

THE PANDAS/PANS DISORDERS. Is It Time for More Allergist-Immunologists to Get Involved?

June 2, 2023

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Learning Objectives

- To define the possible immunologic mechanisms involved in the pathogenesis of the PANDAS/PANS DISORDERS
- To describe potential strategies for diagnosis and clinical management of the PANDAS/PANS DISORDERS
- To define the extent to which allergist-immunologists might be involved in their management

Topics We will Cover

1. How Does Our Immune System Recognize ANY Antigen ("Foreign Agents") and Respond?
2. What is Molecular Mimicry and How Can it Trigger Autoimmune Disorders?
3. What Does Molecular Mimicry Have to do with Neuropsychiatric Conditions in Lyme, PANDAS/PANS, and Long-COVID?
4. Neuropsychiatric Symptoms Resulting from Infection-Triggered Autoimmune Antibodies and their Relevance to Other Chronic Disorders

Lecture Outline

- Introduction
- Clinical features of PANDAS/PANS
- Historical background
- Pathogenesis
 - What Is Molecular Mimicry?
 - Neuroinflammation
- Clinical diagnosis
- Treatment
- Role of the ALLERGIST/IMMUNOLOGIST in management
- Conclusions

Lecture Outline

● Introduction

● Clinical features of PANDAS/PANS

● Historical background

● Pathogenesis

- o What Is Molecular Mimicry?

- o Neuroinflammation

● Clinical diagnosis

● Treatment

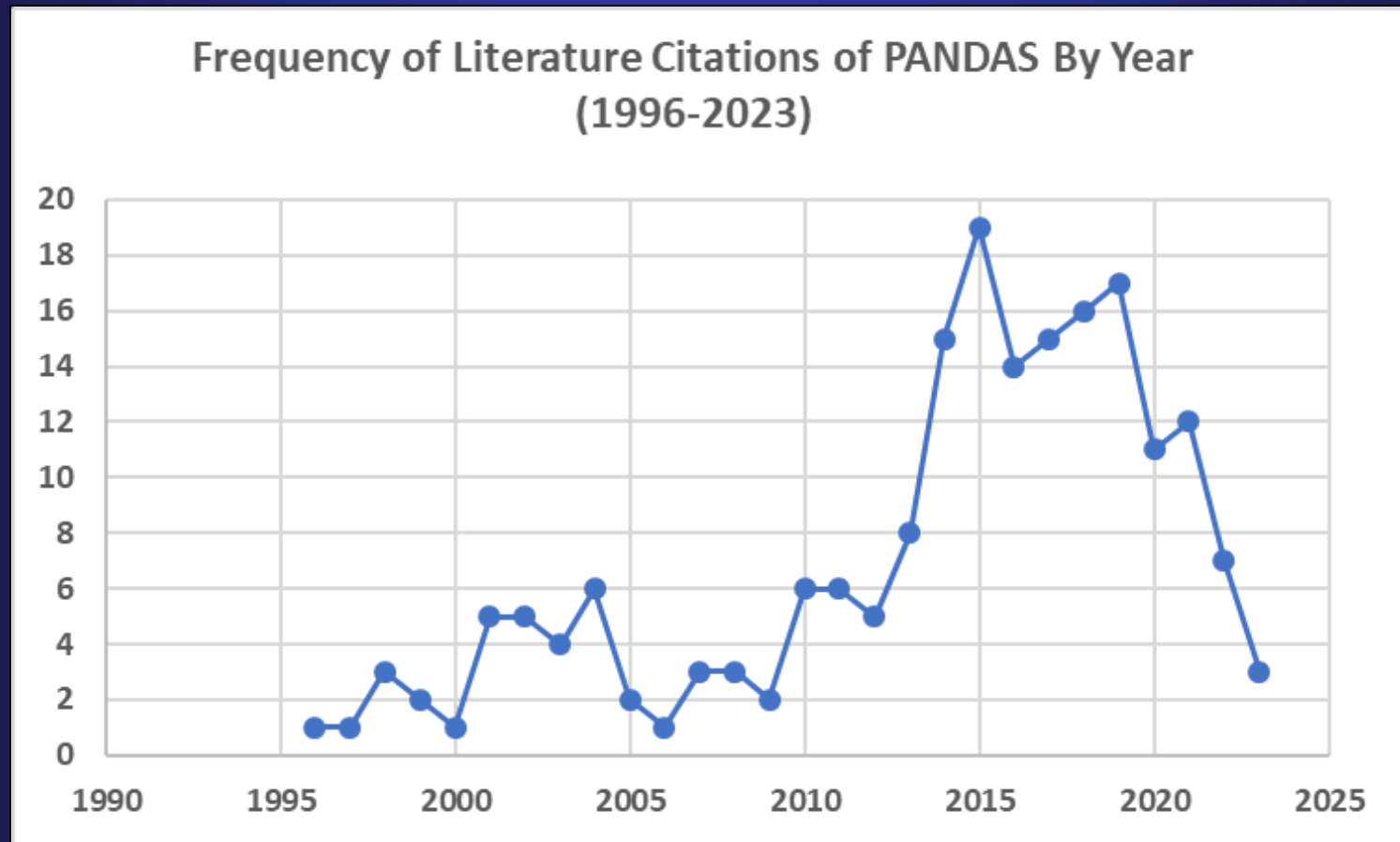
● Role of the ALLERGIST/IMMUNOLOGIST in management

● Conclusions

HERE'S the PANDA WE ALL KNOW ABOUT WHOSE SPECIES IS BECOMING EXTINCT...THE PANDAS WE WILL BE SPEAKING ABOUT TODAY IS A CONDITION WHICH IS BECOMING MORE FREQUENTLY RECOGNIZED



Frequency of Literature Citations of PANDAS by Year (1996-2023)



What are PANDAS/PANS?

- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) and
- PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)
- These are a group of disorders that can cause sudden onset of neuropsychiatric symptoms in children, including obsessive-compulsive (OCD) behaviors, tics, and other psychiatric symptoms.

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PANDAS Criteria 1998	PANS 2012
1. PRESENCE OF DIAGNOSIS OF OCD AND/OR TIC DISORDER	1. ABRUPT, DRAMATIC ONSET OF OCD OR SEVERELY RESTRICTED FOOD INTAKE
<ol style="list-style-type: none"> 1. Prepubertal onset 2. ACUTE onset and episodic course 3. Temporal relationship between symptoms, exacerbations and group A beta-hemolytic streptococcal infections 4. Association with neurological abnormalities (e.g., choreiform movements) 	<ol style="list-style-type: none"> 2. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset, from of at least two of the following seven categories: <ol style="list-style-type: none"> A. Anxiety B. Emotional lability and/or depression C. Irritability, aggression and/or severely oppositional behaviors D. Behavioral (developmental) regression E. Deterioration in school performance F. Sensory or motor difficulties G. Somatic signs/symptoms including sleep disturbances, enuresis, or urinary frequency <p>Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham's chorea (SC), systemic lupus erythematosus, Tourette syndrome, or others</p>

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PANDAS/PANS and Sydenham's Chorea

• In 1998 Dr. Swedo, a pediatric neuropsychiatrist working at NIH described a neuropsychiatric condition in children following infection with Group A streptococci (GAS) that include obsessions, compulsions, tics, hyperactivity, inattention, and mild choreiform movements.

• She named the condition PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections)

• More recently, in 2012, a broader group of patients with a set of symptoms similar to PANDAS but with no streptococcal etiology was described with the acronym PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

PANDAS/PANS and Sydenham Chorea

• Dr. Swedo linked PANDAS with Sydenham chorea (SC), a rare neurological disorder characterized by involuntary movements of the muscles, emotional instability, and behavioral changes that is commonly associated with beta-hemolytic streptococcal infections is a complication rheumatic fever (RF).

