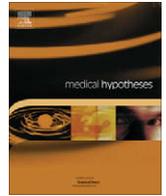


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Clinical trials validate the severity of persistent Lyme disease symptoms

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SUMMARY

Background: Persistent Lyme Disease Symptoms (PLDS) have included fatigue, headaches, poor concentration and memory, lightheadedness, joint pain, and mood disturbances. Evidence-based guidelines committees disagree over the severity of PLDS. The 2004 International Lyme and Associated Diseases Society (ILADS) concluded that PLDS are severe. The 2006 Infectious Disease Society of America (IDSA) guidelines committee concluded that PLDS are nothing more than the “aches and pains of daily living” and an ad hoc International Lyme group concluded that PLDS are “symptoms common in persons who have never had Lyme disease.”

Hypothesis: Clinical trials validate the severity of persistent Lyme disease symptoms.

Evaluation of the Hypothesis: There are 22 standardized instruments used to measure the severity of PLDS among the four published National Institutes of Health (NIH) sponsored double-blind randomized placebo-controlled trials (RCTs).

Validating the hypothesis: All four NIH sponsored RCTs validate the severity of PLDS. PLDS are as severe as symptoms seen in other serious chronic illnesses, and result in a quality of life lower than for the general population as determined by 22 standardized measures of QOL, including fatigue, pain, role function, psychopathology, and cognition. None of the four RCTs support the IDSA hypothesis that PLDS are nothing more than “the aches and pains of daily living” nor the ad hoc International Lyme group conclusion that PLDS are “symptoms common in persons who have never had Lyme disease.”

Implications of the hypothesis: If the QOL of life for these patients is as poor as for patients with other serious chronic diseases, their symptoms need to be addressed by their doctors. Studies differ as to the precise cause of PLDS, the most effective treatments, and whether a cure is possible. But the fact that there is disagreement is not a license for physicians to ignore or turn away patients complaining of PLDS, or to dismiss their symptoms as purely psychosomatic. For physicians, the goal or purpose of treating PLDS should be the same as their purpose in treating other chronic illnesses that result in a poor QOL: vigorous pursuit of a cure, and where a cure proves impossible, amelioration of patients' symptoms and suffering. Even if this hypothesis fails to be apply to more than a fraction of the total Lyme disease population, this still represents a significant number of patients, and these findings could address a neglected aspect of caring for patients with Lyme disease.

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Background

Persistent Lyme Disease symptoms (PLDS) have included fatigue, headaches, poor concentration and memory, lightheadedness, sleep disturbance, joint pain, and mood disturbances. Two retrospective cohorts support the need to assess PLDS. Thirty-four percent of LD patients in a Massachusetts population-based retrospective cohort were symptomatic an average of 6.2 years after treatment [7]. Sixty-two percent of LD patients in a retrospective Westchester cohort were symptomatic an average of 3.2 years after treatment [8]. The cost for individuals with PLDS beyond human suffering can be estimated to be \$16,199 per year for clinically

defined late-stage Lyme disease in Maryland's Eastern Shore [9]. Ninety-five percent of the cost was indirect medical costs, non-medical costs, and productivity losses.

Evidence-based guidelines committees disagree on the severity of PLDS. The 2004 International Lyme and Associated Diseases Society (ILADS) guidelines committee concluded that PLDS are severe [5]. By contrast, the 2006 Infectious Disease Society of America (IDSA) guidelines committee concluded that PLDS are nothing more than “the aches and pains of daily living” [6] and an hoc international Lyme disease group concluded that PLDS are “symptoms common in persons who have never had Lyme disease” [4].

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Hypothesis

Clinical trials validate the severity of persistent Lyme disease symptoms.

