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Title: Use of Pioglitazone to Prevent Intensification of Persistent Symptoms Following Cholestyramine Treatment of Patients with Post-Lyme Syndrome

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Abstract Body:
Many patients with Lyme Disease have persistent symptoms following antibiotic therapy. A recent prospective study of 51 Post-Lyme Syndrome (PLS) patients demonstrating a deficit in visual contrast sensitivity (VCS) showed significant reduction of symptoms when treated with cholestyramine (CSM), but 33% of the PLS patients initially experienced worsening of symptoms. Pretreatment with pioglitazone (pio) in 12 PLS patients prevented the intensification seen with CSM use and reduced plasma levels of TNF alpha. A single site, prospective, clinical trial on pio and CSM use in PLS patients was conducted to confirm benefit of CSM therapy in PLS and determine if pretreatment with pio could prevent intensification.
All 114 patients referred to the study had long-standing symptoms and a clinical and/or laboratory diagnosis of Lyme Disease. Patients were first treated with pio, 45mg daily for 10 days; CSM began on day 6 of pio. Symptoms were monitored and sequential VCS testing was performed. CSM was continued until the endpoints of symptom abatement and maximum improvement in VCS scores were reached. No antibiotics or other treatments were administered during the study.
No patients had adverse effects from pio, including hypoglycemia or abnormal LFT. Only 1 patient experienced significant symptom intensification. 89.3% of patients had at least 75% reduction of symptoms, with resolution of symptoms in 32.1%. VCS deficits prior to treatment were better correlated with symptom abatement than all other diagnostic markers.
The results support the hypotheses that: 1) PLS may be a chronic, neurotoxin-mediated illness; 2) antibiotic treatment of Lyme disease should be followed with the pio/CSM protocol in symptomatic patients; 3)VCS is an effective diagnostic tool that can indicate neurotoxicity in PLS patients; 4) TNF release from adipocytes, induced by CSM, may participate in intensification and 5) the benefit of pio in prevention of intensification, possibly by down-regulation of adipocyte TNF, has implications for an additional mechanism of action for pio in treatment of Type II diabetes associated with a pro-inflammatory cytokine response. A double-blinded, placebo-controlled trial will be required to validate these preliminary findings.

Use of pioglitazone to prevent intensification of persistent symptoms following cholestyramine treatment of patients with Post-Lyme Syndrome.

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Introduction. Since the first description of Lyme disease there have been subsets of patients identified with persistent symptoms, refractory to antibiotics. A recent prospective study of 51 Post-Lyme Syndrome (PLS) patients demonstrating a mid-spatial frequency deficit in visual contrast sensitivity (VCS) showed significant reduction of symptoms with use of a cholestyramine (CSM) treatment protocol. The symptoms and VCS deficits in the PLS patients were similar to those demonstrated by patients with other chronic, neurotoxin-mediated illnesses reported previously. Early in the course of CSM treatment, 33% of the 51 PLS patients experienced a significant intensification of symptoms, a phenomenon not seen with different biotoxin exposures. Pretreatment with pioglitazone (pio), a PPAR agonist known to reduce adipocyte production of TNF alpha, in 12 subsequent PLS patients was shown to prevent the intensification associated with CSM use and to reduce plasma levels of TNF alpha. A single site, prospective, clinical trial on pio and CSM use in PLS patients was conducted to confirm benefit of CSM therapy in PLS and determine if pretreatment with pio could prevent intensification. **Methods.** All patients referred to the study had long-standing symptoms following a known tick bite or exposure to areas where others had tick bites, and a clinical and/or laboratory diagnosis of Lyme Disease. Diagnostic parameters used by referring physicians included a history of erythema chronicum migrans (ECM) rash, ELISA assay, and Borrelia burgdorferi Western blot. Patients with a clinical diagnosis of PLS but without a positive serologic test were included at the discretion of the attending physician. 114 patients were included in the study center at Pocomoke, MD. All patients had past antibiotic treatment, but were still symptomatic. All patients were pretreated with pioglitazone (pio), 45mg daily for 10 days. On day 6 of pio, CSM treatment was initiated. An orally administered checklist monitored symptoms, and sequential VCS testing was performed. CSM was continued until the treatment endpoints of maximum symptom abatement and maximum improvement in VCS scores were noted. No antibiotics or other therapeutic interventions were administered during the study. **Results.** No patients had adverse effects from pio, including hypoglycemia or abnormal liver function tests. Only 1 of 112 patients experienced significant symptom intensification, not severe enough to stop treatment. 89.3% of patients had at least 75% reduction of number of symptoms following use of the CSM protocol, with complete resolution of symptoms in 32.1%. VCS deficits prior to treatment and resolution with treatment were better correlated with symptom abatement than all other diagnostic markers. **Conclusion.** The results support the hypotheses that: 1) PLS may be a chronic, neurotoxin-mediated illness; 2) antibiotic treatment of Lyme disease should be followed by adjuvant treatment with the pio and CSM protocol in patients with persistent symptoms; 3) VCS is an effective diagnostic tool that can indicate neurotoxicity in PLS patients; 4) TNF produced by adipocytes may participate in the intensification reaction and 5) the benefit of pio in prevention of intensification, possibly by down-regulation of adipocyte TNF, has implications for an additional mechanism of action for pio in treatment of Type II diabetes associated with a pro-inflammatory cytokine response. These results must be

