Seizures cause inflammation, and inflammation, in turn, influences seizure occurrence and severity as well as seizure-related neuronal death [26]. Several inflammatory mediators have been detected in surgically resected brain tissue after epilepsy surgery [26]. Although inhibition of neuroinflammation may not alter the underlying cause of epilepsy and accompanying neurodegenerative phenomena in DEEs, it might reduce the production of factors that contribute to neurotoxicity, thereby resulting in clinical benefit.

Disclosure of interest

The authors declare that they have no competing interest.

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The authors declare that they have not used generative AI in writing this paper.

Authors' contributions

RG conceived the review, drafted, and revised the manuscript and the figure. VC drafted the manuscript and prepared the figure. Both authors approved the final version of the manuscript.

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