

Microbes and Mental Illness: Past, Present and Future

- Bransfield RC, Mao C, Greenberg R. Healthcare (Basel). 2023 Dec 29;12(1):83. doi: 10.3390/healthcare12010083.

Infectious Agents with Potential Psychiatric Manifestations

- **Spirochetes:**
- *Borrelia burgdorferi* sensu lato, genus *Borrelia*
 - *Borrelia burgdorferi* sensu stricto (Lyme disease in USA, Europe)
 - *Borrelia afzelii* (Lyme disease mostly in Europe, Asia)
 - *Borrelia garinii* (Lyme disease mostly in Europe, Asia)
- *Relapsing Fever Group* (also known as relapsing fever group *Borrelia*)
- *Leptospira* species (leptospirosis)
- *Treponema pallidum* (syphilis)
- **Other bacteria:**
- *Actinomyces*
- *Bartonella henselae*, and other species (cat scratch disease, bartonellosis)
- *Brucella* species (brucellosis)
- *Chlamydia* species
- *Coxiella burnetii* (Q-Fever and "Post-Q Fever Fatigue Syndrome")
- *Ehrlichia chaffeensis* (human monocytic ehrlichiosis)
- *Helicobacter pylori*
- *Mycoplasma pneumoniae* and other species
- *Rickettsia* species (spotted fever, scrub typhus, African tick bite fever)
- *Streptococcus pyogenes* (group A beta hemolytic strep, PANDAS, Sydenham's Chorea, St Vitus Dance)
- *Tropheryma whipplei* (Whipple's disease)

Infectious Agents with Potential Psychiatric Manifestations II

- **Viruses:**
 - Borna virus
 - Chikungunya virus
 - Coronaviruses (other than SARS-CoV-2)
 - Enterovirus
 - Cytomegalovirus
 - Epstein-Barr virus
 - Tick-borne encephalitis virus
 - Hepatitis C virus
 - Human endogenous retroviruses
 - Human immunodeficiency virus
 - Human T-Cell lymphotropic virus type 1
 - Influenza virus
 - Measles virus
 - Parvovirus B19
 - Poliovirus
 - Rubella
 - SARS-COV-2 coronavirus
 - West Nile virus
- **Parasites**
 - *Plasmodium* species (Malaria)
 - *Babesia* species (*B. microti*, *B. duncani*, other *Babesia* species [Babesiosis])
 - *Filaria* (filariasis)
 - *Leishmania* species (Leishmaniasis)
 - *Toxoplasma gondii* (Toxoplasmosis)
 - *Taenia solium* (Neurocysticercosis or Cysticercosis)
 - *Trypanosoma* sp. (Trypanosomiasis)
- **Fungal**
 - *Aspergillus* species
 - *Candida*
 - *Cryptococcus neoformans* (Cryptococcosis)

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Potential or Postulated Association of Autism with Infectious Agents

- *Babesia*
- *Bartonella*
- Borna virus (mostly animal models)
- *Borrelia burgdorferi* and other tick-borne diseases
- *Chlamydia pneumoniae*
- Cytomegalovirus
- Enterovirus
- Fungi (*Aspergillus*, *Candida*)
- Herpes simplex virus
- Herpes simplex virus-6
- Infections early in childhood
- Intestinal microbiome composition changes
- Maternal infections or immune activation during pregnancy
- *Mycoplasma*: (*M. fermentans*, *M. genitalium*, *M. hominis*, *M. pneumoniae*)
- Measles virus
- *Plasmodium* (malaria)
- *Rubella*
- *Toxoplasma gondii* (Toxoplasmosis)
- Varicella zoster virus
- Viral infectious

Potential or Postulated Association of Schizophrenia with Infectious Agents

- *Aspergillus*
- Bacterial infections
- *Bartonella*
- *Borrelia burgdorferi* (Lyme disease)
- Borna disease virus
- *Candida albicans*
- *Chlamydia*, *C. psittaci*, *C. pneumoniae*
- Coronaviruses
- Cytomegalovirus
- Epstein-Barr virus (EBV)
- Herpes simplex virus
- Human Endogenous Retrovirus
- Infections early in childhood
- Influenza virus
- Maternal infections or immune activation during pregnancy
- Measles virus (Subacute sclerosing panencephalitis)
- Parvovirus
- Poliovirus
- Pneumonia and influenza
- Rubella
- *Taenia solium* (Neurocysticercosis or Cysticercosis)
- *Toxoplasma gondii*
- *Treponema pallidum* (syphilis)

