

Report

Tickbite-associated chronic pruritic lesions in an Afro-descendant population in the Cauca Department, Colombia.**I. Clinical features and impact on health**

Niklas Weber¹, Julian Trujillo-Trujillo², MSc, Jürgen Krücken³, Dr. rer. nat.,
Christiane Michl¹, MD, Maryln E. Hidalgo⁴, PhD, Giovanni Appræez-Ippolito⁵, MD, PhD,
Felipe Castillo⁵, Hermann Feldmeier^{6,*}, MD, PhD and Cord Sunderkötter^{1,7,*}, MD

¹Department of Dermatology and Venereology, University Hospital Halle, Halle, Germany, ²Ministry of Health and Social Protection of Colombia, Bogotá, Colombia, ³Institute for Parasitology and Tropical Veterinary Medicine, Freie Universität Berlin, Berlin, Germany, ⁴Grupo de Enfermedades Infecciosas, Departamento de Microbiología, Pontificia Universidad Javeriana, Bogotá, Colombia, ⁵Secretaria de Salud Cauca, Popayan, Colombia, ⁶Institute of Microbiology and Hygiene, Charite-Universitätsmedizin, Berlin, Berlin, Germany, and ⁷Department of Translational Dermatoinfectiology, University of Münster, Münster, Germany

Correspondence

Niklas Weber
Department of Dermatology and Venereology
University Hospital Halle
Martin-Luther-University Halle-Wittenberg
Ernst-Grube-Str. 40
06120 Halle (Saale)
Germany
E-mail: niklasweber@posteo.de

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*Contributed equally.

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Introduction

Hard ticks (*Ixodidae*) belong to the order of ticks (Ixodida), which are considered to be one of the most significant group of vectors for the transmission of human pathogens worldwide, second to mosquitos.^{1,2} In many areas, the local ticks transmit bacterial and viral infectious diseases, such as Rocky Mountain spotted fever or Ehrlichiosis. Owing to its salivary constituents,

Abstract

Background During a health survey in a remote area in southwest Colombia, it became apparent that a high percentage of the population suffered from chronic pruritus in association with high numbers of ticks and tickbites.

Objective To determine the clinical features and severity of tickbite-associated pruritus.

Method At twotime points – 8 weeks apart to account for seasonal effects – a cross-sectional study was conducted encompassing physical examination of the population, histological analysis of skin biopsies, and determining serum for antibodies against spotted fever (SFG) rickettsiae and typhus group (TG) rickettsiae. Ticks were identified using morphological criteria, and infection by rickettsiae was determined by PCR.

Results About 94.5% of the population (95% CI 92–97%) showed clinical signs of a pruritic arthropod reaction and of chronic pruritus with lichenoid papules and hyper- and hypopigmented nodules on otherwise noninflamed skin. Pruritus markedly impaired the quality of life in terms of sleeping disturbances. No signs for other diseases were observed. Chronic pruritus appeared to be because of repeated tickbites and scratching, but not because of other dermatological or medical conditions. Antibodies against SFG and TG-rickettsiae were detected at 79.0% (95% CI 73–86) and 3.6% (95% CI 0.7–6), respectively. Ticks were identified as *Amblyomma cajennense*.

Conclusion Remarkably high exposure to tick bites caused an unusually high rate of acute and chronic pruritus and markedly impaired quality of life of the investigated rural community. This underlines the necessity of public health measures and surveillance of rickettsial disease.

the tick bite is usually asymptomatic, and the attached tick is not noticed during bloodfeeding.^{3–8}

During a survey on ectoparasitoses, initiated by the Ministry of Health of Colombia, attention was drawn to a remote Afro-Colombian village in south-west Colombia, where people reported about repeated infestations with ticks in the field, associated with an unusually persistent or chronic pruritic dermatosis. These conditions affected almost all inhabitants and

seemed to lead to severe impairment in the quality of life of most, as well as to some individuals' reduced general activity. Such a high prevalence of tick bites associated with incapacitating chronic pruritus is noteworthy and deserves attention, also because ticks are known vectors for rickettsiae in South America,⁶⁻¹² and outbreaks of the spotted fever group rickettsioses have occurred in another area of Colombia.

Aims

The goal of the present study was to analyze this condition more closely. Therefore, our aims were to: (i) assess the prevalence of this chronic pruritic dermatosis and its impact on the quality of life, (ii) explore whether the tickbite-associated pruritus represents a severe form of an arthropod reaction¹³ or a form of chronic pruritus associated additionally with another disease, (iii) determine the tick species, and (iv) look for a possible correlation between pruritus and the prevalence of antibody titers against rickettsiae.

Materials and methods

Study area and study population

The study was performed in three rural Afro-Colombian villages located in south-west Colombia, 70 km from Popayán, the capital of the Cauca department (Fig. 1). The climate is warm (25 °C mean temperature) and humid with an average annual rainfall of 2.208 mm. The vast majority of the population in the study area includes subsistence farmers, cultivating maize, sugarcane, cassava, and passionfruit.

Study design

To account for seasonal effects, two cross-sectional studies were conducted at an interval of 8 weeks. The study was

performed as a door-to-door survey. Based on data from a recent census, the entire population was examined in La Alianza and Cabuyal. In Quilcacé only, households situated in the geographically separated southern part of the community were included in the study.

The aim of the study was explained to community leaders, health personnel, teachers, and other local stakeholders. All individuals encountered in the house at the time of the visit were included. Households were approached several times, but if any individual was not at home at the second and third visit, no further attempts were made, and the individual was excluded from the study. The first cross-sectional study was carried out between May and June 2017 (rainy season), and the second was conducted between August and September 2017 (dry season). The flow chart of the study is depicted in Figure 2. The data were collected through standardized interviews.

