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

- .....
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.

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-1a (human leucocyte function-associated antigen 1), which induce a cross-reactive T-cell response.

Autoimmunity in rheumatic diseases induced by microbial infections increasingly recognised

Autoimmune Diseases
Volume 2012 (2012), Article ID 539282, 9 pages
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Review Article
Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Crossreactivity or Molecular Mimicry

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Received 2 September 2011; Accepted 1 November 2011
Important to consider Borrelia in the differential diagnosis of rheumatoid arthritis

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

Yu-Fan Hsieh, Han-Wen Liu, Tsai-Ching Hsu, James C.-C. Wei, Chien-Ming Shih, Peter J. Krause, and Gregory J. Tsay

ABSTRACT

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

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Potency</th>
<th>PB PP</th>
<th>Definition</th>
<th>Notes</th>
<th>Reference or submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>(23) YSICKSGCFY</td>
<td>0.1-1</td>
<td>nt</td>
<td>Myelin-associated oligoden drocyte basic protein (MOBP)</td>
<td>Third-most-abundant protein in CNS compact myelin</td>
<td>ref. 45</td>
</tr>
<tr>
<td>(61) LHIISKRVEA</td>
<td>0.1-1</td>
<td>70.0</td>
<td>Titin</td>
<td>Giant protein involved in muscle ultrastructure and elasticity</td>
<td>ref. 46</td>
</tr>
<tr>
<td>(62) SFIYSVYCLV</td>
<td>0.1-1</td>
<td>75.7</td>
<td>Somatostatin receptor isoform 1</td>
<td>Somatostatinergic neurotransmission modulates cognitive function and may be defective in Alzheimer disease</td>
<td>ref. 47</td>
</tr>
<tr>
<td>(63) GHIKKKREVIA</td>
<td>1-10</td>
<td>56.5</td>
<td>Transforming growth factor (TGF)-β3</td>
<td>Potent immunosuppressive cytokine; TGF-β3 is mainly expressed in cells of mesenchymal origin</td>
<td>ref. 48</td>
</tr>
<tr>
<td>(64) FNITSSTCEL</td>
<td>0.1-1</td>
<td>66.3</td>
<td>Human C-C chemokine receptor type 7 precursor</td>
<td>Lymphoid-specific EBV-induced G protein-coupled receptor; upregulated during dendritic cell maturation</td>
<td>refs. 49, 50</td>
</tr>
<tr>
<td>(66) ENVKKSRRLI</td>
<td>0.1-1</td>
<td>64.1</td>
<td>Interleukin (L)-1 receptor type 1, precursor</td>
<td>Receptor for IL-1α and IL-1β; type I membrane protein; binding to agonist leads to activation of NFκB</td>
<td>ref. 51</td>
</tr>
<tr>
<td>(71) DNITSSVLFN</td>
<td>0.1-1</td>
<td>60.6</td>
<td>Aminopeptidase A</td>
<td>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</td>
<td>refs. 52, 53</td>
</tr>
</tbody>
</table>


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

"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*

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.


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

“... 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

"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"

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


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

“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.”
Amyloid plaques in Alzheimer’s Disease – protection against microbial infection?

“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

The association between infectious burden and Parkinson's disease: A case-control study.
Bu XL¹, Wang X¹, Xiang Y¹, Shen LL¹, Wang QH¹, Liu YH¹, Jiao SS¹, Wang YR¹, Cao HY¹, Yi X¹, Liu CH¹, Deng B¹, Yao XQ¹, Xu ZQ¹, Zhou HD¹, Wang YJ².


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

“... 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: 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.

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

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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 on its ability to induce chronic lymphocytic proliferation.
Also found in SLE: Parvovirus B19, CMV, HSV, VZV
Diabetes Type 1: B1 strain of Coxsackie B has antigens similar to those in pancreatic beta cells

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

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¹Department of Microbiology-Faculty of Medical Laboratory Sciences-Alzaeim Alazhari University, Sudan.
²Department of Microbiology-Dentistry & Oral Surgery Collage, Alasmaria Islamic University, Libya.
³Department of Microbiology-School of Medical Laboratory Sciences- SharqElneil College, Sudan.
⁴Department of Microbiology-Alribat University Hospital, Sudan.

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Cytomegalovirus is one of the most common microorganisms that cause opportunistic infection that complicate the clinical care and progress of immunocompromised patients. The virus can cause severe diseases with multiple complications including type I diabetes mellitus. The present study is a case control study aimed at determining cytomegalovirus IgG antibodies positive in children. Sera of eighty one (81) children with diabetic condition were studied against eighty five (85) apparently healthy children. 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

Echovirus 4 and type 1 diabetes mellitus.

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 Type 1 diabetes HLA DR susceptibility genes were also exposed to E4 (15.0%). High frequency of E4 antibodies is significantly associated with Type 1 diabetes (p = 0.03). E4 antibodies are more frequent in diabetic patients with islet cell antibodies (ICA) (39.5%) than in controls (0.01%).

CONCLUSION: 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.
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

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

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


### Sarcoidosis: EBV, CMV, HSV ...

<table>
<thead>
<tr>
<th>Box 1 Suspected Causes of Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Tuberculous</td>
</tr>
<tr>
<td>Nontuberculous(\superscript{\text{a}})</td>
</tr>
<tr>
<td>Cell-wall deficient (L-forms)(\superscript{\text{c}})</td>
</tr>
<tr>
<td>Bacteria</td>
</tr>
<tr>
<td>Propionibacterium acnes(\superscript{\text{c}})</td>
</tr>
<tr>
<td>Tropheryma whippelii</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Fungi</td>
</tr>
<tr>
<td>Cryptococcus spp.</td>
</tr>
<tr>
<td>Endemic fungi</td>
</tr>
<tr>
<td>Viruses</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
</tr>
</tbody>
</table>

*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.

Myasthenia Gravis and EBV

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