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Review in Autism and Epilepsy

Mashaal AlKhateeb and Hesham AlDhalaan

Abstract

Autism is a neurodevelopmental disorder of undefined etiology characterized by social, communication deficits, and restricted interests/repetitive or isolated behaviors. The determination of autism is made in early life as the patients create unusual or decreased social interaction and communication, together with stereotypic movement. In most patients, a delay in verbal and nonverbal communication is watched, whereas a few patients never accomplish valuable language. Patients with autism and epilepsy may develop any type of seizure and maybe all type of seizures. Interestingly, not absolutely understood relationship between each and a lot of research in progress concerning these relations. In patients with autism, some they do not develop seizures; however, abnormal paroxysmal electroencephalographic “EEG” activity can be seen in up to 30%. For that reason, important investigation of patients with autistic spectrum disorders, and any kids with language regression, should always include sleep recording EEG in order to exclude acquired epileptic aphasia (Landau-Kleffner syndrome). The complex relationship between autism and epilepsy provides a bridge to further knowledge of shared neuronal networks for both the autisms and the epilepsies We review the literature to elucidate the relationships between epilepsy and autism.

Keywords: epilepsy, autism, EEG, seizure, syndromes, autistic spectrum disorders

1. Epilepsy and autism

Epilepsy is a neurological disorder not uncommon in children especially with Autism Spectrum Disorder (ASD) [1–4] but little is known about how seizures impact the autism phenotype and the co-occurrence of both conditions leads to opens a lot of windows to speculate that [5]. The etiology of this co-morbidity (autism and epilepsy) is in most cases unclear. In some cases both conditions may be entirely independent and acquired together by chance. In other cases, autistic phenotype and epilepsy are associated with genetic disorder (e.g., fragile-X syndrome, Rett syndrome) or the same acquired early cerebral insult (e.g., congenital rubella).

2. What is the prevalence of autism?

The most recent estimate from the Autism and Developmental Disabilities Monitoring (ADDM) ASD prevalence (1.46%) in 2012, with increase from 0.67% in 2000 to 1.47% in 2010. In a large, nationwide population-based study, the estimated ASD prevalence was 2.47% among US children and adolescents in 2014–2016, with no statistically significant increase over the 3 years [6].

3. What is the rate of epilepsy in ASD?

The rate of epilepsy in ASD has long been reported, but prevalence estimates vary from as little as 5% to as much as 46% [1].

4. Is there any connection between autism and epilepsy?

The complex relationship between autism and epilepsy, as reflected in the autism–epilepsy phenotype, provides a bridge to further knowledge of shared neuronal networks for both the autisms and the epilepsies.

The autisms and epilepsies are heterogeneous disorders that have diverse etiologies and pathologies. Some epilepsy syndromes and specific genetic factors involved in those syndromes are associated with a high risk of ASD. For example, patients with tuberous sclerosis, especially TSC2 mutations, Dravet syndrome, caused by mutations in SCN1A, and epilepsy in females mentally challenged or EFMR, found to be auxiliary to PCDH19 mutations that increase the chance to have autistic like features [7].

The increased prevalence of epilepsy and/or epileptiform discharges in individuals with ASD may be an important sign for an underlying neurological abnormality. Until recently, reported rates of interictal epileptiform discharges varied from 6 to 30% of ASD patients. But higher rates of isolated epileptiform EEGs have been reported recently and one study of children referred for video EEG monitoring to evaluate possible seizures found interictal epileptiform abnormalities in 59% [1].

The correlation between ASD and epilepsy suggests an underlying encephalopathy presenting with a combination of neurologic abnormalities.

5. Conceptual framework between autism and epilepsy

Autism includes heterogeneous conditions that affect the developmental trajectory of social cognition and verbal and non-verbal communication. Repetitive behaviors and narrow interests are characteristic of individuals with autism.

