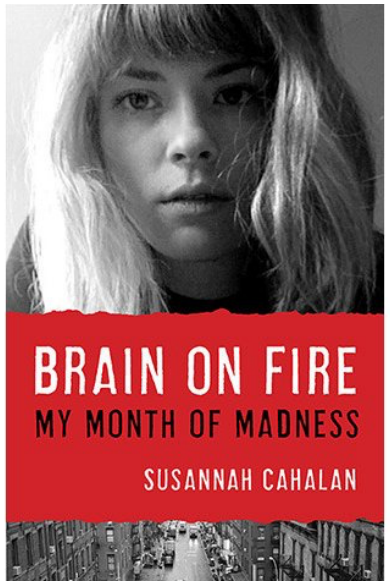
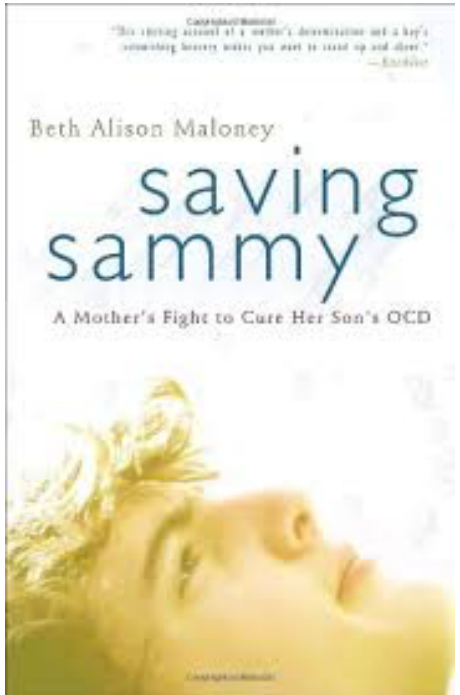
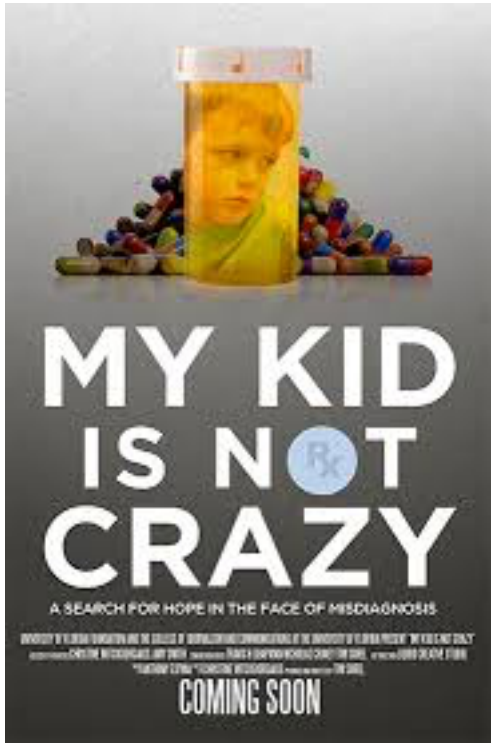
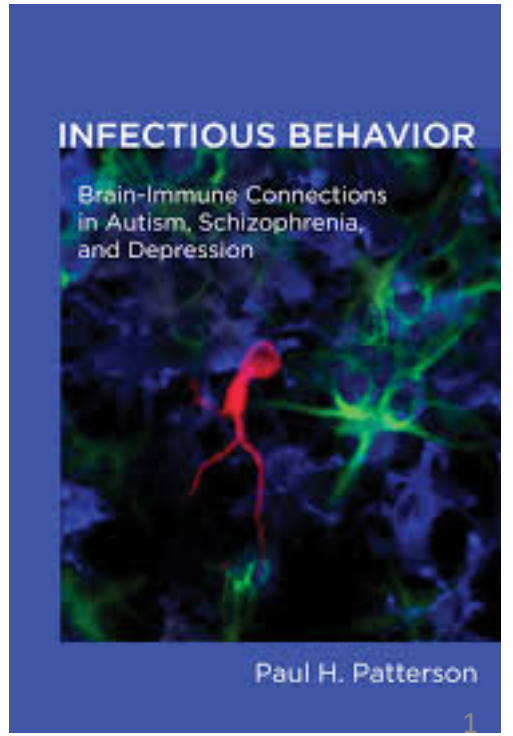
Autoimmune Neuropsychiatric Disorders in Popular Awareness









By Yuval Shafrir MD

Information resources

http://pandasnetwork.org/conferences/

https://www.moleculeralabs.com/pandas-and-pans-physician-resource-center/

https://www.moleculeralabs.com/silver-journal/

https://www.pandasppn.org/diagnose/

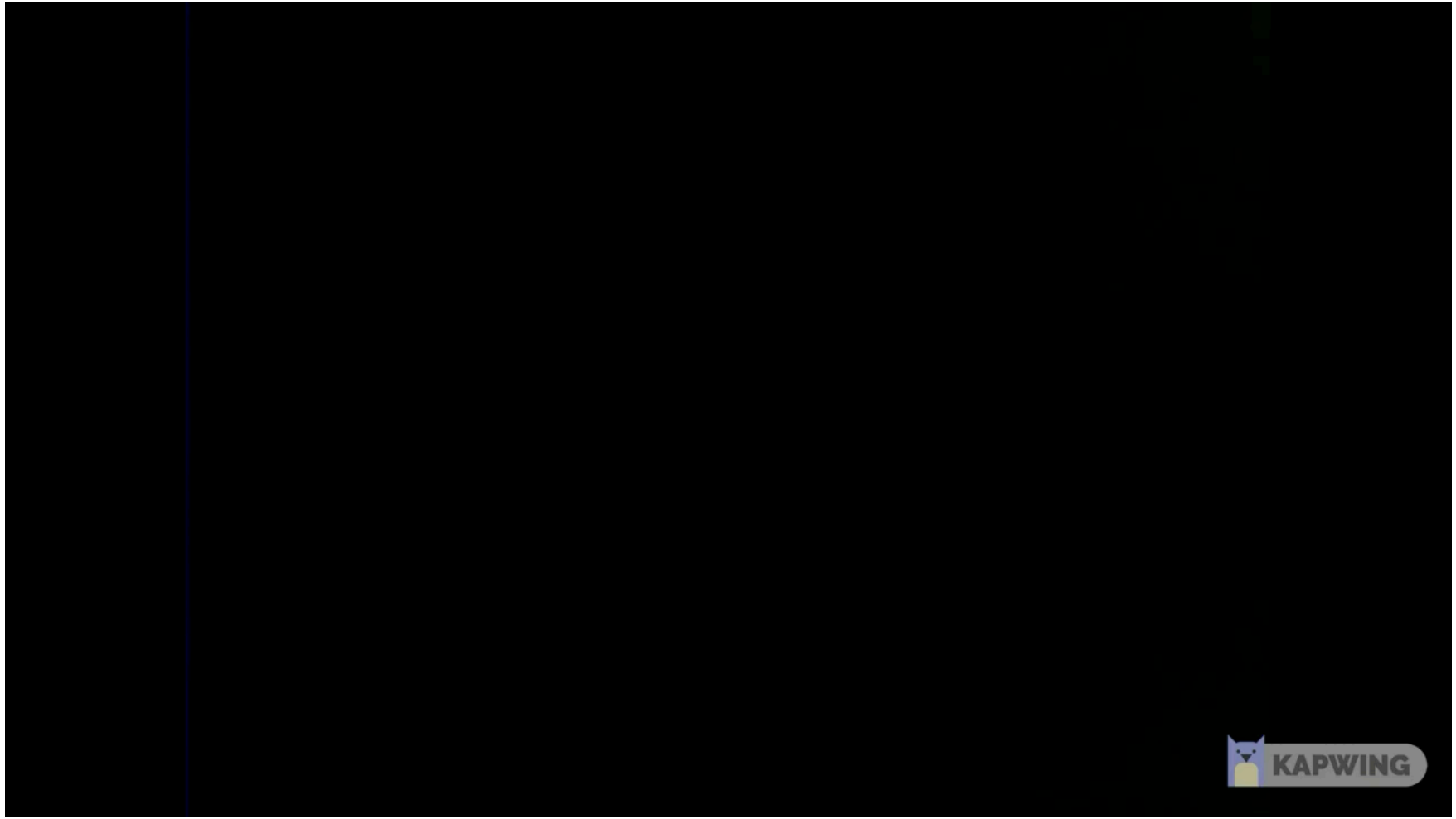
PANDAS/PANS “Controversy”

