Lyme Disease and Viruses: Their Role in Degenerative & Autoimmune Conditions

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Agenda

- Lyme Disease and autoimmunity: mechanisms and focus on specific conditions
- Lyme Disease in degenerative conditions
- Viral involvement in autoimmunity: mechanisms and some specific conditions
- Tailored testing protocols: A few examples

Borrelia is associated with multiple autoimmune conditions

- Rheumatic fever, reactive arthritis, rheumatoid arthritis – all can potentially be forms of Lyme arthritis
- Molecular mimicry in neuroborreliosis
- Neuropathy
- Vasculitis
- Autoimmune thyroid disease/Hashimoto's
- Multiple sclerosis
- .....

Lyme arthritis: the first link between Borreliosis and autoimmune disease

The first indication that treatment-resistant Lyme borreliosis might be an autoimmune disease came from a study analysing MHC (major histocompatibility complex) II alleles (HLA-DR4) in patients with Lyme arthritis. MHC class II molecules play a critical role in activation of the immune system.

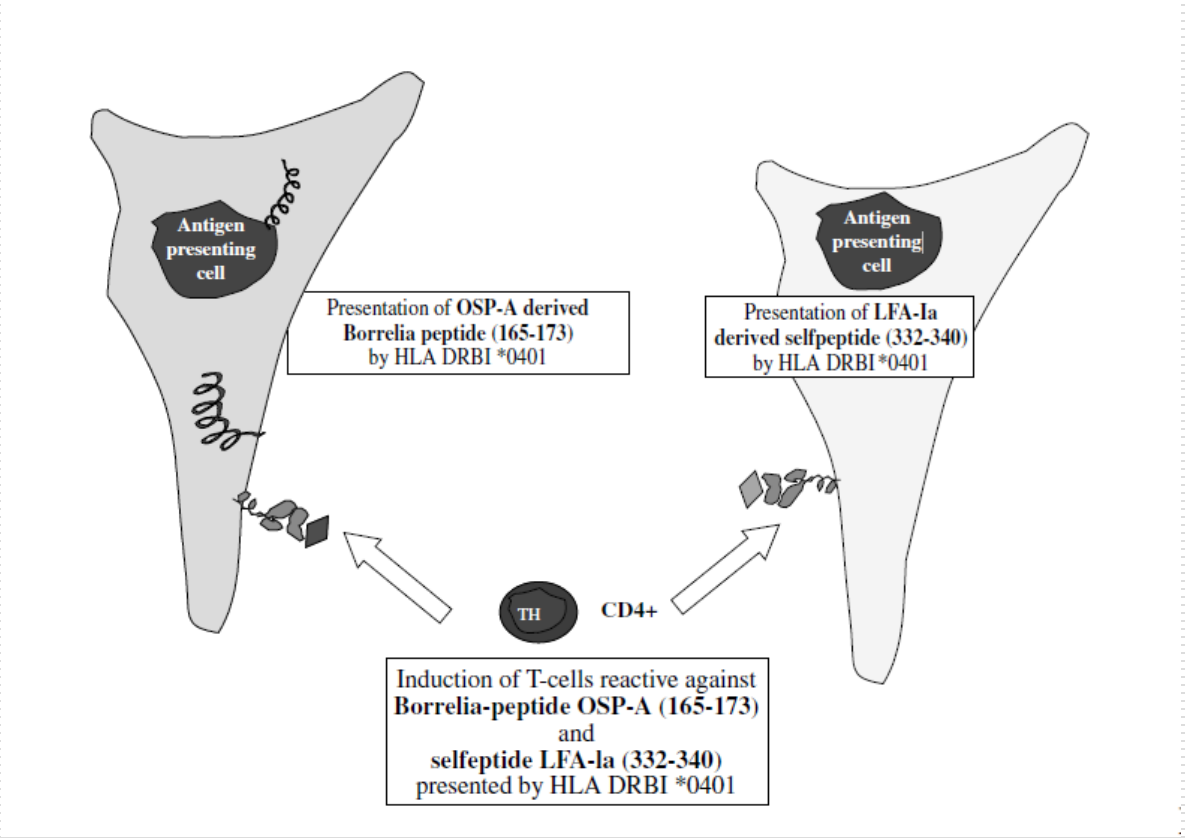
PX with chronic treatment-resistant Lyme arthritis have been found to have MHC II alleles associated with rheumatoid arthritis, partic. HLA-DRB1* 0401 and 0101 alleles.

These PX also develop anti-OspA antibodies correlating with the duration of their arthritis [138], suggesting that OspA may be involved in the autoimmune process.

Gross et al. suggested that LFA-1 (human leucocyte function-associated antigen 1) can serve as a cross-reactive autoantigen for OspA-reactive Th1 cells, leading to treatment-resistant Lyme arthritis. One potential explanation for antibiotic-resistant Lyme disease is thus generation of A/I directly or indirectly mediated by the pathogen and based on molecular mimicry.

Source: Kalish RA, Leong JM, Steere AC. Association of treatment-resistant chronic Lyme arthritis with HLA-DR4 and antibody reactivity to OspA and OspB of Borrelia burgdorferi. Infect Immun 1993; 61: 2774–2779; Gross DM, Forsthuber T, Tary-Lehmann M et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science 1998; 281: 703–706.

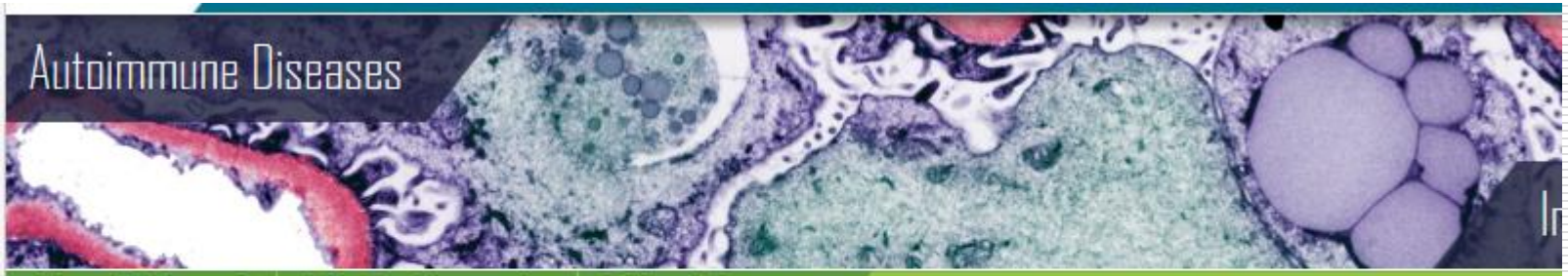
Intracellular persistence of Bb in synovial cells - molecular mimicry in Lyme arthritis



