Autoimmune Encephalitis in Clinical Practice

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Agenda

- Cases
- Define autoimmune encephalitis
- How it is diagnosed
- How it relates to infections
- How to treat it
- Common Mistakes

Case report #1 – So it wasn't a stroke?

- Patient's name: Confusion
- 59 year old woman with 1 year history of various neurologic complaints
  - Fatigue
  - Unsteadiness
  - Speech difficulty
  - Poor Dexterity
  - Cognitive decline
    - Trouble organizing her thoughts
  - Acute onset of focal weakness and speech impairment

Confusion

- Work up
  - MRI
  - CD – normal
  - REEG – bitemporal Spikes
  - Brain SPECT with bitemporal hypoperfusion
  - BW
    - Borrelia Burgdorferi
    - Borrelia Miyamotoi
    - Bartonella Henselae and Quintana
    - Babesia duncani
    - Elevated Voltage gated K+ channel receptor Ab & GAD 65 Ab

Case #2 – Did I do that?

- Patient's Name: Guilt
- 6 year old girl, symptoms age 4
- Fatigue
- Leg Pain
- Regression
  - Thumb sucking
  - Fear of Dark
  - Tantrums
- Bed wetting
- Stomach pain
- Work up: BW – Strep Ab positive

Case report #3 – I am at the end of my rope!

- Patient's Name: Hopelessness
- 21 year old woman, symptoms onset at age 14
- Anxiety
- Psychosis
- Depersonalization
- Seizures
- 3 inpatient involuntary admissions

Hopelessness

- She is followed by a Mass General Psychiatry department with multiple combinations of psychotropic medications without improvement
  - Declining neuropsychiatric status:
    - Hyper-religiosity
    - Intrusive thoughts
    - Severe Anxiety
    - Severe Headaches

Hopelessness

- Work up
  - MRI of the brain - nonspecific white matter changes and a DVA on the left temporal region
  - REEG – normal
  - SPECT scan - hypoperfusion at the tempero parietal region
  - LP – two oligoclonal bands, normal study
  - BW
    - Borrelia Burgdorferi
    - Bartonella Henselae
    - Babesia microti
    - Cunningham Panel
      - Anti Dopamine 1 and 2
      - Anti Lysoganglioside GM1
      - Anti-Tubullin Ab
    - GAD 65 Ab

Case report #4 – I did everything right!

- Patient's Name: Frustration
- 13 yo male with onset of joint pain and toe walking at age 2
- At age 9 he developed
  - Facial motor ticks
  - Cognitive decline
  - Regressive behavior

Frustration

- He was tested for and diagnosed with
  - Lyme
  - Strep
  - Mycoplasma Pneumoniae
  - Bartonella
- Treated on and off with a combination of Abx for 6 months
  - Worsening symptoms
- Clinical Decline
- Test for Autoimmune Encephalitis
  - Moleculera Lab
    - Anti-Tubulin Ab

Frustration

- Started IVIG at 1gm/kg
- Got better initially and then declined
- On retest of his BW he had
  - Decline in IQ through Neurocognitive assessment
  - REEG – mild diffuse encephalopathy
  - MRI brain – normal
  - BW positive for
    - Strep
    - Lyme
    - Babesia duncani & microti
    - Bartonella Henselae
    - Mycoplasma Pneumoniae

Frustration

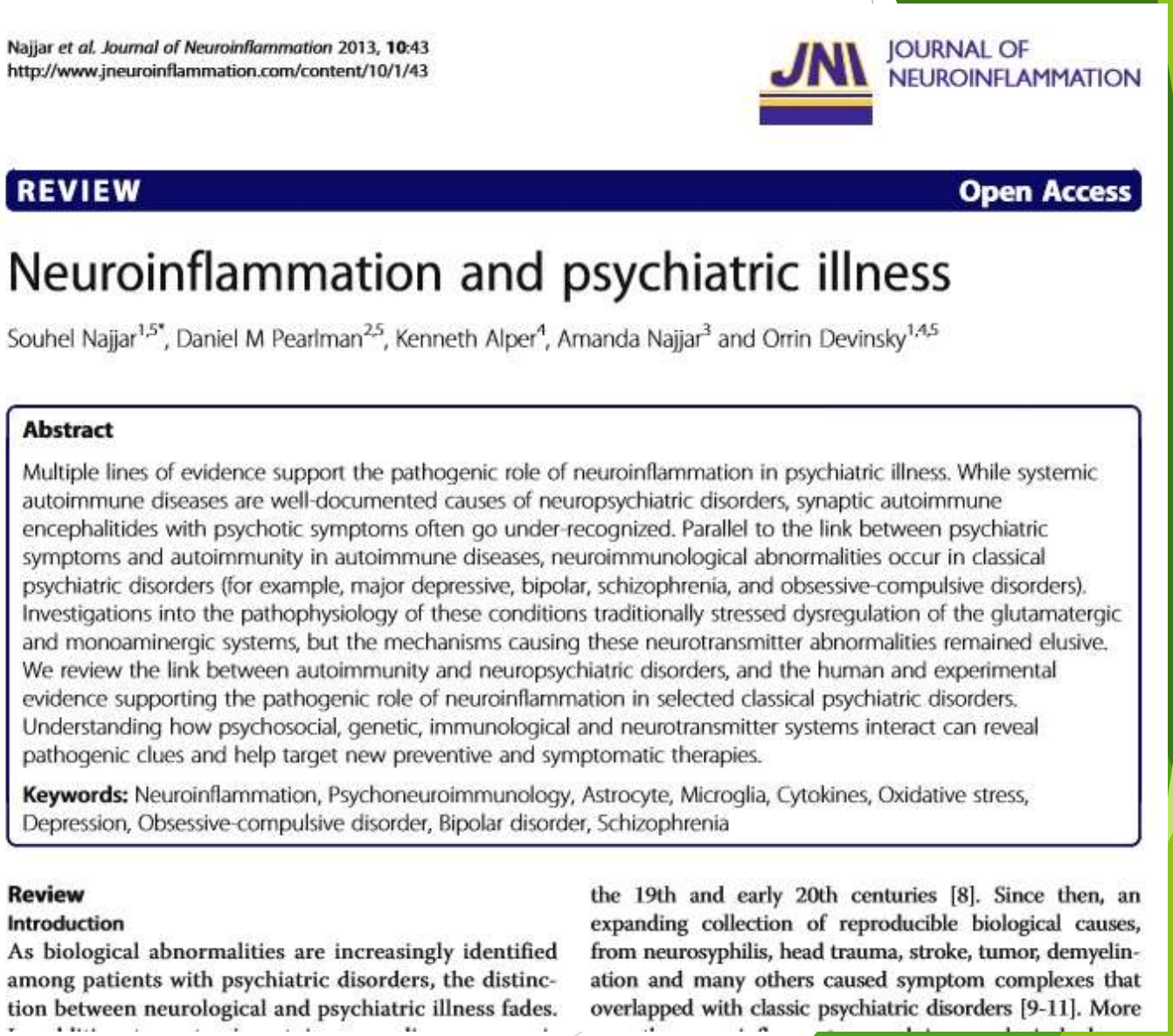
- Positive for Antineuronal antibodies
  - Cunningham Panel
    - Dopamin 1
    - Tubulin
  - Voltage Gated K+ channel receptor Ab
  - GAD 65 Ab
  - Thyroid peroxidase and Thyroglobulin Ab
- What do you do?

