Unraveling Mysteries of Neuropsychiatric Disorders

Elena Frid, MD
Board Certified Neurologist
Board Certified Clinical Neurophysiologist
Autoimmune Neurologist / Lyme Specialist

Agenda

- Define Autoimmune Neurology
- Infections induced autoimmune encephalitis
- Talk About Infections
- Neuropsychiatric presentation
- What to do when you suspect and organic presentation
- Case presentations

Autoimmune Neurology

- Production of antineuronal antibodies that affect
  - Central Nervous system
    - Causing Autoimmune Encephalitis
  - Peripheral Nervous system
    - Neuropathy
    - Autonomic Nervous System Dysfunction
- Break in the blood brain barrier due to insult of the nervous system
  - Causing Disruption of the regular brain matrix
    - Presence of inflammatory cells – Lymphocytes
    - Disruption of Glial cells – supportive neuronal cells
  - Often thought to be idiopathic
  - Consider Infectious/Inflammatory

What is new here?

- The condition is INFECTIONS induced
- NOT post-infectious!

According to R. Bransfield's article on "*Relationship of Inflammation and Autoimmunity to Psychiatric Sequelae in Lyme Disease*"

"No self-perpetuating immune process without persistent infection has ever been scientifically proven."

Why Does it Occur?

- If one is infected with an organism that contributes to a significant portion of ones genome – an autoimmune phenomenon may occur.
- Production of anti-neuronal antibodies

What are some of the triggers?

- Lyme Disease
- Co-Infections
- Candida Albicans
- Strep
- Viruses
- M. Pneumonia

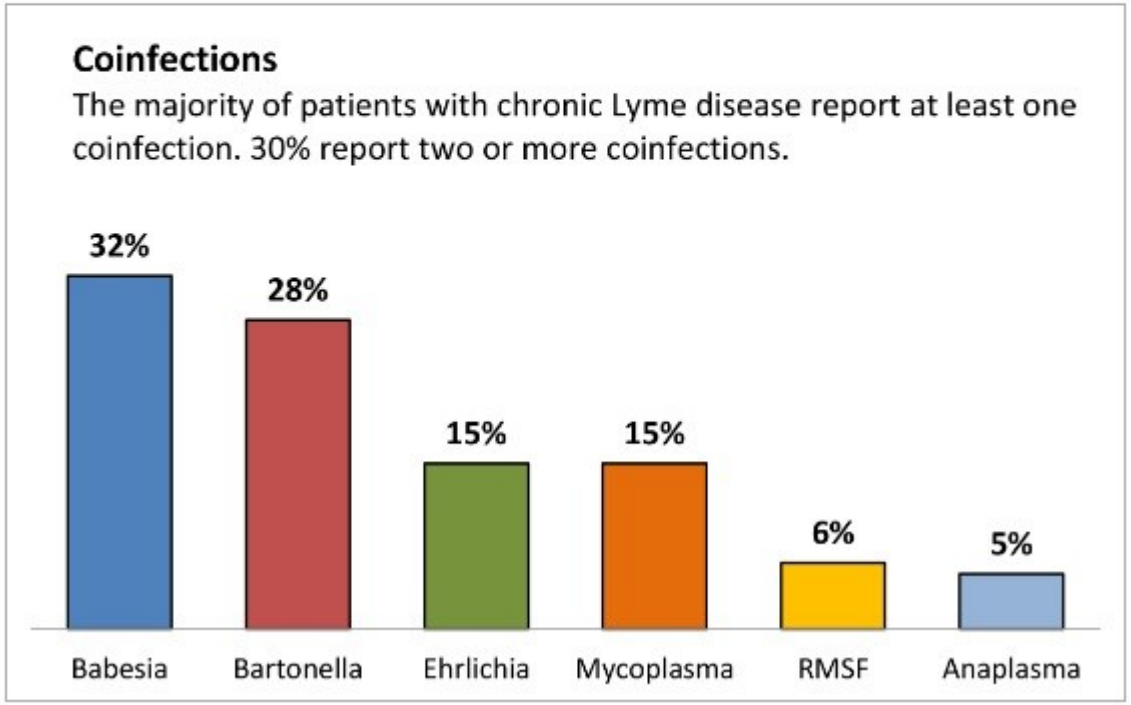
Lyme (*Borrelia burgdorferi*)

- The fastest growing infectious disease and vector borne illness in the US and UK
- Over 300,000 new Lyme cases/year in US
- UK Lyme disease prevalence 1.7 in 100,000
- Reported in all 50 states and 80 countries around the world
- 20-60% of these patients will develop chronic illness

