Seizure Issues in Autism Spectrum Disorders

Jeff Bradstreet MD, MD(H) FAAFP

&

Dan Rossignol, MD FAAFP

Florida, California, Oslo & Dubai

321-259-7111

www.icdrc.org
Lessons from Medical History

• Of the first 11 children Leo Kanner described in 1943 - 18 percent -- had seizures, and one of them died prematurely as a result.

• In 1971, Kanner wrote a follow-up on his historic account of the first 11 cases, and the tale of John F. turned tragic. "John died suddenly in 1966 at 29 years of age."
Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,1,2 Caterina Nascimbene, MD,1–3 Chitra Krishnan, MHS1
Andrew W. Zimmerman, MD,1,4 and Carlos A. Pardo, MD1,2,5

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)–1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Immune transcriptome alterations in the temporal cortex of subjects with autism

Krassimira Garbett, a Philip J. Ebert, a Amanda Mitchell, a Carla Lintas, b, c Barbara Manzi, d Károly Mirnics, a, * and Antonio M. Persico b, c, *

aDepartment of Psychiatry, Vanderbilt University, Nashville, USA
bLaboratory of Molecular Psychiatry and Neurogenetics, University “Campus Bio-Medico”, Rome, Italy
cLaboratory of Molecular Psychiatry and Psychiatric Genetics, Department of Experimental Neurosciences, I.R.C.C.S. “Fondazione Santa Lucia”, Rome, Italy
dDepartment of Child Neuropsychiatry, University “Tor Vergata”, Rome, Italy
eVanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, USA

Received 18 December 2007; revised 23 January 2008; accepted 29 January 2008
Available online 10 March 2008
Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders

Anne M. Connolly, MD, Michael G. Chez, MD, Alan Pestronek, MD, Susan T. Arnold, MD, Shobhna Mehta, BSc, and Ruthmary K. Deuel, MD

(J Pediatr 1999;134:607-13)

Fig 1. A, IgG antibodies from a child with LKSV binding to small blood vessels in human temporal lobe cortex (original magnification ×80). Immunostaining (1:100) demonstrates distinct capillary staining. B, Control serum shows no specific labeling.
## Urinary levels of neopterin and biopterin in autism

S. Messahel\textsuperscript{a, b}, A.E. Pheasant\textsuperscript{a,*}, H. Pall\textsuperscript{b}, J. Ahmed-Choudhury\textsuperscript{a}, R.S. Sungum-Paliwal\textsuperscript{c}, P. Vostanis\textsuperscript{c}

\textsuperscript{a}School of Biochemistry, University of Birmingham, Edgbaston Park Road, Birmingham B15 2TT, UK
\textsuperscript{b}Department of Neurology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
\textsuperscript{c}Department of Child Psychiatry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Neopterin ((\mu\text{mol/mol creatinine}))</th>
<th>Biopterin ((\mu\text{mol/mol creatinine}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic children ((n = 14))</td>
<td>3116 ± 686*</td>
<td>3691 ± 682**</td>
</tr>
<tr>
<td>Siblings ((n = 21))</td>
<td>1490 ± 346</td>
<td>2923 ± 626**</td>
</tr>
<tr>
<td>Control children ((n = 16))</td>
<td>908 ± 201</td>
<td>359 ± 80</td>
</tr>
</tbody>
</table>

Data are the mean ± SEM. Significantly different from controls: *\(P < 0.01\); **\(P < 0.001\).
“The observed increase in urinary native neopterin in autism agrees with our previous observations and indicates activation of cellular immunity in these children thus supporting the possible involvement of autoimmunity in the pathogenesis* of autism.”


*Pathogenesis = the cause of disease
Inflammation is present in the gut of ASD children.
Toxins from gut bacteria and yeast reach the brain. Immune chemicals from Inflammation also reach the brain.
Epilepsy and ASD
Landau Kleffner Syndrome

When seizures occur in sleep in the region of the expressive language cortex. Autoantibodies to endovasculature occur more commonly in autism and LKS. (Connolly et al. J Pediatr. 1999 May;134(5):607-13.)
MEG reflects fissural cortex activity, EEG is dominated by gyral crown activity
Landau Kleffner Syndrome EEG
### LKS: Sources of MEG-spikes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical LKS</strong></td>
<td></td>
<td>N=6</td>
</tr>
<tr>
<td>- Sylvian unilateral</td>
<td></td>
<td>2/6</td>
</tr>
<tr>
<td>- Sylvian bilateral, dependent</td>
<td></td>
<td>3/6</td>
</tr>
<tr>
<td>- Sylvian, bilateral independent</td>
<td></td>
<td>1/6</td>
</tr>
</tbody>
</table>

| **Variant LKS**                |                | N=9  |
| - Sylvian & frontal spikes     |                | 9/9  |

| **Autistic Epileptic Regression** |                | N=100|
| - Sylvian & multifocal          |                | 70/100|

MEG identified epileptiform activity in 41 of the 50 (82%) children with *autism spectrum disorders*.  
(Lewine, *PEDIATRICS* Vol. 104 No. 3 September 1999, 405-418)
Magnetoencephalography in Children with Landau-Kleffner Syndrome and Acquired Epileptic Aphasia

David F. Sobel, Maung Aung, Hiroshi Otsubo, and Michael C. Smith

BACKGROUND AND PURPOSE: Landau-Kleffner syndrome (LKS) is epileptiform aphasia acquired during childhood and occurring in children with previously normal language development. The epileptiform activity in these children is thought to result in a functional ablation of eloquent speech areas. The purpose of this study was to investigate the usefulness of magnetoencephalography (MEG) for localizing the source of epileptiform activity in these patients.

METHODS: Nineteen patients with acquired aphasia and a suspected diagnosis of LKS were referred for MEG evaluation. Patients ranged in age from 4 to 14 years. Fourteen MEG studies were performed on a 74-channel system, four on a 148-channel whole-head system, and one on a 37-channel system.

RESULTS: Thirteen of the 19 patients had perisylvian MEG spikes. In 10 of the patients, the spikes were bilateral, and in three they were unilateral. Four other patients had non-sylvian spikes, and two patients had no spikes recorded. The results of MR imaging were normal or noncontributory for all 19 patients.

