

Autism with epilepsy: A neurodevelopmental association

R Canitano^{1*}

Abstract

Introduction

The association between Autism Spectrum Disorders (ASD) and epilepsy has been extensively documented and the estimated prevalence varies, depending upon the selected population and the clinical characteristics. Children with early-onset epilepsy and early brain damage have a higher risk of presenting ASD compared to those without epilepsy. Genetic abnormalities are likely implicated in the association of ASD and epilepsy, although these abnormalities are currently detectable in only a small percentage of patients. Copy number variants (CNVs) with a low rate of occurrence (so-called rare variants) have been found to be implicated in these conditions as well. Furthermore, some genetic and medical conditions are associated with ASD and epilepsy. Currently the co-occurrence of autism and epilepsy is conceptualized as the result of common abnormal neurodevelopmental pathways. Synaptic dysfunction is likely to be involved in both disorders, as observed in preclinical models. There is no specificity of seizure type to be expected in children and adolescents with ASD compared to other neurodevelopmental disorders or epileptic syndromes. Treatment options include developmentally-based early interventions for ASD and medications for epilepsy. The aim of this article is to provide a brief overview of current research on the association of autism with epilepsy, from molecular basis to clinical characteristics.

Conclusion

Common neurodevelopmental pathways are probably at play in the association of autism with epilepsy. Synaptic abnormalities and genetic variations have been shown to be implicated in this complex condition.

Introduction

Autism Spectrum Disorders (ASD) and epilepsy are frequently associated and the rates of co-occurrence vary greatly in relationship to the selected population and concomitant predisposing factors¹.

Recent studies have reported significant differences, especially in cognitive levels. In a meta-analysis on this association, epilepsy was concomitant with ASD in 21.5% of patients with a type ASD who also had an Intellectual Disability (ID), in a pooled estimate, compared to a much lower prevalence of 8% in subjects without an ID².

A later meta-analysis evaluating the occurrence of epilepsy in ASD detected a prevalence of 8.9% in individuals over the age of 12 yrs without an ID, and a higher prevalence of 23.7% in individuals over the age of 12 years with an ID³. In the opposite association, children with early-onset epilepsy are also at a higher risk for presenting ASD compared to those without epilepsy.

In a population-based study of children with the onset of epilepsy in the first year of life, an elevated risk of ASD was found in those with infantile spasms secondary to a previous pathology⁴. Another study found that 5% of children with epilepsy in childhood also had ASD. Again, in this study infantile spasms were identified as predisposing factors and an ID was the other relevant factor associated with epilepsy and ASD. Furthermore, in patients with normal cognitive

levels, the prevalence of ASD was 2.2%, still higher than that in the general population, thus confirming the pathogenic association between ASD and epilepsy⁵.

Currently, the co-occurrence of ASD and epilepsy is seen as the result of common abnormal neurodevelopmental pathways.

There is evidence that shared mechanisms are responsible for the co-occurrence of epilepsy, autism, and ID^{6,7} and the mechanisms that lead to epilepsy may also negatively interfere with social development and overall cognition. These basic mechanisms and the pathways involved in social and cognitive dysfunctions in ASD, with or without epilepsy, are still under intense investigation.

The aim of this paper is to describe the association of autism with epilepsy and detail the relevant genetic and synaptic abnormalities that are involved in the complex association of autism with epilepsy.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Genetic underpinnings of ASD with epilepsy

The genetic abnormalities of the association of autism and epilepsy fall within the overall pool of abnormalities of ASD. Cytogenetic studies have identified recurrent, maternally

*Corresponding author
Email: r.canitano@ao-siena.toscana.it

¹ University Hospital of Siena, Siena, Italy



inherited duplications of chromosome 15q11-13, which along with other rare chromosomal abnormalities is still considered to be an important cause of ASD. Furthermore, individual genes of major effect, 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% to 2% of children with an ASD. In addition, it must be mentioned that these variants have been observed not only in individuals with ASD but also in patients with an Intellectual Disability (ID)⁸. Currently in a large percentage of patients with ASD, with or without epilepsy, there are still no detectable genetic defects and diagnosis is made solely on clinical grounds.