confirmed in a prospective double-blinded, placebo-controlled clinical trial, with frequent monitoring of TNF levels using validated laboratory protocols.

Pretreatment of patients with Post Lyme Syndrome with pioglitazone before use of cholestyramine prevents intensification: Vision, neurotoxins and cytokines.

Background: A prospective, multisite clinical trial using pioglitazone, an agonist of PPAR gamma, as a pretreatment before giving cholestyramine (CSM) to 250 patients with chronic symptoms and a clinical or laboratory diagnosis of Lyme Disease, refractory to oral and/IV antibiotics, resulted in significant improvement of symptoms in over 92% of patients. A previous study by the authors of 71 patients with Post Lyme Syndrome using cholestyramine alone had shown a significant worsening of symptoms in over 30% of patients, associated with a rise in TNF alpha mRNA and TNF alpha that preceded eventual resolution of their symptoms. Pronounced deficits in visual contrast sensitivity (VCS), not found in asymptomatic controls and not explained by confounding neurotoxicant exposures, resolved with CSM, but not with pioglitazone, coincident with abatement of symptoms. A deficit in capillary perfusion of retina and neural rim of the optic nerve head, documented with the Heidelberg Retinal Flowmeter, also not found in controls or in patients with fatigue due to other causes, resolved with CSM treatment but not with pioglitazone.

Methods: Following informed consent, patients with a history of symptoms refractory to antibiotics following a tick bite or exposure to an area where others had a tick bite, with a history of either an ECM rash, physician diagnosed Lyme Disease or serological evidence of Lyme Disease, were interviewed by a study physician. Symptoms were recorded, physical exam was performed and additional lab testing was done as deemed necessary by the study physician. VCS was recorded. One center, Chico, California, did not require the presence of a deficit in VCS, greatest at the mid-frequencies, for entry into the treatment protocol. The Pocomoke, Md. Center maintained the VCS deficit requirement. Pioglitazone, 45 mg taken once daily for 5 days, together with dietary restriction of amylose and added sucrose, was initiated, followed by CSM, 1 scoop (9 grams), taken four times a day on an empty stomach and pioglitazone for 5 days. Symptoms and VCS scores were recorded. Patients with no evidence of worsening of their symptoms (no intensification) stopped pioglitazone. CSM was continued until VCS deficits and symptoms resolved or until a plateau of no further improvement was noted. Retinal flowmeter measurements were made in some but not all study participants.

