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Fatigue in Patients with Erythema Migrans

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Abstract

Background—Fatigue is a common symptom in patients with Lyme disease.

Objective—The purpose of this study was to characterize fatigue in untreated adult patients presenting with erythema migrans. Selected variables were assessed to determine if any correlated with the presence or severity of fatigue.

Methods—Fatigue was assessed on the day of the evaluation by a visual analogue scale (VAS), over the past 14 days by the 11-item fatigue severity scale (FSS-11) and over the past 28 days based on a question from the 36-item Short Form General Health Survey version 2.

Results—51 patients with erythema migrans whose mean age was 49.8 years, and 33 (64.7%) of whom were male, were evaluated in this study. The three measures of fatigue were positively correlated with one another ($p \leq 0.01$). 26 (51%) had fatigue based on a VAS score above 0. 10 (19.6%) had severe fatigue based on an FSS-11 score of ≥ 4. The strongest correlate for higher fatigue scores was having a greater number of symptoms in addition to fatigue.

Conclusion—Based on the FSS-11 assessment tool, approximately 20% of early Lyme patients have severe fatigue. Having a high total number of symptoms was associated with both the presence and severity of fatigue. Since prior studies have demonstrated the presence of elevated levels of pro-inflammatory cytokines and other molecules in the serum of highly symptomatic

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patients with erythema migrans, the symptom of fatigue in early Lyme disease may be a component of what has been referred to as the acute sickness response.

Keywords

Lyme disease; *Borrelia burgdorferi*; Fatigue; Acute sickness response

Lyme disease is the most common tick-borne infection in North America. Recent estimates suggest that approximately 300,000 cases occur annually in the United States [1,2]. At least 70-80% of patients with Lyme disease in the United States present with the objective skin manifestation, erythema migrans [3]. Approximately 65% of patients with erythema migrans in the United States have additional non-specific complaints such as fatigue, musculoskeletal pains, headaches, and others [4]. Fatigue is a common symptom in patients with both early and late manifestations of Lyme disease, as well as in patients with post-treatment Lyme disease symptoms (PTLDS) [4-9]. Studies of patients with PTLDS have often employed both an 11-item Fatigue Severity Scale (FSS-11) and a visual analogue scale (VAS) to quantitate the level of fatigue [6-8]. A score of ≥ 4 is regarded as severe fatigue on the FSS-11 [6]. However, the FSS-11 has not been used in patients with untreated erythema migrans and, thus, it is unknown what proportion of early Lyme disease patients have severe fatigue based on this assessment tool.

The purpose of this study was to evaluate the results of the FSS-11 and other measures of fatigue severity in adult patients with untreated early Lyme disease presenting with erythema migrans and to determine whether certain clinical or demographic factors in such patients correlate with fatigue severity.

Methods

Adult patients with Lyme disease were enrolled between 2011 and 2015 in a prospective study to assess outcomes. Exclusion criteria included: a history of Lyme disease within 12 months, or on-going symptoms from a more remote bout of Lyme disease; pregnancy or being post-partum; an immunocompromising condition; having a diagnosis of fibromyalgia, chronic fatigue syndrome or traumatic brain injury; any prolonged history of undiagnosed or unexplained somatic complaints; and any underlying disease or condition that might interfere with an evaluation of outcome.

The focus of this analysis was specifically on the subset of enrolled subjects with untreated erythema migrans, who had no evidence of a concomitant objective extracutaneous manifestation of Lyme disease. All patients fulfilled the Infectious Diseases Society of America criteria for erythema migrans [10].

Subjects underwent a systematic evaluation for the presence and severity of fatigue prior to antibiotic treatment. The study was conducted at the Lyme Disease Diagnostic Center at New York Medical College and was approved by the institutional review board at New York Medical College.

