

THE MEDICAL
MANAGEMENT OF
AUTISM

Current and
Theoretical Future Treatments

by

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Disclosures

- Consultant
Forest Laboratories; Inventor Patent
Memantine in Autism
- Speaker
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Autism: Definition

- Clinical Definitions based on observations

- 3 Core Problems:

- Communication;
Socialization;
Stereotypic Behaviors



Autism

- State of California shows increasing diagnosis and service utilization as of 2007-2010 still
- Now > 1:110 births; > 1:80 boys born
- 3/1000 autism, 7 /1000 autistic spectrum
- Cost \$3.5 million per child over lifetime

MEDICAL DEFINITION: Descriptive in DSM; Clinically Lumping vs. Splitting

- TYPE OF AUTISM CLINICALLY
- LOW or HIGH FUNCTIONING
- PRIMARY or SECONDARY TYPE
i.e. is there an underlying or prior medical reason
- REGRESSION or NON-REGRESSION
- CO-MORBID ISSUES: Sleep GI
Immune; Epilepsy; Sleep; Psychiatric

MEDICAL FACTS

- No Current Single Cause
- Multifactorial Theories
- Heterogenous Condition

Medical Facts

- EEG factors: Abnormal/ Normal
- Epilepsy 10-30%
- Immune Markers? Toxins?
- Neuroanatomical Studies Still Limited
- Brain Imaging Findings: functional and static imaging Evolving
- Genetics/ Environment
- Comorbid Facts
- Cognitive Abilities

AUTISM SPECTRUM

- Autism is clearly a clinical spectrum disease much like cancer or dementia not all being exactly from one cause
- In other words not all cases look or act the same
- Therefore no single treatment or behavior strategy will apply to all children with the label

Autism Spectrum

- Caution with “Cookie Cutter” Approach for everyone
- Big clinical differences from low and high functioning, with or without mental retardation, with or without seizures, etc.

Prenatal Factors

- Genetic
- Immune
- Environmental
- In Vitro? In Utero
- Infection and When
- Complication of Pregnancy
- Gestational Age

Genetics

- Genetics study features and link these to chromosome data
- Phenotype: Clinical patterns that describe genetic condition
- Genotype: Actual chromosomal data that correlates to patient genes. May or may not always match phenotype, variants occur, more than one genotype for a phenotype can occur in autism

Genetics

- Have studied twins
- Have studied other diseases with autistic similarities: Angelmann's, Williams, DiGeorge, Smith-Lemli Opitz, tuberous sclerosis, and others
- Also Fragile X and Retts
- These diseases are unique and different than idiopathic autism

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Genetics

- So far > 22 genes have been linked in studies to autism
- There are other genes on the X, 17, 22, 1,7,15, 16, MECP2, MET gene, and other chromosome gene sites
- Family histories of immune or psychiatric conditions
- These genetic findings support a multifactorial problem
- Retroviral Genetics?

Genetics

- Microarrays show numerous changes to genes and are new technology offered
- These chips find 5-10% may have new spontaneous mutation
- There are some that may double the risk of autism related to the immune system on chromosome 6; MET gene
- Recent work 104 families of middle east decent (Parents first degree relative) had 8% abnormalities: genes affecting synapse formation; 5 with sodium channels, 1 child had deletion

Genetics

- Conclusion: Complex
- Not one-gene-one disease
- May not yield single therapy except in cases like perhaps Fragile X (Seaside Pharmaceuticals drug as example)
- More studies on autism and genetics in past decade than any other area of hard science, > 10,000 articles

Environment

- May have environmental factors
- In utero: Infection, immune issues, medications
- Extra-utero: In vitro, toxins, pesticides, heavy metal?, other factors
- Deprivation: Orphanages

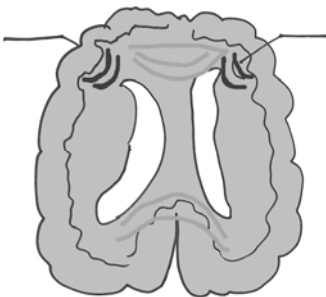
Neuroimaging, Neuroanatomy

- Routine Clinical MRI not very informative in most cases
- Research over the years has implicated various regions
- Cerebellum; Temporal Region; Atypical or poss of asymmetries
- White matter thickening, Accelerated Head Growth, Regional Loss of Neurons or Asymmetry

