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REVIEW ARTICLE

Aspects of neurodevelopment between autism spectrum disorders and epilepsy

Paola Núñez-Contreras[1], Daniela Granado-Rocha[1], Maritza Carvajal-Game[2], and Ana M. Torres-Perez[2]

[1]Hospital Doctor Exequiel González Cortés, [2]Unidad Docente Neurologia Pediátrica. Universidad de Santiago de Chile. Chile

Abstract

There are high incidences of epilepsy and autism in the preschool and school ages, in which the synaptic plasticity and synaptogenesis are more active, a primary interruption of the synaptic function due to injury or genetic mutation may result in the appearance of both pathologies as in Lennox Gastaut S., De Aircadi S, epilepsy with continuous slow waves during sleep and Landau Kleffner S. There is evidence of abnormal brain maturation in autism spectrum disorders (ASD). Normal pruning eliminates faulty connections and optimizes neuronal functioning. In autism, this pruning would result in degrees of anatomical "over-connectivity" that increases or decreases the efficiency of communication between cortical regions. The same occurs with axonal myelination that affects integrated interregional cortical communication and synchronization. Critical and vulnerable mechanisms are appreciated during the peri-neonatal period, with subsequent stabilization of the synapses to form pre-designed neural networks through genetic mechanisms and modified by environmental factors. There are anomalies in different proteins that modulate the first phase of synaptogenesis, mutations in protocadherins, cadherins, and abnormalities in glutamatergic and GABAergic systems that affect the brain. All these aspects are critical for learning, language, and memory in both autism and epilepsy.

Keywords: *Synaptogenesis, Autism, Epilepsy.*

Aspectos del neurodesarrollo entre trastornos del espectro autista y epilepsia

Resumen

Se presentan altas incidencias de epilepsia y autismo en el preescolar y escolar, edades en las que la plasticidad sináptica y sinaptogénesis es más activa, una interrupción primaria de la función sináptica por lesión o mutación genética puede resultar en aparición de ambas patologías como en S. Lennox-Gastaut, S. De Aircadi, Epilepsia con ondas lentas continuas durante el sueño y el S. de Landau Kleffner. Existe evidencia de maduracion anormal del cerebro en TEA. La poda normal elimina conexiones defectuosas y optimiza el funcionamiento neuronal. En autismo, esta poda daría lugar a grados de "sobreconectividad" anatómica que aumentan o disminuyen la eficiencia de la comunicación entre regiones corticales. Igual ocurre con la mielinización axonal que afecta la comunicación cortical interregional integrada y sincronización. Mecanismos críticos y vulnerables durante el período peri-neonatal, con posterior estabilización de las sinapsis para constituir redes neuronales prediseñadas mediante mecanismos genéticos y modificadas por factores ambientales. Existen anomalías en diversas proteínas que modulan la primera fase de la sinaptogénesis, mutaciones en las protocadherinas, cadherinas y

Correspondence:
*Paola Núñez-Contreras,
E-mail: paolagnc@gmail.com

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anomalias en sistemas glutamatergicos y gabaergicos que afectan el cerebro. Todos estos aspectos son críticos para el aprendizaje, lenguaje y memoria tanto en autismo como epilepsia.

Palabras clave: *Sinaptogenesis, Autismo, Epilepsia.*

Introduction

The association between autism spectrum disorders (ASD) and epilepsy has been established in numerous studies. The rate of epilepsy in children diagnosed with ASD is described by 30%, meaning that one in every three patients with autism will develop epilepsy during their lifetime[1].

If children with a diagnosis of autism and without epilepsy symptoms have an electroencephalography (EEG), 10% would have an EEG with epileptic form activity. These anomalies remain over time, continuing in adolescents and young adults with autism[2] (Giovanardi Rossi, 2000). A relationship between the regression of language and epilepsy is associated, and the epileptic form alterations found when performing longer electroencephalographic records.

In rare cases, epilepsy may be responsible for autistic traits, such as in acquired epileptic aphasia, where marked impairment of social communication has been described as autistic, but apparently this is a direct result of epilepsy[3]. To the question of whether autism causes epilepsy, it is argued that autism could cause epilepsy on the basis that, frequently, autism is associated with another comorbid cerebral dysfunction, especially intellectual deterioration, which is also associated with epilepsy. This coexistence of autism and epilepsy is an association, not causation[3].