The commonly used terms Autism spectrum disorders (ASD) or pervasive developmental disorder (PDD) to incorporate children with autistic disorder, pervasive developmental disorders not otherwise specified (PDD-NOS) and those with Asperger disorder (AS). Children with disintegrative disorder (DD) and Rett disorder (RS) are too included beneath the umbrella term of PDD but have features, particularly when examining the relationship of epilepsy to autism, that recognize them from children with AD, PDD-NOS, and AS. With the exemption of RS, these disorders are all behaviorally characterized and most recent studies utilize the term autism interchangeably with that of ASD to incorporate children with AD, PDD-NOS, AS, and DD, but not RS [8].

There's no single no single etiology for autism or for epilepsy. Both are associated with change in behavior, cognitive, and variable outcomes.

6. Genetics of autism

Autism is not a disease but a syndrome with multiple non-genetic and genetic causes.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSMIV-TR) [7] and International Classification of Diseases, Tenth Revision (ICD-10).

(The autistic spectrum disorders [ASDs]), characterized by impairments in 3 behavioral domains:

1. Social interaction.
2. Language, communication, and imaginative play and
3. Range of interests and activities [9].

A number of approaches are being used to elucidate the association between specific genes and autism.

7. Cytogenetics and chromosomes 15q and 7q

Cytogenetic assays used for decades to explore chromosomal defects in patients with autism, and a number of cytogenetic abnormalities besides fragile X have been described [9].

Less than 10% of cases of autism are associated with clear chromosomal abnormalities. Cytogenetic abnormalities found at the 15q11-q13 locus are reported most frequently in patients with autism, up to 1–4%.

Analysts have started to look at the glutamatergic framework within the pathogenesis of autism. A few lines of prove recommend the inclusion of glutamate receptors: (1) Indications of hypoglutamatergia mirror the behavioral phenotypes of autism. (2) Serotonin receptor 2A (5-HT_{2A}) agonists cause behavior comparative to autism, maybe through expression of 5HT_{2A} on glutamatergic-inhibiting GABAergic neurons. (3) Association studies have involved the inclusion of GABAA receptors on 15q11-q13 that in turn balance glutamatergic function. (4) Excessive glutamatergic activity is associated with epileptiform activity, which is highly associated with autism.

The ionotropic glutamate receptor 6 (GluR6) gene on chromosome 6q21 was associated significantly with autism. Also, the metabotropic glutamate receptor GRM8 in the chromosome 7q31-q33 autism susceptibility locus has exhibited linkage disequilibrium LD with autism. These data highlight the need for additional investigations into the relationship between the glutamate system and autism.

The neuromodulator oxytocin (OT) is also potentially relevant to the impaired sociability of autism [9].

Autism genes have been troublesome to recognize, in spite of the fact that well known the high heritability of autism disorders. Up to 10% of autism cases may be due to uncommon sequence and gene dosage variations, for example, mutations in NRXN1, NLGN3/4X, SHANK3, and copy number variants at 15q11-q13 and 16p11.2 [10].

A number of illnesses of known etiology, including Rett disorder, fragile X disorder, neurofibromatosis, tuberous sclerosis, Potocki-Lupski syndrome and Smith-Lemli-Opitz syndrome, are also related with autism. The remaining 90% of autism spectrum disorders, whereas exceedingly familial, have unknown hereditary etiology [10].

8. Genes implicated in autism and epilepsy

The genetic abnormalities in autism and epilepsy not completely identified.

Cytogenetic studies have identified recurrent, maternally inherited duplications of chromosome 15q11-13 along with other rare chromosomal abnormalities is considered to be an important cause of ASD [8].

Some genes, such as NLGN4, NRXN1, and SHANK3, have been identified by array-based methods. Although they collectively account for an estimated 15% of cases, variants at these and other loci are detected in no more than 1–2% of children with an ASD [8].

In addition to that copy number variants (CNVs; e.g., microdeletions, microduplications, insertions) and single gene disorders have been found to be associated to ASD.

