Acrodermatitis chronica atrophicans: clinical and microbiological characteristics of a cohort of 693 Slovenian patients

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Abstract. Ogrinc K, Maraspin V, Lusa L, Cerar Kišek T, Ruzič-Sabljić E, Strle F (University Medical Centre Ljubljana, Ljubljana; University of Primorska, Koper; and University of Ljubljana, Ljubljana, Slovenia). Acrodermatitis chronica atrophicans: clinical and microbiological characteristics of a cohort of 693 Slovenian patients. J Intern Med 2021; https://doi.org/10.1111/joim.13266

Background. Information on large groups of patients with acrodermatitis chronica atrophicans (ACA) is limited.

Methods. We assessed clinical and microbiological characteristics of patients with ACA diagnosed at a single medical centre and compared findings in periods 1991–2004 vs. 2005–2018. The cohort is representative of Slovenian ACA patients.

Results. We assessed 693 patients: 461 females and 232 males, with median age of 64 years. Median duration of ACA before diagnosis was 12 months. In all but 2 patients, the skin lesions were located on extremities, more often on the lower (70.0%) than the upper (45.2%), bilaterally in 42.4%. Reddish-blue discoloration, swelling, thinning and wrinkling of skin were present in 95.2%, 28.1%, 46.4% and 20.5% of patients, respectively. Overall, 64.4% of patients reported constitutional symptoms, 23.1% had local symptoms, and 20.8% had symptoms/signs of peripheral neuropathy. Nodules, arthritis, joint deformity, muscle atrophy and paresis were rare (<3%). Borreliae were isolated from 200/664 (30.1%) skin samples; 92.8% were Borrelia afzelii. B. garinii and B. burgdorferi s.s. were more often isolated from the skin of male patients (OR = 4.17) and from those with arthropathy (OR = 11.74). Patients included in the more recent period were older, complained less often of constitutional symptoms but more often of local symptoms, and more often had local swelling but less often skin atrophy and bilateral involvement, probably as a consequence of earlier diagnosis.

Conclusions. ACA, typically caused by B. afzelii, usually affects older women. Clinical presentation depends on the duration of illness and probably on the Borrelia species causing the disease.

Keywords: acrodermatitis chronica atrophicans, Borrelia afzelii, Borrelia burgdorferi sensu lato, late Lyme borreliosis.
The aim of this study was to obtain comprehensive clinical and microbiological data on a large group of patients with ACA.

Patients and methods
The present study is a retrospective cohort study, encompassing patients diagnosed with ACA at LB Outpatient Clinic of University Medical Centre Ljubljana, Slovenia, in the period 1991–2018. Whilst the information on the patients has been systematically collected since 1991, the database has been created only recently. Consequently, the data for individual patient were considerably complete; however, for initial years (1991–1994) documentation was missing for several patients (Fig. S1). Since a large majority of patients with suspected ACA from central part of Slovenia are referred to our LB Outpatient Clinic, the present case series is most probably well representative of Slovenian ACA patients. The age and sex of 590 patients included in the present study have been reported previously [6].

The study was approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia (No. 0120-520/2017/5).

Patients
We reviewed the medical records of patients ≥15 years of age, diagnosed with ACA at our LB Outpatient Clinic during the 28-year period, 1991–2018, and for whom the medical documentation was available. Diagnosis of ACA was based on 3 criteria: suggestive clinical presentation, demonstration of borrelial serum IgG antibodies and histological findings compatible with ACA. We also included some patients with typical clinical presentation and established borrelial infection but for whom skin histology was not available. We analysed the epidemiological, clinical and microbiological characteristics of all these patients. To test the assumption that knowledge of ACA has improved over the years and that diagnosis is therefore earlier, we compared findings in subgroups of patients assessed in the periods 1991–2004 and 2005–2018.

Clinical evaluation
Basic approaches remained similar during the overall study period. We obtained the demographic, epidemiological and clinical data, paying particular attention to constitutional and local symptoms, tick bites, past manifestations of LB, previous antibiotic treatment, skin changes, and neurological and/or joint involvement. The data were collected prospectively. For the purpose of this study, only information obtained at the initial presentation (before treatment) was used.

Serological evaluation
Up to 2010, we measured serum antibodies to B. burgdorferi s.l. in an indirect immunofluorescence assay (IFA) with a local isolate of B. afzelii as antigen. Serum dilutions ≥1:256 were interpreted as positive, based on results in a control group from the same geographic region [7]. For antibody detection from 2010 onwards, we used an indirect chemiluminescence immunoassay (LIAISON®/Dia-Sorin, Italy) with recombinant antigens OspC and VlsE for IgM and VlsE for IgG; results were graded according to the manufacturer’s instructions.

Cultivation and typing of B. burgdorferi s.l.
Skin biopsy specimens (2.5 × 2 × 2 mm) obtained from ACA lesions were inoculated directly into tubes containing 7 mL of modified Kelly–Pettenkofer medium (MKP). Samples of citrated blood (5 mL until 2000, 9 mL from 2001 onwards) were centrifuged (500 rpm for 10 minutes), and 1 mL samples of plasma were inoculated into tubes containing 7 mL MKP. All samples were incubated at 33°C and examined weekly by dark-field microscopy for the presence of spirochetes (up to 9 weeks for skin, 12 weeks for blood specimens). Isolates were identified to species/strain level using pulsed-field gel electrophoresis after MluI restriction of genomic DNA [8], or by PCR-based restriction fragment length polymorphism of the intergenic region [9].