Autoimmune Encephalitis

- Production of antineuronal antibodies that affect
  - Central Nervous system
    - Causing Autoimmune Encephalitis
- 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
    - Post infectious
    - Malignant
    - Idiopathic
  - Consider Infectious/Inflammatory

Autoimmune Encephalitis

- Published in 2013 in the Journal of Neuroinflammation
- Links Psychiatric disorders with neuroinflammation
- Contributing to
  - Major Depression
  - Bipolar
  - Schizophrenia
  - OCD



Najjar et al. Journal of Neuroinflammation 2013, 10:43
http://www.jneuroinflammation.com/content/10/1/43

JNI JOURNAL OF NEUROINFLAMMATION

REVIEW Open Access

Neuroinflammation and psychiatric illness

Souhel Najjar[1,5*], Daniel M Pearlman[2,5], Kenneth Alper[4], Amanda Najjar[3] and Orrin Devinsky[1,4,5]

Abstract

Multiple lines of evidence support the pathogenic role of neuroinflammation in psychiatric illness. While systemic autoimmune diseases are well-documented causes of neuropsychiatric disorders, synaptic autoimmune encephalitides with psychotic symptoms often go under-recognized. Parallel to the link between psychiatric symptoms and autoimmunity in autoimmune diseases, neuroimmunological abnormalities occur in classical psychiatric disorders (for example, major depressive, bipolar, schizophrenia, and obsessive-compulsive disorders). Investigations into the pathophysiology of these conditions traditionally stressed dysregulation of the glutamatergic and monoaminergic systems, but the mechanisms causing these neurotransmitter abnormalities remained elusive. We review the link between autoimmunity and neuropsychiatric disorders, and the human and experimental evidence supporting the pathogenic role of neuroinflammation in selected classical psychiatric disorders. Understanding how psychosocial, genetic, immunological and neurotransmitter systems interact can reveal pathogenic clues and help target new preventive and symptomatic therapies.

Keywords: Neuroinflammation, Psychoneuroimmunology, Astrocyte, Microglia, Cytokines, Oxidative stress, Depression, Obsessive-compulsive disorder, Bipolar disorder, Schizophrenia

Review

Introduction

As biological abnormalities are increasingly identified among patients with psychiatric disorders, the distinction between neurological and psychiatric illness fades. the 19th and early 20th centuries [8]. Since then, an expanding collection of reproducible biological causes, from neurosyphilis, head trauma, stroke, tumor, demyelination and many others caused symptom complexes that overlapped with classic psychiatric disorders [9-11]. More

Neuroinflammation and Psychiatric Illness – Najjar, 2013

- Defining Autoimmue Encephalitis
  - Clinical presentation
    - Seizures
    - Psychiatric Features
    - Cognitive Decline
  - Pathophysiology
    - Anti-Synaptic Autoantibodies
    - Anti-Intracellular Autoantibodies

Neuropsychiatric autoimmune encephalitides associated with serum anti-synaptic and glutamic acid decarboxylase autoantibodies

Autoimmune encephalitides are characterized by an acute onset of temporal lobe seizures, psychiatric features, and cognitive deficits [2,3,99-108]. The pathophysiology is typically mediated by autoantibodies targeting synaptic or intracellular autoantigens in association with a paraneo plastic or nonparaneoplastic origin [3]. Anti-synaptic autoantibodies target NR1 subunits of the NMDAR [100,108,109], voltage-gated potassium channel (VGKC) complexes (Kv1 subunit, leucine-rich glioma inactivated (LGI1) and contactin associated protein 2 (CASPR2)) [101,102,106], GluR1 and GluR2 subunits of the amino-3-hydroxy-5-methyl-l-4-isoxazolepropionic acid receptor (AMPAR) [6,110,111] and B1 subunits of the γ-aminobutyric acid B receptors ($GABA_BR$) [3,99,103]. Anti-intracellular autoantibodies target onconeuronal and GAD-65 autoantigens [2,3].

How it is diagnosed

- MRI of the head
- EEG
- LP
- BW:
  - Paraneoplastic Panel (Anti Hu, Yo, Ri, Amphiphysin, Tr, CV2, Ta)
  - K channel receptor Ab
  - NMDA receptor Ab
  - GAD 65 Ab (Stiff Person's syndrome/Autoimmune Encephalitis)
  - CASPR- 2 Ab (Limbic encephalitis)
  - Glutamate Receptor Ab (Rasmuseen's encephalitis)
  - LGI1 (Faciobrachial dystonic seizures)
  - S100B (Break in Blood Brain Barrier) - marker of glial activation and blood-brain barrier hyperpermeability in the brain
- Brain SPECT/Brain PET scan
- Neurocognitive Assessment
- Brain Biopsy (Lymphocytes/Glial Cells)

How it is diagnosed

- LP
  - Increased CSF: serum albumin ratio
    - Indicative of BBB hyperpermeability
  - Increased intrathecal synthesis of IgG, IgM, and/or IgA
  - Presence of up to four IgG oligoclonal bands
  - Mild pleocytosis
  - Elevated neopterin levels
  - Elevated cytokines
  - Increased intracranial pressure

Anti Neuronal Antibodies: Journal of Clinical Neurology

J Clin Neurol

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

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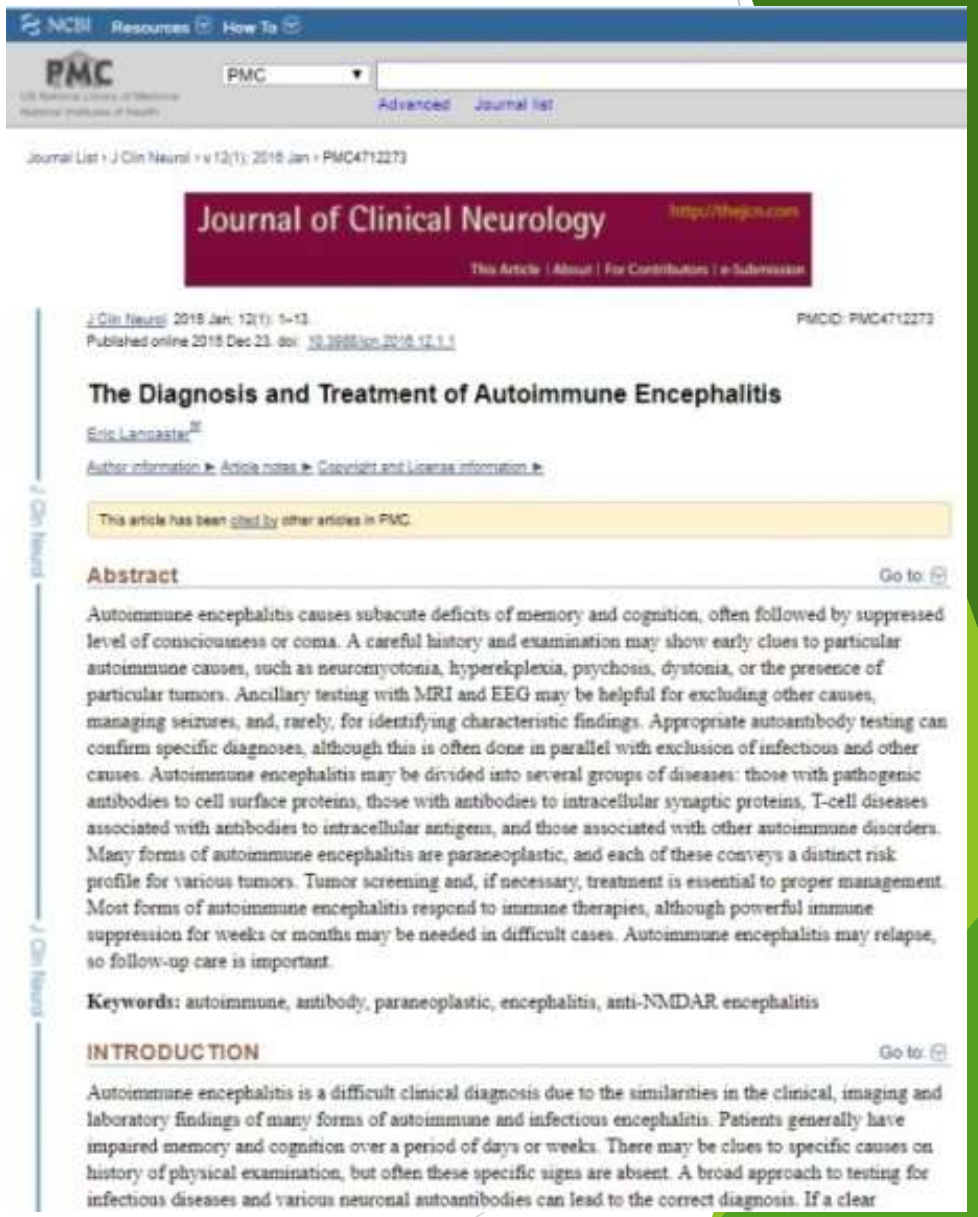
Role of Cunningham Panel

