

# C3a and C4a in Chronic Lyme Disease

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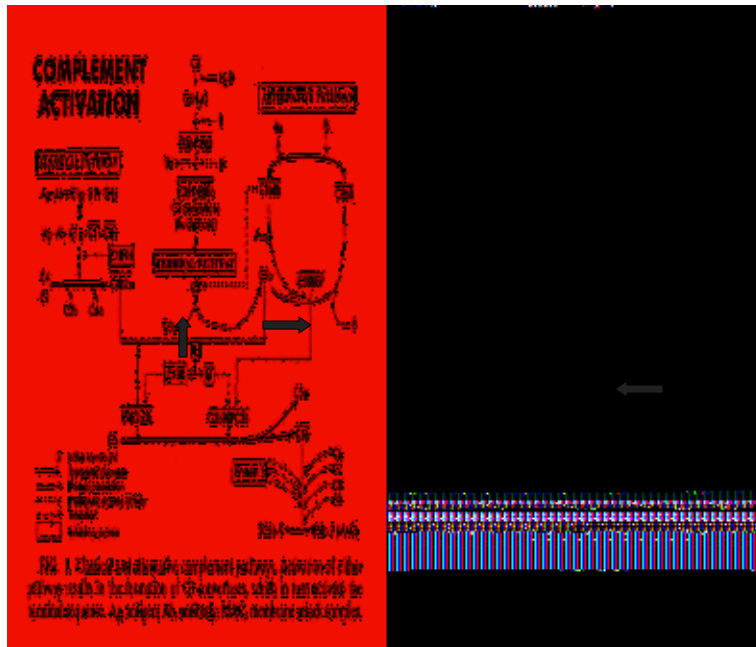


TABLE 2. Products of complement activation

Product and component	Property
<b>Multimolecular complexes</b>	
C1r-C1s-C1Inh	Inactivation product of C1
C3bBbP	Alternative pathway fluid-phase C5 convertase
SC5b-9	Soluble membrane attack complex
<b>Split products</b>	
C4a	Anaphylatoxin, split product of C4
C4d	Inactivated C4b produced by factor I and C4BP
Ba	Fluid-phase activation product of factor B
Bb	Part of alternative pathway C5 convertase
C3a	Anaphylatoxin, split product of C3
iC3b	Inactivated C3b produced by factors I and H
C3c	Split product of C3b or iC3b
C3dg	Split product of C3b or iC3b
C5a	Anaphylatoxin, split product of C5
<b>Components expressing neoantigens</b>	
C4b	Activation product of C4 produced by C1s
C3a, C3a(des Arg)	Anaphylatoxin, split product of C3
iC3b	Inactivated C3b produced by factors I and H
C5a	Anaphylatoxin, split product of C5
C9	Final component of membrane attack complex

## Anaphylatoxins C3a/C4a/C5a

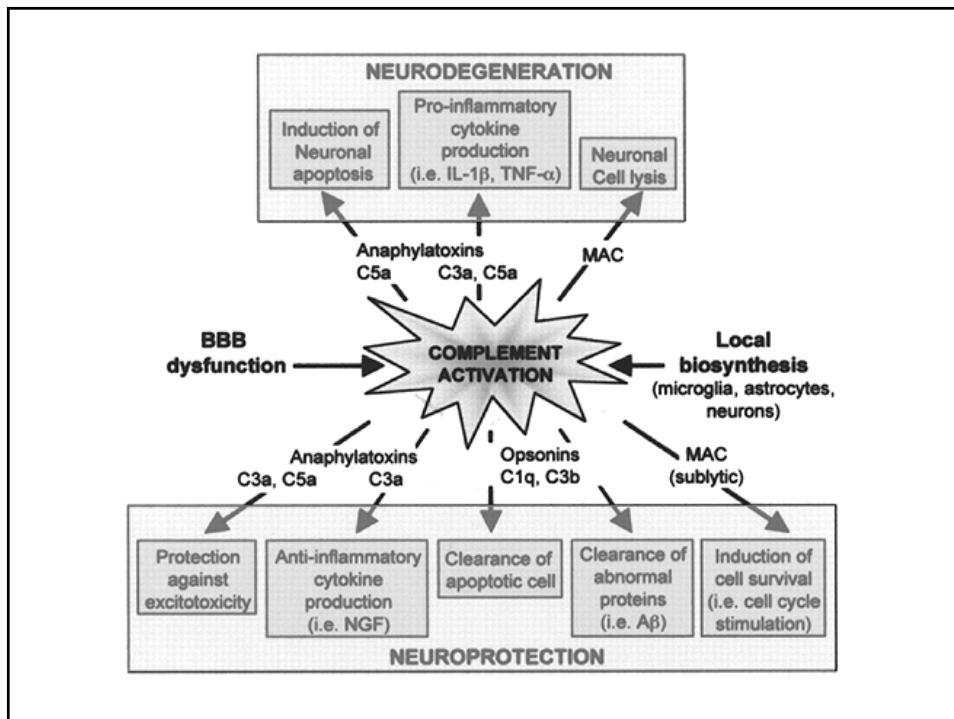
**“The studies derived from these molecules in teleost fish indicate that the basic structure and function of anaphylatoxins and their receptors, have been conserved for more than 300 million years.”**