Lyme and Co-Infections

- Lymedisease.org chart
  - prevalence of co-infections is high

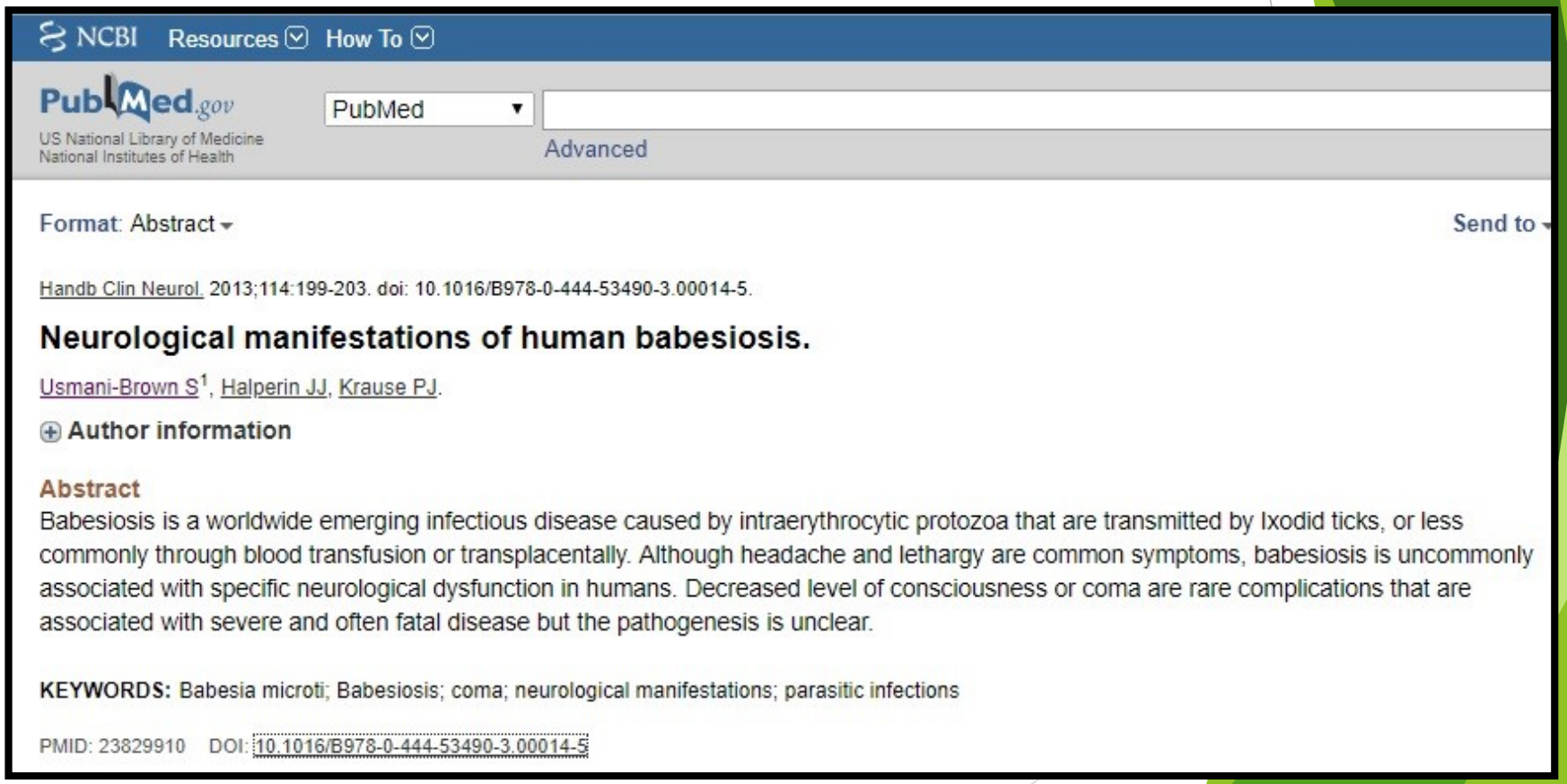
Coinfections may be common – at least among those with chronic Lyme disease. A recently published LDo survey over 3,000 patients with chronic Lyme disease found that over 50% had coinfections, with 30% reporting two or more coinfections. The most common coinfections were Babesia (32%), Bartonella (28%), Ehrlichia (15%), Mycoplasma (15%), Rocky Mountain Spotted Fever (6%), Anaplasma (5%), and Tularemia (1%). A similar study in Canada found similar rates of coinfection in patients with chronic Lyme disease:



https://www.lymedisease.org/lyme-basics/co-infections/about-co-infections/

Babesia Presentation

- Headaches
- Lethargy
- Hematologic Abnormality



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Handb Clin Neurol. 2013;114:199-203. doi: 10.1016/B978-0-444-53490-3.00014-5.

Neurological manifestations of human babesiosis.

Usmani-Brown S[1], Halperin JJ, Krause PJ.

Author information

Abstract

Babesiosis is a worldwide emerging infectious disease caused by intraerythrocytic protozoa that are transmitted by Ixodid ticks, or less commonly through blood transfusion or transplacentally. Although headache and lethargy are common symptoms, babesiosis is uncommonly associated with specific neurological dysfunction in humans. Decreased level of consciousness or coma are rare complications that are associated with severe and often fatal disease but the pathogenesis is unclear.

KEYWORDS: Babesia microti; Babesiosis; coma; neurological manifestations; parasitic infections

PMID: 23829910 DOI: 10.1016/B978-0-444-53490-3.00014-5

Bartonella Henselae Presentation

- **Immunocompetent patients presenting with:**
  - Aphasia
  - Encephalopathy
  - Neuropathy
  - Seizures
  - Transverse myelitis

Ashdin Publishing
Journal of Neuroparasitology
Vol. 3 (2012), Article ID 235640, 15 pages
doi:10.4303/jnp/235640

Review Article

Neurological Manifestations of Bartonellosis in Immunocompetent Patients: A Composite of Reports from 2005–2012

E. B. Breitschwerdt,[1] S. Sontakke,[1,2] and S. Hopkins[3]

[1] *Intracellular Pathogens Research Laboratory, Center for Comparative Medicine and Translational Research, North Carolina State University, Raleigh, NC 27607, USA*
[2] *Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27607, USA*
[3] *Department of Neurology, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE 19803, USA*
Address correspondence to E. B. Breitschwerd, ed_breitschwerdt@ncsu.edu

http://www.lymepa.org/Breitschwerdt_J_Neuroparasitol_Review_2012.pdf

AE an Infections Induced Process

International Journal of Pediatric Otorhinolaryngology 92 (2017) 38–44

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Improvement of psychiatric symptoms in youth following resolution of sinusitis