- For some reasons, the diagnosis and treatment of PANS/PANDAS became very controversial.
- This lead to marked paucity of good studies, which prevented progress in the field, especially when we compare it to the dramatic progress in other forms of non-cancerous autoimmune encephalitis, which was discovered about the same time as PANDAS, but is now part of regular neurological curriculum, many studies, and progress which helped saving many lives.
- Before this discovery of autoimmune encephalitis as a treatable condition many patients died or were left with extreme level of neurological disability.
- The result of this strange controversy is that the patients and their families are left to the mercy of greedy insurance companies, who typically deny the treatment.
- Very sadly, insurance consideration frequently dictate the diagnostic workup in the treatment which are currently sub-optimal.

Historical Perspective

- 1894 – Osler first describes OCD in Sydenham's Chorea (SC) a complication of rheumatic fever
- 1958 – Chapman reported OCD in 8 children with SC
- 1965 – Langlois and Force reported a 6 year old child with tics and SC precipitated by infection that was successfully treated with antibiotics and neuroleptics
- 1978 - Kondo and Kabasawa reported an 11-year-old boy with a tic disorder started abruptly about 10 days after a febrile illness associated with elevated antistreptolysin O (ASO) antibody titers and good response to corticosteroids
- 1989 - Kiessling reported an association of tics during pediatric GABHS outbreaks.
- 1989 – Swedo from NIH reported high number of SC cases with OCS and a fluctuating clinical course
- 1995 - Allen identified a subgroup of children with OCD and/or tic disorders post infection not c/w SC which they named PITANDs (pediatric, infection-triggered, autoimmune neuropsychiatric disorders).
- 1998 - PITANDs subgroup was renamed ''PANDAS''

Sydenham Chorea



History of PANDAS/PANS

- Identified in mid-1990s by NIMH researchers (Swedo and Rappaport)
- Grew out of research on OCD and Sydenham Chorea
- First peer-reviewed studies in 1995, 1998
- Continued research in 1990s, 2000s, 2010s
- 2012: Defined PANDAS and PANS as separate entities
- 2015: Diagnosis and evaluation guidelines (Chang et al, 2015)
- 2017: Treatment guidelines (various authors)

QUESTIONS FOR FAMILIES AND PHYSICIANS

- Treat if syndrome criteria not met?
- Who is treating physician?
- Which antibiotic? How long?
- ?Steroids, NSAIDs, tonsillectomy, IVIG, plasma exchange? "Alternative" treatments?
- How can one get physicians to coordinate care?
- What about family members warrants consideration?
- Immunization
- How to get school accommodations and which?
- How to get insurance to pay for treatment?

Terms

PANDAS = Pediatric Autoimmune Neuropsychiatric Syndrome associated with Streptococcal Infection

PANS = Pediatric Acute-onset Neuropsychiatric Syndrome

CANS = Childhood Acute Neuropsychiatric Symptoms
Autoimmune disease = It is easy it is caused by a misdirected activity of the immune system against the self. Most frequently, it is caused by activation of the system against a real threat. Because every person's immune system is unique and different any other human being, and some situations this misdirected response can occur.

Autoimmune encephalopathy = any brain disorder which is caused by inflammation and autoimmune attack. There are many brain disorders, including PANDAS and PANS, which are autoimmune encephalopathies.

Autoimmune encephalitis= autoimmune encephalopathy in which inflammation can be demonstrated by laboratory tests which include MRI showing changes which are presumed to be inflammatory, spinal fluid examination (obtained by spinal tap) showing inflammatory cells, as well as specific anti-neuronal antibodies which were discovered over the last few years.

Seronegative autoimmune encephalopathy: in which specific antibodies are not identified, but the clinical presentation is suggestive of autoimmune encephalopathy.

The presence of anti-neuronal antibody in the patient's blood does not prove that it is the cause of the patient's symptoms

Definition

Pediatric Acute – Onset Neuropsychiatric Syndrome (PANS) is a clinical condition defined by the usually abrupt onset of obsessive compulsive symptoms and/or severe eating restrictions and at least two concomitant cognitive, behavioral, or neurological symptoms.

Pediatric Autoimmune Neuropsychiatric Disorder associated with streptoccal infections (PANDAS) is a subset of PANS.

Guidelines For Diagnosing PANDAS

- Presence of clinically significant obsessions, compulsions and/or tics
- Unusually abrupt onset of symptoms or a relapsing-remitting course of symptom severity
- Pre-pubertal onset. Symptoms of the disorder first become evident between 3 years of age and puberty
- Association with Group A Streptococcal (GAS) infection.
- Association with other neuropsychiatric symptoms

Consensus PANS Criteria

I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake

II. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories:

1. Anxiety
2. Emotional lability and/or depression
3. Irritability, aggression, and/or severely oppositional behaviors
4. Behavioral (developmental) regression
5. Deterioration in school performance (related to attention deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)
6. Sensory or motor abnormalities
7. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency

III. Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham Chorea.

IV. No age requirement

How autoimmune attack on the brain and brain inflammation cause psychiatric symptoms?

The honest answer is: we have no clue. However, important progress has been made in understanding the mechanisms of these conditions (see Dr. Najjar lecture and other information on PPN)

All we have is clinical data showing the relationship.

The best examples are
- Lupus which has very large range of clinical expression with very variable symptoms, one of them is neuropsychiatric lupus with psychosis

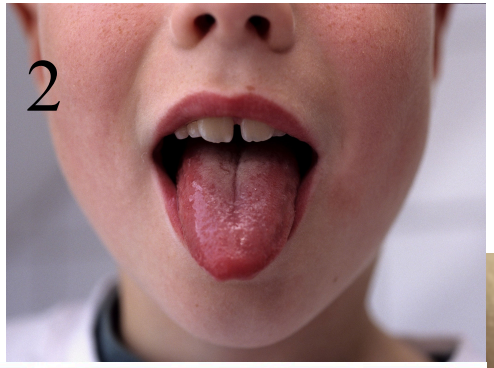
- Cases of autoimmune encephalitis with pure psychiatric presentation in which autoantibodies (antibodies which is produced by the patient's immune system, and ending up attacking the patient's own tissues) can be demonstrated.

