

PANS/CANS and PANDAS

SNPed Lecture 13
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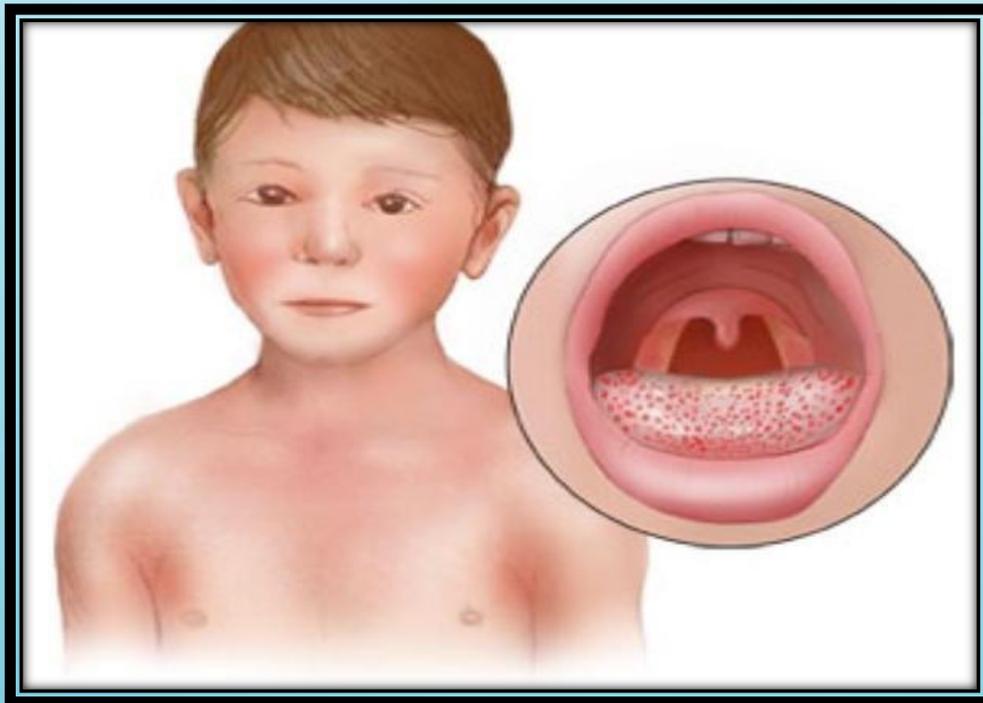
Content Overview

- Definitions
- Symptoms
- Pathophysiology
- Mechanisms
- Testing
- Allopathic Treatments
- Functional Approach