In this way, (i) a comprehensive examination in the population of three communities was conducted and the prevalence of tick-borne dermatitis was ascertained, (ii) its clinical and histological picture as well as its course were analyzed, and (iii) the species and its potential infection with rickettsiae species were determined, and (iv) titers of antibodies against rickettsiae in the affected population were measured.

Clinical examination

To determine the topographic distribution of the lesions, the body was divided into 11 areas, as defined and used previously.^{14,15} Individuals were asked about lesions in the genital, gluteal, and inguinal area, but these private areas were otherwise spared from the examination. Chronic pruritus was diagnosed according to the guidelines¹⁶: pruritus ≥ 6 weeks, history and/or signs of repeated scratching behavior (excoriations or scars, hyper- and hypopigmentation of lesions,

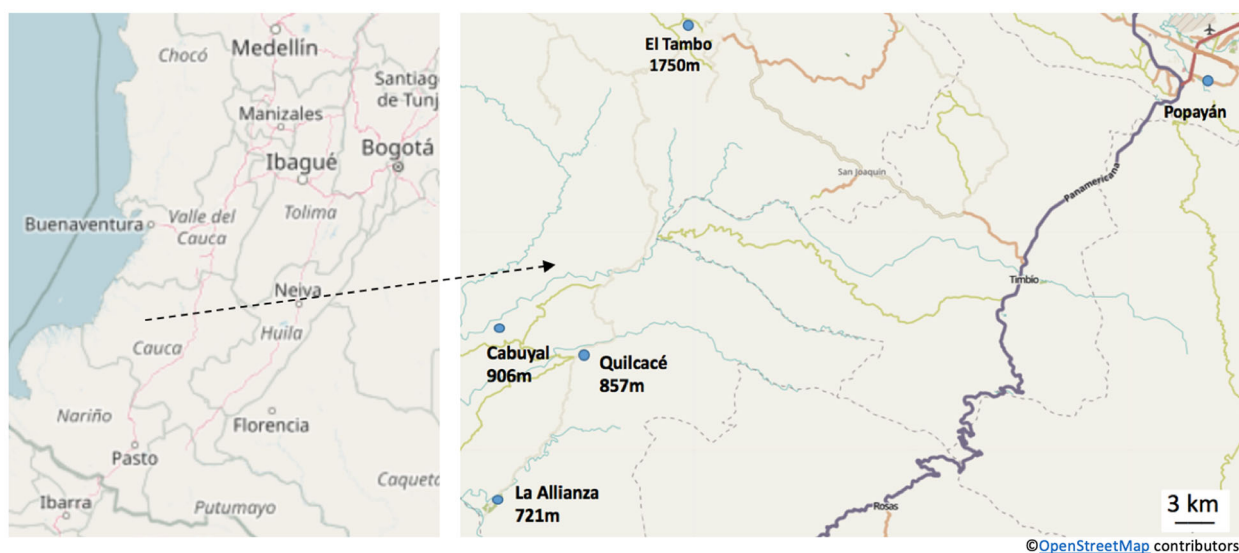


Figure 1 Study area (© OpenStreetMap contributors)