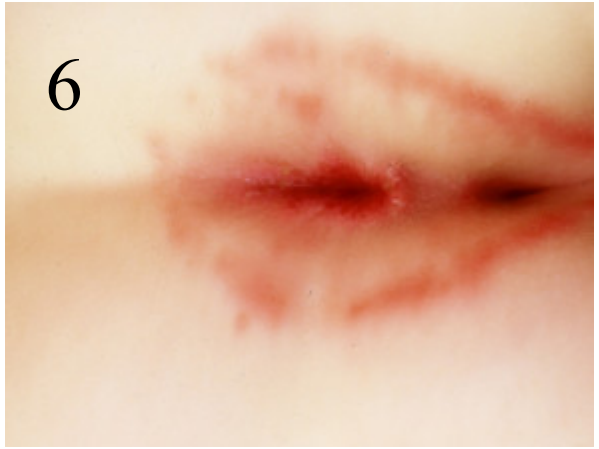
The most important proof for the role of brain autoimmunity and inflammation in psychiatric symptoms in the current stage of scientific knowledge is the dramatic improvement in the psychiatric symptoms with immunomodulatory treatment that suppress autoimmune activity and inflammation.

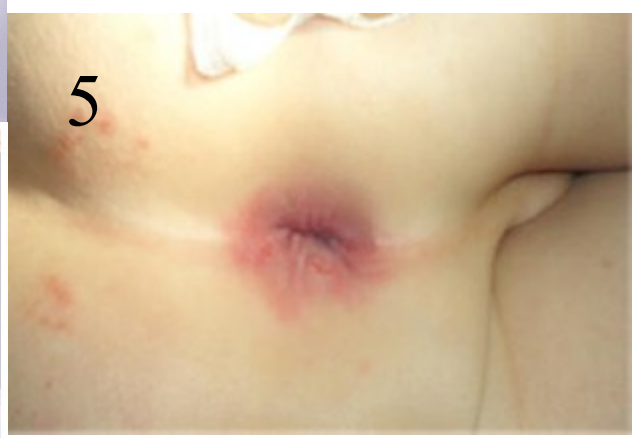
Presentation of streptococcal infection

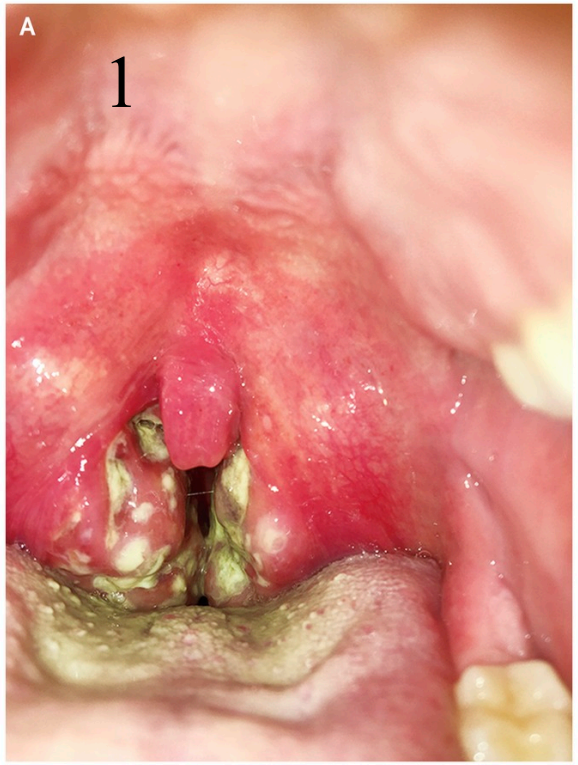
- Pharyngitis or tonsillitis
- sinusitis, ear infection
- Scarlet fever
- Perianal strep
- Impetigo
- abdominal pain
- Stiff neck
- ASYMPTOMATIC

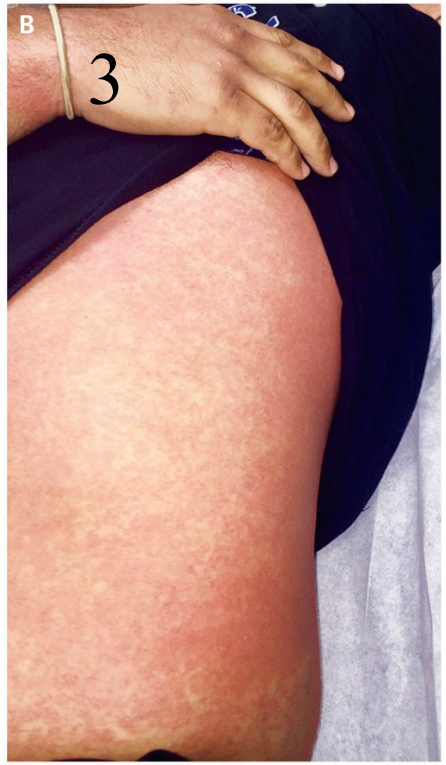
2 Streptococcal antibodies:
antistreptolysin O
anti DNase B
up to 40% of patients with documented streptococcal infection (by culture) would not have elevated antibodies.

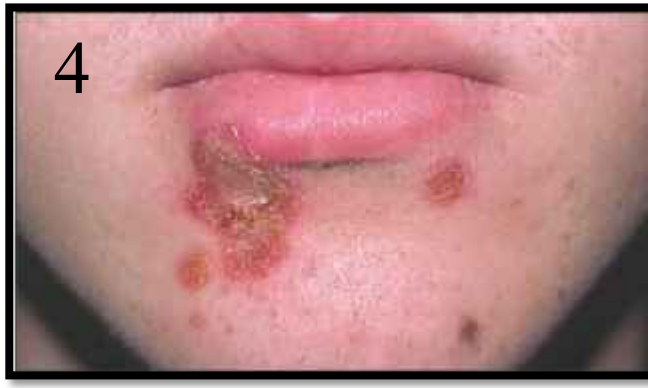












Other neurological presumed autoimmune conditions triggered by streptococcal infection

- Sydenham Chorea
- Basal ganglia encephalitis
- Narcolepsy
- Encephalitis lethargica
- Streptococcal related tics

TABLE 1. PROVISIONAL DETERMINATION OF PRIOR STREPTOCOCCAL INFECTION FOR AN OPERATIONAL DEFINITION OF PANDAS

Adequate for a diagnosis of PANDAS
A rise in serial antibody level, regardless of rapid test or culture result. This definition does not require clinical pharyngitis.
Acute pharyngitis with a positive GAS throat culture, with or without a rising antibody level.[a]
Pharyngitis with characteristic palatal petechiae.[b]
Pharyngitis with a characteristic scarlatinaform rash.[b]
Pharyngitis without a throat swab or serology, but intimate (usually household) exposure to a proven GAS case.[c]
Asymptomatic pharyngeal colonization documented after an intimate exposure.
Asymptomatic pharyngeal colonization after a negative throat swab documented within the prior 3–4 months.
Single ASO or ADB antibody level within 6 months after the initial onset of neuropsychiatric symptoms may be accepted as positive if it is >95th percentile, using the laboratory's normal standard for children of comparable age, or provisionally ASO ≥1:480 or ADB ≥1:1280.[d]
Both ASO and ADB are elevated at >80% percentile for age in the same serum sample within 6 months after the initial onset of neuropsychiatric symptoms.[e]
Culture-documented streptococcal dermatitis.