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

"The Diagnosis and Treatment of AE" 2016

- Three Types of Abs:
  - Paraneoplastic disorders
    - Ab to intracellular antigens
    - Poor prognosis due to irreversible neuronal damage
  - Autoantibodies to extracellular epitopes of ion channels, receptors and other associated Autoantibodies
    - Synaptic
    - Intracellular
  - Other forms of autoimmune encephalitis in which precise antigens are less clearly established (Systemic)



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Journal List › J Clin Neurol › v.12(1); 2016 Jan › PMC4712273

Journal of Clinical Neurology

J Clin Neurol. 2016 Jan; 12(1): 1–13.

Published online 2015 Dec 23. doi:

PMCID: PMC4712273

The Diagnosis and Treatment of Autoimmune Encephalitis

Eric Lancaster

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Abstract

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Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. A careful history and examination may show early clues to particular autoimmune causes, such as neuromyotonia, hyperekplexia, psychosis, dystonia, or the presence of particular tumors. Ancillary testing with MRI and EEG may be helpful for excluding other causes, managing seizures, and, rarely, for identifying characteristic findings. Appropriate autoantibody testing can confirm specific diagnoses, although this is often done in parallel with exclusion of infectious and other causes. Autoimmune encephalitis may be divided into several groups of diseases: those with pathogenic antibodies to cell surface proteins, those with antibodies to intracellular synaptic proteins, T-cell diseases associated with antibodies to intracellular antigens, and those associated with other autoimmune disorders. Many forms of autoimmune encephalitis are paraneoplastic, and each of these conveys a distinct risk profile for various tumors. Tumor screening and, if necessary, treatment is essential to proper management. Most forms of autoimmune encephalitis respond to immune therapies, although powerful immune suppression for weeks or months may be needed in difficult cases. Autoimmune encephalitis may relapse, so follow-up care is important.

Keywords: autoimmune, antibody, paraneoplastic, encephalitis, anti-NMDAR encephalitis

INTRODUCTION

Go to:

Autoimmune encephalitis is a difficult clinical diagnosis due to the similarities in the clinical, imaging and laboratory findings of many forms of autoimmune and infectious encephalitis. Patients generally have impaired memory and cognition over a period of days or weeks. There may be clues to specific causes on history of physical examination, but often these specific signs are absent. A broad approach to testing for infectious diseases and various neuronal autoantibodies can lead to the correct diagnosis. If a clear

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

“A clinical approach to new-onset psychosis associated with immune dysregulation: the concept of autoimmune psychosis” Feb 2018

J Neuroinflammation. 2018; 15: 40.
Published online 2018 Feb 13. doi: 10.1186/s12974-018-1067-y
PMCID: PMC5809809
PMID: 29433523

A clinical approach to new-onset psychosis associated with immune dysregulation: the concept of autoimmune psychosis

Souhel Najjar,[1] Johann Steiner,[2] Amanda Najjar,[3] and Karl Bechter[4]

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Abstract

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Growing data point to the overlap between psychosis and pathological processes associated with immunological dysregulation as well as inflammation. Notably, the recent discovery of antibodies against synaptic and neuronal cell membrane proteins such as anti-*N*-methyl-D-aspartate receptor provides more direct evidence of the etiological connection between autoimmunity and subsequent hazard of psychosis.

J Neuroinflammation

Autoimmune Psychosis Subclasses

- I. Autoimmune Encephalitis associates with synaptic and neuronal cell membrane proteins Ab
  - NMDAR
  - AMPAR
  - GABAbR
  - VGKC (LGI1, CASPR2)
- Clinical presentation
  - Confusion
  - Seizures
  - Memory loss

Autoimmune Psychosis Subclasses

- II. Psychosis associated with Autoimmune and Inflammatory Disorders
  - 1. systemic Autoimmune Disorders: Neuropsychiatric Lupus Erythematosus
    - NMDAR Ab
    - Ribosomal P Ab
  - 2. Neuroinflammatory Disorders:
    - MS, ADEM
      - OCD AB (Oligoclonal bands)
      - MBP AB (Myeline Basic Protein)
      - MOG Ab (Myeline Oligodendrocyte glycoprotein)
  - 3. Hashimoto's Encephalopathy
      - TPO Ab (Thyroperoxidase Ab)
      - Tg Ab (Thyroglobulin Ab)
      - Autoimmune vasculitis and Immune Complex deposition
  - 4. Autoimmune Encephalitis associates with Ab targeting Intracellular Antigens
    - Onconeuronal Ab (HU, MA2, CRMP5, Amphyphisin, GAD Ab, GABAb

Autoimmune Psychosis Subclasses

- III. Seronegative but probable autoimmune encephalitis (SPAP)
  - Unknown Autoantibodies
  - Innate – or T-cell autoimmunity?
- Clinical presentation
  - Encephalopathy
  - Cognitive deceline
  - Memory Impairment
  - Affective Disorder
  - Seizures

"The Diagnosis and Treatment of AE" 2016

- 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
- Cerebellitis
  - Ataxic
    - Gait
    - Limb movements
    - Eye movements
    - Voice
    - Swallowing