Sunyer et al. Vet Immunol Immunopathol. 2005;108:77-89.

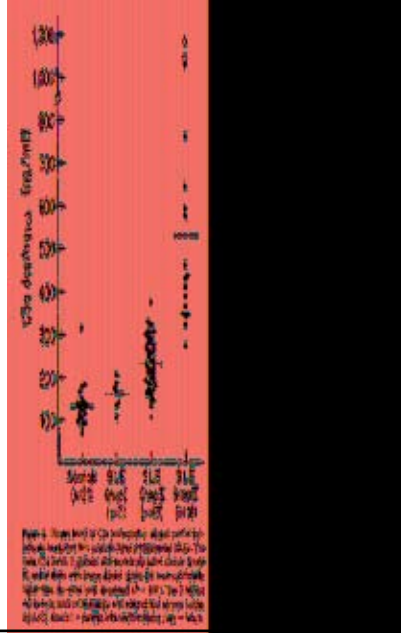
## Complement Activation in the Central Nervous System

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

Van Beek et al. Ann N Y Acad Sci. 2003;992:56-71.

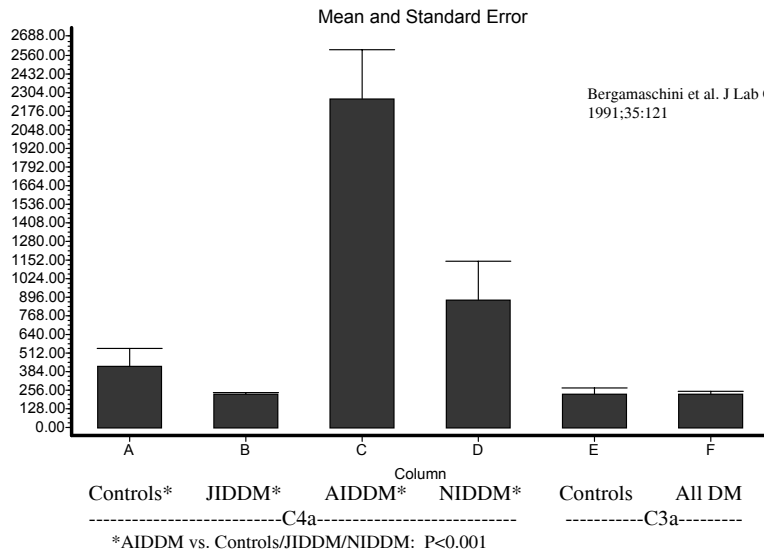


## C3a in Systemic Lupus Erythematosus



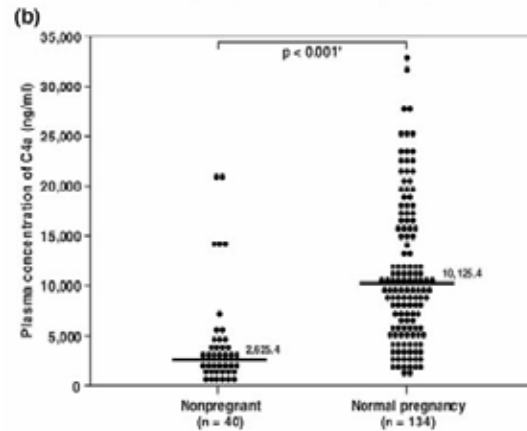
Belmont et al. Arth Rheum 1986;29:1085

## C3a and C4a in Diabetes Mellitus



Bergamaschini et al. J Lab Clin Immunol 1991;35:121

## C4a in Normal Pregnancy



Richani et al. J Matern Fetal Neonatal Med. 2005;17:239-45.