Copy number variants (CNVs; e.g. microdeletions, microduplications, insertions) and single gene disorders have been found to be associated to ASD. CNVs that occur infrequently, so-called rare variants, have been found to be implicated in these conditions⁹. According to a current hypothesis¹⁰, common diseases are the result of multiple rare variants that have great functional effects. This is the case in autism and epilepsy, which both present a marked heterogeneity, and in which a number of rare variants would lead to multiple phenotypes. Further evidence of the importance of the search for rare variants has been found in the disease genes discovered to be closely related to ASD. As many as 103 disease genes have been described as related to ASD, including SHANK3, CNTNAP2 and NLGN4X, and many of them are also implicated in epilepsy¹¹ (Table 1).

Single gene disorders known to be associated with ASD, such as Fragile X Syndrome (FMR1), 22q13 Deletion Syndrome/Phelan-McDermid Syndrome, Rett Syndrome (MECP2), and Tuberous Sclerosis (TSC1, TSC2), are associated with epilepsy in various but significant percentages^{12,13,14,15} (Table 2).

For example, 22q13 deletions/SHANK3 mutations (Phelan-McDermid Syndrome) suggest that the haploinsufficiency of SHANK3 can cause a single gene form of ASD with a frequency of 0.5% to 1%. The clinical phenotype of SHANK3-haploinsufficiency is characterized by neonatal hypotonia, absent or severely delayed language, minor dysmorphic features, gastrointestinal disease, renal abnormalities and ASD. In addition, seizures and epilepsy are present in about 30% of individuals¹⁶.

Although these syndromic ASDs have diverse genetic origins and phenotypes, and they account only for a small fraction (approximately 1-2%) of the whole ASD spectrum, they share common intermediates in the signalling pathways that are probably implicated in synaptic abnormalities and their association with epilepsy.

To further analyse the association of autism with epilepsy, multiplex ASD families were studied, providing significant results. In a recent investigation the prevalence of epilepsy was 12.8% in individuals with ASD and 2.2% in siblings without ASD. The risk of epilepsy in multiplex autism was significantly associated with ID, but not with gender.

In addition, genetic or non-genetic identified risk factors of autism tended to be significantly associated with epilepsy. When children with prematurity, pre- or perinatal insult, or cerebral palsy were excluded, a genetic risk factor was reported for 10.2% of children with epilepsy and 3.0% of children without epilepsy (P = 0.002).

Furthermore, the epilepsy phenotype co-segregated within families (P < 0.0001). As a result, epilepsy in multiplex autism likely has significant genetic components and it may define a different subgroup of clinical characteristics and genetic risks¹⁷.

Excitation/Inhibition(E/I) imbalance in ASD and epilepsy

The co-occurrence of epilepsy, autism, and ID is probably the consequence of functional abnormalities of neurons disrupting the normal balance between excitation and inhibition, interfering with neural functioning^{6,7}. An altered balance between excitatory synapses, mostly expressed by glutamate transmission and inhibitory GABAergic synapses, could affect social cognition during development, as well as a predisposition to epilepsy¹⁸.

Molecular abnormalities in synaptic structures and functions in ASD and epilepsy involve neuroligins and neurexins, proteins that are crucial for aligning and activating synapses along with the SHANK3 scaffolding protein. Multiple genes can contribute to the disruption of GABAergic interneuron development, which may be a point of convergence for both autism and epilepsy. Mutations in GABAA receptor subunit genes have been associated with ASD. The genes coding for the three GABAA receptor subunits $\alpha 5$, $\beta 3$ and $\gamma 3$ (GABRA5, GABRB3 and GABRG3, respectively) are located on the 15q11 chromosome, and single nucleotide polymorphisms (SNPs) in these genes have been associated with ASD¹⁹.

Neurexins (NRXNs) are presynaptic proteins that bind their postsynaptic counterparts, the neuroligins (NLGNs). NRXN-NLGN signalling is consistently involved in postsynaptic differentiation and it controls the balance of inhibitory GABAergic and excitatory glutamatergic signalling. Mutations and chromosomal rearrangements in NRXN1, one of the three genes coding for neurexins, have been associated with ASD²⁰.

Recently, it has been shown that NRXNs can bind not only NLGNs but also GABAA receptors²¹, with the result of decreasing GABAergic transmission. NLGN1, NLGN4X and NLGN4Y neuroligins are localized at glutamatergic synapses, while NLGN2 is located in GABAergic synapses. Mutations in NLGN1, 3 and 4X genes have been identified in ASD and two X-

Competing interests: None declared. Conflict of interests: None declared. All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Table 1: Altered genes in ASD with epilepsy. Modified by Amiet 2013 and Betancur 2011.