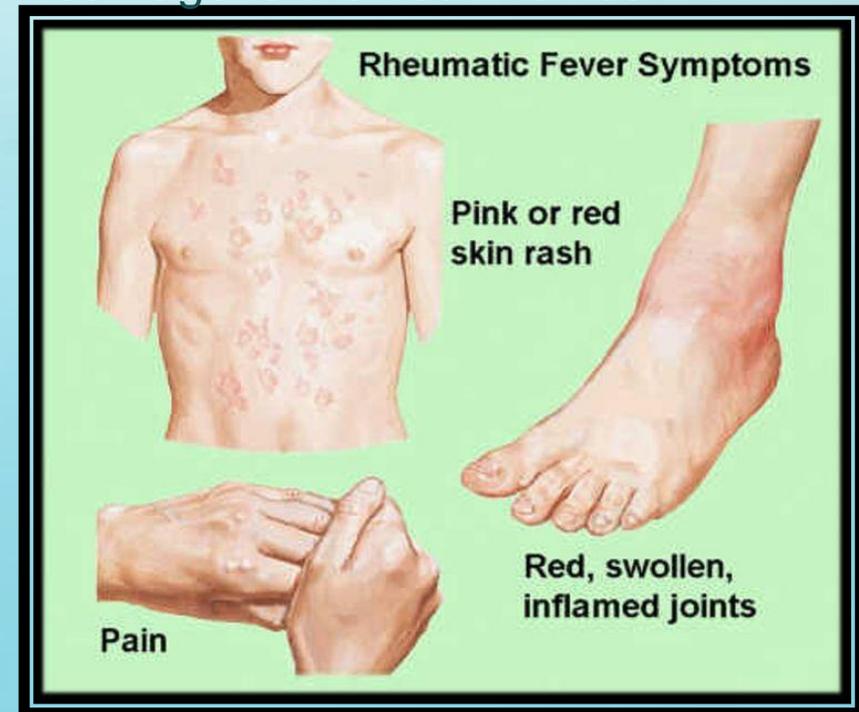
Definitions

GABHS: Group-A Beta-Hemolytic Streptococcal infection – Most commonly known for causing strep throat, but can also lead to Scarlet Fever and Rheumatic Fever (*S. pyogenes* – (pie-og-en-knees)).

Scarlet Fever: Red rashes (sandpaper) appear on the body in reaction to toxins produced by GABHS bacteria; Berry tongue.



Rheumatic Fever: A complication occurring with long-term exposure to these toxins leading to painful, swollen joints and fever. There is also potential damage to the heart valves.



Definitions (continued)

- **SC: Sydenham's chorea (syd-en-hams chor-e-ah)**- A well-characterized manifestation of Rheumatic fever, is considered the prototype of neurologic disorders caused by aberrant immune responses to GABHS. SC patients often exhibit obsessive-compulsive symptoms (OCS) together with other behavioral abnormalities.
- **PITANDs: Pediatric, Infection-Triggered, Autoimmune Neuropsychiatric Disorders** - Presents similarly to SC. Renamed “PANDAS” to reflect a direct association with streptococcus and to provide a set of working diagnostic criteria developed by Swedo et al. in 1998 (not necessarily acute).
- **PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections** - Refers to children with abrupt onset of behavioral abnormalities including tics and/or OCD associated with a recent GABHS infection.

Definitions (continued)

- **PANS: Pediatric Acute Onset Neuropsychiatric Syndrome** -
Comprises the same onset of symptoms as PANDAS, however includes causes other than GABHS (newer name for PITANDS).
- **CANS: Childhood Acute Neuropsychiatric Syndromes** - The most recent and accurate umbrella term used to describe neuropsychiatric symptoms with acute onset in childhood.
 - Variety of potential causes
 - Etiologies include infectious, post-infectious, drug-induced, toxic, traumatic, vascular, autoimmune, hypoxic and psychogenic.

Symptoms

Diagnostic criteria for PANS/CANS/PANDAS:

- An abrupt, dramatic onset of Obsessive Compulsive Syndrome (OCS) and/or severely restricted food intake
- At least two of the following:
 - Anxiety/separation anxiety
 - Emotional lability/depression
 - Oppositional behaviors including aggression and irritability
 - Developmental regression (typically assessed by writing or coloring abilities)
 - Dramatic deterioration of school performance
 - Loss of motor acuity and sleep disturbances
 - Enuresis or urinary frequency
- The child must be at least three years away from the onset of puberty for PANDAS/PANS
- Can also present with repetitive vocalizations of body movements known as TICs, Tourette's Syndrome, attention deficits with motor hyperactivity and choreiform movements.

Choreiform Movements (Chor-e-a-form)



Pathophysiology

- Currently very little is known about the underlying etiology of these abrupt pediatric neuropsychiatric conditions.
- For PANDAS, it has been presumed that the sudden onset is associated with an extreme autoimmune response to the streptococcal (GABHS) infection.
- The concept of T-cell molecular mimicry as the etiology of autoimmune disease has also been suggested for SC and PANDAS.
- For all other non-streptococcus conditions (CANS/PANS), there is some supportive evidence to suggest autoimmune activation of neuronal antibodies, but this data is far from conclusive. Look for concurrent diagnoses of Coxsackie A & B, Lyme disease and Mycoplasma as triggers.