• Sydenham chorea (SC) is commonly associated with beta-hemolytic streptococcal infections, cause strep throat and rheumatic fever (RF).

• It is believed that SC and RF are caused by autoimmune responses to the streptococcal infection in which susceptible individuals, produces antibodies that attack not only the bacteria, but also normal tissues in the body, including the basal ganglia in the brain, leading to inflammation and damage and the symptoms of these disorders

What are PANDAS/PANS?

- PANDAS is considered a subgroup of PANS.
- PANDAS is a more well-defined subtype of PANS with specific diagnostic criteria and is specifically defined with an etiology of preceding beta-hemolytic infection
- PANS encompasses a broader range of neuropsychiatric symptoms that may be associated with various triggers, including infections, autoimmune conditions, metabolic disorders, and environmental factors.
- The relationship between PANDAS and PANS is complex and not fully understood, but they are believed to share a common underlying pathophysiology involving an abnormal immune response leading to inflammation and dysfunction in the brain.

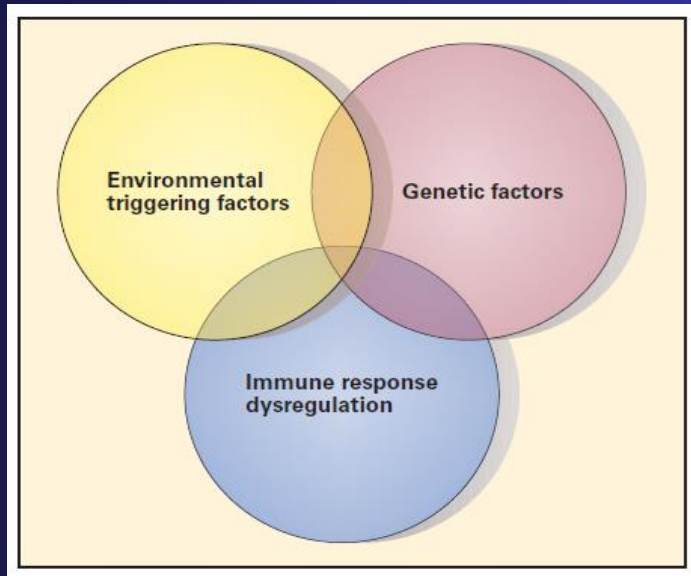
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What is Autoimmunity and Autoimmune Diseases?

- **Autoimmunity** is a condition where the immune responses of an organism are directed against its own healthy cells and tissues
- Any disease that results from such an aberrant immune response is termed an "**autoimmune disease**"
- Autoimmunity emerges when the mechanisms of tolerance fail
- About 5% of the population suffers from autoimmune disease.
- Autoimmune diseases are commonly divided into **organ-specific**, when autoimmune injury is directed against one organ, or **systemic**, when many different organs and tissues are affected.

Etiology of Autoimmunity



It has been postulated that most autoimmune diseases are the result of a complex interplay between:

1. Genetic factors [MHC & Non-MHC genes]
2. Environmental triggers [Microorganisms Viruses Trauma, UV light]
3. Regulatory aberrations of the immune response triggered by epigenetics

Is rheumatic fever a hypersensitivity disorder or an autoimmune disorder

- Rheumatic fever (RF) is an autoimmune disorder rather than a hypersensitivity disorder.
- In autoimmune disorders, the immune system mistakenly attacks and damages the body's own tissues and organs.
- This occurs in RF when the immune system attacks various tissues in the body, including the heart, joints, skin, and brain, in response to a previous infection with *Streptococcus pyogenes*.
- Hypersensitivity disorders, on the other hand, are caused by an exaggerated immune response to a foreign substance or allergen. Examples of hypersensitivity disorders include allergic reactions to food or medication, and autoimmune disorders are different from these types of reactions.

Sydenham Chorea is a Group A Streptococcal-triggered Autoimmune Neuropsychiatric Disorder

Dancing Mania 1564 and engraving 1642

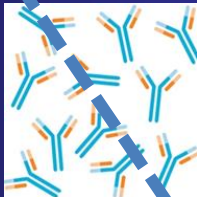
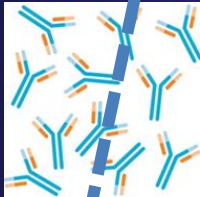


By Pieter Brueghel the Elder - Pieter Bruegel

Sydenham Chorea



Group A Strep



Also known as "St. Vitus' dance"

- abnormal movements
- Loss of fine-motor control
- Loss of emotional control

Thomas Sydenham reported this in 1686 "Sydenham's chorea"

Sydenham Chorea Acute Rheumatic Fever
Basal Ganglia

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What is molecular mimicry?

● Molecular mimicry is a phenomenon where a pathogen or foreign substance has a structure that is similar to a self-molecule in the human body. This similarity can lead to an immune response against both the pathogen and the self-molecule, resulting in autoimmune diseases.

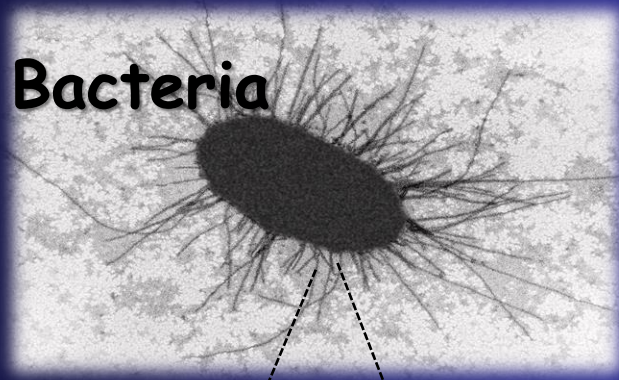
● In molecular mimicry, the immune system recognizes a foreign antigen as a threat and produces antibodies to attack it. However, because the antigen is similar in structure to a self-antigen, the antibodies may also attack the self-antigen, leading to autoimmune reactions.

● Molecular mimicry is also believed to play a role in other autoimmune diseases, such as multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus.

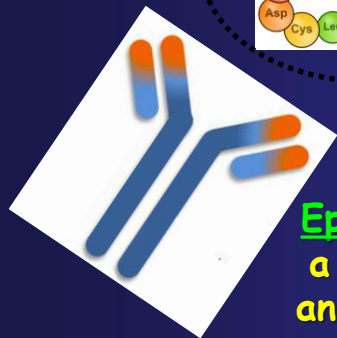
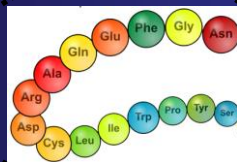
What is molecular mimicry?

- For example, in rheumatic fever, a bacterial infection caused by *Streptococcus pyogenes*, the bacteria produce antigens that mimic the structure of human heart tissue. The resulting immune response can cause damage to the heart, leading to rheumatic heart disease.
- Molecular mimicry is also believed to play a role in other autoimmune diseases, such as multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus.

