PANS/PANDAS

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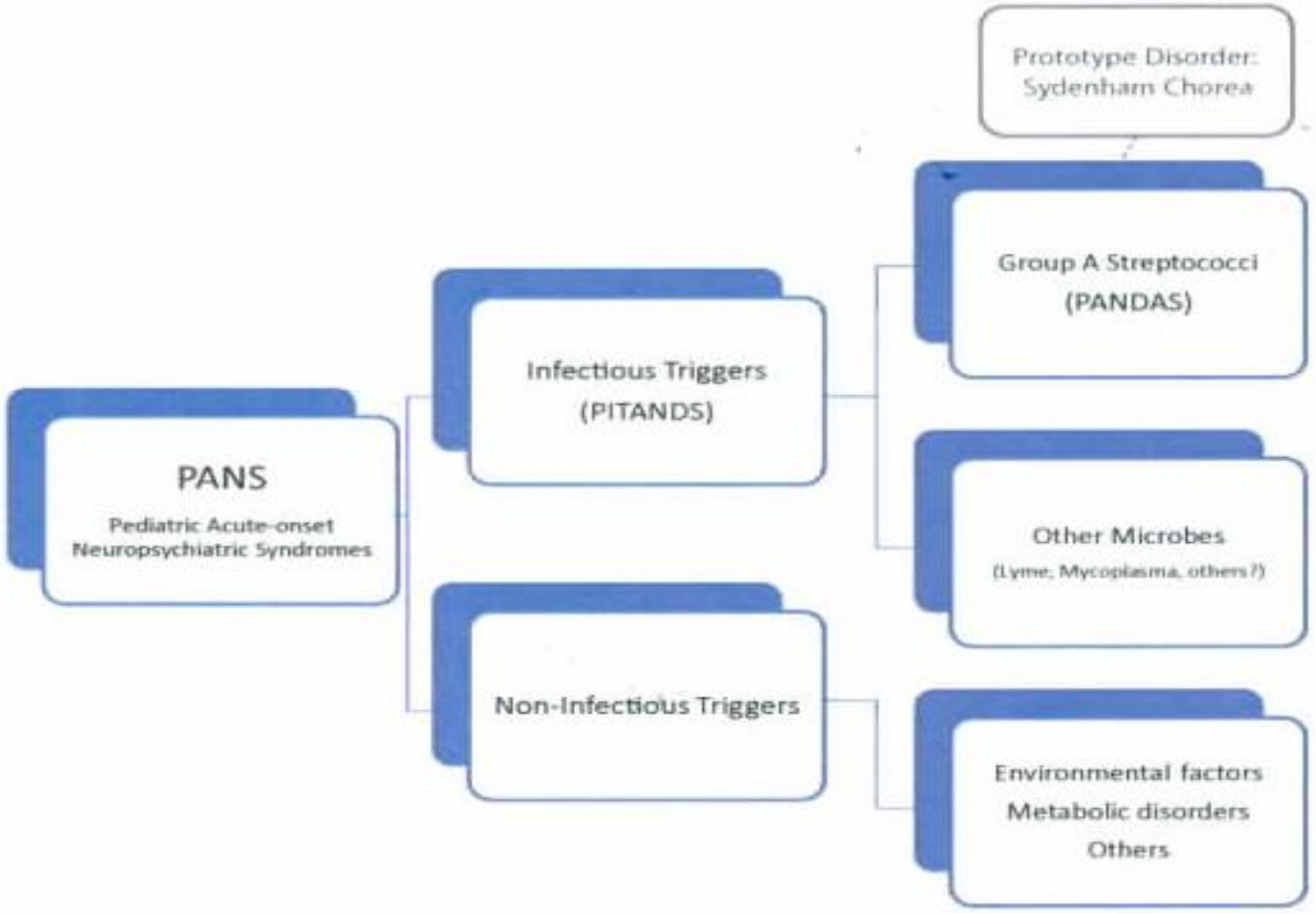
DISCLOSURE

- **Disclaimer**
  - All the information provided in this lecture is strictly for informational purposes only. It is not intended as a substitute for advice from your health care provider or physician. Before beginning any treatment, please consult with your or your child's physician.
- **Disclosures**
  - I do not have any financial arrangements or affiliations with any commercial entities whose products, research, or services may be discussed in this lecture

WHAT IS PANS/PANDAS?

- **PANDAS** = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep
- **PANS** = Pediatric Acute-Onset Neuropsychiatric Syndromes
- **PITANDS** = Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders
- Post-streptococcal Autoimmune Encephalitis (of the basal ganglia)
- Sydenham Chorea
  - Post-Streptococcal Striatal Autoimmune Encephalitis
  - 95% with emotional lability, 50-75% with OCD at initial presentation and 100% with recurrence (Russel Dale & colleagues)

PANS/PANDAS



Swedo et al, Ped Ther, 2012

PANS/PANDAS

- **1 in 150-200 children diagnosed with PANS**
  - Subgroup of those children with OCD (which represents 2% of population)
  - At least 25-30% of OCD and Tic disorders are acute onset
- More prevalent in males than females (2.6:1)
- Increased occurrence with family history of autoimmune disease
  - 64% have 1st degree relative with inflammatory disease

DIAGNOSTIC CRITERIA

- **ACUTE ONSET** of **DRAMATIC** OCD (or anorexia and/or severe, restrictive eating disorder) in addition to TWO of the following neuropsychiatric symptoms (with severe and acute onset):
  - Separation Anxiety
  - Emotional lability
  - Behavioral/developmental regression
  - Sensory/motor abnormalities – handwriting deterioration
  - Deterioration of school performance
  - Urinary symptoms (urgency, frequency, enuresis)
  - Sleep disturbance (difficulty falling asleep, REM disinhibition/restless sleep)
  - Symptoms not better explained by another disorder

Swedo et al, 2012, Pediatric Therapeu; Frankovich et al, J child Adol Psychopharm, 2015

CLINICAL OBSERVATIONS

- Aggression 60%
- Sleep Disorders 80%
- Insomnia, night terrors, inability to sleep alone
- Behavioral Regression
- Separation anxiety 98%
- Learning Difficulties 60%
- Hyperactivity; Inattentiveness 70%
- Inability to concentrate 90%
- Eating Disorder 20%
- Hallucinations 10%
- Terror Stricken look or Hyper-alert appearance 80%
- Urinary Frequency, urgency, urinary accidents 90%
- Handwriting deterioration 90%
- Tics 70%
- Short-term memory loss 60%
- Sensory -hypersensitive or insensitive 40%
- History of repeated UTIs or sinusitis

Toufexis et al, , JACP, 2015

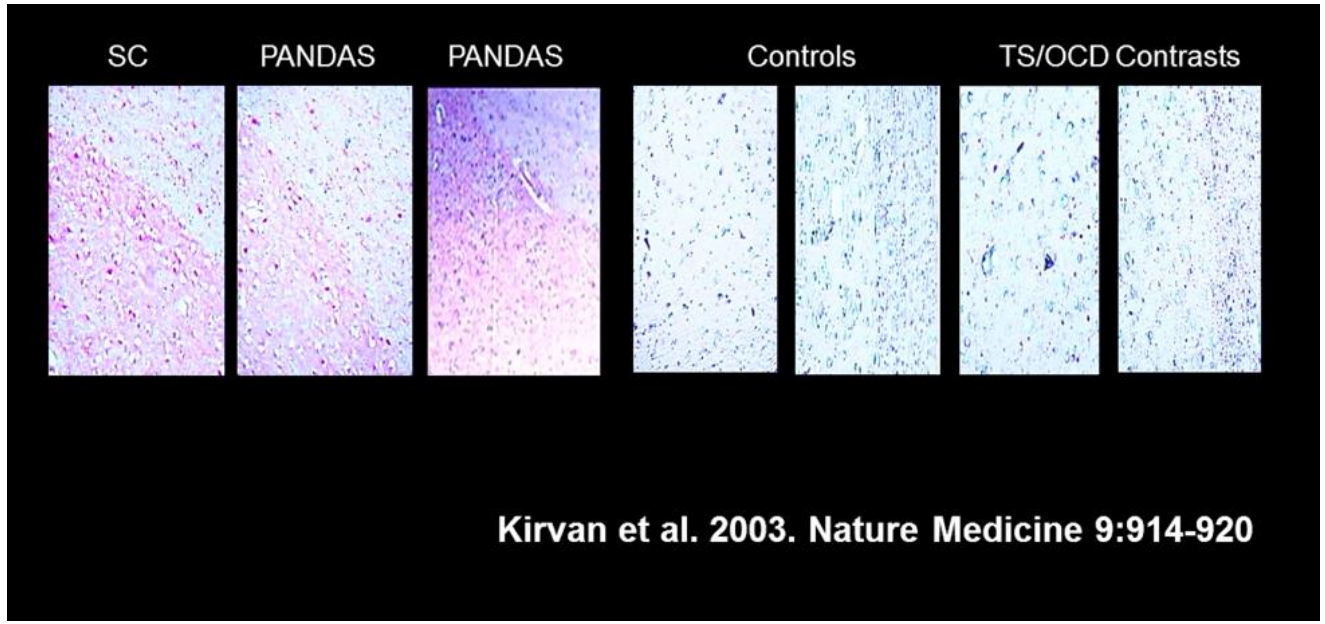
ADDITIONAL OBSERVATIONS

- Margin Drift (left sided neglect)
- Shortened attention span
- Difficulty with memory
- Loss of math visuospatial skills
- Dysgraphia/clumsiness
- Patterns of executive function deficit different than those children with Tourette's
- EEG – 17% show spikes (4/42) or diffuse slowing (3/42) consistent with autoimmune encephalitis
- Sleep study – 85% show nonspecific REM motor disinhibition

