Elias Tembenis

A CONSENSUS STATEMENT FROM THE ELIAS TEMBENIS SEIZURES THINK TANKS

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SHORT TITLE: SEIZURES IN AUTISM SPECTRUM DISORDER

Abbreviations: ASD: autism spectrum disorder; EEG: electroencephalogram; GABA: gamma-aminobutyric acid; SEDs: subclinical electrical discharges.

Keywords: Autism spectrum disorder; seizures; epilepsy; prevalence; subclinical electrical discharges; excitatory-to-inhibitory cortical balance; genetic syndrome; metabolic disorders; treatment

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Authors' Contribution: To develop this summary, we held the Elias Tembenis Seizures Think Tanks at the AutismOne meeting in Chicago in May of 2009 and 2010 and at the Autism Canada meeting in Toronto, Canada in October of 2009. These think tanks included scientists and clinicians with expertise in seizures related to ASD. The participants represented a wide variety of researchers and practitioners who treat ASD. The participants from the initial think tank in May of 2009 provided the basis for the content of the information within this supplement. Individuals in the following two think tanks (October 2009 and May 2010) provided suggestions for the developed document. Individual participants who provided written text for the supplement or contributed in the editing of the document are recognized as authors.

RICHARD FRYE, MD, PHD, is the Director of Autism Research at Arkansas Children's Hospital Research Institute and the Director of the Autism Multispecialty Clinic at Arkansas Children's Hospital. He is a well-recognized expert in the diagnosis and treatment of ASD and other neurodevelopmental disorders. Dr. Frye is fellowship trained in behavioral neurology and psychology and has clinical expertise in the assessment, diagnosis, and treatment of children with ASD. He is the author of over 100 peer-reviewed articles and book chapters on neurological disorders. Over the past two years, Dr. Frye has completed three clinical studies related to ASD, including an open-label trial examining the metabolic and behavioral effects of tetrahydrobiopterin, a clinical study of the metabolic and genetic characteristics of children with ASD and mitochondrial disease, and a clinical study on the prevalence of the folate receptor alpha autoantibody in children with ASD as well as the response to leucovorin treatment in ASD children with the folate receptor alpha autoantibody.

JAMES B. ADAMS, PhD, is a father of a daughter with autism, who was diagnosed in 1994, and that is what led him to eventually shift much of his research emphasis to autism. His research focuses on the medical causes of autism and how to treat it, including addressing nutrition, toxic metals, gut bacteria, and seizures, and he is widely published. He is currently a President's Professor at Arizona State University, where he directs the ASU Autism/Asperger's Research Program. He is the president of the Autism Society of Greater Phoenix and the president and founder of the Autism Conferences of America. Prof. Adams has won multiple awards. He served on the board of directors of the Autism Research Institute and continues to serve as the co-leader of ARI's science advisory committee.

MANUEL CASANOVA, MD, completed his residency in neurology and then did a fellowship in neuropathology at Johns Hopkins Hospital. During his stay at Johns Hopkins, he was in charge of pediatric neuropathology. Dr. Casanova spent several years as Deputy Medical Examiner for Washington, DC, gaining valuable experience in the post-mortem examination of SIDS and child abuse cases. His expertise was recognized by honorary appointments as a scientific expert for the Armed Forces Institute of Pathology and as a professorial lecturer for the Department of Forensic Science at George Washington University. Dr. Casanova helped establish two of the most successful brain banks in this country. He is well published in a multitude of postmortem techniques. His interest shifted toward the study of abnormalities of cortical circuitry. His most recent studies have investigated the presence of abnormalities of minicolumnar organization and lateralization in the brains of patients who exhibit language disturbances, including autism, Asperger's syndrome, and dyslexia.

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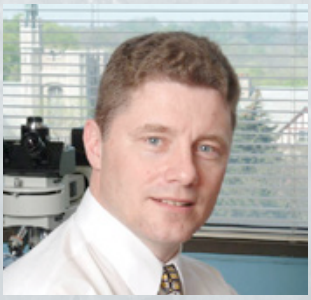

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SEIZURES IN AUTISM SPECTRUM DISORDER

Although autism spectrum disorder (ASD) is a behaviorally defined disorder, research shows that ASD is associated with neurological, genetic, gastrointestinal, and other medical abnormalities. In this article, we discuss the most prevalent neurological abnormality affecting children with ASD -- seizures. To provide insight and knowledge about this subject, we held three Elias Tembenis Seizures Think Tanks that included practitioners who treat children with ASD and seizure disorders using both traditional and non-traditional treatments. This article outlines the summary points of the major agreed upon conclusions of the think tanks. These conclusions were based on the most valid, evidence-based information available on seizures and epilepsy in ASD.