The level and presence of fatigue was evaluated by three different measures:

1. The FSS-11, which is an 11-item self-administered questionnaire about the subject's experience with fatigue over the prior two weeks, with each item scored on a scale of 1 to 7 (7 being most severe).
2. An 8 cm VAS was used to quantitate the level of fatigue that the subject was experiencing on the day of study entry. A score of 0 indicated that fatigue was not present and a score of 8 indicated that the fatigue was extreme/could not be worse. Subjects with positive scores on the VAS were questioned about the duration of fatigue and whether there was another possible explanation for this symptom. One subject with a positive VAS score was not included in this study because fatigue was attributed to a cause other than Lyme disease.
3. The third measure, arbitrarily called the 28 day fatigue scale (28d-FS), was based on a self-administered question from the 36-item Short Form General Health Survey version 2 (SF-36v2) that inquired about how much of the time during the past four weeks the subject felt tired. A score of 0 indicated “none of the time,” 1 indicated “a little of the time,” 2 indicated “some of the time,” and 3 indicated “most of the time,” and a score of 4 indicated “all of the time.”

Other assessments

At the baseline visit, demographic and clinical data were collected, including data on 11 other symptoms in addition to fatigue, such as headache, joint pain, muscle pain, cognitive complaints and others, as described elsewhere [9]. Serologic testing was performed using the C6 Lyme ELISA kit (Immunetics, Inc., Boston, Massachusetts) according to the manufacturer's recommendations. In addition, patients were evaluated for co-infections with *Anaplasma phagocytophilum* and *Babesia microti* by serology (based on a 4-fold rise in titer between acute and convalescent serum samples on testing performed by Focus Diagnostics, Inc., Cypress, California) and in selected cases with highly suggestive clinical features, such as new onset fever while on antibiotic treatment for erythema migrans, by a blood smear or polymerase chain reaction, as described elsewhere [11,12].

Statistical methods

Continuous variables were described using means and standard deviations; categorical variables were described with frequencies and percentages. For univariable comparisons, t-tests assuming unequal variances were used for continuous outcomes. For categorical variables, Fisher's exact test was used. Correlations between symptom and fatigue scales were analyzed using Spearman's correlation (r_s). To examine the agreement between symptom and fatigue scales dichotomized at specific cutpoints, a GEE analysis was performed to account for the within-subject correlations among scales. Because of multiple comparisons, a p value of < 0.01 was considered to be significant.

Results

Fifty-one adult patients with untreated erythema migrans were evaluated in this study. The mean age was 49.8 years (range, 20-86 years) and 33 (64.7%) were male (Table 1). Twenty-one (41.2%) had multiple erythema migrans skin lesions. The mean duration ± SD of the erythema migrans skin lesion was 7.88 ± 5.51 days (median 7 days, range 1-22 days) (patients who presented on the same day as the skin lesion was discovered were regarded as having a duration of 1 day in this analysis).

All three measures of fatigue were directly and significantly correlated (Table 2) (28d-FS vs. FSS-11: $r_s = 0.50$, $p = 0.009$; VAS vs. FSS-11: $r_s = 0.66$, $p < 0.001$; VAS vs. 28d-FS: $r_s = 0.48$, $p = 01.$). When the comparison of fatigue measures was restricted to the 26 subjects (51.0%; 95%CI: 36.6%, 65.2%) with a VAS score of > 0, the correlations all remained significant ($p \leq 0.01$). However, when the sample was restricted to the 10 subjects with an FSS-11 score of ≥ 4, there was no significant correlation among the three measures of fatigue (28d-FS vs. FSS-11: $r_s = 0.07$, $p = 0.85$; VAS vs. FSS-11: $r_s = 0.13$, $p = 0.71$; VAS vs. 28d-FS: $r_s = 0.15$, $p = 0.68$).

Not all of the FSS-11 scores of ≥ 4 correlated with high VAS scores. Although 6 of the 10 subjects with an FSS-11 of ≥ 4 had a VAS score that also exceeded 4, 4 subjects reported lower scores including 1 subject with a score of 0, a second subject with a score of 0.6 and 2 with scores of 3.8. In contrast, there seemed to be greater consistency between high scores on the VAS and higher FSS-11 scores. Of the 8 subjects whose level of fatigue equaled or exceeded 5 on the VAS (representing 15.7% of the 51 subjects enrolled and 30.8% of the 26 with VAS scores above 0), the FSS-11 score was ≥ 4 for 6 and the other 2 had scores close to 4, of 3.45 and 3.27 respectively. Some discrepancies in scores are not unexpected, since the FSS-11 evaluates fatigue over 14 days, whereas the VAS used in this study inquired about fatigue experienced only on the day of study entry.