Buckley et al, NIH, J Clin Sleep Med, 2016

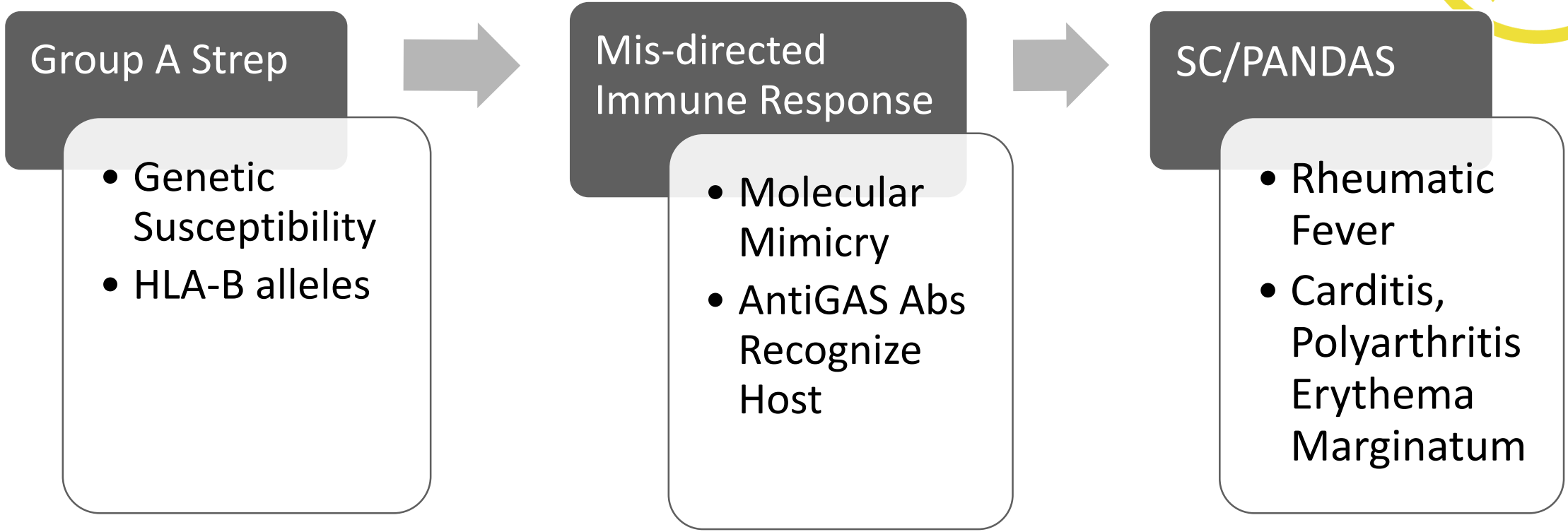
ADDITIONAL OBSERVATIONS

- Studies reveal that 80% of patients diagnosed with PANS have post-infectious autoimmunity and/or neuroinflammation (Swedo et al, 2015)
- Neuroinflammation seen in the caudate/putamen (Kirvan et al, 2003)



DIFFERENTIAL DIAGNOSIS

- Sydenham chorea (acute rheumatic fever)
- Other forms of encephalitis, cerebral vasculitis
- Child abuse, sexual abuse, psychological trauma
- Toxins, medications, illicit drugs
- Tumors, strokes
- Tourette’s, OCD – not ACUTE



PATHOGENESIS

TH17

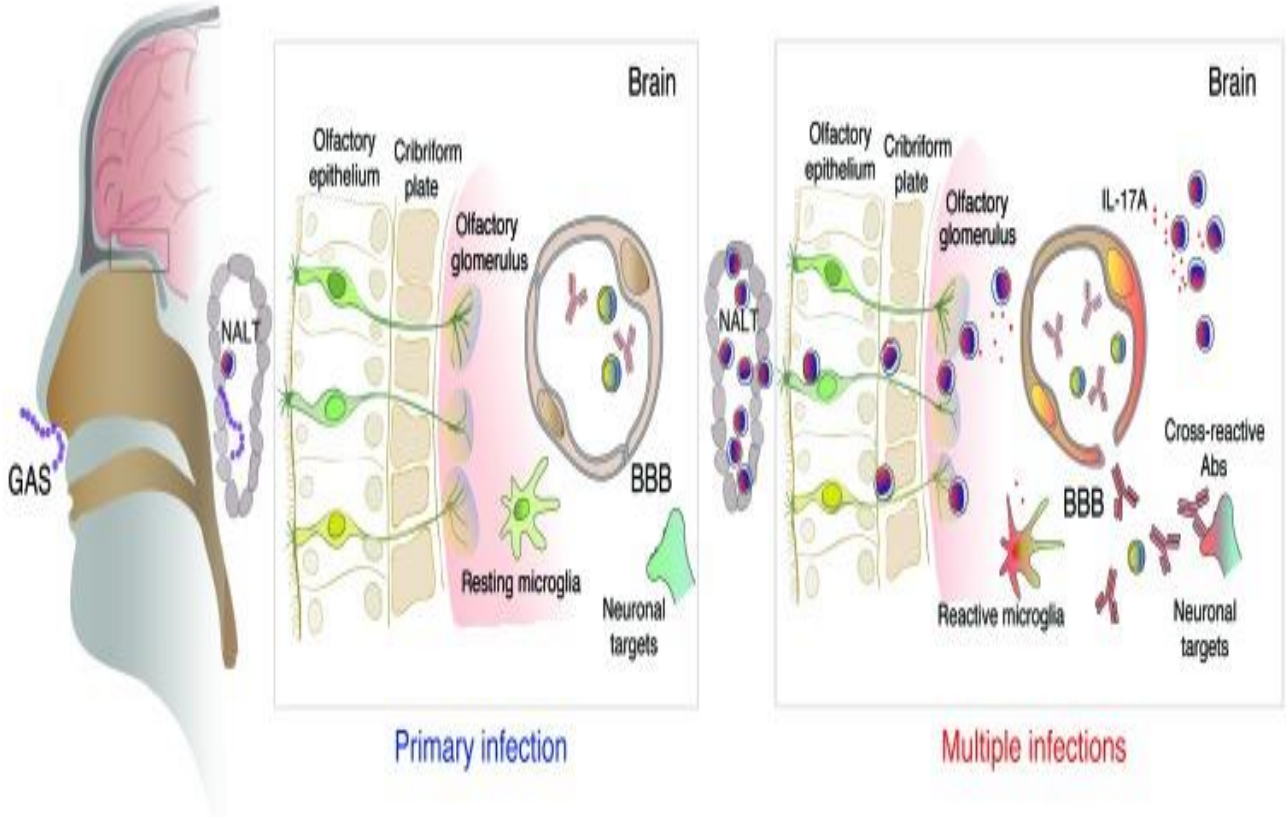
J Clin Invest. 2016 Jan;126(1):303-17. doi: 10.1172/JCI80792. Epub 2015 Dec 14.

Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells.

Dileepan T, Smith ED, Knowland D, Hsu M, Platt M, Bittner-Eddy P, Cohen B, Southern P, Latimer E, Harley E, Agalliu D, Cleary PP.

Abstract

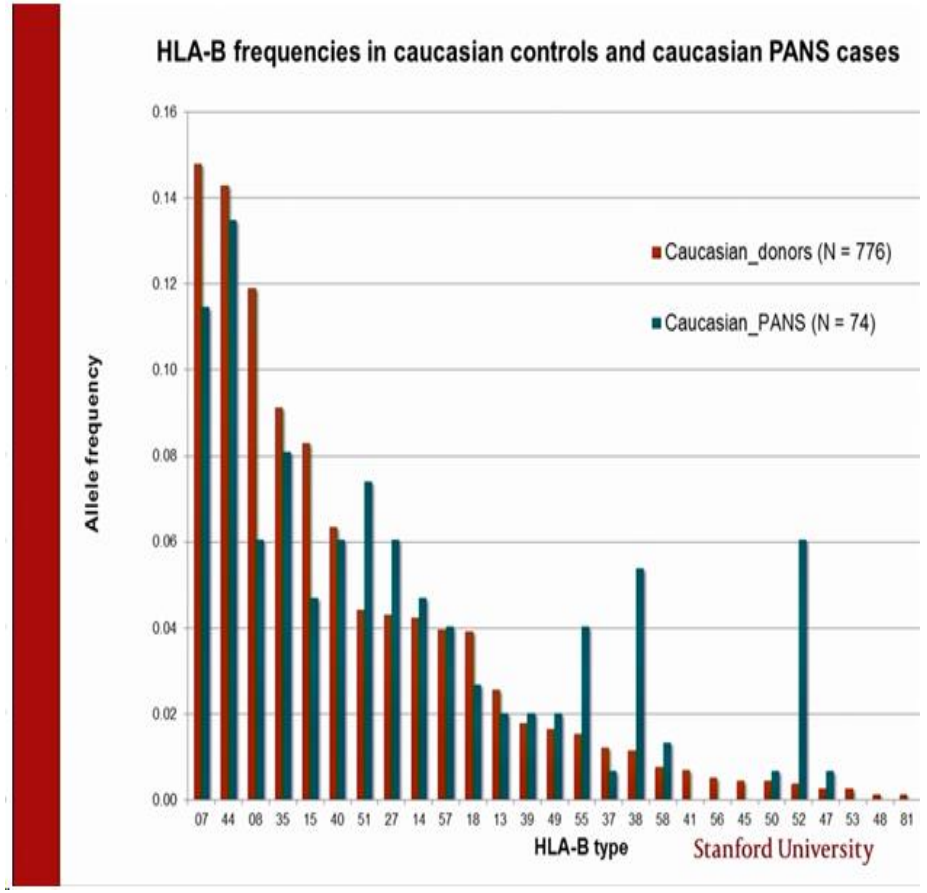
Group A streptococcal (GAS) infection induces the production of Abs that cross-react with host neuronal proteins, and these anti-GAS mimetic Abs are associated with autoimmune diseases of the CNS. However, the mechanisms that allow these Abs to cross the blood-brain barrier (BBB) and induce neuropathology remain unresolved. We have previously shown that GAS infection in mouse models induces a robust Th17 response in nasal-associated lymphoid tissue (NALT). Here, we identified GAS-specific Th17 cells in tonsils of humans naturally exposed to GAS, prompting us to explore whether GAS-specific CD4+ T cells home to mouse brains following i.n. infection. Intranasal challenge of repeatedly GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected in CNS tissue. CD4+ T cells were predominantly located in the olfactory bulb (OB) and in other brain regions that receive direct input from the OB. Together, these findings provide insight into the immunopathology of neuropsychiatric complications that are associated with GAS infections and suggest that crosstalk between the CNS and cellular immunity may be a general mechanism by which infectious agents exacerbate symptoms associated with other CNS autoimmune disorders.