Evaluation of the hypothesis

To be plausible, the “severity of PLDS” hypothesis should be measurable with standardized instruments. There were 22 standardized instruments used to measure the severity of PLDS among the four published NIH sponsored double-blind randomized placebo-controlled trial (RCTs) (1–3). Eleven instruments assessed QOL (1, 3), fatigue (2, 3), pain (1, 3), role function (1), and psychopathology (1, 3) of PLDS. Eleven other instruments assessed cognitive function of PLDS (1–3).

Quality of life

The Fallon and two Klempner RCTs assessed QOL using the medical outcomes study (MOS) 36-item short-form general health survey (SF-36) (1, 3). Thirty-six questions assessed the physical component summary (PCS) and mental component summary (MCS) of QOL. The PCS assessed the ability to perform daily physical activities, e. g., self care, walking, climbing stairs, and vigorous activities; degree to which individual performs typical work/daily activities; intensity, duration, and frequency of bodily pain, and limitations in usual activities due to pain; and personal evaluation of general health, including current and prior health and health outlook. The MCS assessed the personal evaluation of energy and tiredness; the ability to develop, maintain, and nurture social relationships, including family, friends and marital functioning; degree to which emotional problems limit work/daily activities; and a person’s emotional, cognitive, and intellectual status.

Fatigue

The Fallon and two Klempner RCTs assessed fatigue using a reliable, well studied, modified version of the self-administered fatigue severity scale, FSS-11 [10].

Fibromyalgia Impact questionnaire

The two Klempner RCTs measured the severity of PLDS using a modified version of the fibromyalgia impact questionnaire (FIQ). The FIQ “measures difficulties with activities of daily living and symptoms of pain, fatigue, morning tiredness, stiffness, job difficulty, depression, and anxiety along with amount of work missed and overall well-being during the past week” [11].

Ability to perform usual activities

The two Klempner RCTs measured the ability to participate in daily activities using the MOS for role functioning. The role functioning scale measured limitations in daily activities including having to take frequent rests and the need for special assistance [12].

Pain

The Fallon RCT measured the McGill pain questionnaire-short-form (SF-MPQ) [13]. The SF-MPQ uses word descriptors and an intensity scale to generate a score. The words include the sensory qualities of the pain (e.g., throbbing, sharp, stabbing), the affects of the pain (e.g., sickening, blinding, grueling), the overall experience of the pain (e.g., annoying, intense, unbearable), and miscellaneous characteristics of the pain (e.g., radiating, piercing, nagging).

The SF-MPQ has been used for pain assessment in patients with arthritis [12]. The Fallon RCT also measured pain using a visual analogue scale (VAS) consisting of a line 10 cm in length, with end points labeled no pain to severe pain. The patient places a mark on the line corresponding to the intensity of the pain. The two Klempner RCTs assessed the severity of pain using the MOS. “The effect of pain was measured based on its impact on mood, walking ability, sleep, normal work, recreational activity, and life enjoyment using a 5-point Likert-type scale anchored to the frequency of symptoms” [12].

Psychological measures

The Fallon RCT assessed three psychopathology measures. The Beck Depression Inventory (BDI) is an estimate of the severity of depression [14]. The zung anxiety scale [15] is a measure of anxiety. The SCL-90 GSI is a self-reported measure of psychological distress. The SCL-90 GSI is a eight dimension measure: anxiety, agoraphobia, depression, somatic symptoms, distrust and interpersonal sensitivity, anger hostility as well as sleeping disorders [16].

Cognitive function

The Krupp RCT measured the severity of impairment of cognition using the alpha-arithmetic (A–A) Test, a reaction time task. The A–A test was considered to be a sensitive measure of cognitive impairment. Patients with Lyme disease demonstrated slower performances (i.e., greater impairment) on the A–A Test compared to healthy controls in prior studies [17]. The two Klempner RCTs assessed the severity of cognition using an MOS scale which measures problems with reasoning, concentration, confusion, forgetfulness, maintaining attention, and slowed thinking. The Fallon RCT assessed cognition using individual scales and an index based on the following six domains: “motor function (finger tapping, simple reaction time, choice reaction time), psychomotor function (Trail Making A&B; Digit Symbol), attention (Continuous Performance Test, Stroop task), memory (Buschke Selective Reminding Test [verbal memory]; Benton Visual Retention Test [visual memory]), working memory (A, Not B Logical Reasoning Test; N-Back Test), and verbal fluency (Controlled Oral Word Association Test and Category Fluency Test)” [3].

