From Diagnosis to Intervention: ASD & Epilepsy

Gregory Barnes, M.D., Ph.D
Reet Sidhu, M.D.
Nancy Minshew, M.D.
Overview

- Autism Spectrum Disorders (ASD) and the role of the Neurologist
- Epileptiform EEG and the work-up
- Behavior/Cognition and Epileptiform EEG
- Behavior/Cognition and Epilepsy
- ASD: the role of neuroimaging
- Guideline development in ATN
ASD: a disorder of functional connectivity
Inhibitory Tone in ASD Networks

- The function of the region varies as a balance of excitatory vs inhibitory tone.

- Interneurons and excitatory neurons both have reported abnormalities in ASD.
Epileptiform Activity

- 10-30% of individuals with ASD also have epilepsy

- 50-80% of individuals with ASD have epileptiform EEGs

- There are no current estimates of individuals with ASD and epilepsy with normal overnight EEGs. These children do exist (i.e. children with symptomatic generalized epilepsy from the frontal lobe).

- EEG abnormalities and epilepsy tends to occur less frequently after 20 years of age.

- How do we identify those with epileptiform EEGs and those at risk for epilepsy?
Advertisements

- Research Studies
- Dr Haines- Genetics of Autism
- Dr Barnes- Relation of EEG to Cognition and Behavior in Kids with ASD and no seizures
- Dr Barnes- Relation of EEG to Cognition and Behavior
- Seminar on June 23rd, 2011 Thursday night 6:30-8:30 PM
Guidelines for EEG in ASD

- 2000 Guidelines for AAP and AAN: no known role for EEG unless epilepsy/seizures are suspected.
- 2010 ATN EEG Algorithm: development of clinical indicators for EEG in ASD.
- Guided by evidence in the literature and consensus of the ATN Neurology-Genetics-Metabolism Committee.
- 2010 ATN EEG Algorithm currently being tested at 3 ATN sites.
Features of EEG Algorithm

- Targeted to primary care providers (pediatricians, developmental pediatricians, family practitioners).
- Clinical indicators or “red flags” developed to guide practitioner on when to order EEG in ASD.
- Algorithm includes advice on management of both normal and abnormal EEG along with next steps.
- Accompanying text explains each box of algorithm including general educational information about ASD/epilepsy.
EEG algorithm

Draft Text for EEG Algorithm — box numbers reference algorithm location.

1-5 There are many risk factors for epilepsy. In isolation they are not indicators for obtaining an EEG; however, they should be considered when evaluating individuals with ASD. The following is a list of the most common risk factors: family history of epilepsy, mental retardation, tuberous sclerosis, Rett syndrome, Angelman syndrome, Fragile X syndrome, 15q duplication syndrome, microcephaly, focal neurological examination findings, and dysmorphism.

2 Atypical febrile seizures: refers to complex febrile seizures with duration longer than 10-15 minutes or focal in nature or if they recur within one day.

3 Suspicious spells: i.e. periods of altered consciousness or unresponsiveness that are out of the ordinary for the individual or episodic movements accompanied by altered or unresponsiveness. Parents/caregivers are encouraged to videotape any events of concern as it is helpful for the physician to see the event. Videotaping is encouraged as this can provide important clues as to the etiology of the event in question. It is very important to consider other medical causes for unusual spells. Seizures are only one potential cause and special attention should be paid to ruling out other associated medical conditions such as headaches, gastrointestinal disorders, genitourinary conditions, hormonal imbalance/endocrine dysfunction and sleep disturbance. Examples of such medical conditions include, but are not limited to, the following: gastroesophageal reflux disease, pain due to migraine headaches or ear infections, urinary tract infections, dental problems, fractures, hormonal changes, or sleep apnea.

4 Sleep disturbance suspect for seizures: nocturnal seizures may present as unexpected arousals with odd or repetitive hypermotor behavior and/or complex behavioral automatisms, i.e. lip smacking or other facial movements, stereotyped hand movements, unusual posturing, unexpected incontinence, or gelastic (laughing) spells. Nocturnal seizures are not associated with difficulty falling asleep, early morning or multiple awakenings or prolonged periods of wakefulness without altered consciousness or other automatisms. These symptoms are more suggestive of a sleep disorder.

5 Regression of language and/or sociability: commonly referred to as autistic regression, occurs in approximately 30% of children with ASD. Age of onset is difficult to precisely determine as the majority of families report regression as a gradual process rather than a sudden event. It is generally thought to occur between 12-24 months. The majority of children with autistic regression have a history of earlier subtle delays in social and communication domains. Only a very small proportion of children with regression will have shown truly typical development prior to their loss of skills. Regression that is multiple/recurrent or occurring after the age of 2 years is atypical. Active regression is that which is currently underway when the child is being evaluated or that which occurred within the last 12 months accompanied by definitive loss of skills with no recovery.