Main Symptoms

- Anxiety, particularly separation anxiety
- OCD symptoms, rituals, fears
- Emotional liability or depression
- Irritability, aggression, and/or several oppositional behaviors
- Deterioration in school performance. Change in handwriting.
- Food restrictions (without any change in body image; It is not anorexia)
- Sensory abnormalities
- Motor abnormalities (Tics, choreiform movements, repetitive movements)
- Somatic signs/symptoms including sleep disturbances, enuresis, or urinary frequency

OCD

Although patients can have PANDAS without OCD, OCD is the most common psychiatric symptoms in PANDAS, especially in the young children.

In contrast to non-PANDAS OCD which is a chronic condition that may fluctuate but does not go away and has gradual onset, in PANDAS the onset is typically very abrupt, may go away with or without treatment, and may recur.

A young child with abrupt onset of OCD, has not had OCD symptoms before, most probably has PANS/PANDAS, especially when associated with tics. However, those “pure” forms of PANS/PANDAS are the minority, and that many other patients with less distinct clinical presentation.

Common Pediatric Obsessions

- Contamination:
  - Bodily fluids
  - Germs/disease
  - Emetophobia
  - Environmental contaminants
  - Household chemicals
  - Dirt
- Losing Control/Harm:
  - Fear of acting out on impulse to hurt self or others, steal, curse
  - Fear of acting out on horrific images or impulses (suicide, etc)
  - Fear of being responsible for bad outcomes of others (fire, burglary, etc)
- Religious Obsessions (Scrupulosity)
  - Concern with offending God or committing blasphemy
  - Excessive concern with right/wrong or morality
- Perfectionism
  - Concern about evenness or exactness
  - Concern with a need to know or remember
  - Fear of losing information if discarded

Common Pediatric Compulsions

- Washing and cleaning
  - Washing excessively or in certain order
  - Excessive showering, tooth brushing, grooming, toilet routines
  - Cleaning household items or avoiding touching others to theirs
- Checking
  - Did not/will not harm others
  - Did not hurt self
  - Nothing terrible happened
  - Did not make a mistake
  - Body ok
- Mental compulsions
  - Mental review of events to prevent harm (conversations, sequences, etc.)
  - Praying to prevent harm
  - Counting while performing a task, ending a good/lucky/right number
  - Cancelling or undoing (replacing a good word with a bad word)
- Repeating
  - Rereading or rewriting/excessive erasures
  - Repeating routine activities (going up/down stairs, in/out of rooms)
  - Body movements (tapping, touching, blinking, breathing)
  - Repeating in multiples (x4, x8, etc.)

PANDAS Pre-Treatment

Fact or Opinion

Read the story.

Brad and Amy

Brad and Amy are brother and sister. They both like playing sports. Brad is on the soccer team. "Soccer is better than any other sport," Brad says. Amy likes basketball. She plays at the park down the street. Brad and Amy have a little brother named Steve. Steve would rather read a good book than play sports. He does like to watch his brother and sister play. Though. He sits on the sideline and cheers for them. They are both good at their sports!

Decide whether each sentence is a fact (F) or an opinion (O).

F Brad is on the soccer team.
O Soccer is better than any other sport.
F Amy plays basketball at the park.
F Steve is Brad and Amy's little brother.
F Brad and Amy are both good at their sports.
F Steve sits and cheers for his brother and sister.

Write a fact from the story.

Amy plays at the park down the street.

Write an opinion from the story.

Soccer is better than any other sport.

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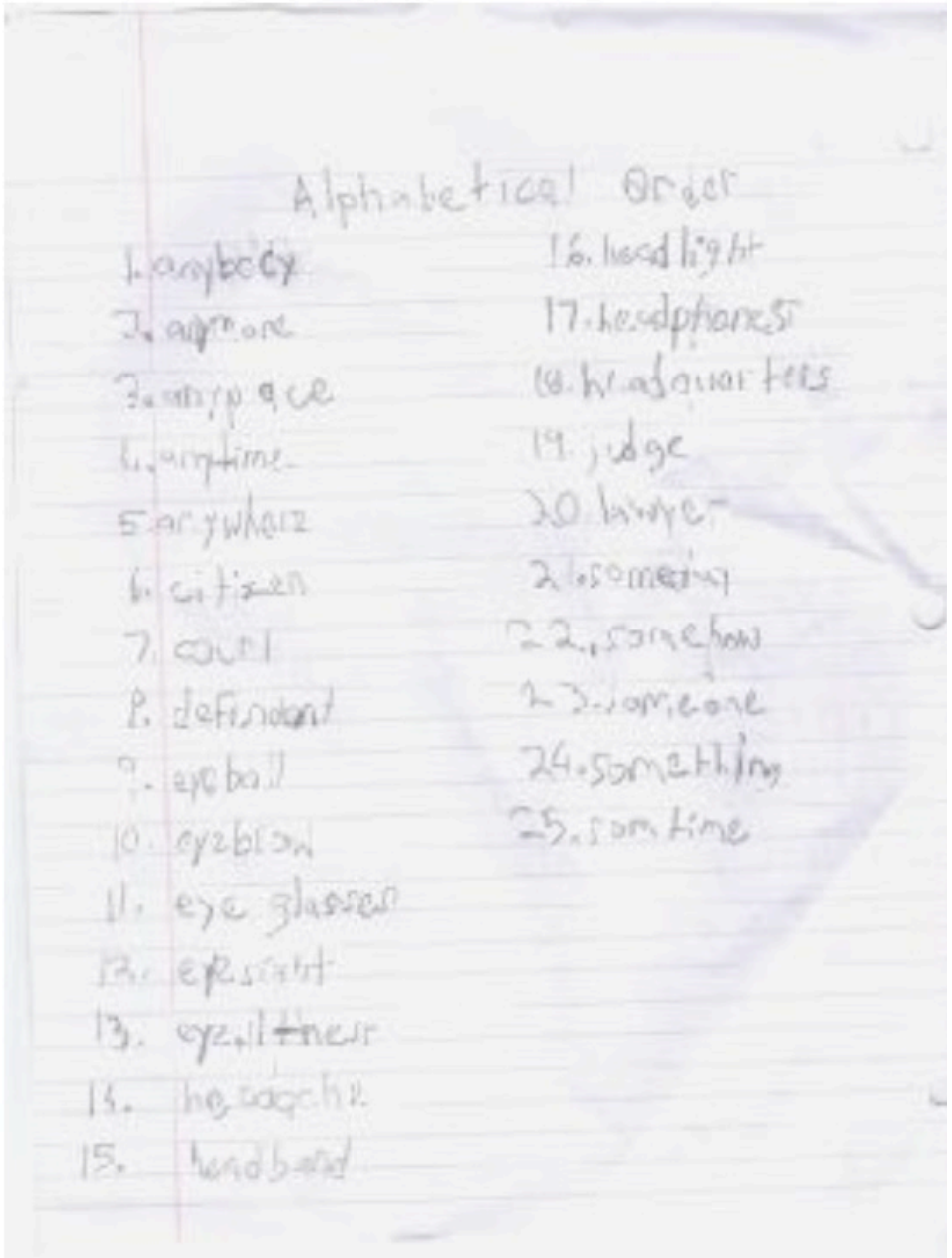
PANDAS Post Treatment



