PANDAS – PANS Autoimmune Disorders That Impact the Brain

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Sydney, Australia

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Overview

- Assessment
 - Autoimmune Disorders
 - PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep)
 - PITANDS (Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders)
 - PANS (Pediatric Acute-Onset Neuropsychiatric Syndromes)
 - Post-streptococcal Autoimmune Encephalitis (of the basal ganglia)
- Treatment



Autoimmune Disorders The Basics

- "Friendly Fire"
- Immune cells target and attack body's own tissues
 - Normal body substance altered by virus, drug, radiation and appears foreign
 - Molecular mimicry
 - Ability of strep antigen to mimic myosin (RF)
 - Best example of post infectious autoimmunity due to molecular mimicry (Sydenham chorea)
 - Cunningham, 2000, M, Clin Microbiol.

Rheumatic Fever

- Streptococcal M protein juts from strep surface, prevents WBC from engulfing, destroying bacteria
- Human immune system coats M protein with antibodies -> summons WBC attack to destroy strep
- Abs that react to M protein also react to myosin in heart (M protein look alike)
- White cells attack both -> autoimmune disease
 - Galvin et al, 2000, *J Clin Invest*.

Examples of Autoimmune Disease

- Thyroiditis (Grave's, Hashimoto's)
 - 1st Autoimmune disease (1912)
 - Prasad's (Hashimoto's presenting as mania)
 - Physical illness with "mental symptoms"
- IDDM, Type I (virally attacked beta cells; Nature Imm, 2002)
- SLE (Hahn et al, 2008, Kelley's Textbook of Rheumatology)
- Myasthenia Gravis (Block acetylcholine receptors; Patrick et al, 1973, Science)
- Sydenham chorea (Abs signal neuronal cells to release DA; Kirvan,2003, Nat Med)
- PANDAS (Abs to basal ganglia; Kurlan et al, 2004, *Pediatrics*)
- PITANDS (Allen et al, 1995, J Am Acad Child Adol Psych)

PANDAS

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep

- Diagnostic Criteria (Swedo et al, 1997, Am J Psychiatry)
 - Acute onset of OCD, tic disorder
 - Pediatric onset of symptoms (prepubertal)
 - Episodic course of symptom severity (relapsing and remitting)
 - Association with Group A Beta-hemolytic strep
 - Association with other neurologic abnormalities (motoric hyperactivity, choreiform movements (piano playing fingers), separation anxiety, NOT chorea)
 - Diagnosis based on symptoms; can be high ASO, AntiDNase
 - Temporal relationship of symptoms with GAS
 - Chmelik et al. 2004 Clin Pediatr

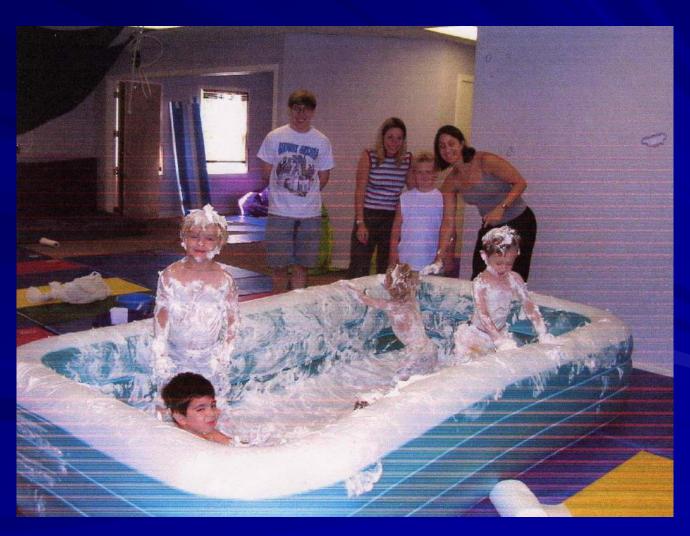
PANDAS – Diagnosis

- Sudden worsening of behaviors
- Not always history of recent strep (for many reasons)
- ASO and AntiDNase Ab may NOT be elevated
- Symptoms may include choreioform movements, tics, OCD, aggression, agitation, hyperactivity, emotional lability, anxiety, cognitive deficits, oppositional behaviors, ADHD
- Can be encephalitic in onset
- Often history of sinus/URI
- Boys outnumber girls
- Family history of autoimmune disease
 - Swedo, 2004, *Pediatrics*

Sites of Host Infection With Immune Stimulation

- Throat (rapid test high false negative rate)
- Tonsils (surface/core)
- Adenoids (surface/core)
 - Discordance between surface and core bacterial isolates (Internat J Ped Otorhinolar, 1987)
- Skin (eczema, psoriasis)
- Urinary Tract
- GI Tract
- Sinuses (cryptic, recalcitrant)

What lies behind us and what lies before us are small matters compared to what lies within us.