8 Conducting overnight EEG: It is optimal for the EEG to include a minimum of one hour of slow wave sleep since many abnormal discharges only appear during slow wave sleep. This requires a prolonged recording if done in an EEG lab. Overnight studies are known to increase the overall yield and should be performed in individuals with suspicious spells, sleep disturbance suspect for seizures, or active/ataypical regression who will be unlikely to fall asleep in a lab setting during the daytime. Access to an overnight EEG may prompt the provider to conduct a routine EEG, depending on the clinical scenario. Similarly, providers may choose to conduct overnight EEG in lieu of routine EEG if it improves coordination of clinical care (i.e. obtaining other diagnostic studies or laboratory investigations at time of EEG or simply more feasible from family or physician perspective).

*Providers may directly refer to a neurologist when considering overnight EEG based on clinical scenario or personal preference.

11 If overnight EEG is normal, proceed to algorithm boxes 12 and 13. These boxes are unrelated and have the same importance as one another in evaluating what the next step for the child should be.

16* Physician should refer to neurologist at any point if their clinical judgment indicates necessity.

11/1/2010
What if your child with ASD has an epileptiform EEG but no seizures?

- Very little data
- Case reports: VNS, AEDs, Steroids improved behavior in ASD
- One RCT (Hollander): Irritability and repetitive behavior improved by Depakote
- In small numbers, hint that those with spikes are better Depakote responders
- Smaller trials-lamictal or levetiracetam- no effect on behavior
- Area of active research- ATN group and the Hollander led group
- No data yet between sleep, EEG and behavior—stay tuned.
Age and Types of Epilepsy

- Two peaks (0-5 years) and (10-15 years)
- 75% partial epilepsies and 25% generalized epilepsies
- Maybe 10% are known genetic syndrome
- Location of epileptiform activity: majority are frontal, central, temporal
- No published data on MRI abnormality rate in ASD/Epilepsy group
What if your child with ASD has an epileptiform EEG and seizures?

- ASD and epilepsy is a heterogeneous patient population.
- We have no information from EEGs yet on who is at risk for epileptogenesis.
- At Risk for Epilepsy: Gender (Female), Intellectual Disability, Receptive language delay, motor dysfunction.
- Role of regression is less certain.
Disorders Co-Morbid with Autism/Epilepsy

- More significant ADHD
- More impaired social interactions/impaired reciprocal communications
- More restricted behavior than ASD alone
- More OCD than ASD alone
- In general, they are poorer sleepers
Sleep Disorders Co-Morbid with Autism/Epilepsy

- Poorly defined as of now. Unclear what percentages of autism/epilepsy patients have sleep disorders.
- Hypermotor seizures and epileptic arousals when treated with AEDs—generally zonegran-improve sleep.
- However most arousals of ASD children in a Peds EMU are not epileptic in nature.
- When in doubt at night, a Peds EMU admission is indicated.
- However, treating sleep disorders in these patients often do not improve their seizure control. Ambien, Melatonin, Lunesta have little effect on seizure control.
- Treating their sleep disorder may have a significant effect on cognition and behavior. Not to mention parental stress.
ASD/Epilepsy Group: Treatment of Epileptiform EEGs and Seizures

- Absolutely no data in the literature
- Following data is from the Vanderbilt Pediatric Epilepsy program
- Parents will know when seizures are going to be a problem because behavior and cognition are worse
- Each AED is recommended based on 1) positive effects on behavior and cognition; and 2) ability to stop seizures/fix EEG
ASD/Epilepsy Group: Treatment of Epileptiform EEGs and Seizures

- AED Recommendations:
  - Partial Epilepsies- Trileptal, Depakote, Lamictal, Zonegran
  - Generalized Epilepsies- Depakote, Lamictal, Zonegran
- ADHD-Strattera, stimulants are OK. No increase in seizures.
- OCD/Aggression- Neuroleptics are OK. No increase in seizures.
ASD/Epilepsy Group: Treatment of Epileptiform EEGs and Seizures

• Some kids—treat the seizures and behavior/cognition is better. With most kids, seizure go away but problems remain.
• One study—Hamaski et al 2010 had data on AED use (79 patients)
  60% (1 AED), 18% (2 AED), 16% (3 AEDs), 6% (Resistant to 4 or more AEDs)
  67% were seizure free for more than two years
  8% had “autistic symptoms improve”
• Congruent with the experience of the Vanderbilt Pediatric Epilepsy program
ASD/Epilepsy Group: Treatment of Epileptiform EEGs and Seizures