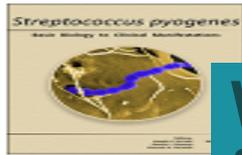
T-Cell Mimicry



Autoimmunity

- When GABHS bacteria avoid host detection using molecular mimicry, the antibodies created to combat the foreign antigen display cross-reactivity, mistaking normal antigens for the foreign ones by mimicking their molecular structure.
- The cross-reactive antibodies created induce an autoimmune reaction, binding to neuronal antigens which can potentially stimulate or inhibit their functions, triggering neuropsychiatric or motor irregularities, typically in the basal ganglion.
- Studies have shown that children with SC have antibodies that cross react with an epitope of the GABHS, epitope N-acetyl-beta-D-glucosamine, in addition to brain rich lysoganglioside and tubulin, suggesting a correlation to the PANDAS presentation (Kirvan, 2003 and Kirvan, 2007).

M Proteins/Receptors? Acetylcholine Connection



Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet].

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What it does: main end-receptor stimulated by acetylcholine from postganglionic fibers in the parasympathetic nervous system.

S. pyogenes is not only an extracellular pathogen, but can survive phagocytosis inside the cells. M-protein-expressing *S. pyogenes* strains, can survive after phagocytosis by human neutrophils and the surface M-anchored protein has been identified as the pivotal factor that affects the phagosomal maturation in macrophages.

Why this matters? *S. pyogenes* induces molecular mimicry because it survives the neutrophil attack and is sensitive to ACH - the chemical that motor neurons of the nervous system release in order to activate muscles. (ALZ and Myasthenia gravis)

Pediatric Streptococcus

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Foreword

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PANDAS Testing

- The extreme autoimmune response to GABHS, the proposed mechanism behind PANDAS onset, can be assessed by testing for anti-streptococcus antibody titers including:
 - ASO (Antistreptolysin O)
 - AntiDNAse-B (Antistreptococcal DNAase B)
 - Anti-A-Carbohydrate

Dopamine Connection

- Dopamine is required for fine motor control, cognition, mood and neurotransmitter balance. (High levels=schizophrenia/paranoia; low levels=Parkinson's)
- Serves as the precursor to the biologic amines norepinephrine and epinephrine.
- Its actions are mostly mediated by DR1 and DR2
 - DR1 mutations have been significantly associated with bipolar disorders (Severino, 2005; Asuni, 2007), ADHD (Misener, 2004; Bobb, 2005) and alcoholism (Limosin, 2003; Kim, 2007).
 - DR2 is associated with adult walking behavior, associative learning, auditory behavior, behavioral responses to cocaine and ethanol, feeding and grooming behavior and myoclonic dystonia that could potentially be responsible for choreiform movements seen in PANDAS.
 - A small subset of PANDAS and SC patients have presented with choreiform movements and all had antibodies against DR2 (Cox, 2013, Ben-Pazi, 2013, Cunningham, 2016).

PANDAS and SC Testing

- The Cunningham Panel is a test developed to assess the level of antibodies to the following neuronal antigens associated with PANDAS/SC.
 - **Tubulin**: A ubiquitous structural protein. Antibodies affect most connective tissue along with neuronal tissue. Anti-Tubulin is associated with the rheumatic endocarditis found in SC and Rheumatic fever.
 - **Lysoganglioside-GM1**: Found throughout the central nervous system and concentrated in neuron membranes. Antibodies are associated with degenerative neurologic conditions such as Guillain-Barre syndrome, which is also believed to have an infectious etiology.
 - **Calcium calmodulin dependent protein kinase II (CaMKII)**: Involved in synthesis and release of neurotransmitters like dopamine. Autoimmune antibodies cause increased activity of the enzyme, subsequently increasing dopamine levels and altering dopaminergic pathways.
 - **DR1 and DR2**: Found to be significantly increased in children with SC; potentially further increases dopamine levels, leading to increases in the adrenergic amines (epinephrine and norepinephrine) which could then result in the anxiety and hyperactivity commonly seen in this population.