How it is diagnosed: Neurology - 2017

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

OPEN

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ABSTRACT

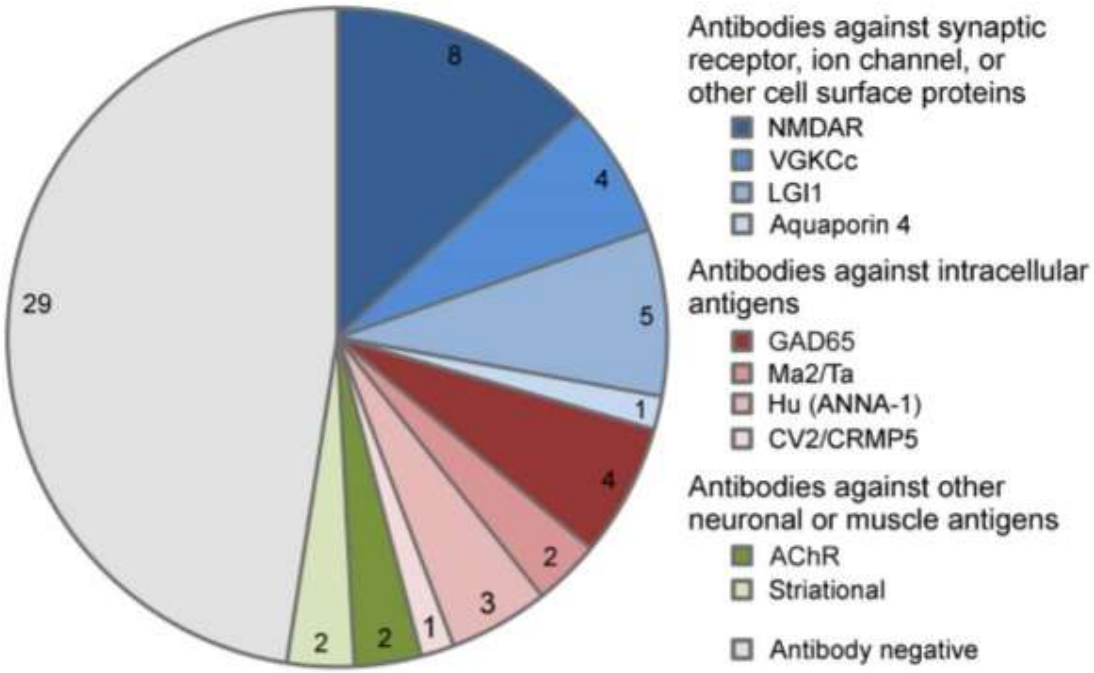
Objective: To compare the rate of abnormal brain metabolism by FDG-PET/CT to other paraclinical findings and to describe brain metabolism patterns in autoimmune encephalitis (AE).

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

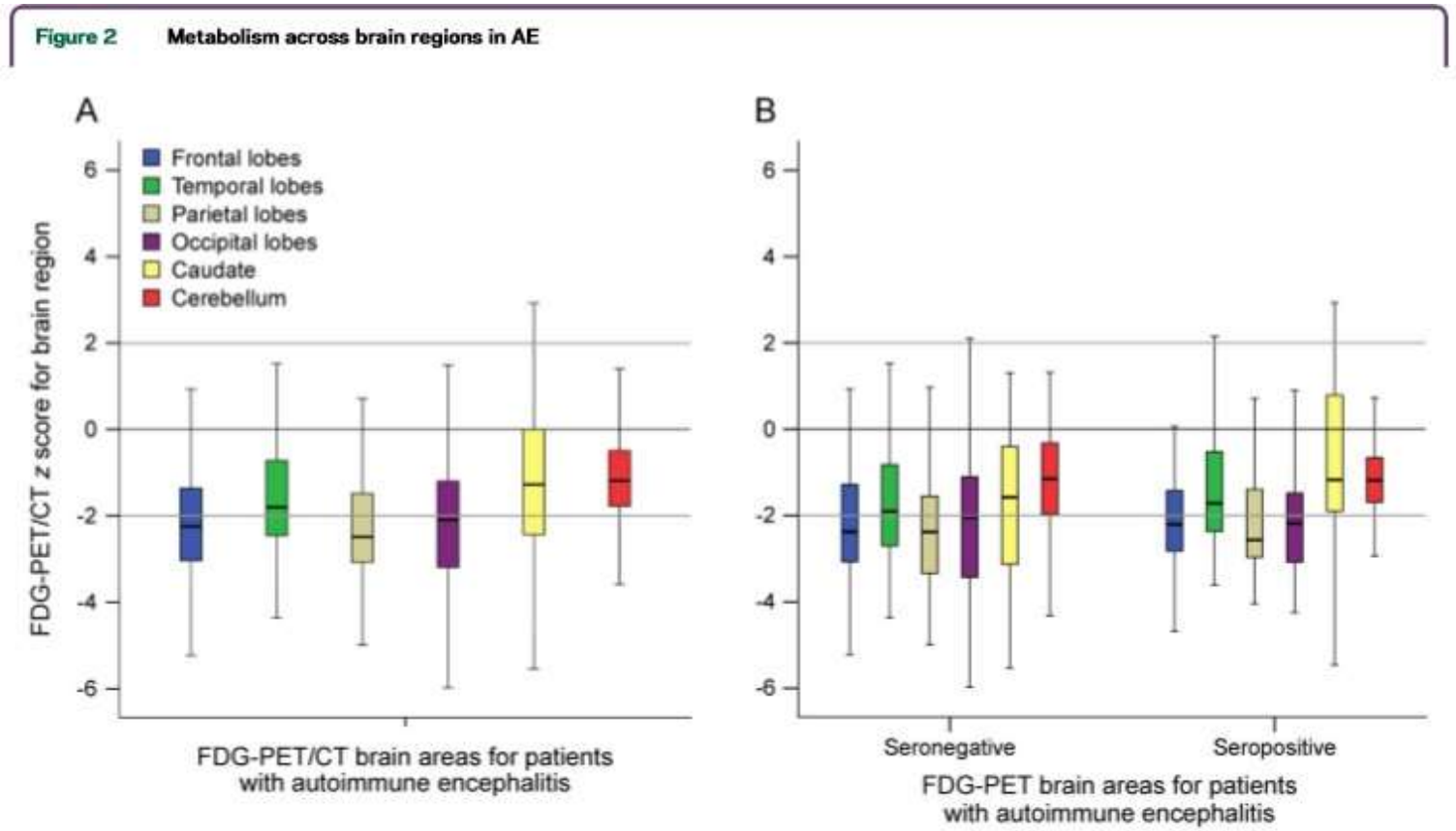
Figure 1 **Antibody status of patients with AE**



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

Diagnosing AE – Brain PET



Boxplots of Z-scores for FDG-avidity for brain areas on dedicated FDG-PET/CT for (A) patients meeting consensus criteria for AE, (B) seronegative and seropositive patients meeting the consensus criteria for AE. Z-scores varied across brain regions for patients with AE ($p < 0.005$), with values for the caudate being greater than those for frontal ($p < 0.005$), temporal ($p = 0.002$), parietal ($p < 0.005$), and occipital ($p < 0.005$) lobes. No difference was noted between seronegative and seropositive patient groups ($p = 0.08$). AE = autoimmune encephalitis.

- No difference in presentation between seronegative and seropositive patients
- Presentation may be heterogeneous
  - Not just mesial temporal lobes hypometabolism

AE an Infections Induced Process

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

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

Improvement of psychiatric symptoms in youth following resolution of sinusitis

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ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form
25 October 2016
Accepted 26 October 2016
Available online 31 October 2016

Keywords:
Sinusitis

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

How it is related to infections?