Antigen-presenting cells (monocytes, macrophages, dendritic cells and synovial fibroblasts) present peptides generated from borrelial OspA and host LFA-Ia (human leucocyte function-associated antigen 1), which induce a cross-reactive T-cell response

Source: Singh SK, Girschick HJ. Lyme borreliosis: from infection to autoimmunity. 2004. Clinical Microbiology and Infection (CMI), 10, 598–614

Autoimmunity in rheumatic diseases induced by microbial infections increasingly recognised



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Autoimmune Diseases
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http://dx.doi.org/10.1155/2012/539282

Review Article

Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Crossreactivity or Molecular Mimicry

Taha Rashid and Alan Ebringer

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Received 2 September 2011; Accepted 1 November 2011

Important to consider Borrelia in the differential diagnosis of rheumatoid arthritis

Clinical and Vaccine Immunology
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Clin Vaccine Immunol. 2007 Nov; 14(11): 1437–1441. PMCID: PMC2168181
Published online 2007 Sep 19. doi: 10.1128/CVI.00151-07

Serum Reactivity against *Borrelia burgdorferi* OspA in Patients with Rheumatoid Arthritis▽

Yu-Fan Hsieh,[1] Han-Wen Liu,[1] Tsai-Ching Hsu,[1] James C.-C. Wei,[2] Chien-Ming Shih,[3] Peter J. Krause,[4] and Gregory J. Tsay[1,2,*]

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ABSTRACT

Go to:

Lyme arthritis and rheumatoid arthritis share common clinical features and synovial histology. It is unclear whether they also share similar pathogenesis. Previous studies have shown that the severity and duration of Lyme arthritis correlate directly with serum concentrations of antibody against outer surface protein A (OspA) of the causative pathogen *Borrelia burgdorferi*. We tested the sera of 68 subjects with rheumatoid arthritis, 147 subjects with other autoimmune diseases, and 44 healthy subjects who had never had Lyme

Molecular mimicry in chronic neuroborreliosis

Hemmer et al. demonstrated that several T-cell clones responded to Borrelia peptides and endogenous host peptides

Table 4 Sequence, potency, and function of human autoantigenic mimics

Sequence	Potency		PB PP[c]	Definition	Notes	Reference or submission
	EC_{50} µg/ml[a]	% of max. response[b]				
(23) YSICKSGCFY	0.1-1	nt	nt	Myelin-associated oligodendrocyte basic protein (MOBP)	Third-most-abundant protein in CNS compact myelin	ref. 45
(61) LHIISKRVEA	0.1-1	70.0	0	titin	Giant protein involved in muscle ultrastructure and elasticity	ref. 46
(62) SFIYSVVCLV	0.1-1	75.7	9	Somatostatin receptor isoform 1	Somatostatinergic neurotransmission modulates cognitive function and may be defective in Alzheimer disease	ref. 47
(63) GHIKKKRVEA	1-10	56.5	0	Transforming growth factor (TGF)-β3	Potent immunosuppressive cytokine; TGF-β3 is mainly expressed in cells of mesenchymal origin	ref. 48
(64) FNITSSTCEL	0.1-1	66.3	1	Human C-C chemokine receptor type 7 precursor	Lymphoid-specific EBV-induced G protein-coupled receptor; upregulated during dendritic cell maturation	refs. 49,50
(66) ENVKKSRRLI	0.1-1	64.1	0	Interleukin (L)-1 receptor type 1, precursor	Receptor for IL-1α and IL-1β; type I membrane protein;binding to agonist leads to activation of NFκB	ref. 51
(71) DNITSSVLFN	0.1-1	60.6	5	Aminopeptidase A	Cleaves acidic amino acids off N terminus of polypeptides (angiotensin II, IL-8, CCK-8); may cleave both IL-7 and IL-7R (N-terminal E); EC 3.4.11.7; genomic structure similar to CD10, CD26; marker of immature B cells, upregulated by IL-7, viral transformation, type I interferons.	refs. 52,53

Source: Hemmer B, Gran B, Zhao Y et al. Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease. Nat Med 1999; 5: 1375–1382

Anti-axonal IgM antibodies have been found in the serum of PX with neurological Lyme Disease

very uncommon (19, 22). The inability to find the organism in biopsies of affected nerve tissue may indicate that very few organisms are present but that they are nonetheless capable of producing signific
isms has been the
23). Vasculitis in
and may be part
tively, or as a con
is no longer, or wa
and that immune
onopathy; we ha
might be an active
Previous studies have demonstrated that patients with LD-associated neuropathy have serum and cerebrospinal fluid antibodies to *B. burgdorferi* flagellin, often binding to the H9724-defined epitope (7); this epitope cross-reacts with human peripheral nerve axon (36). These antibodies bind to a specific axonal target, a protein with an appro
64 kDa (34), now known to be cpn60
protein (8).

We demonstrated that H9724, a m
shared flagellin-cpn60 epitope, modifies in vitro neurite out-

compatible with the premise that H9724 has its effect at a site proximal to effects mediated by cAMP and protein kinase (activated directly by phorbol esters) or that the effect of
ore physiological pathway. Heat shock
spontaneous neuritogenesis, an obser-
n60, or a related protein, may play a