Agalliu, et al. Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells. J Clinical Investestigation. 2016;126 (1)303-17

HLA SUSCEPTIBILITY

- Increase incidence of PANS in subjects which had the following HLA-B alleles:
  - HLA-B 55
  - HLA-B 38
  - HLA-B 52
    - Associated with vasculitis (i.e Behcets)
- Shows genetic predisposition to vulnerability



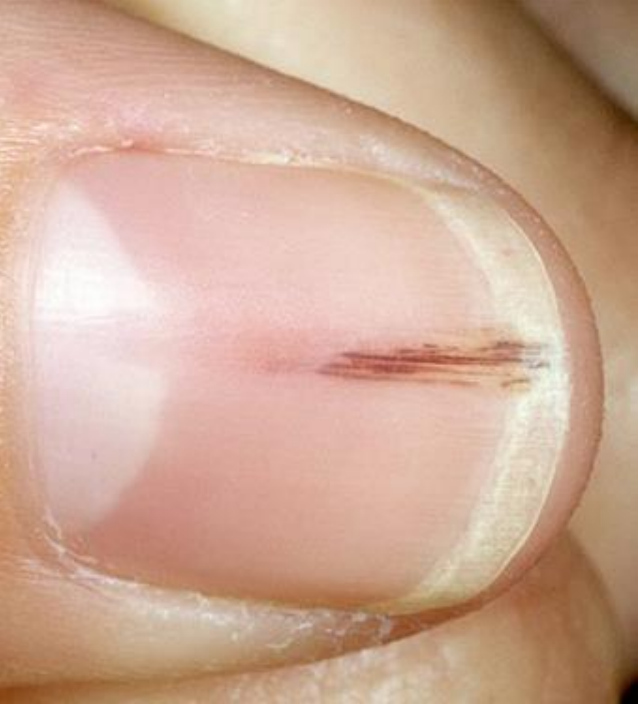
Frankovich, 2016

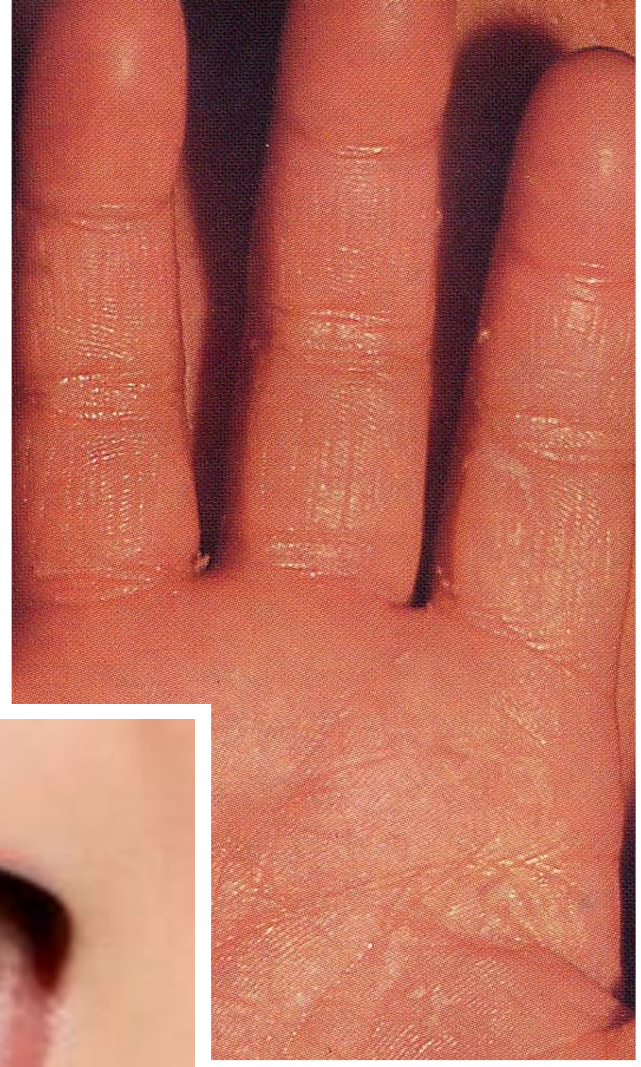
DIAGNOSIS

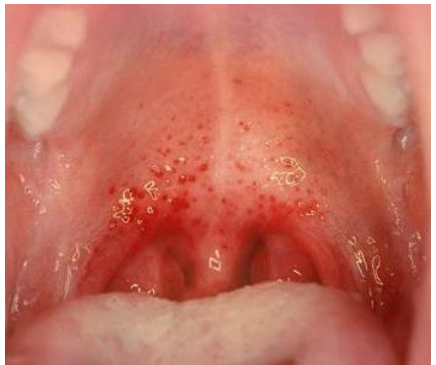
- PANS/PANDAS is a **CLINICAL DIAGNOSIS**
- Based on History and Physical Exam
- Clinical Diagnosis of **ACUTE ONSET** of symptoms
- Evidence of infection/inflammation

HISTORY

- Recent illness before the onset of symptoms
- History of family members being ill around the onset of symptoms
- **IMPORTANT TO NOTE:** Our kids will not always present with the typical acute illness symptoms and may just present with behavioral issues





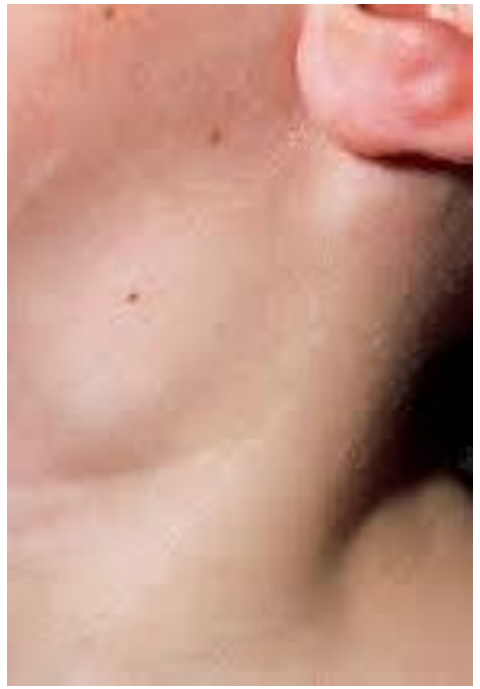


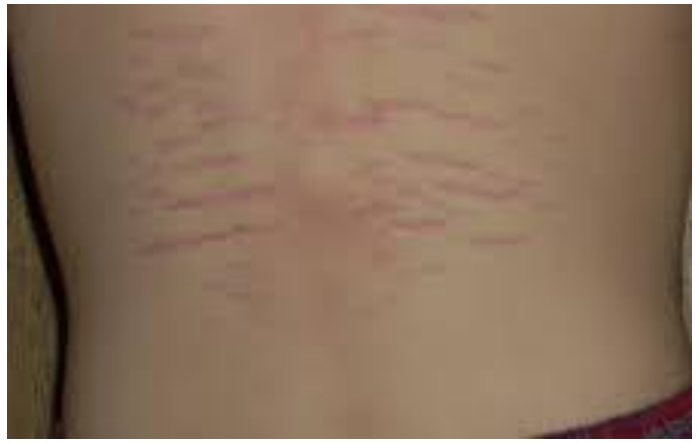
PHYSICAL EXAM

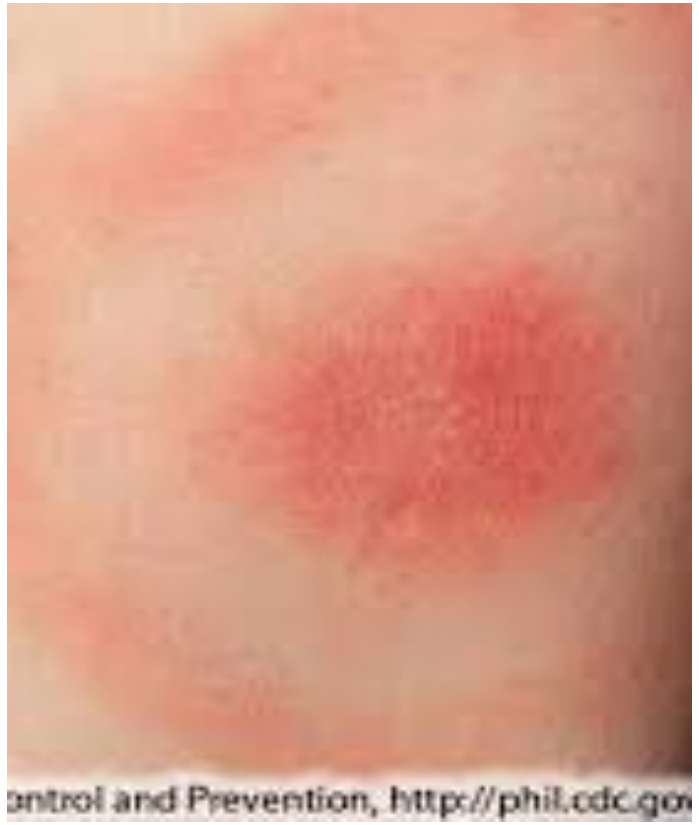
- Choreiform Movements (“piano playing fingers”)
- Strep (PANDAS)
  - Red anal ring
  - Peeling fingers
  - Tongue
  - Palate petechiae
  - Scarlatina Rash
  - Damaged nail bed vasculature