Findings from standardized testing

Quality of life

The SF-36 measure of PCS was 37.1, 33, and 35.8 for the Fallon and two Klempner RCTs respectively. For comparison, the PCS for common chronic conditions are as follows: diabetes (42), heart disease (39), sciatica (46), cancer not skin-related (41), depression (45), osteoarthritis (39), and rheumatoid arthritis (42) [18]. The mean PCS score for the general population of the United States and for the Fallon RCT is 50 and 55.9, respectively.

The SF-36 measure of MCS was 39.2, 43.4, and 46.7 for the Fallon and two Klempner RCTs respectively. For comparison, the MCS for common chronic conditions are as follows: diabetes (48), heart disease (49), sciatica (48), cancer not skin-related (49), depression (37), osteoarthritis (49), and rheumatoid arthritis (48) [18]. The mean MSC score for the general population of the United States and for the Fallon RCT is 50 and 56.2, respectively.

Fatigue

The modified version of the self-administered Fatigue Severity Scale, FSS-11 was 5.5 and 5.2 for the Krupp and Fallon RCTs respec-

tively. Severe fatigue has been defined as an elevated score (≥ 4.0) on the FSS-11 [2]. The means score for the FSS-11 was 2.1 for controls in the Fallon RCT [3].

Fibromyalgia Impact questionnaire

The fibromyalgia impact questionnaire was 47.9 for the two Klemmner RCTs. The average score for the general population is 14 (1), whereas the average fibromyalgia patient scores about 50 and severely afflicted patients are usually 70-plus [19].

Ability to perform usual activities

The role functioning scale using MOS was 53.5 and 56.0 for the two Klemmner RCTs. The role functioning was 44.5 and 12 for chronic tension-type headaches and the general population respectively [20].

Pain

The SF-MPQ measure of pain (13) was 11.6 in the Fallon RCT compared to 1.1 for controls. The VAS measure of pain was 5.2 compared to 0.1 for controls. The MOS measure of pain was 49.4 and 63.0 for the two Klemmner RCTs. The pain was 54.3 and 13.5

for chronic tension-type headaches and controls respectively [20].

Psychological measures

All three psychopathology measures for Lyme disease patients in the Fallon RCT were worse than controls. The BDI of 12.8 for patients with PLDS was worse than the average score of 1.9 for controls. The zung anxiety scale for PLDS of 49.6 showed a higher level of anxiety among Lyme patients than the scores for controls of 32.9. The SCL-90 GSI measure of psychological distress for PLDS of 63.9 was worse than the scores for controls of 42.6.

Cognitive function

The nine measures of cognitive function in the Fallon RCT were significantly worse than controls. The cognitive measure of MOS of 54.2 and 53.3 for the two Klemmner RCTs was also significantly less than controls. The alpha-arithmetical (A-A) Test measure of cognitive function in the Krupp RCT of 4.1 was only mildly worse than healthy controls and less than anticipated from other Lyme disease populations [17].

Table 1
Severity of persistent Lyme disease symptoms (PLDS) for four NIH sponsored RCTs.