Talia Mahony [a], Douglas Sidell [b], Hayley Gans [c], Kayla Brown [a], Bahare Farhadian [a], Melissa Gustafson [a], Janell Sherr [a], Margo Thienemann [d], Jennifer Frankovich [a,*]

[a] Pediatric Divisions of Allergy, Immunology, & Rheumatology, Stanford University School of Medicine, 700 Welch Road, Suite 301, Palo Alto, CA, 94304, USA
[b] Pediatric Division of Otolarynthology, Stanford University School of Medicine, 730 Welch Road, Palo Alto, CA, 94304, USA
[c] Pediatric Division of Infectious Disease, Stanford University School of Medicine, 730 Welch Road, Palo Alto, CA, 94304, USA
[d] Pediatric Divisions of Child & Adolescent Psychiatry, Stanford University School of Medicine, 700 Welch Road, Suite 301, Palo Alto, CA, 94304, USA

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ABSTRACT

Introduction: Accumulating evidence supports a role for inflammation in psychiatric illness, and the onset or exacerbation of psychiatric symptoms may follow non-CNS infections. Here, we provide the first detailed description of obsessive-compulsive and related psychiatric symptoms arising concurrently with sinusitis.

Methods: We reviewed the charts of 150 consecutive patients evaluated in our Pediatric Acute-onset Neuropsychiatric Syndromes clinic for documented sinusitis as defined by the American Academy of Pediatrics guidelines. Sinusitis treatments, sinonasal imaging, and neuropsychiatric symptoms before, during, and after sinusitis onset were noted. Patients were included in the final review if they had a clear

"Improvement of Psychiatric Symptoms in Youth Following Resolution of Sinusitis" 2017

- Patients presented with
  - Anxiety
  - Mood Disorders
  - Panic Attacks
  - Learning Disability
  - OCD
  - And more
- Retrospective study with 150 patients
  - 10/150 presented with neuropsychiatric symptoms at onset of sinusitis
  - 8/10 patients had resolution of their neuropsychiatric symptoms with treatment
  - 1 patient lost to follow up
  - 1 patient did not follow recommendations

Why do these infections develop into a chronic illness?

- One needs to identify all the infections and treat them all at the same time!
  - This is complicated!!!
- Important to identify all co-infections
- Important to identify all offending agents and pathologies

Despite that, a % of patient remain ill…

- There is evidence of an autoimmune phenomenon that occurs in these patients including
  - Arthritis
  - Encephalopathy
  - Neuropathy
  - Neuro-degenerative disorders
  - Neurodevelopmental
  - Neuropsychiatric
  - Thyroid disorders
  - Etc.

Clinical presentation of Autoimmune Encephalitis:

- Seizures
- Psychiatric Features
- Cognitive Decline

Symptoms of Autoimmune Encephalitis:

- Often can be a subacute presentation of
  - Decline in memory
  - Psychiatric symptoms
    - Psychosis
    - Aggression
    - Inappropriate sexual behaviors
    - Panic attacks
    - Compulsive behaviors
    - Euphoria or fear
  - Seizures
- Movement disorder
  - Dystonia
  - Chorea
  - Rigidity
  - Myoclonus
  - Catatonic State
- Cerebellitis
  - Ataxic
    - Gait
    - Limb movements
    - Eye movements
    - Voice
    - Swallowing

Movement Disorders

- Myoclonic jerks
- Dystonia
- Chorea
- Rigidity

Transient Catatonic State

What to do next?

- Work patients up for autoimmune disorders

NAME _____ DOB ____/____/____

☐ I DONT HAVE LYME ☐ I DO HAVE LYME ☐ Other disease or illness (if known diagnoses) _____

What is the primary (chief) complaint? _____

Please rate signs and symptoms below:

Current severity : (1) mild (2) moderate (3) severe
Current Frequency: (+) occasional (++) often (+++) constant

	Initial Visit	Follow-up	Follow-up	Follow-up	Follow-up
DATE:					
Ex.	2++				
Unexplained fevers, sweats, chills or flushing					
Weight change (loss or gain)					
Fatigue					
Hair loss					
Swollen glands					
Sore throat					
Testicular/pelvic pain					
Menstrual irregularity					
Irritable bladder or dysfunction					
Upset stomach/abdominal pain					
Constipation/diarrhea					
Chest pain/rib soreness					
Shortness of breath or cough					
Heart palpitations					
Joint pain/swelling					
Joint stiffness					
Muscle pain/cramps					
Muscle twitching					
Headaches					
Neck creaks/cracks/stiffness					
Numbness/tingling stabbing sensations					
Facial paralysis					
Double vision/loss of vision					
Buzzing/ringing/ear pain					
Vertigo/dizziness					
Lightheadedness / poor balance					
Tremors / twitches					
Difficulty thinking / constr.					
Forgetfulness/poor short term memory					
Disorientations/getting lost					
Difficulty with speech / writing					
Mood swings / depression					
Too much / too little sleep					
Total Score:					

Scoring:
<5 Lyme Borreliosis Unlikely
5-10 Lyme Borreliosis Possible
>10 Lyme Borreliosis Highly Likely

Go to Checklist

My work up for Autoimmune Encephalitis

- MRI of the head
- EEG
- Brain SPECT/Brain PET scan
- BW:
  - Paraneoplastic Panel (Anti Hu, Yo, Ri, Amphiphysin, Tr, CV2, Ta)
  - Gad 65 Ab (Stiff Person's syndrome/Autoimmune Encephalitis)
  - CASPR- 2 Ab (Limbic encephalitis)
  - Glutamate Receptor Ab (Rasmuseen's encephalitis)
  - S100B (Break in Blood Brain Barrier)
- LP
- Neurocognitive testing
- Brain Biopsy (Lymphocytes/Glial Cells)