PHYSICAL EXAM

- Other:
  - Erythema Migrans – BORRELIA
  - Striae that blanches – BARTONELLA
  - Swollen/tender glands
  - Tenderness to palpation of sinuses
  - Whiteness on tongue – YEAST OVERGROWTH
  - Positive Woods Lamp – YEAST OVERGROWTH

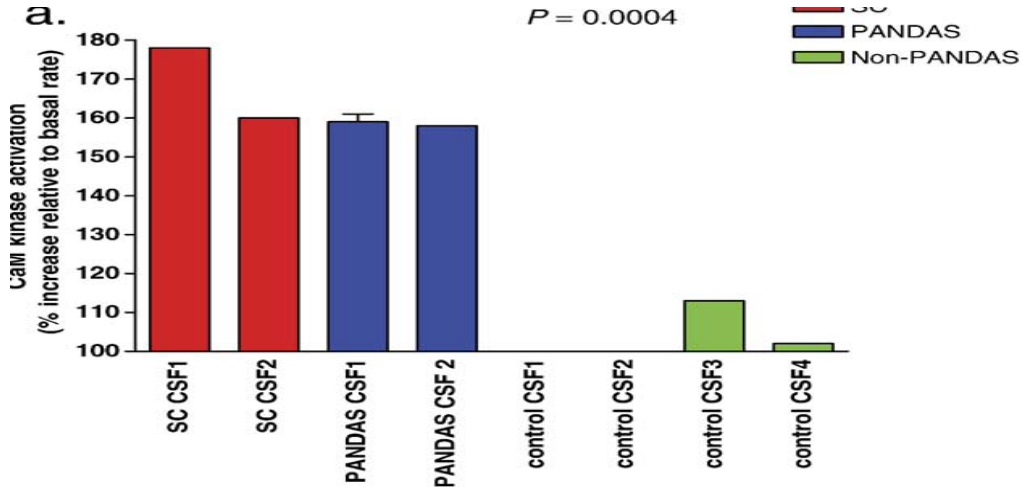


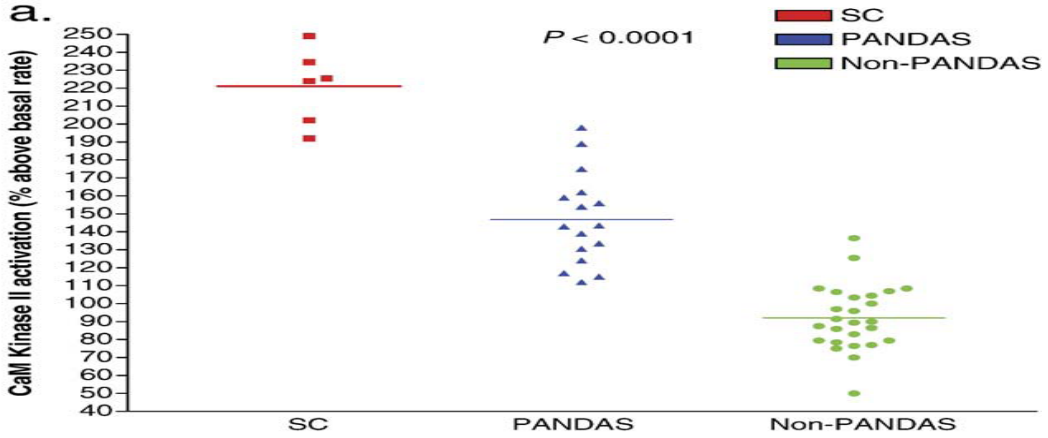


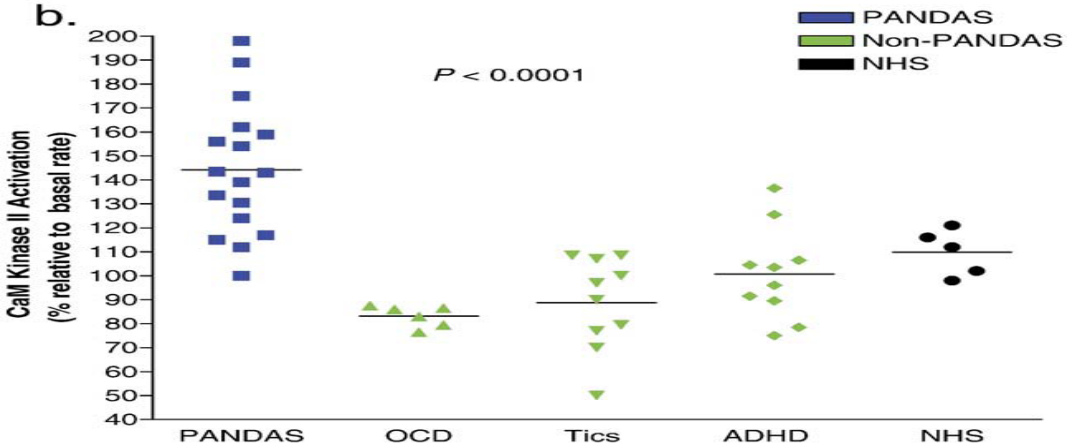


DIAGNOSIS

- Culture of possible sites of infection:
  - Throat (rapid test – high false negative rate)
  - Tonsils and Adenoids (surface/core)
  - Urinary Tract
  - GI Tract/Perianal (Toufexis et al, JCAP, 2013)
  - Sinuses - cryptic, recalcitrant (Mahoney et al, J Ped Otorhinolar, 2017)







DIAGNOSIS

- **Laboratory evidence**
  - Strep markers– ASO, antiDNaseB Ab
    - 6-8 weeks for rise in titers post infection
    - These antibodies only mean that the child has had a previous strep infection. It does NOT mean the child has PANDAS
    - About 40% of children with documented GAS infections do not show a rise in titers – leading to false negatives.
  - Other infectious markers :
    - Mycoplasma IgG/IgM
    - Lyme and Coinfections (Babesia, Bartonella, Ehrlichia)
    - Viral markers – influenza, EBV, CMV, etc.
    - Gut dysbiosis – yeast, parasites
  - Inflammatory markers – hs-CRP, ESR, ANA
    - ANA is positive in > 56 % (Cox et al, JACP, 2015)
- CaM Kinase – Moleculara labs
  - Testing may be helpful when child in a flare or not classical clinical picture

DIAGNOSIS

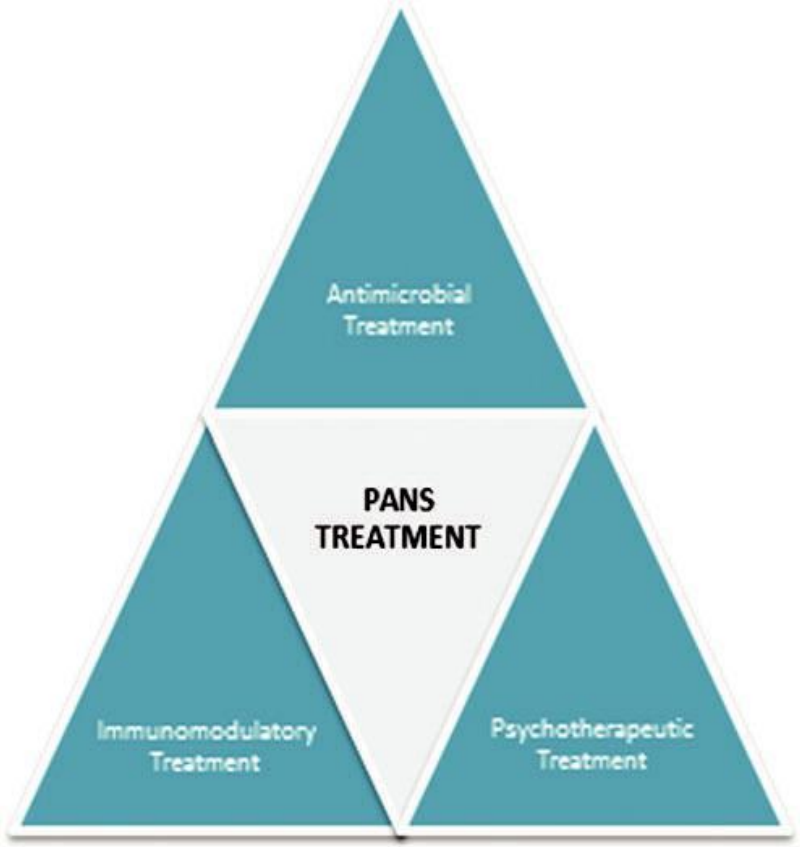
Environmental Exposures:

- MOLD – mycotoxin profile
- Chemical exposures
- Immunizations
- Anesthesia
- Pesticides

Additional Markers:

- Food Allergies
- Celiac screen
- Thyroid abs
- Cerebral Folate Deficiency
- Metabolic markers
- Endocrine markers

TREATMENT



- Treating the symptoms with supportive interventions (CBT, supplements, psychoactive medications)
- Removing the source of the infection – treating with antimicrobials (natural and pharmaceutical)
- Treating immune disturbances with immunomodulatory and/or anti-inflammatory interventions