Histopathological evaluation
Skin samples obtained at sites of ACA were placed directly into formalin-containing tubes and subsequently examined after standard haematoxylin and eosin staining. Dermis atrophy and/or lymphocyte and plasma cell inflammatory infiltrates were regarded as indicative of ACA.

Statistical methods
Categorical variables were summarized with frequencies and percentages and 95% confidence
intervals (CI), numerical variables with medians and interquartile ranges (IQRs). The characteristics of the patients diagnosed in the 1991–2004 period were compared to those diagnosed in the 2005–2018 period using the Mann–Whitney test, Fisher’s exact test or chi-squared test, as appropriate. Several covariates, selected using expert opinion (KO, FS) independently from the observed outcomes, were used for testing associations with three outcomes: the presence of serum borrelial IgM antibodies; positive borrelial skin culture; and B. garinii/B. burgdorferi s.s. versus B. afzelii isolated from the ACA skin lesion (Table S1). For the analyses, univariate and multivariable logistic regression models were employed. The R software was used. The missing values for the duration of ACA and skin histology indicative of ACA were imputed using the observed means; for the other covariates included in the analyses, the information was complete. Sensitivity analysis comparing the results obtained with imputation of means and the results obtained with multiply imputed values for covariates with missing values was performed using mice R package. Since the outcomes obtained with the two imputation methods were very consistent (data not shown), only the results using imputation of the observed means are shown.

Results

A total of 693 patients diagnosed with ACA during the 28-year period qualified for the study: 461 females (66.5%) and 232 males, with median age of 64 (IQR: 55–71) years. The lower number of patients in the early 1990s was mainly due to incomplete medical documentation (Fig. S1). Basic demographic, epidemiological and clinical data were assessed for the periods 1991–2004 and 2005–2018 (Table 1).

Information on tick bites was available for 590/693 patients, most of whom (422/590; 71.5%) recalled a tick bite within a 2-year period before the onset of ACA, but only 37/590 (6.3%) attributed the skin lesion to a particular tick bite, with a median latency period of 6 months.

Amongst the 693 patients, 147 (21.2%) reported having had EM (Fig. 1) and 7 (1.0%) having had Lyme neuroborreliosis before the ACA. In 36/103 (35.0%) patients with available information on the location of EM, the location matched the later ACA; in these patients, the time interval from EM to onset of ACA was shorter than in patients with nonmatching locations (19 vs. 63 months; \( P = 0.005 \)).

The median duration of ACA before diagnosis was 12 months (Fig. 2). In all but 2 patients, ACA was located on the limbs: on 1, 2, 3 and all 4 extremities in 55%, 31.3%, 5.6% and 7.8% of patients, respectively. The lower extremities were involved in 70%, and the upper extremities were involved in 45%. Bilateral involvement occurred in 42.1%, more often on the upper extremities than the lower (51.1% vs. 38.4%; \( P < 0.001 \)).

The most frequent skin signs (in descending order) were as follows: redness, bluish discoloration, thinning, swelling and wrinkling. In 4.8% of patients, only swelling or atrophic changes were noted, but no colour change. Rare findings included nodules (2.2%, most often located on the extensor side of the elbow), arthritis (2.6%), joint deformity (0.4%), muscle atrophy (0.4%) and paresis (0.1%).

Constitutional symptoms were reported by 64.4% of patients and local symptoms by 23.1%; in the majority, the symptoms were mild. At least 1 symptom (pain, burning, paresthesia, hypesthesia) and/or sign (muscle atrophy, paresis) suggesting ACA-associated peripheral neuropathy was present in 144 (20.8%) patients; these symptoms and signs were located exclusively at the site of ACA skin lesions.

Borrelial IgG antibody levels were usually very high. Specific IgM antibodies were also present in 32.4% of patients (Table 2). Univariate and multivariable models found no significant associations between predefined covariates and the presence of borrelial serum IgM antibodies (Table 3). Histological findings in skin lesions were available for 567/693 (81.8%) patients and were indicative of ACA in 498/567 (87.8%) patients (Table 2).