PANDAS - Controversy

- 79% peds would treat presumed strep infection w/o positive cx (Paluck et al, 2001, Can Fam Phys)
- Use of abx without objective laboratory evidence of infection could increase abx resistance (Gabbay et al, 2008, Pediatrics)
- Small # prospective studies (Murphy et al, 2004, Biol Psych)
- Ambiguity and skepticism in establishing GAS relatedness to OCD/tics (Murphy et al, 2010, J Child and Adol Psychopharm)

The Immunobiology of Tourette's Disorder, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus, and Related Disorders: A Way Forward

- OCD and related conditions including TD with associated immune dysfunction has been reported and debated in the literature since the late 80s.
- Grp A Strep assoc (Pro 9; Con 2; Inconclusive 2)
- ABGA (Pro 8; Con 3; Inconclusive 2)
- Immune tx (Pro 6; Con 2; Inconclusive 1)
- Immune markers (Pro 11; Con 2; Inconclusive -1)
- Animal studies (Pro 3; Con 2)
- Non-Group A Streptococcus pathogens (Pro 7; Con 1)

Association between Strep and OCD, TS, Tics (Mell et al, 2005, Pediatrics)

	Cases, n (%)	Controls, n (%)	OR	95% CI
All cases				
Strep within 3 mo of	fonset			
Any	12 (8.3)	24 (3.9)	2.22	1.05, 4.69
Strep within 1 y of c				
Any	32 (22)	78 (13)	1.91	1.20, 3.05
≥2	13 (9.0)	18 (2:9)	3.10	1.77, 8.96
OCD				
Strep within 3 mo of	fonset			
Any	2 (6.1)	3 (2.3)	2.66	0.54, 29.5
Strep within 1 y of c	onset			
Any	5 (15)	20 (16)	1.10	0.37, 3.26
≥2	1 (3.0)	4 (3.1)	1.21	0.12, 12.1
TS, no OCD				
Strep within 3 mo o	fonset			-
Any	3 (7.3)	6 (3.3)	2.21	0.45, 8.89
Strep within 1 y of c	onset			200
Any	6 (15)	20 (11)	1.20	0.44, 3.31
≥2	6 (15)	5 (2.8)	5.26	1.43, 19.3
Tic disorder only				
Strep within 3 mo o	fonset			
Any	7 (10)	15 (5.0)	2.03	0.77, 5.33
Strep within 1 y of c				
Any	21 (30)	38 (13)	2.81	1.52, 5.19
≥2	6 (8.6)	9 (3.0)	3.16	1.01, 9.83

Strep and OCD, TS, Tics

- Case-control study of children 4 to 13 years old receiving their first diagnosis of OCD, TS, or tic disorder between January 1992 and December 1999 at Group Health Cooperative outpatient facilities.
- Cases were matched to controls by birth date, gender, primary physician, and propensity to seek health care.
- Results Patients with OCD, TS, or tic disorder were more likely than controls to have had prior streptococcal infection (OR: 2.22; 95% CI: 1.05, 4.69) in the 3 months before onset date.
- Risk was higher among children with multiple streptococcal infections within 12 months (OR: 3.10; 95% CI: 1.77, 8.96).

PANDAS - Diagnosis

- Group A beta-hemolytic Streptococcus titer elevations were associated with worse performance on tasks of neurocognitive and executive ability
 - Stroop Color-Word Interference Test
 - Visuospatial memory
 - Fine motor speed (finger tapping)
 - Elevated obsessive-compulsive symptom severity
 - Lewin et al, 2011, J Neuropsych Clin Neurosci

Physical Exam Clues

- Strep (PANDAS)
 - Red anal ring
 - Peeling fingers

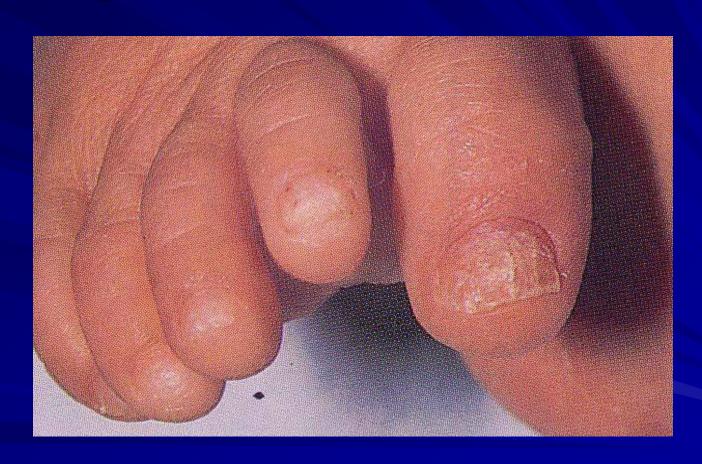


Physical Exam Clues

- Strep (PANDAS)
 - Red anal ring
 - Peeling fingers
- Infectious etiologies (PITANDS)
 - Skin findings (warts, molluscum, ringworm)
 - Peeling, wet rash
 - Tongue
 - Anal rash
 - Ridged nails