Having a higher number of symptoms (inclusive of the symptom of fatigue itself) was associated with significantly greater fatigue scores on all 3 scales (Table 3) ($p<0.0001$). Other characteristics (Tables 3 and 4), such as younger age, having multiple erythema migrans skin lesions and seroreactivity at enrollment, were associated with at least a trend toward higher levels of fatigue (for seroreactivity and for the C6 ELISA value, this was found only for the FSS-11). Gender, body mass index (BMI), and size and duration of the erythema migrans skin lesion did not correlate with fatigue severity.

Of particular interest are the associations and predisposing factors for severe fatigue. A comparison of the 10 (19.6%) (95% CI = 9.8%, 33.1%) subjects with severe fatigue based on a score of at least 4.0 on the FSS-11 with the 41 other subjects showed no significant differences in age, sex, BMI, presence of multiple erythema migrans skin lesions, duration of erythema migrans, area of the largest skin lesion, frequency of C6 ELISA reactivity, C6 ELISA value, or the presence of a co-infection (all p values > 0.25) (Table 5). Severe fatigue based on an FSS-11 score of ≥ 4 did, however, directly correlate with the number of symptoms the subjects had at the time of the visit (those with an FSS-11 ≥ 4 had a mean ±

SD of 7.5 ± 3.06 symptoms versus 2.24 ± 2.58 symptoms for those with an FSS-11 score of < 4, $p < 0.001$).

A comparison of the 26 subjects with a VAS score above 0 with the 25 whose score was 0 also found no significant differences in any of the parameters listed in Table 5 (data not shown), except for the total number of symptoms (mean ± SD number of symptoms in those subjects with a VAS score of > 0 was 5.38 ± 3.32 versus 1.08 ± 1.58 in those with a VAS score of 0, $p < 0.001$). There was a trend for subjects to be younger who had VAS scores of > 0 (mean ± age of subjects with a VAS score > 0 was 46.3 ± 13.7 years versus 53.4 ± 16.8 years for those with a VAS score of 0, $p = 0.10$).

A limitation of the 28d-FS is that it potentially captures any event causing fatigue over a 4 week period and thus would seem to be more likely to generate a larger number of positive responses with some of these unrelated to early Lyme disease. In this study 44 (86.3%) of the 51 subjects had a 28d-FS score of >0 compared with 36 (70.6%) who had an FSS-11 score of >1 and with 26 (51.0%) who had a VAS score of >0 (28d-FS vs. FSS-11: $p = 0.02$; 28d-FS vs. VAS: $p < 0.001$; FSS-11 vs. VAS: $p = 0.005$). The significance of the overall comparison was $p < 0.0001$ (Figure 1).

The duration of fatigue was assessed only for the 26 subjects whose VAS score was > 0; the mean ± duration was 8.08 ± 7.79 days (median = 5.5, range = 1-36) (the mean duration of the erythema migrans skin lesion for this subgroup was very similar at 7.92 ± 5.29 days). There was a trend toward greater fatigue severity in subjects with longer durations of fatigue ($r_s = 0.46$, $p = 0.02$ for the FSS-11; $r_s = 0.39$, $p = 0.053$ for the VAS; and $r_s = 0.50$, $p = 0.011$ for the 28d-FS). However, the small sample size limited more detailed analyses.

Discussion

Fifty-one adult patients with erythema migrans were assessed by three different measures of fatigue. An 8 cm VAS assessed the presence and severity of fatigue on the day of the visit. The FSS-11 assessed the severity of fatigue over the prior 14-days. What we have termed the “28d-FS” determined the frequency that fatigue was experienced over a 28-day time frame. Based on a positive score on the VAS, 26 (50.1%) had fatigue on the day of study entry. Based on the FSS-11, 10 (19.6%) of the enrolled subjects had severe fatigue. Severe fatigue by this criterion was significantly associated with having more total symptoms ($p<0.001$), but was not associated with age, gender, BMI, having multiple erythema migrans skin lesions, the duration of the erythema migrans skin lesion at the time of evaluation, the area of the largest erythema migrans skin lesion, seropositivity by the C6 ELISA, or the presence of a co-infection.