Borreliae were successfully isolated from 200/664 (30.1%) skin samples and 4/408 (1.0%) blood samples: B. afzelii predominated (92.8%) in skin, whereas 3 of 4 blood isolates were B. garinii (Table 2). In univariate analyses, isolation of borreliae from skin was positively associated with the presence of oedema and location of ACA on the lower extremities, whilst the association was negative for antibiotic treatment within 6 months.
|                        | 1991–2004 | 2005–2018 |   | 1991–2018 |
|------------------------|-----------|-----------|---|-----------|
|                        | N = 295   | N = 398   | P | N = 693   |
| Female sex             | 187 (63.4; 57.6–68.9) | 274 (68.8; 64.0–73.4) | 0.155 | 461 (66.5; 62.9–70.0) |
| Age (years)            | 62 (53–69) | 65 (57–74) | < 0.001 | 64 (55–71) |
| Female                 | 64 (57–70) | 67 (59–74) | 0.002 | 65 (58–72) |
| Male                   | 60 (48–67) | 61 (53–73) | 0.037 | 61 (50–69) |
| Annual number of tick  | 1 (0–4)<sup>a</sup> | 1 (0–4)<sup>b</sup> | 0.761 | 1 (0–4) |
| bites                  |           |           |    |           |
| Tick bite in 2-year    | 191/254 (75.2; 69.4–80.4) | 231/336 (68.8; 63.5–73.7) | 0.104 | 422/590 (71.5; 67.7–75.1) |
| period before ACA      |           |           |    |           |
| Time interval from     | 5 (4–12)<sup>d</sup> | 6 (2–14)<sup>e</sup> | 0.883 | 6 (2–14) |
| tick bite to ACA       |           |           |    |           |
| (months)               |           |           |    |           |
| Past EM                | 57 (19.3; 15.0–24.3) | 90 (22.6; 18.6–27.0) | 0.340 | 147<sup>f</sup> (21.2; 18.2–24.4) |
| Time from EM to ACA    | 19 (6–56)<sup>g</sup> | 96 (36–178)<sup>h</sup> | < 0.001 | 55 (18–150) |
| (months)               |           |           |    |           |
| Matching location of   | 19/48 (39.6; 25.8–54.7) | 17/55 (30.9; 19.1–44.8) | 0.475 | 36/103 (35.0; 25.8–45.0) |
| ACA and preceding EM   |           |           |    |           |
| Time from EM to ACA    | 9 (3–22)<sup>i</sup> | 54 (6–177)<sup>j</sup> | 0.024 | 19 (3–55) |
| in patients with       |           |           |    |           |
| matching locations     |           |           |    |           |
| (months)               |           |           |    |           |
| Past LNB<sup>k</sup>   | 1 (0.3; 0–1.9) | 6 (1.5; 0.6–3.3) | 0.126 | 7<sup>j</sup> (1.0; 0.4–2.1) |
| Antibiotic therapy     | 23/290 (7.9; 5.1–11.7) | 33 (8.3; 5.8–11.4) | 0.976 | 56/688 (8.1; 6.2–10.4) |
| with anti-borrelial     |           |           |    |           |
| activity in the 6      |           |           |    |           |
| months prior to        |           |           |    |           |
| presentation           |           |           |    |           |
| Duration of ACA        | 12 (6–24) | 8 (4–18) | < 0.001 | 12 (5–24) |
| (months)               |           |           |    |           |
| Constitutional         | 237 (80.3; 75.3–84.7) | 209 (52.5; 47.5–57.5) | < 0.001 | 446 (64.4; 60.7–67.9) |
| symptoms<sup>m</sup>   |           |           |    |           |
| Arthralgia             | 180 (61.0; 55.2–66.6) | 118 (29.6; 25.2–34.4) | < 0.001 | 298 (43.0; 39.3–46.8) |
| Headache               | 95 (32.2; 26.9–37.9) | 79 (19.8; 16.0–24.1) | < 0.001 | 174 (25.1; 21.9–28.5) |
| Myalgia                | 97 (32.9; 27.5–38.6) | 48 (12.1; 9.0–15.7) | < 0.001 | 145 (20.9; 18.0–24.1) |
| Fatigue                | 68 (23.1; 18.4–28.3) | 69 (17.3; 13.7–21.4) | 0.076 | 137 (19.8; 16.9–22.9) |
| Vertigo                | 42 (14.2; 10.5–18.8) | 32 (8.0; 5.6–11.2) | 0.013 | 74 (10.7; 8.5–13.2) |
| Memory/                | 21 (7.1; 4.5–10.7) | 15 (3.8; 2.1–6.1) | 0.073 | 36 (5.2; 3.7–7.1) |
| concentration          |           |           |    |           |
| disorder               |           |           |    |           |
| Duration of            | 10 (5–24) | 6 (3–12) | 0.007 | 9 (4–24) |
| constitutional         |           |           |    |           |
| symptoms (months)      |           |           |    |           |
| Local symptoms         | 56 (19.0; 14.7–23.9) | 104 (26.1; 21.9–30.7) | 0.034 | 160 (23.1; 20.0–26.4) |
| Description of skin lesion                | 1991–2004          | 2005–2018          | 1991–2018          |
|-------------------------------------------|--------------------|--------------------|--------------------|
|                                           | N = 295           | N = 398            | N = 693            |
| Pain                                      | 27 (9.2; 6.1–13.0) | 37 (9.3; 6.6–12.6) | 0.946 64 (9.2; 7.2–11.6) |