Potential or Postulated Association of Bipolar Illness with Infectious Agents

- *Babesia*
- *Bartonella*
- *Borrelia burgdorferi*
- Human Endogenous Retroviruses
- *Mycoplasma*
- Parvovirus B19
- SARS-CoV-2
- Tick-borne diseases
- *Toxoplasma gondii*
- *Treponema pallidum* (syphilis)

Potential or Postulated Association of Depression with Infectious Agents

- *Babesia*
- *Bartonella*
- Borna disease virus
- *Borrelia burgdorferi*
- Cytomegalovirus
- Enterovirus
- Hepatitis C virus
- Human immunodeficiency virus (HIV)
- Human T-Cell lymphotropic virus type 1 (HTLV-1)
- Infections early in childhood
- Measles virus (subacute sclerosing panencephalitis)
- *Plasmodium* (malaria)
- SARS-CoV-2 and other coronaviruses
- *Taenia solium* (Neurocysticercosis or Cysticercosis)
- *Treponema pallidum* (syphilis)
- West Nile virus

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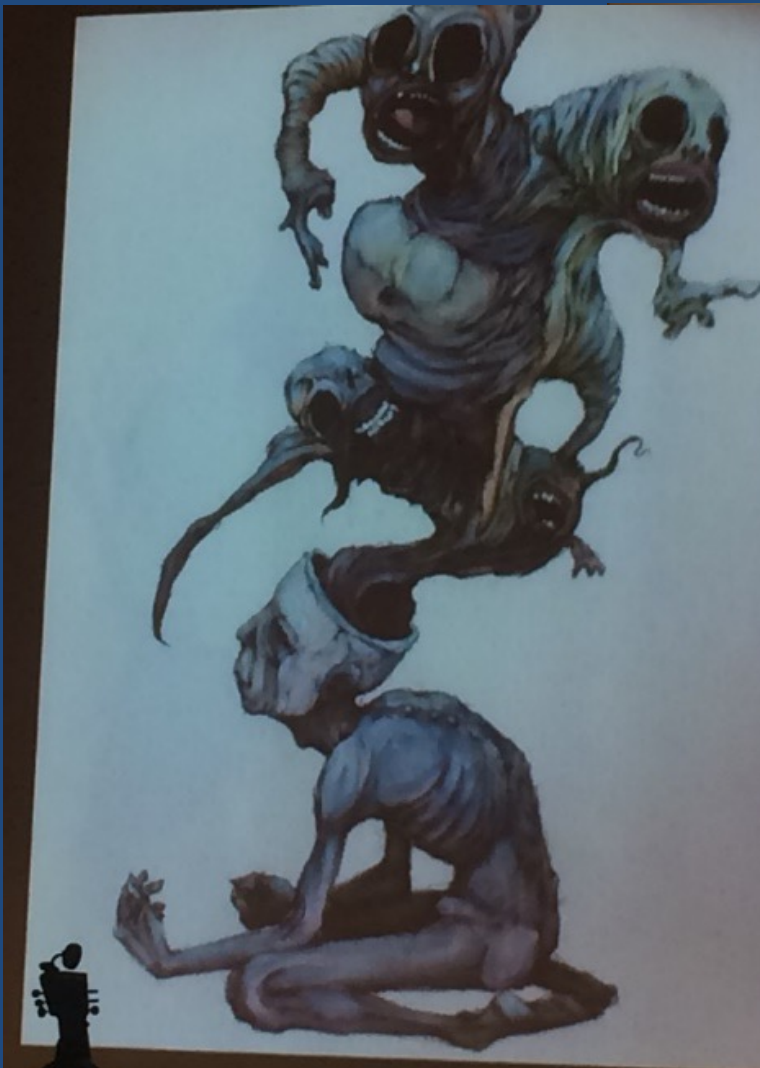
Potential or Postulated Association of Anxiety with Infectious Agents

- *Bartonella*
- *Borrelia burgdorferi*
- Epstein-Barr virus
- Human T-Cell lymphotropic virus type 1
- *Mycoplasma pneumoniae*
- SARS-CoV-2
- *Streptococcus pyogenes* (Group A Strep)
- *Treponema pallidum* (syphilis)

Potential or Postulated Association of Suicide with Infectious Agents

- All infections requiring hospitalization (including infections requiring hospitalization for COPD)
- *Bartonella*
- *Borrelia burgdorferi*
- Cytomegalovirus
- Hepatitis C virus
- Herpes Simplex Virus Type 1 (HSV-1)
- Human immunodeficiency virus (HIV)
- Influenza virus
- SARS-CoV-2
- *Streptococcus pyogenes* (group A)
- *Toxoplasma gondii*