Potential Genetic Targets

- Other potential antibody titer candidates include non-HLA B cell markers such as D8/17, a monoclonal antibody first found in relation to Scarlet Fever.
- High levels of these antibodies are found in significant numbers in the following conditions: SC, PANDAS, OCD, tic conditions, autism, anorexia nervosa and adult onset OCD (Moretti, 2008).
- Further, positive D8/17 cells are inherited in an autosomal recessive fashion, which is a different mode of inheritance from typical Major Histocompatibility Complex (MHC) cells, indicating a genetic predisposition for these conditions (Khanna, 1989).
- In addition to the dopamine receptor issues and pathway genomics, alterations in genes that regulate mannose-binding lectin and the FcRγIIA receptor may result in an inability to clear immune complexes from the blood, another proposed mechanism for autoimmunity (Cunningham, 2016).

Genomics to Consider

- For more information on the Dopamine Receptors – please reference the neurotransmitters and nutrigenomics lecture – Part 1.
- DR1: rs4867798, rs251937, rs686, rs5326, rs4532, rs265981
- DR2: rs6277, rs1799732
- DR3: rs167771
- DR4: rs916457, rs752306, rs11246226, rs3758653, rs1800443, rs4331145
- FcRγIIA: rs2251746, rs2427824, rs10489854
- B cell marker D8/17: Blood test – antibody rapid detection (not tested for at 23 and me); Genetic predisposition to rheumatic fever.
 - Close to the HLA-DQ region – so what disease is highly concurrent? Celiac!

Conventional Treatments

- **Antibiotics:** Currently there is insufficient data to support routine use of antibiotic prophylaxis as studies have been inconclusive or poorly controlled!!! Extended use of powerful antibiotics can also compromise a growing child's gut microbiome, wreaking havoc on their developing metabolism and weakening their immune system.
- **Tonsillectomy/adenoidectomy:** There have been multiple case reports on the benefit of these procedures in mitigating symptoms of PANDAS, however research does not demonstrate a positive impact on children with OCD or tics, regardless of a PANDAS diagnosis.
- **Combination of SSRIs and Cognitive Behavioral Therapy:** Although proven effective in treatment of OCD, whether or not triggered by GABHS, many patients are still non-responsive or have an unsatisfactory response to treatment, including those in the PANDAS subgroup.
- **Immune-modulating treatments:** Plasma exchange and IVIG (intravenous immunoglobulin therapy) demonstrated a significant reduction in severity of OCD symptoms in one study of PANDAS patients, however, adverse effects such as nausea, vomiting and headache occurred in about two-thirds of those in the treatment groups (Perlmutter, 1999). Additionally, a subsequent study failed to demonstrate a benefit of IVIG over placebo (Williams, 2016). The hefty price tag and risk for infection that accompanies the use of IV therapy makes this a questionable choice.