| Burning                                   | 15 (5.1; 2.9–8.2)  | 42 (10.6; 7.7–14.0)| 0.014 57 (8.2; 6.3–10.5) |
| Paresthesia                               | 20 (6.8; 4.2–10.3) | 25 (6.3; 4.1–9.1)  | 0.914 45 (6.5; 4.8–8.6) |
| Itching                                   | 10 (3.4; 1.6–6.1)  | 26 (6.5; 4.3–9.4)  | 0.095 36 (5.2; 3.7–7.1) |
| Hypoesthesia                              | 2 (0.7; 0.1–2.4)   | 5 (1.3; 0.4–2.9)   | 0.364 7 (1.0; 0.4–2.1) |
| **Localization of ACA**                   |                    |                    |                    |
| Lower extremity                           | 203 (68.8; 63.2–74.1) | 282 (70.9; 66.1–75.3) | 0.620 485 (70.0; 66.4–73.4) |
| Foot                                      | 88 (43.3; 36.4–50.5) | 157 (55.7; 49.7–61.6) | 0.010 245 (50.5; 46.0–55.1) |
| Ankle                                     | 84 (41.4; 34.5–48.5) | 167 (59.2; 53.2–65.0) | < 0.001 251 (51.7; 47.2–56.3) |
| Shin                                      | 149 (73.4; 66.8–79.3) | 177 (62.8; 56.8–68.4) | 0.018 326 (67.2; 62.8–71.4) |
| Knee                                      | 51 (25.1; 19.3–31.7) | 75 (26.6; 21.5–32.2) | 0.795 126 (26.0; 22.1–30.1) |
| Thigh                                     | 49 (24.1; 18.4–30.6) | 100 (35.5; 29.9–41.4) | 0.010 149 (30.7; 26.6–35.0) |
| Buttocks                                  | 3 (1.5; 0.3–4.3)   | 8 (2.8; 1.2–5.5)   | 0.251 11 (2.3; 1.1–4.0) |
| Lower extremity – bilateral involvement   | 111 (54.7; 47.6–61.7) | 75 (26.6; 21.5–32.2) | < 0.001 186 (38.4; 34.0–42.8) |
| Upper extremity                           | 157 (53.2; 47.3–59.0) | 156 (39.2; 34.4–44.2) | < 0.001 313 (45.2; 41.4–49.0) |
| Hand                                      | 146 (93.0; 87.8–96.5) | 150 (96.2; 91.8–98.6) | 0.325 296 (94.6; 91.4–96.8) |
| Forearm                                   | 32 (20.4; 14.4–27.5) | 49 (31.4; 24.2–39.3) | 0.036 81 (25.9; 21.1–31.1) |
| Elbow                                     | 26 (16.6; 11.1–23.3) | 27 (17.3; 11.7–24.2) | 0.980 53 (16.9; 12.9–21.6) |
| Upper arm                                 | 15 (9.6; 5.4–15.3)  | 19 (12.2; 7.5–18.4) | 0.572 34 (10.9; 7.6–14.8) |
| Upper extremity – bilateral involvement   | 102 (65.0; 57.0–72.4) | 58 (37.2; 29.6–45.3) | < 0.001 160 (51.1; 45.4–56.8) |
| Trunk                                     | 9 (3.1; 1.4–5.7)   | 10 (2.5; 1.2–4.6)  | 0.846 19 (2.7; 1.7–4.2) |
| Face                                      | 1 (0.3; 0–1.9)     | 1 (0.3; 0–1.4)     | 0.615 2 (0.3; 0–1.0) |
| Description of skin lesion                |                    |                    |                    |
| Redness                                   | 199 (67.5; 61.8–72.8) | 290 (72.9; 68.2–77.2) | 0.144 489 (70.6; 67.0–73.9) |
| Bluish discoloration                      | 175 (59.3; 53.5–65.0) | 207 (52.0; 47.0–57.0) | 0.066 382 (55.1; 51.3–58.9) |
| No colour change                          | 26 (8.8; 5.8–12.6)  | 7 (1.8; 0.7–3.6)   | < 0.001 33 (4.8; 3.3–6.6) |
| Swelling                                  | 56 (19.0; 14.7–23.9) | 139 (34.9; 30.2–39.8) | < 0.001 195 (28.1; 24.8–31.6) |
| Shining                                   | 47 (15.9; 11.9–20.6) | 44 (11.1; 8.1–14.6) | 0.077 91 (13.1; 10.7–15.9) |
| Thin / atrophic                           | 176 (59.7; 53.8–65.3) | 144 (36.2; 31.5–41.1) | < 0.001 320 (46.4; 42.4–50.0) |
| Wrinkled                                  | 95 (32.2; 26.9–37.9) | 47 (11.8; 8.8–15.4) | < 0.001 142 (20.5; 17.5–23.7) |
| Venous prominence                         | 43 (14.6; 10.8–19.1) | 53 (13.3; 10.1–17.1) | 0.716 96 (13.8; 11.4–16.7) |
| At least 1 clinical sign of skin atrophy  | 223 (75.6; 70.3–80.4) | 183 (46.0; 41.0–51.0) | < 0.001 406 (58.6; 54.8–62.3) |
| Nodule                                    | 5 (1.7; 0.6–3.9)    | 10 (2.5; 1.2–4.6)  | 0.640 15 (2.2; 1.2–3.5) |
| Peeling                                   | 7 (2.4; 1.0–4.8)    | 11 (2.8; 1.4–4.9)  | 0.937 18 (2.6; 1.5–4.1) |
| Arthritis                                 | 7 (2.4; 1.0–5.3)    | 11 (2.8; 0.8–4.2)  | 0.937 18 (2.6; 1.3–3.8) |
| Joint deformity                           | 8 (2.7; 1.2–5.3)    | 3 (0.8; 0.2–2.2)   | 0.042 11 (1.6; 0.8–2.8) |
The multivariable model showed significant association only for antibiotic treatment within 6 months before skin biopsy (odds ratio (OR) 0.13; 95% CI, 0.05–0.37; \( P < 0.001 \)). In a skin culture-positive subgroup, multivariable analysis found that isolation of *B. garinii* or *B. burgdorferi s.s.* was associated with patient sex (OR for male sex 4.17; 95% CI, 1.18–14.29, \( P = 0.027 \)) and arthropathy (OR = 11.74; 95% CI, 1.48–93.07; \( P = 0.020 \)). Further information is given in Table 3.

