PANDAS & PANS
An Integrative Approach

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Conventional
Approach
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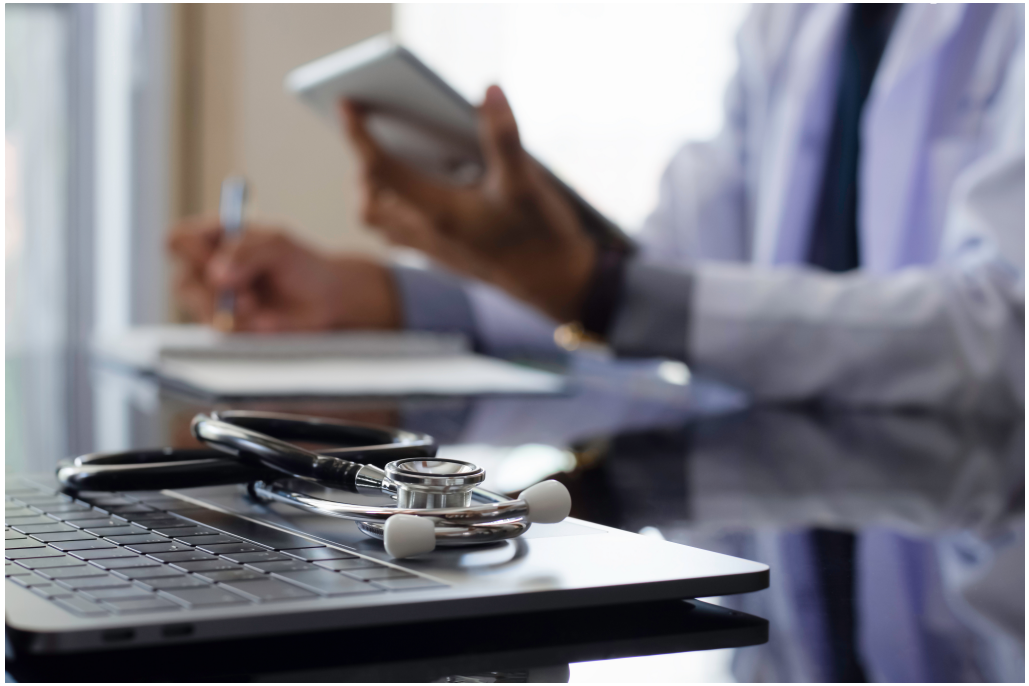

Course Outline

1. Symptoms
2. Mechanisms
3. Diagnostics
4. **Conventional treatment approach**
5. Integrative treatment approach
6. Recovery essentials
7. Cases

Conventional management

1. Control inflammation
   NSAIDs, steroids
2. Prevent/treat infection
   Prophylactic Abx + perianal Strep tx
3. Remove reservoirs of infection
   Tonsillectomy
4. Correct neurotransmitters
   SSRIs/SNRIs
5. Manage behaviors
   CBT
6. Immune modulation
   IVIG, Rituximab, CellCept, Plasmapheresis

Flowchart from PANDAS Physician Network website

Control inflammation

Ibuprofen ~

NSAID. MOA: non-selective inhibitor of cyclooxygenase (COX) which is required for the synthesis of prostaglandins via the arachidonic acid pathway.

Trial period/flare management

10mg/kg bid-tid x 2 weeks.

Maintenance dose varies (Naproxyn may be used for maintenance.)

Tell parents this is intended as prescription strength, may not match OTC dosing, so watch closely for s/e's

S/E - nausea, reflux, bloating, tinnitus, edema, and stomach, intestinal or unusual bleeding

If significant improvement from trial dose, then you know that "taming the flame" is an important target of tx.
Variety of options other than, or used with, NSAIDs

Control inflammation

Corticosteroids ~

Dexamethasone. MOA: glucocorticoids modulate the inflammatory response by repressing the expression of pro-inflammatory cytokines by immune cells.
C/I - hypersensitivity to dexamethasone, uncontrolled infection, systemic fungal infection
S/E - thrush, acne, increased risk of infection, dyspepsia, insomnia, wt gain, h/a, htn, hyperglycemia, confusion/amnesia, vertigo, growth stunting, bone loss, bruising, muscle atrophy

Oral Burst/Taper ~ PANDAS Physician Network

Oral prednisone 2 mg/kg for 1 week
-then taper to 1 mg/kg the second week
-0.5 mg/kg the third week
-0.5 mg/kg QOD for the final week
The maximal initial starting dose is 60 mg per day.
Am dosing and/or before 3pm to mitigate problems with sleeping

Per Stanford PANS clinic “for autoantibody-mediated encephalitis, NSAIDS and oral steroids often won’t come close.”