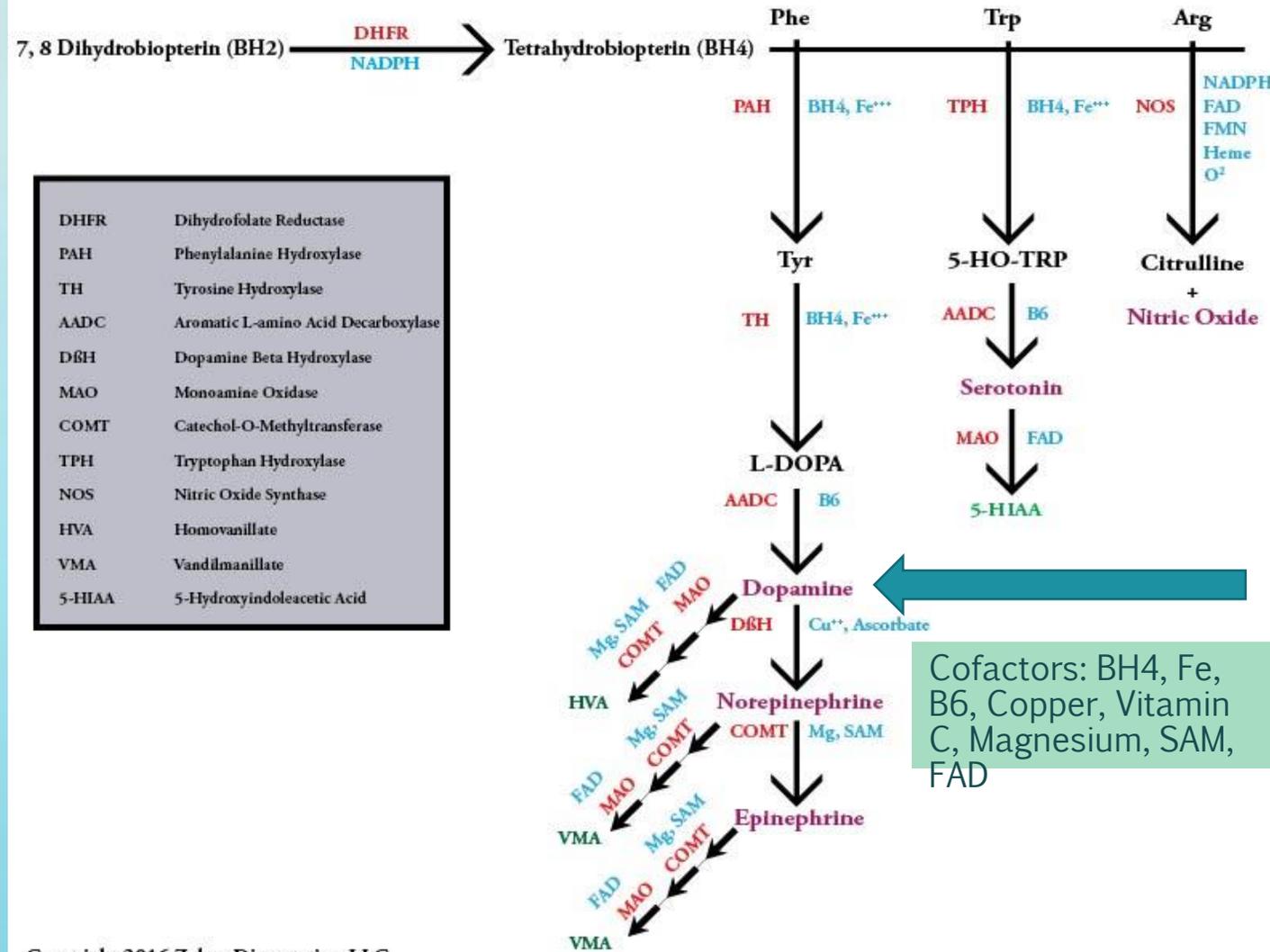
Functional Approach

- Autoimmune 5R program: Leaky gut=Leaky Brain! Remove, Replace, Reinoculate, Repair, Rebalance (please see dysbiosis lecture for more details)
- Identify and remove all known environmental allergies and food allergies to alleviate the improper activation of the immune system. Begin with removal of major allergens like gluten, dairy, soy, corn and eggs.
- Natural anti-microbials such as olive leaf, oil of oregano, berberine and immuno-modulation of the gut by lactoferrin, provides a much less severe approach to eradicating pathogens.
- Probiotics: *S. salivarius K12* is known to inhibit the pathogenic *Streptococcus pyogenes* found in the majority of PANDAS cases. Prophylactic inoculation with probiotic supplements containing *S. salivarius K12* may prevent the colonization of *S. pyogenes* and thus decrease the auto-antibody response in children with PANDAS.
- Zinc carnosine could also confer benefits in mitigating symptoms and repairing the gut mucosa.
- Reduce Inflammation! Fish oil, antioxidants, curcumin
- Modulate any preexisting dopaminergic pathway abnormalities to re-create balance.

Remember the Dopamine Pathway?

DHFR is the precursor to both the folate and neurotransmitter cycles....thus removing gluten reduces folic acid and assists in detoxication and proper synthesis.