CONCLUSIONS: MEG can play a useful role in evaluating children with LKS and acquired epileptiform aphasia, both in diagnosis and in aiding presurgical localization of epileptiform activity when surgery is being considered.
Unilateral abnormalities on MEG auditory evoked fields in children with Landau-Kleffner Syndrome

E.W. Pang\textsuperscript{a,b,*}, H. Otsubo\textsuperscript{a,b}, R. Sharma\textsuperscript{a}, A. Hunjan\textsuperscript{a}, B. Chu\textsuperscript{a}, O.C. Snead\textsuperscript{a,b}

\textsuperscript{a} Division of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada
\textsuperscript{b} Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada


Abstract. Landau-Kleffner Syndrome (LKS) is known to disrupt auditory processing but the exact nature of these disruptions has not been established. We compared the MEG auditory evoked fields (AEF) to monaural tone stimulation in a group of 4 children (aged 7–10 years) with LKS and a group of age-matched clinical controls. In all 4 control children, bilateral AEFs were observable and dipoles localizable to both superior temporal gyri. In the children with LKS, an AEF was observable only over one hemisphere (3 left temporal lobes; 1 right). The AEF generated in the other hemisphere demonstrated non-dipolar topographies that were not localizable. Furthermore, in the group of children with LKS, the hemispheric concordance between EEG and AEF abnormality was 50%. Our evidence concurs with the literature that there are unilateral auditory processing abnormalities in LKS. We add to the existing data by further describing the nature of these abnormalities. © 2007 Elsevier B.V. All rights reserved.
Drawbacks of MEG

- Requires anesthesia for children
- Not usually paid by insurance
- Few Scanners available
- Some think it is too sensitive
Wavelet Analysis of EEG Spiking
Video EEG
fMRI Imaging of Language

Normal

Autistic 6 yr. old

Autistic 7 yr. old
Autonomic Nervous System

PARASYMPATHETIC NERVES
“Rest and digest”
- Constrict pupils
- Stimulate saliva
- Slow heartbeat
- Constrict airways
- Stimulate activity of stomach
- Inhibit release of glucose; stimulate gallbladder
- Stimulate activity of intestines
- Contract bladder
- Promote erection of genitals

CHOLINERGIC - USE ACETYLCHOLINE

SYMPATHETIC NERVES
“Fight or flight”
- Dilate pupils
- Inhibit salivation
- Increase heartbeat
- Relax airways
- Inhibit activity of stomach
- Stimulate release of glucose; inhibit gallbladder
- Inhibit activity of intestines
- Secrete epinephrine and norepinephrine
- Promote ejaculation and vaginal contraction

USE NORADRENALINE TRANSMITTERS

Acetyl Choline Nicotine effect
Noradrenaline effect
Reduced cardiac parasympathetic activity in children with autism.

Brain Dev. 2005 Oct;27(7):509-16
Ming X, et al

Department of Neuroscience, New Jersey Medical School, UMDNJ, Newark, 90 Bergen Street, DOC 8100, NJ 07103, USA. mingxu@umdnj.edu

Many of the clinical symptoms of autism suggest autonomic dysfunction. **results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone** in children with autism whether or not they have symptoms or signs of autonomic abnormalities.
# Autonomic Dysfunction in Epilepsy

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac/thoracic</strong></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal/abdominal</strong></td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
</tr>
<tr>
<td><strong>Genital</strong></td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
</tr>
<tr>
<td><strong>Pupillary</strong></td>
</tr>
<tr>
<td><strong>Secretory</strong></td>
</tr>
</tbody>
</table>

[Link](http://emeds.c.medscape.com/article/1186872)
Bradycardia and Cardiac Arrest

• Sustained cardiac bradyarrhythmias and asystole associated with seizures are most likely secondary to parasympathetic autonomic dysfunction.
• Cardiac bradyarrhythmias and arrest have been documented in both generalized and CP seizures (Phizackerley, 1954).
• Nashef et al reported bradycardia in most patients who experienced central apnea during seizure (Nashef, 1996).
• Patients with epilepsy have a mortality rate that is 2-3 times that of the general population because of epilepsy-related deaths. The phenomenon of SUDEP may account for 8-17% of deaths in patients with epilepsy (Ficker, 1998). Age range 20-40.
## Anti-Seizure Medication and Their Side Effects

<table>
<thead>
<tr>
<th>BRAND NAME (generic name)</th>
<th>SOME SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBATROL (extended release carbamazepine)</td>
<td>Dizziness, drowsiness, blurred or double vision, nausea, skin rashes, abnormal blood counts (rare)</td>
</tr>
<tr>
<td>DEPAKENE (valproate)</td>
<td>Upset stomach, altered bleeding time, liver toxicity, hair loss, weight gain, tremor</td>
</tr>
<tr>
<td>DEPAKOTE (divalproex sodium)</td>
<td>Upset stomach, altered bleeding time, liver toxicity, hair loss, weight gain, tremor</td>
</tr>
<tr>
<td>DIASTAT (diazepam rectal gel)</td>
<td>Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior changes</td>
</tr>
<tr>
<td>DILANTIN (phenytoin)</td>
<td>Clumsiness, insomnina, motor twitching, nausea, rash, gum overgrowth, hairiness, thickening of features</td>
</tr>
<tr>
<td>KEPPRA (levetiracetam)</td>
<td>Sleepiness, fatigue, poor coordination, loss of strength, dizziness</td>
</tr>
<tr>
<td>KLOPONIN (clonazepam)</td>
<td>Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior changes</td>
</tr>
<tr>
<td>LAMICTAL (lamotrigine)</td>
<td>Dizziness, headache, blurred vision, clumnsiness, sleepiness, nausea, skin rash</td>
</tr>
<tr>
<td>MYOSLINE (primidone)</td>
<td>Clumsiness, dizziness, appetite loss, fatigue, drowsiness, hyperirritability, insomnia, depression, hyperactivity (children)</td>
</tr>
<tr>
<td>NEUROPTIN (gabapentin)</td>
<td>Sleepiness, dizziness, clumsiness, fatigue, twitching</td>
</tr>
<tr>
<td>PHENOBARBITAL (phenobarbital)</td>
<td>Drowsiness, irritability, hyperactivity (children), behavioral problems, difficulty concentrating, depression</td>
</tr>
<tr>
<td>TEGRETOL (carbamazepine)</td>
<td>Dizziness, drowsiness, blurred or double vision, nausea, skin rashes, abnormal blood counts (rare)</td>
</tr>
</tbody>
</table>
Common Anti-seizure Medications May Increase Risk of Cardiovascular Problems

ScienceDaily (Mar. 23, 2009) — An important clinical repercussion in the treatment of epilepsy has been discovered by a research team led by Scott Mintzer, M.D., assistant professor in the Department of Neurology and the Jefferson Comprehensive Epilepsy Center at Jefferson Medical College of Thomas Jefferson University.

The team has determined that two of the most commonly prescribed anti-seizure medications may lead to significantly increased levels of cholesterol, C-reactive protein and other markers of cardiovascular disease risk. The finding – set to be published in the March 18th online edition of Annals of Neurology – may help doctors manage the care of patients with seizures more effectively by prescribing different anti-seizure medications that will not adversely affect cardiovascular health.