Gene	Locus	Type of mutation	Transmission	Molecular abnormalities
SCN1A	2q24	Point mutation	De novo	Na-channel
SCN2A	2q23–q24.3	Deletion	De novo	Na-channel
KCNMA1	10q22	Point mutation	Dominant inheritance	K-channel
NLGN4X	Xp22.31	Point mutation	Inherited	Synapse formation
NRXN1	2p16.3	Deletion Point mutation	Recessive inheritance De novo	Synapse formation
CNTNAP2	7q35	Deletion Point mutation	Recessive inheritance De novo	Synapse formation
SYNGAP1	6p21.3	Point mutation	De Novo	Synapse RasGAP
ARX	Xp22.13	Duplication	Inherited De novo	Aristaless-related homeobox protein

linked neuroligin mutations have been associated with familial ASD²².

All these studies highlighted abnormal synaptic GABAergic signaling, establishing the vanguard of current research on molecular abnormalities in ASD and epilepsy.

Alterations of neocortical minicolumns (namely, morphological changes of GABA interneurons associated with reduced width of minicolumns) have been demonstrated in ASD. Minicolumns are anatomically characterized by vertical arrays of pyramidal neurons with dendrite and axon projections. Pyramidal cell arrays are accompanied by their GABAergic interneurons that establish synapses with pyramidal cell bodies, axons and dendrites. A narrowing of these cortical minicolumns has been demonstrated in ASD patients.

It was hypothesized that this reduced intercolumnar distance was dependent on structural/anatomical defects in GABAergic interneurons surrounding principal pyramidal cortical neurons^{23,24}. In addition, a significant decrease in GABA_A receptor $\alpha 4$, $\alpha 5$, $\beta 1$ and $\beta 3$ subunits²⁵ in ASD brains has been observed.

GABAB receptors were also reduced in restricted regions of the cerebral cortex from ASD patients. However, current research in humans is still at the stage of preliminary investigations. Advanced neuroimaging techniques are developing this field. For example, ¹H-magnetic resonance spectroscopy (¹H-

MRS) is a non-invasive neuroimaging technique that allows for the estimation of specific in vivo neurochemical metabolites of GABA.

In a recent study, creatine-normalized GABA⁺ ratios (GABA⁺/Cr) were measured in a group of 17 children with ASD, and in a control group of 17 typically developing children, for motor, auditory and visual regions of interest. In the ASD group, deficits in GABA⁺/Cr were demonstrated at approximately 11% in motor regions and at approximately 22% in auditory regions²⁶. These findings support a model of regional brain differences in GABA⁺/Cr in ASD with an imbalance in the inhibitory component.

Clinical characteristics of epilepsy in ASD

On clinical grounds, the occurrence of seizures in children and adolescents with ASD is unpredictable, and seizures typically occur in otherwise healthy children/adolescents.

The exception is the occurrence of early onset seizures in infants that have an early epileptic syndrome and who later develop an ASD. Seizures appear as an additional clinical burden to ASD in the first case and, as a rule, neither trigger factors nor concomitant relevant events are identified. Epilepsy is an additional problem in ASD that must be considered by clinicians and family members, since some interventions should be made readily available to the child^{1,27}.

A set of assistance measures should be explained to the family, including emergency and prophylactic norms that are the same as those used in the general care of children with epilepsy.

In the evolution of seizures, the causes and clinical course remain elusive and they are not helpful in the choice of treatment, nor in clinical consultation. Seizures are heterogeneous and they vary individually, as any kind of seizure may appear in young people with ASD with an unpredictable course.

There is a wide range of possible evolutions, from rare to only one lifetime seizure, or to intractable epilepsy, as is commonly found in epilepsy without autism. Thus, caution is always warranted in management and outcome prediction in each individual case. Epilepsy is a further burden for ASD individuals with already varying degrees of adaptive difficulties, warranting a careful approach by clinicians.

Epileptiform abnormalities without seizures are as frequent as 20-30% in individuals with ASD and epilepsy, however, their role in the development of the nuclear disturbances of autism is controversial⁷.