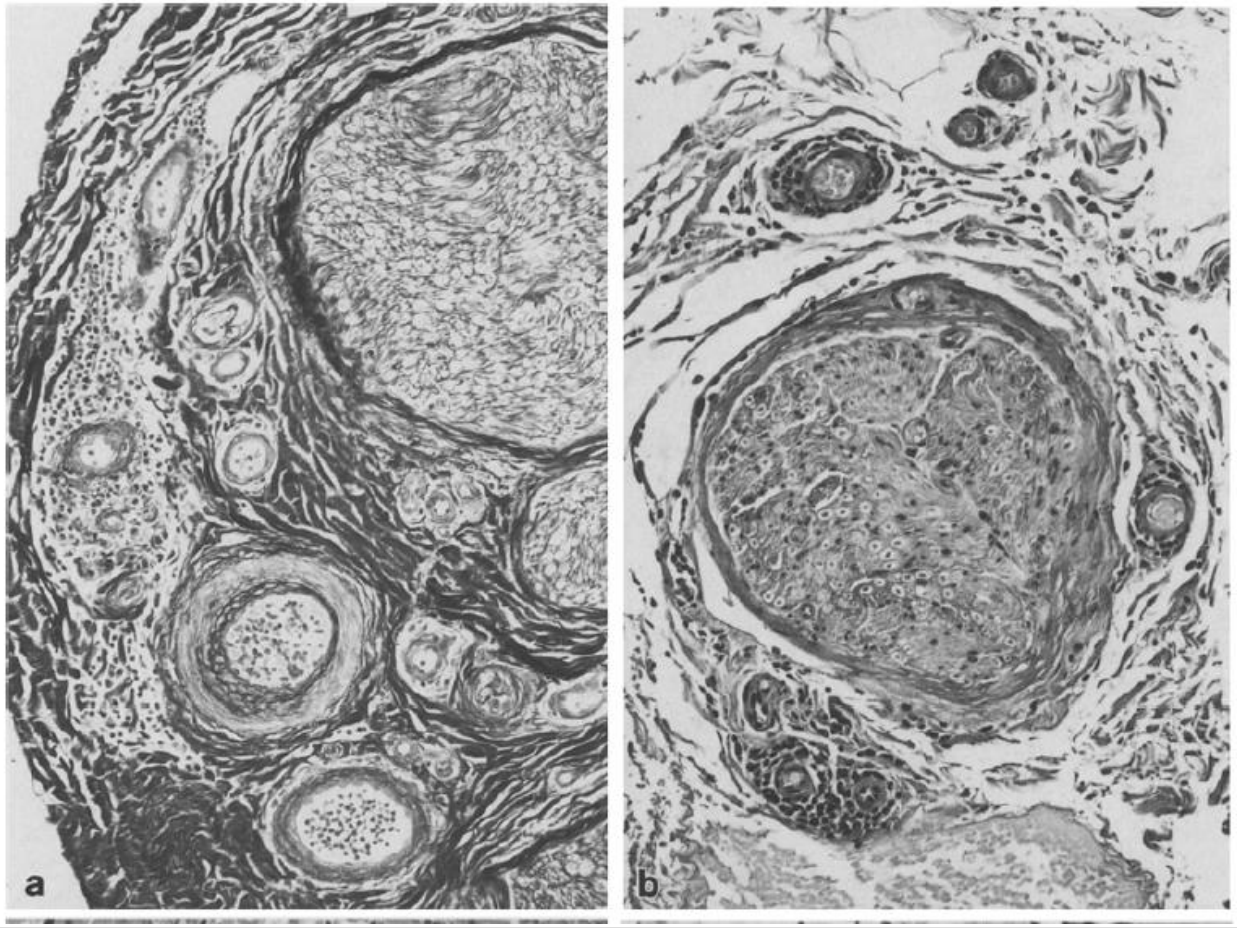
an intracellular protein, although in
r a homolog, can be expressed on the
ed on other studies, including surface
ography, we have concluded that the
nulated SK-N-SH cells is intracellular (data not shown). Certainly, it would be difficult to explain interference with neurite formation on the basis of surface binding of H9724, but that remains a possibility. Our results are compatible with the premise that H9724 is capable of entering the live cultured cells being studied without perma-
ntibody into living neu-
ously (12, 13, 21) and in
ediated by surface Fcγ
ffect on neuritogenesis,
the effects of H9724 are antigen specific and do not represent

"Previous studies have demonstrated that patients with LD-associated neuropathy have serum and **cerebrospinal fluid antibodies** to *B. burgdorferi* flagellin, **often binding to the H9724-defined epitope**"

The H9724-defined epitope cross-reacts with human peripheral nerve axons*

*Source: Sigal LH[1], Williams S A monoclonal antibody to Borrelia burgdorferi flagellin modifies neuroblastoma cell neuritogenesis in vitro: a possible role for autoimmunity in the neuropathy of Lyme disease Infect Immun. 1997 May;65(5):1722-8. ; Dai, Z. Z. (1993). Definition of the Epitope on the 41-kDa Flagellin of Borrelia burgdorferi for a Monoclonal Antibody H9724 and Identification of a H9724-Reactive ProteinFromCalf Adrenal Gland, PhDThesis, Rutgers University 4; * :Sigal, L. H., and A. H. Tatum. 1988. Lyme disease patients' serum contains IgM antibodies to Borrelia burgdorferi that cross-react with neuronal antigens. Neurology 38:1439–1442*

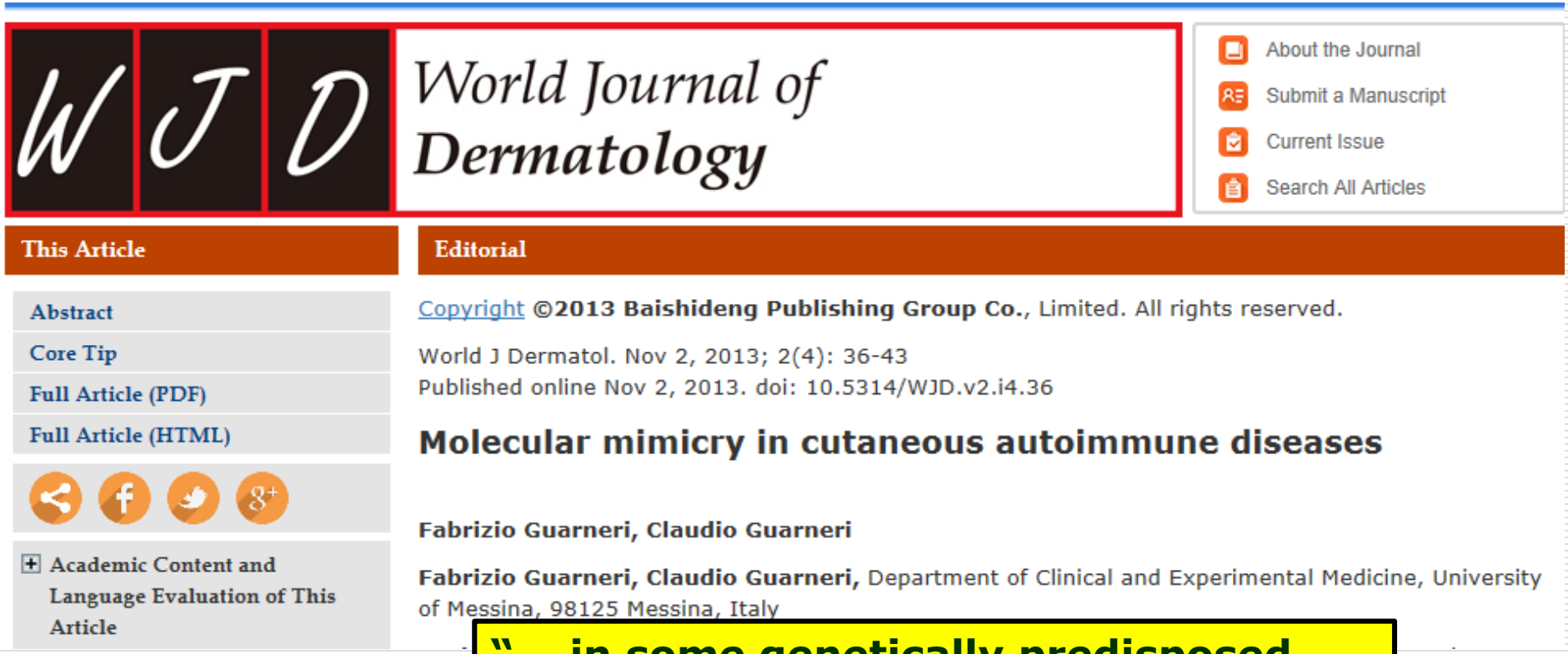
Vasculitis in affected nerves has been reported as part of the neuropathological process