BH4 and Neurotransmitter Synthesis



Anorexia Nervosa Presentation

- While OCD is more commonly recognized as a CANS symptom, sudden onset of severe eating restrictions can be a defining feature in some cases.
- These aberrant food restrictions are usually driven by obsessive fears including:
 - Contamination fears (poison, germs, allergens, fats, excess calories)
 - Fears of vomiting, choking or swallowing
 - Fear of weight gain may also transpire secondary to development of body image distortions.
- Some presentations can start out mimicking classic anorexia symptoms
 - A case report of an 8 year old male describes his concern of weight gain, believing he was “too fat” and looking at himself in the mirror multiple times a day. He then developed suspicion of his mother contaminating his food and began eating only packaged products (Calkin, 2007).
- Others display unfounded thoughts or behaviors leading to restrictive intake
 - One young female presented with extreme guilt, constantly apologizing when she had done nothing and became convinced that she “did not deserve to eat” leading to food refusal, especially of anything she considered a ‘treat’ (Toufexis, 2015).

Adult onset PANS/PANDAS?

- There is some, very minimal evidence that suggests that there may be an adult-onset version of these conditions, however, the delineation between the DSM-V diagnostic for Obsessive Compulsive Disorder (OCD) and acute onset is blurred in adults.
- The major criteria for PANDAS/CANS/PANS is OCD and/or Anorexia.

OCD-DSM-V

- To receive an OCD diagnosis, you must meet these general criteria:
 - You must have obsessions and compulsions
 - The obsessions and compulsions must significantly impact your daily life
 - You may or may not realize that your obsessions and compulsions are excessive or unreasonable
- Your obsessions must meet specific criteria:
 - Intrusive, repetitive and persistent thoughts, urges, or images that cause distress
 - The thoughts do not just excessively focus on real problems in your life
 - You unsuccessfully try to suppress or ignore the disturbing thoughts, urges, or images
 - You may or may not know that your mind simply generates these thoughts and that they do not pose a true threat
- Your compulsions must meet specific criteria:
 - Excessive and repetitive ritualistic behavior that you feel you must perform, or something bad will happen. Examples include hand washing, counting, silent mental rituals, checking door locks, etc.
 - The ritualistic compulsions take up a least one hour or more per day
 - You perform these physical rituals or mental acts to reduce the severe anxiety caused by the obsessive thoughts.

This is a typical presentation in PANS/CANS/PANDAS – Thus, they meet to diagnostic criteria for OCD – could it just be pediatric onset?? Especially in CANS/PANS?

What Causes OCD?

- Imbalance in neurotransmitters, including serotonin, dopamine, glutamine, GABA and glutamate
- Certain genes – some overlap in PANDAS
- So what is the difference?
 - In PANDAS – the OCD occurs very suddenly, seemingly overnight, and has a very immediate, severe impact on the child's life. “Regular” pediatric OCD has a gradual presentation – occurring over many weeks, months or years.

Connective Tissue Disease Associations?

- Generally speaking – collagen deficiencies result in not only stretchy ligaments and fibers, but also of all the other soft tissues in the body, including the GI mucosa and the blood brain barrier.
- Flanagan, 2015 suggests that alterations in the craniocervical junction alter not only the hydrodynamics of spinal fluid, but can also impact disease such as Alzheimer's disease, Parkinson's disease, MS, and ALS, as well as many other neurological conditions including hydrocephalus, idiopathic intracranial hypertension, migraines, seizures, silent-strokes, affective disorders, schizophrenia, and psychosis.
 - This juncture is also where we look at Arnold Chari malformation – A common comorbidity of connective tissue disease.
- Lujan–Fryns syndrome (LFS) includes a Marfanoid habitus and psychosis like behavioral abnormalities. Marfan Syndrome, Osteogenesis Imperfecta and Ehlers Danlos Syndrome all have neurological associations that could increase the incidence of CANS/PANS/PANDAS.

Vaccine Connections?