Paroxysmal epileptiform abnormalities are thought to be involved in cognitive disturbances and in the social core difficulties of ASD, but the issue is still unclear. An initial overgrowth of white matter in the first 2 years of life is followed by arrested/abnormal growth of the dendritic tree.



Table 2: Known genetic syndromes with ASD and epilepsy (modified by Abrahams and Geschwind, 2008).

Genetic Syndrome	Genes	% with ASD	Seizures	Intellectual Disability
Rett	MECP2	80%	++++	yes
Fragile X	FMR1	25%M – 6%F	++	yes
Tuberous Sclerosis	TSC1, TSC2	20%	+++++	yes
22q13.3(Phelan-Mc Dermid Syndrome)	SHANK3	80%	+++	yes
Angelman or 15q dup	UB3A	40%	+++	yes
Cortical Displasia Focal epi	CNTAP2	70%	+++++	yes

In ASD, reduced dendritic connections are probably implicated in limiting widespread paroxysms and may be a plausible explanation for the high prevalence of epileptiform abnormalities without seizures²⁸.

Consistent with this hypothesis, neuroimaging with MRI tensor imaging methods and fMRI investigations have shown reduced/abnormal connectivity between several areas of the brain, further supporting the hypothesis of underconnectivity between cortical areas²⁹.

The relationship between epileptiform abnormalities and diagnosis, history of regression, communication skills, and other features associated with ASD has been investigated. Interestingly, a higher incidence of epileptiform activity was found in children with stereotypies and aggressive behaviour. The incidence of epileptiform abnormalities was significantly lower in higher functioning ASD individuals compared to autistic patients with ID. In this study, the overall increasing severity of symptoms was associated with a higher frequency of epileptiform abnormalities³⁰.

Autism with regression and epilepsy

Autism with regression has been reported in one third of children with ASD, in those with previously normal or nearly normal development who later developed the typical social and language impairments of autism. This condition is characterized by the loss of language, usually at the stage of single words, and social withdrawal during the second to third year of age

in the absence of apparent concomitant emotional or environmental factors, without antecedents of specific pathologic events.

In a percentage of these children, a so-called autistic epileptiform regression occurs, associated with epileptic disorders. The Continuous Spikes and Waves during Slow-wave Sleep syndrome (CSWSS) and Landau-Kleffner (LKS) syndrome are two rare epileptic encephalopathies that share common clinical features, including seizures and regression with autistic features³¹.

Interestingly, many genetic abnormalities found in this study (e.g. CNTNAP2, CTNNA3, DIAPH3, GRIN2A, SHANK3 etc.) are those that have been associated with ASD or language impairment, underscoring the overlapping of these disorders at both the clinical and genetic levels. The relationship of autistic regression to epilepsy or to epileptiform EEG findings is still unclear and needs more research, since some studies have reported higher rates of epilepsy and epileptiform abnormalities in children with ASD and regression, while others did not find significant relationships^{30,32}.

Interventions in ASD and Epilepsy

With respect to intervention in children with the association of ASD and epilepsy, there is a growing concern about appropriate treatment, especially at a young age. In the global approach to interventions in children with ASD, programs for improving social cognition and social skills should be started quickly after diagnosis since it has been observed

that early interventions can consistently modify the development of these children.

Current research on early intervention in ASD has highlighted that children who have received a developmentally-based intervention for ASD (namely, the Early Start Denver Model) have shown significant improvements in IQ, adaptive behaviour, and overall autism symptoms. Conversely, an untreated group showed greater developmental delays, including less adaptive behaviour; improvements in core social abnormalities were also reported in these children, albeit to a lesser extent³³.

In a later study by the same authors, a normalization of EEG brain activity was demonstrated in ASD children, measured by event-related potentials and spectral power analysis³⁴. However, this study involved children with ASD who were not affected by epilepsy, thus caution is warranted in extending these results to include children with both disorders. When seizures occur in ASD, antiepileptic medications must be administered according to clinical features and current guidelines for epilepsy. Careful supervision to guarantee treatment compliance and the safety of patients is warranted.