Peeling Feet

Ridged, Discolored Nails



Testing

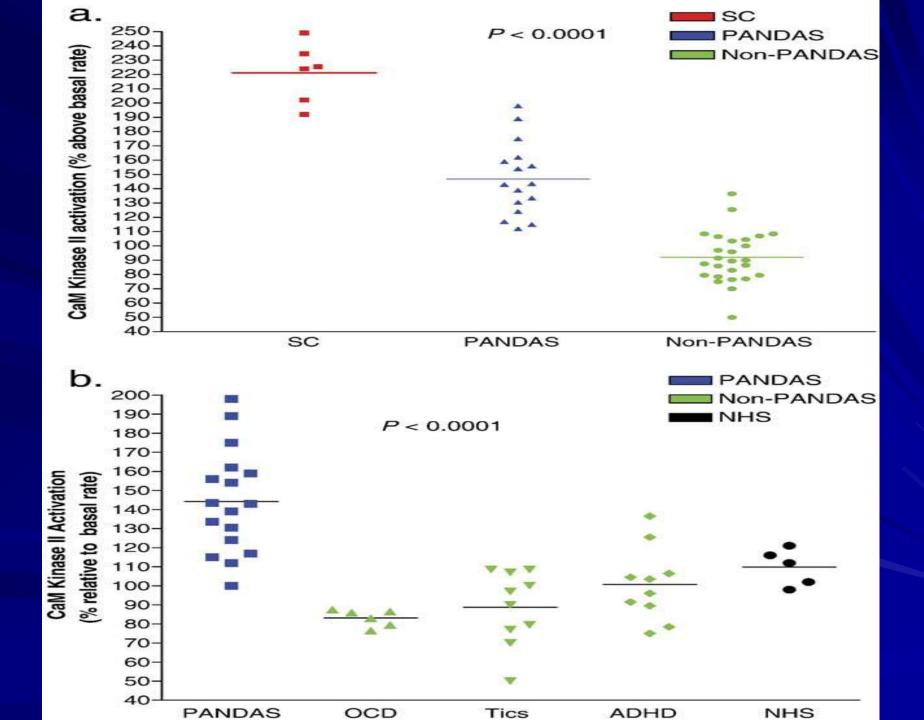
- Elevation ASO, AntiDNase Ab (repeat in 4-6 weeks)
 - Only ASO elevation assoc with increased risk of PANDAS/OCD (59% vs 3&%, p value = 0.03; Murphy et al, 2011, *J Peds*)
 - 150 children studied 38% with tics and high ASO vs 2% in control group (Cardona et al, 2001, J Peds)
- Autoimmune conditions decreased number of Tregs; 56% with positive ANA (Kawikova, 2007, Biol Psych)
- Difference between TD and controls in gene expression of IFN response, viral processing, NK and cytotoxic T cells (Lit et al, 2007, Am J Med Genet B Neuropsych Genet)
- Subgroup of Tourette's patients enhanced immunologic response to GAS antigens (Bombaci et al, 2009, PLoS One)
- D8/17 no longer molecular marker for genetic susceptibility so still trying to understand who is susceptible

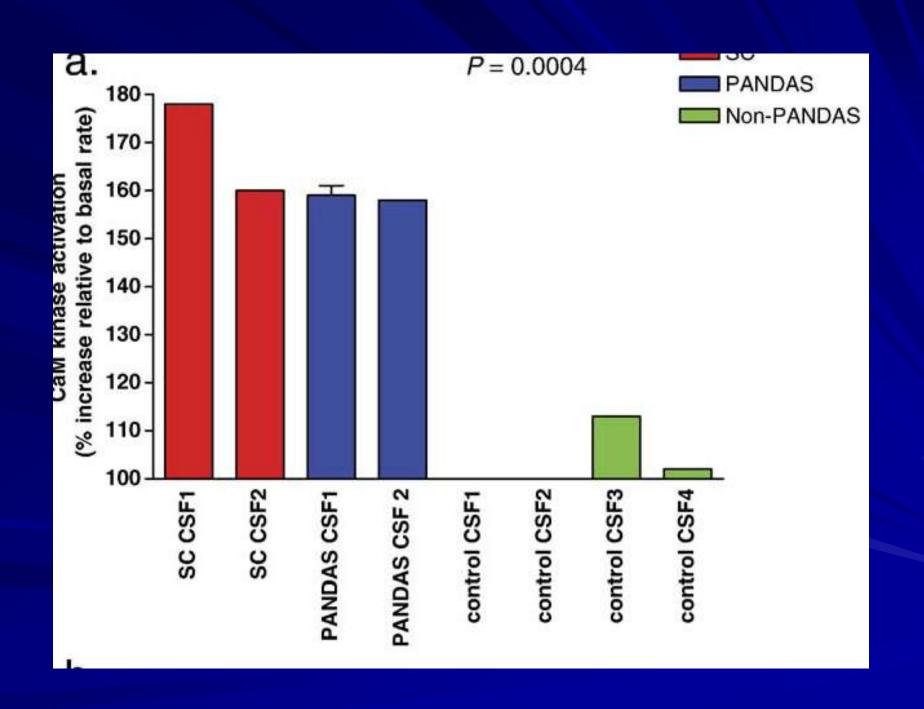
Further testing

- Basal Ganglia inflammation in children with neuropsychiatric symptoms increased activated microglial cells, suggesting underlying neuroinflammation, in bilateral caudate nuclei in children with PANDAS and TS; in bilateral lentiform nuclei in PANDAS patients only; differences in the pattern and extent of neuroinflammation signify a possible difference in pathophys between PANDAS and TS. (Kumar et al)
- AutoAb -> activate CaM kinase II -> increase DA release -> inhibit suppressive functions of Tregs -> autoimmune inflammation of basal ganglia -> further activation of immune cells and release of inflammatory mediators - -> tics, OCD, behavioral and movement issues
 - Cunningham et al, 2008, Cong of Neuroimm