- Borrelia Burgdorferi
- Prevalence >300,000 new Lyme disease cases per year in the US
- GOV.UK – Publik Health England 2013:
  - “Lyme borreiosis is the most common vector – borne human infection in England and Wales.”
- Complex Pathophysiology
  - Causing Direct Infection
  - Inflammation
  - Autoimmune process

Relationship of inflammation and autoimmunity to Psychiatric sequela of Lyme disease - Bransfield

Relationship of Inflammation and Autoimmunity to Psychiatric Sequelae in Lyme Disease

Robert C. Bransfield, MD, DLFAPA

The causative spirochete of Lyme disease, *Borrelia burgdorferi*, is the most common human tick-borne pathogen in the Northern hemisphere. It is also probably the most complex bacteria known, as it has 132 genes and 21 plasmids, with 90% of this genetic material unrelated to any known bacteria.

These genes facilitate adaptation of the organism in different forms and in different hosts with multiple mechanisms to evade and weaken host defenses. By comparison, the spirochete *Treponema pallidum pallidum* (the organism that causes syphilis) is a comparatively simple organism, with only 22 genes and much less adaptive capability.

Lyme disease is currently viewed as being a mostly zoonotic tick-borne disease. The human mouth contains 400 different species of bacteria, as well as viruses and parasites. By contrast, ticks live in filth and feed on the blood of rodents and a variety of other animals, meaning that there are likely numerous other human pathogens besides

LATE-STAGE IMMUNE CNS EFFECTS

The three principal mechanisms leading to the injury of neuronal cells are: 1) the secretion of cytotoxic substances by leucocytes and glial cells; 2) direct cytotoxicity; and 3) autoimmune-triggered processes via molecular mimicry. An interaction between *B. burgdorferi* and the neural cells can cause dysfunction by adherence, invasion, and cytotoxicicity of neural cells. In addition, *B. burgdorferi* outer surface protein A induces apoptosis and astrogliosis. *B. burgdorferi* spirochetes interacting with Schwann and glial cells also appear to produce nitric oxide, and the spirochetes can induce cytokines such as IL-6 or TNF-alpha in glial cells, both of which are neurotoxic and might provoke autoimmune reactions.[3]

When there is inflammation within the CNS, the chemokine CXCL13, which is produced by monocytes and dendritic

Autism

Autism spectrum disorders have been associated with a number of infections, including LYD/TBD. Both inflammatory and autoimmune processes that adversely affect developing fetal neural tissue appear to be involved in the pathophysiology. Effects upon the developing fetus from the mother's immune system and infection of the infant that adversely alters developing neural tissue are both possible pathophysiologic processes.[26-28]

The inflammatory response elicited by* B.burgdorferi *in glial cells contributes to damage of oligodendrocytes that are vital for the functioning and survival of neurons.

CONCLUSIONS

Most symptoms associated with Lyme disease and other tick-borne diseases are immune mediated. A progressive sequence of immune effects is associated with a progressive development of cognitive, psychiatric, neurologic, and somatic symptoms. These progressive immune effects include persistent inflammation with cytokine effects, the release of proinflammatory lipoproteins from the outer coat of *B. burgdorferi*, and autoimmunity.

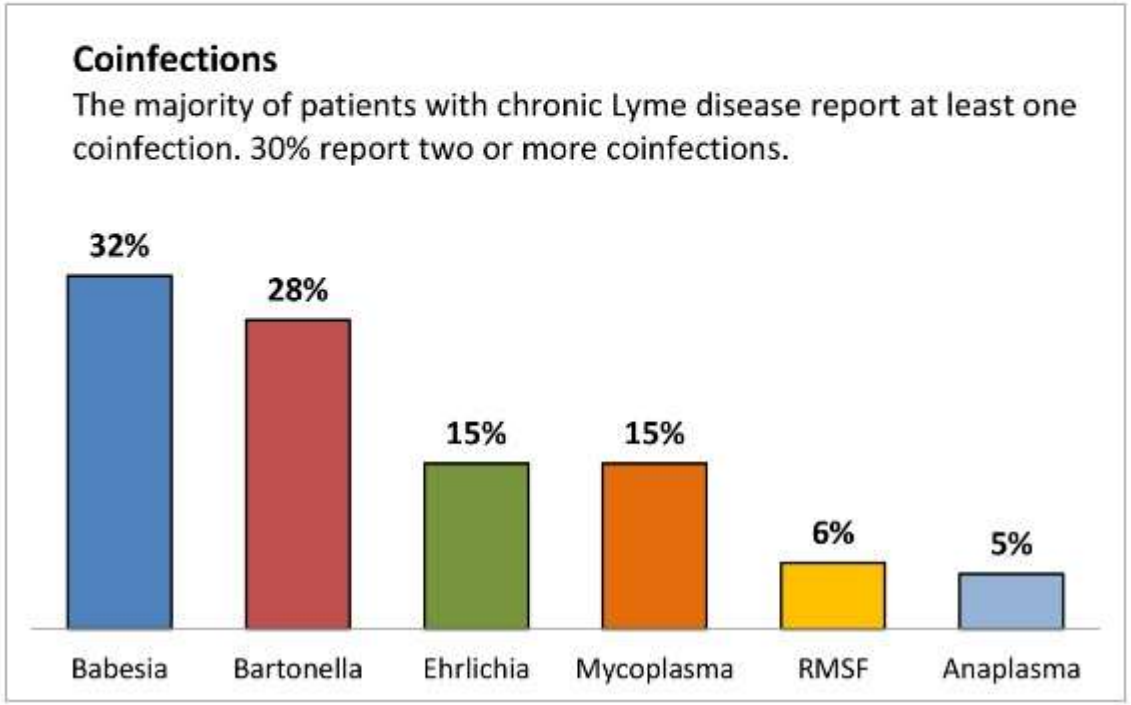
Prolonged inflammation, particularly the type associated with chronic infection within the CNS, is associated with further cognitive impairments, more severe psychiatric symptoms, gliosis, and dementia. Autoimmune effects also can be present at the same time and can include antineuronal antibodies and *B. burgdorferi* lipoproteins that can disseminate from the periphery to inflame

- Immune Mediated symptoms
  - Inflammation with cytokines
  - Proinflammatory lipoproteins
  - Autoimmunity