Anti Neuronal Antibodies: Journal of Clinical Neurology

Table 1

Clinical clues in the recognition of particular types of autoimmune encephalitis

Clinical finding	Associated autoantibody disorders
Psychosis	NMDAR, AMPAR, GABA-B-R
Dystonia, chorea	NMDAR, Sydenham chorea, D2R
Hyperekplexia	GlyR
Status epilepticus	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common; may occur in other types as well
New onset type 1 diabetes	GAD65
Fasciobrachial dystonic seizures	LGI1
Neuromyotonia, muscle spasms, fasciculations	Caspr2
Stiff-person syndrome and/or exaggerated startle	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)
CNS (myoclonus, startle, delirium) and gastrointestinal hyper-excitability	DPPX
Cranial neuropathies	Ma2, Hu, Miller-Fisher, Bickerstaff (but also infections like Sarcoidosis, Lyme, TB)
Cerebellitis	GAD65, PCA-1 (Yo), ANNA-1 (Hu), DNER (Tr), mGluR1, VGCC

J Clin Neurol

www.ncbi.nlm.nih.gov/pmc/articles/PMC4712273

Role of Cunningham Panel

- Shows presence of Anti-Neuronal Antibodies
  - Dopamine 1
  - Dopamine 2
  - Lysoganglioside
  - Tubulin
- Induced by infections:
  - Strep
  - Lyme
  - Mycoplasma Pneumoniae
  - And more
- Causing PANS/PANDAS

How it is diagnosed: Neurology - 2017

Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis

OPEN

John C. Probasco, MD
Lilja Solnes, MD
Abhinav Nalluri, BS
Jesse Cohen, BA
Krystyna M. Jones, MD
Elcin Zan, MD
Mehrbod S. Javadi, MD
Arun Venkatesan, MD, PhD

Correspondence to Dr. Probasco: jprobas1@jhmi.edu

ABSTRACT

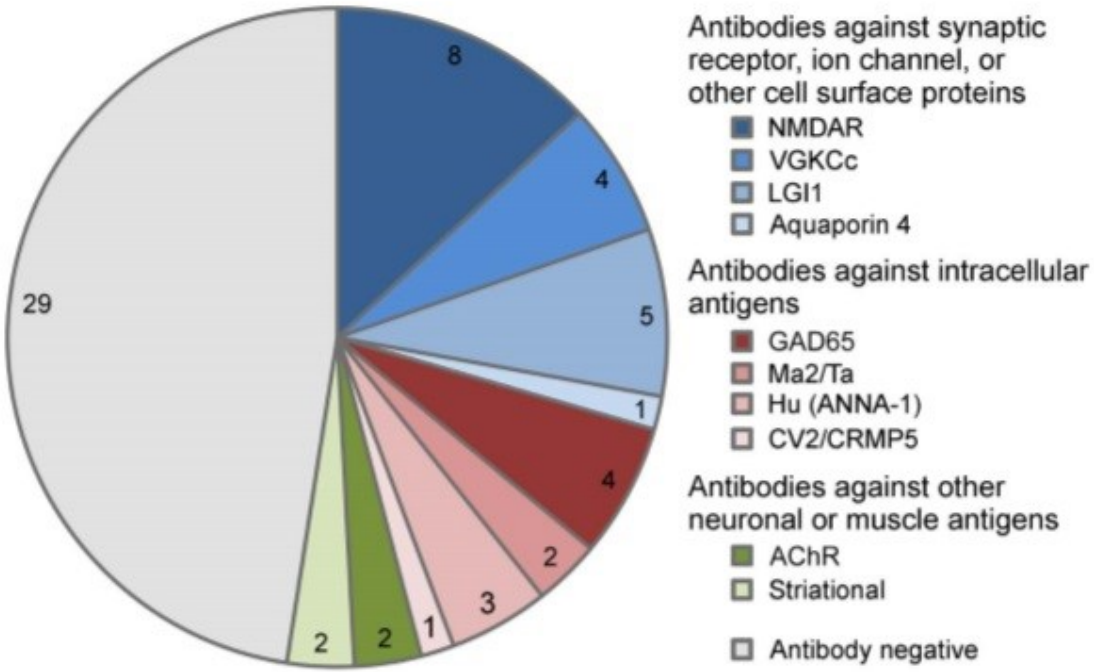
Objective: To compare the rate of abnormal brain metabolism by FDG-PET/CT to other paraclinical findings and to describe brain metabolism patterns in autoimmune encephalitis (AE).

Methods: A retrospective review of clinical data and initial dedicated brain FDG-PET/CT studies for neurology inpatients with AE, per consensus criteria, treated at a single tertiary center over 123 months. Z-score maps of FDG-PET/CT were made using 3-dimensional stereotactic surface projections with comparison to age group–matched controls. Brain region mean Z-scores with magnitudes ≥2.00 were interpreted as significant. Comparisons were made to rates of abnormal initial brain MRI, abnormal initial EEG, and presence of intrathecal inflammation.

Results: Sixty-one patients with AE (32 seropositive) underwent brain FDG-PET/CT at median 4 weeks of symptoms (interquartile range [IQR] 9 weeks) and median 4 days from MRI (IQR 8.5 days). FDG-PET/CT was abnormal in 52 (85%) patients, with 42 (69%) demonstrating only hypometabolism. Isolated hypermetabolism was demonstrated in 2 (3%) patients. Both hypermetabolic and hypometabolic brain regions were noted in 8 (13%) patients. Nine (15%) patients had normal FDG-PET/CT studies. CSF inflammation was evident in 34/55 (62%) patients,

Diagnosing AE – Brain PET

Figure 1 **Antibody status of patients with AE**



Antibody status of patients with AE who underwent dedicated brain FDG-PET/CT (N = 61). AE = autoimmune encephalitis; ANNA-1 = anti-neuronal nuclear antibody 1; CRMP5 = collapsin response mediator protein 5; GAD65 = 65 kDa glutamic acid decarboxylase enzyme; VGKCc = voltage-gated potassium channel-complex antibodies different from leucine-rich inactivated 1 protein (LGI1) and contactin-associated protein-2 (CASPR2); AChR = acetylcholine receptor antibody.