Perivasculitis of epineurial vasa nervorum in sural nerve biopsies from patients with PNS complications of Lyme-Borreliosis

Source: Meier, C., F. Grahmann, A. Engelhardt, and M. Dumas. 1989. Peripheral nerve disorders in Lyme-borreliosis: nerve biopsy studies from eight cases. Acta Neuropathol. 79:271–278; Camponovo F, Meier C (1986) Neuropathy of vasculitic origin in a case of Garin-Bujadoux-Bannwarth syndrome with positive borrelia antibody response. J Neurol 233: 69- 72

Borrelia burgdorferi can cross-react with thyroid tissue triggering Hashimoto's



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Editorial

World J Dermatol. Nov 2, 2013; 2(4): 36-43
Published online Nov 2, 2013. doi: 10.5314/WJD.v2.i4.36

Molecular mimicry in cutaneous autoimmune diseases

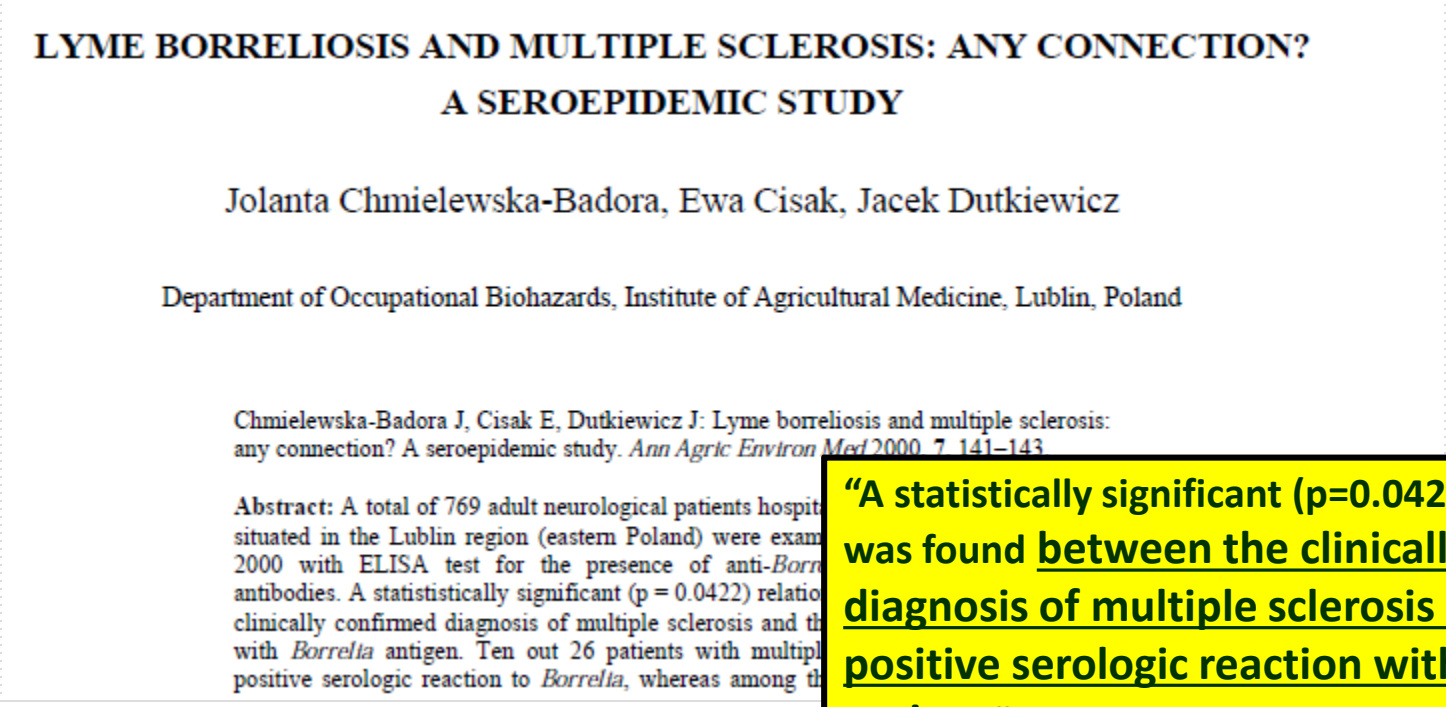
Fabrizio Guarneri, Claudio Guarneri

Fabrizio Guarneri, Claudio Guarneri, Department of Clinical and Experimental Medicine, University of Messina, 98125 Messina, Italy

"... in some genetically predisposed subjects, Borrelia infection can be the trigger of Hashimoto's thyroiditis and/or lichen sclerosus"

IgG antibodies that cross-react with myelin basic protein discovered in sera from Lyme disease PX

Sera from Lyme disease patients contain antibodies to Bb that crossreact with nervous tissue antigens. Sigal and Tatum found IgM antibodies that cross-reacted with axonal antigens, and Garcia-Monco et al. found IgG antibodies that cross-reacted with myelin basic protein



LYME BORRELIOSIS AND MULTIPLE SCLEROSIS: ANY CONNECTION?
A SEROEPIDEMIC STUDY

Jolanta Chmielewska-Badora, Ewa Cisak, Jacek Dutkiewicz

Department of Occupational Biohazards, Institute of Agricultural Medicine, Lublin, Poland

Chmielewska-Badora J, Cisak E, Dutkiewicz J: Lyme borreliosis and multiple sclerosis: any connection? A seroepidemic study. *Ann Agric Environ Med* 2000, 7, 141–143