Further Testing

- CaM Kinase testing (Ab induces increase in calcium/calmodulin-dependent protein kinase II – in both PANDAS and SC)
 - Ab fluctuates with OCD sx (Murphy, Biol Psych, 2004)
 - PANDAS and SC groups have high reactivity against DOPAMINE 2 receptors (D2 and D1)
 - Moleculara Labs If not classic clinical picture, then testing can be helpful in making diagnosis
 - If sick for long time, antibodies may be negative
- Inflammatory markers CRP, ESR, ANA
- PANDAS/PITANDS
 - Other germs mycoplasma, lyme extended western blot, culture
 - IgG from GAS-exposed rats injected into naïve rats ->behavioral/motor reactions, reacted with DA and ST receptors (Lotan et al)
 - Ab from PANDAS children injected into mice caused perseverative behaviors
 - (Kirvan et al. 2006. *J Neurolmm*)





Further Animal Model

- Rats exposed to GAS antigen exhibited motor symptoms (impaired food manipulation and beam walking) and compulsive behavior (increased induced-grooming).
- Symptoms alleviated by D2 blocker (haloperidol) and SSRI (paroxetine) used to treat motor symptoms and compulsions in PANDAS/PANS
- Streptococcal exposure resulted in antibody deposition in the striatum, thalamus, and frontal cortex; alterations in dopamine and glutamate levels in cortex and basal ganglia, consistent with pathophysiology of SC/PANDAS.
- Autoantibodies (IgG) of GAS rats reacted with tubulin and caused elevated CamKinase
 - (Brimberg et al. 2012. *Neuropsychopharmacology*)

PANDAS – TREATMENT

- Probiotics
- Xylitol
- Saccharomyces Boulardii/Alkalinization/Charcoal
- Antibiotics
 - IM Bicillin (1.2 million units-perhaps monthly)
 - Penicillin, Amoxicillin-Clavulanate, Azithromycin, Cefdinir, Clindamycin
 - Antibiotic Prophylaxis with Penicillin or Azithromycin
 - EKG with Azithromycin
- Antimicrobial herbs (Berberine, Neem, Banderol)

PANDAS - TREATMENT

- Immune Modulators (March et al, 2004, Arch Ped Adol Med)
 - Oral immunoglobulins (Schneider et al, 2006; Handen et al, 2009)
 - Minocycline (NIH study at 1.4 mg/kg, max of 50 mg bid; teeth discoloration; no significant improvements)
 - IVIG No improvements in sham IVIG group; significant decrease in OCD severity in IVIG and plasmaphoresis groups after 1 month (Perlmutter)
 - Plasmaphoresis (Snider LA, Swedo SE, 2004, Mol Psych)
 - Helminth therapy (<u>www.biomerestoration.com</u>)

Antibiotics

- Penicillin
 - 35% failure to eradicate Streptococcal infection (Casey et al, 2004, *Pediatrics*)
- Cephalexin; Cefdinir
 - Superiority over strep in post- strep illnesses (Hahn et al, 2005, Am Fam Phys)
- Amoxicillin/Clavulanate
 - Clavulanate affects DA and glutamate systems may not just be antibiotic effect
 - Increase in yeast overgrowth in susceptible children
- Azithromycin
 - Protection against other infectious agents (strep, staph, atypicals)
- Clindamycin
 - Anaerobes, Babesia, PCP
 - Snider et al, 2005, Biol Psych

Treatment

Steroids

- Short burst used therapeutically and diagnostically
- Temporary fix in some; need to do for 30 days
- Proves inflammatory reaction
- May increase inclination to continue antibiotics or pursue further treatment

Plasmophoresis

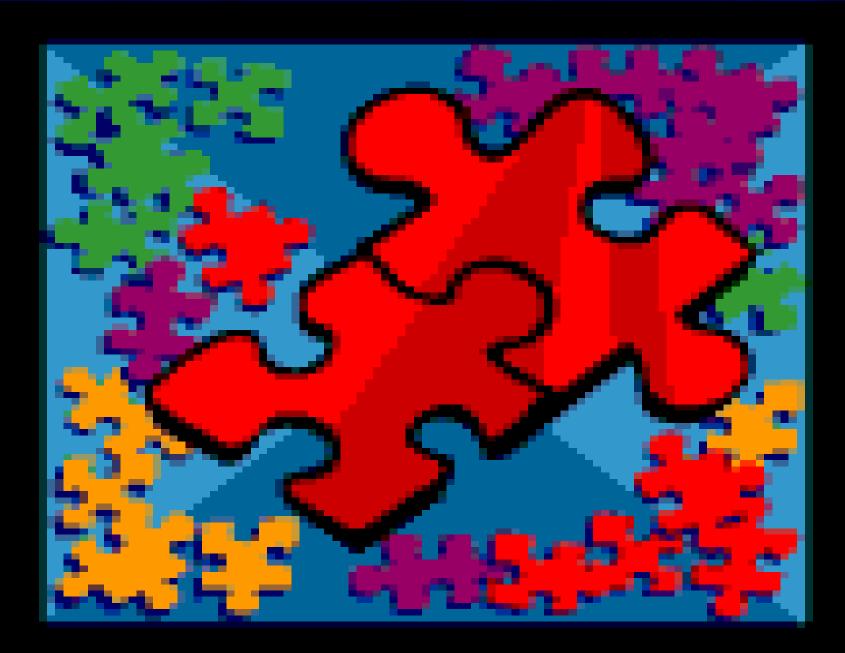
- Remove antibodies
- Rapid cessation of symptoms
- Recreation of antibodies in some cases
 - Perlmutter et al, 1999, Lancet