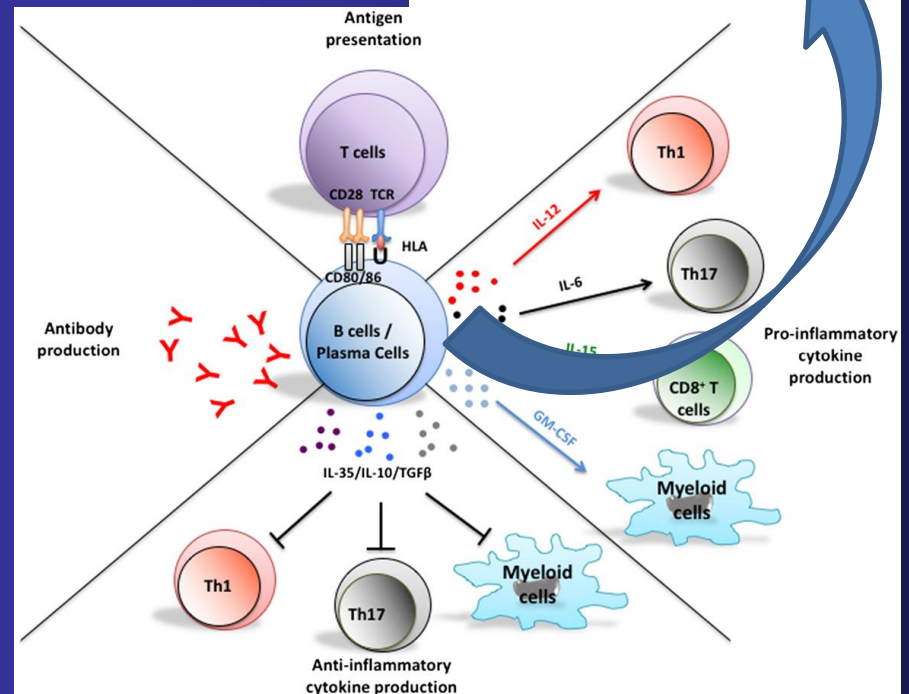
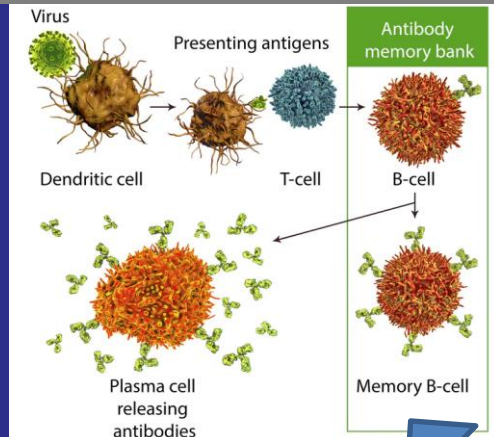
Antibodies Recognize Epitopes on Infectious Agents



Epitope

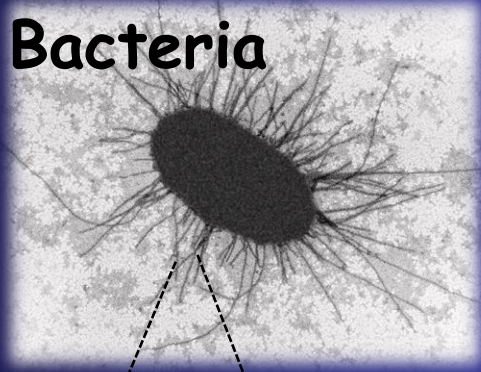


Epitope: the part of a molecule to which an antibody attaches itself

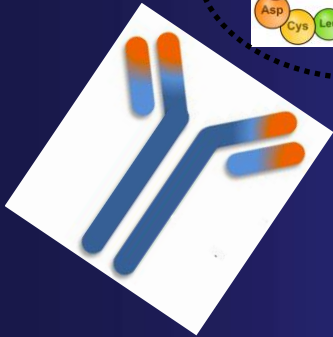
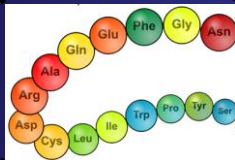


Similar Epitopes Occur Between Infectious Agents and Self Antigens

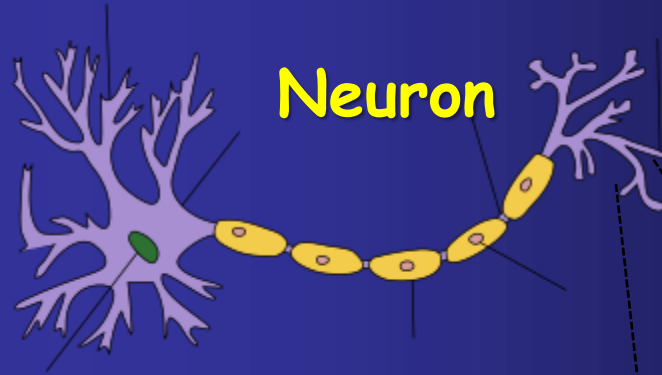
Bacteria



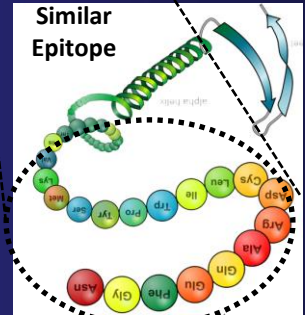
Epitope



Neuron



Similar Epitope



*Autoimmune response through
"Molecular Mimicry"*

Other Autoimmune Disorders Associated through Molecular Mimicry*

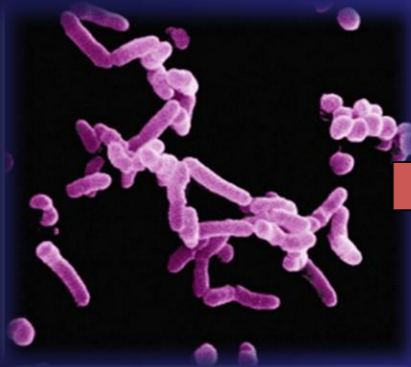
- **Guillain-Barré Syndrome**
 - **Campylobacter jejuni**
- **Sydenham Chorea**
 - **Group A Streptococcus**
- **Systemic Lupus Erythematosus**
 - **Epstein-Barr virus (EBV nuclear antigen -1)**
- **Multiple Sclerosis**
 - **EBV, measles and HHV-6**
- **Myasthenia Gravis**
 - **Herpes Simplex Virus Type 1 (gpD)**
- **Cardiomyopathy (myocarditis)**
 - **Coxsackie virus, Group A Streptococcus**
- **Crohn's Disease**
 - **Gram-positive bacterial peptidoglycans**
- **Diabetes Type 1**
 - **Coxsackie B virus, rubella, herpesvirus, rotavirus**
- **Psoriasis**
 - **Streptococcus pyogenes (Streptococcal M Protein)**

What Does Molecular Mimicry
Have to do with
Neuropsychiatric Conditions in
Lyme, PANDAS/PANS, and
Long-COVID?