IV: 3mg/kg/d by continuous IV infusion x 3d/mo x 6mo
Follow with Rituximab or Cellcept (mycophenolic acid/mold derivative)

Prevent infection

Prophylactic Antibiotics ~
- Triggering event is long gone
- GABHStrep is target = “cell wall” beta-lactam antibiotics
- ex: Penicillins, Cephalosporins, Cephamycins
- Per some specialists, dose *really* matters, don’t go too low
  - Ie: Augmentin (875mg amoxicillin + 125mg clavulanate) bid
  - Clavulanate - also beta-lactamase inhibitor
  - S/E - diarrhea, candida, liver/kidney toxicity

Per Stanford PANS Clinic, to keep in remission ~
- IM Penicillin (long-acting) q2-3 weeks
- Even if were compliant on oral AB
- Sydenham’s chorea similarity
- More fitting for PANDAS than PANS?

PMID: 33728634 2021 Cochrane Review. Different antibiotic treatments for Group A Streptococcal pharyngitis.

Perianal Strep

Commonly persistent. Tonsils/gut serve as co-infected reservoirs.

Studies show that treating all the potential reservoir locations, rather than just a topical cream, is most effective.

Topical silver sulfadiazine or pharmaceutical antibiotics *Along* with oral antimicrobials, until there's no sign of infection on culture.

ALWAYS re-culture to make certain is eradicated.

PMID: 30627524

Antimicrobial sources

Many are derived from mold, some are actual mycotoxins
- Compare to enviro testing (if available) before prescribing
- Will affect susceptibility and side-effects if use same source Rx as environment.

Penicillium
- Penicillin, amoxicillin

Acremonium
- *Cephalosporins

Actinomycetes/actinobacteria
- Tetracyclines, macrolides, aminoglycosides, rifamycins

Actinobacteria
- Ivermectin

Side-effects as mold clues

Penicillin

Allergy - IgE-mediated pruritus, rash, GI
Correlated with exposure to environmental Penicillium

"IgE-mediated allergy wanes over time, with 80% of patients becoming tolerant after a decade."…why? tolerance or move?

"Cross-reactivity between penicillin and cephalosporin drugs occurs in only about 2% of cases."

+penicillin skin testing, high-risk anaphylactic cases, +spores

∴ Low- to moderate-risk missed w skin testing, +mycotoxins

PMID: 30644987, 405332

Side-effects as mold clues

Tetracyclines

S/E - photophobia
Correlated with mold exposure
Vitamins A & D deficiency also correlated,
common in mold-exposed patients,
esp if being treated with LT Rx binders

PMID: 14650691, 26269110

Side-effects as mold clues

Macrolides

S/E - Tinnitus
Correlated with mold exposure
Neurotoxic. “First pass" effect at the sinuses
Cavernous sinus - many nerve pass-throughs
Internal carotid artery, abducens nerve (cranial nerve VI)
Cranial nerves III, IV, V1, V2, (oculomotor, trochlear, ophthalmic, and maxillary)

S/E - Cholestatic hepatitis
Inflam/congestion of bile ducts also correl with mold exposure

Remove reservoirs of infection

Tonsils and sinuses can become reservoirs of infection.

Much scientific debate about tonsillectomy. In a survey conducted by the PANDAS Physician Network, parents reported anecdotal evidence that tonsillectomy may have benefit.

IME some benefit, and some don't. Leaves parents conflicted over whether surgery is the right decision.

Where I've seen clear benefit of tonsillectomy are in the children with a specific combination of factors:

- Free of perianal Strep, verified by culture.
- Been dairy free for more than 6 weeks. (Common cause of enlarged, chronically infected tonsils.)
- Free of cavities or dental infections.
- Gut microbiome has been addressed.
- Tonsils have been aggressively tx'd, yet remain large, boggy, cryptic, and may form tonsilloliths.
- Tonsils are large enough to cause snoring or obstructive sleep apnea.