1. INTRODUCTION

The prevalence of autism spectrum disorders (ASD) is high with recent Center for Disease Control studies estimating the prevalence at 1 in 88[1]. Although ASD is a behaviorally defined disorder, children with ASD often suffer from comorbid medical conditions, including abnormalities in the peripheral nervous, musculoskeletal, endocrine, gastrointestinal, immune, detoxification, redox regulation systems and mitochondrial function.[2,3] It is not known whether these medical abnormalities are part of the etiological processes that cause ASD or whether they arise as a consequence of other pathological processes that arise after the development of ASD. Regardless, it is crucial to understand these comorbid medical abnormalities in order to optimally manage children with ASD and assist them toward a pathway that promotes developing more typical cognitive function. Seizures are the most prevalent neurological disorder associated with ASD4. To provide insight and knowledge about this subject, we held three Elias Tembenis Seizures Think Tanks that included practitioners who treat children with ASD and seizure disorders with both traditional and non-traditional treatments for ASD. The first Elias Tembenis Seizures Think Tank was held at the AutismOne meeting in Chicago in May of 2009. Work continued on this project during similar think tanks held at Autism Canada in Toronto in October 2009 and AutismOne in Chicago in May 2010. The think tanks included a wide variety of scientists and clinicians with expertise in ASD and seizures. The summary points below represent the major agreed upon conclusions of the think tanks. These conclusions were based on the most valid, evidence-based information available on seizures and epilepsy in ASD.

2. SUMMARY POINTS

Summary point 1, Prevalence: Seizures are a significant concern and are relatively common in individuals with ASD. While 1-2% of children in the general population develop epilepsy, the prevalence of epilepsy in ASD is much higher with estimates varying widely from 5% to 38%.[5-9] Some individuals with ASD develop seizures in childhood, some at puberty, and some at adulthood. Although the prevalence of seizures by age is not well studied, recent studies suggest the risk of seizure into adulthood remains high. Seizures are associated with increased mortality and morbidity in individuals with ASD[10] and are the leading cause of mortality in adults with ASD.[11] Certain subgroups of individuals with ASD have a higher risk for developing seizures and epilepsy; these subgroups include individuals with comorbid intellectual disabilities, single gene defects, or brain malformations.[5]

Summary point 2, Subclinical Electrical Discharges: Electroencephalographic (EEG) subclinical electrical discharges (SEDs), not necessarily associated with clinical seizures, appear to be very prevalent in individuals with ASD. The prevalence of these abnormalities is high in ASD, varying from 30%[12] to 61%[13] in studies that have used long-term EEG monitoring and varying from 82%[14] to 100%[15] in studies that have used magnetoencephalography (MEG). Studies using non-ASD populations have shown that SEDs are associated with cognitive and behavioral abnormalities, and controlled studies have shown improvement in cognition and behavior with anti-epileptic drug (AED) treatment of SEDs in children with epilepsy.[16,17] Thus, the authors believe there is evidence to support the notion that SEDs could contribute to the cognitive and behavioral

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morbidity associated with ASD and, thus, deserve careful study in the future.

Summary point 3, Pathophysiological processes: Many pathophysiological processes are related to both ASD and seizures, and the majority of these pathophysiological processes act through altering the excitatory-to-inhibitory balance of the cortex. Many single gene defects and metabolic disorders change this excitatory-to-inhibitory balance by altering γ-aminobutyric acid (GABA) or glutamate neurotransmission. The neuropathology associated with ASD has also demonstrated defects in GABA neurotransmission at the cortical level, potentially leading to an elevation in the excitatory-to-inhibitory balance of the cortex, thereby resulting in seizures. Other pathological processes such as vitamin and mineral deficiencies, oxidative stress, and immune abnormalities may contribute to the development of seizures, but the exact mechanisms by which they might cause seizures requires further study.

Summary point 4, EEG Assessment: Subtle symptoms of seizures are very difficult to differentiate from abnormal behaviors commonly associated with ASD. Some individuals with ASD may not have any clear or subtle symptoms of seizures despite having SEDs.[18] Thus, it is reasonable to consider a screening EEG in children with ASD in order to detect subtle seizure activity and/or SEDs. An extended overnight EEG should be strongly considered as a screening test since (1) routine 1-2 hour studies are very often unsuccessful due to patient agitation or the need for sedative medications for electrode placement and (2) several seizure syndromes associated with autistic regression require a prolonged recording of sleep.