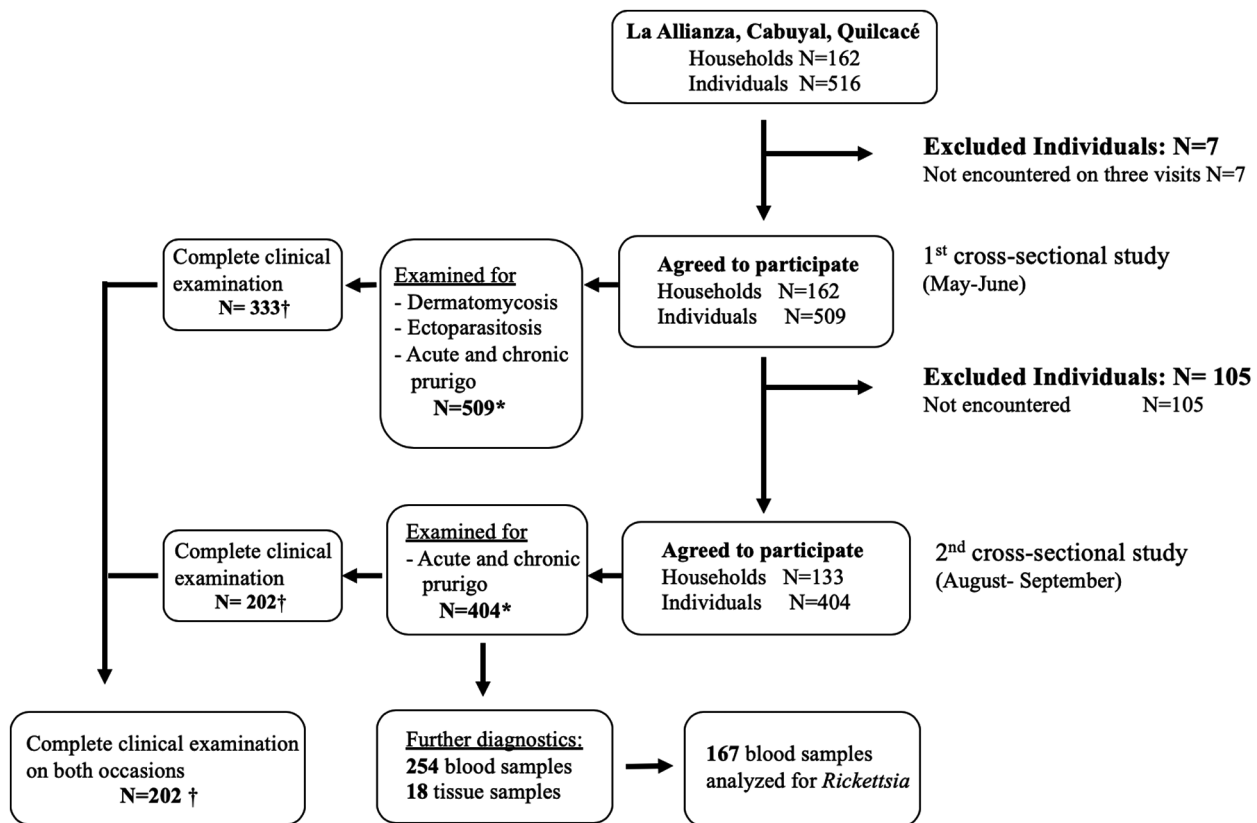


Figure 2 Flow-chart. *Including 176 participants, of whose the whole body except the upper leg was examined. †Participants, of whose the whole body was examined

and multiple pruritic papules or nodules [localized or generalized]).

Intensity of pruritus

Study patients were asked to scale their itching semiquantitatively, using a visual analogue scale (VAS), as absent (zero points), slight (one point), moderate (two points), important (three points), and severe (four points). The VAS has been validated in illiterate patients before.¹⁷ Established scales as mentioned in the prurigo guidelines,¹⁶ like the 10-point VAS, proved to be too complicated for the local population. Insomnia was classified by the patients as absent (zero points), slight (one point), moderate (two points), and severe (three points) (Fig. 3).

Biopsies and blood samples

Biopsies were taken from acute and chronic lesions with 3 mm biopsy punches (Kai Medical, Seki, Japan). Biopsies were preserved in 10% formaldehyde solution. Sections were stained with haematoxylin-eosin and then evaluated using microscopy and an image analyzer (Mirax Desk; CARL ZEISS MICROSCOPY, Göttingen, Germany).

Peripheral venous blood was obtained at the end of the second cross-sectional examination, centrifuged, and serum

was stored at -60°C . It was examined for IgG antibodies against SFG rickettsiae and TG rickettsiae using indirect immunofluorescence assays. As a cut-off level for SFG rickettsiae, an IFA-IgG titer of 1/128 was used, according to the manufacturer's recommendation for endemic areas¹⁸ (Rickettsia IFA IgG; FOCUS DIAGNOSTICS, Cypress, CA, USA); for TG rickettsiae, an IFA IgG-Cut off level of 1/64 was used.

Identification of ticks and molecular-biological analysis of ticks regarding rickettsia

To find out whether the local ticks are infected with rickettsial species of the SFG- or TG-variety, we collected 85 ticks of different developmental stages (69 larvae, 11 nymphs, and 5 adults). The collected ticks were either removed from the patient's body (73 ticks from 9 patients) or collected individually intra- and peridomiliary (i.e., found in and around patients' houses) (12 ticks). Ticks were conserved in 80% ethanol. Domestic animals were not examined for the presence of ticks. Ticks were identified by species using morphological criteria under a stereo-microscope.¹⁹ DNA was processed and analyzed for rickettsia using a PCR targeting the citrate synthase gene *gltA*.²⁰ Briefly, a 676 bp fragment was amplified using Phusion Hot Start II High Fidelity polymerase, and the