- Does vaccine injury precipitate PANDAS?
 - The majority of PANS/CANS/PANDAS parents can pinpoint to the day and hour when their child began showing symptoms; Most can often correlate this to a recent vaccine – “back to school shots”. This vaccine injury at first appears “normal”, however, the immune system is activating – it has been exposed to a pathogenic species and is concurrently being hindered by all of the excipients that were also in the vaccine. This hyperactivation of the immune system, stimulates molecular mimicry on the part of the pathogen, which then stimulates the same autoimmune reaction when the child is further exposed to another pathogen – like Strep.
- What is vaccine injury?
 - When the child has ANY adverse reaction, even those that are considered “normal” such as excessively crying (typically brain swelling), no or limited affect (they won’t look you in the eyes or connect), rash, swelling, fever, lethargy, etc.!

Vaccine Connections?

- A pilot case-control study found a temporal association of some neuropsychiatric disorders following vaccination such as those with newly diagnosed anorexia nervosa being more likely than controls to have had a vaccination in the 3 months prior. Other such findings were a history of influenza vaccinations during the previous 3, 6 and 12 months being associated with diagnoses of anorexia, OCD and anxiety (Leslie, 2017).
- However, Cai et al., 2015 found in a meta-analysis that psychosis occurred more often in the adult children of mothers who experienced gestational influenza, advocating the importance of flu vaccinations.
- A review by Gasparini et al., 2015 recognizes that severe neurological diseases may occur simply by chance, promoting a causal relationship as an “urban myth”. It highlights the important point that case reports producing this conclusion have almost always displayed only a temporal association between vaccination and neurological events. Controlled studies either excluded these associations or have not been able to endorse a causal link.

Autism Association?

- In children with autism, it is estimated that over 30% may also have PANDAS.
 - Recognition and diagnosis of PANDAS may be more challenging given the overlap of symptoms. It could also be mistaken as classic OCD, a common co-morbidity of autism.
 - Brain swelling from neuronal antibodies may also cause severe pain and induce head-banging, a commonly overlooked manifestation of autism.
- The monoclonal antibody D8/17 related to GABHS infections are also found in higher rates in children with autism. Additionally, severity of repetitive behaviors was significantly correlated with D8/17 expression, suggesting it may have a relationship with reactive autoimmunity (Hollander, 1999).

Case Study

- 15 year old female of Hispanic/Asian decent with a 3-time history of strep. She is the oldest of 5 children and the middle three children have recently been diagnosed with Scarlet Fever. She began menstruating 6 months ago and her periods have been irregular. She is underweight and small for her age at 4'10 and 85 lbs. Her father has osteopenia that was diagnosed in childhood. She presents with:
- Urinary incontinence. She would walk into the bathroom and urinate on the floor.
- She has intrusive thoughts that she is doing something “bad”. This is interfering with her ability to have a spiritual relationship – which is very important in her family. She often becomes “paralyzed” when she has these thoughts and will stare off for several minutes. There is a family history of epilepsy.
- She has compulsions to not bend forward – she believes that she is bowing down to the devil.
- She has a regression in school work and is unable to complete her tasks – there has been no regression of writing/drawing skills.

Case Study Presentation Continued:

- She is constantly curling her fingers and grimacing.
- She is positive for mycoplasma and chlamydia pneumonia with a h/o pneumonia, recent EBV, Lyme and CMV
- She is fully vaccinated
- She complains of no longer enjoying activities with her friends/family
- She has great difficulty sleeping and sleeping alone
- She has extremely bad reactions (intensification) after eating Chinese Food – 1x/week.
- She has acidic urine, signs of hypochlorhydria, dysbiosis, folate trapping and a high level of Insulin-like growth factor and her alkaline phosphatase is consistently between 400-500 (optimal is 70-100; assoc. w/bone loss/dysbiosis/biliary obstruction) (serum zinc is low).
- She is negative for ASO (Antistreptolysin O), AntiDNAse-B (Antistreptococcal DNAase B) and Anti-A-Carbohydrate and has thyroid conversion issues.