The purpose of this review is to describe the different relational elements shared between ASD and epilepsy, as brain mechanisms, which include the regulation of gene transcription, cell growth, synaptogenesis, and the role of glutamatergic and GABAergic systems. It should also be taken into consideration that there are also metabolic, mitochondrial, and genetic defects that underlie ASD and epilepsy.

Methods

Bibliographic search in PubMed, ScienceDirect, Springer Link, Cochrane, textbooks, referring to Epilepsy, Autism and Neurodevelopment, 70 articles were found, only five establish a relationship between them; it is for this reason that we consider it important to review this relationship.

Autism background

Leo Kanner, in 1943, described the autistic disorder, now called ASD[4], where deficiencies are found in socio-emotional reciprocity, deficiencies in non-verbal communicative behaviors, used in social interaction, deficiencies in the development, maintenance, and understanding of relationships, in addition to restrictive and repetitive patterns of behavior, interests, and activities; symptoms that must be present from the earliest stages of development[5]. Associated with these, there are serious impairments in the ability to relate, adapt and interact socially, as well as in neurocognitive development[1-6].

ASDs can occur with or without medical, genetic, neurodevelopmental, mental, or behavioral disorders. Together, they have a prevalence of 0.6% in the general population[7]. The estimated prevalence of ASD was 2.24% (1 in 45), in 2014, established by Centers for Disease Control[8].

According to the Ministry of Health of Chile, it is estimated that for 240,569 live births registered in 2007 (DEIS), the approximate number of people diagnosed with ASD in Chile was 2156 children (1 in 111) five according to the Department of Statistics and Information of Health of the Ministry of Health. Fombonne et al. (2016) determined the prevalence of autism in Mexico, concluding that 1 in every 115 children would have this disorder[5].

Biological mechanisms described in autism

Considering autism a neurodevelopmental disorder, there is an abnormal maturation of the brain[9,10]. In the normal brain, initial growth, neuronal loss, and synaptic pruning are timed so that activity and experience support the organization of functional networks (Kandel et al., 2000)[11]. While normal pruning could help eliminate faulty connections and optimize coordinated neuronal functioning, pruning in autism would possibly result in some degree of anatomical “over-connectivity” that could increase or decrease the efficiency of communication between cortical regions. In autism, the absence of neuronal structures, including apoptosis, axonal pruning and dendritic degeneration, as well as increased neurogenesis, would explain the autism clinic, in combination with specific genetic alterations.

Lewis and Elman (2008)[12] postulate that the abnormalities in these maturation processes are consistent with the findings of increased brain size in autism in the early stages of development, the largest increase being in the frontal cortex. A compensatory process that would reduce the functional impact of the increase in brain size would be a reduction in the proportion of long-distance connections.

Adam et al. (2012)[9] propose a lack of integrity of the tracts of the white matter that carry information between the different brain regions, affecting the interregional cortical communication. Another mechanism affected is the myelination of axons that also affect integrated interregional cortical communication and synchronization.

Geschwind and Levitt (2007)[10] express that biological mechanisms affect connectivity; several microstructural processes could explain the impediments in the functional and anatomical connectivity observed in autism. A series of initial processes of neurodevelopment, such as neuronal migration and the establishment of synapses, could individually or in combination lead to anomalies in the development of connectivity.

Herbert et al. (2004)[13] suggest that the corpus callosum is usually smaller in autism, this decrease in size could be an index of white matter deficit that could contribute to damage cortical connectivity. Vargas et al. (2005)[14] found evidence of astroglial and microglial activation and neuroinflammation in the gray and white matter (in samples taken from the middle frontal gyrus, anterior cingulate gyrus and posterior cerebellar hemispheres) and the symmetry of the temporal planes in postmortem case studies.