Alphabetical Order

1. anybody
2. anyone
3. anyplace
4. anytime
5. anywhere
6. citizen
7. court
8. defendant
9. eyeball
10. eyebrow
11. eye glasses
12. eyesight
13. eyelashes
14. headache
15. headband
16. headlight
17. headphones
18. headquarters
19. judge
20. lawyer
21. someday
22. somehow
23. someone
24. something
25. sometime

What differentiates autoimmune encephalitis from PANDAS

We have to remember that PANDAS is a form of autoimmune encephalitis.

- In the more severe cases of autoimmune encephalitis the patient is very sick, maybe comatoes, have repeated seizures which are difficult to control, or severe movement abnormalities (which may, at times, require restraints). The patient typically requires intensive care unit admission (practically not seen in pandas).

- Seizures are practically not seen in pandas. They are quite common in autoimmune encephalitis.

- In milder cases of autoimmune encephalitis, psychiatric problems most prominent. It is then more difficult to distinguish it from pandas.

- In pandas, the relationship to infection is more common. Treatment of the infection and prevention of recurrent infections a major part of the treatment in pandas. However, in many cases of autoimmune encephalitis, preceding infection can be identified

- However, the treatment of acute symptoms is identical.

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

Dalmou J, Graus F. NEJM 2018; 378: 840-851.

Differential Diagnosis

- Stress reaction, such as school stress the family stressors. It should be considered only after medical conditions were ruled out. The diagnosis should only be made by a trained psychologist who saw the child for several sessions
- Obsessive compulsive disorder
- Acute Psychosis
- Anorexia nervosa
- Avoidant/restrictive food intake disorder (ARFID)
- Tourette syndrome
- Transient tic disorder
- Bipolar disorder
- Onset of Schizophrenia
- Sydenham chorea
- Autoimmune encephalitis
- Systemic autoimmune disease (for example, psychosis associated with lupus cerebritis)
- Wilson's diseasea

Laboratory Testing

The diagnosis is purely clinical. Laboratory tests are only confirmatory.

There is no relationship between levels of streptococcal antibodies or Mycoplasma antibodies and the severity of the disease.

- CBC with diff, CMP, ESR, UA, CRP, throat culture strep, ASO (anti-streptolysin), antiDNAse B
- PANDAS: culture Group A Strep
- PANS: mycoplasma (serology and PCR), Influenza (rapid testing vs PCR), EBV serology, Lyme (serology and PCR for patients with history Lyme disease or live in tick infested areas.
- Other measures of autoimmunity: ANA, immunoglobulins
- Easily accessible tests for autoimmune causes of behavioral changes: thyroid function tests, thyroid antibody panel, anti-GAD 65 antibodies, celiac disease antibody panel
- Test for autoimmune encephalitis: Mayo clinic (very difficult to access); Quest diagnostics

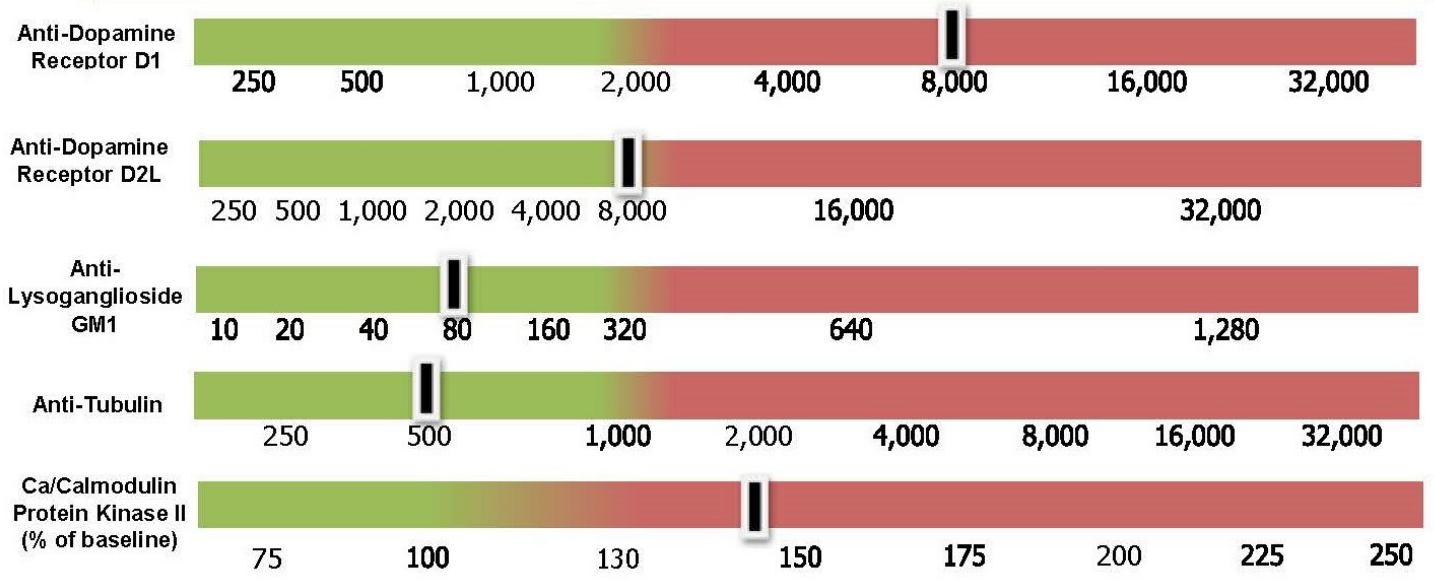
Labs: The Cunningham Panel

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	**1:8,000**	**1:8,000**	**1:80**	**1:500**	**145**
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	**ELEVATED**	**BORDERLINE**	**NORMAL**	**NORMAL**	**ELEVATED**

***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS



Treatment

Tragically, the policies of insurance companies greatly affect what we do.

Treatment

With complete lack of understanding of the pathophysiology of the disease the treatment is empiric, based on successful treatment of other conditions.

The treatment is directed by the severity of the symptoms. When the child is in very poor shape,

I'm very aggressive in the treatment even if the diagnosis is not fully established. The alternative, not to do anything, is not acceptable to me, but is acceptable to many other physicians.

- Treatment of acute infection
- prevention of recurrent infection
- immunomodulatory treatment
- treatment of specific symptoms
    - psychiatric treatment including therapy and psychiatric medications
    - treatment of sleep disorder

Treatment of Symptoms with Psychiatric Medications

OCD symptoms • Food or fluid intake restriction • Tics • Irritability, aggression • Anxiety • ADHD symptoms • Sleep disturbances • Depression • Pain

Although psychiatric medications are much less effective when the causes autoimmune encephalopathy, and the complete lack of response is frequently an important diagnostic clue, it does not mean that we should give up and not try to treat the suffering child with psychiatric medications.