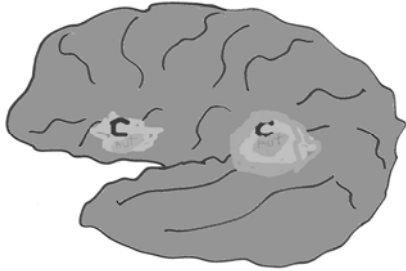
Functional Neuroimaging

- SPECT Inconclusive overall; sleep studies with EEG abnormalities do correlate 80% of time; Possible microvascular issues
- PET: Again inconclusive to date
- MEG: Possible decrease in sylvian fissure or atypical occult spikes
- fMRI: Atypical activation
- Mirror Neurons

Brain Schematic U fibers thicker



fMRI Differences in Activation:
Yellow (Control)/ Green (Autism)



Neuroanatomy

- Findings so far are limited to few brain samples available, may not represent the entire current spectrum
- See Purkinje cell and pontine changes/ retrograde changes?
- Hypercellular and abnormal temporal regions
- Neuroglial changes

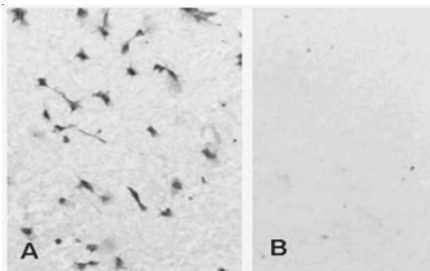
Neuroanatomy

- Differences in Receptors:
- Perry in England found decreased frontal and parietal nicotinic (alpha and beta) and frontal M1 & parietal muscarinic M2 receptor density in Autistic Brain (*Perry, et al 2001*)
- Excess Glutaminergic activity in Brain Tissue
- AMPA excitation and signaling (Frag X)

Neuroimmunology

- Since that time there is now evidence of elevated cytokine inflammation and neuroglial activation in some autistic tissue and CSF samples.
- Elevated TNF-Alpha, TNF-Alpha R1 receptors, MCP-1, IL-1, IL-6
- Prior CNS anti-bodies against capillary lining tissue and Anti-BDNF

Anti-CNS Antibodies: A =autism
B=control serum



Role of Innate Autoimmune Neuroglial System

- This may be primary or secondary pathological factor
- May affect neuromigration or development; Synaptogenesis
- NMDA receptors may be important end-stage of glutamate damage to neurons
- Cholinergic nicotinic receptors now thought to be involved in potential repair mechanism of white matter damage due to inflammation

Do Vaccines Cause Autism

- Probably not directly; Not as claimed in lay public
- Can autoimmune issues that are present in mother in utero or in infant predisposed yield aberrant response in innate neuroglial reaction: Perhaps
- Mercury not likely the causes for vaccine issues
- Perhaps underlying /immune issues also

Neuroimmune System

- Potential Future Treatment Target
- May Represent Major Source of Autism Epidemic Increase
- Theoretically May be 30-40% clinical cases; Regression; Recurrence in Families?
- More on Treatment Later

Electrophysiology and Autism

- 1943 Kanner patients 3/11 had seizures
- Also Subsequent studies show 10-30% of patients develop seizures in lifetime
- If seizures present 60-80% may have EEG abnormalities
- What about patients who are under age 5 years? What about regression?

EEG and Autism Spectrum

The Clinical Need for an EEG in Children with Language Developmental Delays and Pervasive Developmental Disorders or Autism:

What Does an Abnormal EEG Potentially Mean?

EEG and Autism Spectrum

- EEG abnormalities may represent dysfunction or inflammation causing epileptogenesis
- EEG abnormalities may represent GABA deficits or Glutamate excess
- EEG abnormalities may be part of a spectrum of clinical presentation/ worsen morbidity

EEG and Autism Spectrum

- A relationship between regressive PDD and epileptiform disorder was suggested in 1997 by Tuchman and Rapin
- Tuchman and Rapin (1997) saw centrotemporal spikes in children with language regression, regardless of the presence of epilepsy.
 - no differences in the localization of EEG discharges in AR and epilepsy.
- Rapin reported that by adulthood, 1/3 of those with autism will develop epilepsy
 - Risk peaks in adolescence

EEG and AUTISM/ MEG Findings

- Lewine et al. studied 50 children with AR or LKS in 1999 using MEG
 - Abnormalities found in 93% with AR and epilepsy
 - Abnormalities found in 77% with AR and no epilepsy
 - Primary or secondary sites of activity in the intrasylvian and perisylvian regions
 - Multifocal abnormalities observed in 75% of AR patients.
 - MEG Localization May predict Treatment Response to EEG treatment with Steroids (Lewine and Chez 2009).