Results: No serious intensification reactions occurred in pioglitazone pretreated patients. Patients had an average of 12 symptoms, not related to duration of illness or prior therapy. 92.8% of patients showed a significant reduction of symptoms with complete resolution in 60%. A deficit in VCS occurred in 95% of all patients with symptoms, independent of serological results. Mild intensification was noted in 25% of patients treated with CSM after pioglitazone, with a deficit on VCS in the highest frequencies noted to develop just prior to onset of the intensification, with abatement of the high frequency deficit occurring shortly prior to resolution of intensification. No patients dropped out of the trial due to intensification. Retinal flow measurements showed a marked reduction of capillary perfusion in the retina and neural rim of the optic nerve head. Patients without the VCS deficit had more persistent symptoms than those with the VCS deficit. Patients with coinfection due to Babesia also had more post-treatment

symptoms than those without coinfection. Resolution of the capillary hypoperfusion in retina and optic nerve head matched resolution of the VCS deficit and paralleled the resolution of symptoms. 12-month follow-up has not shown relapse of symptoms in the absence of reexposure.

Conclusion: VCS and HRF measurements, previously shown by the authors to be of benefit as indicators of the effect of neurotoxins on contrast and capillary perfusion respectively, correlated with the presence of elevated levels of pro-inflammatory cytokines, including TNF alpha and IL-1B, are useful adjuncts to the diagnostic approach to Post Lyme Syndrome. The prevention of intensification, mediated by pro-inflammatory cytokines, seen in these patients may be due to the known effect of pioglitazone as an agonist of PPAR gamma which downregulates production of TNF alpha under transcriptional control of cytokine nuclear receptors in adipocytes, but not in macrophages. CSM has been shown to relieve symptoms in patients with exposure to other known biotoxins. The improvement in the study patients with chronic symptoms refractory to antibiotics suggests that the Post Lyme Syndrome is a neurotoxin-mediated illness. Additional study is required to explain the lack of presence of VCS deficit in some study patients and to define the reasons for failure to improve in some of the Lyme-Babesia co-infected patients.

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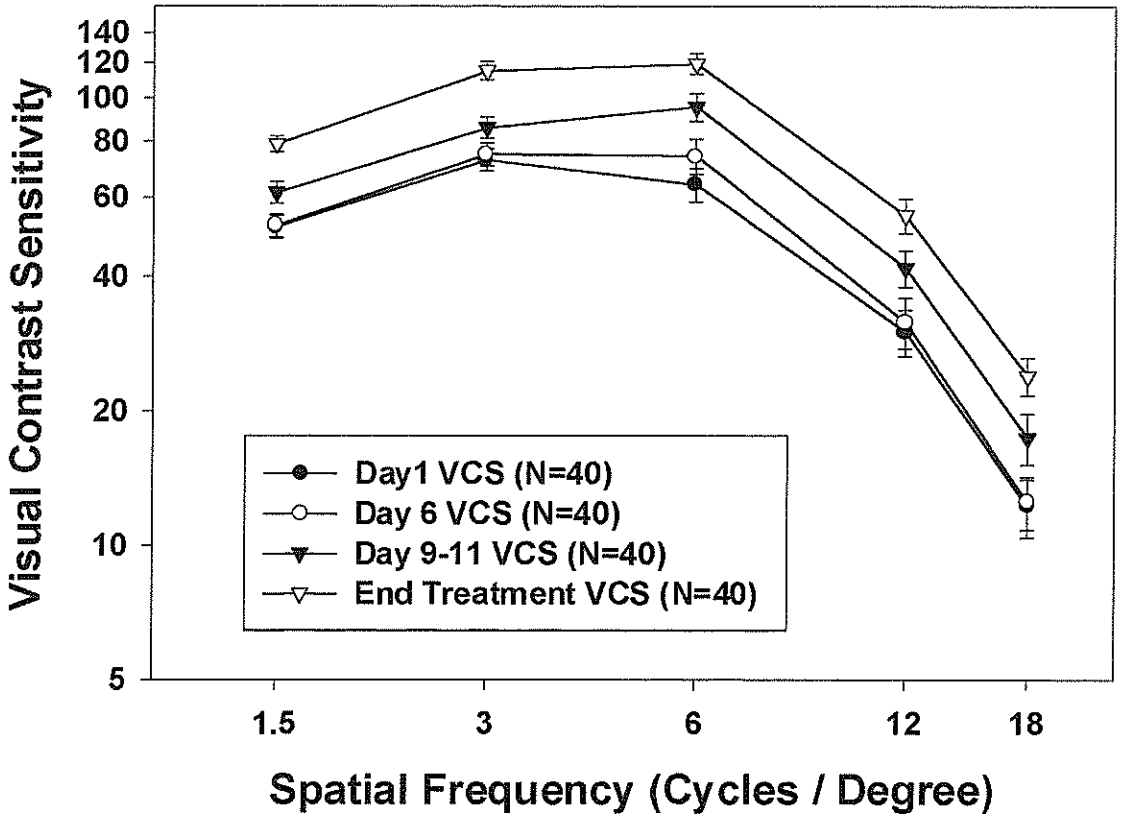
VCS in Post-Lyme: Day 1 (Begin Pio), Day 6 (Pio & Begin CSM), Day 9-11 (Continue Pio & CSM), End Treatment (4-8 Weeks)