Treatment of infection and prevention of recurrences

- Treatment of acute infection.

Treatment of strep. The initial treatment should be Augmentin (amoxicillin + clavulanic acid). It is not the standard treatment of strep infection, but I prefer to use it.

Side effects include:
- allergic reaction
- yeast infection, especially vaginal in girls. Oral thrush is less frequent.
- Diarrhea, bloating, abdominal distention
- The most feared side effect is a potentially life-threatening condition called pseudomembranous colitis, which may result in “toxic megacolon” and is caused by infection with a bacteria called Clostridium difficile. This is a result of the disruption in the balance of the bacterial populations in the gut. It can occur with any antibiotic, but clindamycin (which is frequently used in pandas) and Augmentin are the most common of oral antibiotics causing this condition.

It is believed that the use of probiotics together with antibiotics may decrease the risk for these complications.

ANTIBIOTIC RCTS FOR PANS/PANDAS

- **Penicillin v. Placebo** - Garvey et al. 1999
  - 4 months RCT, 37 children with PANDAS
  - No significant difference in improvement between groups.
  - Limitations
    - Carryover/order effects
    - Too many received treatment while in placebo arm
- **Penicillin v. Azithromycin v. Placebo** – Snider et al. 2005
  - 12 month parallel design, n=23
  - Decreased number of exacerbation and strep infections compared with pre-treatment year
- **Azithromycin v. Placebo** – Murphy et al. 2017
  - 4 weeks RCT, 31 children with PANS
  - Significant reduction in OCD severity (CGI-S OCD)
    - Tic severity moderated treatment response
    - Increase in QTc observed
- **Cefdinir v. Placebo** – Murphy et al. 2014
  - 30 days, n=19
  - OCD and tics improved following 30 day treatment
    - Moderate treatment effects observed with tic symptoms
    - No significant group differences

The use of long term antibiotics

- It is somewhat more controversial.
- It is based on the experience in rheumatic fever, in which it was proven to dramatically decrease recurrences and prevent long-term cardiac damage.
- There is only one study performed in the NIH in the late 90s showing that prolonged treatment with penicillin or erythromycin decrease the number of occurrences of PANDAS.
- Empiric experience suggests that in many patients, stopping antibiotics is followed by an exacerbation of PANDAS. However, exacerbation of PANDAS frequently occur while the patient takes antibiotics. In this situation, we frequently switch to stronger more white spectrum antibiotics such as Augmentin or clindamycin.
- Never use low dose antibiotics!
- The most feared side effect is pseudomembranous colitis, which maybe life-threatening. Milder side effects include diarrhea, abnormal swelling, used infection (oral thrush vaginitis)
- The use of probiotics with long-term antibiotic treatment is crucial.

Antibiotic treatment in cases without evidence of strep infection

- This is even more controversial.

- Mycoplasma is an intra-cellular microorganism which is not affected by penicillin. Penicillin works through disruption of the bacterial cell wall. Mycoplasma does not have cell wall. The treatment of choice is erythromycin or tetracyclines. Tetracyclines should be used only in children older than 9.
- Tetracycline and erythromycins may have anti-inflammatory effects

Tonsillectomy and adenoidectomy

- A procedure is frequently associated with quite dramatic improvement in symptoms.
- It is also important for prevention of future infections with strep.

However, it is not universally accepted treatment modality, and obviously it is quite controversial. We frequently do it because it is available, and the insurance companies are less likely to interfere with it, although they may.

Immunomodulatory Treatment

Ibuprofen

Prednisone

IVIG

Plasmapheresis

Rituximab

Cytotoxic medications used in cancer

Ibuprofen

- Effectiveness is viable and unpredictable, but in many cases it can be quite effective in few small studies.

- Parents can started on their own. It is an over-the-counter medication.

- The dose is 5 – 10 mg per kilogram per dose. It is given three times a day, ideally every eight hours. One tablet over the counter of ibuprofen, such as Advil, is 200 mg. The liquid is hundred milligrams per 5 ML.

- Short treatment of 7 – 10 days have very little side effects other than stomach irritation. Prolonged treatment has significantly more side effects. However, children with different forms of arthritis take very high doses for long period of time.

Prednisone

The insurance company will not interfere with his treatment because it is cheap.

There are no studies. A high dose should be used (2 mg per kilogram with decreasing doses over time) for at least 2-4 weeks. Short five day treatment typically used for asthma attack (dose-pack) is unlikely to work.

The common side effects are inevitable, and are part of the physiological effect of this hormone (Cushing's syndrome). They include

- hypertension
- increased sugar level
- weight gain, puffy red face, "Buffalo hump"

With prolonged use for more than several months, major side effects can appear including

- severe bone disease
- cataract
- diabetes

It is important to remember that 5% of patients will have psychiatric side effects including mania and psychosis. If this occurs, the medication must stop.

In order to decrease the side effects, several regimens were tried, such as high dose once a week.

Intravenous steroids (Methylprednisolone)

In autoimmune encephalitis, a regimen of 3-5 days of very high dose IV steroids is quite effective. Studies of this treatment has not been published in PANDAS.

The insurance companies are unlikely to restrict this medication, but it should be given under close medical supervision, and administration in an infusion center is quite likely to be denied by the insurance companies.

Steroid sparing treatments

Because of the side effects of steroids, in many autoimmune conditions including autoimmune encephalitis and occasional cases of PANDAS, oral cytotoxic medications are used in order to decrease or even stop the treatment with steroids. Those medications, azathioprine (Immuran) or mycophenolate (CellCept), have much less side effects than steroids, although they still have serious side effects. The most concerning is the fact that the increased the risk of cancer later in life. This risk is maximally children who have many years to live

IVIG

- This treatment has much less side effects than steroids. It is a crime against our children when we have to use steroids instead of for IVIG in order to maintain the profits of the insurance companies and the bonuses for their senior executives.

- It is used for several decades to treat autoimmune conditions. It is unclear how it works.

- The dose used for pandas is "borrowed" from the treatment of other autoimmune conditions (mainly a condition called immune thrombocytopenic purpura). The dose is 2 g per kilogram. Ideally, it should be given over five days in a hospital, but we rarely do it because of the interference of the insurance companies. It is typically given over two days, because this is what the insurance company allows.

- There are no studies which were performed in PANDAS patients to determine the optimal dose.

- The use of low dose IVIG (typically 400 mg per kilogram) should not be used in PANDAS. It is a treatment for hypogammaglobulinemia.

- Parents must be very careful in making sure that the medication is maintained in low-temperature during transport from the specialty pharmacy and kept in the refrigerator until it is diluted and infused.