Comparison of demographic, epidemiological, clinical and laboratory characteristics in the 2 time periods (1991–2004 vs. 2005–2018) showed that patients treated in the more recent period were older, had shorter duration of ACA (Fig. 2), reported constitutional symptoms less often but local symptoms more often, presented more frequently with swelling and less frequently with skin atrophy and deformation of joints, and had bilateral ACA less frequently. Also in the later period, patients more frequently had borreial IgM antibodies in serum and histological findings suggestive of ACA (Tables 1 and 2).

### Discussion

Several articles on ACA have appeared in recent decades, but the reported series are relatively small and most relate to specific clinical or microbiological aspects of ACA. In North America, only sporadic cases imported from Europe have been described [10–13].

Our study encompasses 693 patients \( \geq 15 \) years old who presented with ACA at our LB Outpatient Clinic in a 28-year period, 1991–2018. In that same period, EM was diagnosed in 17,654 patients, indicating > 25 cases of EM per 1 case of ACA, and corroborating the appraisal that amongst adult patients with LB, ACA represents < 4% of cases [14, 15]. It is of interest that each year we diagnose more cases of ACA than proven Lyme neuroborreliosis [16].

Amongst our ACA patients, the age and sex distribution, localization on dorsal distal parts of extremities and proportion of patients recalling EM before the onset of ACA were similar to those reported elsewhere [16–20]; however, several other findings differed (Table 4). For some distinctions in

### Table 1 (Continued)

|                     | 1991–2004 | 2005–2018 | \( P \) | 1991–2018 |
|---------------------|-----------|-----------|--------|-----------|
| Muscle atrophy\( ^a \) | 3 (1.0; 0.2–2.9) | 0 (0–0.9) | 0.077 | 3 (0.4; 0.1–1.3) |
| Muscle paresis\( ^a \) | 1 (0.3; 0–1.9) | 0 (0–0.9) | 0.426 | 1 (0.1; 0–0.8) |

Data are medians (interquartile range) or frequencies (percentage; 95% confidence interval). \( P \) values were obtained with the Mann–Whitney test for numerical variables and with Yates’s corrected chi-squared test or two-tailed Fisher’s exact test for categorical variables.

ACA, acrodermatitis chronica atrophicans; EM, erythema migrans; LNB, Lyme neuroborreliosis.

\( ^a \)Data available for 93 patients.

\( ^b \)Data available for 260 patients.

\( ^c \)Patients who attributed ACA to specific tick bite.

\( ^d \)Data available for 4 patients.

\( ^e \)Data available for 33 patients.

\( ^f \)83 patients treated according to recommendations (azithromycin in 27 patients, doxycycline in 9, ceftriaxone in 6, cefuroxime in 3, amoxicillin in 2, penicillin in 1 and unknown antibiotic in 35); 61 patients not treated, data on treatment not available for 3 patients.

\( ^g \)Data available for 38 patients.

\( ^h \)Data available for 64 patients.

\( ^i \)Data available for 18 patients.

\( ^j \)Data available for 15 patients.

\( ^k \)4 months to 20 years prior to ACA.

\( ^l \)All patients treated according to recommendations.

\( ^m \)Mostly of low intensity.

\( ^n \)Findings at presentation.

\( ^o \)Thin/atrophic and/or wrinkled and/or shining skin and/or venous prominence.
the present study (such as the lower proportion of patients with symptoms/signs of peripheral neuropathy or joint involvement), the shorter duration of ACA (12 months) in comparison with previous reports (≥2 years) might be a reliable explanation, but for the more frequent bilateral involvement and some other distinctions we do not have convincing explanations. For example, peripheral neuropathy and/or arthropathy are reported to occur primarily in the area of impaired skin but in some patients may also occur at other skin sites [21, 24, 28]; in the present study, these complications were found exclusively in the areas of affected skin. We also observed differences within our patient group: those diagnosed more recently (2005–2018) were older, had shorter duration of ACA that was less frequently bilateral, reported constitutional symptoms less often but local symptoms more often, and more frequently had swelling but less frequently had atrophy compared with patients treated earlier (1991–2004) (Table 1). Most of these differences probably relate to the earlier recognition of the disease in more recent years.