IVIG

- Clinical Trial of IVIG vs placebo in treatment of PANDAS
- Used for autoimmune and encephalitic illnesses
- Interference with emergence of B cells from BM
- Modulation of B cell antibody production
- Control of B and T cell proliferation
- Modulation of activation of T cells
- Neutralization of pathogenic auto-antibodies
- Neutralization of bacterial toxins and super-antigens
- Only one dose if no immunodeficiency (repeat only if reinfection or flare)
 - Kessel et al, 2007, *J of Immun*
 - Perlmutter, 1999, *Lancet*

Course of Treatment

- Initial course of antibiotics (up to 30 days)
- Steroids in recalcitrant cases (up to 80 mg/day)
- IVIG/plasmophoresis in severe cases
- Antipsychotic, SSRI medications
- Cognitive Behavioral Therapy
- Antibiotic prophylaxis
 - Post pubertal or until age 21
 - Risk of more severe reaction with reinfection
 - Reduction in neuropsychiatric exacerbations
 - Snider et al, 2005, *Biol Psych*
 - Gabbay et al, 2008, *Pediatrics*



PITANDS

- Viral infections (Perrin et al, 2004, Arch Ped Adol Med)
- Sinusitis (Leslie et al, 2008, J Am Acad Chil Adol Psych)
- Mycoplasma (Ercan et al, 2008, J Child Neuro)
- Lyme (Rhee et al, 2012, Internat J Gen Med)
- Psychosocial stress
 - potential to disrupt psychoimmune balance
 - Tait et al, 2008, *J Leuko Biol*

PITANDS

- Viral
 - titers often not helpful
 - clinical diagnosis
 - Trials of antimicrobials in "n of 1" (vitamin A, OLE, lysine, monolaurin, amantadine, valcyclovir)
- Sinusitis consider yeast if recalcitrant
- Mycoplasma check titers and IFA if IgM +
 - Azithromycin, Clarithromycin, Ciprofloxacin
- Lyme (clinical diagnosis)
 - Extended western blot and coinfections
 - Igenex
 - Advanced Lab culture

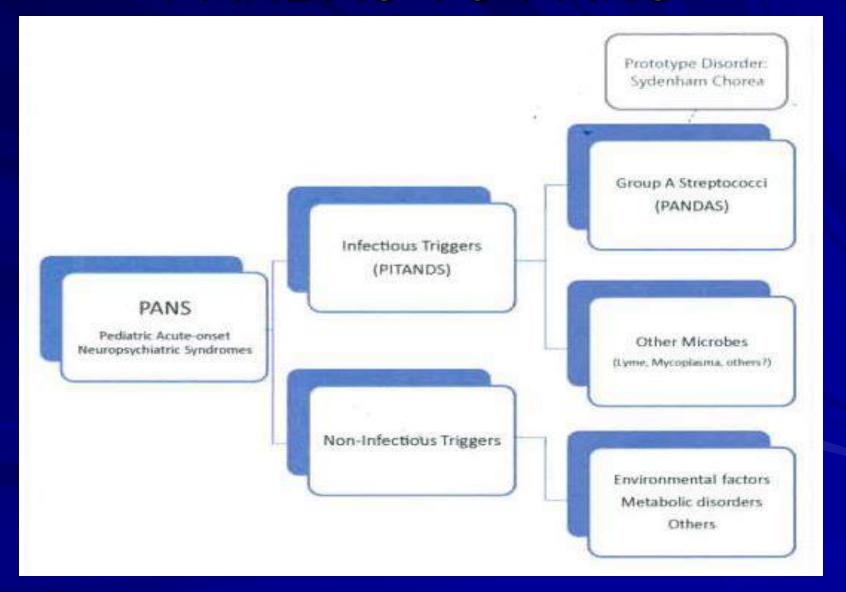
Lyme – Multi Systemic Infectious Disease Syndrome

- Infections
- Immune Dysfunction (HLA-DR, ANA, high IL1, IL6, TNF)
- Toxicity
- Allergies
- Nutritional deficiencies
- Mitochondrial dysfunction
- Endocrine and metabolic abnormalities
- Gastrointestinal issues
- Psychosocial stress true in all cases

Lyme – Autoimmune Disease (PITANDS)

- Antimicrobial treatment
 - Short term failure rate 25-71%
 - 100 days
 - Two month symptom free
 - Antifungals (Nystatin, herbals (OOO)
 - Liver protection (milk thistle, adaptogens)
 - Treat co-infections and all phases
 - Detox Charcoal, Epsom salts, Ibuprofen
- Immunotherapy
 - Diet Anti-inflammaotry
 - Probiotics, prebiotics
 - Aloe, Curcumin, Luteolin, Quercetin, Resveratrol
 - Herbals OLE, elderberry, astralagus