EEG and Autism

- 2007; 2009: Spence et al at NIH show high percentage of sleep abnormalities in young Children > 50% (about 100 children)
- 2006: Chez, et al show abnormal rate at least 61% over 10 year study in 889 children with autism or PDD-NOS Largest Study to date)
- Chez 2007 presents 60% abnormality rate in PDD-NOS and autism, around 80% PDD-NOS; 45% Autism in kids under 6 years (N=50)

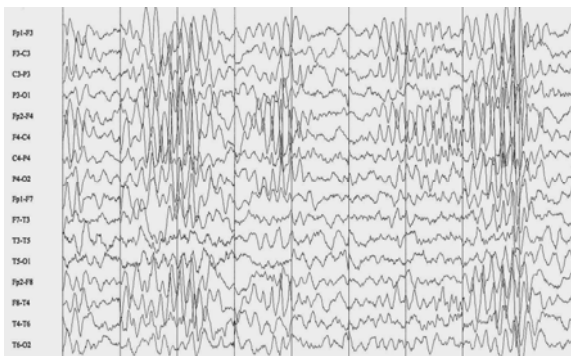
Treatment of EEG Abnormalities

- Studies by Hollander et al in autism shows benefits in behavior, however no EEG correlation
- Treatment with Valproate
 - Pliopys in 1994 described it to be possibly effective in improving language and social skills in children with autism and abnormal EEGs.
- Chez, et al shows several studies with EEG correlation of clinical and EEG response
- Studies in Benign Focal epilepsy and Temporal Lobe epilepsy show cognitive gains treating EEG (Kossoff et al 2009)
- Future: Treatment with Valproic Acid placebo controlled study planned Autism Treatment Network/ Multi-center Study

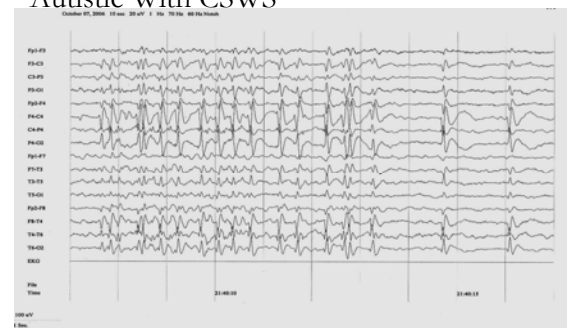
Spikes in Autism



Spikes in Sleep



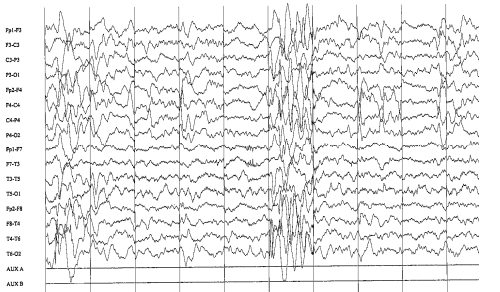
Recent Autistic With CSWS



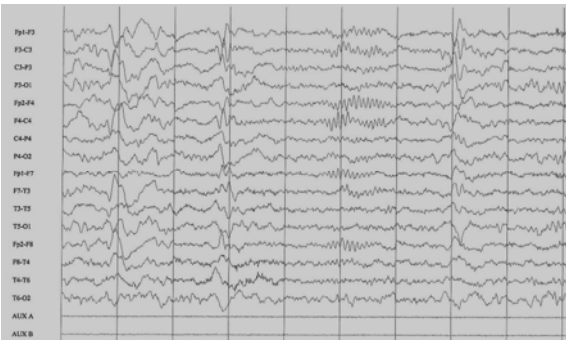
Treatment Results

- Chez, et al 2006
- 176 patients treated with valproic acid formulations after first abnormal EEG.
 - Normalization in 82 (46.6%)
 - Improvement without normalization in 30 (17.0%)
 - No change in 64 (36.3%).
 - None worsened by follow-up overnight EEG.
 - Performed on average 10.1 months after first study

Autism Pre-Treatment



Autism Post-Treatment With Valproic Acid: Normalized Sleep EEG



EEG and Autism

- The data should encourage early screening of patients with ASDs using prolonged sleep EEGs
- It should dispel the myth that children with ASDs cannot participate in prolonged EEG studies
- Treatment can change EEG and Behavioral Outcomes and Language Core Issue

Medical Management: Goals

- No Cure, Quality of Life and maximize function
- Need to assess Individually
- Core Symptoms:
 - Language/Communication
 - Behavioral Issues
 - Socialization