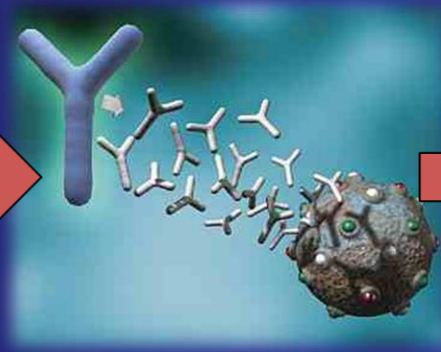
An Autoimmune Mechanism for Neuropsychiatric and Behavioral Disorders



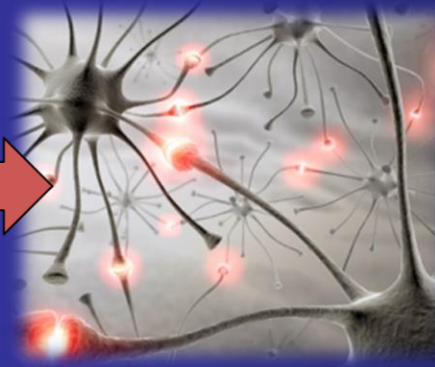
Microbial, Viral,
Fungal Infection
Occurs



Body Produces
Antibodies That
Recognize Infectious
Agent



Antibodies Cross-
React
With Neurologic
Receptors
(molecular mimicry)



Reaction Disrupts
Brain Function
(friendly fire)



Neuropsychiatric Symptoms
Including Anxiety, Aggression,
Rage, OCD, Tics, Depression,
Hyperactivity, Insomnia, Phobias

Immunoneuropsychiatry — novel perspectives on brain disorders

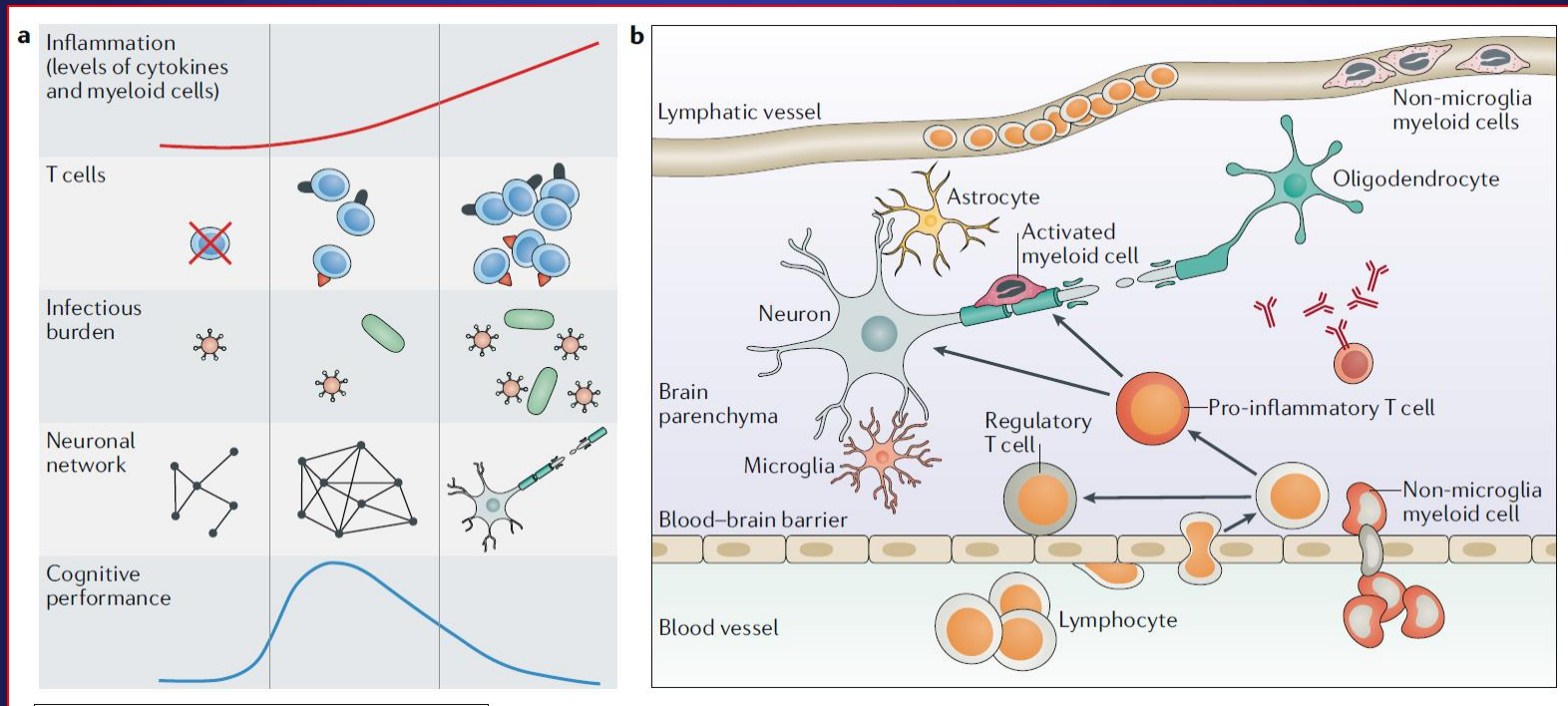
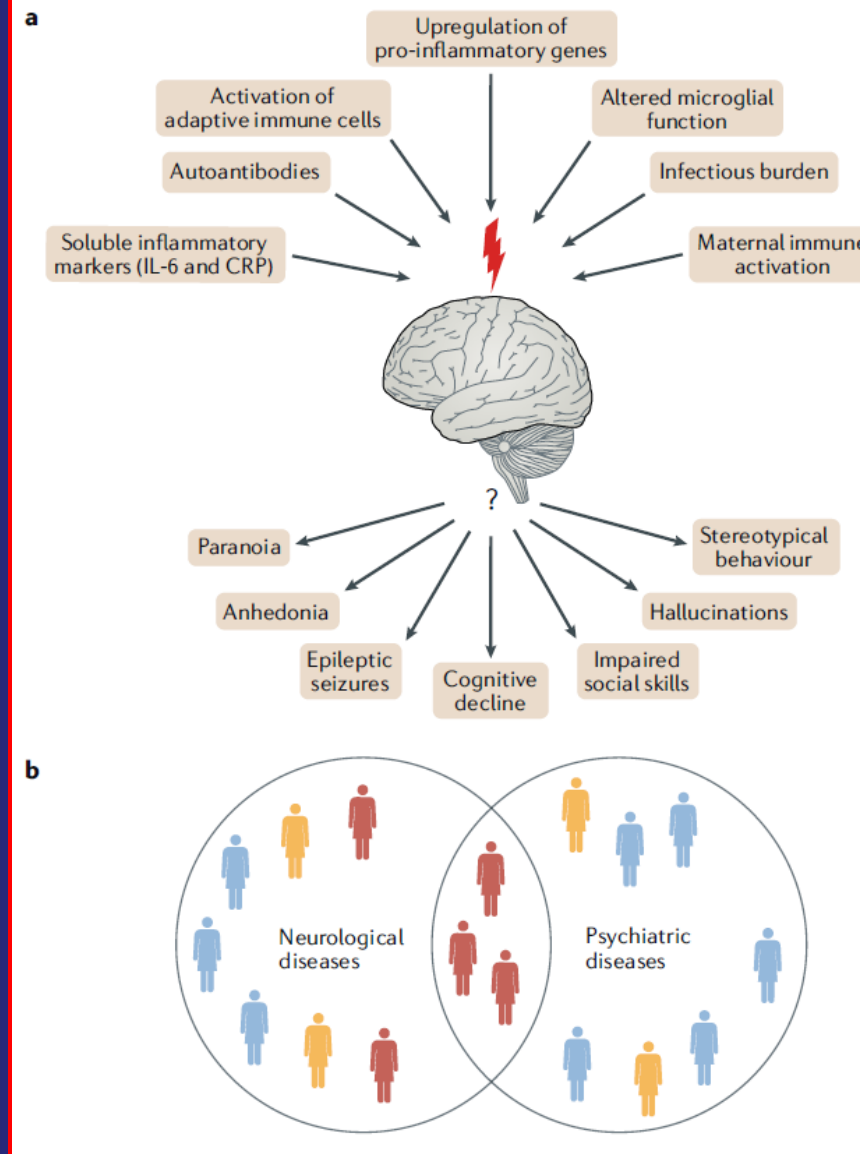


Fig. 1 | The interplay between the immune system and the CNS. a | A certain level of inflammation and autoimmunity is necessary for optimal function of the CNS, but an overwhelming immune reaction leads to neuronal loss and impaired cognition.