Tonsillectomy in these cases reduces infection and recurrence of autoimmune flares, and improves sleep.

Culture or NGS-PCR test the removed tissue.

- If + for biofilm species, must be treated or may persist in other tissues/sinuses.
- Prevotella - Gram neg anaerobe - most commonly found by Dr. Trifiletti.
- Also commonly find Pseudomonas and Klebsiella.

PANDAS Physician Network Website: Tonsillectomy

"While there have been no published research on the effect of tonsillectomy on PANS or PANDAS patients, there has been unpublished findings and anecdotal evidence that show tonsillectomy may have benefit. ***Many PANS/PANDAS patients have damaged or cryptic tonsils, but the potential benefit of tonsillectomy is not limited to patients with those tonsil characteristics*.**

In an unpublished research study done at Georgetown Medical Center, PANDAS patients had their tonsils removed, analyzed, and the children subsequently tracked for over six months. The tonsils relative to non-PANDAS patients had many pathogens, most prominent being staphylococcus (staph). ***Streptococcus pyogenes was not found in PANDAS patients but was present in non-PANDAS controls***. Other notable pathogens included MRSA, E. coli, Pseudomonas and Serratia marcens. ***The absence of Streptococcus in the PANDAS cohort suggests that once the patient has been "sensitized" other pathogens can induce neurologic symptoms in susceptible patients.***

In addition, the ***tonsils belonging to PANDAS patients contained elevated levels of TH17***, indicating a consistent immune response to the pathogens lodged within the tonsils. TH17 has been found in animal PANDAS research to be a potential agent for opening the blood brain barrier, allowing inflammation in targeted regions of the brain.

The Georgetown study and physician experience indicates that removal of the tonsils can provide remission of PANS and PANDAS symptoms for some patients. There is no marker to determine which patient a tonsillectomy will result in remission of PANS/PANDAS symptoms.

A clear benefit of tonsillectomy that was found in the Georgetown study and further observed by practitioners who see many PANS/PANDAS patients, is that ***those PANS/PANDAS cases that have undergone tonsillectomy, have a significantly lower chance of recurrence post-immunotherapy such as IVIG*.** Since immunotherapy suppresses the potential cause of basal ganglia encephalitis and in some cases like IVIG "reboots" the immune response, then removing a consistent infectious trigger housed within the tonsil or removing a repository for new pathogen agitators would most likely be beneficial."

What factors lead to the benefit?

2016 Review by Windfuhr. *Tonsillectomy remains a questionable option for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).*

"The positive outcome after TE as reported in case studies may be influenced by the postoperative medication and is not supported by the results of large-scale studies. In the light of the considerable postoperative morbidity rate, it appears wise to indicate TE for PANDAS only in supervised clinical studies."

Options to address sinus and tonsil health is covered in the next module.

PMID: 28025607

Correct neurotransmitters

SSRIs/SNRIs
- Ultra low dose required (consistent with toxin-based syndromes)
- Postulate that flare increases permeability of BBB
- Equates to “sprinkles” of typical initial dose, ie: 1/8-1/4 normal dose
  ex: 6.25mg sertraline, 2mg fluoxetine
- Tendency to increase dose bc not responding = miss therapeutic window
- Often will cut dose rather than increase
- Also must account for normal wax/wane of dz

Must weigh the costs to the brain living in torture vs S/Es of Rx
- “Never belittle the history” & “assess for safety” (behaviors/nourishment)
- Views rage attacks as “defensive aggression” ie: cornered animal
- Often won’t remember bc “no one’s home” during the event
- Safety for all is imperative. Monitor triggers (hunger, fatigue, infection risk)
- Dr. Margot Thienemann, Stanford PANS Clinic
- *Recommend Stanford CME she offers: 1st steps when you meet w PANDAS/ PANS pt

EMDR - helpful also for parents who are perpetually in dread, waiting for next flare

Manage behaviors

CBT ~
Cognitive-Behavioral Therapy
My bias - worsens limbic imbalance
False ‘belief’ or wiring? Or are they reacting to triggers we haven’t yet identified.
Highlights the need for paradigm shift - recognize trauma-induced vs physiologically-induced behaviors
I encourage a middle ground - honor the sensory input and tamper the reaction.
Utilize CBT or other like measures with modification to help the child gain skills.