- In this study
  - 29 out of 61 = **47.5%** of patient were seronegative

How to treat it?

- Check for Infections
  - Treat all infections at the same time
- Assess patient's immune/inflammatory status
  - Detox routines
  - Pro-inflammatory states
    - i.e Mast Cell Activation syndrome
  - Environmental Toxins
- Immune modulating treatment
  - IVIG
  - Plasmapheresis
- Use of Hyperberic O2 treatment
  - Anti inflammatory effect
  - Stimulates production of stem cells

Diagnosing and Treating Infections Induced Autoimmune Encephalitis in patients with persistent Lyme Symptoms

Elena Frid, M.D.[1]
Charles Ray Jones, M.D.[2].
[1]Neurology Associates of New York, New York, New York.
[2]New Heaven, Connecticut.

ABSTRACT

Background: Increased number of cases of persistent Infections Induced Autoimmune Encephalitis in patients with Lyme disease and Tick Borne Illnesses despite appropriate treatment with antibiotics.

Objectives: Identify and treat patients with persistent symptoms of Infections Induced Autoimmune Encephalitis in the Lyme and Tick Borne Diseases patient population.

Methodology: We have identified and treated 30 patients over the last 2 years who initially presented with Lyme Disease and Tick Borne Illnesses however after months of treatment with antibiotics had persistent symptoms of headaches, insomnia, visual complains, cognitive impairment, dizziness and fatigue. These patients were evaluated for Infections Induced Autoimmune Encephalitis with MRI of the head, brain SPECT scan, EEG, LP and blood markers including paraneoplastic panel, NMDA receptor Antibodies, Potassium Channel Receptor Antibodies, GADGS, S100B, CASPR 2 Antibodies, and Glutamate Receptor Antibodies. Once diagnosed with Infections Induced Autoimmune Encephalitis the patients were started on immune modulating doses of IVIG therapy.

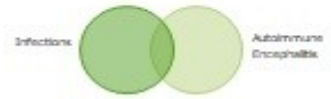
Results: After six to nine months of treatment with combination of antibiotics and immune modulating doses of IVIG at 1.5-2gm/kg divided over two consecutive days to be administered monthly, patients started experiencing significant improvement in their overall wellbeing.

Conclusion: In patients who continue to complain of neurologic symptoms despite proper course of antibiotics, one should consider a diagnosis of Infections Induced Autoimmune Encephalitis and treat with IVIG at immune modulating doses to achieve desired results while continuing appropriate antibiotic therapy.

BACKGROUND

Increased number of cases of persistent Infections Induced Autoimmune Encephalitis in patients with Lyme disease and Tick Borne Illnesses despite appropriate treatment with antibiotics.

Infections Induced Autoimmune Encephalitis



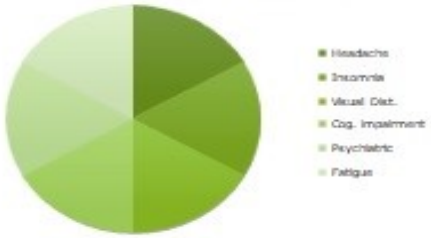
OBJECTIVE

Identify and treat patients with persistent symptoms of Infections Induced Autoimmune Encephalitis in the Lyme and Tick Borne Diseases patient population.

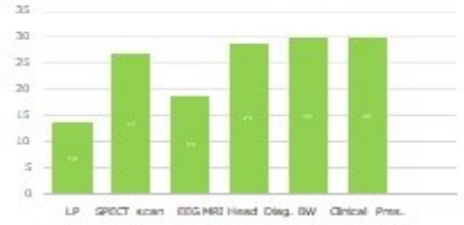
METHODS

We have identified and treated 30 patients, ages 4-74, over the last 2 years who initially presented with Lyme Disease and Tick Borne Illnesses, however after months of treatment with antibiotics had persistent symptoms of headaches, insomnia, visual complains, cognitive impairment, psychiatric symptoms and fatigue. These patients were evaluated for Infections Induced Autoimmune Encephalitis with MRI of the head, brain SPECT scan, EEG, LP and blood markers including paraneoplastic panel, NMDA receptor Antibodies, Potassium Channel Receptor Antibodies, GADGS, S100B, CASPR 2 Antibodies, and Glutamate Receptor Antibodies. Once diagnosed with Infections Induced Autoimmune Encephalitis the patients were started on immune modulating doses of IVIG therapy.