Alterations in synaptogenesis and autism

Juan-Jose García-Peñas et al. (2012)[15] conducted a review on alterations of synaptogenesis in autism; it is known that the first functional synapses in the human brain are evident from the 40th day of embryonic life and later undergo a complex process of structural and functional maturation. These mechanisms are especially critical and vulnerable during the perinatal and neonatal period, then there is stabilization of the synapses to constitute pre-designed neural networks through genetic mechanisms and modified by environmental factors.

Suda et al. (2011)[16] described histochemical studies in brains of autistic children and adolescents, where anomalies have been revealed in various proteins that modulate the first phase of synaptogenesis, including ephrins type EFNA4 and EFNB3, plexin PLXNA4, and ROBO2 and ROBO3 (roundabout 2 and 3), mainly in the primary motor cortex and the anterior cingulate cortex.

SynCAM1 (membrane protein of the Ig superfamily) that functions as an adhesion molecule is located symmetrically in both membranes of the synapses and binds to them through an extracellular domain to form a homophilic component of cell adhesion. Zhiling (2008) described missense mutations in the SynCAM1 gene in autistic people.

N-cadherin (CDH2) acts as a basic adhesion molecule for the development of excitatory and inhibitory synapses, protocadherins are essential in the development of synaptic specificity. Morrow and Bhalla (2008) described mutations in the protocadherins PCDH9 and PCDH10 and in cadherins CDH15 and CDH18 in subjects with autism and mutations in protocadherin PCDH8, which interacts with the kinase TAOK2 (serine/threonine-protein kinase TAO2) and MAPK3 (mitogen-activated protein kinase 3), which map in the region 16p11.2, one of the most important loci of susceptibility for autism, this alteration of PCDH8 would produce an internalization of the synaptic receptors AMPA, which would modify the normal development of the synapses.

Glutamatergic-GABAergic systems and autism

The glutamatergic and GABAergic systems are important foci of pathology in the brain of patients with autism. Many investigations stand out the deregulation of several proteins involved in this pathway (Fatemi et al., 2012)[17].

The GABA A receptors are responsible for the mediation of rapid inhibitory action of GABA in the brain. GABA B receptors play an important role in maintaining an excitatory/inhibitory balance in the brain. The GAD protein is responsible for the conversion of Glutamate to GABA. It has been shown that GAD 65 and 67 are reduced in the cerebellum of adults with autism. In the cerebellum, concordant reductions have been observed in mRNA and in the protein levels of GABA R1 receptor in adults with autism[18].

Concurrent reductions were also observed in GABA A and GABA B receptors in Brodmann areas 40 and 9, decreased densities of the GABA A receptors in the anterior cingulate cortex and GABA B in the fusiform gyrus.

Reelin (serine protease of the extracellular matrix) is expressed in the GABAergic and glutamatergic cells; regulates the lamination of neurons during embryonic

development; and helps in the processes of neuronal migration in the early development, modulation of synaptic plasticity throughout life, and maintenance of long-term potentiation.

Many studies have shown abnormal expression of reelin in autism and reproduced these results evidencing polymorphisms of the RELN gene, decreased reelin mRNA in the upper frontal cortex and cerebellum, and decreased expression of Reelin in blood analyzes[19]. Reelin also binds to very low-density lipoprotein (VLDLR) receptors, apolipoprotein receptor 2, and $\alpha 3\beta 1$ integrin. Through these, it is capable of activating Dab-1 (Disabled-1), an intracellular adapter protein that facilitates the signal between the reelin-secreting cells and the pyramidal cells. VLDLR is upregulated in the upper frontal cortex and cerebellum of adult patients with autism, while Dab-1 is significantly reduced in these areas, suggesting the alteration of signaling in the reelin pathway.

Epilepsy background

According to the ILAE 2017, epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"[20]. It is the clinician's first task to determine that an event has the characteristics of a seizure and not one of the many imitators of seizures. The next step is classification into a seizure type, the electroclinical syndrome, and determine the treatment consistent with the physiopathological mechanisms of each of the different epilepsies[21].

The epidemiology varies according to the underdeveloped or developed countries, being the average in developed countries of 5.8/1000 habitants, while in low-resource countries, it is 10.3/1000 in urban areas and 15.4/1000 in rural areas[22].