Lyme Disease and Suicide



Artwork by Daniel J. Levy with permission from Adam Levy

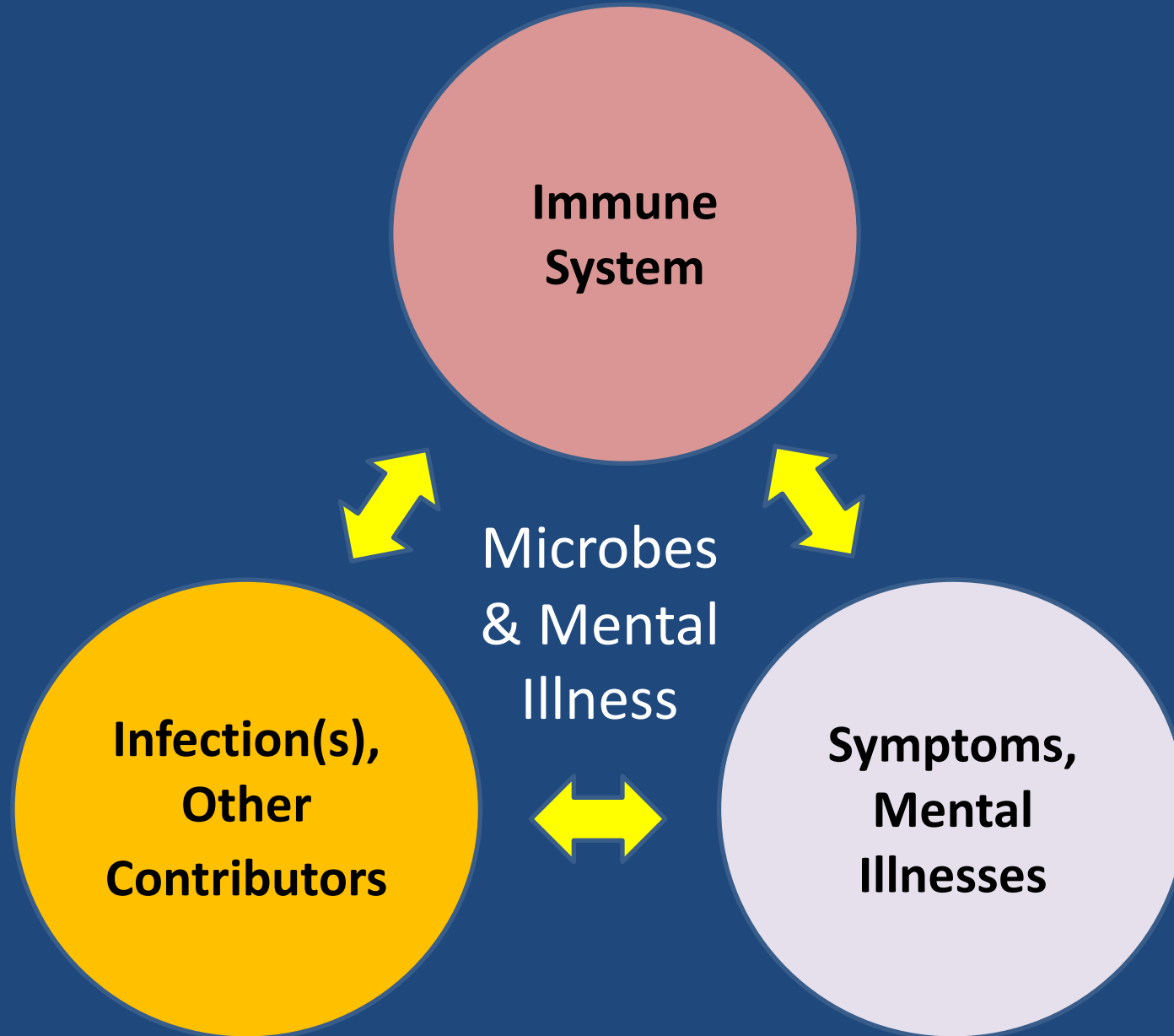
Potential or Postulated Association of Aggressiveness with Infectious Agents

- *Babesia*
- *Bartonella*
- *Borrelia burgdorferi*
- Encephalitis lethargica agent
- Hepatitis E virus
- Herpes simplex virus
- Infection during childhood
- Measles virus
- *Mycoplasma*
- Parvovirus
- *Plasmodium* (Malaria)
- Rabies virus
- *Streptococcus pyogenes* (group A Strep)
- *Toxoplasma gondii* (Toxoplasmosis)
- *Treponema pallidum* (syphilis)
- viral encephalitis
- Animal models of infections associated with aggression include *Borrelia burgdorferi* in dogs, *Bartonella henselae* in dogs, *B. henselae* in horses, *B. burgdorferi* postulated in chimpanzee in lay news, rabies virus in multiple animal species, and gut microbiota changes in dogs, horses, and pigs.