All of the assessment tools had certain limitations. A limitation of the FSS-11 is the difficulty that subjects may have had in filling out this form if they were not experiencing fatigue at all. For example, one of the questions on the FSS-11 asks to what extent you agree with the statement that “fatigue interferes with carrying out certain duties and responsibilities” which could be interpreted as true even if you do not have fatigue when the questionnaire was administered. This assessment tool was intended to quantitate the level of

fatigue in subjects who actually had this symptom. A possible illustrative example of an inaccurate FSS-11 score is that of the seven subjects who had a score of 0 on both the VAS and the 28d-FS, one, nevertheless, had an FSS-11 score of 2.09.

The 28d-FS also appeared to over-estimate the frequency of fatigue due to Lyme disease because it assessed a much longer time period than is typical for early Lyme disease patients prior to consulting with a health care provider. The VAS tool only asked about fatigue on the day of the evaluation and thus some patients with fatigue from Lyme disease on preceding days might have been missed based on this measure of fatigue.

There was a trend toward greater levels of fatigue based on all 3 fatigue scales in patients with disseminated Lyme disease as defined by the presence of multiple erythema migrans skin lesions. However, neither the presence of fatigue by the VAS, nor a high level of fatigue severity based on an FSS-11score of ≥4 was associated with disseminated *B. burgdorferi* infection. This finding is consistent with a previous study of 104 patients with culture-confirmed erythema migrans that failed to show that fatigue was significantly more common among patients infected with the subgroup of borrelial strains most often associated with hematogenous dissemination, compared with patients who were infected with other strains (based on a ribosomal spacer typing system that differentiates United States strains of *B. burgdorferi* into 3 distinct subsets) [13].

In the present study, the presence of fatigue by the VAS and severe fatigue based on the FSS-11 were both strongly associated with having a greater number of total symptoms, suggesting that fatigue is a component of what is referred to for other infectious diseases as the “acute sickness response,” which appears to be caused by the presence of pro-inflammatory cytokines and other acute phase proteins [14,15]. Prior studies in the United States of patients with erythema migrans have found evidence for increased serum levels of interferon (IFN)-gamma, interleukin-6 (IL-6), CXCL9 and/or CXCL10, depending on the particular study, in more symptomatic patients [16-18]. Higher serum levels of certain cytokines and chemokines were correlated with the presence of a particular single nucleotide polymorphism (SNP) in the gene encoding Toll-like receptor 1 [17]. Patients with this SNP who were infected with certain borrelial strains had even higher levels of these cytokines and chemokines and were uniformly symptomatic [17]. In patients without this SNP, however, borrelial strain differences did not affect the likelihood of a symptomatic versus asymptomatic infection [17]. These observations suggest that there is a potentially important interaction between the strain of borrelia causing Lyme disease and host factors in contributing to the development of non-specific symptoms such as fatigue.

Fatigue is a common complaint in many other infectious diseases, including other deer tick transmitted infections [12,19-21]. In certain other infections, emerging data suggest that a SNP in the IFN-gamma gene is significantly associated with experiencing severe fatigue per se [15], a topic that should be considered for potential investigation in Lyme disease patients as well.

In conclusion, in this study, as in others [4], fatigue was a common symptom in adult patients with early Lyme disease associated with erythema migrans. The prevalence of this

symptom was influenced by the choice of the assessment measure. Based on the FSS-11 assessment tool approximately 20% of such patients may experience severe fatigue. Having more numerous symptoms was significantly associated with reporting the symptom of fatigue and specifically with having severe fatigue as defined by a score of ≥4 on the FSS-11. The symptom of fatigue in early Lyme disease is likely to be a component of what has been referred to as the acute sickness response.

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HIGHLIGHTS

1. Fatigue was assessed in patients with Lyme disease presenting with erythema migrans (EM).
2. Over 50% of patients with EM had fatigue, and ~20% had severe fatigue based on the FSS-11 scale.
3. Having a large number of symptoms was associated with both the presence and severity of fatigue.
4. This finding suggests that fatigue with EM may be a component of the acute sickness response.