In high-income countries, incidence rates in the general population are between 30 and 50/100,000 people. In low- and middle-income countries, this figure can be up to twice as high[23]. In Mexico, the prevalence in the centers of the Priority Epilepsy Program is 11.4-20.3/1000 (2004)[24]. In Chile, the prevalence of epilepsy is 10-17.7 × 1000 (Lavados et al.)[25].

Epileptogenesis

Epileptogenesis is the process by which the previously normal brain is functionally altered and biased toward the generation of abnormal electrical activity that leads to chronic epileptic seizures. The concept of "mechanism of epilepsies" refers to any biological characteristic of the brain that drives or supports recurrent and unprovoked crises.

Epileptogenesis is a dynamic process, in which the genetic and structural alterations in the brain lead to a cascade of molecular and cellular changes, which are associated with the appearance of spontaneous epileptic seizures, such as changes in neurogenesis, neurodegeneration, gliosis, dendritic plasticity, axonal damage, damage to the blood-brain barrier, inflow of inflammatory cells to the brain tissue, reorganization of the extracellular matrix, and reorganization of neuronal activity. Glial abnormalities, including glial scars, various gliomas, and microglia and chronically activated astrocytes, can lead to epileptogenesis due to increased neuronal excitability and inflammatory processes.

The process of epileptogenesis can be divided into three phases[26]. The first is associated with the occurrence of injury or event, the second latent phase leads to the appearance of abnormal epileptic brain activity, and in the third phase occurs spontaneous epileptic seizures. The factors that have the most important role in the molecular basis of epileptogenesis are as follows: the brain-derived neurotrophic factor-tropomyosin-related kinase B (TrkB, also known as NTRK2) signaling, the mammalian target of rapamycin (mTOR), the repressor element 1 (RE1), and Silencing Transcription Factor, also known as Neuron-Restrictive Silencer Factor.

The imbalance between excitatory and inhibitory neurotransmitters explains the induction of epileptic seizures. GABA A controls the entry of chloride into the cell, and GABA B increases the potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters. The concepts of tripartite neuron explain the pathophysiology of epilepsy, with relevance in the anomalies in the GABAergic function in genetic and acquired animal models of epilepsy, reductions or inhibition mediated by GABA, activity of glutamate decarboxylase, and binding to GABA A sites, this has been reported in studies of human epileptic brain tissue. Abnormalities of GABAergic function, including synthesis, synaptic release, composition, and metabolism of the receptor, lead to a hyperexcitable epileptic state.

Relationship between epilepsy and autism

Sundelin et al. have documented a greater frequency of epileptic seizures in ASD. The frequency range varies from 7% to 42%, currently an association of one third of children with ASD is considered to develop epilepsy[27]. In our series, we found a prevalence of 30% of children with ASD and Epilepsy[28]. There is a bimodal

distribution of onset of crisis in patients with ASD and epilepsy: one in the early childhood (before 5 years old) and the other in adolescence after 10 years old[29].

The variability in the prevalence of epileptic seizures would probably be due to three factors: (1) the age groups studied, finding a higher percentage of epileptic seizures in studies that include adolescents and young adults, (2) the most severe cognitive disability is related with a higher percentage of epileptic seizures, and (3) the type and degree of language dysfunction, with the highest percentage of epileptic seizures occurring in individuals with verbal auditory agnosia.

All types of seizures can be associated with autism. Keller et al. (2017)[30] report partial seizures, atypical absences, myoclonic, and tonic–clonic seizures as the most prevalent, while Tuchman and Rapin (2002)[29] show tonic–clonic seizures and atypical absences, in genetic cases as the most common. Matson and Neal (2009)[31] found a relationship between autistic regression in patients diagnosed with Epilepsy and ASD. Spurling and Tuchman (2015)[32] comments that there is no evidence to suggest that epilepsy is the cause of autistic regression; however, it recommends the importance of detecting other deficits, such as language, cognitive, behavioral, and not only to treat seizures. It suggests that there are multiple variables that can guide clinical management where epilepsy, autism, and regression overlap, such as the type of regression, age of onset of crisis, epileptic form activity and the location, orientation, and amount of epileptic form activity.