Summary point 5, Systematic Workup: Since specific genetic and metabolic syndromes are associated with both ASD and seizures, children with ASD and comorbid seizures or SEDs should have a systematic workup for these known syndromes. A chromosomal microarray with testing for fragile X and Rett syndrome in boys and girls, respectively, should be highly considered as initial genetic testing. Genetic testing for tuberous sclerosis complex as well as Angelman, Prader–Willi, velocardiofacial, Smith-Lemli-Opitz syndromes should be conducted as indicated based on specific dysmorphological findings. Several metabolic syndromes that have been suggested to have a high prevalence in ASD such as mitochondrial dysfunction and cerebral folate deficiency can also be associated with seizures and should be highly considered in children with ASD and seizures. Other metabolic disorders that are considered rare, such as succinic semialdehyde dehydrogenase deficiency, adenylosuccinate lyase deficiency, creatine metabolism disorder, phenylketonuria, pyridoxine dependent and responsive seizures, and urea cycle disorder, are associated with both seizures and ASD; such disorders should be considered if supporting clinical characteristics exist.

Summary point 6, Seizure Treatments: Traditional treatments for seizures and epilepsy have not been well studied in the ASD population. Since children with ASD may be sensitive to cognitive and behavioral adverse effects of treatments, it is wise to carefully consider the safety profile of treatments. One large survey study investigated the perceived effect of many different types of treatments for seizures in individuals with ASD.[19] In this study, specific antiepileptic drugs (AEDs) and non-AED treatments were rated as improving seizures. AEDs, including lamotrigine, levetiracetam, valproic acid, and ethosuximide were rated as improving seizures and not negatively affecting mood and behavior as much as other AEDs. Non-AED therapy, including the ketogenic diet and Atkin's diet, were rated as improving seizures and positively affecting other important clinical factors such as mood and behavior. In addition, adverse effects of specific AEDs may be minimized by co-treatment with specific vitamins. For example, carnitine can help with valproic acid metabolism, and pyridoxine can mitigate adverse behavioral effects of levetiracetam. Overall, it was found that research on treatment for seizures in children with ASD is needed.

Summary point 7, Treatment of Subclinical Electrical Discharges: Several controlled studies have shown improvement in cognitive function and behavior with AED treatment of SEDs in children with epilepsy. Studies have demonstrated improvement in SEDs in children with ASD using AED treatment, but, unfortunately, there are no studies focusing on the behavioral or cognitive effects of AED treatment of SEDs in children with ASD. Given the excellent safety profile of newer AEDs, the authors believe that the risk/benefit ratio is reasonable to consider in the treatment of SEDs in a careful and controlled fashion with close follow-up and frequent clinical reevaluation. It is likely that SEDs work in concert with underlying neuropathology to exacerbate ASD symptoms; thus, although AED treatment may improve ASD symptoms, it is not likely that AED treatment of SEDs will result in complete resolution of ASD symptoms.

Summary point 8, Alternative Seizure Treatments: Some alternative treatments commonly prescribed to children with ASD, such as vitamin supplementation, may, theoretically, have a positive influence on some of the pathological processes known to cause seizures in ASD. However, empirical evidence for efficacy for the great majority of these treatments is lacking. Thus, certain treatments that have excellent safety profiles may be worth considering for treating seizures in ASD. However, for safety reasons, such treatment should be used as an adjunct or add-on therapy with standard therapies when treating clinical seizures.

Summary point 9, Future Research: There are several areas that are ripe for future research efforts. These include **1)** further defining the pathophysiological causes of seizures in ASD, particularly with respect to the pathophysiology that may cause both behavioral and cognitive aspects of ASD as well as seizures, **2)** evaluation of the tolerability, safety, and efficacy of standard and alternative treatments for seizures, **3)** the natural history of seizures and epilepsy in children with ASD, particularly with respect to the influence of hormonal fluctuations during adolescence, and **4)** investigation into the significance and treatments of SEDs. Dietary manipulations and transcranial magnetic stimulation are particular treatments that were felt to be promising and deserving of more study.

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3. HIGHLIGHTS (SUMMARY FOR PARENTS)

Incidence of Epilepsy: Epilepsy and seizures are significantly more common in children, adolescents, and adults with autism. The incidence of developing seizures appears to continue to increase into adulthood, so it is important to be aware of seizure symptoms in individuals with ASD regardless of age.

