NINDS epilepsy and autism spectrum disorders workshop report

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ABSTRACT

The association of epilepsy and autism spectrum disorders (ASD), although well-recognized, is poorly understood. The purpose of this report is to summarize the discussion of a workshop sponsored by the National Institute of Neurological Disorders and Stroke, with support from the National Institute of Child Health and Human Development, Autism Speaks, and Citizens United for Research in Epilepsy, that took place in Bethesda, Maryland, on May 29 and 30, 2012. The goals of this workshop were to highlight the clinical and biological relationships between ASD and epilepsy, to determine both short- and long-term goals that address research and treatment conundrums in individuals with both ASD and epilepsy, and to identify resources that can further both clinical and basic research. Topics discussed included epidemiology, genetics, environmental factors, common mechanisms, neuroimaging, neuropathology, neurophysiology, treatment, and research gaps and challenges in this unique population. **Neurology® 2013;81:1630-1636**

GLOSSARY

AED = antiepileptic drug; **ASD** = autism spectrum disorders; **CNV** = copy number variant; **DTI** = diffusion tensor imaging; **FMRP** = fragile X mental retardation protein; **FXS** = fragile X syndrome; **GABA** = γ -aminobutyric acid; **ID** = intellectual disability; **IED** = interictal epileptiform discharge; **LTD** = long-term depression; **mTOR** = mammalian target of rapamycin; **mTORC1** = mTOR complex 1; **NDAR** = National Database for Autism Research; **RTT** = Rett syndrome; **TSC** = tuberous sclerosis complex.

Epilepsy and autism spectrum disorders (ASD) frequently occur together; there may be common underlying mechanisms as well as common genetic and environmental risk factors that converge and can enhance the understanding of both disorders. A workshop on ASD and epilepsy sponsored by the National Institute of Neurological Disorders and Stroke, with support from the National Institute of Child Health and Human Development, Autism Speaks, and Citizens United for Research in Epilepsy, took place in Bethesda, Maryland, on May 29 and 30, 2012. The purpose was to highlight the need to better understand the complex relationships between ASD and epilepsy; to determine both short- and long-term goals that address research and treatment conundrums in individuals with both ASD and epilepsy; and to identify resources that can further both clinical and basic research. The following questions were addressed:

1. What do we know about individuals with both ASD and epilepsy?
2. What causes ASD and epilepsy to occur together? What do we know about contributions of genetics, environmental factors, and immunology?
3. What can we learn about mechanisms from syndromes in which both ASD and epilepsy commonly co-occur?
4. Neuroimaging, neuropathology, and neurophysiology: what do they tell us?
5. What are the issues unique to this population in designing clinical studies?
6. What resources are available for clinical research?
7. What are the short- and long-term goals for addressing gap areas and research opportunities?

EPIDEMIOLOGY ASD and epilepsy are common neurologic disorders with prevalence estimates of approximately 1% of the population and with considerable overlap between both disorders.¹⁻³ Both ASD and epilepsy account for a significant proportion of child and adult neurologic burden of disease. Intellectual disability (ID),

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defined as an IQ of less than 70, occurs in approximately 55% of individuals with ASD.⁴ Epilepsy and ID commonly coexist and it has been suggested that the prevalence of epilepsy in individuals with ASD and of ASD in epilepsy is accounted for by the degree of ID.⁵

Individuals with ASD. In a meta-analysis of studies conducted from 1963 to 2006, the pooled prevalence of epilepsy was 21.5% in individuals with ASD with ID vs 8% in ASD without ID.⁶ A meta-analysis of 16 recent studies, in which only one study overlapped with the previous meta-analysis, found that in children and adolescents above the age of 12 years with autism, with and without ID, there was an increase in the rate of epilepsy compared to those below age 12 years.⁷ The pooled estimate of those having epilepsy with no ID at follow-up was 8.9%; in those ASD individuals with ID, the estimate was 23.7%. Seizures starting after age 12 years and continuing into adulthood may be more likely in ASD as compared to other populations of individuals at risk for epilepsy.⁸ The highest rate of epilepsy in ASD is in those with ID but in individuals with ASD and no ID the risk of developing epilepsy is 8 times higher than would be expected in the general population.