Study	Year	Size	Patient population	Primary outcome variable	Severity of PLDS	
					Cases	Controls
Klemmner (1)	2001	78	Seropositive LD with persistent symptoms in Northeast (NE) US	SF-36 quality of life (QOL), mean (SD)		
				PCS	33.1 (9.9)	
				MCS	43.4 (11.6)	
				Medical outcome study (MOS), mean (SD)		
				Pain	49.9 (24.3)	
				Cognition	54.2 (21.5)	
				Role functioning	53.5 (33.4)	
				Fibromyalgia impact questionnaire – FIQ, mean (SD)	58.4 (19.7)	
				Psychopathology measure, mean (SD)	11.2 (7.1)	
				Depression (BDI)		
Klemmner (1)	2001	51	Seronegative LD with persistent symptoms in NE US	SF-36 QOL, mean (SD)		
				PCS	35.8 (8.6)	
				MCS	46.7 (9.7)	
				MOS score, mean (SD)		
				Pain	63.0 (21.6)	
				Cognition	53.3 (20.0)	
				Role functioning	56.0 (32.9)	
				Fibromyalgia impact questionnaire - FIQ, mean (SD)	47.9 (15.2)	12.9 (7.2)
				Psychopathology measure, mean (SD)		
				Depression (BDI)		
Krupp (2)	2003	55	LD with disabling fatigue in NE US	Fatigue, mean (SD)	5.7 (1.4)	
				Cognitive function, mean (SD)	4.1 (1.7)	
Fallon (3)	2007	37	LD with cognitive dysfunction NE US	Fatigue,% (SD)	5.2 (1.5)	2.1 (0.5)
				Neurocognitive results mean, (SD)		
				Motor	-0.23 (1.34)	0.58 (0.63)
				Psychomotor	-0.21 (0.75)	0.98 (0.75)
				Attention	-0.12 (0.76)	0.35 (0.85)
				Memory total	-0.75 (1.07)	0.56 (0.43)
				Buschke	-1.13 (1.33)	0.38 (0.76)
				Benton	-0.36 (1.21)	0.73 (0.46)
				Workin memory	-0.92 (1.09)	0.34 (0.69)
				Fluency	-0.73 (0.94)	0.48 (0.66)
				Index	-0.49 (0.63)	0.55 (0.40)
				SF-36 QOL, mean (SD)		
				Physical component summary (PCS)	37.1 (8.6)	55.9 (3.6)
				Mental component summary (MCS)	39.2 (11.6)	56.2 (2.9)
				Pain, mean (SD)		
				McGill	11.6 (7.8)	1.1 (2.5)
				Visual analogue scale	5.2 (3.1)	0.1 (0.2)
				Psychopathology measures, mean (SD)		
				Depression	12.8 (8.6)	1.9 (2.4)
				Anxiety (zung index)	49.6 (11.6)	32.9 (6.7)
				Global (GSI of SCL-90)	63.5 (11.5)	42.6 (7.2)

Validating the hypothesis

All four NIH sponsored RCTs validate the severity of PLDS Table 1 [5]. PLDS are as severe as symptoms seen in other serious chronic illnesses and result in a QOL lower than that of the general population as determined by 22 standardized measures (1, 3), fatigue (2, 3), pain (1, 3), role function (1), psychopathology (1, 3), and cognition [1–3]. None of the four RCTs support the IDSA hypothesis that PLDS are nothing more than “the aches and pains of daily living” (6) nor the ad hoc International Lyme group conclusion that PLDS are “symptoms common in persons who have never had Lyme disease” [4].

Implications of the hypothesis

If the QOL of life for these patients is as poor as for patients with other serious chronic diseases, their symptoms need to be addressed by their doctors. Studies differ as to the precise cause of PLDS, the most effective treatments, and whether a cure is possible. But the fact that there is disagreement is not a license for physicians to ignore or turn away patients complaining of PLDS, or to dismiss their symptoms as purely psychosomatic. For physicians, the goal or purpose of treating PLDS should be the same as their purpose in treating other chronic illnesses that result in a poor QOL: vigorous pursuit of a cure, and where a cure proves impossible, amelioration of patients' symptoms and suffering. Even if this hypothesis fails to be apply to more than a fraction of the total Lyme disease population, this still represents a significant number of patients, and these findings could address a neglected aspect of caring for patients with Lyme disease.

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