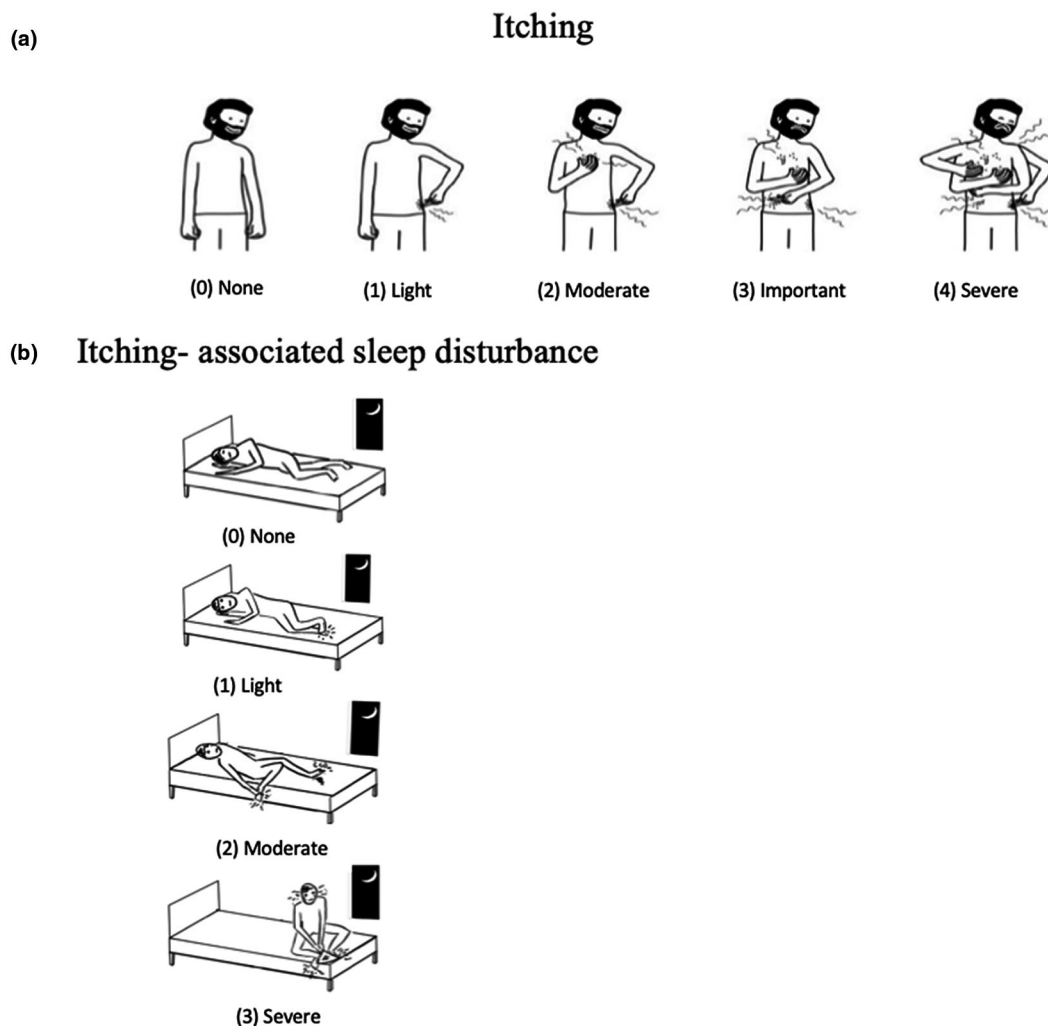


Figure 3 Visual scale for itching (a) and itching-related sleep disturbance (b)

detection limit of the PCR was established to be <5 copies/reaction.

Data storage and analysis

The data were entered in an Excel database (Excel Version 2011; Mac, Redmont, WA, USA). The statistical software STATA (Version 14, 2015; StataCorp LLC, College Station, Texas, USA) was used for data analysis. In descriptive statistics, the absolute and relative frequency of the binary variable were used. The Wilson method was used for calculating the 95% confidence intervals. Based on nonparametric data, median values and interquartile ranges (IQR) were used to indicate the average and the dispersion of tickbite lesions.

Ethical approval

The ethical approval was obtained by the Ethics Committee of the “Escuela Superior de Oftalmología del Instituto Barraquer de América”, Bogotá, Colombia. The patients as

well as parents or custodians, if patients were underaged, were informed about the objective and procedures of the study in their mother language and had the right to withdraw consent at any given time. Consent was obtained via signature from patient or the legal guardian. Examination of the skin and interrogation were performed in private and in case of children, in the presence of their caregivers. Treatment of dermatitis and other ectoparasitoses were provided free of charge and independent from potential withdrawal.

Results

Characteristics of the study population

At the end of the rainy season, 509 individuals (living in 162 households) were examined, and 404 individuals (living in 131 households) were re-examined in the dry season (drop-outs of 105) (Fig. 2).

Table 1 Demographic characteristics of households ($n = 162$) and household members ($n = 509$) at baseline

Characteristics	Community, n (%)			Total, n (%)
	La Alianza	Cabuyal	Quilcacé	
Number of households	77 (47.9)	65 (40.1)	20 (12.4)	162 (100)
Sex				
Female	128 (55.9)	98 (49.5)	33 (40.2)	259 (50.9)
Male	101 (44.1)	100 (50.5)	49 (59.8)	250 (49.1)
Age (years) ^a				
<1–4	20 (8.7)	13 (6.6)	7 (8.5)	40 (7.9)
5–10	26 (11.4)	23 (11.7)	8 (9.8)	57 (11.2)
11–20	39 (17.0)	40 (20.3)	16 (19.5)	95 (18.7)
21–40	67 (29.3)	48 (24.4)	13 (15.9)	128 (25.2)
41–60	46 (20.1)	40 (20.3)	25 (30.5)	111 (21.9)
>60	31 (13.5)	33 (16.8)	13 (15.9)	77 (15.1)
Persons per household				
1–2	30 (38.9)	27 (41.5)	3 (15.0)	60 (37.0)
3–4	37 (48.1)	26 (40.0)	11 (55.0)	74 (45.7)
≥5	10 (13.0)	12 (18.5)	6 (30.0)	28 (17.3)
Median	3	3	4	3
Children per household ^b				
0	35 (45.5)	34 (52.3)	9 (45.0)	78 (48.2)
1–2	36 (46.8)	26 (40.0)	9 (45.0)	71 (43.8)
3–4	6 (7.8)	5 (7.7)	2 (10.0)	13 (8.0)
Median	1	1	0	1
Educational achievement ^c				
Never went to school or primary				
School not completed	92 (61.3)	78 (61.4)	29 (52.7)	199 (59.9)
Primary school completed	39 (26.0)	35 (27.6)	12 (21.8)	86 (25.9)
Secondary school completed	19 (12.7)	14 (11.0)	14 (25.5)	47 (14.2)
Ethnicity ^d				
Afro-descendant ^e	225 (98.3)	198 (100)	82 (100)	505 (99.2)
Mestizo ^e	4 (1.7)	0 (0)	0 (0)	4 (0.8)

^aOne missing observation.

^b<16 years.

^cOnly adults ≥ 18 years ($n = 332$).

^dDetermined by self-classification.

^eReflects a population self-defined ethnicity according to the National Department of Statistics of Colombia.

The demographic characteristics of the three communities were similar (Table 1). Almost all (99%) of the residents were of African origin, calling themselves “*afro-descendientes*”, and 1% were of other ethnic origin. The median age was 30 years (range 92). About 60% of the participants had an education level that did not go beyond primary education. In 92.6% of the households, the monthly household income was less than the official minimum wage (239 US \$ per month at the time of the study); 99.2% of the male householdheads worked as farmers on a subsistence level.