Many disease genes have been described as related to ASD, for example: SCN1A, SCN2A, KCNMA1, NLGN4X, NRXN1, SYNGAP1, ARX, SHANK3, CNTNAP2, NLGN4X, and play important role in epilepsy [11].

9. Genetic syndromes with ASD and epilepsy

Gene disorders known to be associated with ASD, such as Rett Syndrome (MECP2Fragile X Syndrome (FMR1), 22q13 Deletion Syndrome/Phelan-McDermid Syndrome), and Tuberous Sclerosis (TSC1, TSC2), and cortical dysplasia focal epilepsy syndrome (CDFE) a recessive nonsense mutation in CNTNAP2 are associated with epilepsy [12].

CNTNAP2 (also known as CASPR2) encodes a neuronal transmembrane protein member of the neurexin superfamily involved in neuron-glia interactions and clustering of K⁺ channels in myelinated axons. This is supported by the imaging and pathology data in patients with CDFE, in whom nearly half manifest presumed neuronal migration abnormalities on MRI, confirmed by histological analysis of brain tissue resected from patients who underwent surgery for epilepsy.

It is rare disorder resulting in epileptic seizures, language regression, intellectual disability, hyperactivity, and, in nearly two-thirds of the patients, autism [13].

The Continuous Spikes and Waves during Slow-wave Sleep syndrome (CSWSS) and Landau-Kleffner (LKS) syndrome are two epileptic encephalopathies that share common clinical features, including seizures and regression with autistic features. Both LKS and Regressive ASD patients experience an onset of regression. In LKS, the regression is specific to language skills but in Regressive ASD, it is a global. The important difference between both, the age of onset of regression for LKS is between the ages of 3 and 9 years, whereas for Regressive ASD the onset is before 2 years of age.

10. The autism-epilepsy phenotype

The characteristics of the autism-epilepsy phenotype propose that there are fundamental etiologies and pathologies dependable for both the seizures and the socio-cognitive and communicative behaviors that characterize autism. Understanding of neuronal systems and the part of cellular dysfunction, and molecular derangements common to both autism and epilepsy.

10.1 Neural networks in epilepsy and autism

Both epilepsy and autism may be consequences of disorders of large-scale neural networks with alterations in cortical-subcortical systems connectivity.

Alterations in subcortical systems such as basal ganglia-substantia nigra connectivity, may lower the seizure threshold, contribute to cognitive impairments and to the motor stereotypies commonly found in autism.

A disorder in which abnormalities of interneurons are hypothesized and in which both autism and epilepsy commonly coexist is infantile spasm [14].

Malformations of cortical development (MCD), due to focal disruption of normal cortical organization are commonly lead to epilepsy, which also can lead to autism, as is highlighted in tuberous sclerosis in which both autism and epilepsy co-exist [14].

10.2 Biomarker for autism gives hope for future autism treatment

The clinical heterogeneity and molecular complexities of autism spectrum disorders have increasing interest into biomarkers and endophenotypes, measurable quantitative parameters able to facilitate more reliable diagnoses and may help in the treatment of ASD.

‘Biomarkers’ can be defined as biological variable or cellular alteration associated with the disease and measurable directly using sensitive and reliable quantitative procedures [15].

Elevated blood serotonin (5-HT) levels, and serotonin transporter (SERT) consistently recorded in individuals with ASD [16].

11. Conclusions

The progression of biomarker research in autism mirrors that of other neurologic disorders in that it is still in its infancy and marked largely by discovery rather than validation.

The search for biomarkers for autism will proceed, given the profundity and extend of their potential benefits for individuals with autism and their families. If effective, biomarkers for autism may one day demonstrate important for finding out chance, helping with determination and/or recognizing therapeutic interventions.

Finally, Biomarker research has great heuristic potential in targeting autism diagnosis and treatment.

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