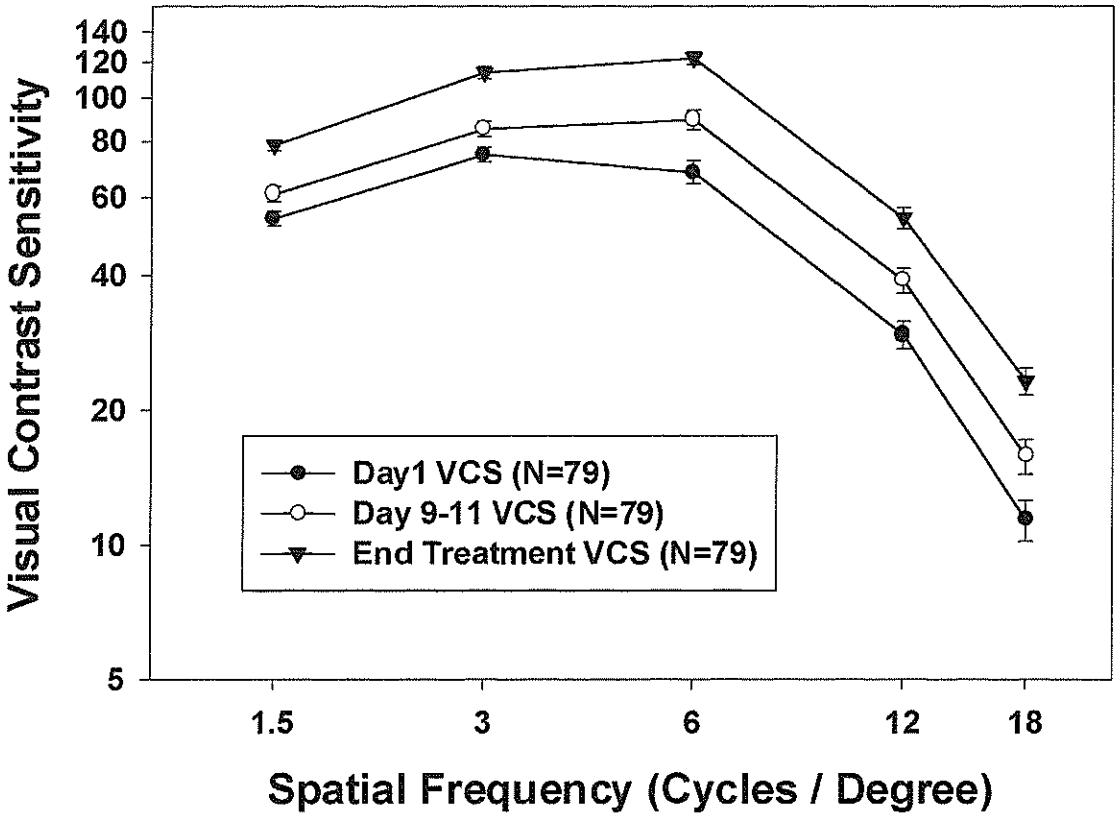
 # Symptoms
Before Rx = 11.3
After Rx = 1.4