Clinical findings

The clinical picture in all age groups comprised the eruption of mostly papules, few nodules (Fig. 4), and sometimes revealed a slight surrounding erythema (not always well detectable on dark skin). Affected patients showed a median of four papular

lesions (IQR 7). In a few cases, ticks were observed on the skin. Patients confirmed that lesions arose at the site of the tick bite or that they had observed ticks on their skin prior to new lesions. Correspondingly, some papules were reported to have been acquired a few days prior to our physical examination in conjunction with tick bites, others to have been present for up to 6–8 weeks.

Depending on the persistence of lesions, some had a small central erosion, compatible with acute pruritic lesions in terms of an arthropod reaction. Others showed larger erosions or excoriations or a lichenoid appearance because of scratching in response to marked itching. The nodules and healing lesions revealed peripheral hyperpigmentation and mostly central hypopigmentation (Fig. 5) (each patient had a median of 19 hyperpigmented lesions [IQR 27]) and reportedly had persisted for longer than 6 weeks. Predilection areas for acute and

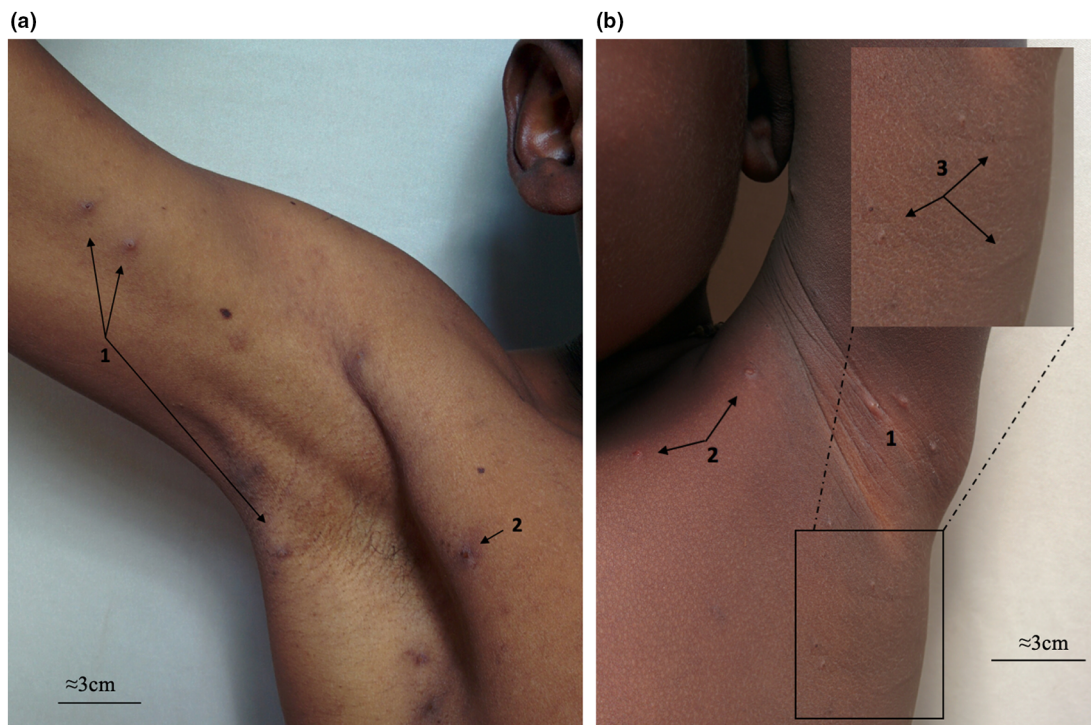


Figure 4 Clinical presentation of acute and chronic tick-borne dermatitis. (a) Acute tick-borne dermatitis at the right upper arm and axilla of an adult patient with multiple excoriated papular eruptions combined with a hemorrhagic crust (1) and a hyperpigmented halo (2). (b) Acute and chronic tick-borne dermatitis at left axilla of a child with multiple excoriated papules (1). Some lesions show a tiny central hemorrhagic crust (2). Chronic lesions with hyperpigmented halo and faint scratch marks are visible (3)

chronic tick bite lesions were in descending order of frequency the lower leg, upper leg, upper arm and lower arm, abdomen, back, and feet. Only few lesions were observed on the thorax and axilla. No lesions were encountered on the hands or head (Fig. 6). Private body areas that were excluded from the systematic medical examination, such as the gluteal and the inguinal area, also showed tickbite lesions. Affected individuals reported that papules or nodule eruptions had re-occurred in the same anatomical areas for several years. The remaining skin in most cases showed no other signs of inflammation or of another dermatosis that is associated with pruritus. Topographic distribution patterns indicate that the development of pruritic lesions was related to tick bites and that pruritus appeared to be permanently present, partially because of recurrent tick bites (Fig. 6) but partially also because of chronically itchy, lichenoid papules and pruritic nodules. The clinical pattern was therefore compatible with arthropod reactions and with chronic pruritus on primary nondiseased or noninflamed skin.

Chronic severe pruritus and pruritic lesions also occurred in the 1% non-“*afro-descendant*” participants.

Prevalence

Overall, 94.5% (95% CI 92–97%) of the population showed lesions compatible with acute or chronic pruritus. They all

confirmed that they had been in contact with ticks some time before the examination. So almost every examined individual had experienced a pruritic tickbite-induced papule, which owing to severe and repeated scratching had led to lichenoid, hyperpigmented, or hypopigmented lesions. Among all participants, 47.5% (95% CI 42–53%) additionally presented fresh papules after tick bites. In the dry season, the percentage of individuals affected with fresh papules rose to 62.9% (95% CI 56–70%).