Lyme and Co-Infections

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

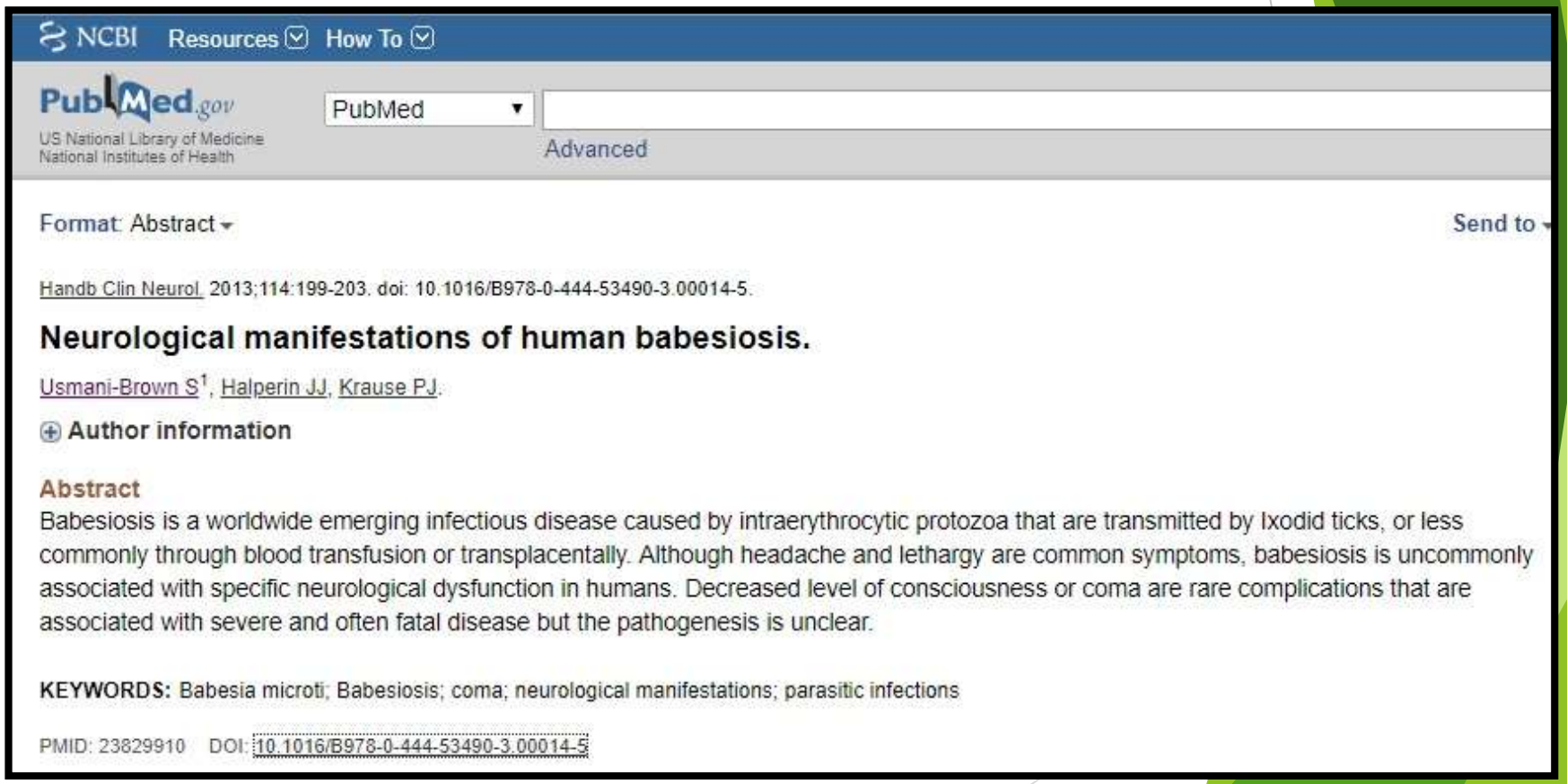
Coinfections may be common – at least among those with chronic Lyme disease. A recently published LDo survey over 3,000 patients with chronic Lyme disease found that over 50% had coinfections, with 30% reporting two or more coinfections. The most common coinfections were Babesia (32%), Bartonella (28%), 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

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

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

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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, GAD65, S100B, CASPR 2 Antibodies, and Glutamate Receptor Antibodies. Once diagnosed with Infections Induced Autoimmune Encephalitis the patients were started on immune modulating dose 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

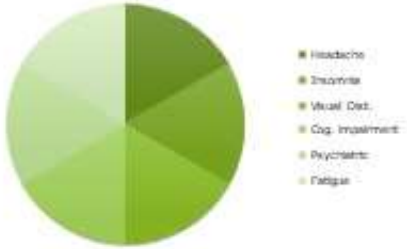
OBJECTIVE

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

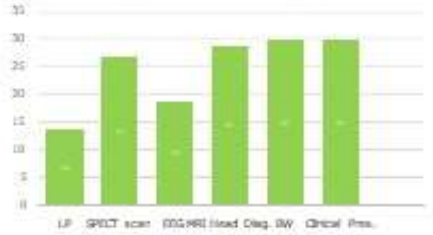
METHODS

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, GAD65, S100B, CASPR 2 Antibodies, and Glutamate Receptor Antibodies. Once diagnosed with Infections Induced Autoimmune Encephalitis the patients were started on immune modulating dose of IVIG therapy.

DIAGNOSTIC TOOLS



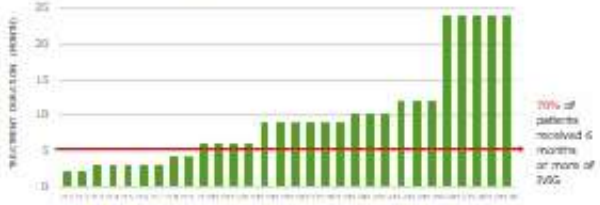
POSITIVE MARKERS



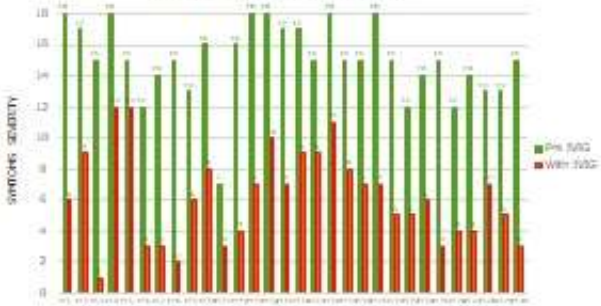
RESULTS

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.

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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

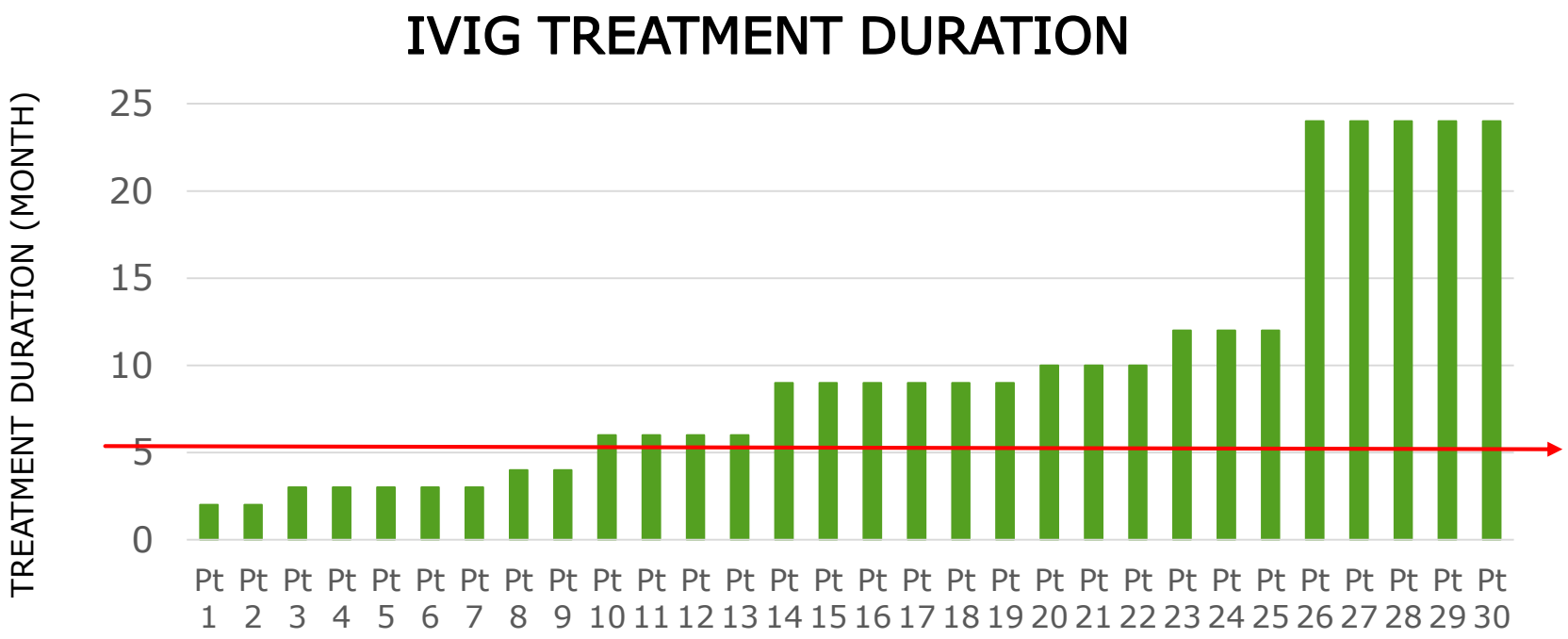
Diagnosing and Treating Autoimmune Encephaitis in patients with persistent Lyme Symptoms