Visual Acuity
No Change

VCS
Treatment
F(1,106)=190.36
p<0.001

Treatment x SF
F=(4,103)=33.93
p<0.001

VCS in Post-Lyme: Day 1 (Begin Pio), Day 6 (Pio & Begin CSM) - Not Shown, Day 9-11 (Continue Pio & CSM), End Treatment (4-8 Weeks)



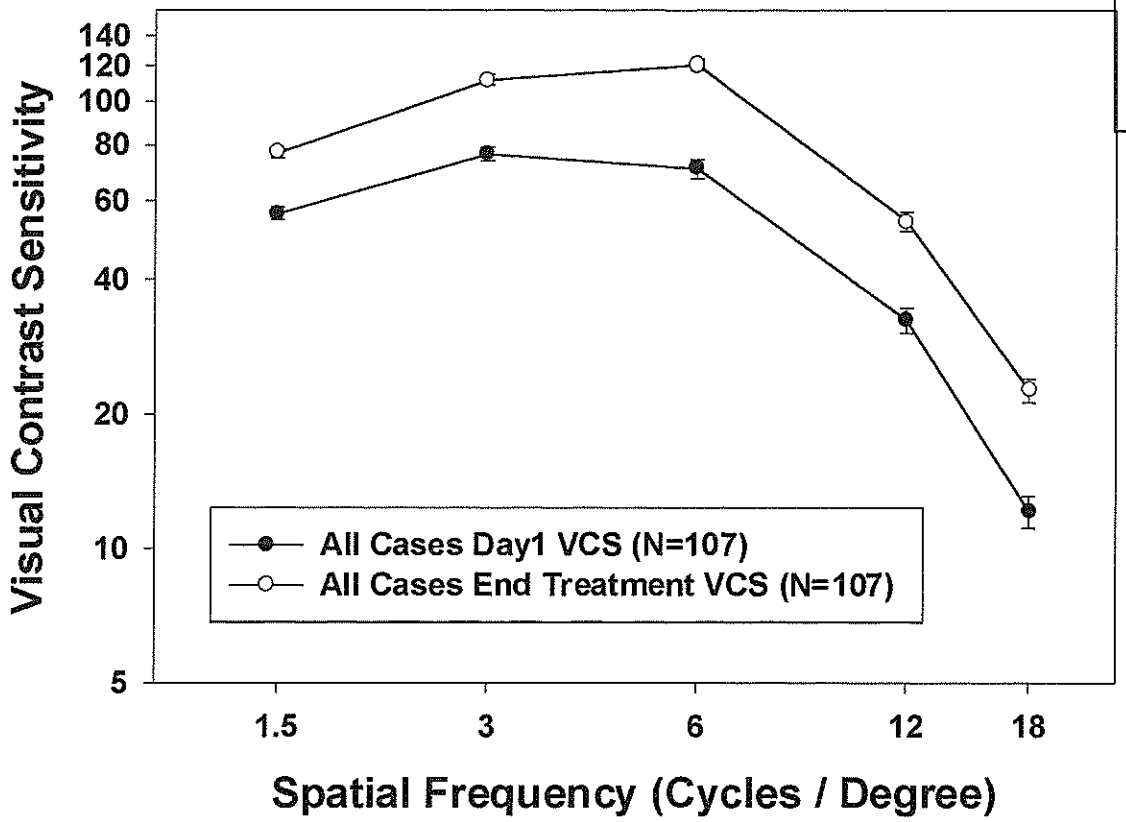
Clinically Significant Symptom Intensification:
Day 9-11 = 2 (2.5%)