The pathogenesis of ACA is not well elucidated. It is postulated that ACA does not heal spontaneously, in contrast to the majority of other manifestations of LB [35, 36]. ACA is frequently the only manifestation of LB. Its incubation period is uncertain. In tick-transmitted infection, incubation signifies the

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**Fig. 1** Erythema migrans in patients with acrodermatitis chronica atrophicans. Abbreviations: EM, erythema migrans; ACA, acrodermatitis chronica atrophicans. a11/33 (33.3%) patients treated with antibiotic for EM. b27/42 (64.3%) patients treated with antibiotic for EM. cData are medians (interquartile range). dSignificant difference in the time interval from EM to onset of ACA between the two groups (P = 0.005).

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**Fig. 2** Duration of ACA prior to enrolment in the study. Numbers in the columns represent number of patients according to duration of ACA prior to diagnosis in the two time periods.
time from a tick bite to the onset of disease. In the current study, >70% of patients reported tick bites in the 2 years before onset of ACA, but only 6% of patients associated a specific bite with subsequent ACA developing 6 (2–14) months after the bite. However, tick bites are numerous, not all bites are noticed and/or remembered, and only some ticks are infected. Moreover, just a small proportion of ticks harbouring borreliae successfully transmit the causative agent to humans, resulting in clinical illness. It is very difficult, therefore, to establish a bite causally associated with ACA. Data on EM, which develops within a month after a bite, enable more reliable assessment. Nevertheless, the assumption that prior EM is related to ACA may not be always valid. The chances are probably higher if ACA occurs at the site of previous EM, especially if the EM was not adequately treated. Amongst our patients, 147/693 (21%) reported having EM prior to ACA. In 36/103 (35%) patients with information on EM location, the locations of ACA and EM matched; in these patients, the time interval from EM to the onset of ACA was shorter than in patients with nonmatching locations (median 19 vs. 63 months; \( P = 0.005 \)), implying nonuniform association between EM and subsequent ACA. These findings suggest that the incubation time for ACA is long, ranging from a few months to a few years.

Our study shows that, as for EM, ACA is more common on the lower extremity than on the upper extremity. The fact that EM develops at the site of a tick bite, and that tick bites in adults are more common on the lower than on the upper part of the body, implies localized illness at the site of tick bite not only for EM but also for ACA.

It is not known why patients with ACA are mostly older, why women are more commonly affected than men, and why the distal parts of the limbs are mainly involved. However, female predominance is not a complete surprise; as in several European countries, including Slovenia, LB is more common.
in women than in men. Closer insight shows that female predominance is valid only for cutaneous manifestations of LB (EM and ACA, which are by far the most common clinical signs and account for ≥90% of all LB cases in Slovenia), but not for Lyme neuroborreliosis and Lyme arthritis, which are more common in males [16]. A recent hypothesis suggests that ACA occurs in older individuals because they are likely to have age-related anatomic/physiological skin changes in the distal

| Covariate                                  | Univariate analysis OR (95% CI), P | Multivariable analysis OR (95% CI), P |
|--------------------------------------------|-----------------------------------|-------------------------------------|
| Female sex                                 | 1.00 (0.72–1.41), 0.987           | 1.01 (0.72–1.43), 0.949             |
| Age                                        | 0.99 (0.98–1.01), 0.428           | 1.00 (0.98–1.01), 0.510             |
| Duration of ACA<sup>b</sup>                 | 1.00 (1.00–1.01), 0.106           | 1.00 (1.00–1.01), 0.092             |
| Previous EM                                | 0.98 (0.66–1.44), 0.908           | 0.95 (0.64–1.41), 0.785             |
| Antibiotic therapy in previous 6 months    | 0.92 (0.31–1.60), 0.772           | 0.94 (0.54–1.65), 0.841             |
| Constitutional symptoms<sup>c</sup>        | 1.19 (0.85–1.66), 0.313           | 1.20 (0.85–1.68), 0.294             |
| Local symptoms<sup>d</sup>                 | 1.13 (0.77–1.64), 0.537           | 1.13 (0.77–1.65), 0.523             |
| Local swelling                             | 1.13 (0.80–1.61), 0.484           | 1.17 (0.81–1.68), 0.401             |

### Serum Borrelia IgM antibodies

| Covariate                                  | Univariate analysis OR (95% CI), P | Multivariable analysis OR (95% CI), P |
|--------------------------------------------|-----------------------------------|-------------------------------------|
| Female sex                                 | 1.32 (0.92–1.89), 0.130           | 1.36 (0.94–1.99), 0.106             |
| Age                                        | 0.99 (0.97–1.00), 0.059           | 0.99 (0.97–1.00), 0.102             |
| Duration of ACA<sup>b</sup>                 | 1.00 (0.99–1.01), 0.914           | 1.00 (0.99–1.01), 0.801             |
| Antibiotic therapy during previous 6 months | 0.13 (0.05–0.38), < 0.001         | 0.13 (0.05–0.37), < 0.001           |
| Local symptoms<sup>d</sup>                 | 1.38 (0.94–2.02), 0.097           | 1.28 (0.86–1.91), 0.222             |
| Local swelling                             | 1.46 (1.02–2.09), 0.038           | 1.33 (0.90–1.95), 0.148             |
| Signs of skin atrophy<sup>f</sup>          | 1.12 (0.80–1.57), 0.511           | 1.36 (0.94–1.97), 0.099             |
| Upper extremity involvement                | 0.68 (0.48–0.95), 0.025           | 0.75 (0.45–1.24), 0.259             |
| Lower extremity involvement                | 1.49 (1.02–2.17), 0.039           | 1.13 (0.65–1.96), 0.659             |