Case Study Continued

- Her ND puts her on 600mg of NAC BID – she has a noticeable improvement. She is on a gluten, dairy and shellfish free diet – but the family is not very strict with the gluten exposures (Chinese food 1x/week)
- Her physician prescribes the following: Augmentin, Diflucan for suspected vaginal fungal overgrowth (vaginosis- negative for chlamydia) , Alinia for suspected protozoan/parasitic infection/green stools with IBS-M presentation with an expected prescription for Rifampin for anti-viral/bacterial protection. She has been on this regiment for 4 months.
- She has been taking Swanson Oral Probiotic with Blis K12 for 5 weeks and has not had any recurrent infections. Patient and parents report improvement in the last month or so.
- She has been taking 100 mg of 5-HTP, 3 mg of melatonin, Speak nutrients fish oil, a mix of magnesium, vitamin C, D3, *S. boulardii* and Curamed (turmeric)
- How do you intervene? Does she fit the criteria for PANDAS/CANS/PANS?

Case Study Intervention

- Order OAT/UAA/ IgG food allergy test along with 23 and me
- Refer for DEXA – Juvenile osteoporosis can be secondary – caused by Celiac, diabetes, blood cancers and osteogenesis imperfecta – once genome is back – full connective tissue disease evaluation – also check hydroxyproline on OAT; check for HLA's associated with diabetes and Celiac.
- Place family on very strict gluten free/dairy free diet until testing is returned – then remove any additional offenders.
- Modify supplements – Keep These
 - Allergy Research Group Buffered Vitamin C – 1000mg – 2x/day
 - Pure Encapsulations Vitamin D3 1,000 IU – 3 drops/day - Bring down to 2 drops per day
 - Pure Encapsulations *Saccharomyces boulardii* – 1 capsule/day - please take everyday
 - Swanson Oral Probiotic Formula with Blis K12 Strawberry Flavor- please take everyday
 - Speak by Speech Nutrients (EPA, DHA, GLA, Vit E and Vit K) – 4/day
- Order Growth Hormone, 24 hour free cortisol and potentially refer for a dexamethasone suppression test – IGF being elevated could indicate an issue in the pituitary and /or adrenals.
- Increase dark leafy vegetable and citrus fruits for acidic urine.

Supplements to help until testing is returned

- P5P50 (activated B-6) by Pure Encapsulations- 1 capsule once per day with a meal. This is the co-factor that targets both of the anxiety genes, and also the glucose regulation.
- CogniMag by Pure Encapsulations- take 1 capsule, twice daily, before a meal and at bedtime. This is the form of magnesium that crosses the blood brain barrier.
- 5-Hydroxy Gaba by Priority One Vitamins-Take one capsule 30 minutes before bedtime This should replace bedtime supplements (Melatonin at that dosage should not be sustained).
- Bone Strength Take Care tiny tabs by New Chapter-Take three tiny tabs, one at each meal. This will help preserve bone loss
- L-Theanine 100 mg by Integrative Therapeutics-1 capsule once per day Or as needed for anxiety. Do not take more than 2 capsules per day.
- Zinc-Carnosine by Integrative Therapeutics-1 capsule once per day; This helps with the tight junctions in the GI system. Fix the leaky gut, help the leaky brain.
- Activated B-12 Guard™ 2000 mcg by Perque-1 lozenge once per day under tongue and let dissolve.
- NAC by NOW-One per day; The selenium in this product will help with the poor thyroid conversion and the molybdenum assists with turning cystathionine into taurine as well as glutathione (SUOX – sulfur metabolism). This will reduce any additional stress placed on this system that could result in sulfur intolerance and an increase in cortisol/glutamate. We may consider increasing or reducing this dosage once the genomic data and labs have been evaluated.
- Ther-Biotic Children's Chewable (60 tablets) by Klaire Labs-1 chew once per day 30-60 minutes following a meal.
- Consider Dopatropic by Biotics Research

Upcoming SNPed Lectures

New times to come: 7:30 pm on Thursday nights
and 12 pm on Friday's.

- 4/26- Detoxification: Phase I (JP)
- 5/10 – Mitochondrial SNPs part 3 (CW)
 - 5/24- Organic Acids Part 1 (JP)
 - 6/7 – Amino Acids part 1 (CW)
 - 6/28 – Organic Acids part 2 (JP)
 - 7/12 – Amino acids part 2 (CW)