Individuals with epilepsy. Two large prospective studies have looked at rates of ASD within an epilepsy population and found that approximately 4% to 5% of children with epilepsy had ASD.^{9,10} In a nationally representative population-based study of individuals with epilepsy 16 years and older, examining the burden of neurodevelopmental and psychiatric comorbidities, the prevalence of ASD was 8.1%; after adjusting for verbal IQ, an individual with epilepsy had a sevenfold increase in the odds of having an ASD.¹¹ The highest risk of ASD in epilepsy is in those with ID.⁵ However, even in the absence of ID, the risk of epilepsy in ASD as well as ASD in epilepsy is significantly higher than found in the general population.

WHAT CAUSES THIS TO HAPPEN? GENETICS, ENVIRONMENT, AND IMMUNOLOGY The combination of ASD, ID, and epilepsy may result from the same pathophysiologic mechanisms that lead to abnormal synaptic plasticity and excitatory/inhibitory imbalance in the developing brain. These conditions are found in syndromic disorders such as fragile X syndrome (FXS), Rett syndrome (RTT)/CDKL5, and tuberous sclerosis complex (TSC), and in rare copy number variants (CNVs) and other rare mutations associated with ASD (e.g., neuroligin/neurexin and Shank3 mutations and “interneuronopathies” from ARX and neuropilin 2 mutations).¹² CNV abnormalities that overlap between epilepsy and

ASD include 5q14.3, 15q13.3, 16p13.11, 16p11.2, and 17q12.¹³ Single gene overlaps include *JARID1C*, *PCDH19*, *SLC9A6*, *PHF6*, *RBA39B*, *SCN1A*, *ALDH7A1*, *CNTNAP2*, *FOXG1*, and *SYN1*.¹⁴ Although the same mutations may be found in children with epilepsy and ASD, there is large variation in phenotypic severity in carriers, and these mutations are not necessarily associated with a specific clinical subtype and also occur in healthy individuals.¹⁵ Few (if any) of the CNVs or mutations are specific to both ASD and epilepsy, and they all overlap with ID.¹⁶ This will be important to keep in mind when evaluating cohorts of children with ASD plus epilepsy that can serve as the basis for future genetic studies from which genetic etiologies can be determined.

Independent of and in addition to genetic disruptions of synaptic plasticity, there may be changes resulting from epileptogenesis or seizures in the developing brain that may alter synaptic plasticity and contribute to ASD. For example, changes associated with epileptogenesis and seizures may disrupt normal activity-dependent developmental processes in the brain, including synaptic pruning, dendritic and axonal refinement, and receptor and ion channel maturations; depolarizing γ -aminobutyric acid (GABA) currents are critical for Ca^{++} -dependent developmental processes including neuronal proliferation, migration, targeting, and synaptogenesis.¹⁷ Early-life seizures accelerate the switch of GABA effects from depolarizing to hyperpolarizing in hippocampal CA1 neurons¹⁸ and are associated with spatial learning deficits.¹⁹ Since depolarizing GABA currents are critically important for a variety of normal developmental processes, this accelerated switch could have major impact on neurodevelopment. Thus, an altered balance between excitatory synapses and inhibitory synapses could affect learning and social behavior as well as contribute to epilepsy. It is thus likely that abnormalities in excitatory and inhibitory neurotransmission, genetic or acquired, contribute to epilepsy, ID, and autism in the immature brain.¹²

Environmental risk factors common to both epilepsy and ASD include low birthweight, young gestational age, and maternal and paternal advanced age, with a stronger effect of these risk variables in ASD than in epilepsy. Immunologic risk factors common to both ASD and epilepsy include those with neuroinflammatory components; studies have demonstrated increased activation of microglia and astroglia, as well as differential expression of cytokines in the brains of individuals with ASD²⁰ or those with epilepsy.²¹

The literature on the genetic, environmental, and immunologic factors common to both ASD and epilepsy often lacks the critical elements of consistent case definition and inclusion criteria. Much of the uncertainty in the literature on the epidemiology

and causal mechanisms in ASD–epilepsy research relates to variable definitions on both the epilepsy and ASD sides. Clear working criteria and operational definitions should be specified for all key study groups: epilepsy only, ASD only, overlap (ASD + epilepsy), and control groups.