Animals such as dogs, horses, and donkeys were seen to be heavily affected by tick infestation but were not examined systematically.

Symptoms and impact on quality of life

Itching was reported by 39.9% (95% CI 35–45%) of the population at the end of the rainy season and by 45.1% (95% CI 38–52%) in the dry season. Among the patients with pruritic tickbite lesions, 52.3% suffered an important to severe form of pruritus.

Those individuals who denied itching at the time of questioning presented mostly with lesions of chronic pruritus, rather than acute pruritus, while stating that they had had pruritus in the past. Affected children were reported to have attention deficits at school. Furthermore, affected patients complained about the

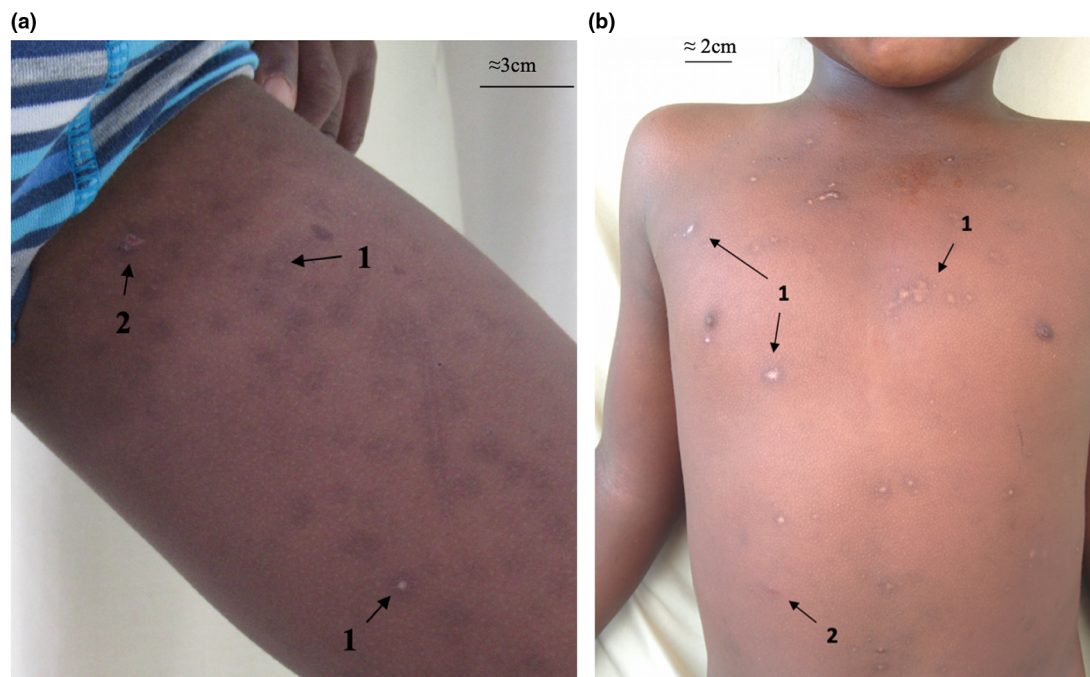


Figure 5 Clinical presentation of a chronic tick-borne dermatitis. (a) Left upper leg of a boy with multiple hyperpigmented lesions (>30). Lesions show a central hypopigmentation with a peripheral hyperpigmentation (1) and excoriations (2). (b) Thorax of a boy with multiple hypopigmented lesions with a hyperpigmented surrounding (1) and papule (2)

cosmetic appearance of multiple lesions and tried to cover them with long clothing.

In 76.6% of the population pruritus, started immediately after noticing a tick bite, while in 22.5%, itching began after 1–5 hours. More than half of the individuals reported the pruritus was intense throughout the day. Severe pruritus was responsive to antihistamines (cetirizine, loratadine, 100 mg/day). At follow-up visits, each household received a hand-out related to: (i) the ticks' life-cycle, (ii) infectious pathogens, and (iii) tickbite prevention, such as regular bush and weed control, avoidance of livestock in and around the households, and treatment of livestock according to the local official recommendations.

Histopathology

Biopsies were obtained from 18 patients. Seven biopsies were taken from papules shortly after tick bites. They revealed an acanthotic epidermis and dense perivascular and interstitial infiltrates of eosinophils in the stratum papillare and reticulare. In one case, “flame figures” were seen in the stratum reticulare (Fig. 7a). Eleven biopsies were obtained from chronic (older) hyperpigmented or hypopigmented lesions. They showed hyperkeratotic and acanthotic epidermis with a perivascular and interstitial infiltration of sparse lymphocytes but not eosinophils (Fig. 7b) around dilated vessels of the superficial vascular plexus and capillaries.

These findings were compatible with an acute arthropod reaction and chronic prurigo papules or nodules, respectively. No characteristic signs for foreign body reaction, eczema, delayed hypersensitivity (DTH) reaction (no spongiosis), or infection (no accumulation of neutrophils or plasma cells) were revealed.

Serology for *Rickettsia* in the population

In 79.0% (95% CI 73–85%) of 167 serum samples, the presence of antibodies against SFG-rickettsiae was demonstrated, but no clinical case of rickettsiosis was observed.

Antibodies against the TG-rickettsiae were detected in 3.6% (95% CI 0.7–6%).