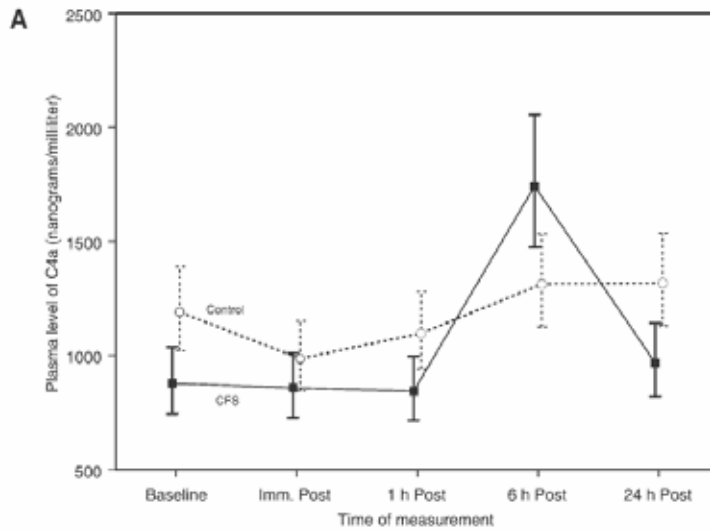
### Complement activation in a model of chronic fatigue syndrome.

Sorensen B, Streim JE, Strand M, Make B, Giclas PC, Flesher M, Jones JF  
Complement activation in a model of chronic fatigue syndrome  
*Journal of Allergy and Clinical Immunology* 2003; 112:397-403.

#### Summary

The symptoms of CFS are similar to those seen in a systemic infection or in an inflammatory disease. Previous studies have attempted to identify alterations in immune function, levels of cytokines, and mediators of inflammation that could contribute to the pathogenesis of CFS. However, the frequency and type of the immune alterations vary from study to study, suggesting a need for a more focused approach. One approach is to observe patients in a situation known to induce an increase in symptoms. One such symptom trigger, also part of the CFS definition, is physical exertion; the other trigger known to reproduce symptoms of CFS is exposure to allergens. Both exercise and allergens also induce a variety of changes in physiologic function mimicking an infectious or inflammatory state.

**“Exercise challenge induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the CFS group ( $P < 0.01$ ), regardless of allergy status....Further research concerning the biology of C4a is necessary to understand its role in the pathophysiology of CFS.”**