Neuropsychiatric Disorders: Overlap of Neurologic diseases and Psychiatric Disorders

Pape K, et al. Immunoneuropsychiatry - novel perspectives on brain disorders. Nat Rev Neurol. 2019;15:317-328.

Factors contributing to autoimmunity: molecular mimicry

AN IMMUNOLOGICAL CROSS-REACTION BETWEEN GROUP-A STREPTOCOCCAL CELLS AND HUMAN HEART TISSUE

MELVIN H. KAPLAN

M.D. Harvard

ASSOCIATE PROFESSOR OF MEDICINE

MARY MEYESERIAN

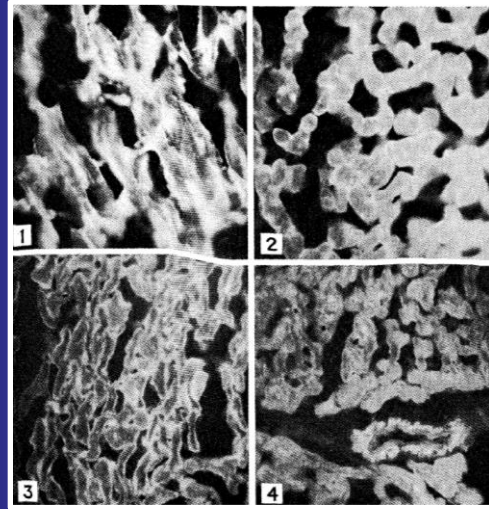
B.A. Rochester

RESEARCH ASSISTANT

WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE

- In 1962, Kaplan published his ground-breaking article of an 11-yr-old boy with rheumatic fever who died of heart failure with pathologic findings of immunoglobulin deposits in the cardiac muscle
- Subsequent examination of sera from rabbits immunized with group A streptococcal cells were found to be reactive with samples of human heart tissue, resulting in the first description of molecular mimicry .

Factors contributing to autoimmunity: molecular mimicry



• Immunofluorescent staining of several different myocardium sections of autopsy specimen from the 11-year boy who died of acute rheumatic fever (ARF) and a normal heart. Direct staining with IgG deposition in subepicardial myocardium of ARF patient (Panel 1); Direct staining with IgG deposition in ventricular myocardium of ARF patient (Panel 2); Indirect staining with an anti-cell-wall serum showing IgG deposition of myofibers of a normal heart (Panel 3); Indirect staining with an anti-cell-wall serum showing IgG deposition of smooth muscle an arterial wall and cardiac myofibers of a normal heart (Panel 4).

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Neuroinflammation

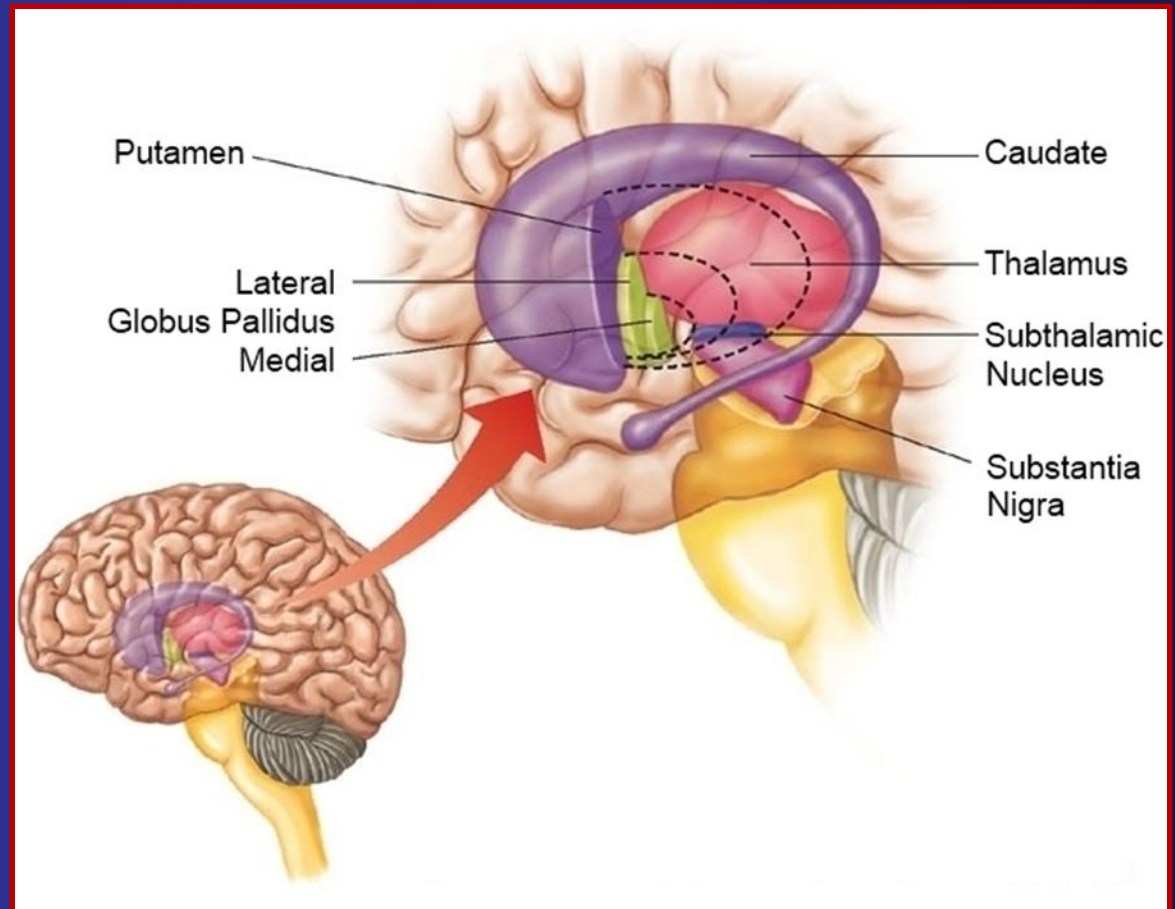
• Sydenham's Chorea (SC), PANDAS, and PANS are postinfectious neuroinflammatory diseases involving basal ganglia with OCD as a major clinical manifestation

• **Cortico-basal ganglia-thalamo-cortical (CBGTC)** circuitries become disrupted by immune dysfunction, producing autoantibodies thought to be triggered by infections (most notably Group A Strep), to cross-react with neural antigens within the basal ganglia, and to modulate neuronal activity