Medical Management of Autism

- Clinically assess subtype of autism
- Regression or not
- Behavioral Problems to be addressed
- Family History: Psychiatric, Autoimmune
- Comorbid Issues: Immune, GI, Sleep
- Seizures or epileptiform EEG
- Genetics
- Prior Treatments tried

Medical Treatments

- Clinical Model: Assessment First
- History and Physical
- Genetic Screening where appropriate:
Fragile X, Karyotype, microarray, mitochondrial genetics
- Overnight sleep EEG
- Medical Laboratory data as needed: General labs and metabolic(rare)

Medical Assessment: Present and Future

- Neuroimaging: MRI most common usually normal
- May in future do more lumbar punctures:
- Study CSF for Neurotransmitters, folinic acid deficiency, amino acids, inflammatory markers in future may be standard procedure; Serum immune or maternal immune studies?
- Cell typing/genotyping?? Future possibilities for Stem cell therapies?

Medical Management

- If EEG abnormal, do MRI
- If EEG abnormal consider medical treatment options: such as Valproic acid etc. Studies in autism to support trials of valproic acid, more in progress soon
- Once try this establish clinical and EEG improvements
- Need to keep levels high therapeutic with valproic acid for example(90-110mg/ml)
- Aim to improve EEG; Improve moods and receptive language observed goals to date

Medical Management: Language

Core Symptom

- Speech Therapy Is Standard
- Language: May improve with treatment of abnormal EEG
- Receptive language first response with valproic acid
- May improve with L-carnosine Published study receptive language gains
- May improve with certain medications that treat Alzheimers currently: Acetyl Choline esterase inhibitors or NMDA Antagonists may help expressive and receptive language

Medical Management

- Use of these medications are currently being considered off-label as autism language therapy.
- Memantine being studied in double blind fashion for FDA approval currently
- Prior Double blind placebo controlled studies in literature for donezepil, and L-Carnosine
- Open label studies for memantine, rivastigmine, donezepil, amantidine, and others

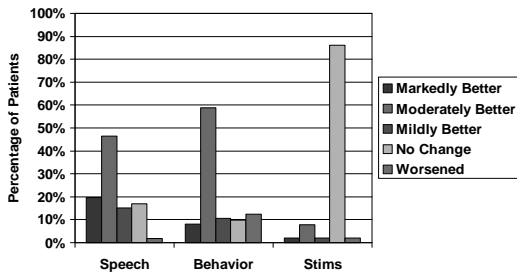
NMDA Receptors

- Possible Glutamate excess in autism
- NMDA mechanisms in epilepsy
- Many children in spectrum have epileptic spikes on EEG or clinical epilepsy
- Perhaps NMDA could play a role modulating behaviors; Neuroprotective?

NMDA RECEPTOR

- NMDA may play a role in neuroglial activation
- May modulate some cytokine activity and in turn be modulated by some cytokine
- Important in neuronal migration and Synaptic Formation
- End point of glutamate regulation in inflammation

Clinical Experience: M. Chez, MD Efficacy: CGI- Autistic Patients



Memantine and NMDA

- Studies to develop for FDA approval in progress. Still many physicians are using off label for now
- Other new data for anxiety, OCD: Riluzole another NMDA antagonist is being studied.
- D-cycloserine, amantidine, dextromethorphan
- High Dose N-acetyl Cysteine As Add On Therapy also

Treatment of Autism/ Aggression and Irritability

- Behaviors of aggression and agitation:
- Also tics and anxiety and OCD or "manic" symptoms
- Use of atypical antipsychotics; previously used older antipsychotics
- Risperidone and aripiprazole have FDA approval
- Other atypicals also useful, these all block various dopamine receptors and some agonist/antagonist for dopamine and serotonin too.
- Biggest Risks are Metabolic and weight gain issues

AUTISM: Aggression and Irritability

- Future
- Ar-Baclofen affects GABA receptor selectively
- Studies in Fragile X and Autism underway
- Suggest improved irritability and anxiety
- Fenobam therapy and other future AMPA Receptor agonists (fragile X) may also help behaviors
- All undergoing phase 2 and phase 3 studies

Anxiety, Depression

- Mainly use SSRIs
- Some benefit mainly at low dose, higher doses tend to activate or induce manic type or agitated behaviors in autism
- OCD usually better managed with atypical antipsychotics, perhaps NMDA drugs, as SSRIs have only had limited success overall in autism population,
- SSRIs may work better in Asperger or high functioning group

MOOD Disorder/ Bipolar Type in ASD

- May need > 2-3 medications
- May need atypical antipsychotic
- May need Mood stabilizer VPA, Lithium, Lamictal, Carbamazepine
- May need SSRI or Stimulants sometimes
- Sleep Aids too