The study involved two of the most widely-prescribed anticonvulsants – phenytoin (Dilantin®) and carbamazepine (Tegretol®, Carbatrol®) – which have potent effects on many enzymes in the body involved in different areas of metabolism, compared to two newer anti-seizure drugs which do not widely affect enzymes – lamotrigine (Lamictal®) or levetiracetam (Keppra®). Just 6 weeks after the patients' drugs were switched, there were significant declines in total cholesterol, non-high-density lipoprotein (commonly referred to as 'bad') cholesterol, triglycerides and C-reactive protein.
Two randomized vitamin D trials in ambulatory patients on anticonvulsants: impact on bone.


Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan Gel-H.

Adult and Pediatric Epilepsy Program, Department of Pediatrics, American University of Beirut Medical Center, Beirut, Lebanon. mamikati@aub.edu.lb

METHODS: We conducted two parallel, randomized, controlled trials in 72 adults (18 to 54 years old) and 78 children and adolescents (10 to 18 years) on long-term AED therapy. They received either low-dose vitamin D 400 IU/day or high-dose vitamin D 4,000 IU/day (adults) and 2,000 IU/day (children/adolescents). Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry.

RESULTS: In adults, baseline BMD was lower than that of age- and gender-matched controls vs either a Western or an ethnically identical population. After 1 year, there were significant increases in BMD at all skeletal sites compared to baseline in the high-, but not in the low-dose treatment group. However, BMD at 1 year remained below normal. In children, baseline BMD was normal vs age- and gender-matched controls and showed significant and comparable increases in both treatment groups. CONCLUSIONS: In ambulatory adults on antiepileptic drugs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites. In children, both doses resulted in comparable increases in bone mass.
Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet.


Bergqvist AG, Schall JI, Stallings VA, Zemel BS.

Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. bergqvist@email.chop.edu

BACKGROUND: The ketogenic diet (KD) is a high-fat, low-carbohydrate, and protein diet that effectively treats intractable epilepsy (IE). OBJECTIVE: The purpose of this study was to measure the change in bone mineral content (BMC) in children with IE treated with the KD for 15 mo. DESIGN: Prepubertal children >or=5 y of age with IE were eligible. A 4:1 ketogenic diet was maintained for 15 mo, and whole-body and spine BMCs were measured with dual-energy X-ray absorptiometry. Z scores were generated by comparing the children with IE with a cohort of 847 healthy children. Other measurements included demographics, anthropometry, serum 25-hydroxyvitamin D (25-OHD), intact parathyroid hormone, electrolytes, and dietary intake. RESULTS: Growth and bone health status were suboptimal as were serum 25-OHD concentrations and dietary intake of calcium and vitamin D. Body mass index (BMI; in kg/m(2)) z score, age, and ambulation were positive predictors of BMC, which declined sharply over 15 mo of KD treatment. CONCLUSION: Bone health in children with IE was poor... The KD resulted in progressive loss of BMC.
Hippocampal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity.


Medical school, University of Tampere, Finland.

Previously celiac disease (CD) and gluten sensitivity (defined as the presence of anti-gliadin antibodies and positive immunogenetics) has been associated with cerebellar degeneration and epilepsy with occipital calcifications. Hippocampal sclerosis (HS) in temporal lobe epilepsy (TLE) is a potentially progressive disorder with unknown etiology, and autoimmunity has been implicated in TLE+HS as one of the possible mechanism leading to HS. We measured anti-gliadin, anti-tTG and anti-EMA and celiac type HLA (DQ2 and DQ8) in 48 consecutive patients with therapy resistant localisation-related epilepsy. The patients were categorised TLE+HS (N=16), TLE-HS (N=16) and extratemporal epilepsy (N=16) based on ictal eletro-clinical characteristics and high resolution MRI. Patients with suspected CD or gluten sensitivity underwent duodenal biopsies. The association was very robust in this well characterized group of patients; thus gluten sensitivity should be added to the list of potential mechanism leading to intractable epilepsy and HS.
Successful treatment of epilepsy and celiac disease with a gluten-free diet.


Mavroudi A, Karatza E, Papastavrou T, Panteliadis C, Spiroglou K.

Department of Pediatrics, 3rd Pediatric Clinic, Division of Digestive Diseases, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece.

Celiac disease is a gluten-sensitive enteropathy, which recently has been described in association with epilepsy or other neurologic disturbances. This study describes a case of a 7-year-old female with intractable-to-treatment epilepsy and late-onset celiac disease, who was treated successfully with a gluten-free diet plus antiepileptic therapy. It is important for children with intractable cases of epilepsy and weight loss to undergo screening for celiac disease.
Effect of magnesium chloride and magnesium L-aspartate on seizure threshold in rats under conditions of dietary magnesium deficiency.


Spasov AA, Iezhitsa IN, Kharitonova MV, Kravchenko MS.

Institute of Pharmacology, Department of Pharmacology, Volgograd State Medical University.

We studied the effect of Mg-L-aspartate, MgCl2, and their combinations with vitamin B6, magneB6, and MgSO4 on seizure threshold in rats with dietary Mg2+ deficiency. Mg2+ deficiency was followed by a decrease in the threshold dose of corazol (from 79.20 to 49.48 mg/kg), shortening of the latency of the first jerk (by 33.6%, p=0.012), and reduction of the time to the first episode of clonic seizures (by 32.6%, p=0.011). Seizure threshold and latencies of the first jerk and first episode of clonic seizures increased over 3 weeks after peroral administration of Mg2+ salts. The combination of Mg2+ salts and pyridoxine (B6) was most effective in this respect.
Dose-dependent anticonvulsant effects of linoleic and alpha-linolenic polyunsaturated fatty acids on pentylenetetrazol induced seizures in rats.


Taha AY, Filo E, Ma DW, McIntyre Burnham W.

Department of Pharmacology, Faculty of Medicine, University of Toronto, Toronto, Canada. a.taha@utoronto.ca

PURPOSE: Linoleic and alpha-linolenic polyunsaturated fatty acids, derived from plant oils, have been reported to reduce neuronal excitability ex vivo and in cell culture. The evidence derived from animal seizure models, however, has been contradictory. The goal of the present study was to assess the dose-dependent anticonvulsant effects of a fatty acid mixture containing linoleic and alpha-linolenic acids in a 4 to 1 ratio (the "SR-3" compound). RESULTS: Daily intraperitoneal injection of SR-3 for 21 consecutive days raised omega-3 polyunsaturated fatty acid (n-3 PUFA) composition in the unesterified fatty acid fraction of brain lipids (p < 0.05), and increased latency to seizure onset when administered at 200 mg/kg (p < 0.05), but not at 40 mg/kg (p > 0.05). CONCLUSION: Linoleic and alpha-linolenic polyunsaturated fatty acids in a 4 to 1 ratio raises n-3 PUFA composition in the unesterified fatty acid fraction of brain lipids, and increases latency to seizure onset when administered at 200 mg/kg.
Brain-Derived Neurotrophic Factor and Autoantibodies to Neural Antigens in Sera of Children with Autistic Spectrum Disorders, Landau-Kleffner Syndrome, and Epilepsy


**Background:** Brain derived neurotrophic factor (BDNF) elevation in newborn sera predicts intellectual/social developmental abnormalities. Other autoantibodies (AAs) to endothelial cells (ECs) and myelin basic protein (MBP) are also elevated in some children. We tested relationships between BDNF, BDNF AAs, and other AAs in children with these disorders.