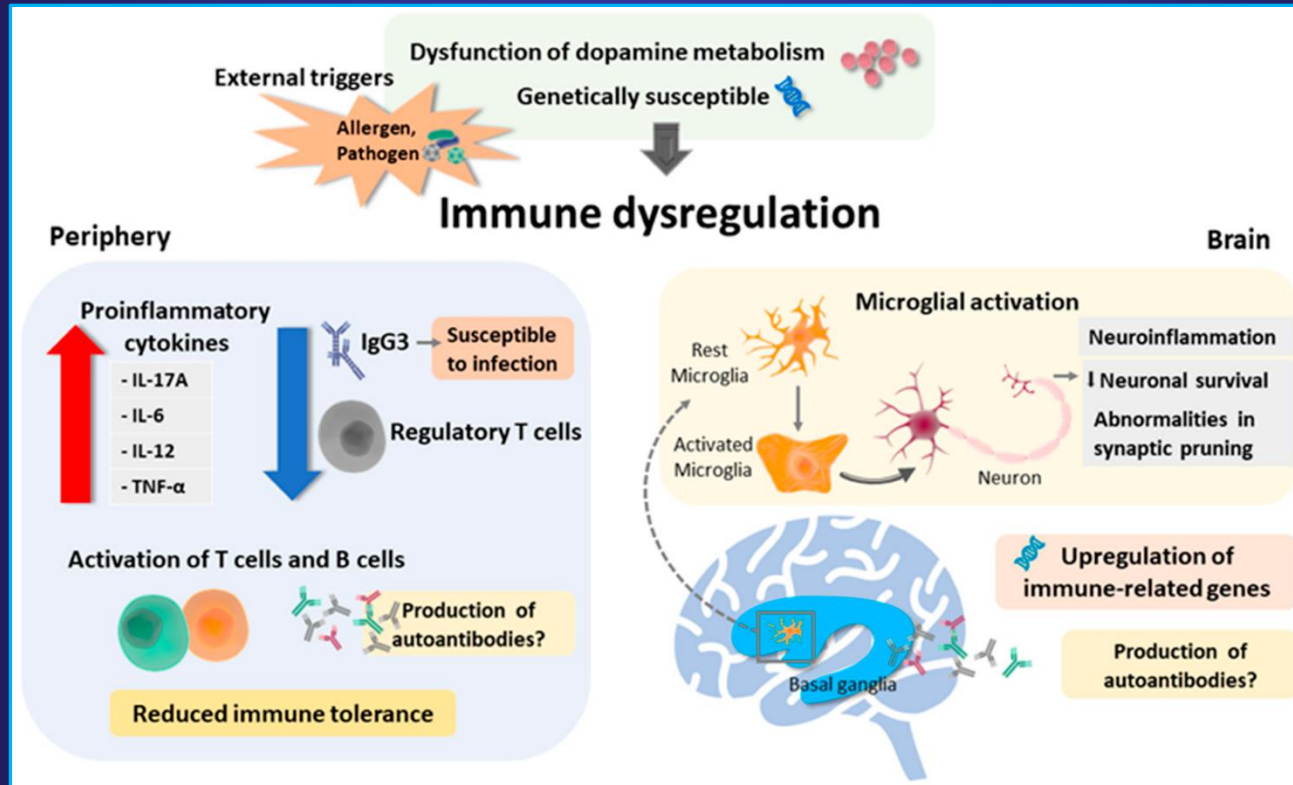
Role of Basal Ganglia in PANDAS/PANS

Basal Ganglia are Responsible for:

- Voluntary motor control
- Procedural learning
- Cognitive functions
- Emotional functions
- Eye movement



Proposed Underlying Immune Dysfunction Mechanism(s) in PANDAS/PANS Disorders



Proposed Underlying Immune Dysfunction Mechanism(s) in PANDAS/PANS Disorders

Predisposing conditions include:

- Dysfunction of dopamine metabolism and genetic susceptibility.
- External triggers such as allergen and microbial pathogens may facilitate peripheral and brain immune dysregulation.
- In the periphery, diminished Treg cells may contribute to increased production of proinflammatory cytokines
- Activation of T-cells and B-cells may lead to reduced immune tolerance
- Additionally, any decrease in humoral (e.g., IgG3) immunity may lead to defective immune clearance of pathogens resulting in persistent inflammation

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CLINICAL DIAGNOSIS

- PANDAS and PANS are typically seen in children between 5 and 12 yrs who present with the acute onset of OCD or tics
- Patients may experience very mild choreiform hand movements ,clumsy motor control, or sudden deterioration in the quality of their handwriting.
- Patients often exhibit comorbid symptoms as seen in SC, including emotional lability, depression, irritability, anxiety, motoric hyperactivity, distractibility, or impulsivity

SUGGESTED DIAGNOSTIC TESTS

Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference

Kiki Chang, MD,^{1,*} Jennifer Frankovich, MD,^{2,*} Michael Cooperstock, MD, MPH,³
Madeleine W. Cunningham, PhD,⁴ M. Elizabeth Latimer, MD,⁵ Tanya K. Murphy, MD,⁶
Mark Pasternack, MD,⁷ Margo Thienemann, MD,⁸ Kyle Williams, M
D,⁹ Jolan Walter, MD,¹⁰ and Susan E. Swedo, MD¹¹; From the PANS Collaborative
Consortium

Chang K, et al. J Child Adolesc Psychopharmacol. 2015; 25:3-13.

COMORBID SYMPTOMS WITH PANDAS

- Emotional lability (66%)
- Separation anxiety (46%)
- Night-time fears and bedtime rituals (50%)
- Cognitive deficits
- Deterioration in school performance (60%)
- Deterioration in math skills (26%)

SUGGESTED DIAGNOSTIC WORKUP

- Family history
- Medical history and PX
- Psychiatric evaluation
- Infectious disease evaluation
- Assessment of symptoms and HX suggesting need for further evaluation of immune dysregulation (autoimmune disease, inflammatory disease, immunodeficiency)
- Neurological assessment
- Assessment of somatic symptoms, including possible sleep evaluation
- Genetic evaluation

DIFFERENTIAL DIAGNOSIS

- Obsessive compulsive disorder
- Anorexia nervosa
- Avoidant/restrictive food intake disorder (ARFID)
- Tourette syndrome
- Transient tic disorder
- Bipolar disorder
- Sydenham chorea
- Autoimmune encephalitis
- Systemic autoimmune disease^a
- Wilson's disease^a

^aRelatively rare conditions

LABORATORY TESTS

All patients meeting PANS criteria should have the following:

- Complete blood cell count with manual differential
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Comprehensive metabolic panel
- Urinalysis (to assess hydration and to rule out inflammation for children with urinary complaints; clean-catch urine culture for those and anti-with pyuria)
- Throat culture, anti-streptolysin O (ASO) and anti-DNase B

LABORATORY TESTS

- The laboratory workup by the allergist-immunologist should include an immunodeficiency evaluation

- Since, a majority of these patients have evidence for frequent infections and the finding of an immunoglobulin deficiency, for example, could provide further justification for IVIG administration.