Swedo et al, J Child Adol Psychopharm, 2017

PRINCIPLES OF TREATMENT

Establish the correct diagnosis

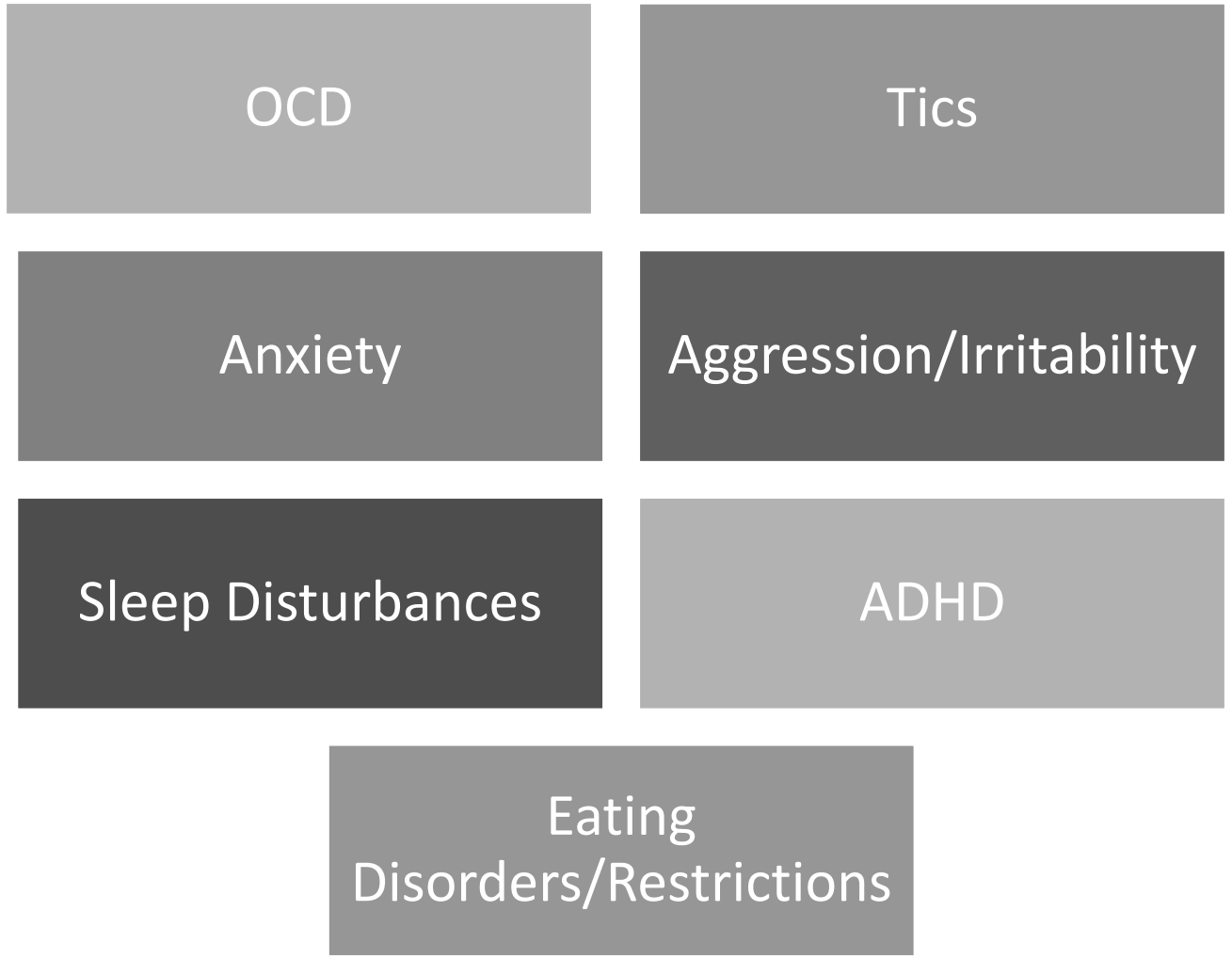
Provide symptomatic relief and comprehensively treat symptoms causing the most distress (Thienemann et al, J Child Adol Psychopharm, 2017)

Treat infections – therapeutic and prophylactically (Cooperstock et al, J Child Adol Psychopharm, 2017)

Treat neuroinflammation and post-infectious autoimmunity with anti-inflammatory and immunomodulatory interventions (Frankovich, J Child Adol Psychopharm, 2017)

Evaluate effectiveness of treatment, modifying as warranted by relapsing and remitting symptoms (Swedo et al, J Child Adol Psyhopharm, 2017)

TREATMENT FOR SYMPTOMS



OCD

- **N-Acetyl Cysteine (NAC)**
- **Inositol**
  - 18 grams/day found to decrease OCD (Palatnik et al, J Clin Psychopharm, 2001)
- **CBD (Hemp Oil) – Cannabidiol**
  - Reverses mCPP-induced marble burying in mice (Nardo et al, 2013; Delana et al, Psychopharm, 2012)
- **Lithium Orotate** (O'Donnell et al, Eur Neuropsychopharm, 2003)
- **Passionflower** – helps to calm of mind of repetitive thoughts
- **Ashwagandha**
  - Comparable efficacy in mice models to fluoxetine (Asian Pac J Trop Med, 2012)
- **GABA**
  - Modulates glutamate that has been found to be significantly higher in CSF of subjects with OCD compared to controls(Pittenger et al, 2011)
- **Mindfulness** (Hansteded et al, J Nerv Ment Dis, 2008)
- **Exercise** (Otto et al Oxford Univ Press, 2011)

Review
http://dx.doi.org/10.9758/cpn.2015.13.1.12
Clinical Psychopharmacology and Neuroscience 2015;13(1):12-24
pISSN 1738-1088 / eISSN 2093-4327

N-Acetyl Cysteine in the Treatment of Obsessive Compulsive and Related Disorders: A Systematic Review

Georgina Oliver[1], Olivia Dean[1,2,3], David Camfield[4,5,6], Scott Blair-West[1], Chee Ng[1], Michael Berk[1,2,3,4], Jerome Sarris[1,4]

[1]Department of Psychiatry, The Melbourne Clinic, The University of Melbourne, Melbourne, [2]Innovation in Mental and Physical Health and Clinical Treatment: Strategic Research Centre, School of Medicine, Deakin University, Geelong, [3]The Florey Institute of Neuroscience and Mental Health, [4]Centre for Human Psychopharmacology, Swinburne University, Melbourne, [5]Illawarra Health & Medical Research Institute (IHMRI), [6]School of Psychology, University of Wollongong, Wollongong, Australia

Objective: Obsessive compulsive and related disorders are a collection of debilitating psychiatric disorders in which the role of glutamate dysfunction in the underpinning neurobiology is becoming well established. N-acetyl cysteine (NAC) is a glutamate modulator with promising therapeutic effect. This paper presents a systematic review of clinical trials and case reports exploring the use of NAC for these disorders. A further objective was to detail the methodology of current clinical trials being conducted in the area.

Methods: PubMed, Web of Science and Cochrane Library Database were searched for human clinical trials or case reports investigating NAC in the treatment of obsessive compulsive disorder (OCD) or obsessive compulsive related disorders. Researchers with known involvement in NAC studies were contacted for any unpublished data.

Results: Four clinical trials and five case reports/series were identified. Study durations were commonly 12-weeks, using 2,400-3,000 mg/day of NAC. Overall, NAC demonstrates activity in reducing the severity of symptoms, with a good tolerability profile and minimal adverse effects. Currently there are three ongoing randomized controlled trials using NAC for OCD (two adults and one pediatric), and one for excoriation.

Conclusion: Encouraging results have been demonstrated from the few pilot studies that have been conducted. These results are detailed, in addition to a discussion of future potential research.

OCD

- **Pharmaceuticals**
  - SSRI's (Selective Serotonin Reuptake Inhibitors) prescribed for OCD
    - Low dose with slow titration (Coffey, 2007)
    - Study found that 30% of patients have treatment-refractory (Goddard et al., 2008)
    - Reason to implement natural interventions!
    - Possible benefit from additional treatment that addresses other neurochemical pathways (i.e dopamine and glutamate)
  - Memantine (Namenda)
    - NMDA receptor antagonist and regulates glutamate (excitatory neurotransmitter)
    - Study showed improvement in OCD and impulsivity (Ghaleiha et al, 2013)
    - Animal models show anti-inflammatory benefits
  - Amantadine
    - NMDA receptor antagonist that decreases glutamate to help with OCD (Hosenbocus and Chahal, 2013)

ANXIETY

- 5-HTP
- GABA
- L-Theanine
- B6
- B complex
- Magnesium
- Probiotics
- Multi-mineral
- EFA

- L-MTHF (if MTHFR mutation OR CFD)
- Ashwagandha
- Lemon Balm
- Motherwort
- Passionflower
- Mimosa Bark
- Hemp oil
- EXERCISE
- Meditation
- Classical Homeopathy

ANXIETY

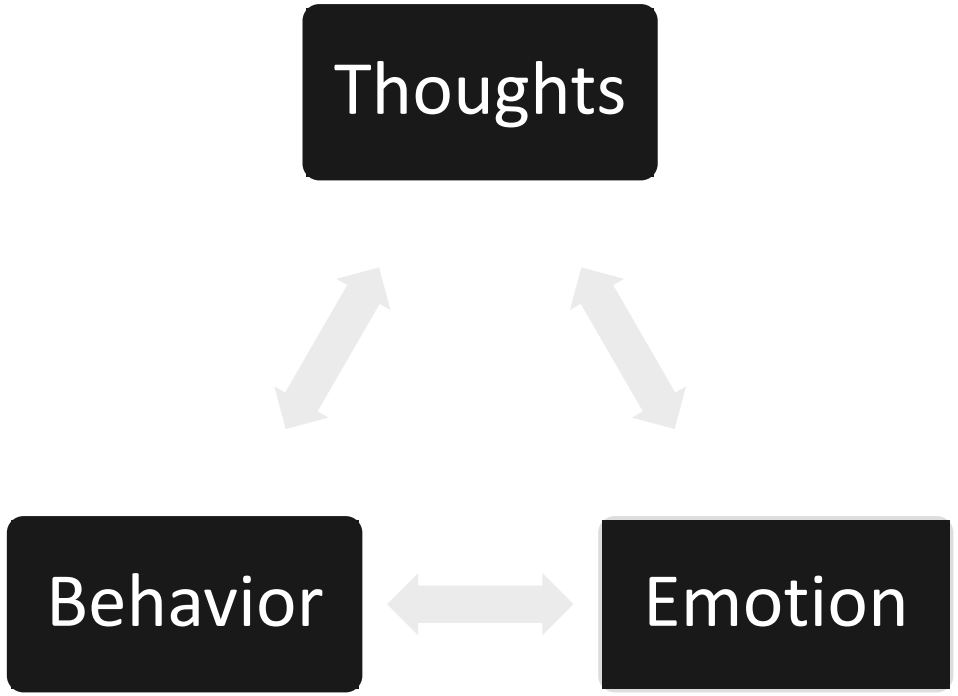
- Dosages based on TD children
- Start at low dosage and slowly titrate up
- SSRIs most successful treatment for TD youth with anxiety
- SSRIs used in ASD population but lack of double-blind placebo controlled trials
- Data from SSRI trials report behavioral activation (increased activity, impulsivity, insomnia, etc.) in children with ASD (Walkup and Labellarte, 2001).

