NINDS Autism and Epilepsy Workshop
May 29-30, 2012
Bethesda Maryland

Cosponsored by NICHD, Autism Speaks and CURE

AS-CURE-ILAE: Autism-Epilepsy Scientific Research Synergies from a Global Perspective, December 2010

- Define scope of problem
- Need to involve researchers from both fields
- Plan for next steps.

Topics for May 2012 NIH workshop

- Who are these children?
- What causes this to happen?
- Are there environmental/immunologic risk factors?
- What can we learn about mechanisms from syndromes with both features?
- What do we know and need to know about neuroimaging, neuropathology, and neurophysiology?
- How do we design studies unique to this population?
- What resources are there for clinical research?
- What are the short and long- term goals, next steps?

Who are these children- Epidemiology

Epilepsy in those with ASD (Tuchman and Rapin 2002):

- Peak in childhood more associated with intellectual disability, peak in adolescence less so
- Cumulative risk 67% by age 10 in autism +severe MR+CP
- 27% with autism and severe MR
- 8% with autism only

ASD in those with epilepsy (Berg 2011):

- Normal cognition- 2.2% with ASD
- MR- 10.6% WITH ASD

What causes this to happen?

- ASD, Epilepsy and intellectual disability could result from the same mechanisms, resulting in an abnormality of synaptic plasticity, or abnormalities of excitatory and inhibitory balance, e.g. TSC, Fragile X, neuroligin mutations
- Early in life there could be either delayed maturation of inhibitory receptors or early maturation of excitatory receptors
- Seizures may result in abnormalities of neurotransmission that could contribute to learning and social behavioral deficits

Infantile spasms

- Early epilepsy syndrome where common outcome is intellectual disability and autism
- Could be used to study how early intervention could prevent the autistic symptoms

EEG and autism

- Epileptiform EEGs (with interictal epileptiform discharges), even without seizures, may impact cognition and behavior, based on extensive animal data and limited human data.
- EEG endophenotypes exist for epilepsy but not clear yet whether they exist in ASD
- Genetic factors may be operant in EEG endophenotypes for autism but not yet identified. Several models were proposed. Overlap of genes and gene pathways may be illuminating

Sleep issues also related

- Significant interdependent relationships among sleep, IEDs, and seizures which impact neural circuitry output (cognition and behavior).
- Sleep abnormalities and IEDs have both regional and long distant effects on neural circuits/functional connectivity.

Possibility for intervention or prevention trials

- 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.
- Possible interventions include valproate, lamotrigine or oral steroids. (Risperidone as an active control, rather than placebo, was also discussed.)
- Primary endpoint could be improvement in language or behavior, compared with baseline. Secondary endpoints could include reduction in EEG spikes, compared with baseline, confirmed by central EEG review.

Designing clinical studies unique to this population

- Animal models not effective as they should be.
- Can EEG or functional MRI be used to identify intellectual disability?
- EEG can identify at risk groups but is not a primary outcome, potentially can be used to measure connectivity.
- Need to appreciate the common comorbidities. Treatment trials need to be applicable to all.

Resources for clinical research

- The potential for use of stem cells as a clinical research resource
- NIH approaches to brain tissue banking
- Autism Tissue program
- Databases and managed care
- Registries- autism speaks treatment network
- NDAR
- Christine database for epilepsy

Short term goals- opportunities for sharing resources

- Look for overlaps in both autism databases and epilepsy databases
- Integration of existing clinical, genomic and imaging datasets
- Look at populations with autism to understand what epilepsy does to the phenotypes; what kind of epilepsy do autistic children have? How can we better characterize?
- In single gene variants can try to modify disease, may later benefit more people.
- Identification of novel drug targets

Long term goals

- Integration of the two expertises and fields
- Search for shared mechanisms. Need to study commonalities at the genetics and neurological level; neural networks that are affected.
- Search for genomic and environmental factors for both
- Development of treatments that are disease-preventing; the objective is curative therapy.
- Clinical trials to develop evidence for best treatments; test combinations of behavioral and drug therapies

Summary

- Benefit to studying both disorders- understanding underlying mechanisms
- Also benefit to intervention and treatment plans, addressing the two related conditions.
- Follow-up plans for collaborative research