### Positive Borrelia skin culture result (results available for 664 patients)

| Covariate                                  | Univariate analysis OR (95% CI), P | Multivariable analysis OR (95% CI), P |
|--------------------------------------------|-----------------------------------|-------------------------------------|
| Female sex                                 | 0.28 (0.09–0.86), 0.025           | 0.24 (0.07–0.85), 0.027             |
| Age                                        | 0.97 (0.94–1.01), 0.164           | 0.97 (0.93–1.02), 0.279             |
| Duration of ACA<sup>b</sup>                 | 0.93 (0.86–1.01), 0.067           | 0.93 (0.86–1.01), 0.072             |
| Previous EM                                | 2.06 (0.65–6.51), 0.218           | 1.92 (0.47–7.79), 0.361             |
| Constitutional symptoms<sup>c</sup>        | 1.21 (0.39–3.76), 0.740           | 0.95 (0.26–3.51), 0.935             |
| Local symptoms<sup>d</sup>                 | 0.70 (0.19–2.63), 0.601           | 0.45 (0.01–21.97), 0.690            |
| Symptoms and/or signs of peripheral neuropathy<sup>h</sup> | 0.77 (0.20–2.87), 0.692 | 1.35 (0.03–65.13), 0.880 |

### Table 3

| Covariate                                  | Univariate analysis OR (95% CI), P | Multivariable analysis OR (95% CI), P |
|--------------------------------------------|-----------------------------------|-------------------------------------|
| Female sex                                 | 1.49 (1.02–2.17), 0.039           | 1.13 (0.65–1.96), 0.659             |

B. garinii or B. burgdorferi s.s. versus B. afzelii isolated from skin (B. afzelii isolated from 179 patients, B. garinii or B. burgdorferi s.s. from 14)
extremities that may predispose to the development of ACA in those particular body parts [16]. However, if this were the case, why do later similar lesions also appear on the distal part of some other limb and why does this happen contralaterally more often than ipsilaterally, resulting in bilateral, more or less symmetrical lesions that are more often present on hands than on feet? A possible theoretical explanation is that the initial localized infection disseminates early on, before the humoral immune response. Consequently, borreliae are present in other parts of the body as early as during the initial infection, but manifest as clinically visible primary ACA after a longer delay because the skin in these areas is less damaged than at the primary location. Alternative hypotheses are that borreliae spread slowly and continuously from the site of primary infection through the skin or along nerves to other parts of the body, or that despite a pronounced humoral immune response intermittent haematogenous dissemination of borreliae occurs in the course of ACA; in both cases, the infection becomes clinically evident on locations with the most ‘favourable’ conditions for ACA. A further possibility would be reinfection, that is new localized infection at the ‘vulnerable’ site with a long delay until clinical manifestation. However, all these hypotheses are only partial explanations and have several weaknesses.

Several other simple questions remain unanswered, such as why do ACA lesions progress from the distal part of the extremity to more proximal sites, why is spreading so slow, and why is bilateral involvement more often on hands than on feet?

Diagnosis of ACA is based on the suggestive clinical presentation, demonstration of borrelial serum IgG antibodies and histological findings compatible with ACA. Although the histopathological pattern of ACA is not diagnostic per se, it is sufficiently characteristic to alert the experienced pathologist [15, 37]; in our patient group, histological findings were indicative of ACA in nearly 90%, whilst in the remainder it was suggestive (Table 2). We found at least one clinical sign of skin atrophy in 59% of our patient group overall. As expected, atrophy was associated with duration of the lesions: signs of atrophy were present in 51% of patients with ACA duration up to a year and in as many as 70% of patients with longer duration ($P < 0.001$). However, we also found signs of skin atrophy in some patients with relatively short ACA duration.

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### Table 3 (Continued)

| Covariate                                      | Univariate analysis OR (95% CI), $P$ | Multivariable analysis$^g$ OR (95% CI), $P$ |
|------------------------------------------------|-------------------------------------|-----------------------------------------------|
| Local swelling                                 | 3.76 (1.20–11.71), 0.023             | 3.80 (0.99–14.53), 0.051                       |
| Signs of skin atrophy$^f$                      | 0.88 (0.29–2.63), 0.814             | 1.24 (0.33–4.62), 0.751                       |
| Signs of arthropathy$^i$                       | 3.56 (0.68–18.67), 0.133             | 11.74 (1.48–93.07), 0.020                      |
| Skin histology indicative of ACA$^b$           | 0.51 (0.10–2.50), 0.406             | 0.30 (0.05–1.91), 0.204                       |

OR, odds ratio, CI, confidence interval, ACA, acrodermatitis chronica atrophicans, EM, erythema migrans.

$^a$Intercept: estimated coefficient 0.48 (95% CI: 0.20–1.15), $P = 0.099$.