**Methods:** BDNF levels and IgG/IgM autoantibodies to BDNF, ECs, MBP, and histones were measured in children with autism, childhood disintegrative disorder (CDD), pervasive developmental delay-not otherwise specified (PDD-nos), acquired epilepsy, Landau-Kleffner syndrome (LKS); healthy children (HC), and children with non-neurological illnesses (NNI).

**Results:** Mean BDNF levels were elevated in children with autism and CDD, \(p \leq 0.0002\) compared to HC or NNI. Mean IgG and IgM BDNF AAs were elevated in children with autism, CDD and epilepsy \(p \leq 0.0005\) compared to HC but not to NNI. Mean IgM AA EC titers detected by immunocytochemistry were higher in autism, PDD-NOS, epilepsy, and LKS \(p \leq 0.005\) compared to HC and NNI. While mean ELISA IgG EC AAs were higher in autism and PPD-NOS \(p < 0.005\) compared to HC but not NNI, ELISA IgM EC AAs were higher in children with autism, CDD, PDD-NOS, and epilepsy compared to both HC and NNI \(p < 0.0005\). Mean anti-MBP IgG and IgM titers were higher in all study groups \(p < 0.005\) except for LKS compared to both HC and NNI.

**Conclusion:** Children with developmental disorders and epilepsy have higher AAs to several neural antigens compared to controls. The presence of both BDNF AAs and elevated BDNF levels in some children with autism and CDD suggests a previously unrecognized interaction between the immune system and BDNF.
Galantamine and nicotine have a synergistic effect on inhibition of microglial activation induced by HIV-1 gp120.

Giunta B, et al. Neuroimmunology Laboratory, College of Medicine, University of South Florida, 3515 E. Fletcher Avenue, Tampa, FL 33613, USA.

Chronic brain inflammation is the common final pathway in the majority of neurodegenerative diseases and central to this phenomenon is the immunological activation of brain mononuclear phagocyte cells, called microglia. This inflammatory mechanism is a central component of HIV-associated dementia (HAD). Recent data from our laboratory indicates that cultured microglial cells also express this same receptor and that microglial anti-inflammatory properties are mediated through it and the p44/42 mitogen-activated protein kinase (MAPK) system. Here we report for the first time the creation of an in vitro model of HAD composed of cultured microglial cells synergistically activated by the addition of IFN-gamma and the HIV-1 coat glycoprotein, gp120. Furthermore, this activation, as measured by TNF-alpha and nitric oxide (NO) release, is synergistically attenuated through the alpha7 nAChR and p44/42 MAPK system by pretreatment with nicotine, and the cholinesterase inhibitor, galantamine. Our findings suggest a novel therapeutic combination to treat or prevent the onset of HAD through this modulation of the microglia inflammatory mechanism.
Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

Michael G. Chez, MD, Quinn Burton, MS, Timothy Dowling, Mina Chang, MS, Pavan Khanna, MS, and Christopher Kramer, MS

Autism and Pervasive Developmental Disorder Not Otherwise Specified are common developmental problems often seen by child neurologists. There are currently no cures for these lifelong and socially impairing conditions that affect core domains of human behavior such as language, social interaction, and social awareness. The etiology may be multifactorial and may include autoimmune, genetic, neuroanatomic, and possibly excessive glutaminergic mechanisms. Because memantine is a moderate affinity antagonist of the N-methyl-D-aspartic acid (NMDA) glutamate receptor, this drug was hypothesized to potentially modulate learning, block excessive glutamate effects that can include neuroinflammatory activity, and influence neuroglial activity in autism and Pervasive Developmental Disorder Not Otherwise Specified. Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. To generate a clinician-derived Clinical Global Impression Improvement score for language, behavior, and self-stimulatory behaviors, the primary author observed the subjects and questioned their caretakers within 4 to 8 weeks of the initiation of therapy. Chronic maintenance therapy with the drug was continued if there were no negative side effects. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects.

Keywords: autism treatment; pervasive developmental disorders; memantine
The Methylation and Transsulfuration Pathways Provide the Reduced Glutathione (GSH) to Repair Oxidative Damage.

**FOLATE CYCLE**
- B6
- 5,10-CH₂-THF
- THF
- MS
- MSR
- B12
- Trimethylglycine
- SAH
- SAM
- Methyl acceptor
- Methyl transfease
- Methylated Product (DNA, RNA, Protein, neurotransmitters)
- Adenosine
- CBS
- Cystathionine
- B6
- Cysteine
- GSH
- GST M1
- GSSG

**TRANSMETHYLATION**
- Methionine
- SAM
- Methyl acceptor

**TRANS-SULFURATION**
- Homocysteine
- SAHH
- 5-CH₃-THF
- MTHFR
- 5,10-CH₂-THF
- Trimethylglycine
- B12

**Cell membrane**
- Reactive Oxygen Species: Peroxides
- Cell membrane

**Glutathione Peroxide**
- Glutathione
- GST M1
- GSSG

*Courtesy of Jill James, PhD, University of Arkansas*
Interaction of Choline with Methylation and Transsulfation

**Figure 1.**
Choline metabolism and links to methionine and folate metabolism. The pathways described are all present in the liver, with other tissues having one or more of these pathways. PEMT, phosphatidylethanolamine N-methyltransferase; CHDH, choline dehydrogenase; BHMT, betaine homocysteine methyltransferase; MTHFR, methylene tetrahydrofolate reductase; MTHFD, methylene tetrahydrofolate dehydrogenase.