Abstract: A total of 769 adult neurological patients hospit
situated in the Lublin region (eastern Poland) were exam
2000 with ELISA test for the presence of anti-*Borr*
antibodies. A statististically significant (p = 0.0422) relatio
clinically confirmed diagnosis of multiple sclerosis and th
with *Borrelia* antigen. Ten out 26 patients with multipl
positive serologic reaction to *Borrelia*, whereas among th

"A statistically significant (p=0.0422) relationship was found between the clinically confirmed diagnosis of multiple sclerosis and the positive serologic reaction with Borrelia antigen"

Source: Meier, C., F. Grahmann, A. Engelhardt, and M. Dumas. 1 studies from eight cases. Acta Neuropathol. 79:271–278; Sigal, IgM antibodies to Borrelia burgdorferi that cross-react with neuronal antigens. Neurology 38:1439–1442; Garcia-Monco JC, Coleman JL, Benach JL (1988) Antibodies to myelin basic protein in Lyme disease. J Infect Dis 158 : 667- 668

Multiple Sclerosis

Multiple Sclerosis, myelopathies, polyneuropathies, brain tumor, encephalopathy. (Neurosurgery.1992 May;30(5): 769-73)

1986 (USA): Relapsing fever/Lyme disease – Multiple sclerosis. Medical Hypotheses, volume 21, issue 3, pages 335-343

2000 (Poland): Lyme borreliosis and Multiple sclerosis: Any Connection? A Seroepidemic study. Ann Agric Environ Med. issue 7, 141-143

2001 (Norway): Association between Multiple sclerosis and Cystic Structures in Cerebrospinal Fluid. Infect 29:315

2004 (Switzerland): Chronic Lyme borreliosis at the root of Multiple sclerosis – is a cure with antibiotics attainable?

Borrelia burgdorferi as well as viruses associated with neurological disease

- Clear role in neurodegenerative and neurobehavioural conditions: likely driver/s
- Alzheimer's
- Parkinson's/Parkinsonism
- Even found in ALS/motor neurone disease
- …

Professor Garth Nicolson: clear role of Bb in neurodegenerative and neurobehavioural disease

BJMP.org
British Journal of Medical Practitioners

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioral, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 1

Garth L. Nicolson and Jörg Haier

Cite this article as: BJMP 2009:2(4) 20-28
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Abstract

Chronically ill patients with neurodegenerative, n
central nervous system bacterial and viral infectio
are routinely found, such as fatiguing and autoim
bacterial and viral infections that could be import
severity of signs and symptoms. Evidence of *Myc*
herpesvirus-1, -6 and -7 and other bacterial and
were not found in controls. Although the specific
have not been carefully determined, the data sug
progressive chronic diseases.

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioural, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 2

Garth L. Nicolson and Jörg Haier

Cite this article as: BJMP 2010;3(1):301
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"Evidence of *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls."

Abstract

Chronically ill patients
central nervous syste
are routinely found, s
bacterial and viral inf
signs and symptoms.
-6 and -7 and other b
controls. Although th
carefully determined, the data suggest that chronic bacterial and/or viral infections are common features of progressive chronic diseases.

Abbreviations: Ab Beta Amyloid; AD Alzheimer's Disease; ADHD Attention-Deficit Hyperactivity Disorder; ALS Amyotrophic Lateral Sclerosis; ASD Autism Spectrum Disorders; EBV Epstein-Barr Virus; CFS Chronic Fatigue Syndrome; CFS/ME Chronic Fatigue Syndrome/Myalgic Encephalomyopathy; CI Confidence Interval; CMV Cytomegalovirus; CSF

Spirochete-stimulated brain tissue evidences reactive astrogliosis/inflammation in the brain parenchyma

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Am J Pathol. 2008 Nov; 173(5): 1415–1427.
doi: 10.2353/ajpath.2008.080483
PMCID: PMC2570132

Interaction of the Lyme Disease Spirochete *Borrelia burgdorferi* with Brain Parenchyma Elicits Inflammatory Mediators from Glial Cells as Well as Glial and Neuronal Apoptosis

Geeta Ramesh,* Juan T. Borda,† Jason Dufour,‡ Deepak Kaushal,* Ramesh Ramamoorthy,* Andrew A. Lackner,† and Mario T. Philipp*

Author information ► Article notes ► Copyright and License informati

"The high number of significantly perturbed transcripts of genes that regulate immune function, as revealed in our microarray analysis of live spirochete-stimulated brain tissues, subscribes to the notion that spirochetes can have a powerful effect on the regulation of inflammation in the brain parenchyma."

Abstract

Lyme neuroborreliosis, caused by the spirochete ***Bor***
neurocognitive deficits. As a possible mechanism for
burgdorferi induces the production of inflammatory
concomitant neuronal and/or glial apoptosis. To test
consisted of freshly collected slices from brain corte
to penetrate the tissue. Numerous transcripts of genes that regulate inflammation as well as oligodendrocyte and neuronal apoptosis were significantly altered as assessed by DNA microarray analysis. Transcription level increases of 7.43-fold ($P = 0.005$) for the cytokine tumor necrosis factor-α and 2.31-fold ($P = 0.016$)

Amyloid plaques in Alzheimer's Disease – protection against microbial infection?

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RESEARCH ARTICLE | ALZHEIMER'S DISEASE

Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease

Deepak Kumar Vijaya Kumar[1,*], Se Hoon Choi[1,*], Kevin J. Washicosky[1,*], William A. Eimer[1], Stephanie Tucker[1], Jessica Ghofrani[1], Aaron Lefkowitz[1], Gawain McColl[2], Lee E. Goldstein[3], Rudolph E. Tanzi[1,†] and Robert D. Moir[1,†]

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* These authors contributed equally to this work.

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Rehabilitation of a β-amyloid bad boy

A protein called Aβ is thought to cause neuronal death in Alzheimer's disease (AD). Aβ

Science Translational Medicine
Vol 8, Issue 340
25 May 2016
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"When you look in the plaques, each one had a single bacterium in it," says Tanzi. "A single bacterium can induce an entire plaque overnight."

"Our findings raise the intriguing possibility that Alzheimer's pathology may arise when the brain perceives itself to be under attack from invading pathogens"

Numerous studies have found connections with Parkinson's/Parkinsonism

Parkinsonism Relat Disord. 2015 Aug;21(8):877-81. doi: 10.1016/j.parkreldis.2015.05.015. Epub 2015 May 30.

The association between infectious burden and Parkinson's disease: A case-control study.

Bu XL[1], Wang X[1], Xiang Y[1], Shen LL[1], Wang QH[1], Liu YH[1], Jiao SS[1], Wang YR[1], Cao HY[1], Yi X[1], Liu CH[1], Deng B[1], Yao XQ[1], Xu ZQ[1], Zhou HD[1], Wang YJ[2].