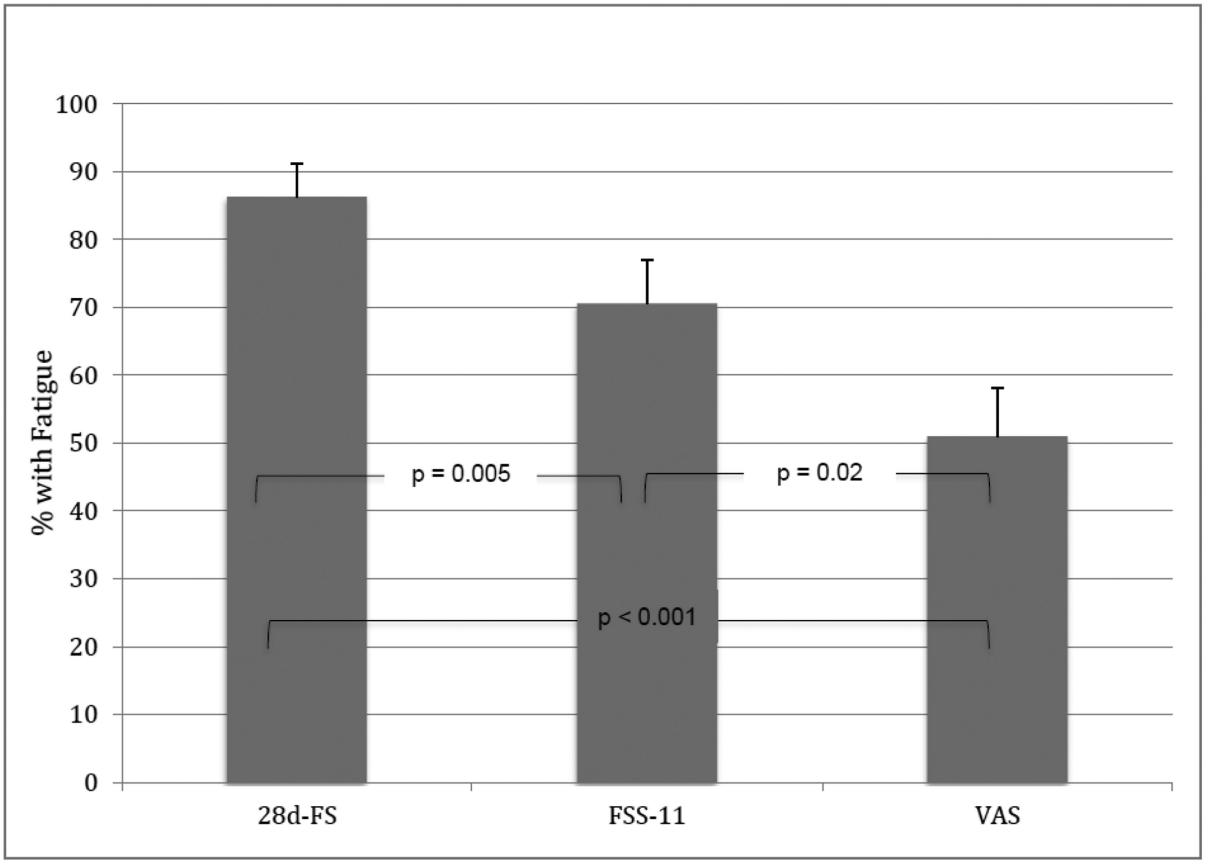

Figure 1.

Comparison of the proportion of 51 early Lyme disease patients with a positive score for the presence of fatigue based on three different assessment measures (28d-FS vs FSS-11, p=0.005; 28d-FS vs VAS, p<0.001; FSS-11 vs VAS p=0.02). An overall comparison of the three prevalence figures showed a highly significant difference (p<0.0001).

Table 1

Selected Demographic and Clinical Characteristics of 51 Untreated Patients with Erythema Migrans.

Characteristic	Findings
% male	64.7
Mean age ± SD in years (median, range)	49.8 ± 15.6 (50, 20-86)
% with multiple erythema migrans skin lesions	41.2
Mean area ± SD of largest erythema migrans skin lesion in square cm* (median, range)	179.8 ± 200.8 (99, 11-900)
Mean duration of erythema migrans ± SD in days at time of evaluation (median, range)	7.88 ± 5.51 (7, 1-22)
% with symptoms at study entry	76.5
Mean number of symptoms ± SD (median, range)	3.27 ± 3.38 (2, 0-12)
Mean body mass index ± SD (median, range)	25.2 ± 3.9 (25.1, 17.2-38.4)
% with reactive C6 Lyme serology**	64.7
Mean C6 ELISA value ± SD	4.3 ± 3.7
% with *Babesia microti* co-infection	7.8
% with *Anaplasma phagocytophilum* co-infection	0

*Area defined as the maximum width times the maximum length

**Test result was positive or equivocal

Table 2

Comparison of Three Measures of Fatigue in 51 Untreated Patients with Erythema Migrans.