Letter to the Editor

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

S. Jill James, Stepan Melnyk, Stefanie Jernigan, Mario A. Cleves, Charles H. Halsted, Donna H. Wong, Paul Cutler, Kenneth Bock, Marvin Boris, J. Jeffrey Bradstreet, Sidney M. Baker, and David W. Gaylor

1Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas
2Genome and Biomedical Sciences Facility, West Health Science Drive, University of California Davis, Davis California
3Elmwood Ave., Niagara Falls, New York, New York
4Rhinebeck Health Center, Rhinebeck, New York, New York
5Froelich Farm Blvd., Woodbury, New York, New York
6International Child Development Resource Center, Hibiscus Bldg, Melbourne, Florida
7Sag Harbor, New York, New York
8Department of Biostatistics, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas

TABLE II. Transmethylation and Transsulfuration Metabolites in Autistic Cases and Controls

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control (n = 73)</th>
<th>Autistic (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine (μmol/L)</td>
<td>28.0 ± 6.5</td>
<td>20.6 ± 5.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAM (mmol/L)</td>
<td>93.8 ± 18</td>
<td>84.3 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAH (μmol/L)</td>
<td>18.8 ± 4.5</td>
<td>23.3 ± 7.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAM/SAH ratio</td>
<td>5.5 ± 2.8</td>
<td>4.0 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adenosine (μmol/L)</td>
<td>0.19 ± 0.13</td>
<td>0.28 ± 0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>6.0 ± 1.3</td>
<td>5.7 ± 1.2</td>
<td>0.03v</td>
</tr>
<tr>
<td>Cystathionine (μmol/L)</td>
<td>0.19 ± 0.1</td>
<td>0.24 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cysteine (μmol/L)</td>
<td>207 ± 22</td>
<td>165 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cysteinylglycine (μmol/L)</td>
<td>39.4 ± 7.3</td>
<td>38.9 ± 11</td>
<td>0.78</td>
</tr>
<tr>
<td>Total GSH (μmol/L)</td>
<td>7.53 ± 1.7</td>
<td>5.1 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Free GSH (μmol/L)</td>
<td>2.2 ± 0.9</td>
<td>1.4 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GSSG (μmol/L)</td>
<td>0.24 ± 0.1</td>
<td>0.40 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total GSH/GSSG ratio</td>
<td>28.2 ± 7.0</td>
<td>14.7 ± 6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Free GSH/GSSG ratio</td>
<td>7.9 ± 3.5</td>
<td>4.9 ± 2.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; GSH, glutathione; GSSG, glutathione disulfide.

*aMeans ± SD.
Efficacy and prognosis of a short course of prednisolone therapy for pediatric epilepsy.


You SJ, Jung DE, Kim HD, Lee HS, Kang HC.

Department of Pediatrics, Epilepsy Center, University College of Medicine, Korea

PURPOSE: To evaluate the efficacy and safety of adjunctive prednisolone therapy in children with cryptogenic epileptic encephalopathy, other than infantile spasms, and to determine its prognosis. METHODS: Prednisolone, 2mg/kg per day for 6 weeks, tapered for a further 2 weeks, was given in combination with previously prescribed antiepileptic drugs. A retrospective assessment of 41 children thus treated included measurements of seizure frequency, electroencephalographic findings, global assessments of cognitive function, and adverse drug events. Long-term patient prognoses over a mean follow-up period of 3 years and 5 months (range, 14-90 months) were also examined. RESULTS: After prednisolone therapy, 73% (30/41) of patients showed a reduction in seizure frequency of >50%, and 59% (24/41) became seizure free. Most adverse events were transient, or were tolerated well with conservative management, with maintenance of the medication. CONCLUSION: Prednisolone therapy may be a safe and effective adjunct in patients with cryptogenic epileptic encephalopathies, but the high relapse rate is of concern.
Brief Report: Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics¹

Sudhir Gupta,² Sudeepa Aggarwal, and Cathy Heads
Division of Basic and Clinical Immunology, University of California, Irvine
Journal of Nutritional & Environmental Medicine  

CLINICAL RESEARCH  

Improvement in children with autism treated with intravenous gamma globulin  

MARVIN BORIS, MD¹, ALLAN GOLDBLATT, PA-C² & STEPHEN M. EDELSON, PhD³  

¹New York University School of Medicine, New York, USA, ²Truro College, New York, USA, and ³Autism Research Institute, 4182 Adams Ave, San Diego, CA 92116, USA
Intravenous immunoglobulins in refractory childhood-onset epilepsy: effects on seizure frequency, EEG activity, and cerebrospinal fluid cytokine profile.

Epilepsia. 2007 Sep;48(9):1739-49.


Laboratory of Experimental Transplantation, University of Leuven, Leuven, Belgium.

PURPOSE: Several studies have reported favorable effects of intravenous immunoglobulins (IVIG) in refractory epilepsy. Evidence substantiating an immunomodulatory action is scarce. In an open-label study, we prospectively investigated the effect of IVIG on clinical, EEG and serum/CSF immunological parameters in patients with refractory childhood-onset epilepsy. CONCLUSIONS: Despite unchanged EEG spike counts, substantial reductions in seizure frequency occurred in 7 of 13 patients, suggesting that IVIG hinder progression of central epileptic activity into clinical seizures. Intrathecal presence of IL-8 and IL-6 was documented in all patients, but was unaffected by IVIG, suggesting that their production is directly related to electrical seizure activity and that IVIG may act through interference with immune pathways downstream to IL-6 and IL-8.
Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

James Jeffrey Bradstreet a,*, Scott Smith a, Doreen Granpeesheh b, Jane M. El-Dahr c, Daniel Rossignol d

a International Child Development Resource Center, Melbourne and Florida Hospital, Celebration, 1688 West Hibiscus Boulevard, Melbourne, FL 32901, United States
b Center for Autism Related Disorders, Tarzana, CA, United States
c Tulane University Health Sciences Center, Departments of Pediatrics and Medicine, Section of Pediatric Allergy, Immunology and Rheumatology, New Orleans, LA, United States
d University of Virginia, Department of Family Medicine, P.O. Box 800729, Charlottesville, VA, United States
**Table 2** Summary of the proposed effects of spironolactone on autism findings

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Autism finding</th>
<th>Effect of spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon gamma</td>
<td>$\uparrow$ [19]</td>
<td>$\downarrow$ [55]</td>
</tr>
<tr>
<td>TNF-α</td>
<td>$\uparrow$ [24,25]</td>
<td>$\downarrow$ [54,55]</td>
</tr>
<tr>
<td>MCP-1</td>
<td>$\uparrow$ [34]</td>
<td>$\downarrow$ [54,56]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>$\uparrow$ [27,34]</td>
<td>$\downarrow$ [53,55]</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>$\uparrow$ [57]</td>
<td>$\downarrow$ [62]</td>
</tr>
<tr>
<td>Testosterone effects</td>
<td>$\uparrow^a$ [5–7]</td>
<td>$\downarrow$ [59]</td>
</tr>
</tbody>
</table>

$^a$ Elevated in a subset of autistic individuals.
Steroids in childhood epilepsy