There is evidence that valproate, lamotrigine, and levetiracetam are the most effective and tolerable medications for individuals with ASD. Among the specific treatments for genetic and metabolic syndromes associated with ASD and seizures, there are still only a few studies of the effectiveness of treatments for seizures³⁵.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Furthermore, antiepileptic medications have been used for targeting the common epileptiform abnormalities in ASD and for treating some behavioural symptoms of ASD, such as irritability. In a meta-analysis on seven studies, no significant differences were found between medication and placebo in four studies targeting irritability/agitation and three studies investigating global improvement³⁶. However, the lack of power and the use of different medications in the examined studies prevent firm conclusions. Additional research is needed, particularly in the subgroup of patients with epileptiform abnormalities.

Conclusion

Current thought regarding the association of ASD with epilepsy considers the overlapping of common neurodevelopmental pathways as a new paradigm, replacing the original concept of two distinct, coexisting major disorders. A growing number of genes that appear etiologically relevant to ASD and epilepsy have been discovered, strengthening the likelihood of a neurodevelopmental association of ASD with epilepsy.

Abnormalities in synaptic plasticity early in development, as the result of either early seizures or genetic variants, may be a common mechanism for the development of autism and epilepsy. The role of CNVs, or structural genomic changes such as deletions and duplications, has been important in reinforcing this developmental association, and it suggests a possible “double hit” mechanism involving more than one gene in the development of the two disorders and co-occurring pathologic determinants, such as early onset epilepsies and/or brain damage.

The impairment of inhibitory neurotransmission and the resulting imbalance in the excitation/inhibition ratio in the developing brain is also likely to be implicated in both ASD and epilepsy. Dysfunctions of GABAergic interneurons and of

related mini-columns are thought to be pathogenic mechanisms in the association of ASD with epilepsy.

However, a direct demonstration of GABAergic brain dysfunction is still lacking and it should be promptly addressed. Great efforts are needed to further investigate the complexity of the association of ASD with epilepsy, in order to shed light on the basic mechanisms involved and on the most effective interventions for improving overall outcomes in children with both disorders.

References

1. Tuchman R. Autism and social cognition in epilepsy: implications for comprehensive epilepsy care. *Current Opinion in Neurology*. 2013, Apr; 26(2): 214-218.
2. Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biological Psychiatry*. 2008, Oct;64(7):577-82
3. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. *Developmental Medicine and Child Neurology*. 2012, Apr;54(4):306-12.
4. Berg AT, Plioplys S, Tuchman R. Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study. *Journal of Child Neurology*. 2011, May;26(5):540-
5. Saemundsen E, Ludvigsson P, Rafnsson V. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. *Epilepsia*. 2008, Nov;49(11):1865-70.
6. Brooks-Kayal A. Epilepsy and autism spectrum disorders: are there common developmental mechanisms? *Brain & Development*. 2010, Oct;32(9):731-8.
7. Tuchman R, Cuccaro M. Epilepsy and autism: neurodevelopmental perspective. 2011, Aug;11(4):428-34.
8. Abrahams BS, Geschwind DH. Connecting genes to brain in the autism spectrum disorders. *Archives of Neurology*. 2010, Apr; 67(4): 395-9.
9. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R et al. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*. 2010, Jul 15;466(7304):368-72.
10. Abrahams BS, Geschwind DH. Connecting genes to brain in the autism spectrum disorders. *Archives of Neurology*. 2010, 67(4): 395-9
11. Betancur C. Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. *Brain Research*. 2011, Mar 22;1380:42-77.
12. Hagerman R, Hoem G, Hagerman P. Fragile X and autism: Intertwined at the molecular level leading to targeted treatments. *Molecular Autism*. 2010, Sep 21;1(1):12.
13. Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F et al. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics*. 2007, Jan;39(1):25-7.
14. Banerjee A, Castro J, Sur M. Rett syndrome: genes, synapses, circuits, and therapeutics. *Frontiers in Psychiatry*. 2012, May 8;3:34.
15. Sahin M. Targeted treatment trials for tuberous sclerosis and autism: no longer a dream. *Current Opinion in Neurobiology*. 2012, Oct;22(5):895-901.
16. Soorya L, Kolevzon A, Zweifach J, Lim T, Dobry Y, Schwartz L et al. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. *Molecular Autism*. 2013, Jun 11;4(1):18.
17. Amiet C, Gourfinkel-An I, Laurent C, Bodeau N, Génin B, Leguern E et al. Does epilepsy in multiplex autism pedigrees define a different subgroup in terms of clinical characteristics and genetic risk? *Molecular Autism*. 2013, Dec 1;4(1):47.
18. Sgadó P, Dunleavy M, Genovesi S, Provenzano G, Bozzi Y. The role of GABAergic system in

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.