	VAS	FSS-11	28d-FS
Mean ± SD score (median, range)	1.85 ± 2.32 (0.4, 0-8)	2.57 ± 1.85 (1.73, 1-7)	1.63 ± 1.04 (2, 0-4)
Mean ± SD scores for the 26 patients with a VAS score > 0 (median, range)	3.63 ± 2.02 (3.6, 0.4 – 8)	3.46 ± 1.89 (3.32, 1-7)	2.15 ± 0.97 (2, 1-4)
Mean ± SD scores for the 10 patients with FSS-11 ≥ 4 (median, range)	4.6 ± 2.64 (5.2, 0-8)	5.76 ± 0.99 (5.55, 4-7)	2.40 ± 0.97 (2.5, 1-4)

Table 3

Correlation between Fatigue Scales and Selected Clinical and Demographic Characteristics.

Characteristic	VAS	FSS-11	28d-FS
	r_s value; p value	r_s value; p value	r_s value; p value
Number of symptoms	+0.78; < 0.0001	+0.72; < 0.0001	+0.64; < 0.0001
Age	−0.28; 0.04	−0.28; 0.05	−0.40; 0.003
BMI	+0.15; 0.30	−0.07; 0.63	−0.01; 0.93
EM area	−0.08; 0.56	+0.05; 0.75	−0.07; 0.63
EM duration	−0.08; 0.56	+0.05; 0.75	−0.07; 0.63
C6 ELISA value	+0.14; 0.35	+0.32; 0.02	+0.20; 0.16

BMI = Body mass index

EM = Erythema migrans; EM area = maximum width time maximum length

Table 4

Fatigue Severity in Relation to Selected Clinical and Demographic Characteristics.

	Characteristic		P value
Scales*	**Male**	**Female**	
VAS	2.03 ± 2.49	1.52 ± 2.01	0.43
FSS-11	2.51 ± 1.83	2.67 ± 1.93	0.78
28d-FS	1.64 ± 1.11	1.61 ± 0.92	0.93
	Single EM	**Multiple EM**	
VAS	1.28 ± 1.97	2.67 ± 2.58	0.05
FSS-11	2.02 ± 1.53	3.35 ± 2.01	0.02
28d-FS	1.40 ± 1.04	1.95 ± 0.97	0.06
	Reactive C6**	**Non-reactive C6**	
VAS	2.16 ± 2.38	1.28 ± 2.17	0.19
FSS-11	2.98 ± 1.89	1.81 ± 1.55	0.02
28d-FS	1.76 ± 1.09	1.39 ± 0.92	0.21

*Scores are shown as mean ± SD

**Positive or equivocal

Table 5

Comparison of the 10 subjects with erythema migrans who had an FSS-11 score of ≥ 4 with the other 41 subjects.

Characteristic	FSS-11 ≥ 4 n=10	FSS-11 < 4 n=41	P value
% male	50	68.3	0.30
Mean age ± SD in years	46.3 ± 17.6	50.6 ± 15.1	0.49
Mean ± SD body mass index	24.0 ± 13.5	25.5 ± 3.9	0.25
% with symptoms at study entry	100	70.7	0.09
Mean number of symptoms ± SD	7.5 ± 3.0	2.2 ± 1.26	< 0.001
% with multiple erythema migrans skin lesions	60	36.6	0.28
Mean duration ± SD of erythema migrans skin lesion in days	8.9 ± 7.1	7.6 ± 5.2	0.60
Mean area ± SD of largest skin lesion in square cm*	187.7 ± 256.9	177.9 ± 188.4	0.91
% with reactive C6 Lyme serology**	80	61	0.46
Mean ± SD C6 ELISA value	5.0 ± 3.5	4.1 ± 3.8	0.50
% with co-infection	10.0	7.3	1.0

*Area defined as the maximum width times the maximum length

**Test result was positive or equivocal