DIAGNOSTIC TOOLS



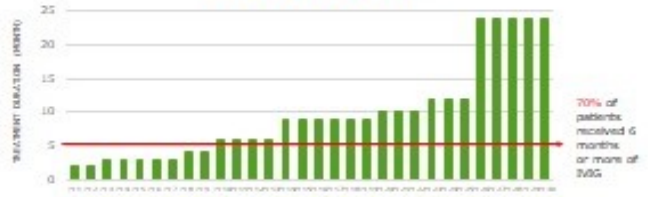
POSITIVE MARKERS



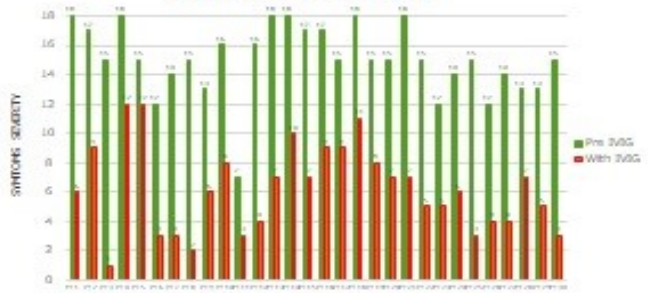
RESULTS

After six to nine months of treatment with combination of antibiotics and immune modulating doses of IVIG at 1.5-2gm/kg divided over two Consecutive days to be administered monthly, patients started experiencing significant improvement in their overall wellbeing.

IVIG TREATMENT



SYMPTOMS SEVERITY



CONCLUSIONS

In patients who continue to complain of neurologic symptoms despite proper course of antibiotics, one should consider a diagnosis of Infections Induced Autoimmune Encephalitis and treat with IVIG at immune modulating doses to achieve desired results while continuing appropriate antibiotic therapy.

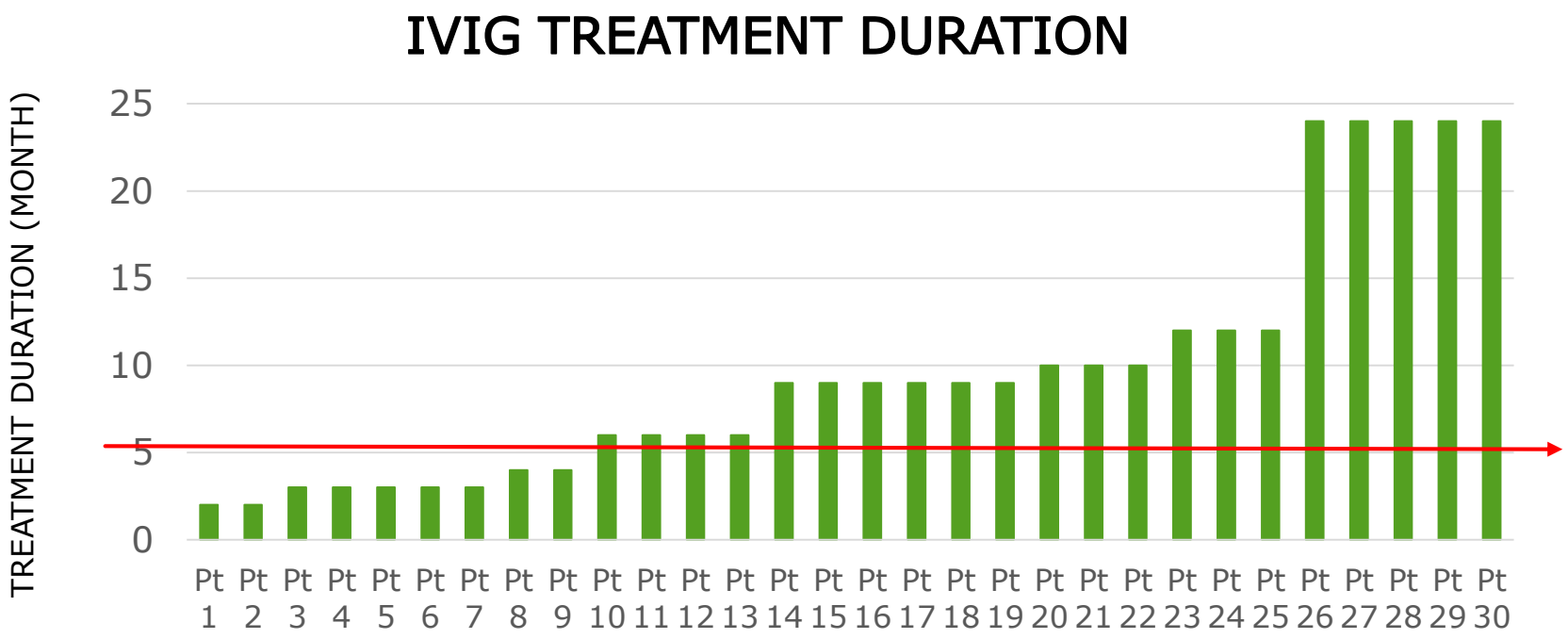
For additional information please contact:

Dr. Elena Frid
Pediatric and Adult Neuro-Lyme Specialist
Neurology Associates of New York
info@elenafridmd.com

Diagnosing and Treating Autoimmune Encephaitis in patients with persistent Lyme Symptoms