Late-stage Borreliosis and Substance Abuse

- Late-stage borreliosis is associated with multiple symptoms that may contribute to an increased risk of substance abuse and addictive disorders. More effective diagnosis and treatment of borreliosis, and attention to substance abuse potential may help reduce associated morbidity and mortality in patients with borreliosis, particularly in endemic areas

Treatment



Examples of Microbes Associated with Mental Illness

- Five infectious diseases described as examples of microbes associated with mental illness are **syphilis** (a sexually transmitted spirochetal disease); **toxoplasmosis** (a zoonotic parasitic disease caused by *Toxoplasma gondii*); COVID-19 (a respiratory-transmitted viral disease); **Lyme borreliosis and associated infections (zoonotic vector-borne disease)**; and **group A beta hemolytic streptococcal infections and PANDAS/PANS** (an autoimmune disease induced by infection and other provocations).

Infections and Psychiatric Illness

- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)
- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)

- First described in a landmark paper by Dr. Susan Swedo and her team at the NIMH in the American Journal of Psychiatry Feb. 1998

30% of Acute Rheumatic Fever (ARF) patients have Sydenham Chorea; of those, about 70% will develop OCD.

Criteria for PANDAS

- Presence of OCD and/or tics, particularly multiple, complex or unusual tics
- Age Requirement (Symptoms if the disorder first become. Evident between 3 years of age and puberty)
- Acute onset and episodic (relapsing-remitting) course
- Association with Group A Beta-hemolytic Streptococcal Infection (GAS)
e.g. positive throat culture or history of scarlet fever
- Association with Neurological Abnormalities (e.g. physical hyperactivity or unusual, jerky movements that are not in the child's control)

Other symptoms associated with PANDAS episodes

Youth with PANDAS experience 1 or more of the following in addition to their OCD or tic disorder:

- Symptoms of ADHD
- Separation anxiety
- Mood changes e.g. irritability, sadness, emotional lability
- Trouble sleeping
- Nighttime bed wetting, frequent daytime urination or both
- changes in motor skills, such as handwriting
- joint pains

What Causes PANDAS?

PANDAS may result from the molecular mimicry of Group A streptococcal bacteria, which stimulates production of antibodies that then cross-react with antigens in the brain, producing a variety of neurologic and psychiatric manifestations.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

- Does not specify a trigger
- Thought to be an immune reaction to one of a number of physiological stressors including Group A Streptococcal infection, Mycoplasma pneumonia infection, influenza, upper respiratory infections, sinusitis, and psychosocial stresses.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

Diagnostic Criteria

- 1) Abrupt onset or abrupt recurrence of OCD or Restrictive Eating Disorder

Restrictive Eating

- 1 in 5 children with PANS will have restricted food intake.
 - may be contamination fears associated with the food
 - obsessional fears of choking or vomiting
 - fears harm will come to himself or others, such as his parents, if he eats; in these cases, the child may be afraid to speak of the association because of additional obsessional fears.
 - refuse to eat because of a new obsession with body image or weight.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

Diagnostic Criteria

- 2) Co-morbid neuropsychiatric symptoms (at least 2) with a similarly acute onset: anxiety, sensory amplification or motor abnormalities, behavioral regression, deterioration in school performance, mood disorder, urinary symptoms and/or sleep disturbances
- 3) Symptoms are not better explained by a known neurologic or medical disorder