Causes of Epilepsy: The causes of most seizures are unknown, but many medical abnormalities associated with ASD, including genetic and metabolic disorders, are associated with brain hyperexcitability, a state that is likely to predispose an individual with ASD to have seizures. Thus, patients with ASD and epilepsy should undergo a comprehensive genetic and metabolic workup for underlying causes.

Subclinical Electrical Discharges: Seizure-like activity has been reported to occur with a high prevalence in individuals with ASD even if they do not have obvious seizures. It is very possible that these abnormal electrical discharges may interfere with attention, cognition, and learning. Thus, we recommend an overnight electroencephalograph for **all** patients with autism due to the high prevalence of these abnormalities and the inability to adequately detect symptoms of these abnormalities during a clinical evaluation. In addition, several clinical studies support treating subclinical electrical discharges. Thus, a treatment trial is reasonable if subclinical electrical discharges are found on electroencephalogram.

Seizure Treatments: Certain specific treatments, including specific antiepileptic drugs (lamotrigine, levetiracetam, valproic acid, and ethosuximide) and diets (ketogenic diet, modified Atkin's diet), appear to be rated as improving seizures without significant adverse effects. Other nutritional supplements and non-traditional treatments may also be beneficial but have not been studied. Thus, in patients with epilepsy and seizures, non-traditional treatments should be used as add-on therapy rather than primary therapy at this point.

Future research: More research is needed on the causes of seizures, with a focus on metabolic abnormalities. Also, more research is needed on new treatments, including dietary treatments and possibly transcranial magnetic stimulation.

Appendix A: Participants of the Elias Tembenis Seizures Think Tanks

Participant	Speciality	May 2009	Oct 2009	May 2010
Richard Frye, MD, PhD	Child and Behavioral Neurology	■	■	■
Derrick MacFabe, MD	Neurology, Neurophysiology	■	■	■
Paul Hardy, MD	Child Neurology	■	■	■
James Adams, PhD	Biochemistry	■	■	■
Manuel Casanova, MD	Neuropathology	■	■	■
Jeffrey Lewine, PhD	Neuropsychology, Neurophysiology	■	■	■
Maya Shetreat-Klein, MD	Child Neurology	■	■	■
Tapan Audhya, PhD	Vitamin Supplementation	■	■	■
Gregory Brown, MD	Alternative Medicine	■	■	■
Vicki Martin, RN	Alternative Medicine	■	■	■
Rob Coben, PhD	Neuropsychology, Neurophysiology	■	■	■
Harry Schneider, MD	Neuroimaging	■	■	■
Dan Rossignol, MD	Family Medicine	■	■	■
Theoharis Theoharides, PhD	Pharmacology, Internal Medicine, Biochemistry, Immunology	■	■	■
Martha Herbert, MD, PhD	Child Neurology	■	■	■
Stephen Edelson, PhD	Alternative Medicine	■	■	■
Seyyed Hossein Fatemi, MD, PhD	Psychiatry, Cell Biology and Neuroanatomy	■	■	■
Cindy L. Griffin, DSH-P, DIHom	Homeopathy	■	■	■
Lindyl Lanham, DSH-P, HD	Homeopathy	■	■	■
Jon Poling, MD, PhD	Neurology, Neurophysiology	■	■	■
Allan Sosin, MD	Alternative Medicine	■	■	■
Aristo Vojdani, PhD	Immunology	■	■	■
William Walsh, PhD	Biochemistry	■	■	■
Harumi Jyonouchi, MD	Allergy/Immunology	■	■	■
Georgia Davis, MD	Neurology, Psychiatry, Pathology	■	■	■
Jeffrey Bradstreet, MD	Alternative Medicine	■	■	■
Sargent Goodchild	Biofeedback	■	■	■
Nancy Mullan, MD	Psychiatrist	■	■	■
Natalie King Wilson, DO	Chiropractor	■	■	■
Daniel Barth, PhD	Electrophysiology, Neuroimmunology	■	■	■
Dan Pavel, MD	Neuroimaging, Nuclear Medicine	■	■	■
Alexander Rotenberg, MD, PhD	Child Neurology, Neurophysiology	■	■	■
Evdokia Agnostou, PhD	Psychologist	■	■	■

■ Attended Specific Meeting
■ Did Not Attend Specific Meeting

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