⊕ Author information

Abstract

INTRODUCTION: The etiology of Parkinson's disease (PD) remains unclear. The aim of this study was to examine the association between common pathogenic infections and PD.

METHODS: Antibody titers to common infectious pathogens including cytomegalovirus (CMV), Epstein Barr virus (EBV) , herpes simplex virus type-1 (HSV-1), Borrelia burgdorferi (B. burgdorferi), Chlamydophila pneumoniae (C. pneumoniae) and Helicobacter pylori (H. pylori) were measured by ELISA in serum of 131 PD patients and 141 normal controls. Infectious burden (IB) was defined as a composite serologic measure of exposure to these common pa

RESULTS: Seropositivities to

of normal controls while in 4%, 61% and 35% of PD pa

h PD. Schwab and England (S&E) scores were n

matory cytokines (interleukin-1β and interleukin-

CONCLUSIONS: IB consisting of CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae and H. pylori is associated with PD. This study supports the role of infection in the etiology of PD.

"Infectious burden consisting of CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae and H. pylori is associated with PD. This study supports the role of infection in the etiology of PD."

Drosophila-like 4 gene, which is associated with inflammation and neuronal death and is up-regulated in Parkinson's disease, was up-regulated in spirochete-stimulated tissues by 9.98-fold*

*Source: * Ramesh G et al. Interaction of the Lyme Disease Spirochete Borrelia burgdorferi with Brain Parenchyma Elicits Inflammatory Mediators from Glial Cells as Well as Glial and Neuronal Apoptosis. Am J Pathol. 2008 Nov; 173(5): 1415–1427*

Even MND may be associated with Borrelia and coinfections – patient recovered when treated accordingly

Acta Neurol Scand. 2007 Feb;115(2):129-31.

Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy.

Harvey WT[1], Martz D.

⊕ Author information

Abstract

This report summarizes what we believe to be the first verifiable case of a significant and progressive motor neuron disease (MND) consistent with amyotrophic lateral sclerosis that resolved during treatment with i.v. ceftriaxone plus oral atovaquone and mefloquine. The rationale for use of these antibiotics was (i) positive testing for Borrelia burgdorferi and (ii) red blood cell ring forms consistent with Babesia species infection. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain.

Comment in

Motor neuron disease. [Acta Neurol Scand. 2008]

"… positive testing for Borrelia burgdorferi ….. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain."

Viral involvement in autoimmunity is well documented

- Viruses: molecular mimicry, bystander activation or viral persistence? – possibly a perfect storm of all three
- Examples:
  - SLE (Lupus)
  - Type 1 Diabetes
  - Sarcoidosis
  - Myasthenia Gravis
  - Graves Disease

Viruses have cross-reactive epitopes with host self proteins

Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease

Robert S. Fujinami[1,*], Matthias G. von Herrath[2], Urs Christen[2] and J. Lindsay Whitton[3]

Author Affiliations

SUMMARY

Virus infections and autoimmune disease have long been linked. These infections often precede the occurrence of inflammation in the target organ. Several mechanisms often used to explain the association of autoimmunity and virus infection are molecular mimicry, bystander activation (with or without epitope spreading), and viral persistance. These mechanisms have been used separately or in various combinations to account for the immunopathology observed at the site of infection and/or sites of autoimmune disease, such as the brain, heart, and pancreas. These mechanisms are discussed in the context of multiple sclerosis, myocarditis, and diabetes, three immune–medicated diseases often linked with virus infections.

Molecular mimicry: A foreign antigen shares a sequence or structural similarities with self-antigens. This can result not only in the production of antibodies against the virus, but can also lead to autoantibodies against the human cells due to the similarities in the proteins

Bystander activation: An indirect or non-specific activation of autoimmune cells caused by the inflammatory environment present during infection. When one part of the immune system becomes activated this leads to the activation of other parts which can kill both viral-infected cells, and healthy cells as well

Source: Fujinami RS et al. Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease. Clin. Microbiol. Rev., Jan 2006; 19: 80 -94.; Fujinami, R. S. et al. 1983. Molecular mimicry in virus infection: Cross-reaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. Proc. Natl. Acad. Sci. USA 80:2346–2350.

EBV and SLE

Arthritis Research & Therapy

RESEARCH ARTICLE | OPEN ACCESS

Patients with systemic lupus erythematosus have abnormally elevated Epstein–Barr virus load in blood

Uk Yeol Moon[†], Su Jin Park[†], Sang Taek Oh, Wan-Uk Kim, Sung-Hwan Park, Sang-Heon Lee, Chul-Soo Cho, Ho-Youn Kim, Won-Keun Lee and Suk Kyeong Lee

[†] Contributed equally

Arthritis Res Ther 2004 **6**:R295 | **DOI:** 10.1186/ar1181

Received: 4 November 2003 | **Accepted:** 1 April 2004 | **Published:** 7 May 2004

Abstract

Various genetic and environmental factors appear to be involved in systemic lupus erythematosus (SLE). Epstein–Barr virus (EBV) is among the environmental factors that are suspected of predisposing to SLE, based

Also found in SLE: Parvovirus B19, CMV, HSV, VZV

Medicine (Baltimore). 2008 Nov;87(6):311-8. doi: 10.1097/MD.0b013e31818ec711.

Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature.

Ramos-Casals M[1], Cuadrado MJ, Alba P, Sanna G, Brito-Zerón P, Bertolaccini L, Babini A, Moreno A, D'Cruz D, Khamashta MA.