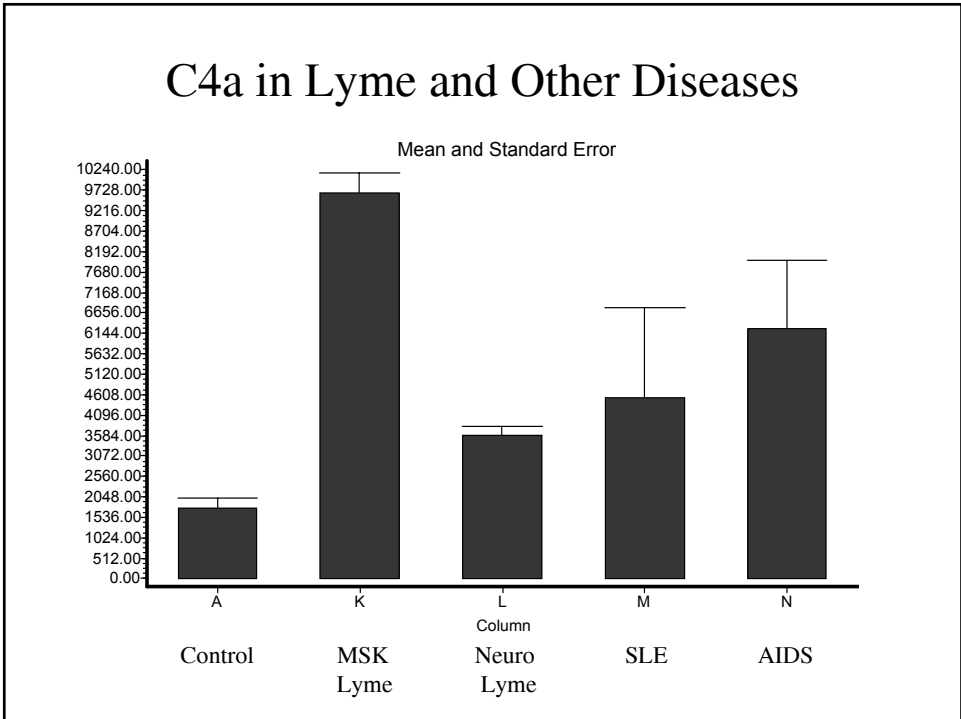
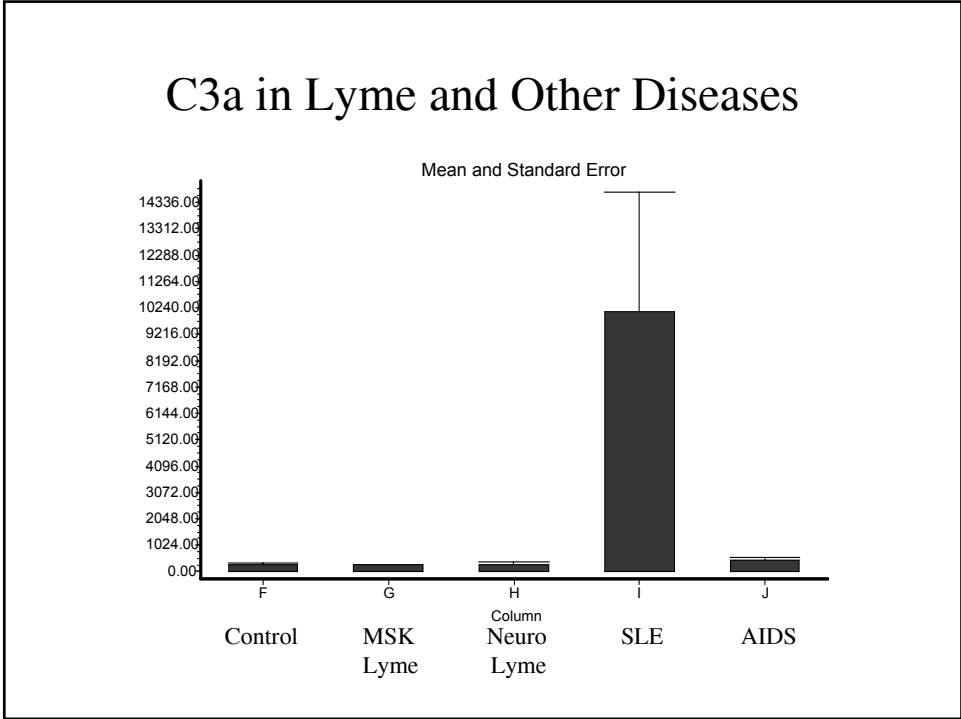
Could C4a be a marker of  
chronic Lyme disease?

## Study Population

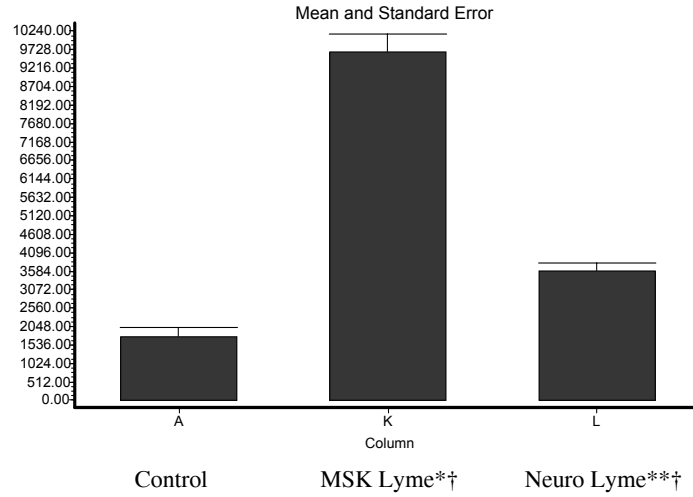
<u>Patient Group</u>	<u>Number</u>
1. Controls	13
2. Chronic Lyme Disease:	311
A. Predominant musculoskeletal symptoms	215
B. Predominant neurologic symptoms	96
3. Systemic Lupus Erythematosus (SLE)	4
4. AIDS	6

## C3a/C4a Assays

- Radioimmunoassay performed by Clinical Immunology Laboratory, National Jewish Medical & Research Center, Denver, CO.
- Subjects tested at baseline and 3-6 months on treatment. Response assessed by symptom score and CD57 natural killer cell level.
- Normal Ranges:
  1. C3a: 0-940 ng/ml
  2. C4a: 0-2830 ng/ml