WHAT CAN WE LEARN ABOUT MECHANISMS FROM SYNDROMES WITH AUTISTIC FEATURES AND EPILEPSY? TSC, FXS, and RTT are monogenic disorders with some overlapping symptoms with ASD and although they are phenotypically different they provide good clinical models to understand the relationship between epilepsy, ASD, and ID.²² Molecular pathways and cellular mechanisms aberrant in these disorders are beginning to be understood. In addition, some individuals with these single-gene disorders may be diagnosed before birth or at the time of birth, and from a treatment perspective, US Food and Drug Administration–approved compounds with potential to treat both ASD and epilepsy in these disorders are becoming increasingly available.^{23,24}

In TSC, approximately 50% of affected individuals have associated ASD, and 80% to 90% have seizures, although risk factors for developing ASD in TSC are poorly understood and are strongly linked to ID.²⁵ TSC is caused by mutations in the *TSC1* or *TSC2* genes, also known as hamartin and tuberlin, respectively, which together inhibit the serine-threonine kinase mammalian target of rapamycin (mTOR) pathway. The TSC/mTOR pathway plays an important role in neuronal cell growth including dendritic arborization and spine morphogenesis as well as axon guidance, myelination, and synaptic plasticity and function.²⁶ Consistent with this role, mice deficient in *Tsc1* or *Tsc2* reveal aberrant axonal projections and disrupted neuronal connectivity; in addition, *Tsc* mutant mice show profound deficits in mGluR-dependent long-term depression (LTD) which, in concert with the structural defects, may contribute to the pathogenesis of TSC as well as to ASD and epilepsy.²⁴ Diffusion tensor imaging (DTI) studies in patients with TSC indicate diffuse white matter abnormalities possibly leading to aberrant neuronal connectivity in this disorder.²⁶ A recent mouse model with conditional knockout of the *Tsc1* gene in GABAergic interneurons specifically addresses the hypothesis that functional deficiency in these interneurons leads to many hallmarks of the disease including decreased seizure threshold; the abnormalities may involve increased mTOR complex 1 (mTORC1) signaling in GABAergic neurons and point to a potential common molecular mechanism accounting for ASD and epilepsy in TSC.²⁷ In a rodent model of neonatal seizures, treatment with the mTORC1 inhibitor rapamycin immediately

before and after seizures reversed many of the early increases in glutamatergic neurotransmission and signs of pathology including the increase in seizure susceptibility, and attenuated later-life epilepsy and autistic-like behavior.²⁸

FXS is caused by an expanded CGG repeat (>200) in the *FMR1* gene, located on the X-chromosome, which leads to transcriptional silencing of FMR1 and loss of the fragile X mental retardation protein (FMRP). The absence of FMRP, an mRNA binding protein that normally acts to repress translation, leads to excessive and dysregulated mRNA translation of several other key synaptic proteins that control synaptic development and plasticity.²⁹ Approximately 30% of males with FXS meet criteria for autistic disorder.³⁰ Investigators are beginning to unravel the molecular overlap between FXS and ASD. Using a genome-wide approach to identify FMRP targets, Darnell et al.³¹ recently found that FMRP interacts with many proteins implicated in autism including components of the ERK and mTOR signaling pathways (e.g., Pten, Nf1, Tsc2) and synaptic and plasticity-related proteins such as Shank3, Arc, and mGluR5. Mice lacking FMRP reveal excessive AMPA receptor internalization, exaggerated mGluR-dependent LTD, and impairments in the GABAergic system leading to imbalances in excitatory and inhibitory neurotransmission in the brain.³² These physiologic findings are accompanied by defects in dendritic and spine structure.