Author information

Abstract

Few studies have evaluated the impact of viral infections on the daily management of patients with systemic lupus erythematosus (SLE). We analyzed the etiology and clinical features of acute viral infections arising in patients with SLE and their influence on the diagnosis, prognosis, and treatment of SLE. Cases occurring within the last 5 years were selected from the databases of 3 large teaching hospitals. Acute viral infections were confirmed by the identification of specific antiviral IgM antibodies and subsequent seroconversion with detection of specific IgG antibodies. In autopsy studies, macroscopic findings suggestive of viral infection were confirmed by direct identification of the virus or viruses in tissue samples. We performed a MEDLINE search for additional cases reported between January 1985 and March 2008. We included 88 cases (23 from our clinics and 65 from the literature review) of acute viral infections in patients with SLE. Twenty-five patients were diagnosed with new-onset SLE (fulfillment of the 1997 SLE criteria) associated with infection by human parvovirus B19 (n = 15), cytomegalovirus (CMV; n = 6), Epstein-Barr virus (EBV; n = 3), and hepatitis A virus (n = 1). The remaining 63 cases of acute viral infections arose in patients already diagnosed with SLE: in 18 patients, symptoms related to infection mimicked a lupus flare, 36 patients, including 1 patient from the former group who presented with both conditions, presented organ-specific viral infections (mainly pneumonitis, colitis, retinitis, and hepatitis), and 10 patients presented a severe, multiorgan process similar to that described in catastrophic antiphospholipid syndrome-the final diagnosis was hemophagocytic syndrome in 5 cases and disseminated viral infection in 5. Twelve patients died due to infection caused by CMV (n = 5), herpes simplex virus (n = 4), EBV (n = 2), and varicella zoster virus (n = 1). Autopsies were performed in 9 patients and disclosed disseminated herpetic infection in 6 patients (caused by herpes simplex in 4 cases, varicella in 1, and CMV in 1) and hemophagocytic syndrome in 3. A higher frequency of renal failure (54% vs. 19%, p = 0.024), antiphospholipid syndrome (33% vs. 6%, p = 0.023), treatment with cyclophosphamide (82% vs. 37%, p = 0.008), and multisystemic involvement at presentation (58% vs. 8%, p < 0.001); and a lower frequency of antiviral therapy (18% vs. 76%, p < 0.001) were found in patients who died, compared with survivors. The most common viral infections in patients with SLE are parvovirus B19 (predominantly mimicking SLE presentation) and CMV (predominantly presenting in severely immunosuppressed patients). CMV infection may mimic a lupus flare or present with specific organ involvement such as gastrointestinal bleeding or pulmonary infiltrates. Other herpesviruses are common in immunosuppressed SLE patients and may produce a wide range of manifestations. Physicians should examine the pharynx, eyes, skin, and genitalia and should conduct serologic and molecular studies to improve early detection of viral infection in patients with SLE.

Diabetes Type 1: B1 strain of Coxsackie B has antigens similar to those in pancreatic beta cells

Source: Kalish RA, Leong JM, Steere AC. Association of treatment-resistant chronic Lyme arthritis with HLA-DR4 and antibody reactivity to OspA and OspB of Borrelia burgdorferi. Infect Immun 1993; 61: 2774–2779; Gross DM, Forsthuber T, Tary-Lehmann M et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science 1998; 281: 703–706.

Association with Cytomegalovirus …

Associations of cytomegalovirus with type I diabetes mellitus among children in Khartoum State

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Cytomegalovirus is one of the most common microorganisms that cause opportunistic infection that complicate the clinical care and progress of immunecompromised patients. The virus can cause severe diseases with multiple complications in[illegible] The present study is a case control study aimed at determining c[illegible]ese children. Sera of eighty one (81) childre[illegible] the study group and 54 (66.7%) from appare[illegible]ted for IgG anti-cytomegalovirus using enzy[illegible]2%) of the total population of study were se[illegible]6%) were diabetic patients, the results indic[illegible]rus IgG antibodies with type I diabetes mell[illegible]lue 0.003) of cytomegalovirus IgG antibodies

"the results indicate significant association (*P* value 0.025) of cytomegalovirus IgG antibodies with type I diabetes mellitus in children. The study reveals significant relation (*P* value 0.003) of cytomegalovirus IgG antibodies with type I diabetes mellitus in age group (5-9 years)."

… and with other enteroviruses: Echovirus

Autoimmunity. 2001;34(4):275-81.

Echovirus 4 and type 1 diabetes mellitus.

Díaz-Horta O[1], Bello M, Cabrera-Rode E, Suárez J, Más P, García I, Abalos I, Jofra R, Molina G, Díaz-Díaz O, Dimario U.

⊕ Author information

Abstract

AIMS/HYPOTHESIS: To determine the association between exposure to enteroviruses and Type 1 diabetes.

METHODS: We measured neutralizing antibodies to the following enteroviruses: Coxsackievirus CA9, CB1, CB2, CB3, CB4, CB5, CB6, and Echovirus E4, E6, E9, E11 in the sera of (1) Type 1 diabetic patients at diagnosis (n = 33), (2) healthy offspring of parents with Type 1 diabetes without islet cell antibodies (ICA) (n = 43) and (3) normal controls (n = 57). All subjects were less than 20 years old. We performed the neutralization test determining the cytopathogenic effect on Vero cells. HLA DR serotyping was also performed in Group 2.

RESULTS: Type 1 diabetic patients showed a higher frequency (21.2%, $p < 0.01$) of neutralizing antibodies to E4 in relation to controls (1.8%), although there were no differences comparing with offspring of Typ… 1 diabetes HLA DR susceptibility genes were also exposed to E4 (15.0%). High frequ… ound in the control group.

CONCLUSION: This study shows the association between Type 1… virus 4, suggesting the possible participation of this virus as an environmental trigger … ays high frequencies of exposure to enterovirus (including CB4) although th… tants).

"This study shows the association between Type 1 diabetes and the presence of neutralizing antibodies to Echovirus 4, suggesting the possible participation of this virus as an environmental trigger of this autoimmune disease."

Also Rotavirus, Rubella, Mumps …

Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes.

M C Honeyman, B S Coulson, N L Stone, S A Gellert, P N Goldwater, C E Steele, J J Couper, B D Tait, P G Colman **and** L C Harrison

[+] Author Affiliations

Diabetes 2000 Aug; 49(8): 1319-1324. http://dx.doi.org/10.2337/diabetes.49.8.1319

^ Gale EAM. Congenital rubella – citation virus or viral cause of type 1 diabetes? Diabetologia 2008;51:1559–66

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^ Rubinstein P et al. The HLA system in congenital rubella patients with and without diabetes. Diabetes 1982;31:1088–91

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Sarcoidosis: EBV, CMV, HSV …

Box 1 Suspected Causes of Sarcoidosis	
Infectious	**Noninfectious**
Mycobacteria	Dusts
Tuberculous	Clay
Nontuberculous*	Pine
Cell-wall deficient (L-forms)*	Pollen
Bacteria	Talc
Corynebacterium spp.	Mixed*
*Propionibacterium acnes**	Metals
Tropheryma whippleii	Aluminum
Others	Beryllium‡
Fungi	Zirconium
Cryptococcus spp.	
Endemic fungi	
Viruses	
Cytomegalovirus	
Epstein-Barr virus	
Herpes simplex virus	
Others	

*These organisms have been the focus of most recent studies, but no single agent is confirmed. It is very possible that several disparate agents induce similar reactions leading to sarcoidosis.