In studies of multiple models of epilepsy suggest that the balance between the excitatory and inhibitory networks are interrupted, and that the composition and excitatory synaptic efficacy are enhanced, directly, or indirectly. A important excitatory synapses regulator is the glutamate receptor, which is also critical for learning and memory. Therefore, dysregulation induced by an epileptic seizure of glutamate receptor function itself, or that of a "upstream and downstream" mediator can have important effects on learning and cognition.

Ictal activity may provide greater excitability to disrupt synaptic homeostasis, even a brief ictal activity may impair learning, possibly the most sensitive period for seizures that affect cognitive function is during brain development. At that time, the mechanisms of synaptic plasticity are maximum, and excitatory mechanisms predominate on inhibitory. Since the cascades involved in learning and memory are mostly dependent on the activity of neural networks, there is a possibility that this excessive neuronal activity has unexpected effects on normal synaptic function. On the other hand, synaptogenesis is maximal in the developing brain, and it seems to share many of the same mechanisms with those of synaptic plasticity.

The preschool and grade school ages present high incidences of epilepsy, and this is also the period, in which autism manifests itself. This age window is the natural "critical period," where synaptic plasticity and synaptogenesis are at the highest level of life. In addition, both epilepsy and autism are partly due to a consequence of a dysregulated synaptic development. When epilepsy and autism co-occur, it is assumed that they may have been the result of a primary interruption of synaptic function due to injury or genetic mutation[30]. What is not known is whether epileptic activity, which could further disrupt synaptic function, may contribute to the secondary symptomatology of autism.

Glutamate plays a role during the development of the brain by regulating multiple processes, (neurogenesis, neuronal growth, survival of neurons, and synaptogenesis). It is important in the acquisition of emotional behavior. NMDA glutamate receptors are responsible for long-term potentiation, learning, and memory, which altered processes in subjects with autism. In addition, the imbalance between GABA/glutamate can cause epileptic disorders in autism. Genetic studies have found positive associations between autism and a series of polymorphisms in glutamate receptors and transporters, including the mitochondrial glutamate-aspartate transporter (SLC25A12) and the glutamate ionotropic receptor kainate type subunit 2[17].

Mutations in GABA A receptor subunits or mutations in non-GABA A receptor subunit genes that alter GABAergic neuronal activity are associated primarily with epilepsy, but also with autism or both. Genetic mutations other than GABA A receptor subunits, such as tuberous sclerosis, Fragile X Syndrome (FXS) Rett Syndrome, show altered GABAergic signaling. Studies of animal models indicate that the loss of SCN1A function causes significant reductions of sodium in inhibitory GABAergic neurons, suggesting GABAergic circuits that would explain the presence of epileptic seizures in these entities.

The altered expression of GAD 65 and 67 in the GABAergic system has been associated with epilepsy, schizophrenia, ischemia, and traumatic brain injury. In Autism, the level of GAD protein isoforms is reduced (Fatemi et al., 2012)[17]. Studies of MRI and neuropathology suggest that the altered proliferation and migration of neuroblasts, the cortical organization, and the development of projection neurons and GABAergic interneurons within the focal brain regions, forming common abnormal neuronal circuits, that would explain the phenotypic manifestations in autism and epilepsy.

Giannotti et al. (2008)[33] reported that epilepsy and epileptiform abnormalities in the EEG were more frequent in children with regression (with loss of neurocognitive abilities in expressive, semantic and pragmatic language, communicative intention, working memory, executive functions, playful abilities, and socialization).

Due to the wide range of age and phenotypes of the ASD group, no single EEG biomarker has been identified that consistently distinguishes individuals with ASD from those without ASD. Wang et al. (2013)[34] identified a possible "U" grafoelement within the EEG alterations, with the excess voltage viewed at the theta and gamma frequencies and reduced voltage at medium frequency bands compared to individuals with normal development. The authors speculated that it could result from an abnormal GABAergic tone in inhibitory circuits.