TABLE 1 Summary of Medications for the Treatment of Anxiety in Youth With ASD

Symptoms[a]	Medication[b]	Dose Range[b]		References
		Starting Dose	Maximum Dose	
Core anxiety symptoms	Sertraline[c]	12.5 mg daily	200 mg daily	Reviews in typically developing youth: Mohatt et al (2013), Strawn et al (2014)
	Fluoxetine[c]	2.5–5 mg daily	60 mg daily	
	Citalopram[c]	2.5–5 mg daily	40 mg daily	
	Escitalopram[c]	1.25–2.5 mg daily	20 mg daily	
Specific anxiety symptoms[d]				
Sleep disturbance	Melatonin	2 mg hs	10 mg hs	Guenoe et al (2011)
	Clonidine	0.05 mg hs	0.2 mg hs	Nguyen et al (2014)
	Trazodone[e]	12.5–25 mg hs	100 mg hs	
Physiologic symptoms[f]	Clonidine[f]	0.05 mg hs for 1 week then bid-qid	0.1 mg tid-qid	No data in TD or ASD youth; recommendations based on clinical consensus
	Guanfacine[f]	0.05 mg hs for 1 week then bid-qid	1 mg tid	
	Clonidine ER[f]	0.1 mg hs or qam	0.2 mg hs or qam[g]	
	Guanfacine ER[f]	1 mg hs or qam	4 mg hs or qam[g]	
	Propanolol	10 mg bid-tid or prn	30 mg tid	
Behavioral dysregulation[f]	Clonidine	0.05 mg hs for 1 week then bid-qid	0.1 mg tid-qid	Reviews by: Mahajan et al (2012), Ji and Findling (2014)
	Clonidine ER	0.1 mg daily	0.2–0.3 mg daily	
	Guanfacine	0.5 mg hs for 1 week then bid tid	1 mg tid	
	Guanfacine ER	1 mg hs[g]	4 mg hs or qam	
Situational anxiety[g]	Lorazepam	0.25–0.5 mg prn	2 mg prn	No data in TD or ASD youth; recommendation based on clinical consensus
	Propanolol	5–10 mg prn	20 mg prn	

ANXIETY

- Modified CBT (MCBT) is an effective treatment of children and adolescents with high-functioning ASD and anxiety disorders
- Can be administered individually or in a group and often includes parental involvement
- This therapy includes affective education, cognitive restructuring, reducing avoidance behaviors, relaxation, modeling, and exposure to the feared stimuli (with response prevention)

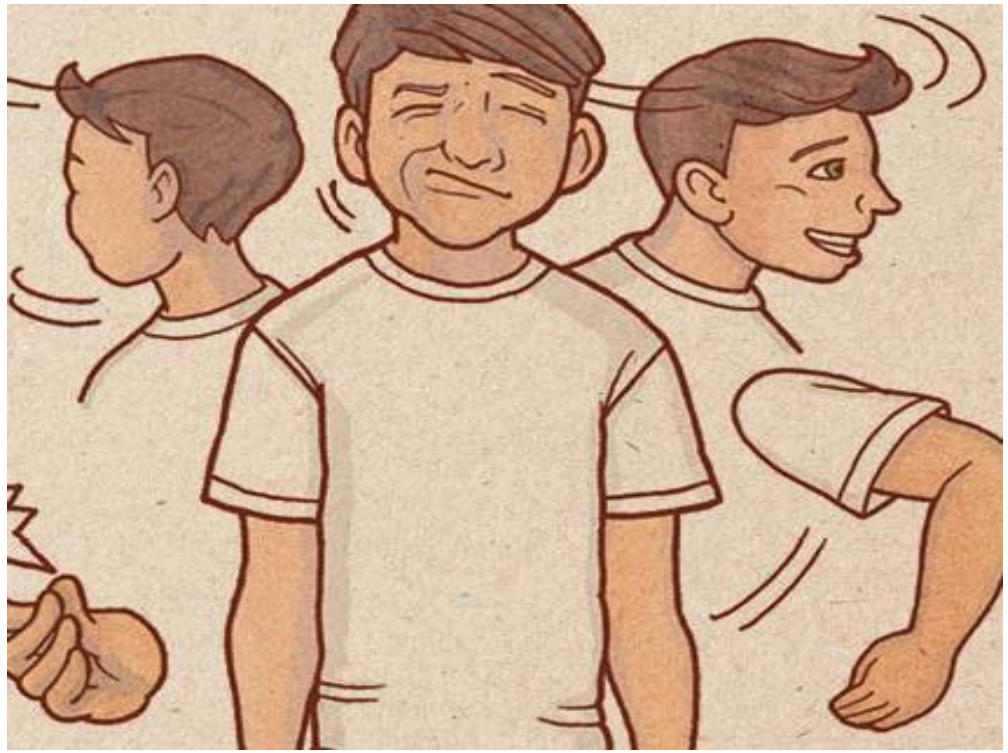


SLEEP DISTRUBANCES

- **Herbals:**
  - Passionflower
  - Skullcap
  - Oat
  - Chamomile
  - Valerian
  - Chinese Skullcap
  - Kava
  - Lavender
  - Ashwagandha
- **Nutrients:**
  - Melatonin
  - GABA
  - Magnesium
  - 5-HTP
  - L-theanine
- **Homeopathy:**
  - Constitutional Remedy
  - Coffea Cruda 30c

TICS

- Oral or IV Magnesium (Garica-Lopez et al, 2009)
- GABA
- L-Theanine
- B6 (Garica-Lopez et al, 2009)
- Essential fatty acids (Gabbay et al, 2012)
- CBD (Seif Kanaan et al, 2017)
- Homeopathy
  - Constitutional Homeopathy
  - Agaricus Muscaris 30c
- Exercise
- Acupuncture (Ma et al, 2006)



FOOD RESTRICTIONS

- ZINC
- Increasing PROTEIN in diet (i.e protein powders)
- MCT OIL
- Digestive bitters
  - Ginger
  - Gentian
  - Anise

ANTIMICROBIAL TREATMENT

- Subjects with new onset of PANDAS and positive rapid strep test/throat cultures treated with appropriate antibiotics – their OCD resolved.

Arch Pediatr Adolesc Med. 2002 Apr;156(4):356-61.

Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS).

Murphy ML[1], Pichichero ME.

Author information

Abstract

BACKGROUND: The current diagnostic criteria for pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS) are pediatric onset, neuropsychiatric disorder (obsessive-compulsive disorder [OCD]) and/or tic disorder; abrupt onset and/or episodic course of symptoms; association with group A beta-hemolytic streptococcal (GABHS) infection; and association with neurological abnormalities (motoric hyperactivity or adventitious movements, including choreiform movements or tics).

OBJECTIVE: To assess new-onset PANDAS cases in relation to acute GABHS tonsillopharyngitis.

DESIGN: Prospective PANDAS case identification and follow-up.

RESULTS: Over a 3-year period (1998-2000), we identified 12 school-aged children with new-onset PANDAS. Each patient had the abrupt appearance of severe OCD behaviors, accompanied by mild symptoms and signs of acute GABHS tonsillopharyngitis. Throat swabs tested positive for GABHS by rapid antigen detection and/or were culture positive. The GABHS serologic tests, when performed (n = 3), showed very high antideoxyribonuclease antibody titers. Mean age at presentation was 7 years (age range, 5-11 years). In children treated with antibiotics effective in eradicating GABHS infection at the sentinel episode, OCD symptoms promptly disappeared. Follow-up throat cultures negative for GABHS were obtained prospectively after the first PANDAS episode. Recurrence of OCD symptoms was seen in 6 patients; each recurrence was associated with evidence of acute GABHS infection and responded to antibiotic therapy, supporting the premise that these patients were not GABHS carriers. The OCD behaviors exhibited included hand washing and preoccupation with germs, but daytime urinary urgency and frequency without dysuria, fever, or incontinence were the most notable symptoms in our series (58% of patients). Symptoms disappeared at night, and urinalysis and urine cultures were negative.

CONCLUSION: To our knowledge, this is the first prospective study to confirm that PANDAS is associated with acute GABHS tonsillopharyngitis and responds to appropriate antibiotic therapy at the sentinel episode.

PMID: 11929370

ANTIMICROBIAL TREATMENT

Antibiotics

- IM Bicillin
- Penicillin, Amoxicillin-Clavulanate, Azithromycin, Clarithromycin, Cephalexin, Cefadroxil, Clindamycin (Shulman et al, Clin Inf Dis, 2012)
- Cefdinir
  - Randomized Trial of CEFDINIR vs. Placebo found that the Cefdinir group had significant improvement in tics and OCD over placebo group (Murphy et al. J of Child & Adol Psychopharm, 2015)
- Azithromycin
  - For long term use must have EKG to rule out prolonged QT interval
  - Is effective against Mycoplasma and has immunomodulatory properties (Obregon et al, Neuropsych, 2012; Murphy et al, J Antimicrob Chemoth, 2008)
- Antibiotic Prophylaxis with Penicillin or Azithromycin

J Child Adolesc Psychopharmacol. 2017 Sep;27(7):640-651. doi: 10.1089/cap.2016.0190. Epub 2017 Mar 30.