Rajesh Ramachandranair
Division of Paediatric Neurology, McMaster Children’s Hospital, McMaster University, 1200 Main St W, Hamilton, Ontario, Canada L8N 3Z5

Abstract

Treatment of epileptic encephalopathies can be very challenging as most anticonvulsant drugs fail to achieve good seizure control. Steroids are disease modifying as well as anticonvulsant in these conditions. Though steroids are accepted as the first-line treatment for infantile spasms, there are many unanswered questions with regard to the preparation, dose and duration of treatment. In this review a re-exploration of the literature is attempted. Putative mechanism of action of steroids in infantile spasms is also discussed. As steroids are being increasingly used in other epileptic encephalopathies and Rasmussen’s encephalitis, a brief discussion on the role of steroids in these conditions is attempted. The review ends with the discussion on newer neuroactive steroids in the management of epilepsy.
Abstract

West syndrome (WS) is a severe age-dependent intractable epilepsy in infants that frequently results in mental retardation. ACTH or glucocorticoids are among several effective treatments in WS, but the relative advantages and disadvantages of these two therapies are still unknown. In a previous study, liposteroid (LS; dexamethasone palmitate) was used for the treatment of WS and compared with ACTH therapy in relation to therapeutic effect and adverse reactions. In this study, a new regimen of LS therapy was tried for WS and its related syndrome in an attempt to hasten the onset of the therapeutic effect and reduce the relapse rate. A single intravenous injection of LS (0.25 mg/kg) was administered 12 times in 1 month (total dosage 3.0 mg/kg) to four patients with WS and with post-WS aged 5–25 months, and one patient with Lennox–Gastaut syndrome (post-WS) aged 84 months. All five patients had daily seizures uncontrolled by conventional antiepileptic drugs, such as VPA, CZP or ZNS. Nodding spasm and hypsarrhythmia on EEG disappeared in one patient with WS within four doses. More than 50% decrease in seizures, and EEG improvement, were found in other two patients. No notable effects were seen in the other two patients. There were no clinically significant adverse reactions throughout the therapy. Efficacy can be determined in this new experimental LS therapy earlier than with conventional LS therapy. In this small study, a new protocol for LS therapy could be completed safely. This regimen may be useful for those susceptible to adverse reactions from conventional treatment or those unresponsive to other treatments.

© 2007 Elsevier B.V. All rights reserved.
ACTH

Hypothalamus

CRH

Pituitary gland

ACTH

Brain stem

Medulla

Adrenal gland

CORTISOL

To immune system
Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone

*Sara Kivity, †Pinchas Lerman, ‡Raya Ariel, §Yardena Danziger, ¶Marc Mimouni, and ||Shlomo Shinnar

*Pediatric Epilepsy Unit and EEG Laboratory, †Department of Mental Health, §Departments of Pediatric Day Care and Emergency Room, Schneider Children’s Medical Center of Israel, Petah Tiqwa, and Sackler School Medicine, Tel Aviv University, Tel Aviv, and ‡EEG Laboratory, Rabin Medical Center, Petah Tiqva, Israel; and ¶Departments of Neurology and Pediatrics and the Comprehensive Epilepsy Management Center, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York, U.S.A.

Summary: Purpose: To evaluate the outcome of children with cryptogenic infantile spasms treated with high-dose synthetic adrenocorticotropic hormone (ACTH) and the relation between early treatment, within 1 month of onset, and outcome. Methods: We assessed the long-term cognitive and seizure outcomes of 37 patients with cryptogenic infantile spasms (onset, age 3 to 9 months) receiving standardized treatment regimen of high-dose etractocactide depot, 1 mg IM every 48 h for 2 weeks, with a subsequent 8- to 10-week slow taper and followed by oral prednisone, 10 mg/day for a month, with a subsequent slow taper for 5 months or until the infant reached the age of 1 year, whichever came later. Development was assessed before treatment. Seizure outcomes were followed up prospectively. Cognitive outcomes were determined after 6 to 21 years and analyzed in relation to treatment lag and pretreatment regression.

Results: Twenty-two infants were treated within 1 month of onset of infantile spasms, and 15 after 1 to 6.5 months. Normal cognitive outcome was found in all 22 (100%) patients of the early-treatment group, and in 40% of the late-treatment group. Normal cognitive outcome was found in all 25 (100%) patients who had no or only mild mental deterioration at presentation, including four in the late-treatment group but in only three of the 12 patients who had had marked or severe deterioration before treatment.

Conclusions: Early treatment of cryptogenic infantile spasms with a high-dose ACTH protocol is associated with favorable long-term cognitive outcomes. Once major developmental regression lasts for a month or more, the prognosis for normal cognitive outcome is poor. Further studies are needed on the optimal treatment regimen for this disorder. Key Words: Cryptogenic infantile spasms—ACTH—Prognosis.
Drug Price Soars from $1,650 to $23,000 Per Vial To Treat Babies with Infantile Spasms

September 17, 2007 -- Reston, VA and Boston, MA

When the price for a single vial of medication used to treat infantile spasms (IS), a rare form of epilepsy, went from $1,650 to $23,000 the immediate reactions in the medical community ranged from anger and shock to relief that a company was going to keep the drug on the market.

The drug in question, manufactured by Questcor Pharmaceuticals, Inc. www.questcor.com, is called H.P. Acthar Gel®, a natural form of adrenocorticotropic hormone (ACTH). While it is the drug of choice in the United States for this devastating condition, which affects about 2,000 babies a year between the ages of 3 months and 9 months in the US alone, it is not approved by the Food and Drug Administration (FDA) for IS.

Steve Cartt, Executive Vice President for Corporate Development at Questcor, said: “The main reason that we moved Acthar to more of an orphan-style pricing model -- and we recognize that it is a fairly dramatic move – was to make sure that the product continues to be available for patients for the long term.”
Transcranial Magnetic Stimulation?
Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat.


Rotenberg A, Muller P, Birnbaum D, Harrington M, Riviello JJ, Pascual-Leone A, Jensen FE.

Department of Neurology, Children's Hospital, Harvard Medical School, 300 Longwood Avenue Fegan 9, Boston, MA 02115, USA.

OBJECTIVE: To test the anticonvulsive potential of a range of repetitive transcranial magnetic stimulation (rTMS) frequencies by novel methods for simultaneous EEG and rTMS in a rat seizure model.

RESULTS: KA-induced seizures were abbreviated by 0.75 Hz (P=0.019) and 0.5 Hz (P=0.033) active EEG-guided rTMS. In contrast, neither active 0.25 Hz rTMS nor the control conditions affected seizure duration (P>0.2).