PANDAS TO PANS



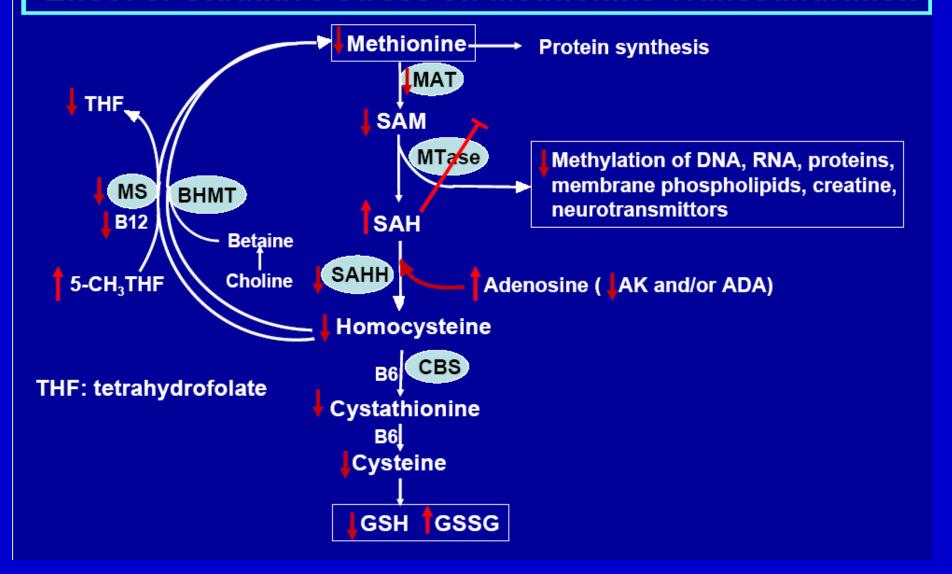
- Pediatric Acute-onset Neuropsychiatric Syndrome
- Does not replace PANDAS
- PANDAS to CANS (Childhood Acute Neuropsychiatric Syndrome)
 - Singer et al, *J Pediatr*, 2012
- Expanded to include metabolic, environmental and all infectious etiologies
 - Swedo et al, *Pediat Ther*, 2012

From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

Despite continued debates about the role of Group A streptococcal infections in the etiopathogenesis of PANDAS... experts on both sides of the controversy agree that a subgroup of children with OCD have an unusually abrupt onset of symptoms, accompanied by of a variety of comparably severe and acute neuropsychiatric symptoms. The acuity of symptom onset is the hallmark feature of their clinical presentation and the basis for the name proposed for an expanded clinical entity. .. Modifying the PANDAS criteria to eliminate etiologic factors and to clarify the initial clinical presentation produced three potential diagnostic criteria for PANS. Swedo et al. 2012 *Ped Ther*. 2(2):1-8.

- Toxic exposures (pesticides, metals, chemicals)
- Mitochondrial changes
 - Anesthesia
 - Vaccines
- Metabolic changes
 - Decreased levels of reduced glutathione
 - Vitamin and mineral deficiencies (including B12, B6, folate, zinc, magnesium)
 - Changes in diet (gluten, casein, soy)
 - Hormonal changes
 - James et al, 2004, Am J Clin Nutr

Effect of Oxidative Stress on Methionine Transsulfuration



Diagnostic Criteria for PANS

- Abrupt, dramatic onset of OCD, anorexia
- Concurrent presence of neuropsychiatric sx with severe and acute onset – Two of the following
 - Separation Anxiety
 - Emotional lability
 - Behavioral/developmental regression
 - Sensory/motor abnormalities handwriting deterioration
 - Somatic sx (sleep disturbance, enuresis, urinary frequency/urgency)
- Sx not better explained by another disorder (SC, SLE, TD)
 - Swedo et al, 2012, *Pediatric Therapeu*