The EEG can also report the neurophysiological mechanisms of the disease in genetic variants of high risk. In duplications of chromosome 15q11.2-q13.1, a subgroup of children exhibits a classic EEG pattern of excessive beta-frequency activity, this characteristic probably reflects the up-regulation of several GABA receptor genes located in the duplicated region. Studies are underway to better characterize this excessive beta-activity, investigate, whether it is characteristic of the EEG, relate to or predict clinical outcomes, particularly the development of epilepsy or ASD.

In addition, they want to find a relationship between specific patterns of EEG with essential deficits or individual behaviors within the ASD, to facilitate clinical stratification[32].

Patterns, even controversial, that could distinguish infants with high and low risk of ASD have been identified. The studies have quantified the differences in the trajectories of EEG development, particularly in the gamma band, which reflects the union of neural information from different networks. Other studies have identified an atypical pattern of hemispheric organization based on the asymmetry of the alpha range as well as less functional connectivity between the frontal and parietal regions, in high-risk children compared to low-risk children, independent of the diagnosis of ASD[32].

Epileptic syndromes and autism[35]

Children with ASD who have epilepsy may have epileptic seizures that do not meet the criteria for specific electroclinical syndromes. However, several specific syndromes of epilepsy seem to be risk factors for the subsequent diagnosis of ASD. These are described below.

Aircadi Goutieres syndrome (SAG)[36]

Rare autoimmune genetic disorder affects the brain and skin. Manifestations may present in utero or postnatal in childhood, characterized by subacute encephalopathy and loss of acquired skills. Severe neurological dysfunction arises as progressive microcephaly, spasticity, dystonia, and cognitive impairment. Associated symptoms include epileptic seizures and glaucoma. Most patients have abnormalities in neuroimaging, including white matter abnormalities and cerebral calcifications, mainly in the basal ganglia.

There are seven known genetic subtypes, caused by mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, or IFIH1; each gene is involved in the intracellular metabolism of normal RNA/DNA. Mutations of TREX1, RNASEH2 A/B/C, SAMHD1, ADAR1, and IFI are associated with developmental delay, regression, and epileptic seizures[37].

Infantile spasms

The prevalence of ASD in children with a history of infantile spasms is not consistent, but an association between both is clearer in the tuberous sclerosis complex (TSC1 and 2) and duplications of FOXG1:

In TSC1 and TSC2, hamartina and tuberina, join, and form, a protein complex involved in the regulation of mTOR. The loss of function of the TSC results in the absence of normal inhibition of mTOR, with an increase in Rheb activity and subsequent hyperactivity in mTOR, which leads to disinhibition of protein synthesis and cell growth. The neurological manifestations of TSC include epilepsy, intellectual disability and ASD, as well as specific cerebral malformations and cortical tubules, nodules and subependymal giant cell astrocytomas. Epilepsy occurs in more than 80-90% of patients with TSC. Infantile spasms occur in approximately 20-38% of patients with TSC and are associated with a worse prognosis. ASD is found in 20-60% of individuals with TSC and is equally common in men and women in this population[35].

Children with duplications of FOXG1 on chromosome 14q12 have long-term developmental abnormalities that include autistic features. FOXG1 is a specific transcriptional repressor protein that regulates the dorsal-ventral pattern and neurogenesis; its overexpression in the developing anterior brain is associated with thickening of the neuroepithelium, and the evidence supports a role inline change in neuroprogenitor cells. However, the mechanisms that lead to epilepsy and associated

developmental disorders due to changes in the number of copies of this gene are not known[38].