Source: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

Myasthenia Gravis and EBV

Ann Neurol. 2010 Jun;67(6):726-38. doi: 10.1002/ana.21902.

Epstein-Barr virus persistence and reactivation in myasthenia gravis thymus.

Cavalcante P[1], Serafini B, Rosicarelli B, Maggi L, Barberis M, Antozzi C, Berrih-Aknin S, Bernasconi P, Aloisi F, Mantegazza R.

⊕ Author information

Abstract

OBJECTIVE: Increasing evidence supports a link between Epstein-Barr virus (EBV), a ubiquitous B-lymphotropic human herpesvirus, and common B-cell-related autoimmune diseases. We sought evidence of EBV infection in thymuses from patients with myasthenia gravis (MG), an autoimmune disease characterized by intrathymic B-cell activation.

METHODS: Seventeen MG thymuses (6 follicular hyperplastic, 6 diffuse hyperplastic, 5 involuted) and 6 control thymuses were analyzed using in situ hybridization for EBV-encoded small RNAs (EBERs), immunohistochemistry for EBV latent and lytic proteins, and polymerase chain reaction for EBV DNA and mRNA.

RESULTS: All 17 MG thymuses showed evidence ...vere infected. Cells expressing EBERs (12 of 17) and EBV latency proteins (EBN ...filtrates and in germinal centers. Cells expressing early (BFRF1, BMRF1) and late ...MG thymuses. Latency (EBNA1, LMP2A) or lytic (BZLF1) transcripts (often both) were present in all MG thymuses, and EBV DNA (LMP-1 gene) was detected in 13 MG thymuses. We also found CD8+ T cells, CD56 + CD3-natural killer cells, and BDCA-2+ plasmacytoid dendritic cells in immune infiltrates of MG thymuses, but not germinal centers, suggesting an attempt of the immune system to counteract EBV infection.

INTERPRETATION: Dysregulated EBV infection in the pathological thymus appears common in MG and may contribute to the immunological alterations initiating and/or perpetuating the disease.

"Dysregulated EBV infection in the pathological thymus appears common in Myasthenia Gravis"

Grave's Disease and EBV

Viral Immunol. 2011 Apr;24(2):143-9. doi: 10.1089/vim.2010.0072.

The influence of Epstein-Barr virus reactivation in patients with Graves' disease.

Nagata K[1], Fukata S, Kanai K, Satoh Y, Segawa T, Kuwamoto S, Sugihara H, Kato M, Murakami I, Hayashi K, Sairenji T.

Author information

Abstract

In Graves' disease, the IgG class autoantibody against thyrotropin receptor (TRAb) is produced excessively and induces hyperthyroidism. Epstein-Barr virus (EBV) is one of the human herpesviruses that persists for life, mainly in B lymphocytes, and is occasionally reactivated. Therefore, EBV may affect the antibody production of B lymphocytes that would normally produce TRAb. The purpose of the present study was to evaluate the association of EBV reactivation with the etiology of Graves' disease. Serum levels of EBV antibodies and IgE were determined by ELISA. TRAb levels were determined by radioreceptor assay. We performed in-situ hybridization (ISH) of EBV-encoded small RNA (EBER)1 on the thyroid tissue of one of our patients. In Graves' disease patients with TRAb levels ≥ [illegible] but significantly correlated with the levels of TRAb, and weakly but s[illegible] had EBV-infected lymphocytes infiltrating the thyroid gland. EBV rea[illegible] TRAb, and this may contribute to or exacerbate the disease.

"In Graves' disease patients with TSH receptor antibodies (TRAb) levels ≥ 10%, EA antibody levels, which indicate EBV reactivation, were moderately but significantly correlated with the levels of TRAb"

Tailored testing protocols – a few examples

- Rheumatoid arthritis
- Hashimoto's ?
- MS
- Alzheimer's/Dementia
- Parkinson's/Parkinsonism
- SLE (Lupus) ?
- Type 1 Diabetes ?
- Sarcoidosis ?
- Myasthenia Gravis ?
- Graves Disease ?

Rheumatoid Arthritis: Laboratory tests suggested

1. Borrelia SeraSpot + Borrelia EliSpot + CD57-cells
2. Chlamydia pneumoniae IgG/IgA antibodies + Chlamydia pneumoniae EliSpot
3. Chlamydia trachomatis IgG/IgA-antibodies + Chlamydia trachomatis EliSpot
4. Mycoplasma pneumoniae IgG/IgA antibodies
5. Ehrlichia/Anaplasma IgG/IgM antibodies + Ehrlichia/Anaplasma EliSpot
6. Rickettsia IgG/IgM antibodies
7. Yersinia IgG/IgA antibodies + Yersinia EliSpot
8. Coxsackie Virus IgG/IgA antibodies
9. HHV6 IgG/IgM antibodies
10. ANA (antinuclear antibodies) + CCP (cyclic citrullinated peptide) antibodies

Hashimoto's: Laboratory tests suggested

1. Borrelia SeraSpot + Borrelia EliSpot + CD57-cells
2. Yersinia-antibodies + Yersinia EliSpot
3. ?
4. ?
5. ?

Multiple Sclerosis: Laboratory tests suggested

1. Borrelia SeraSpot + Borrelia EliSpot + CD57-cells
2. Chlamydia pneumonia IgG/IgA antibodies + Chlamydia pneumoniae EliSpot
3. Mycoplasma pneumoniae IgG/IgA antibodies
4. Bartonella IgG/IgM antibodies
5. Coxsackie Virus IgG/IgA antibodies
6. EBV EliSpot
7. CMV EliSpot
8. HHV6 IgG/IgM antibodies

Alzheimers / Dementia

1. Borrelia SeraSpot + Borrelia-EliSpot + CD57 cells
2. Chlamydia pneumoniae IgG/IgA antibodies + Chlamydia pneumoniae EliSpot
3. Mycoplasma pneumoniae IgG/IgA antibodies
4. Coxsackie Virus IgG/IgA antibodies
5. Herpes simplex virus 1 / 2 IgG/IgA/IgM antibodies + Herpes simplex virus EliSpot
6. EBV EliSpot
7. CMV EliSpot

Parkinsonism

1. Borrelia SeraSpot + Borrelia EliSpot + CD57 cells
2. Chlamydia pneumoniae IgG/IgA antibodies + Chlamydia pneumoniae EliSpot
3. Mycoplasma pneumoniae IgG/IgA antibodies
4. Bartonella IgG/IgM antibodies
5. Coxsackie Virus IgG/IgA antibodies
6. EBV EliSpot
7. CMV EliSpot

Thank you very much for your attention!

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DIAGNOSING TICK-BORNE DISEASES

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