Approximately 10% to 25% of individuals with FXS have epilepsy, with varied seizure types that are often easily controlled, and children with FXS and epilepsy are more likely to have ASD.³³ The molecular basis of the epilepsy in FXS may involve a voltage-gated inward current, $I_{mGluR(V)}$, induced by the overactivation of mGluR5 in the absence of FMRP translational control at multiple synapses; this heightened electrical excitability in combination with a dampened GABAergic response leads to a pronounced excitatory–inhibitory imbalance in brain circuits, which can predispose to the development of epilepsy.³⁴ Potential therapeutics in FXS with potential impact for individuals who also have ASD and epilepsy include mGluR5 antagonists such as a selective mGluR5 receptor antagonist (fenobam) and negative allosteric modulators (STX107), as well as GABAR agonists that potentiate GABA_A transmission (ganaxolone), block GABA uptake (riluzole), potentiate GABA_A transmission–extrasynaptic δ (gaboxadol), or activate postsynaptic GABA_B transmission (arbaclofen).³⁵

RTT is caused by mutations in the gene encoding methyl-CpG-binding protein 2 (*MECP2*) located in the Xq28 chromosome.³⁶ MeCP2 regulates gene expression by binding to methylated CpG sites on DNA and may act as a transcriptional repressor or transcriptional activator by mechanisms still being

elucidated. The loss of *MECP2* function, as occurs in RTT, leads to impairments in synaptic functioning and plasticity, as well as altered expression of several neurotransmitter systems with a net effect of perturbing excitatory-inhibitory balance.³⁷ Although RTT and ASD are not phenotypically the same, autistic behaviors are commonly seen in RTT, and alterations in the *MECP2* gene have been associated with idiopathic autism.³⁸ Approximately 50% of patients with RTT have seizures at some time in life.³⁹ Seizures in RTT are age-dependent, found in 15% <2 years, 50%–70% 5–20 years, and in 48% >30 years.⁴⁰ The molecular basis of epilepsy in RTT may involve an imbalance of excitatory and inhibitory neurotransmission in neural circuits. Mice lacking *MECP2* exhibit pronounced network hyperexcitability in areas CA1 and CA3 of hippocampus, along with increased seizure susceptibility, presumably due to impaired GABAergic recruitment in these circuits.⁴¹

Similar to the TSC phenotype, mice lacking *MeCP2* specifically from GABAergic neurons recapitulate many features of RTT and reveal GABAergic dysfunction including the loss of GABA synthesizing enzymes.⁴² Recent data suggest that *MeCP2* mediates activity-dependent synaptic scaling, and that loss of this homeostatic plasticity mechanism may lead to a pathologic increase in neuronal excitability and increased seizure susceptibility.⁴³ Several questions that may be important for ASD–epilepsy in RTT include a better understanding of *MeCP2* function in GABAergic neurons, understanding how *MeCP2* dysfunction disrupts neural circuits in a region-specific manner, and characterizing circuit level function and how non-neuronal CNS cells interact with neurons to cause pathology in RTT.⁴⁴

NEUROIMAGING, NEUROPATHOLOGY, AND NEUROPHYSIOLOGY: WHAT DO THESE MODALITIES TELL US AND HOW DO WE USE THEM? Epilepsy and ASD have been conceptualized as disorders of large-scale neural networks with alterations in cortical-subcortical connectivity.⁴⁵ Alterations in neocortical minicolumns and selective sparsity of GABAergic interneurons may account for shared mechanisms in ASD and epilepsy.⁴⁶ The role of DTI in delineating abnormalities of white matter tracts during early development in both ASD and epilepsy is being explored.⁴⁷ Malformations of cortical development, cellular disorganization, heterotopias, and dysplasia, reflecting abnormalities in neurogenesis and neuronal migration, are commonly found in children with epilepsy and ASD.⁴⁸