- These patients were evaluated for Infections Induced Autoimmune Encephalitis
  - MRI of the head (29/30)
  - Brain SPECT scan (27/30)
  - EEG (19/30)
  - LP (14/30)
  - Blood markers (30/30)
    - Paraneoplastic panel
    - NMDA receptor Ab,
    - VGKC Ab (CASPR 2)
    - GAD65
    - S100B
    - Glutamate Receptor Antibodies.

Diagnosing and Treating Autoimmune Encephaitis in patients with persistent Lyme Symptoms

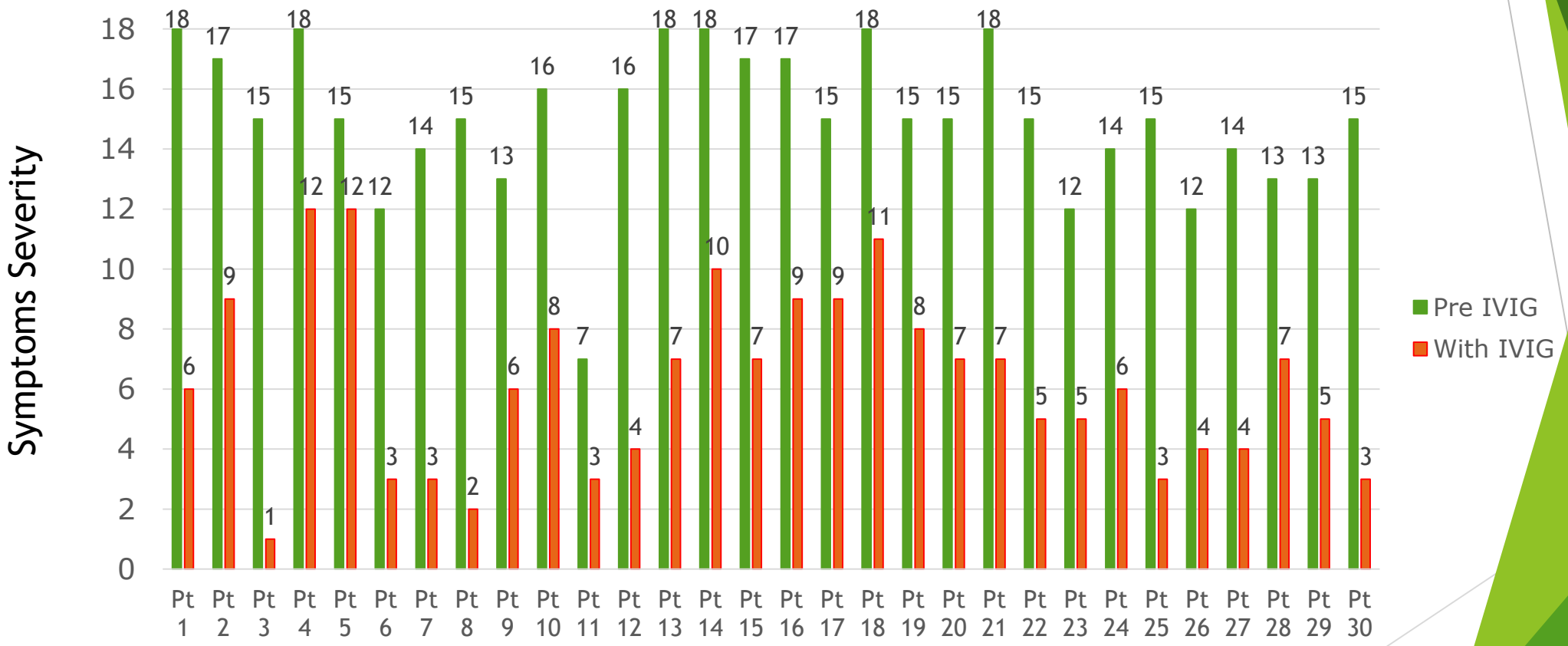
- Treatment:
  - Continue Treatment of Infections
  - Add immune modulating dose of IVIG

Results



70% of patients received 6 months or more of IVIG

SYMPTOMS SEVERITY AND IMPROVEMENTS



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

How to treat it – IVIG protocol

APPENDIX C: Use of corticosteroid-sparing agents in PANS (From Frankovich et al[5])

	DESCRIPTION/BENEFIT	ADVERSE EFFECTS	DOSING
Intravenous Immunoglobulin (IVIG)	IVIG is derived from pooled plasma from human donors and processed using rigorous purification steps. Several potential immunomodulatory roles including effects on Fc receptor activity (saturating FcR) and F(ab)2 activity (anti-idiotypic antibodies) and other mechanisms. Benefit: Broadly impacts immune function and autoimmune responses and may help moderate the autoantibody responses. Caution: The authors report rare cases of worsening PANS symptoms following IVIG when IVIG is given around the time of a new viral illness.	Common infusion related side effects include nausea, myalgia, fever, chills, rigors, chest discomfort, and hypotension (often dose related or due to rapid administration). Post-infusion headaches (HA)[a] are common including aseptic-like meningitis. Aggressive hydration pre/post and half-way through IVIG infusion can help minimize HA. Use of OTC NSAIDs or corticosteroids during and after IVIG can also help prevent/manage HA. A transient fever can be seen in the first 24 hours. Rarely, symptomatic hemolysis can occur and manifest up to 1-week post-infusion. Anaphylaxis can occur, especially in patients with IgA deficiency (if IgA deficient, use formulation that does not contain IgA). Other rare side-effects include renal failure, thrombosis (including sinus venous thrombosis), dermatologic reactions, hemolytic reactions, neutropenia, renal failure, transfusion-related lung injury, and seizures.	Induction: 1.5 - 2 g/kg, max dose 70 g/dose. If patient has clear improvement and then recrudesces, subsequent doses should be dosed at 1 g/kg. 2nd & 3rd doses have been given at 4-6 week intervals by PANS consortium members. Some patients are treated with rheumatology protocols which utilize 2 g/kg monthly (max dose 70 g/dose). If patient becomes dependent on IVIG to maintain good baseline, consider adding in or replacing with Rituximab or MMF.