CONCLUSIONS: We demonstrate that EEG-guided rTMS can suppress seizures in the rat KA epilepsy model, and that the effect is frequency dependent, with 0.75 and 0.5 Hz rTMS being superior to 0.25 Hz rTMS.

SIGNIFICANCE: These data support the use of rat seizure models in translational research aimed at evaluation and development of effective rTMS anticonvulsive protocols. We also offer a proof of principle that real-time analysis of EEG can be used to guide rTMS to suppress individual seizures.
Twelve patients with comorbid posttraumatic stress disorder (PTSD) and major depression underwent repetitive transcranial magnetic stimulation (rTMS) to left frontal cortex as an open-label adjunct to current antidepressant medications. rTMS parameters were as follows: 90% of motor threshold, 1 Hz or 5 Hz, 6,000 stimuli over 10 days. Seventy-five percent of the patients had a clinically significant antidepressant response after rTMS, and 50% had sustained response at 2-month follow-up. Comparable improvements were seen in anxiety, hostility, and insomnia, but only minimal improvement in PTSD symptoms. Left frontal cortical rTMS may have promise for treating depression in PTSD, but there may be a dissociation between treating mood and treating core PTSD symptoms.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2002; 14:270-276)
12 yo girl with autism

- Almost complete lack of speech, which did not progress while other symptoms were improving over time
- Staring spells
- Improved speech was observed with the addition of lamotrigine after SPECT scan performed
6 yo boy with autism

- Slow to progress with standard biomed
- However, did respond to anti-inflammatories
- Severe refractory self-stimulatory behavior
- SPECT performed due to slow progress
- Improvement in speech and almost complete cessation of stimming with Gabapentin
6 yo girl with autism

• Had essentially no words
• Significant self-stimulatory behavior, very mild OCD
• Somewhat hyperactive
• Very slow to improve with basic biomedical treatment
• Increase in hyperactivity with HBOT that went away after ~20 sessions
3 yo boy with autism

- Significant obsessive-compulsive behavior, severe self-stimulatory behavior, and hyperactivity
- Speech delay, stuttering, searching for words
- “Ring of fire” pattern on SPECT and seizure foci
- Large improvement in speech with lamotrigine
3 yo boy with autism

• In this child, copro level doubled on lamotrigine, but preco and other porphyrin levels did not change significantly

• Child also has PANDAS, had large improvement with weekly Azithromycin
7 yo boy with autism

- Speaks in sentences
- Occasional starting spells
- Some self-stimulatory behavior
- Extreme anxiety
- SPECT scan shows seizure focus and also significantly increased activity in the basal ganglia, often seen with anxiety patterns
CNS Anti-inflammatories

• Things active in the gut may not cross into the brain, ie: 5-ASA (sulfasalazine) type meds.
• Nonsteroidals may work but at the risk of further worsening esophagitis and gastritis.
• Steroids may be effective but long term problems limit use.
• IVIG often effective but expensive and insurance coverage limited.
• Novel Agents; Pioglitazone (Actos), Nicotine, Galantamine, Spironolactone, Minocycline and others.
Carnosine, a precursor of histidine, ameliorates pentylenetetrazole-induced kindled seizures in rat.


Wu XH, Ding MP, Zhu-Ge ZB, Zhu YY, Jin CL, Chen Z.

Department of Pharmacology, School of Medicine, Zhejiang University, Hangzhou 310031, China.

Carnosine (beta-alanyl-l-histidine) has been characterized as a putative neurotransmitter. However, so far, understanding of the role of carnosine in the brain is very limited. The objective of this study was to examine the effects of carnosine on the development of pentylenetetrazol (PTZ) kindling seizures and protection against the PTZ kindled seizures in rats. Injection of carnosine (200, 500 mg/kg, i.p.) significantly decreased seizure stage, and prolonged the latencies for myoclonic jerks, in a dose- and time-dependent manner. In the seizure development process, 500 mg/kg carnosine also significantly delayed the onset of PTZ kindled seizures. These results indicate that carnosine can protect against PTZ-induced seizures in both the development of kindling and the challenge process in rats. The results suggest that carnosine might be an endogenous anticonvulsant factor in the brain and can be used as a new antiepileptic drug in future.
Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders.


Chez MG, Buchanan CP, Aimonovitch MC, Becker M, Schaefer K, Black C, Komen J.

Research Division, Autism and Epilepsy Specialty Services of Illinois, Ltd, Lake Bluff, IL 60044, USA. mchezmd@interaccess.com

L-Carnosine, a dipeptide, can enhance frontal lobe function or be neuroprotective. It can also correlate with gamma-aminobutyric acid (GABA)-homocarnosine interaction, with possible anticonvulsive effects. We investigated 31 children with autistic spectrum disorders in an 8-week, double-blinded study to determine if 800 mg L-carnosine daily would result in observable changes versus placebo. After 8 weeks on L-carnosine, children showed statistically significant improvements on the Gilliam Autism Rating Scale (total score and the Behavior, Socialization, and Communication subscales) and the Receptive One-Word Picture Vocabulary test (all P < .05). Improved trends were noted on other outcome measures. Although the mechanism of action of L-carnosine is not well understood, it may enhance neurologic function, perhaps in the enterorhinal or temporal cortex.
Microglial Cells in Culture Express a Prominent Glutathione System for the Defense against Reactive Oxygen Species

Johannes Hirrlinger  Jan Mirko Gutterer  Lothar Kussmaul
Bernd Hamprecht  Ralf Dringen
Physiologisch-Chemisches Institut der Universität, Tübingen, Germany
Glutathione, oxidative stress and neurodegeneration

Jörg B. Schulz, Jörg Lindenau, Jan Seyfried and Johannes Dichgans

Neurodegeneration Laboratory, Department of Neurology, University of Tübingen, Germany
Neuronal Mitochondria Fuel Nerve Signal Impulses

Mitochondria

Synaptic vesicles

Synaptic cleft
Evidence of Mitochondrial Dysfunction in Autism and Implications for Treatment

Daniel A. Rossignol, J. Jeffrey Bradstreet
International Child Development Resource Center, 3800 W. Eau Gallie Blvd., Suite 105, Melbourne, FL 32934

Abstract: Classical mitochondrial diseases occur in a subset of individuals with autism and are usually caused by genetic anomalies or mitochondrial respiratory pathway deficits. However, in many cases of autism, there is evidence of mitochondrial dysfunction (MtD) without the classic features associated with mitochondrial disease. MtD appears to be more common in autism and presents with less severe signs and symptoms. It is not associated with discernable mitochondrial pathology in muscle biopsy specimens despite objective evidence of lowered mitochondrial functioning. Exposure to environmental toxins is the likely etiology for MtD in autism. This dysfunction then contributes to a number of diagnostic symptoms and comorbidities observed in autism including: cognitive impairment, language deficits, abnormal energy metabolism, chronic gastrointestinal problems, abnormalities in fatty acid oxidation, and increased oxidative stress. MtD and oxidative stress may also explain the high male to female ratio found in autism due to increased male vulnerability to these dysfunctions. Biomarkers for mitochondrial dysfunction have been identified, but seem widely under-utilized despite available therapeutic interventions. Nutritional supplementation to decrease oxidative stress along with factors to improve reduced glutathione, as well as hyperbaric oxygen therapy (HBOT) represent supported and rationale approaches. The underlying pathophysiology and autistic symptoms of affected individuals would be expected to either improve or cease worsening once effective treatment for MtD is implemented.
Mitochondrial Dysfunction May Play a Role in Autism Spectrum Disorders Etiology

Caroline Cassels

Medscape Medical News 2008. © 2008 Medscape

April 15, 2008 (Chicago, IL) — New research suggests mitochondrial dysfunction may play a role in the etiology of autism spectrum disorders (ASD) in a subset of this patient population.