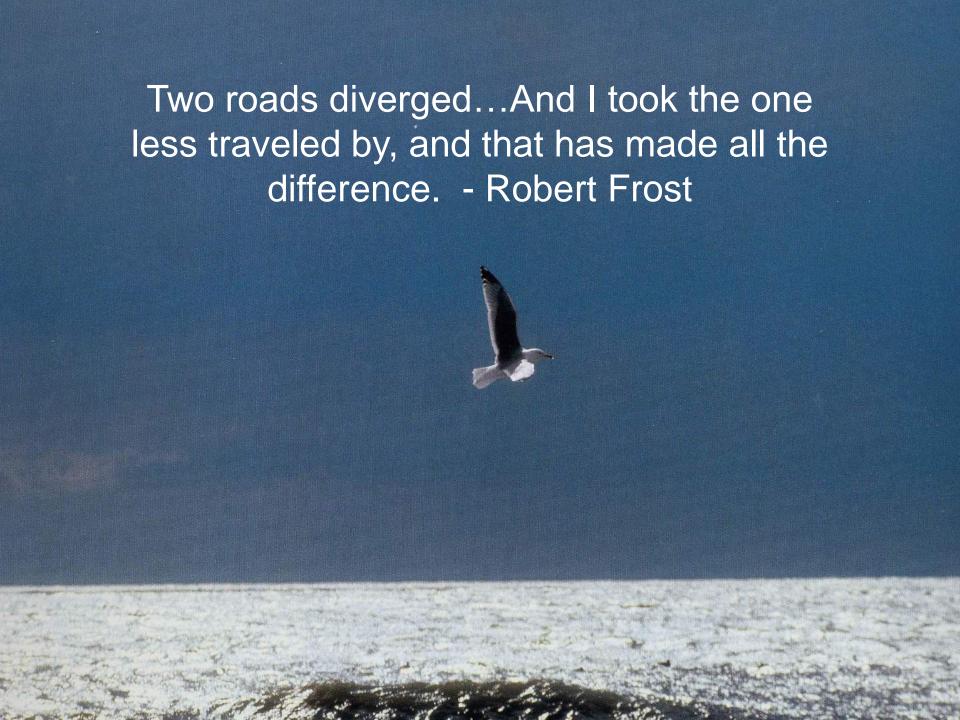
PANDAS

- Throat cultures
 - Negative cultures are not the gospel
 - Look beyond the throat
 - Check family members
- Antibiotic prophylaxis may need to be continued throughout the year and until adulthood
 - Snider et al, 2005, Biol Psychiatry
- Importance of immunotherapy
 - Swedo et al, 2005, *J Child Psychol Psychiatry*
 - Oral colostrum, Probiotics, Aloe
 - Steroids
 - Helminth therapy (Epidemic of Absence)
 - IVIG (1.5-2 gm/kg vs 400 600 mg/kg)

- PANDAS
- Other infectious etiologies
- Environmental and metabolic etiologies
 - Look for each of these in ACUTE onset OCD, tics, aggression, regression in behaviors or movement, anorexia, somatic symptoms
 - Look at specific individual and family history
 - Importance of comprehensive interventions

- Clinical diagnosis confirmed (or not) by laboratory evidence
 - Strep titers
 - Lyme testing
 - Mycoplasma
 - Immune markers (CRP, ESR, ANA, thyroid antibodies, immunoglobulins including subclasses, strep pneumococcal serotypes)
 - Urine organic acids
 - Cysteine, methylation profile (DD)
- Use treatment as diagnostic tool as well as therapeutic intervention (antimicrobials, steroids)

- Treat each child as an individual not a protocol
- Identify underlying problems by looking at his/her individual history, physical exam clues and laboratory data
- See treatments as clinical trials with an N of one



Where Do We Begin?

One Child

Caleb 5 Year Old with new onset tics

- Sudden onset of vocal tics ("excuse me" every 5 seconds)
- Repeated at variable pitch, tone and level of exclamation
- Included during sleep periods (with any brief waking he would repeat phrase)
- Motor tics (itching and smelling his buttocks; touching his shoulders in sequence)
- Change in personality, anxiety and attention
- Began putting everything in his mouth
- Frequent urination (no pain, no change in color of urine, no change in drinking or eating)

Caleb - Past History

- Normal pregnancy and birth
- Breastfed but initial poor latching
- Healthy with few infections
- Normal developmental milestones prior to onset of tics
- Some sensory issues (sensitivities to noises, modulation of moods)
- Alternative vaccination schedule
- Organic diet, no known exposures
- No surgeries, injuries, anesthesia
- No previous lab tests
- Family history of arthritis, cancer, IDDM

Caleb - Recent History

- Sore throat at end of March (strep culture negative)
- MMR vaccine (1st) at end of April
- 1 ½ weeks after MMR, he developed violent vomiting and fever for 2 days
- Sibling with positive Strep culture in early May
- Symptom onset (as per previous slide) in early May
- No tick exposure
- No other infectious symptoms or exposures

What is Differential?

- PANDAS
- PITANDS (Lyme, Mycoplasma, Virus)
- PANS (Metabolic)
- Seizure
- Tourette's

Caleb - Treatment

- Seen by Pediatrician and placed on Azithromycin
 - no change in tics
- Blood work done by pediatrician
 - Negative ASO, AntiDNase B
 - Negative Lyme Screen and Western Blot
 - Normal CBC, ESR

Caleb - Presented to our office 6 weeks later

- Started Probiotic, EFAs
- IV GLUTATHIONE given at time of blood work
- Repeat Blood work done
 - Strep and Lyme titers (including co-infections)
 - Mycoplasma and viral titers (including MMR)
 - CBC, CMP, mitochondrial markers
 - ESR, C3D
 - Vitamin A, D (25 OH), MMA
 - Cysteine



Cysteine, Serum

63 Zillicoa Street Asheville, NC 28801 © Genova Diagnostics



Improving Healthcare for Chronic Disease

Order Number: F0200288

Completed:

Received: .
Collected:

MRN: 0001552768

Patient:

DOB:

Sex: M

Nancy OHara, MD Nancy O'Hara MD 3 Hollyhock Ln Wilton, CT 06897

Cysteine, Serum

Inside Range Outside Range

Reference Range

Cysteine, Serum

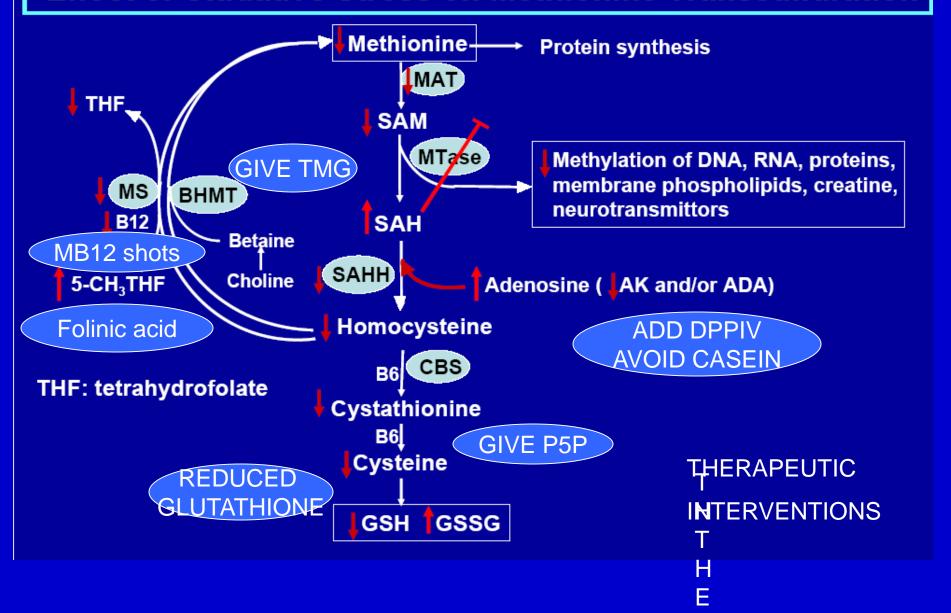
0.36

0.46-1.20 mg/dL

Commentary

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with * as cleared by the U.S. Food and Drug Administration, assays are For Research Use Only.

Effect of Oxidative Stress on Methionine Transsulfuration



Caleb - Returned 2 weeks later

- Tics completely resolved after IV GSH
- All lab work normal except cysteine
- Placed on methylation support
 - Broccoli Seed Extract
 - N Acetyl Cysteine
 - Glycine
 - B12, folinic
 - Continued probiotics, EFAs

Daniel- 8 year old with PDD

- Sudden change in behavior
- Uncontrolled agitation, aggression
- OCD behavior
- Ritualistic
- Verbal tics
- Hyperactivity
- Recurrent sore throats
- Multiple antipsychotic medications and hospitalizations

PANDAS – TREATMENT

www.pandasnetwork.org

- Probiotics
- Saccharomyces Boulardii/Alkalinization/Charcoal
- Antibiotics
 - -Penicillin
 - -Antibiotic Prophylaxis with Zithromax
- Immunotherapy IVIG x 1
- Symptoms resolved



And Then...

- Moved to NC
- Started Abilify 10 mg
- Stopped prophylaxis
- 6/13 psychiatric hospitalization for aggression
 - Auditory sensitivity, acting out with characters from favorite shows
 - Sleep irregular

Diagnosis

- Testing
 - High Mycoplasma IFA, IgM (18.9), IgG (13.8)
 - Negative ASO, antiDNase, lyme, co-infections
- Much improved with AZITHROMYCIN
- Multiple additional interventions (including depakote, increase Abilify, Intuniv, Clonidine, Ashwagandha, Folate, melatonin, Prozac)
- Increase in agitation with steroid trial
- IVIG

Moving Forward Prior to IVIG

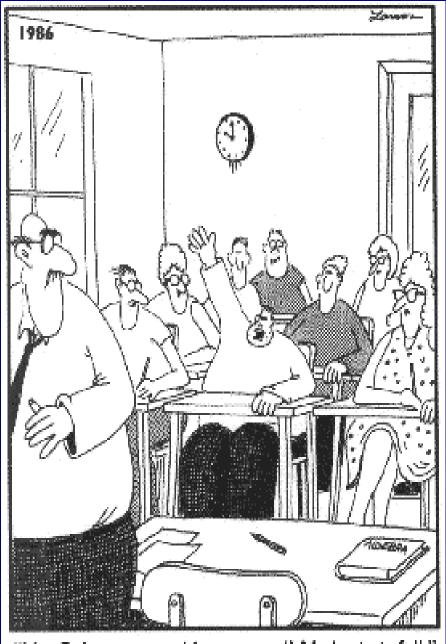
- Extreme anxiety
- Severe sensory seeking computer OCD
- Up at night excessive talking and running up stairs and house. Says he "wants" to sleep but can't. Intermittently break into sweats. Acts impulsively-Imaginary friends.

Post IVIG

- Calmer presentation. Less self talking, redirectable. Less confrontational and threatening.
- Better connected and engaging than prior.
- Anxiety still present with behaviors but he is "trying" to manage and work it through independently.

PANDAS to PANS

- Assessment and Treatment
 - PANDAS
 - PITANDS
 - PANS
 - Autoimmune Encephalitis



"Mr. Osborne, may I be excused? My brain is full."