- neurodevelopmental disorders: a focus on autism and epilepsy. *International Journal of Physiology, Pathophysiology & Pharmacology*. 2011, Sep 30;3(3):223-35
19. Buxbaum JD, Silverman JM, Smith CJ, Greenberg DA, Kilifarski M, Reichert J et al. Association between a Gabrb3 Polymorphism and Autism. *Molecular Psychiatry*. 2002, 7(3):311-6.
20. Kim HG, Kishikawa S, Higgins AW, Seong IS, Donovan DJ, Shen Y et al. Disruption of Neurexin 1 Associated with Autism Spectrum Disorder. *The American Journal of Human Genetics*. 2008, Jan;82(1):199-207
21. Zhang C, Atasoy D, Arac D, Yang X, Fucillo MV, Robison AJ et al. Neurexins Physically and Functionally Interact with Gaba(a)Receptors. *Neuron*. 2010, May; 66(3):403-416.
22. Lawson-Yuen A, Saldivar JS, Sommer S, Picker J. Familial deletion within NLGN4 associated with autism and Tourette syndrome. *European Journal of Human Genetics*. 2008, May;16(5):614-8.
23. Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW et al. Minicolumnar abnormalities in autism. *Acta Neuropathologica*. 2006, Sep;112(3):287-303.
24. Casanova M, Trippe J. Radial Cytoarchitecture and Patterns of Cortical Connectivity in Autism. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2009, May 27;364(1522):1433-6
25. Fatemi SH, Reutiman TJ, Folsom TD, Rooney RJ, Patel DH, Thuras PD. mRNA and protein levels for GABAAalpha4, alpha5, beta1 and GABABR1 receptors are altered in brains from subjects with autism. *Journal of Autism and Developmental Disorders*. 2010, 40(6),743-50.
26. Gaetz W, Bloy L, Wang DJ, Port RG, Blaskey L, Levy SE, Roberts TP. GABA estimation in the brains of children on the autism spectrum: Measurement precision and regional cortical variation. *Neuroimage*. 2013 pii: S1053-8119(13)00568-5.
27. Canitano R. Epilepsy in autism spectrum disorders. *Eur Child Adolesc Psychiatry*. 2007, Feb;16(1):61-6.
28. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Current Opinion in Neurobiology*. 2007, 17,103-111
29. Anagnostou E, Taylor MJ. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. *Molecular Autism*. 2011; 2,4
30. Mulligan C, Trauner D. Incidence and Behavioral Correlates of Epileptiform Abnormalities in Autism Spectrum Disorders. *J Autism Dev Disord*. 2014, Feb;44(2):452-8. doi: 10.1007/s10803-013-1888-6. Jul 20 [Epub ahead of print].
31. Lesca G, Rudolf G, Labalme A, Hirsch E, Arzimanoglou A, Genton P et al. Epileptic encephalopathies of the Landau-Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism. *Epilepsia*. 2012, 53,1526-1538.
32. Hrdlicka M. EEG abnormalities, epilepsy and regression in autism: a review. *NeuroEndocrinolLett*. 2008, Aug;29(4):405-9
33. Dawson G, Jones EJ, Merkle K, Venema K, Lowy R, Faja S et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012, 51(11), 1150-1159.
34. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*. 2010, 125(1), e17-23.
35. Frye RE, Rossignol D, Casanova MF, Brown GL, Martin V, Edelson S et al. A Review of Traditional and Novel Treatments for Seizures in Autism Spectrum Disorder: Findings from a Systematic Review and Expert Panel. *Frontiers in Public Health*. 2013, Sep 13;1:31. eCollection 2013.
36. Hirota T, Veenstra-Vanderweele J, Hollander E, Kishi T. Antiepileptic Medications in Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *J Autism Dev Disord*. 2013, Sep 29.

Competing interests: None declared. Conflict of interests: None declared. All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Licensee OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: Canitano R. Autism with epilepsy: A neurodevelopmental association. *OA Autism* 2014 Apr 08;2(1):7.