Here at the American Academy of Neurology 60th Annual Meeting, a retrospective analysis of 41 children with ASD who were being evaluated for suspected mitochondrial disease showed that 32 (78%) had defects in skeletal muscle oxidative phosphorylation (OXPHOS) enzyme function and 29 of 39 (74%) harbored abnormalities in the OXPHOS proteins.

"We're very excited by these findings, and, based on these results, we will continue to pursue this [mitochondrial dysfunction] as a potential cause in a segment of the autistic population," principal investigator John Shoffner, MD, owner of Medical Neurogenetics, in Atlanta, Georgia, told Medscape Neurology & Neurosurgery.
Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

Jacqueline R. Weissman1, Richard I. Kelley2, Margaret L. Bauman3, Bruce H. Cohen4, Katherine F. Murray5, Rebecca L. Mitchell6, Rebecca L. Kern2, Marvin R. Natowicz1,4,5,6,*

1 Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, Ohio, United States of America, 2Department of Pediatrics, Johns Hopkins University Medical Center and Division of Metabolism, Kennedy Krieger Institute, Baltimore, Maryland, United States of America, 3 Department of Pediatrics and Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS), Massachusetts General Hospital, Boston, Massachusetts, United States of America, 4 Neurological Institute and Pediatrics Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, 5 Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America, 6 Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, United States of America

Abstract

**Background:** Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

**Methodology/Principal Findings:** We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex II (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

**Conclusions/Significance:** Although all patients’ initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These and prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.
Relative Carnitine Deficiency in Autism


Pauline A. Filipek,1,2 Jenifer Juranek,1 Minh T. Nguyen,1 Christa Cummings,1 and J. Jay Gargus1,3,4

A random retrospective chart review was conducted to document serum carnitine levels on 100 children with autism. Concurrently drawn serum pyruvate, lactate, ammonia, and alanine levels were also available in many of these children. Values of free and total carnitine (p < 0.001), and pyruvate (p = 0.006) were significantly reduced while ammonia and alanine levels were considerably elevated (p < 0.001) in our autistic subjects. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, is suggestive of mild mitochondrial dysfunction. It is hypothesized that a mitochondrial defect may be the origin of the carnitine deficiency in these autistic children.

Significantly increased NH3 and Alanine with mild increase in Lactate = Mitochondrial Dysfunction
Increased excretion of a lipid peroxidation biomarker in autism.
Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC.
Department of Neurosciences, UMDNJ-New Jersey Medical School, Newark, 07103, USA.

Fig. 1. Urinary excretion of isoprostane and 8-OHdG in children with autism and controls. *P<0.05, Student’s t-test.
Oxidative Biomarkers and Treatment

- **Isoprostanene** = oxidized fatty acid membranes
- **8 OHG** = oxidized RNA
- **Biopterin** = oxidation due to inflammation
- **Neopterin** = immune activation which will lead to oxidation
- **Cysteine and Glutathione (Methionine)** deficiency
- **Porphyrrins** = coproporphyrin may rise from oxidation not just metal related events.
- **Ammonia & lactic acid** link to mito dysfunction
- **Dysbiosis** markers may impact these issues too.
Mitochondrial Cocktail

- D-Ribose: generates ATP via a bypass of the pentose phosphate shunt pathway. ATP = energy storage.
- B Vitamins
- Acetyl L Carnitine: Fuels CNS mitochondria better than plain carnitine.
- UBQH: more active form of CoQ10, a facilitator of mitochondrial activity.
- Antioxidants: protect mitochondrial OXPHOS
- Multiple small feedings per day – no large meals – constant supply of energy
- Moderation of protein intake – expensive for cells to get rid of extra ammonia.
## Antioxidant Effect per 1 gram of whole food

<table>
<thead>
<tr>
<th>Food</th>
<th>Antioxidant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscadine Grape Seed**</td>
<td>559</td>
</tr>
<tr>
<td>Acai*</td>
<td>387</td>
</tr>
<tr>
<td>Goji Berry*</td>
<td>253</td>
</tr>
<tr>
<td>Noni*</td>
<td>151</td>
</tr>
<tr>
<td>Pomegranates*</td>
<td>105</td>
</tr>
<tr>
<td>Raspberries*</td>
<td>82</td>
</tr>
<tr>
<td>Blueberries*</td>
<td>77</td>
</tr>
<tr>
<td>Red Grapes*</td>
<td>74</td>
</tr>
<tr>
<td>Prunes*</td>
<td>57</td>
</tr>
<tr>
<td>Cherries*</td>
<td>67</td>
</tr>
<tr>
<td>Strawberries*</td>
<td>36</td>
</tr>
</tbody>
</table>


Take Home Message: Part 1

• ASD is associated with both brain inflammation & seizures.
• Early control of inflammation and resulting oxidative stress may improve outcome and reduce the risk of seizures.
• Various anti-inflammatory (steroids, IVIG, etc) have been reported to help both autism and seizures.
• Nutritional support is important in both ASD and Seizures. Carnosine may be protective in both.
• AED may promote inflammation.
Take Home Message: Part 2

• Fatty Acids Omega 3 and 6 especially if given with NSAID or COX-2 agent may reduce inflammation and seizures.
• Vitamin D is important in epilepsy to prevent bone loss from both KD and AED medication.
• Magnesium, Zinc, Folate, B6 & B12 may reduce side-effects of medication and decrease seizures.
• Avoid MSG and Excitotoxins in Food.
• Gluten can increase the risk of seizures in certain at risk populations (Celiac).
Seizure Issues in Autism Spectrum Disorders

Jeff Bradstreet MD, MD(H) FAAFP

&

Dan Rossignol, MD FAAFP

Florida, California, Oslo & Dubai

321-259-7111

www.icdrc.org