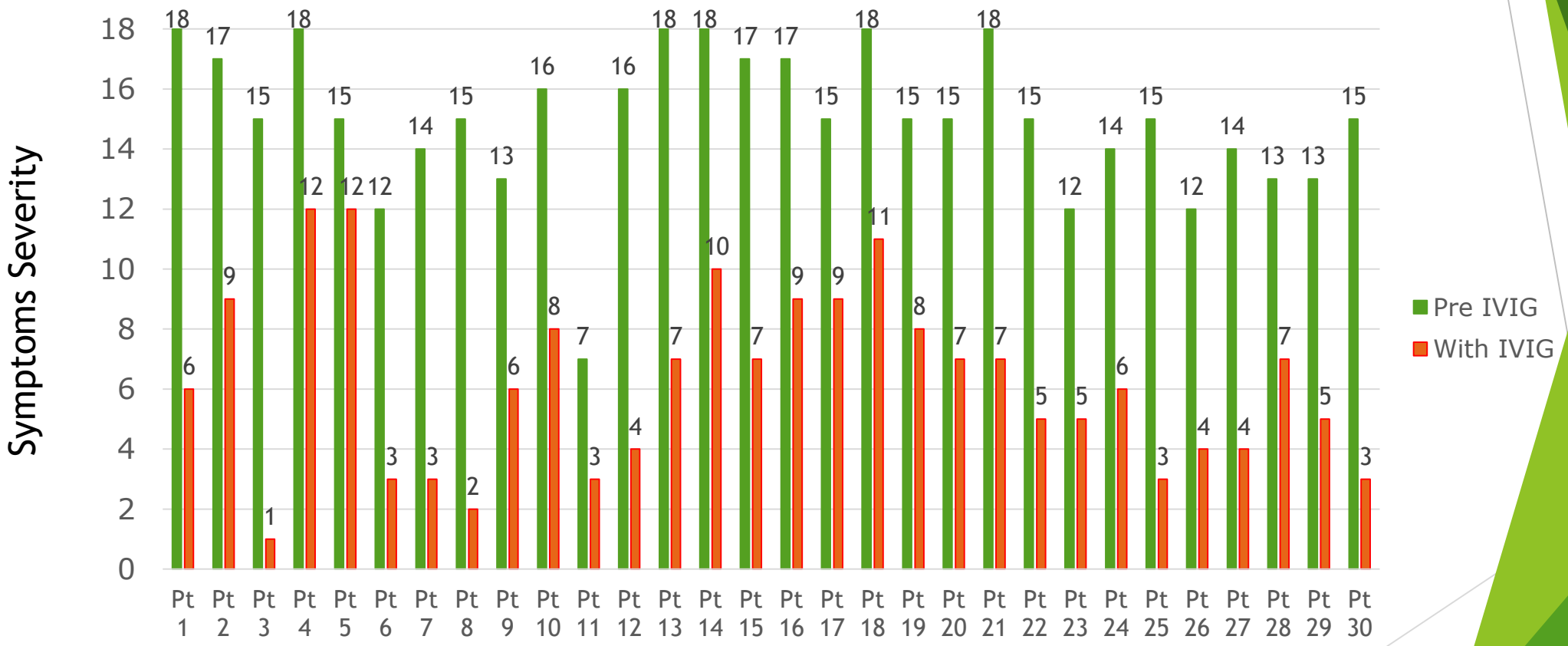
- 30 patients over 2 years with:
  - Lyme Disease & Tick Borne Illnesses
  - Treated with months of antibiotics
  - Had persistent symptoms:
    - Headaches
    - Insomnia
    - Visual Complaints
    - Cognitive impairment
    - Fatigue
    - Psychiatric Features

Results



70% of patients received 6 months or more of IVIG

SYMPTOMS SEVERITY AND IMPROVEMENTS



Common mistakes

- Lower doses of IVIG = immune replacement therapy
  - 500-750mg IVIG/Treatment
- This will stimulate production of more anti-neuronal antibodies
- Not treating the infectious component at the same time as the autoimmune component
- Not treating long enough
  - Improvement in 7-9 months
  - Most patient treated for at least 2 years
- Adding immune suppressive therapy to treatment regiment

Case #1

- 22 year old girl with over 3 in patient psychiatric hospitalizations in the last 7 years.
- She has
  - *Hyperreligiocity*
  - *Delusions of grandeur*
  - *No concept of time*
  - *Depressed*
  - *Feeling of depersonalization*
  - *Headaches /Brain Fog*

- MRI of the head revealed non specific white matter changes
- Brain SPECT –Hypoperfusion at the temporo parietal junction
- Blood Work:
  - Bb, B. Henselae and B. microti
- Cunningham Panel:
  - Positive for 3 out of 4 antinueronal antibodies

Case #2

- 13 year old boy with 10 year history of join aches, toe walking and being sick all the time.
- Two years ago he developed facial ticks
  - OCD
  - Anxiety
  - Motor Ticks
- Diagnosed with PANS/PANDAS
- Diagnosed with Autoimmune encephalitis with (Abnormal MRI brain, EEG, SPECT scan, Cunningham panel, GAD 65 and thryroperoxidase antibodies)
- Also: Strep, Lyme, Babesia duncani and microti, B. henselae and history of Mycoplasma pneumoniae

Case #3

- 21 year old with developmental delay and autism at age 4
- 3 years ago started exhibiting aggressive behavior, decline in verbal output and was expelled from school
- Despite working with his psychiatrist and trial of multiple prescription and alternative medications there is no improvement
- CT head negative
- Blood work tested positive for: Lyme, B. microti, B. Henselae and Coxsackievirus


DrFrid
Pediatric & Adult Autoimmune Neurologist & Lyme Specialist
Can't see Dr. Elena Frid in person? She offers phone consults to help you address your health issues, no matter where you are.
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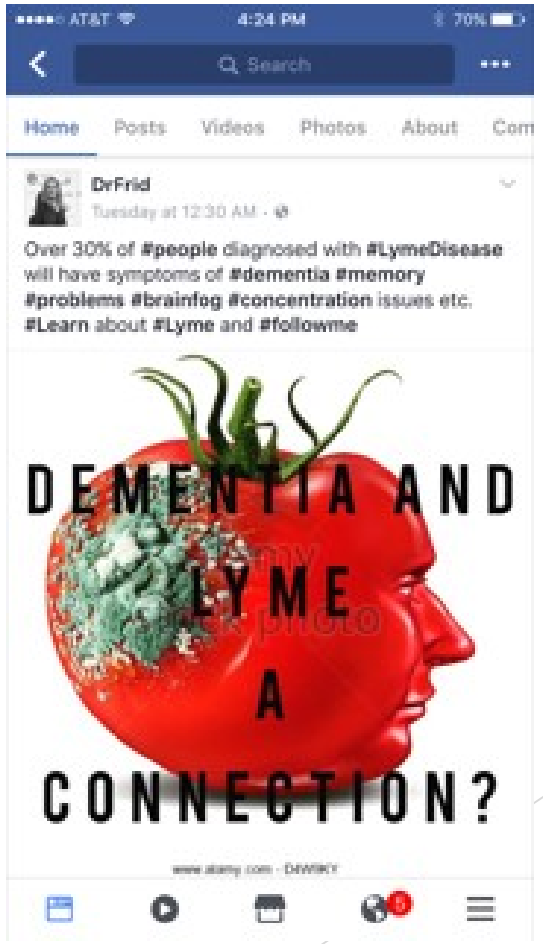