There have been many questions raised about the role of the EEG in children with ASD with and without seizures. Epileptiform EEGs are common in children with ASD, but it is not clear whether this is part

of the basic pathophysiology or an epiphenomenon. Interictal epileptiform discharges (IEDs) are far more common in children with ASD than controls; in ASD, frontal lobe IEDs predominate. In experimental studies, interictal spikes result in transitory cognitive impairment by impairing single unit firing and replay during waking and sleep. In addition, these studies suggest that in the immature brain, interictal spikes may result in long-standing alterations in neuronal network function, impaired short- and long-term potentiation, and possibly decreased neurogenesis or cell loss of specific populations.⁴⁹

The term epileptic encephalopathy implies that epileptic activity itself contributes to severe cognitive and behavioral impairments, above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.⁵⁰ These impairments may be global or selective and may occur along a spectrum of severity. The development of the brain is a dynamic process that is site-specific and influenced by sex within relatively narrow timeframes.^{51–53} CNV alterations in genomic regions or associated genes were recently reported in children with continuous spike and waves during slow-wave sleep syndrome and in Landau-Kleffner syndrome, suggesting that clinical and molecular pathway overlaps may exist between ASD and this group of epilepsies.⁵⁴

There are significant interdependent relationships among sleep, IEDs, and seizures that impact neural circuitry output (cognition and behavior).⁵⁵ Sleep abnormalities and IEDs have both regional and long distant effects on neural circuits/functional connectivity. Spike suppression in one neural circuit may decrease the output of another circuit. Genotype data need to be linked with databases containing phenotype data such as neurophysiology, sleep, behaviors, and cognitive data to determine putative target molecular pathways during selected vulnerable developmental epochs. Some sleep and IED abnormalities may have critical periods during which neural circuit dysfunction is reversible and after which intervention is less useful (i.e., language).

DESIGNING CLINICAL STUDIES UNIQUE TO THIS POPULATION AND RESOURCES FOR CLINICAL RESEARCH Several issues were discussed regarding designing clinical studies unique to the ASD–epilepsy population. Current epilepsy treatments in ASD are limited, and there is no suggestion that treating epilepsy with standard antiepileptic drugs (AEDs) reverses encephalopathy. In general, conventional AEDs are not effective at suppressing interictal abnormalities. For a randomized controlled clinical trial of AED therapy, one would need to rigorously define terms, such as epileptiform EEG, and define the

target primary outcome. Quantifying improvement of the target primary outcome, for example, language or normalization of EEG, is challenging. The inclusion/exclusion criteria would need to take into account age, duration of symptoms, prior treatment, and degree of ID. Outcome assessments should be masked and validated. Confounders are likely to be an issue; for example, children are likely to be receiving applied behavioral analysis and other treatments. Recent studies suggest that a comprehensive developmental behavioral intervention for improving outcomes of toddlers with ASD can increase IQ by 15 points, improve adaptive behavior, and ameliorate the ASD diagnosis.⁵⁶ These improvements in social behaviors are associated with normalized patterns of brain activity,⁵⁷ suggesting that interventions on ASD–epilepsy need to be comprehensive and include both behavioral and pharmacotherapeutic interventions.

Clinicians question whether pharmacologic intervention designed to improve the EEG in patients with epileptiform EEGs without seizures should be used in subjects with ASD. Patients with ASD and epileptiform EEGs, without seizures or with well-controlled seizures, could be subjects in a prospective, randomized, double-blind, placebo-controlled trial. EEGs of 24 hours duration that should include sleep would likely be needed at baseline and outcome. An interventional study could also include other EEG measures (such as EEG coherence). Genotypic and phenotypic information on subjects should be included, ideally to delineate copy number variations, *de novo* point mutations, and inherited mutations. For this reason, exome sequencing of both parents, the affected child (or children), and one unaffected child if available would be ideal, and has proven powerful in the study of ASD alone.⁵⁸