Landau–Kleffner syndrome/continuous spike and wave during slow wave sleep (CSWS). The Landau–Kleffner syndrome is an epilepsy-aphasia syndrome of unknown etiology characterized by language regression and continuous spike-wave during slow wave sleep on the EEG. Some children with severe language apraxia have autistic characteristics with a predominance of severe deficit of receptive language. Studies have detected: (1) copy number variants (CNVs) in exogenous deletions of NRXN1, HDAC4, SYNGAP1, ARID1B, SHANK2, CHD2, SHANK3, PTCHD1 intragenic duplication of NRXN1, IL-1RAPL1, and DMD exonic duplication of DMD, duplication partial of DMD, *de novo* CVN, (2) chromosomal abnormalities: unbalanced translocation, 1q duplication syndrome, ring chromosome 8, Down syndrome, and XYY syndrome, (3) genomic disorders with recurrent breakpoints: deletion syndromes 1q21.1, 10q11.21-q11.23, 15q13.3, 16p11.2, 16p13.11, 22q11 (DiGeorge syndrome), 7q11.23 (Williams Syndrome), 17p11.2 (Smith Magenis syndrome) duplication syndromes 1q21.1, 15q11-q13, 16p11.2, 17q12, and 22q11. Xq28 duplication including GDI1 4, 15q25 distal deletion syndrome, and (4) genomic disorders with non-recurrent breakpoints: 9p terminal deletion, 9q34.3 deletion (Kleefstra syndrome), Jacobson syndrome (11q deletion), Mc Dermid Phelan syndrome (22q13 deletion), and GRIN2A mutations in patients with phenotypes of epilepsy-aphasia.

ASD and epilepsy in genetic syndromes[34]

Several genetic mutations are related to the development of ASD and/or epilepsy and exert their influence on various aspects of neuronal function, not only limiting ion channels and synaptic physiology. These mutations affect proteins involved in all phases of neuronal excitability: anchoring of the synaptic complex, management of the release of synaptic vesicles, control of subcellular signaling pathways, regulation of neuronal migration, and organization of network connections[30]. Conditions caused by variation in the number of genomic copies or mutations in single genes have been associated with ASD and epilepsy.

Genomic disorders

Trisomy 21 (Down syndrome [SD])

5-9% of individuals with DS comply the criteria for ASD. The diagnosis of ASD in this group is a challenge. The prevalence of epilepsy in patients with DS is 8-13%[39]. Children with DS and ASD tend to have a general decrease in brain function, and an increased risk of epileptic seizures.

15q11-q13 Duplication Syndrome inherited from the mother. It is the most frequent chromosomal alteration reported in patients with ASD (0.5-3%).

There would be a deregulation of inhibitory synapses, genes that encode the GABA receptor subunits (GABRA5, GABRB3, and GABRG3) in the duplicated 15q11q13 region, which explains the pathogenesis of epilepsy and ASD phenotypes.

CNVs

Some pathogenic CNVs are associated with ASD and epilepsy. 15q11.2 and 16p11.2 deletions and 16p13.11 duplication have been detected with high frequency in individuals with ASD. A possible mechanism of ASD/epilepsy associated with these CNVs is a second mutation in the non-suppressed allele.

Phelan-McDermid syndrome/SHANK3 deletion

The 22q13.3 deletion containing the SHANK3 gene has been associated with early hypotonia, developmental and speech delay, autistic features, lymphedema, and dysmorphisms. The prevalence of epilepsy in these patients is unknown. SHANK3 encodes scaffold proteins found in the postsynaptic space, which regulates the expression of the metabotropic glutamate receptor 5 (mGluR5), regulates the recycling of AMPA receptors and long-term synaptic potentiation, and interacts with the voltage-gated potassium channels Kvβ2 in postsynaptic space. Mice deficient in SHANK3 show autistic behavior and have anomalies in the synapses of the striatum and corticostriatal circuits. Deletions of SHANK1 and mutations in SHANK2 have also been reported in patients with ASD[40].

Single gene disorders

FXS

It is considered the main monogenic disorder associated with ASD. Occurs when the expansion of a triplet repeat (CGG) leads to the inactivation of the FMR1 gene, resulting in the loss of expression of FMRP (RNA-binding protein, located in the dendritic ribosomes), plays a role in the remodeling synaptic, necessary for normal learning and memory.

The cognitive profile includes hyperactivity, anxiety, tactile defensiveness, gaze avoidance, and socialization difficulties. Epilepsy is reported in 10-20% of individuals. The crisis patterns resemble Benign focal Rolandic epilepsy and typical central-temporal spikes can be observed in up to 60% of patients with FXS with seizures and in 23% of patients without clinical crisis[41]. It has been proposed that an ionic current controlled by voltage participate in epileptogenesis by the activation of the mGluR5 receptor. The activation of mGluR5 across multiple synapses in the context of poor FMRP translation control leads to greater electrical excitability.