Visual Acuity
No Change

VCS (Days 1,9-11)
Treatment
F(1,78)=20.63
p<0.001

Treatment X SF
F(4,75)=5.12
p=0.001

VCS in Post-Lyme: Day 1 (Begin Pio), Day 6 (Pio & Begin CSM) - Not Shown, Day 9-11 (Continue Pio & CSM) - Not Shown, End Treatment (4-8 Weeks)



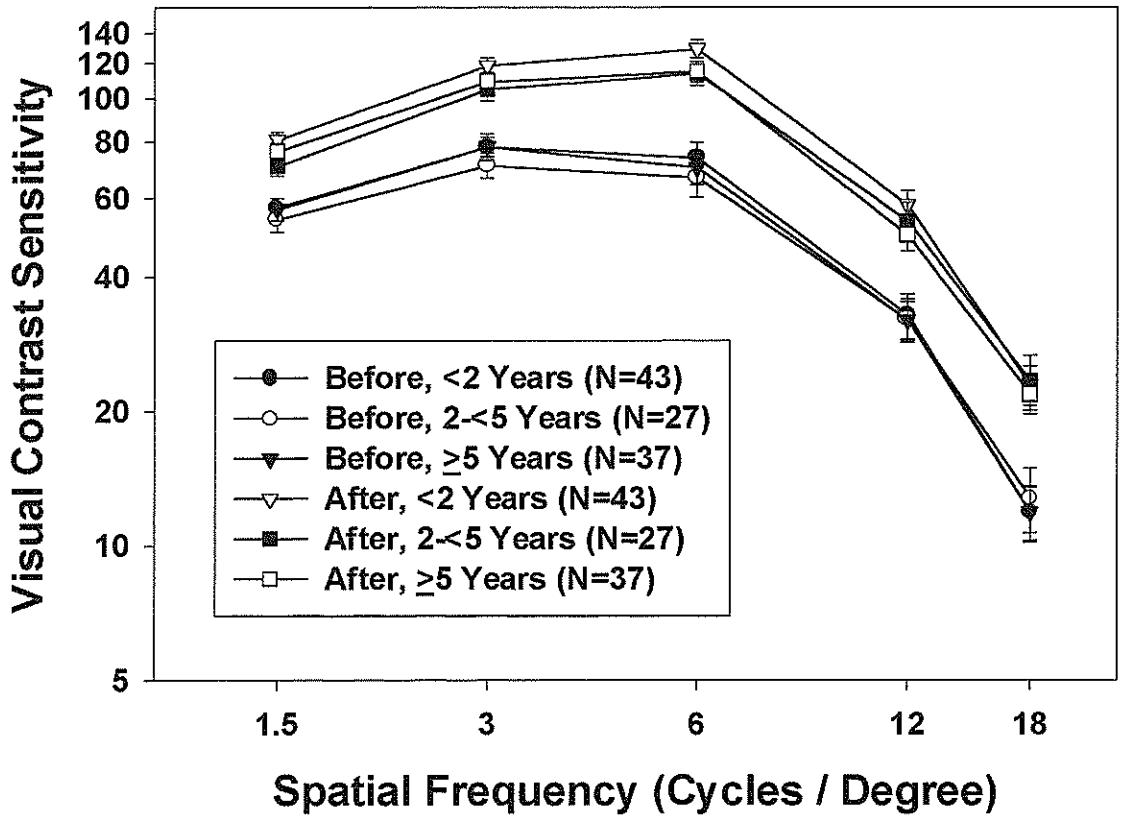
Clinically Significant Symptom Intensification:
Day 6 = 4 (11%)
Day 9-11 = 2 (5%)

Visual Acuity
No Change

VCS (Days 1,6,9-11)
Treatment
$F(2,38)=12.71$
$p<0.001$

Treatment X SF
$F(8,32)=2.35$
$p=0.041$

VCS in Post-Lyme:
Before & After Treatment By Illness Duration - <2, 2-<5 and ≥5 Years