ATTENTION

- Troublesome
- Sometimes language deficit, auditory processing issue
- Sometimes opposite effects with stimulants or atomoxetine
- Stimulants perhaps 30-40% affective, again better in higher functioning older group and Aspergers overall in my and others experiences
- Clonidine, Tenex also have role sometimes

GI Issues

- Most patients with autism have not got sensitivity to milk or wheat or gluten, very rare actual issues.
- However some do have rare food allergies, spastic colon, encoporesis, GE reflux, and also lactose intolerance
- Prudent pediatric care or referral for GI specialty care is important if symptoms are present

GI Issues

- Rigidity about textures, sensory issues, poor diet for meats etc can yield iron deficiency which can cause problems.
- Gluten Casein Diets need to be carefully monitored for nutrition as well as problems with various high dose vitamin supplementation
- Appetite suppression can occur with certain megavitamin therapy, Mg toxicity etc.
- Dietician monitoring these diets is essential
- Variation on low or complex carbohydrate diets may be mechanism

Sleep Issues

- > 50% can have sleep issues
- Onset and maintenance issues occur for sleep
- EEG abnormalities can occur
- If wake up screaming in first couple hours possible night terrors, later in evening of sleep could be seizures

Sleep Issues

- Onset treatment: Melatonin, clonidine, tizanidine, rozerem
- Hyponotics less desired
- Maintain sleep: Make sure not restless legs, iron/ferritin deficiency
- If not seizure or sleep apnea or restless legs may be lack of deep sleep as seen in other psychiatric conditions

Sleep Issues

- May need medications for anxiety or depression
- May need medications that change sleep cycles: Tricyclics, Gabapentin, others
- Obviously sleep behavior modifications are included as first steps to any sleep problem
- EEG or polysomnogram may be helpful

IMMUNE THERAPY

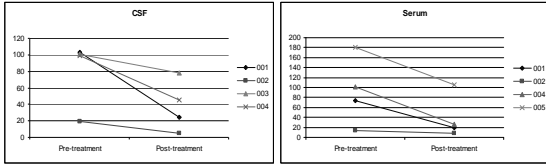
- Corticosteroids
- IVIG
- Future: Targeted drugs for cytokines
- One study lenalinamide shows promise so far(Chez et al 2010)
- Stem Cell Therapy

TNF-Alpha

- Chez, MG et al 2007 show that TNF-alpha in CSF vs. Serum is elevated
- Current Research looking at TNF-alpha inhibitor in autism
- Lenalinomide(Revlimid)
- 6 ADOS proven autism patients open label
- Treat 2.5 mg daily for 12 weeks
- All patient had regression autoimmune family history, elevated CNS or serum cytokines
- 1 had abnormal EEG

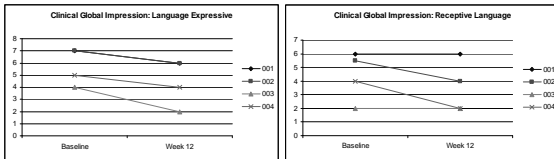
Results

■ TNF-alpha



Results

■ Clinical Global Impression



Future Treatments

- Again more updates on NMDA receptors
- Immune Mechanisms: Prenatal diagnosis of at risk mothers or early screening for those at autoimmune risk
- Treatment for those with regression or autoimmune cytokine markers? Recent Data published by Chez et al showing improvement with lenalinomide therapy in FDA phase 2 trial with regression and immune markers
- Stem Cells/ Targeted immune therapy

Future Treatments

- Treatments to reverse genetic defects specific in Fragile X; Rampamycin therapy
Tuberous Sclerosis
- Neurotransmitter problems, folinic acid therapy; Tetrahydrobiopterin
- Socialization: Possible Effects Oxytocin or even Vasopressin Not yet commercially testing

Medical Management Conclusions

- Autism is Spectrum Disorder
- Not one type of treatment
- Future treatments will look at core mechanisms or reversal of genetic or environmental factors
- Current therapy aimed at quality of life
- Early medical interventions aid other therapeutic and educational efforts

Conclusions

- EEG abnormalities are common in Autism Spectrum Disorders
- Treatment May Change Quality of Life/ Offer Potential Seizure or Neuroprotection
- NMDA Receptors and Glutamate Modulation may be important Therapeutic targets

Conclusions

- Cytokine elevation and modulation may offer clinical treatment target and change outcomes: More research critical on this aspect innate neuroimmune system
- More research desperately needed for effective intervention strategies based on these findings: Genetic; Stem Cells

Dr. Chez's Book JKP 2008