IVIG- Side effects

- Acute allergic reaction which can be life-threatening. Therefore, the first round of treatment must be given in the presence of the physician, nurse practitioner, a very experienced RN in infusion center, never at home.
- Ideally, the first treatment should be given in the hospital, but this is rarely done because the hospital are reluctant to do it for various reasons, including fear not to be reimbursed by the insurance company. In the Washington DC area, the office of Dr. Elizabeth Latimer is probably the safest available outpatient IVIG infusion center for children, but this is also frequently limited by the insurance companies, who usually insist that the medication will come from their pharmacy.
- There are rare slightly delayed side effects such as transfusion related lung injury (TRLI), serum sickness, kidney injury and other.
- There is an increased risk of blood clotting because the blood become "thicker" and hyper- viscous because of increased level of immunoglobulins after the infusion. This may lead to a stroke. This complication is very rare in children. The risk can be decreased by giving 10-20 mL per kilogram of saline prior to the infusion.

IVIG- Side effects

Relatively common, very unpleasant side effect is "allergic meningitis". It can occur at any time within the first 10 days following the IVIG. It presents with severe headaches and recurrent vomiting. Typically, the attack last several hours and then it goes away. It is not life-threatening but may require hospitalization for uncontrolled pain or dehydration.

In order to prevent it, I typically give 10 days of prednisone in decreasing doses.

It responds to typical migraine treatment with a combination of ibuprofen, Tryptan (such as sumatriptan) and anti-emetic medication (anti-vomiting) such as Reglan or Compazine.

Beware of acute dystonic reaction in response to Reglan or Compazine (not present with Zofran).

After giving IVIG, there is no point for any immunological tests such as serological test for infections including streptococcal antibodies for several months, as the results represent the donors antibodies and not the patient's antibodies.

The response to IVIG

The response is not immediate. Typically, the positive effects are seen after 2 to 3 weeks. The only controlled study of the effects of IVIG in PANDAS was performed in the NIH in the late 90s. The study compared the response to a single dose of 2 g per kilogram of IVIG to plasmapheresis. It showed positive effect. Another study was performed recently in the NIH with less impressive results.

- We don't know how to predict the response to IVIG. If the patient responded well to steroids, the likelihood of response to IVIG's higher.

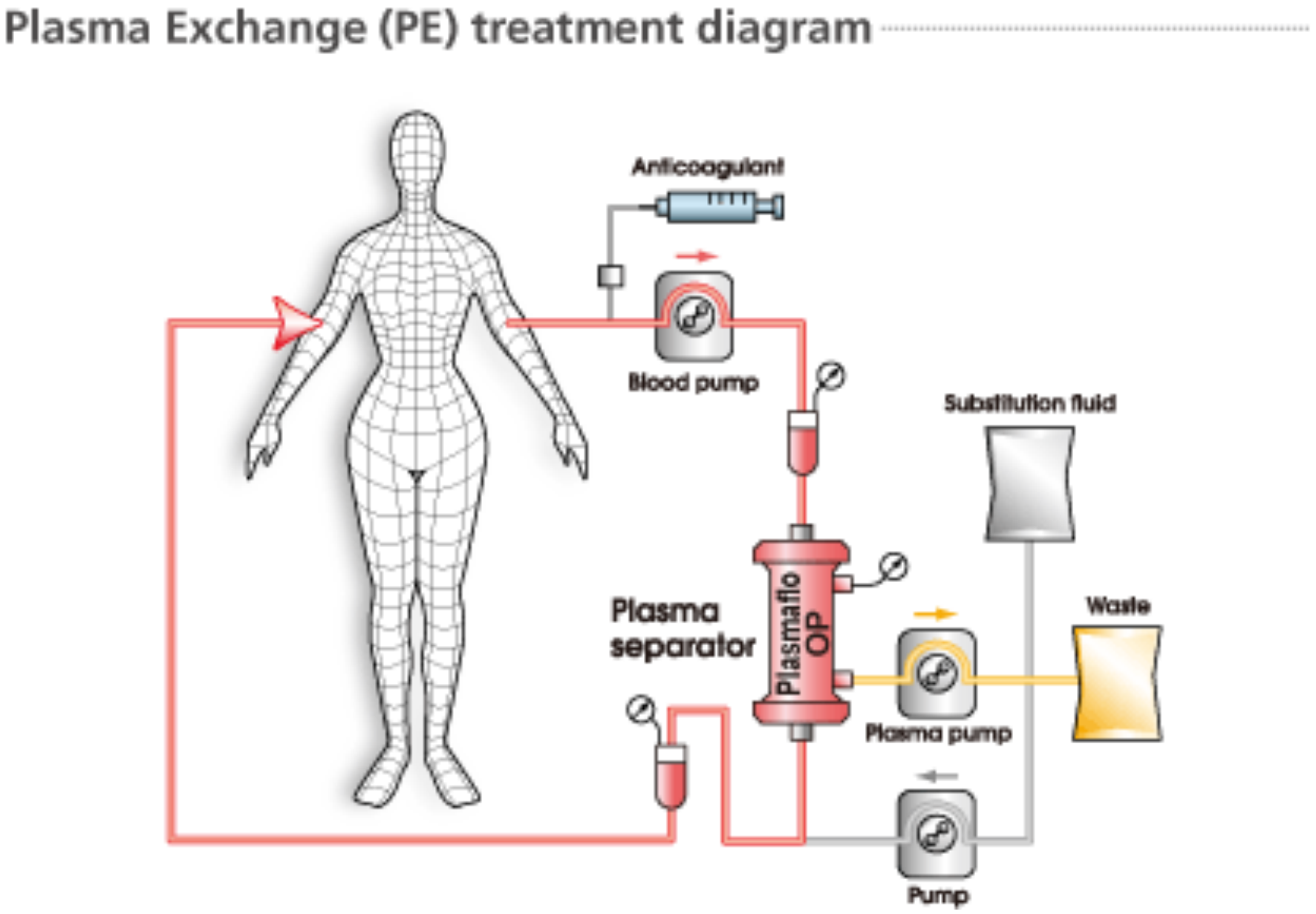
- In many patient's single treatment is enough.

- In other patients, a pattern of recurrence of symptoms and overall deterioration is seen several weeks to months after the treatment. In those patients, the infusion can be repeated and we typically expect success.

- Some patient will end up on a regimen of repeated infusions of IVIG. There are absolutely no studies of such a treatment. However, in those patients the symptoms can be controlled, and eventually the intervals between the infusions can be gradually increased until the treatment is stopped completely.

- Yet in other patients, we see that the response to IVIG gradually decreases and finally there is no help at all.

Plasmapheresis



Plasmapheresis

- This treatment removes the pathologic antibodies from the bloodstream. If those antibodies are the cause of the patient's symptoms, resolution of the symptoms are expected.

- It is a very invasive procedure, typically requiring a week in the hospital.

- It has significantly more side effects than IVIG.

- It produces a faster effect, but probably the duration of the effect is shorter (no well controlled data)

- It may be used with psychiatric emergencies, when very rapid responses necessary. However, it may be very difficult to perform the procedure on patients with severe behavioral problems, irritability or psychosis. General anesthesia for long period of time may be required in such situations.

- It is very rarely used for PANDAS, especially with the availability of rituximab.

Rituximab

Rituximab is a chimeric monoclonal antibody (antibody which is produced by creating an artificial molecule which is part human IgG and part mouse IgG) against the protein CD20, which is primarily found on the surface of immune system B lymphocytes, which are the cells of the immune systems that produce antibodies. When it binds to this protein it triggers cell death. It depletes the body of its B cells.