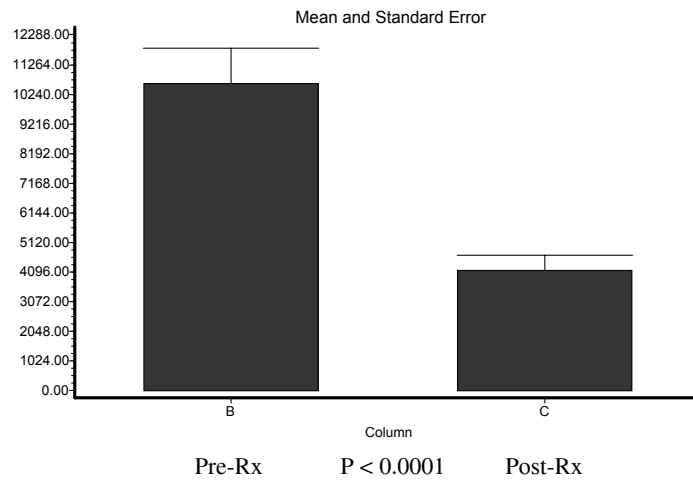


## C4a in Chronic Lyme Disease



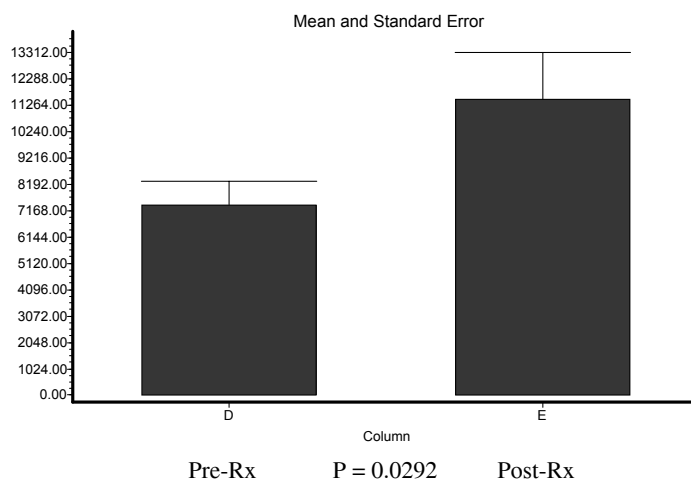
\*P < 0.001 \*\*P < 0.001 vs. Control †P < 0.001 MSK vs. Neuro

## C4a Pre/Post Successful Rx in Lyme Disease

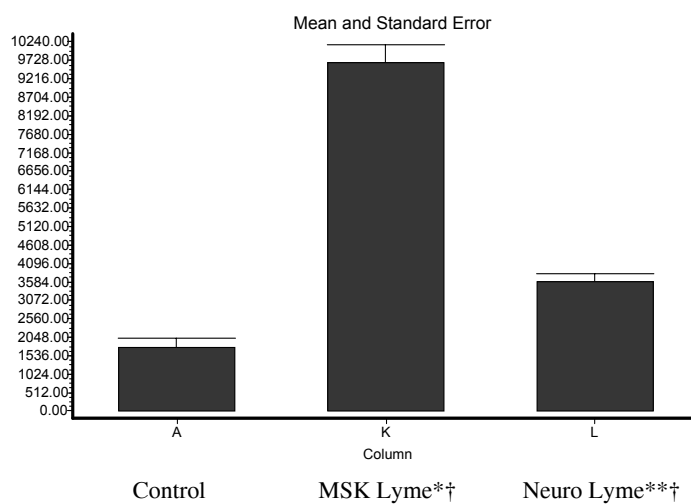


P < 0.0001

## C4a Pre/Post Unsuccessful Rx in Lyme Disease



## C4a in Chronic Lyme Disease



\*P < 0.001 \*\*P < 0.001 vs. Control †P < 0.001 MSK vs. Neuro

## Conclusions

- Increased C4a, but not C3a, appears to be a useful marker for chronic Lyme disease.
- In chronic Lyme disease, C4a levels are higher in patients with predominant musculoskeletal symptoms versus predominant neurologic symptoms.
- Response to treatment in chronic Lyme disease is associated with a decrease in C4a levels.
- The role of increased C4a in chronic Lyme disease merits further study.

## How to Order C3a/C4a

- C3a - LabCorp Code# 840702
- C4a - LabCorp Code# 857334
  
- Directly from National Jewish Medical & Research Center (NJMRC), Denver, CO

## Acknowledgments

- Patricia Giclas, PhD NJMRC
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