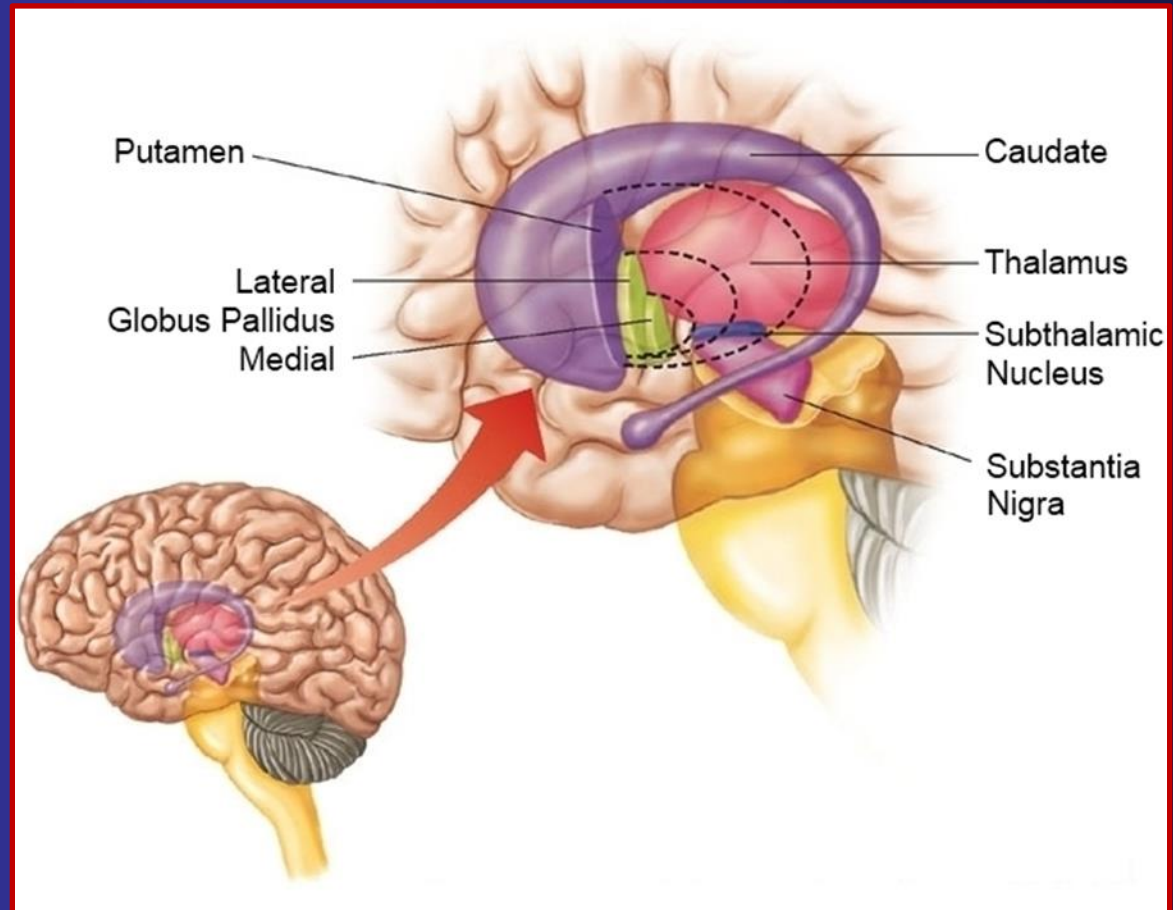
CUNNINGHAM PANEL?

- Measures autoantibodies to five neuronal components cortico-basal ganglia-thalamo-cortical (CBGTC) circuitries
- Although test results are said to provide valuable information to help DX and RX patients, the test has been somewhat controversial
- A report by Hesselmark et al (26) found the assay to have very poor positive and negative predictive values.
- Another issue is that its clinical utility and accuracy have not been fully established through large-scale studies or clinical trials

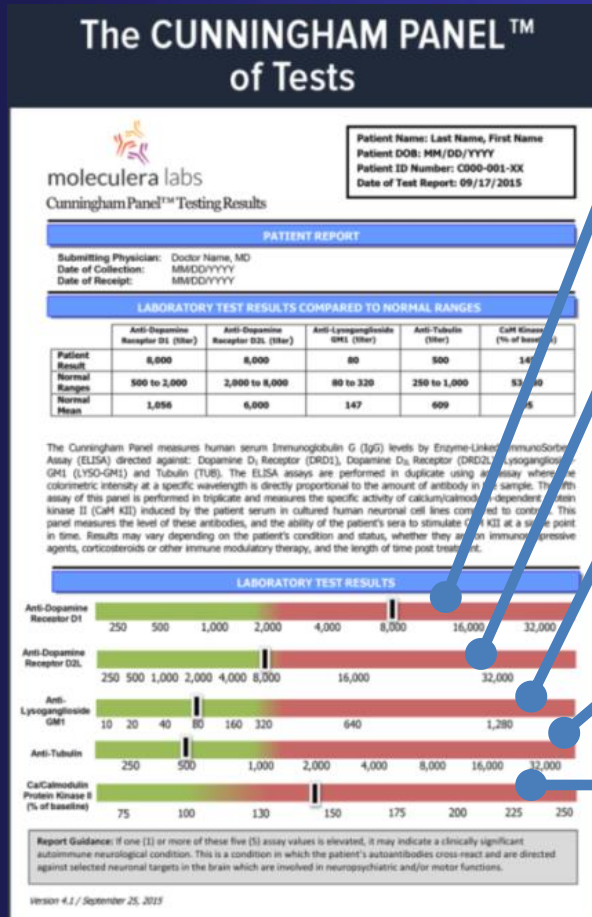
FIVE CORTICO-BASAL GANGLIA-THALAMO-CORTICAL (CBGTC) RECEPTORS TARGETED IN THE CUNNINGHAM PANEL

Autoantibodies directed to FIVE CBGTC targets:

- Dopamine D1
- Dopamine D2L
- Lysoganglioside GM1
- Tubulin
- CaM KII



The Cunningham Panel™ Autoantibody Targets



1) Anti-Dopamine D1

Often positive with psychiatric symptoms including psychosis⁽¹⁾

2) Anti-Dopamine D2L receptor

Often positive with movement disorders and impulsivity⁽¹⁾

3) Anti-Lysoganglioside GM1

Often positive with neuropathic symptoms including tics⁽¹⁾

4) Anti-Tubulin

Often positive with cognitive complaints, OCD and brain fog⁽¹⁾

5) CaM KII Activity

Often positive with involuntary movements and any symptom of adrenergic activation ⁽¹⁾

