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Original article

Pathogenetic implications of the age at time of diagnosis and skin location for acrodermatitis chronica atrophicans

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ABSTRACT

Background: The pathogenesis of acrodermatitis chronica atrophicans (ACA) is not well understood.
Objective: The purpose of this study was to gain a better understanding of ACA by utilizing a large data set of adult Slovenian patients with Lyme borreliosis.
Methods: The age of 590 ACA patients was compared with that of patients with other manifestations of Lyme borreliosis. The location of the ACA lesion on the body was compared with that of erythema migrans (EM).
Results: Patients diagnosed with ACA were on average 14.3 years older than patients with EM ($p < 0.001$). ACA patients were also significantly older than patients with Lyme neuroborreliosis or Lyme arthritis ($p < 0.001$). The average delay in diagnosis of ACA was 1.6 years (range 0.1–20 years). For 572 (96.9%) of the ACA patients, the site of the skin lesion(s) was confined to an extremity vs. 79.6% for patients with EM, $p < 0.001$. For the 20 ACA patients who reported a preceding untreated EM lesion at the same body site, the mean time between the development of the EM and the onset of ACA was 3.0 ± 4.4 (median 1.3, range 0.1–15.0) years.
Conclusions: ACA is more likely to be diagnosed in older individuals than any other manifestation of Lyme borreliosis. ACA is more likely than EM to be localized anatomically to the extremities. Available data favor the hypothesis that ACA occurs most often on the extremities of older individuals because of predisposing age-related anatomic or physiologic changes, but more data are needed to define the latency period and other aspects of the pathogenesis of this skin condition.

1. Introduction

The most common clinical manifestation of Lyme borreliosis (LB) is a characteristic skin lesion, erythema migrans (EM), which occurs at the site of inoculation of *Borrelia burgdorferi* sensu lato by *Ixodes* spp. ticks. EM is a manifestation of early LB that develops within days to weeks after an infected tick bite and can be caused by infection with any of the commonly encountered species of *B. burgdorferi* s.l. Acrodermatitis chronica atrophicans (ACA) is considered a late skin manifestation of LB; it is most commonly caused by *Borrelia afzelii*, a species of *B. burgdorferi* s.l. not present in the United States (Stanek et al., 2012; Müllegger, 2004; Asbrink, 1993).

To gain a better understanding of ACA, we have taken advantage of large data set on ACA and other clinical manifestations of LB compiled by the LB research group at the academic medical center in Ljubljana, Slovenia.

Abbreviations: ACA, acrodermatitis chronica atrophicans; EM, erythema migrans; LB, lyme borreliosis; LNB, lyme neuroborreliosis; LA, lyme arthritis.

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Table 1
Cases of Lyme borreliosis included in this analysis.

Manifestation	Years when diagnosed	Total Number	Number of Females (%)	Number of Males (%)
Erythema migrans	1990–2009	10,539	6245 (59.3)	4294 (40.7)
Acrodermatitis chronica atrophicans	1991–2015	590	386 (65.4)	204 (34.6)
Lyme neuroborreliosis	2005–2012	130	51 (39.2)	79 (60.8)
Lyme arthritis	2001–2012	60	15 (25.0)	45 (75.0)

2. Materials and methods

Data on the demographics and selected clinical features of ACA and various other clinical manifestations of LB for patients at least 15 years of age were obtained from the Department of Infectious Diseases of the University Medical Center Ljubljana, Slovenia. Data extraction was restricted to periods when information on a specific manifestation of LB was systematically collected.

Patients with ACA had the characteristic clinical picture and supportive histologic findings on skin biopsy, in conjunction with IgG seropositivity to borrelial antigens. Data on ACA patients diagnosed from 1991 to 2015 were included in this analysis (Table 1). Patients with EM, Lyme neuroborreliosis (LNB) or Lyme arthritis (LA) were diagnosed using conventional criteria as described elsewhere (Stanek et al., 2011) during the years shown in Table 1.