It eradicates the part of the immune system that makes antibodies.

It is used to treat several types of blood cancers (certain types of leukemia and lymphoma), where its side are much less than typical cytotoxic chemotherapy drugs. It is also approved to be used for the treatment of severe rheumatoid arthritis. The dose in PANDAS and in autoimmune encephalitis is "borrowed" from the treatment of rheumatoid arthritis.

It is used in PANDAS for patients with severe symptoms who do not respond to IVIG.

While having potentially severe and even life-threatening side effects, it has been a "miracle drug", saving many lives of patients with hematological malignancies or severe autoimmune diseases. It is frequently used in neurology for different forms of autoimmune brain diseases.

Rituximab - Side effects

Rituximab has many serious and potentially life-threatening side effects, both acute and chronic. It should never be given at home (although some insurance companies suggested that).

Acute side effects, which often occur within two hours of the medication being given, include rash, itchiness, low blood pressure, and shortness of breath.[3]

Other severe side effects include reactivation of hepatitis B in those previously infected, progressive multifocal leukoencephalopathy (a severe, frequently fatal neurological disorder), and toxic epidermal necrolysis

It makes the patient immunodeficient for several months. Typically we see gradual recovery of the number of lymphocytes carrying CD 20 protein. This is typically measured by a test called lymphocyte subpopulations. Typically a different protein is tested (CD19) which has similar distribution to CD20.

During the period of immunodeficiency, the patient can suffer from severe and potentially life-threatening infections.

Supplements

Supplements never cure PANS or PANDAS.

It can be very detrimental to the child medications aimed at treating the medical condition are avoided because parents want to "try supplements first". Remember, as in any other autoimmune encephalopathy earlier treatment is associated with better results.

- Some treatments such as vitamin B12 injections or fluconazole should be avoided.
- Fish oil, omega-3, phospholipids (such as phosphatidyl choline, Vayarin), vitamin D, magnesium are likely to be helpful although there were not studied.
- Anti-inflammatory diet can be helpful.
- Avoid expensive procedures even if they cannot hurt the child. Better concentrate and spend the money on something that can help.
- CBD oil is not actually a supplement. It is symptomatic treatment that can be quite effective or behavioral difficulties such as anxiety and irritability, but does not cure the pathological condition. It does have some anti-inflammatory effects.

Less well-defined cases.

Psychiatric disorders suspected to be autoimmune/inflammatory in nature.

This is a very new field in neurology and psychiatry. There are no well-defined criteria for diagnosis.

It opens a window of hope to many patients with severe disabling psychiatric disorders who had no effective treatment, and there is growing number of such desperate patients reported to greatly improved on immunomodulatory treatment.

- Patients with positive anti-neuronal antibodies and pure psychiatric symptoms, without encephalitis.
- Patient with “seronegative autoimmune encephalitis” who have clinical presentation typical to autoimmune encephalitis no antibodies is found.
- Patients with psychiatric picture that raises the possibility of autoimmune disease, in whom all the tests for autoimmune encephalopathy (serology, MRI, spinal tap, EEG) are all negative.

See Dr. Najjar lecture on PPN

Diagnostic challenges in identifying this subpopulation of patients:

- Frequent absence of CNS hyperexcitability (e.g., hyperekplexia, tremors, myoclonus), abnormal movements, seizures, or autonomic instability
- Frequent absence of focal neurological deficits
- Frequent absence of diagnostic findings on conventional MRI studies
- May not be associated with CSF pleocytosis or OCBs

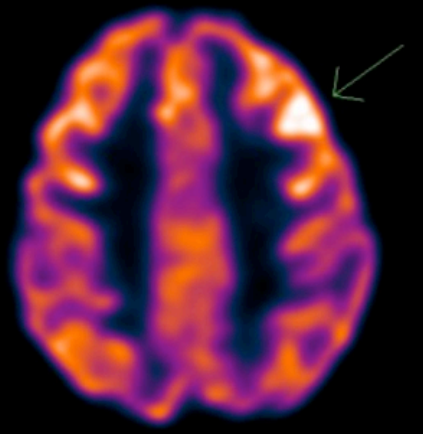
Many time, the treatment is shot in the dark, based on the severity of the patient's situation in severity of the symptoms and the possibility, based on the clinical history and characteristics, that the cause for the psychotic symptoms are autoimmune.

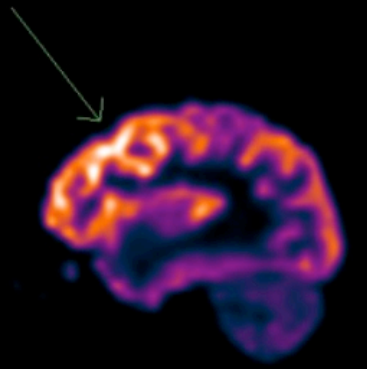
Many physicians look at this approach as a heresy, breaking the dogma of first understand, then treat.

However, this is not "alternative medicine" or "functional medicine" were dishonest physicians, naturopaths, nutritionists, chiropractors etc. claim that they understand the disease and recommend treatments which bear no relationship to any potential cause of the patient's symptoms

PET is another diagnostic modality that can help in establishing the diagnosis of autoimmune psychiatric disorder. Beware of SPECT which is frequently offered by fraudsters.

- 21 year old right handed man presented with subacute-onset refractory psychiatric symptom (depression, anxiety, psychosis associated with cognitive impairment about 2 weeks following viral illness
- No prior personal or family history of psychiatric illness
- DIAGNOSTIC FINDINGS:
  - EEG: Intermittent frontotemporal slowing, L>R
  - BRAIN MRI: normal
  - Serology and CSF::normal





PET in PANDAS Was studied by Kumar, Williams and Chugani (Journal of Child Neurology, Vol 30, Issue 6, 2015

What can we learn from this case?

Although it is well demonstrated that patients are doing much better with early treatment, autoimmune psychiatric disorder can still be successfully treated many years after their onset.

Genetic versus autoimmune

- This year, an amazing publication described 4 girls who were previously diagnosed with developmental delay, and suffered a dramatic deterioration in the function with irritability, psychotic symptoms, and deterioration of language and communication, typically with strong autistic features. At least two of them were diagnosed with pandas. All were found to have mutations in a specific location in the gene called SHANK-3. However, before the diagnosis was made, they were given immunomodulatory treatment (steroids, IVIG, rituximab, and one even received cyclophosphamide, a cancer drug) with dramatic positive response.

- We still don't know what to make of this. Especially when it comes to autism. There is no understanding why the responded so well to the immunomodulatory treatment. However, the verdict: "this is genetic, there is nothing to do", is not as decisive as it was before this publication

Prognosis

- Similar to rheumatic fever, PANDAS is a self-limiting condition, which means that sooner or later it should go away even without treatment.

- In rheumatic fever, the residual damage (the damage that is left after the disease has resolved) is a major problem.

- We don't have long-term studies on pandas to tell us what the overall prognosis is, but it is quite likely, based on observation of many physicians, that it may leave the patient with permanent psychiatric disorders such as OCD or anxiety.