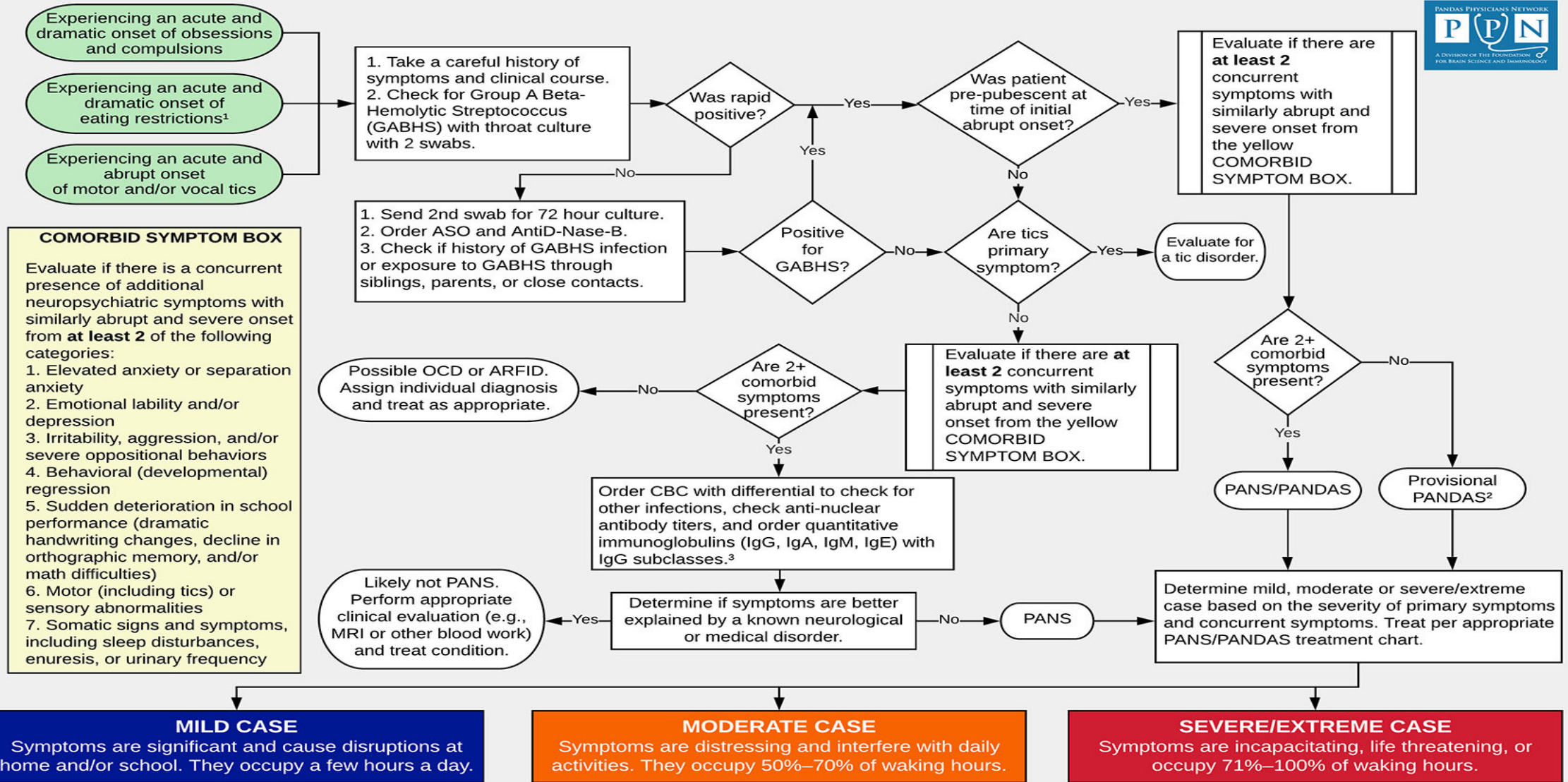
Etiology of PANS

- Dysfunction of the basal ganglia (specifically, the caudate, putamen and globus pallidus).
- One theory is that serum antibodies cross the blood brain barrier, cross-react with neuronal antigens and dysregulate basal ganglia functions.
- Another theory suggests that neuroglial immune cells in the brain incite basal ganglia inflammation. Neurons connecting to the basal ganglia affect motor function, emotion, behaviors, procedural learning, cognition and sensory issues

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PANS/PANDAS Diagnostic Flowchart



COMORBID SYMPTOM BOX

Evaluate if there is a concurrent presence of additional neuropsychiatric symptoms with similarly abrupt and severe onset from **at least 2** of the following categories:

1. Elevated anxiety or separation anxiety
2. Emotional lability and/or depression
3. Irritability, aggression, and/or severe oppositional behaviors
4. Behavioral (developmental) regression
5. Sudden deterioration in school performance (dramatic handwriting changes, decline in orthographic memory, and/or math difficulties)
6. Motor (including tics) or sensory abnormalities
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency

¹ If your patient is experiencing severe restrictive eating and/or ARFID (Avoidant/Restrictive Food Intake Disorder), determine if hospitalization is needed due to dramatic weight loss or if intravenous hydration is required.

² An official diagnosis of PANDAS includes an episodic course; however delaying treatment until a second onset is not recommended.

³ PANS does not exclude the possibility that the patient has or had strep. Approximately 35% of pediatric patients will not generate ASO or Anti-DnaseB titers and therefore can be a false negative for strep (Chet 2003). Throat cultures are only reliable to the extent of the rigor and approach of the practitioner and both vary greatly.