Over the 25 year time frame different serological methods were used. Initially, IgG seropositivity in serum to *B. burgdorferi* s.l. required either a positive immunofluorescence assay (Wilske et al., 1984) or a positive enzyme linked immunosorbent assay with a positive supplemental IgG immunoblot (Strle and Stanek, 2009). In the past few years testing has been based on an indirect chemiluminescence immunoassay (LIAISON®, Diasorin, Italy) using the VlsE (variable major protein-like sequence expressed) and OspC recombinant antigen (Marangoni et al., 2008), following the manufacturer's recommendations.

2.1. Ethics statement

The investigation was conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No 117/11/12). The Ethics Committee waived the need for written informed consent.

2.2. 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, either the Fisher's exact test or the chi square test was used. A p value of <0.05 was considered to be significant.

3. Results

Information on the age of patients at the time of diagnosis of various clinical manifestations of LB was available for 10,539 patients with EM, 590 patients with ACA, 130 patients with LNB, and 60 patients with LA (Table 1). Females with ACA were on average 14.3 years older than females with EM ($p < 0.001$) and males with ACA were on average 14.3 years older than males with EM ($p < 0.001$) (Table 2). Both female and male patients were also significantly older at the time of diagnosis of ACA than were patients of their respective genders who were diagnosed with LNB or LA ($p < 0.001$) (Table 2).

Because patients with ACA, at the time of diagnosis, may have already had their skin lesion(s) for a considerable period of time, we further compared the mean age of patients with ACA at the time of the reported onset of the skin lesion with that of EM patients at the time of diagnosis of EM. Of the 590 patients with ACA, the age at time of onset of the skin lesion was known for 327 of the females and for 161 of the males. The average duration between onset of the ACA skin lesion and diagnosis was 1.6 ± 2.3 (median 1, range 0.1–20) years for females and 1.6 ± 2.6 (median 0.8, range 0.1–20) years for males. The differences in mean ages of patients with EM at time of diagnosis and that of patients with ACA at time of lesion onset, however, remained highly significant, irrespective of gender (ages of EM vs. ACA at time of onset of ACA: 49.1 ± 14.5 years vs. 61.7 ± 12.4 years in females, $p < 0.001$; and 44.9 ± 15.0 years vs. 57.3 ± 13.6 years in males, $p < 0.001$).

Of the 10,258 patients with EM from this data set who had a single EM skin lesion, the EM lesion was located on an extremity in 7759 (75.6%). In contrast, for 572 (96.9%) of the 590 patients diagnosed with ACA, the site of the skin lesion(s) was confined exclusively to one or more extremities ($p < 0.001$ for the comparison with EM patients). 17 patients had ACA on other parts of the body in addition to the extremities, and 1 patient had an ACA lesion confined to the thorax. The mean age of ACA patients with the skin lesion confined only to the extremities was similar to that of ACA patients whose skin lesion involved another anatomic site besides the extremities (62.1 ± 12.4 years vs. 59.4 ± 13.5 years; $p = 0.41$).

Because ACA is primarily caused by *B. afzelii* (Strle and Stanek, 2009; Ružić-Sabljić et al., 2002), we also compared the mean ages at time of diagnosis of 200 patients with a single EM skin lesion caused by this species of *B. burgdorferi* s.l. based on culture of a skin biopsy sample, with that of the 590 ACA cases. Both females and males with ACA (63.4 ± 11.9 and 59.2 ± 13.1 years, respectively) were significantly older at the time of diagnosis than females and males with

Table 2
Age of patients with acrodermatitis chronica atrophicans in comparison to the age of patients with other clinical manifestations of Lyme borreliosis.

Females	Males
ACA vs. EM: 63.4 (±11.9) vs. 49.1 (±14.5) p < 0.001	ACA vs. EM: 59.2 (±13.1) vs. 44.9 (±15.0) p < 0.001
ACA vs. LNB: 63.4 (±11.9) vs. 55.5 (±14.3) p < 0.001	ACA vs. LNB: 59.2 (±13.1) vs. 46.7 (±18.2) p < 0.001
ACA vs. LA: 63.4 (±11.9) vs. 49.0 (±12.3) p < 0.001	ACA vs. LA: 59.2 (±13.1) vs. 46.8 (±14.4) p < 0.001

Data are presented as means ± SD.
ACA = acrodermatitis chronica atrophicans; EM = erythema migrans; LNB = Lyme neuroborreliosis; LA = Lyme arthritis.