Identification of ticks and molecular-biological analysis of ticks regarding rickettsia

Local ticks were collected and identified as *Amblyomma cajennense*. Further, *Rhipicephalus microplus* was observed attached to cattle and horses that were kept by the villagers. *Rhipicephalus microplus* mainly parasitizes livestock, hence only *Amblyomma cajennense* were processed and tested by PCR for rickettsiae. None of the DNA pools ($n = 17$) was tested positive for DNA of rickettsiae of the spotted fever group and typhus group, indicating that the collected local ticks did not harbor these rickettsiae at time of capture.

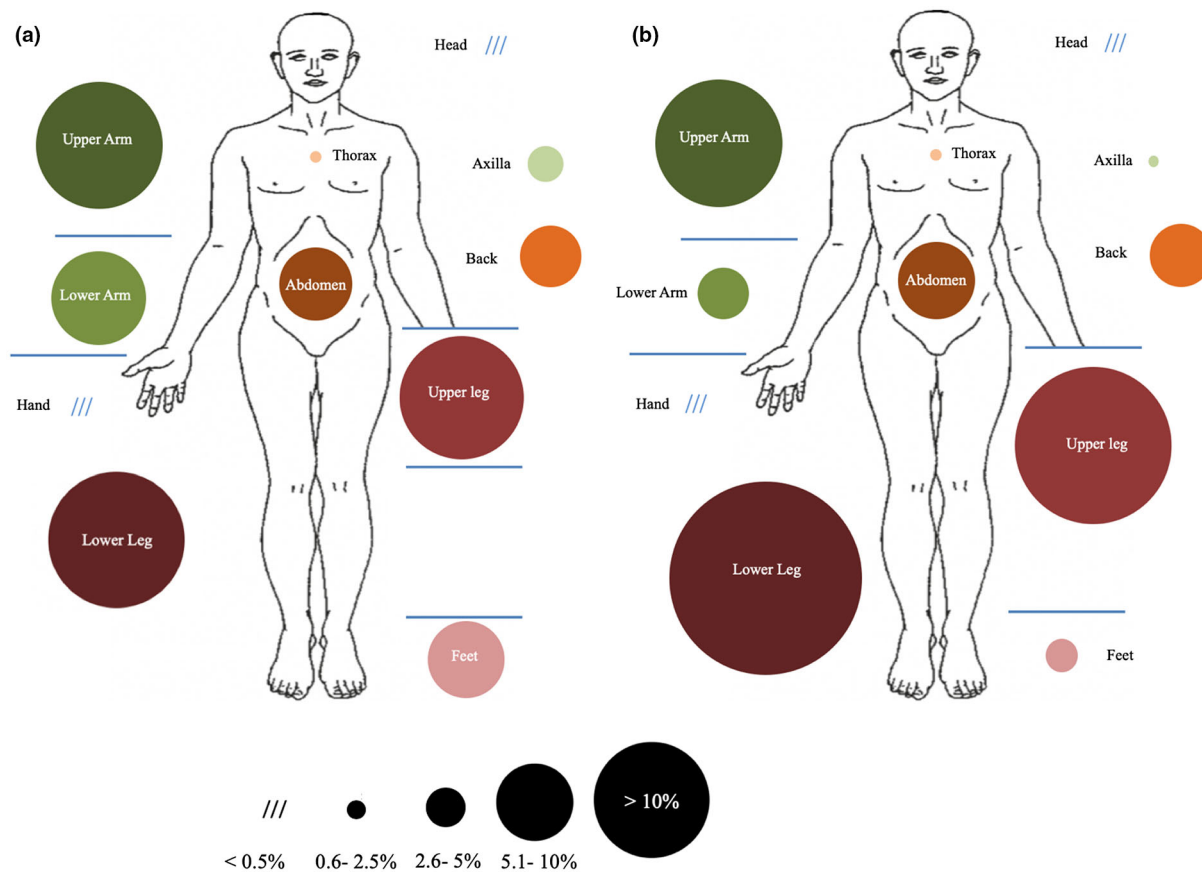


Figure 6 Comparison of topographical distribution of all acute tick-borne lesions^a (a) and all hyperpigmented and hypopigmented lesions^b at baseline. ^aTotal number of acute lesions: 1,070 in 158 patients. ^bTotal number of chronic lesions: 8,444 in 315 patients

Discussion

Our field study showed that a high percentage of the population suffered from both acute arthropod reaction and chronic pruritus on primary nondiseased or noninflamed skin. In about half of the cases, pruritus was intense and lasting, which considerably impaired the life quality of affected patients, including sleep disturbances and their sequela. Patients felt ashamed because of the cosmetic appearance of multiple lesions, which they consequently covered with long clothing.

The clinical, epidemiological, and histopathological observations were compatible with a primary arthropod reaction as a result of numerous and repeated tickbites and ensuing chronification of several pruritic lesions. It did not present a form of pruritus independent from tick bites, for example, owing to an underlying disease or condition.

Attachment of hard ticks is usually painless.³⁻⁸ In some cases, an ensuing immediate reaction of the host may occur manifesting as acute pruritic papular dermatitis,⁸ but this is not a common or inevitable reaction (in contrast to e.g., most

mosquito bites). There have been single reports of patients presenting multiple pruritic tickbite lesions, in the form of papules²¹⁻²³ and nodules^{24,25} (Southern Kentucky, USA,²¹ Japan,^{22,23} Madras, India,²⁴ and Belize²⁵). Most of the cases were caused by larvae and were initially often misdiagnosed as scabies or pubic lice. In contrast to the high prevalence and persistence in our population, the pruritic reaction in these reports appears to have been temporary and restricted to individual cases.

While the high number of lesions determined in our study population was remarkable in itself, clinical characteristics of tickbite-related chronic pruritic skin diseases have, to our knowledge, not been described before on a population level.