Mutations in PTEN[42]

PTEN is a double specificity phosphatase and a tumor suppressor gene, it affects the blocking of the G1 cell cycle and inhibits the PI3K/AKT/mTOR pathway. Macrocephaly and ASD have been reported in children with germline PTEN mutations.

Seizures have been reported in patients with PTEN mutations, including a number with focal cortical dysplasia. Epilepsy seems to be a part of the phenotype for many of the megalencephaly disorders associated with deregulation of the PI3K-AKT-mTOR pathway, but the exact role of mutations in specific genes in this pathway related to seizures and ASD should be clarified.

Disorder related to MECP2 (Rett syndrome)

It predominantly affects women, characterized by intellectual disability, postnatal microcephaly, loss of expressive language, stereotyped movements in hands, and autistic features. The onset of symptoms and regression occur at 6 to 18 months of age after a period of apparently normal development. MECP2 is a transcriptional activator during brain development. Mutations result in "downregulation" of many target genes, loss of MECP2 function reduces GABAergic transmission, and alteration of the glutamatergic unit in specific populations of inhibitory interneurons.

50-90% have epileptic seizures. The type of crisis is variable, the age of onset is rare before 2 years, and the severity of the seizures seems to decrease after adolescence. Mutations specific for MECP2 (p.T158M and p.R106W) were more highly associated with epilepsy.

Disorder related to CDKL5[43]

X-linked disorder, characterized by early onset of epilepsy, with infantile spasms, and severe neurodevelopmental delay with postnatal microcephaly, absence of expressive language, and stereotypies of hands. Girls share some characteristics of ASD. The inability to concomitant development and the phenotype of epilepsy are greater than those typically seen in children with classic forms of ASD. The role of the protein CDKL5 (serine-threonine kinase) has to do with the development of dendritic microcolumns, macrocolumns, and adhesion molecules involved in the stabilization of the post-synaptic membrane.

Disorder related to MEF2C

There are mutations with loss of function and deletions of MEF2C on chromosome 5q14.3, characterized by severe intellectual disability, epilepsy, stereotyped movements, and features of ASD.

In most, the cephalic perimeter and brain morphology are normal. The percentage of epilepsy is variable, 20% present infantile spasms, 33% childhood myoclonic epilepsy, 24% generalized epilepsy in childhood, and 23% without epilepsy.

MEFC2 plays several roles during brain development, and is a marker of cortical lamination driven by Tbr1. MEFC2 recognizes a binding site of the synaptic activity response element, which activates a series of genes for synaptic development, dorsal glutamatergic, and ventral GABAergic.

Disorders related to SCN2A

SCN2A encodes the sodium channel voltage dependent Na (v) 1,2 predominantly expressed in excitatory neurons, the mechanism by which there is loss of function of this channel with secondary hyperexcitability is unclear. The deletion of chromosome 2q24.3 containing SCN2A was reported for the first time in a child with autistic characteristics and intellectual disability[44]. At the same time, several children were identified with a spectrum of severe epilepsies of the early life including Ohtahara syndrome, malignant migratory partial seizures of childhood, and infantile spasms with mutations in SCN2A. In other children, benign neonatal-infantile epilepsy and generalized epilepsy with febrile seizures plus have been reported.

Conclusion

The underlying neurobiological mechanisms for ASD and epilepsy allow us to frequently find both associated pathologies.

This perspective finds support in new genetic mutations discovered for autism and epilepsy that highlight the presence of anomalies in the formation of synapses and the functions that entail an imbalance between excitation and neuronal inhibition.

Every time we diagnose a child on the autistic spectrum, we should consider the possibility of having an epilepsy. It is recommended that patients with diagnosis of epilepsy undergo a neuropsychological evaluation that includes neurocognitive aspects, social, and behavioral skills and interpersonal relationships. The early detection of the association of both pathologies will allow us to provide a better treatment for children and adolescents. It is recommended to perform a directed search and clinical follow-up of this population considering an electroencephalographic follow-up and early intervention in case of diagnosis of epilepsy.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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