A Double-Blind Randomized Placebo-Controlled Pilot Study of Azithromycin in Youth with Acute-Onset Obsessive-Compulsive Disorder.

Murphy TK[1,2,3], Brennan EM[1], Johnco C[4], Parker-Athill EC[1], Miladinovic B[5], Storch EA[1,2,3,6,7], Lewin AB[1,2].

Author information

Abstract

OBJECTIVES: Sudden and severe onset of obsessive-compulsive disorder (OCD) may present secondary to infectious and/or immune-mediated triggers. We assessed the preliminary efficacy, tolerability, and safety of azithromycin compared with placebo in the treatment of OCD and associated symptoms in children with pediatric acute-onset neuropsychiatric syndrome (PANS).

METHODS: Thirty-one youth aged 4-14 years (M = 8.26 ± 2.78 years, 62.5% male) were randomized to receive either placebo or azithromycin for 4 weeks (10 mg/kg up to 500 mg per day). Both groups were administered twice daily probiotics. The primary outcome, obsessive-compulsive symptom severity, was assessed using the OCD Clinical Global Impressions Severity (CGI-S OCD) and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

RESULTS: Participants in the azithromycin group (n = 17) showed significantly greater reductions in OCD severity on the CGI-S OCD than the placebo group (n = 14) posttreatment (p = 0.003), although there were no significant differences on the CY-BOCS. Significantly more participants in the azithromycin condition met treatment responder criteria on the CGI-I OCD at the end of week 4 (41.2%, n = 7) in comparison to the placebo group (7.1%, n = 1; p = 0.045). Tic severity moderated treatment response, with greater tic severity being associated with enhanced treatment response on the CGI-S OCD. Azithromycin was well tolerated with minimal adverse effects and no study dropouts due to side effects. However, the azithromycin group showed a trend toward significantly greater electrocardiography QTc (p = 0.060) at the end of week 4, and significantly more reports of loose or abnormal stools (p = 0.009).

CONCLUSION: This double blind pilot study suggests that azithromycin may be helpful in treating youth meeting the PANS diagnosis, especially those with elevated levels of both OCD and tic symptoms. Azithromycin was well tolerated, but the potential for cardiac risks suggests that additional monitoring may be needed to ensure safety.

ANTIMICROBIAL HERBS FOR STREP

- **Usnea**
  - Activity against strep species (Abachi et al, 2016)
- **Taiga** – Pine needle extract
  - Antimicrobial/antifungal activity (Lee et al, 2005)
- **Berberine (Goldenseal)**
  - Berberine sulfate blocks adherence of Streptococcus pyogenes to epithelial cells, fibronectin, hexadecane (Sun D et al, 1988)
- **Neem**
  - Neem extract effective against four Streptococcus species responsible for causing dental caries (Chava et al., 2012).
- **Oregano Oil**

ANTIMICROBIAL HERBS FOR STREP

- **Cordyceps**
  - Medicinal mushroom containing mycelium which showed to protect against strep (Kou et al., 2005)

- **Allium sativum (Garlic)**
  - Effective against multi-drug resistant bacteria including strep species (Iwalokun et al., 2004)
- **Coptis (Goldenthread)**
  - Antimicrobial properties against strep mutans (Choi et al., 2007)
  - Benefits against parasites as well

- **Capsicum** (Cichewicz and Thorpe, 1996)
- **Achillea** (Candan et al, 2003)
- **Ligusticum** (Xiao et al, 2004)
  - Antibacterial and antiviral support

- **Strep Throat Formula** - *Hydrastis*, *Echinacea*, *Myrrha*, and *Phytolacca*

ANTIMICROBIAL INTERVENTIONS FOR MYCOPLASMA

- Silvercillin
- Berberine/Goldenseal
- Houttuynia
- Isatis
- Reishi
- Pomegranate juice
- Brazil Nuts
- Homeopathic Mycoplasma Nosode

ANTIVIRAL INTERVENTIONS

- Vitamin A
- Vitamin D
- Vitamin C
- L-Lysine
  - amino acid that decreases viral load
- Monolaurin
  - Interferes with virus assembly and viral maturation
  - Do not use if coconut allergy
- Zinc
  - Inhibits viral replication
- Elderberry
  - Hemagglutinin protein has been shown to stop a virus' capability to replicate by inhibiting its ability to penetrate the cell wall (Serkedjieva J and Manolova N, 1999)
  - Do not consume raw elderberries - contain cyanogenic glycosides and must be cooked sufficiently to avoid risk of cyanide toxicity

ANTIVIRAL INTERVENTIONS

- **Glycyrrhiza (Licorice)**
  - Glycyrrhizic acid present in the plant inhibits virus growth and inactivates virus particles (Arora R. et al, 2011)
- **Ginger**
  - Increase levels of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase and TNF-alpha
- **Olive Leaf**
  - Prevents virus shedding, budding, and assembly of cell membranes
- **Lemon Balm**
  - Inhibits virus replication (Pourghanbari et al, 2016)
- **Echinacea**
  - To increase antibody production, increase and stimulate the activity of white blood cells (Brinkeborn et al, 1998)
- Implement acute viral protocols at onset of viral illnesses (i.e vitamin A, D, Zinc, L-lysine, enzyme defense, etc)

OTHER INTERVENTIONS

- **Vitamin D**
  - Deficiency associated with increased frequency infections (Thornton et al, 2013)
  - Downregulate autoimmune processes (Rolf et al, 2014)
- **Ibuprofen/NSAIDS** (Spartz et al, 2017)
- **Xylitol**
  - Inhibits growth of strep mutans and Streptococcus pneumoniae (Tapianien et al, 2001)
  - Effective against yeast
- **Probiotics**
- **BLIS K12**
- **Essential Oils**

Noro Psikiyatr Ars. 2016 Mar;53(1):33-37. doi: 10.5152/npa.2015.8763. Epub 2016 Mar 1.

Vitamin D Deficiency in Obsessive-Compulsive Disorder Patients with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections: A Case Control Study.

Çelik G[1], Taş D[2], Tahiroğlu A[1], Avci A[1], Yüksel B[3], Çam P[2].

Author information

Abstract

INTRODUCTION: Previous studies have indicated that vitamin D deficiency is common in psychiatric patients, particularly in those with neuropsychiatric disorders such as autism and schizophrenia. Vitamin D is an important neurosteroid hormone and immunomodulatory agent that also has bone metabolic effects. There has been an increasing interest in immune-related neuropsychiatric symptoms that are triggered by group A beta-hemolytic streptococcal infections. In this study, we aimed to compare the serum levels of vitamin D between obsessive-compulsive disorder (OCD) patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and control subjects.

METHODS: Thirty-three OCD patients with PANDAS and 20 healthy controls were enrolled in the study. Serum 25-hydroxyvitamin D (25-(OH) D), calcium, phosphorus, alkaline phosphatase, and parathormone levels of the two groups were compared. Serum 25-(OH) D levels of <15 ng/mL were classified as vitamin D deficiency. The children's Yale-Brown Obsessive Compulsive Scale (YBOCS) and Clinical Global Impression (CGI) were used to assess the severity of OCD symptoms.

RESULTS: There was no significant difference in serum 25-(OH) D levels between the patient and control groups. However, vitamin D deficiency was significantly more frequent in the patient group than in the control group (48.5% vs. 20.0%; p=0.038). Moreover, OCD patients with vitamin D deficiency had higher rates of comorbid ADHD than those without vitamin D deficiency (87.5% vs. 52.6%; p=0.027). While serum phosphorus levels were negatively correlated with age as well as alkaline phosphatase and ASO levels, they were positively correlated with the YBOCS total score and global severity score. Serum parathormone levels were positively correlated with the YBOCS total score, compulsion score, obsession score, and global severity score.

CONCLUSION: This study supports the hypothesis that an association between vitamin D metabolism and PANDAS-related OCD exists. We suggest that biochemical parameters predicting metabolic bone diseases are more common in PANDAS patients. There is a need for prospective studies to show a clear association between PANDAS and bone metabolic turnover based on autoimmune mechanisms.

Drug Healthc Patient Saf. 2014 Feb 13;6:15-20. doi: 10.2147/DHPS.S59665. eCollection 2014.

Use of Streptococcus salivarius K12 in the prevention of streptococcal and viral pharyngotonsillitis in children.

Di Pierro F[1], Colombo M[2], Zanvit A[3], Risso P[4], Rottoli AS[5].

Author information

Abstract

BACKGROUND: Streptococcus salivarius K12 is an oral probiotic strain releasing two lantibiotics (salivaricin A2 and salivaricin B) that antagonize the growth of S. pyogenes, the most important bacterial cause of pharyngeal infections in humans also affected by episodes of acute otitis media. S. salivarius K12 successfully colonizes the oral cavity, and is endowed with an excellent safety profile. We tested its preventive role in reducing the incidence of both streptococcal and viral pharyngitis and/or tonsillitis in children.

MATERIALS AND METHODS: We enrolled 61 children with a diagnosis of recurrent oral streptococcal disorders. Thirty-one of them were enrolled to be treated daily for 90 days with a slow-release tablet for oral use, containing no less than 1 billion colony-forming units/tablet of S. salivarius K12 (Bactoblis®), and the remaining 30 served as the untreated control group. During treatment, they were all examined for streptococcal infection. Twenty children (ten per group) were also assessed in terms of viral infection. Secondary end points in both groups were the number of days under antibiotic and antipyretic therapy and the number of days off school (children) and off work (parents).