MCBT more fitting

CBT is best for the parents!

Cautionary Tale

Intravenous Immunoglobulin Therapy (IVIG)

Not every child with PANDAS or PANS needs this to recover.

Hesselmark et al, cohort of Swedish patients: Antibiotics and IVIG were rated as the most successful treatments by participants and were associated with higher patient satisfaction.

The purpose is suppression of Ig production, resulting in loss of autoantibodies/memory cells.

Dose and route of administration are paramount.
Dose: 1.5-2 g/kg given over 2 days given IV [note: dose typo in my book]

Needs to be high dose to accomplish suppression. SQ cannot hit the peak plasma level required for suppression.

Requires repetition to maintain the suppression - IME q 4-8 weeks. The “one and done” has not been durable.

Insurance often pressures you to use the typical supportive dose or SQ. This is NOT recommended. Can flare autoimmunity.

Must check IgA w subclasses (as well as IgG w subclasses) to choose IVIG brand. Some include IgA (risk of thrombosis if not also IgA deficient.)

I suggest referring to collaborative Allergist/Immunologist for administration. Home health services are available, but I don’t recommend this if you don’t have the specialty, and especially not for the first few rounds.

PMID: 31009235

IVIG supportive care

IVIG side effects ~

Occur on days of infusion + a few days following.
Low-grade fever, headache, flushing, itching, back pain, increased blood pressure, and fatigue.
May also see a temporary autoimmune thyroiditis, which tends to go away once the child is done with treatments after 6-9 mo's.

S/E management ~

Diphenhydramine, ibuprofen on infusion days + few days following.
May use IV glutathione push or steroids to prevent severe headaches.
Write on the order *SLOW INFUSION RATE* ~ 6-8 hours per day: many AEs can be prevented.
Home health nurses will go faster if not stipulated every time.

Many side effects can be prevented with 3 simple things ~

IV hydration - 500 mL hydration IV bag just before the IVIG
Slow drip rate
Glutathione

IVIG genetic prognostics?

Is it possible to screen for who will respond best to IVIG and who might respond better using it as step therapy to Rituximab or Plasmapheresis?

Empirically, best responders have genetic snp of Fcγ Receptors. Could Ig senescence be a contributing factor for persistence?

2010 Review: “Possible mechanisms of action of IVIg in autoimmune and inflammatory diseases are: *intact Fc-dependent blockage of IgG* (as in ITP), inhibition of membrane attack complexes (C5b-C9) and activated components C3b and C4b (as in Kawasaki's disease), and anti-idiotypes against autoantibodies (as in acquired hemophilia due to autoantibodies against factor VIII). IVIg also contains various cytokines and natural antibodies that may act against pathogens, altered molecules, cells, autoreactive B cell clones, and tumors.”

PMID: 19590986

Immune modulation

Rituximab ~

Humanized chimeric anti-CD20 monoclonal antibody, which is expressed on the surface of pre-B and mature B-lymphocytes. After binding to CD20, rituximab mediates B-cell lysis.

“we still do not fully understand the mechanisms of action … Direct signaling, complement dependent cellular cytotoxicity and antibody dependent cellular cytotoxicity all appear to play a role.”

Plasmapheresis ~ **Ochratoxin**

“Blood cleaning” procedure - child’s blood is removed through IV catheter and processed by a plasmapheresis machine, which spins it to separate the formed elements (RBCs, WBCs, platelets) from the plasma. The plasma is removed and replaced with equal volumes of albumin. The albumin is mixed with the child’s blood components and returned to his body through a second IV catheter. Multiple procedures are needed, often requires insertion of a central line. Carries significant, but manageable risks, it should be done only in pediatric apheresis centers.

PMID: 20350658. Other Sources: PANDAS Physician Network, Journal of Child and Adolescent PsychopharmacologyVol. 25, No. 1


Conventional Approach
Next up: Integrative Approach
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