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Campaign raising awareness for Lyme Disease in the month of May

@LymeDiseaseChallenge

Dr. Frid in the Press / Radio / Media

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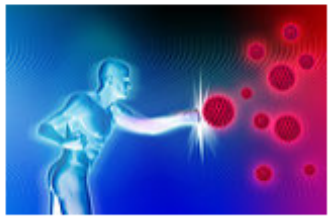
A KEY TO YOUR HEALTH

February 12, 2018 | Elena Frid MD



Over the last few months I have been reflecting on which direction medicine has been heading in the last few decades. It is clear that patients like consumers are looking for immediate response and results from their healthcare professionals. Intern, I see a trend of people moving toward urgent care centers, telemedicine and local pharmacist for questions and advice on issues that arise acutely such as common colds, headaches, stomach aches and flu shots.

But what about the patients with chronic conditions such as diabetes, hypertension, Alzheimer's and Lyme disease, just to name a few, who are they turning to? Well because most of these patients get a 5 to 10 minute in person appointment with their healthcare provider they look for support and answers to many of their questions from the social media community of fellow patients who are going through the same thing or have been through something similar in the past.

Despite all the advances we've made in technology and medicine in the last millennia, it appears that our chronic and more complicated patients are getting less personalized and lower quality care then they did 50 years ago. More often than not they are receiving medical advice from a fellow patient often whom they know very little about.

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A KEY TO YOUR HEALTH

February 12, 2018

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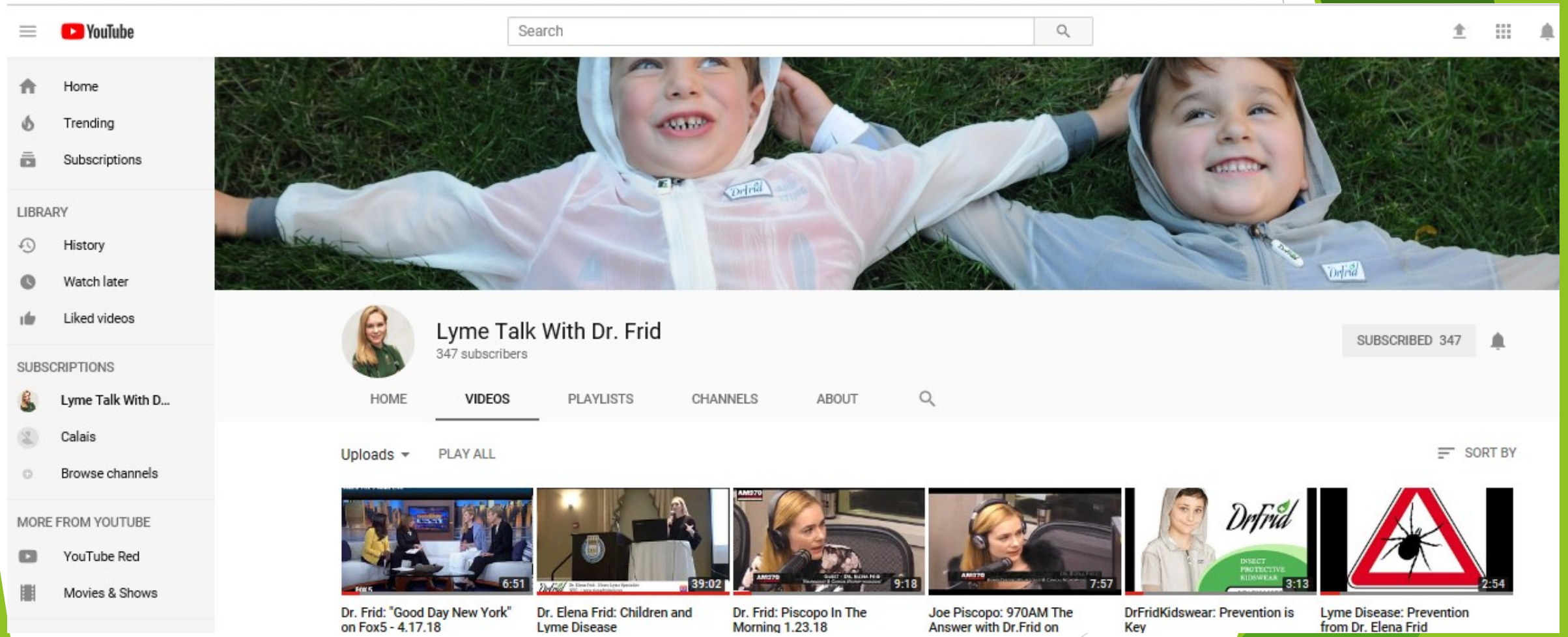

ELENA FRID, M.D.

Pediatric and Adult Neuro-Lyme Specialist

Board Certified Neurologist

Board Certified Clinical Neurophysiologist

New York City | 212-288-8832

www.elenafridmd.com