RESULTS: The 30 children who completed the 90-day trial with Bactoblis® showed a significant reduction in their episodes of streptococcal pharyngeal infection (>90%), as calculated by comparing the infection rates of the previous year. No difference was observed in the control group. The treated group showed a significant decrease in the incidence (80%) of oral viral infections. Again, there was no difference in the control group. With regard to secondary end points, the number of days under antibiotic treatment of the treated and control groups were 30 and 900 respectively, days under antipyretic treatment 16 and 228, days of absence from school 16 and 228, and days of absence from work 16 and 228. The product was well tolerated by the subjects, with no side effects, and only one individual reported bad product palatability and dropped out.

CONCLUSION: Prophylactic administration of S. salivarius K12 to children with a history of recurrent oral streptococcal disease resulted in a considerable reduction of episodes of both streptococcal and viral infections and reduced the number of days under antibiotic and/or antipyretic therapy and days of absence from school or work.

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In Vitro Antibacterial Activity of Essential Oils against *Streptococcus pyogenes*

Julien Sfeir,[1] Corinne Lefrançois,[1,2] Dominique Baudoux,[3] Séverine Derbré,[4,*] and Patricia Licznar[1]

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Abstract

Go to:

Streptococcus pyogenes plays an important role in the pathogenesis of tonsillitis. The present study was conducted to evaluate the *in vitro* antibacterial activities of 18 essential oils chemotypes from aromatic medicinal plants against *S. pyogenes*. Antibacterial activity of essential oils was investigated using disc diffusion method. Minimum Inhibitory Concentration of essential oils showing an important antibacterial activity was measured using broth dilution method. Out of 18 essential oils tested, 14 showed antibacterial activity against *S. pyogenes*. Among them *Cinnamomum verum, Cymbopogon citratus, Thymus vulgaris CT thymol, Origanum compactum*, and *Satureja montana* essential oils exhibited significant antibacterial activity. The *in vitro* results reported here suggest that, for patients suffering from bacterial throat infections, if aromatherapy is used, these essential oils, considered as potential antimicrobial agents, should be preferred.

IMMUNOMODULATORY TREATMENT

- **Steroids** (oral vs IV; length of course depends on symptom severity)
  - Short burst – used therapeutically and diagnostically
  - Temporary fix in some; need to do for 30 days with taper +/- pulses
  - Transient worsening typical
- **Helminth Therapy** – immunotherapy with the use of HDCs
  - www.biomerestoration.com
  - helminthictherapywiki.org
- **Plasmophoresis** – process that filters the blood and removes harmful antibodies
  - severe-extreme disease (Dalmau et al, 2011)
- **Rituximab** – works by turning off a part of the immune system that is not working properly in autoimmune disease
  - Deteriorating, moderate-extreme disease & previous responsiveness & autoimmunity (Chang et al, 2015)

Med Hypotheses. 2019 Apr;125:110-118. doi: 10.1016/j.mehy.2019.02.042. Epub 2019 Feb 19.

Helminth therapy for autism under gut-brain axis- hypothesis.

Arroyo-López C[1].

Author information

Abstract

Autism is a neurodevelopmental disease included within Autism Syndrome Disorder (ASD) spectrum. ASD has been linked to a series of genes that play a role in immune response function and patients with autism, commonly suffer from immune-related comorbidities. Despite the complex pathophysiology of autism, Gut-brain axis is gaining strength in the understanding of several neurological disorders. In addition, recent publications have shown the correlation between immune dysfunctions, gut microbiota and brain with the behavioral alterations and comorbid symptoms found in autism. Gut-brain axis acts as the "second brain", in a communication network established between neural, endocrine and the immunological systems. On the other hand, Hygiene Hypothesis suggests that the increase in the incidence of autoimmune diseases in the modern world can be attributed to the decrease of exposure to infectious agents, as parasitic nematodes. Helminths induce modulatory and protective effects against several inflammatory disorders, maintaining gastrointestinal homeostasis and modulating brain functions. Helminthic therapy has been previously performed in diseases such as ulcerative colitis, Crohn's disease, diabetes, multiple sclerosis, asthma, rheumatoid arthritis, and food allergies. Considering gut-brain axis, Hygiene Hypothesis, and the modulatory effects of helminths I hypothesized that a treatment with Trichuris suis soluble products represents a feasible holistic treatment for autism, and the key for the development of novel treatments. Preclinical studies are required to test this hypothesis.

IMMUNOMODULATORY TREATMENT

Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections.

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Abstract

OBJECTIVE: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are hypothesized to occur as a result of cross-reactive antibodies produced in response to group A streptococcal infections. Previous research suggests that immunomodulatory therapies, such as intravenous immunoglobulin (IVIG), may lead to rapid and sustained symptom improvement in patients with PANDAS.

METHOD: A total of 35 children meeting criteria for PANDAS and moderate to severe obsessive-compulsive disorder (OCD) were enrolled in a randomized-entry, double-blind, placebo-controlled, 6-week trial of IVIG (1 g/kg/day on 2 consecutive days), followed by optional open-label treatment for nonresponders, with follow-up at 12 and 24 weeks. Primary outcome measures were the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Clinical Global Impressions-Improvement (CGI-I) rating. "Responders" were defined, a priori, by a ≥ 30% decrease in CY-BOCS total score, and a "much" or "very much" improved rating on CGI-I.

RESULTS: During the double-blind phase, the mean decrease in CY-BOCS score was 24% ± 31% in the IVIG group (n = 17) and 12% ± 27% in the placebo group (n = 18), with six responders in the IVIG group (35%) versus four (22%) in the placebo group; these differences were not statistically significant. Twenty-four participants met criteria for nonresponse to double-blind infusion and received open-label IVIG at week 6. Among all participants, the mean CY-BOCS improvement from baseline was 55% ± 33% at week 12 and 62% ± 33% at week 24.

CONCLUSION: IVIG was safe and well tolerated. Between-group differences were smaller than anticipated, and the double-blind comparison failed to demonstrate superiority of IVIG over placebo. The observed open-label improvements indicate that future trials would benefit from larger sample sizes designed in part to aid in the identification of biomarkers predictive of a positive response to immunotherapy. Future investigations focused on the natural history of PANDAS are also warranted. Clinical trial registration information-Intravenous Immunoglobulin for PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections); http://clinicaltrials.gov/;

Transl Psychiatry. 2018 Aug 10;8(1):148. doi: 10.1038/s41398-018-0214-7.

Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism.

Connery K[1], Tippett M[1], Delhey LM[1], Rose S[1], Slattery JC[2], Kahler SG[1], Hahn J[3,4], Kruger U[3], Cunningham MW[5], Shimasaki C[6], Frye RE[7,8].

Author information

Abstract

The identification of brain-targeted autoantibodies in children with autism spectrum disorder (ASD) raises the possibility of autoimmune encephalopathy (AIE). Intravenous immunoglobulin (IVIG) is effective for AIE and for some children with ASD. Here, we present the largest case series of children with ASD treated with IVIG. Through an ASD clinic, we screened 82 children for AIE, 80 of them with ASD. IVIG was recommended for 49 (60%) with 31 (38%) receiving the treatment under our care team. The majority of parents (90%) reported some improvement with 71% reporting improvements in two or more symptoms. In a subset of patients, Aberrant Behavior Checklist (ABC) and/or Social Responsiveness Scale (SRS) were completed before and during IVIG treatment. Statistically significant improvement occurred in the SRS and ABC. The antidopamine D2L receptor antibody, the anti-tubulin antibody and the ratio of the antidopamine D2L to D1 receptor antibodies were related to changes in the ABC. The Cunningham Panel predicted SRS, ABC, parent-based treatment responses with good accuracy. Adverse effects were common (62%) but mostly limited to the infusion period. Only two (6%) patients discontinued IVIG because of adverse effects. Overall, our open-label case series provides support for the possibility that some children with ASD may benefit from IVIG. Given that adverse effects are not uncommon, IVIG treatment needs to be considered cautiously. We identified immune biomarkers in select IVIG responders but larger cohorts are needed to study immune biomarkers in more detail. Our small open-label exploratory trial provides evidence supporting a neuroimmune subgroup in patients with ASD.

IMMUNOMODULATORY TREATMENT

- **Probiotics and Prebiotics**
  - Lactobacillus, Bifidobacterium, Bacillius
  - Saccharomyces Boulardii
- **Essential Fatty Acids**–Omega 3 (EPA/DHA) & 6 (GLA)
  - Eat Sardines!
  - Modulation of inflammatory reactions, lowering triglycerides, nerve transmission (Belluzzi et al, 1996)
- **Aloe**
  - Anti-oxidant properties to decrease ROS (Landmead et al, 2004)
- **Curcumin**
  - Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: A randomized, double-blind, placebo-controlled study (Lopresti et al, 2017)
- **CBD Oil**
  - suppression of cytokines and chemokines at inflammatory sites and upregulation of $FoxP3^{+}$ regulatory T cells (Nagarkatti et al, 2009)
- **Flavonoids - Quercetin, Luteolin, Rutin**
  - Potent mast cell stabilizer inhibits release of histamine & inflammatory mediators
  - Prevents excessive release of histamine(Chuenkityanaon et al, 2010)

CLOSING REMARKS

- PANS/PANDAS is a **CLINICAL DIAGNOSIS**
- Think PANS/PANDAS with **ACUTE ONSET** of symptoms (tics, OCD, anxiety, regression, etc.)
- Not every child will present with all of these symptoms
- Treatment plan should include antimicrobial interventions, immunomodulatory interventions, and therapy
- Relapsing and remitting course of symptoms
- Best to combine conventional and natural interventions
- **TAKE CARE OF YOURSELF – YOUR CHILDS HEALTH DEPENDS ON IT!**

THANK YOU!

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