file:///C:/Users/anton/Dropbox/Articles/Treatment%20of%20PANS%20with%20IVIG-Plasmapheresis.pdf

Plasmapheresis Protocol

Therapeutic Plasma Exchange (TPE)	**Removes autoantibodies triggering immune responses leading to brain inflammation.** **TPE is a process of separating blood components using centrifugation and a semipermeable membrane. This allows for disease promoting blood components to be removed while the remaining components are returned to the patient. Plasma proteins, including antibodies promoting disease, can be removed from the patient's blood.** **Benefit: Rapidly removes antibodies from plasma and quickly eliminates autoreactive immune responses caused by antibodies.**	**TPE often requires an intensive care admission and this may be psychiatrically traumatizing to some children.** **Related to IV access: pain, bleeding, infection, and, thrombosis. Risks of sedation. Risks of fluid shifts. Complications related to citrate anticoagulation/calcium chelating and replaced with albumin. Risks of exposure to blood products.** **Syncope, pseudoseizures, and pain-amplification have been reported immediately following TPE.** **TPE can cause hypogammaglobulinemia.**	**1 volume therapeutic exchanges every other day for 10- 12 days (5-6 runs) (Perlmutter et al. 1999).** **1.5 volume therapeutic exchanges over 3-5 days (3-4 runs) (Latimer et al. 2015).** **As soon as TPE is stopped, autoantibodies will continue to be produced (if autoimmune disease present), thus adjunct therapy is recommended. In infection triggered PANS, TPE alone can be effective if infectious driver is eliminated.**

file:///C:/Users/anton/Dropbox/Articles/Treatment%20of%20PANS%20with%20IVIG-Plasmapheresis.pdf

Immune modulating doses of ivig

Immunology 2002 **107** 387–393

REVIEW ARTICLE

Immunomodulatory action of intravenous immunoglobulin

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INTRODUCTION

Intravenous immunoglobulin (IVIg) is a blood product prepared from the serum of between 1000 and 15 000 donors per batch. It is the treatment of choice for patients with antibody deficiencies. In this indication, IVIg is used at a 'replacement dose' of 200–400 mg/kg body weight, given approximately 3-weekly. In contrast, 'high-dose' IVIg (hdIVIg), given most frequently at 2 g/kg/month, is used as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders. Initial use of hdIVIg was for idiopathic thrombocytopenic purpura (ITP) in children.[1] Despite a lack of double-blind, randomized, placebo-controlled trials, many other conditions are managed with hdIVIg, including numerous haematological, rheumatological, neurological and dermatological disorders.[2] In

donor preparations, but there was no difference between standard IVIg preparations and cytomegalovirus hyperimmune globulin.[4]

Both antigen-dependent and antigen-independent responses are inhibited by IVIg in a dose-dependent manner.[5] T-cell proliferation in response to anti-CD3 or tetanus toxoid was shown to be inhibited by IVIg in a dose-dependent manner over a range of IgG concentrations (0–10 mg/ml).[6] The inhibition was reversible by exogenous interleukin-2 (IL-2) and the authors concluded that the effects were a result of interference with cytokine-mediated T-cell proliferation.

Both pooled normal human immunoglobulin, and single donor immunoglobulin were shown to reduce pokeweed mitogen (PWM) -induced plaque-forming cell formation following 300 mg/kg infusions into patients with common variable immu-

- Published in 2002
  - Immunomodulatoy agent = 2gm/kg/month
  - Immune replacement = 200-400mg/kg/weekly

IVIG followed by Plasmapheresis is safe & effective – 2002

- Patients got Plasmapheresis followed immediately by IvIg
- Concentration of IgG dropped by 40%
  - Restored 24h later to 16% reduction in IVIG treated patients
  - Stayed at 32% reduction in none treated patients

Therapeutic Apheresis
6(2):154–158, Blackwell Publishing, Inc.
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The Effectiveness of Intravenous Human Immunoglobulin Treatment After Plasmapheresis in Restoring Serum Immunoglobulin Levels: A Preliminary Study

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Abstract: This study was performed to examine the effects of intravenous human immunoglobulin (IVIG) on the level of serum immunoglobulin G (IgG) and its subclasses after plasmapheresis in patients with autoimmune disorders. Twenty-nine patients with predominantly rheumatoid arthritis were enrolled in this study. The plasmapheresis was performed by the use of double-filtration plasmapheresis (DFPP). Immediately after DFPP, IVIG (2.5 g, 50 ml) was intravenously administered. The treatment with IVIG had almost no effect on subjective and objective symptoms. Immediately after DFPP, the total of serum IgG was decreased by approximately 40%. After 24 h, the total of serum IgG recovered to 16% reduction in IVIG-treated patients whereas it remained at 32% reduction in nontreated patients. The beneficial effect of IVIG was significantly observed in patients who had shown 1,000–1,800 mg/dl IgG in their sera. After DFPP, IgG subclasses were decreased without change in the ratio of subclasses. Twenty percent to 30% of IgG subclasses were supplemented by the treatment with IVIG without change in the ratio of subclasses. These results suggested that the treatment with IVIG at minimal amount was safe and effective to supplement IgG for hypogammaglobulinemia after DFPP. **Key Words:** Autoimmune disorders—Human immunoglobulin preparation—Hypogammaglobulinemia—Immunoglobulin G subclass levels—Plasmapheresis—Serum immunoglobulin G levels.

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


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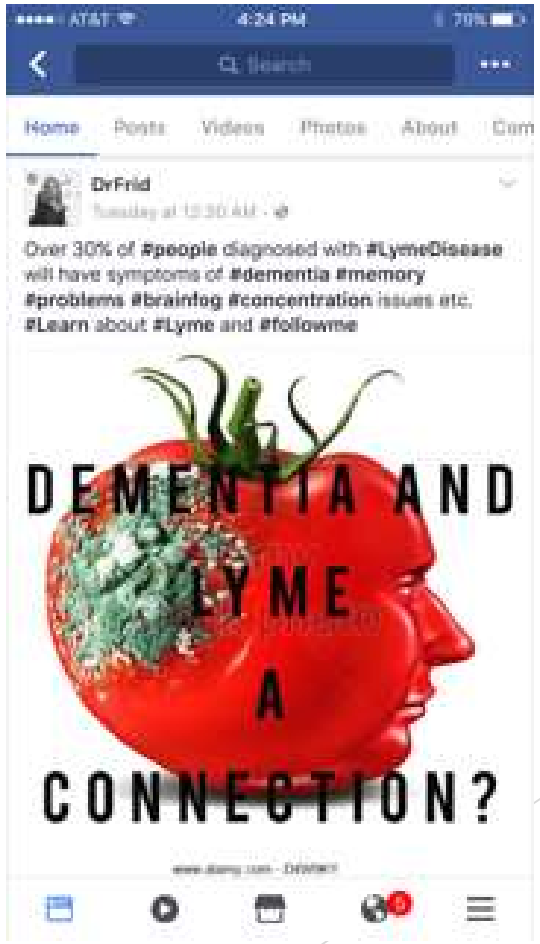

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Campaign raising awareness for Lyme Disease in the month of May

@LymeDiseaseChallenge

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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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