$^b$For duration of ACA (no information available for 84/693 patients) and skin histology indicative of ACA (information not accessible for 126/693), the mean of missing values was imputed. The information was complete for the other covariates included in the analyses.

$^c$Arthralgia and/or headache and/or myalgia and/or fatigue and/or vertigo and/or memory/concentration disorder.

$^d$Pain and/or burning and/or itching and/or paresthesia and/or hypesthesia.

$^e$Intercept: estimated coefficient 0.60 (95% CI: 0.21–1.69), $P = 0.335$.

$^f$Thin/atrophic and/or wrinkled and/or shining skin and/or venous prominence.

$^g$Intercept: estimated coefficient 1.85 (95% CI: 0.05–67.24), $P = 0.736$.

$^h$Pain and/or burning and/or paresthesia and/or hypesthesia and/or muscle paresis and/or muscle atrophy at the site of ACA skin lesion.

$^i$Arthritis and/or joint deformity.
duration, suggesting that in such patients the process of atrophy may begin within the first few months after onset of ACA. Nevertheless, as the onset is gradual, appreciation of the presence of the lesion may be delayed and assessment of its duration underestimated.

| Table 4 | Comparison of our results with previous reports on ACA |
|---------|--------------------------------------------------------|
| Number of patients | 693 | 50 (15–111)\(^b\) |
| Sex and age | Female 66% | ~ |
| | Median age 64 years | Asbrink [18] |
| | | Brehmer-Andersson et al. [19] |
| | | Hulshof et al. [20] |
| | | Strie et al. [16] |
| Duration | 12 months | ≥ 24 months |
| | | Asbrink et al. [17] |
| | | Kindstrand et al. [21] |
| | | Lenormand et al. [22] |
| | | Picken et al. [23] |
| Location | Distal parts of extremities | ~ |
| | | Asbrink et al. [17] |
| | | Kindstrand et al. [21] |
| | | Kristoferitsch et al. [24] |
| Bilateral involvement | 42% | 20% |
| | | Tazelaar et al. [25] |
| Previous EM | 21% | 18–55%\(^c\) |
| | | Asbrink et al. [17] |
| | | Lenormand et al. [22] |
| | | Moniuszko-Malinowska et al. [26] |
| | | Picken et al. [23] |
| ACA–EM location matching | 35% | 18–24%\(^c\) |
| | | Asbrink [27] |
| | | Asbrink et al. [17] |
| | | Picken et al. [23] |
| Symptoms of peripheral neuropathy | 20% | 33–64%\(^c\) |
| | | Hopf [28] |
| | | Kindstrand et al. [21] |
| | | Kristoferitsch et al. [24] |
| | | Tazelaar et al. [25] |
| Signs of peripheral neuropathy | 0.4% | 9–11%\(^c\) |
| (muscle atrophy or paresis) | | Hopf [28] |
| | | Kindstrand et al. [21] |
| Signs of arthropathy | 4% | 26% |
| | | Hovmark et al. [29] |
| Positive skin culture | 30% | 22–40%\(^c\) |
| | 33% (without previous antibiotic) | Asbrink et al. [30] |
| | | Lenormand et al. [22] |
| | | Picken et al. [31] |
| | | Picken et al. [23] |
| Borrelia species | B. afzelii >>> B. garinii, B. burgdorferi s.s. | B. afzelii predominated |
| isolated from skin | | Picken et al. [23] |
| | | Rijpkema et al. [32] |
| | | Ružić-Sablić et al. [33] |
| Positive blood culture | 1% | 3 blood isolates (2 B. afzelii, B. garinii) |
| | | Maraspin et al. [34] |

\(^a\) Similar results.
\(^b\) Most studies reported specific clinical or microbiological aspects of ACA.
\(^c\) Range.

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Clinical presentation depends on the duration of most common, but not exclusive, causative agent. Usually affects older women.

ACA is a late manifestation of European LB that causes skin manifestations of LB (EM) is higher where the proportion of non-B. burgdorferi s.s. from the skin was comparable with EM isolation rate from skin was comparable with previous reports [22, 23, 30, 31]. Skin culture was more likely to be positive in patients with signs of arthropathy. Concerning blood isolates, 3 out of 4 were B. garinii, which is hard to explain, but the total number of blood isolates was small. Until now, only 3 blood isolates (2 B. afzelii, 1 B. garinii) have been reported from patients with ACA [34].

Our study is descriptive, but we hope our insights will encourage analysis of the clinically relevant mechanisms behind the findings. Our results are applicable to European regions with similar ratios of borrelial genospecies causing LB in humans but may not entirely apply to regions where the proportion of non-B. afzelii borreliae causing skin manifestations of LB (EM) is higher [23, 32].

Conclusions

ACA is a late manifestation of European LB that usually affects older women. B. afzelii is by far the most common, but not exclusive, causative agent. Clinical presentation depends on the duration of the ACA skin lesions and probably also on the Borrelia species causing the disease.

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Conflicts of interest

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Supporting Information
Additional Supporting Information may be found in the online version of this article:

Figure S1. Number of patients.

Table S1. Covariates used for testing associations with different outcomes.