Binding Assays

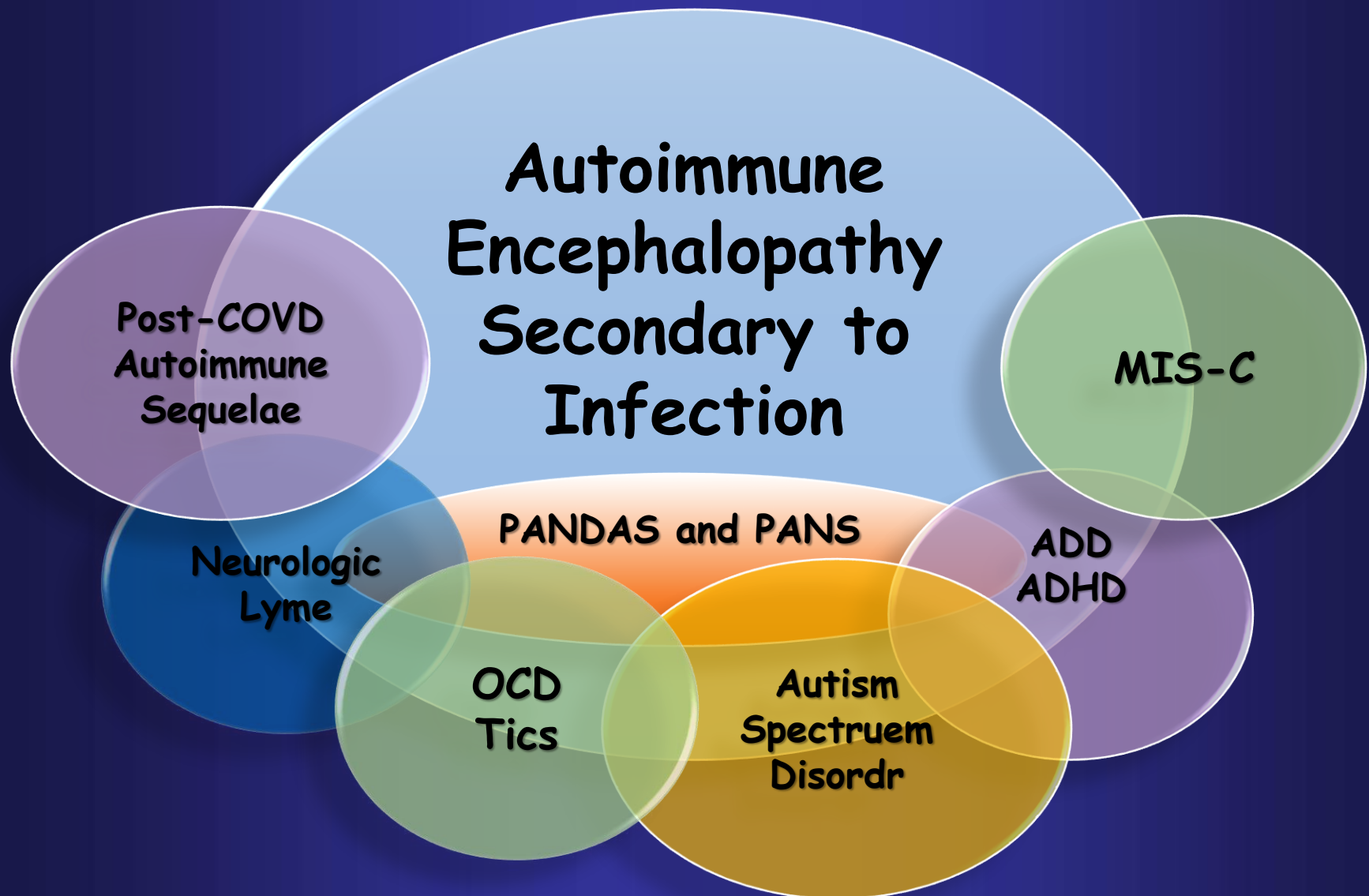
Cell Stimulation Assay

Ref: (1) Reported by Dr. Amiram Katz based upon his 112 patients studied and our patient responses

CUNNINGHAM PANEL?

- Another potential issue is its high cost, as a specialized test it may not be covered by all insurance plans.
- Other panels are available at Mayo Clinic Laboratories (Rochester, MN) and Quest Laboratories (Secaucus, NJ). which use more validated markers
- Overall, while the Cunningham Panel may have some it is important to consider the limitations with any of these anti-neuronal antibody assays and to consider the range of available testing options and select the most appropriate one on the patient's specific symptoms, medical history, and clinical presentation.

Infection Triggered Autoimmune Responses may be a Medical Model for Portions of Many other Neuropsychiatric Disorders



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Treatment

Based on the proposed pathogenesis of the PANDAS/PANS disorders 3 different treatments include:

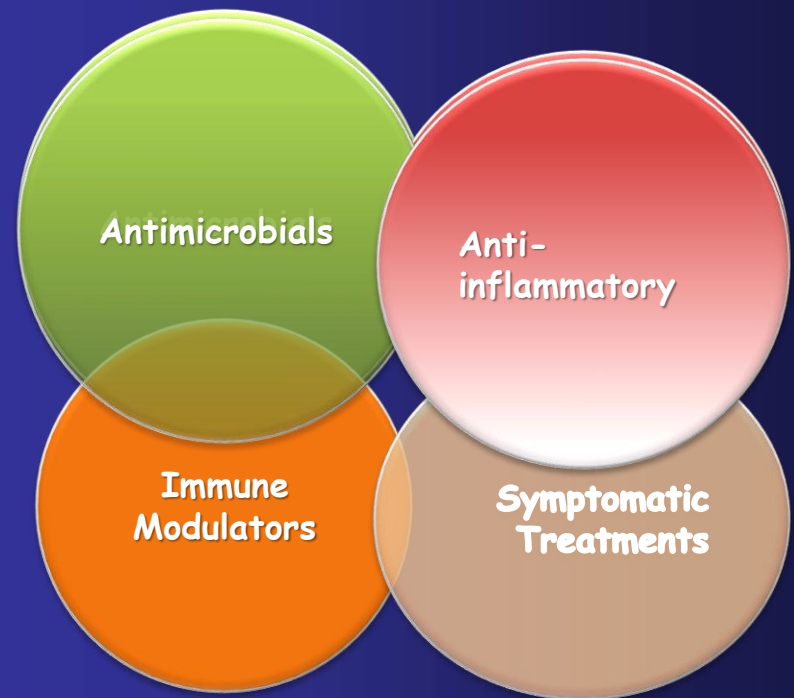
- 1) antimicrobial therapy
- 2) antiinflammatory and immunomodulatory RX
- 3) psychotherapy

However, the literature on treatment of these conditions is diverse, and clinical consensus regarding optimal treatment strategy is lacking

In severe cases, hospitalization may be necessary for DX and RX. In such cases, LP MRI, and EEG may be helpful diagnostics.

Existing Treatments for PANDAS/PANS

- Anti-microbials
- Steroids and NSAIDs
- Plasmapheresis (Plasma exchange)
- Intravenous Immunoglobulins (IVIG)
- Immune modulating medications
- Symptomatic Treatment
- Cognitive Behavioral Therapy
- Low dose SSRIs



TREATMENT	SUMMARY OF SEVERAL CASE REPORTS	CONCLUSION
Antibiotics	Antibiotics reported to be effective in 8-52%.	Overall evidence is inconclusive.
Therapeutic plasma exchange (TPE)	Only 6/25 treated patients reported improvement..	Overall evidence for TPE is inconclusive.
Intravenous immunoglobulin	IVIG was reported "very effective" in 49% of Rxd patients, "somewhat effective" in 25%	Overall evidence for using IVIG is inconclusive.
Tonsillectomy and adenoidectomy (T&A)	T&A has been evaluated in multiple case reports. Not been tested in controlled studies.	Evidence for treating PANDAS with T/A weak.
Cognitive behavior therapy (CBT)	Possible CBT RX could be beneficial but not tested in a controlled setting.	Evidence for CBT is inconclusive.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Many case reports suggest improvement with NSAIDS. In 23% of 302 RX "very effective" and 10% discontinued due to lack of efficacy.	No controlled trials therefore overall evidence is inconclusive.
Corticosteroids	CXs described in multiple case studies. 50% of the treated patients in the survey study reported "very effective".	Evidence for CXS as treatment of PANS is inconclusive.
Selective serotonin reuptake inhibitors (SSRIs)	In study of 265 treated patients, 17% reported "very effective", 20% dc'd due to lack of efficacy and 25% cd'd due lack of tolerability.	Evidence is inconclusive. However, SSRIs are evidence-based treatments for OCD.

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ROLE OF THE ALLERGIST/IMMUNOLOGIST

- The allergist/immunologist can assist in providing a comprehensive and coordinated approach to the management of these patients
- By providing anti-inflammatory and immunomodulatory interventions when indicated
- By supporting the emotional needs of patients and families by promoting rehabilitation and referral to services that focus on improving physical, mental, and social well-being.

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- Role of the ALLERGIST/IMMUNOLOGIST in management
- Conclusions

Conclusions

- Families of patients with PANDAS/PANS often report fear, frustration, and feelings of not being heard and their struggles are being increasingly reported in the news and other media.
- Patients and their families may feel marginalized and suffering from many of life's dimensions (physical, emotional, psychological, social, financial and spiritual) and are striving to get well and feel better.

Conclusions

- The PANDAS/PANS disorders have become a uniquely challenging disease complex for growing numbers of patients, families, HCPs and is a particular challenge for the allergist/immunologist who is increasingly being called upon for the evaluation and management of these patients
- Although neurologists and psychiatrists are primarily involved in the management of these patients, allergist-immunologists have the requisite specialized training and therapeutic knowledge to improve the health of patients afflicted with these disorders.

***ARE YOU WILLING TO TAKE UP THE
CHALLENGE?***