- ~5% of autism/epilepsy patients
- Medication resistant epilepsy- If dysplasia, use resective epilepsy surgery. It works well. May not change other problems.
- Medication resistant epilepsy- If not surgical, this is a big problem. If ESES or Lennox Gastaut syndrome does not respond of AEDs, alternative treatment often do not help behavior or seizures
- Continued seizures with worsening behavior is highly resistant to all epilepsy treatment. Increased risk of SUDEP in this situation.
Guidelines for MRI in ASD

- 2000 Guidelines for AAP and AAN: no role for MRI in routine diagnostic testing of ASD.
- 2010 ATN MRI Algorithm: development of clinical indicators for MRI in ASD.
- Guided by evidence in the literature and consensus of the ATN Neurology-Genetics-Metabolism Committee.
- 2010 ATN MRI Algorithm will be tested at ATN sites in 2011.
ASD: what do we know about brain structure and function?

- ASD are now considered disorders of the development of the connectivity of the neurons of the cerebral cortex which results in disturbances in the highly specialized connections that provide for uniquely human abilities.

- Studies of brain structure have implicated multiple events in prenatal and postnatal brain development, particularly neuronal organizational events.

- Generalized enlargement of the brain resulting from premature overgrowth attests to the broadness of the involvement of the brain, precluding focal brain theories and single primary deficit theories.

- Discovery of 15-20 mostly rare genes that act on molecular signaling pathways involved in the development and maintenance of neuronal and synaptic connections have reinforced the centrality of disruption of cortical connectivity in ASD.

- Brain mechanisms causing ASD are largely at the level of connections among neurons and thus not detectable on gross structural neuroimaging.
ASD: clinical rationale for neuroimaging

- An attempt to determine a specific etiopathological diagnosis for an individual.
- In a minority of cases, the detection of an abnormality of the brain may lead to determination of a specific cause for the child’s ASD.
- This is true especially if the lesion is pathognomonic for a given disorder, i.e. a neurocutaneous syndrome.
- Abnormalities on neuroimaging are not necessarily causally related to the autism spectrum disorder. In many cases, the etiology of the brain abnormality is still unknown and the relationship to the ASD unclear.
- Nonetheless, the MRI may help guide more focused etiological investigations that could further lead to specific diagnoses in a limited number of cases.
- For this reason, imaging is not a routine part of the evaluation of individuals with ASD.
ASD: what are the risks of MRI?

- Must balance the potential value of the information that might be obtained with the risk of the procedure itself.
- Most children or young adults with ASD are unable to tolerate such a procedure without some type of sedation.
- Children and individuals with disabilities of all ages can react paradoxically to medications used for sedation purposes.
- Behavior can be affected for several hours following the procedure and may result in the need for more significant behavioral interventions.
- Experience may be recalled unpleasantly, adding to preexisting daily anxieties.
- Individuals who require general anesthesia may have potential complications including vomiting, aspiration, or cardiorespiratory compromise.
- These are very rare occurrences but do need to be considered when counseling families about risks of procedures.
ASD: what type of MRI is needed?

- Standardized methods of image acquisition and analysis must be developed and universally adopted so that data can be readily compared across sites.

- Recommended that a minimum number of sequences are obtained when performing MRI on an individual with ASD. MRI should include at least 3 different sequences (T1, T2, and FLAIR) in 3 different planes.

- MRS should be considered in those individuals presenting with multisystem disease.

- In individuals with seizures or suspected seizures, MRI should include FLAIR sequences and T1 thin cuts (1mm) in the coronal plane.
Features of MRI Algorithm

- Targeted to primary care providers (pediatricians, developmental pediatricians, family practitioners)
- Clinical indicators or “red flags” developed to guide practitioner on when to order MRI in ASD.
- Algorithm includes advice on management of both normal and abnormal MRI along with next steps.
- Accompanying text explains each box of algorithm including general educational information about ASD/epilepsy.
Summary

• Autism Spectrum Disorders (ASD) are a heterogeneous group of neurodevelopmental disorders of brain structure and function.

• Epilepsy and epileptiform EEG occur in a subset of ASD.

• Not all individuals with ASD require diagnostic testing but there is a role for performing MRI and EEG in a subset of children with ASD.
Summary

• Guidelines are being developed in the ATN to advise practitioners about neurological testing in ASD.

• Goal of EEG and MRI algorithms:
  • Improve clinical care and outcomes for children with ASD.
  • Advance understanding of appropriateness of current indicators or “red flags”.

• Long term goal: consensus-based guidelines evolve into evidence-based guidelines as data is collected through ATN.