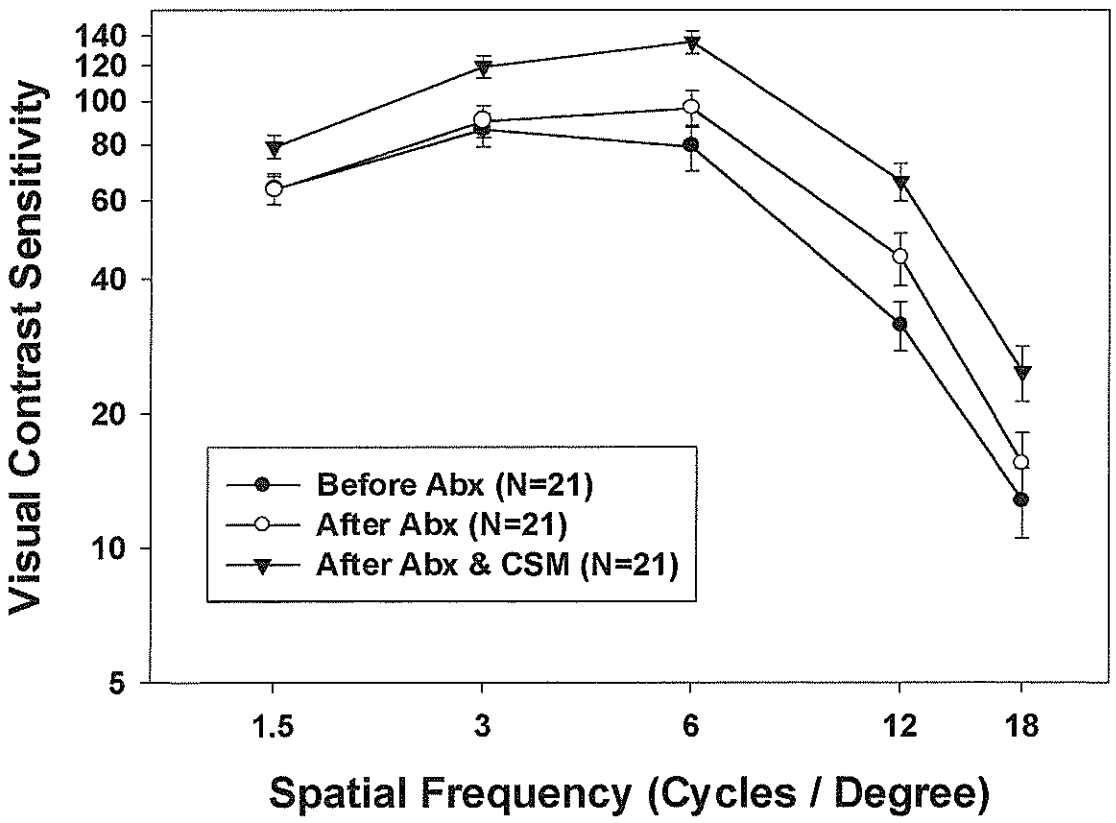
 # Symptoms
Before/After Rx
<2 Yrs = 10.2/0.7
2-<5 Yrs = 11.2/1.5
>5 Yrs = 12.7/2.2

Visual Acuity - No Treatment or Duration Effect

VCS (No Duration or DxT Effect)
Treatment
F(1,104)=179.30
p<0.001

Treatment X SF
F(4,101)=31.97
p<0.001

VCS in Post-Lyme:
Before Antibiotics,
After Antibiotics,
After Antibiotics & CSM



 # Symptoms

Before Abx = 10.3

After Abx = 10.3

After Abx&CSM= 0.7

Visual Acuity

No Change

VCS

Abx Treatment

F(1,20)=2.64

p=0.12

CSM Treatment

F(11,20)=51.91

p<0.001

CSM Trmt X SF

F(4,17)=9.94

p<0.001