CLINICAL RESEARCH TOOLS AND RESOURCES The use of induced pluripotent stem cells as a clinical research tool was reviewed, including the process of harvesting skin cells, reprogramming those skin cells into pluripotent stem cells, introducing mutations, and converting those stem cells into neurons, and then phenotyping the final product to uncover the functional significance of the induced mutations. The NIH approach to brain tissue banking was discussed; information can be found at <http://www.ninds.nih.gov>. Resources available through Autism Speaks, such as the Autism Tissue Program and Autism Speaks Treatment Network, were discussed; information regarding these resources can be found at <http://www.autismspeaks.org>. The National Database for Autism Research (NDAR) is an NIH-funded research data repository that aims to accelerate progress in ASD research through data sharing, data harmonization, and the reporting of research results. NDAR also serves as a scientific

community platform and portal to multiple other research repositories, allowing for aggregation and secondary analysis of data (see <http://ndar.nih.gov>). Christine Database is an advanced pharmacogenetics clinical decision support program available through Cincinnati Children's Hospital Medical Center.⁵⁹

DISCUSSION OF SHORT- AND LONG-TERM GOALS: NEXT STEPS, GAP AREAS, AND RESEARCH OPPORTUNITIES The workshop concluded with a discussion on how to ultimately improve the quality of life of children and adults with these highly prevalent disorders. Keeping in mind that many of the individuals with the most disabling features of ASD and epilepsy also have ID, what are the next steps to build onto the rapidly growing knowledge base of the biology of ASD and epilepsy? The consensus of the workshop is that shared pathophysiology connects all 3 disorders. A better understanding of the underlying etiologies, pathways, and circuits should eventually result in improved outcomes. There is a need for better animal models and effective collaborations across laboratories and clinical consortia. Improved and novel models would be useful to investigate correction of neural circuit dysfunction, which may require 1) AED/spike suppression, 2) synaptic modulators, or 3) agents that will do both.

One challenge for the future is the historic separation and alignment of the biomedical disciplines, medical school departments, and patient advocacy groups. Not surprisingly, one suggestion of the workgroup was better communication. Short-term goals include defining the clinical characteristics of ASD in epilepsy and epilepsy in ASD, better characterization of the seizure patterns found in ASD, and elucidation of the role of ID in the outcomes of both ASD and epilepsy. One immediate focus was on development and use of a large overlapping database as well as integration of existing clinical, genomic, and imaging datasets.

Long-term goals include a search for genomic and environmental factors important to these developmental brain disorders, identification of novel drug targets, and translational research to bring novel therapies to patients. In both ASD and epilepsy, current pharmacologic therapy has variable success in suppressing symptoms but does not cure these disorders. Experience in other neuropsychiatric disorders suggests that a combination of behavioral intervention and drug therapy provides the best outcome and it was strongly suggested that such combinations be tested in future clinical trials, with special attention to individuals with ID. Specific suggestions for future research needs and opportunities include focusing on therapy to treat underlying disease, in addition to

symptom control and on improvements in quality of life throughout the lifespan, development of endophenotypes for both epilepsy and ASD, and ASD-epilepsy endophenotypes,⁶⁰ as well as the use of genomic studies to search for protective factors. It was suggested that a good model to study could be infantile spasms, as an epilepsy syndrome where early therapy might prevent ASD. With a continued search for shared mechanisms, we can overcome the challenge of divergent approaches and expertise in these overlapping developmental brain disorders.

AUTHOR CONTRIBUTIONS

Dr. Tuchman was co-chair of the workshop and wrote the initial draft of the report and contributed to all further revisions and final draft of the manuscript. Dr. Hirtz was co-chair of the workshop and contributed to the initial draft of the report and to all further revisions and final draft of the manuscript. Dr. Mamounas contributed to critical revisions of the manuscript for important intellectual content.

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