The reasons for the acute and persistent pruritus are not well known. Intense immediate pruritus in conjunction with tick bites is remarkable, as components secreted along with saliva usually inhibit pruritus and pain, thus preventing the host from perceiving the blood feeding tick.³⁻⁷ We can only speculate whether the saliva of the local *Amblyomma cajennense* (*A. cajennense* is a complex encompassing at least six different

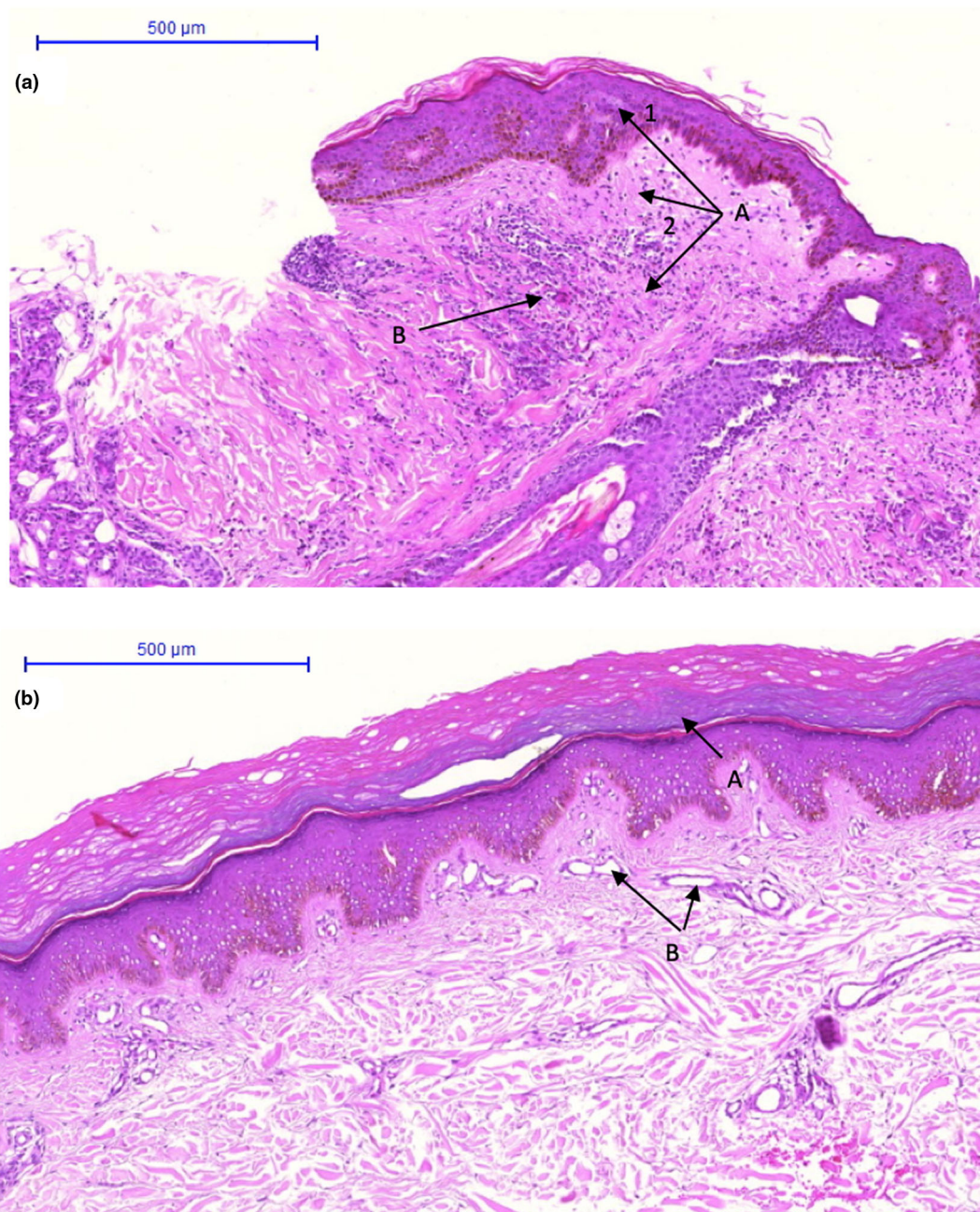


Figure 7 Histopathology of acute (a) and chronic (b) tick-borne dermatitis after hematoxylin and eosin staining (magnification $\times 10$). (a) Acute arthropod reaction with an eosinophilic infiltration in epidermis (A1) and stratum papillare and stratum reticulare of the dermis (A2) and a flame figure (B). (b) Chronic arthropod reaction with a hyperkeratotic and severe acanthotic epidermis (A). Superficial vascular plexus and capillaries are dilated (B)

species,²⁶ of which *Amblyomma patinoi* is present in Colombia and reported to be a main vector of rickettsia²⁷) would contain less anesthetic and itch-suppressing properties than the saliva of other ticks, for example in central Europe. Although this may entail a putative evolutionary disadvantage, because pruritus

eventually disturbs the tick's blood meal, this argument seems less convincing when one considers that livestock are the primary hosts of *A. cajennense* in South America,²⁸ which cannot remove ticks from their body parts as efficiently as affected humans.

A further hypothesis could suggest a genetically determined susceptibility within the rural, formerly isolated, population. However, since the 1% non-“afro-descendent” participants presented similar clinical symptoms as the “Afro-Colombian” patients, this assumption is not well supported.

Yet, the chronic pruritus is likely a result of additional factors. One component is certainly the lasting exposure to repeated tickbites, which provokes a vicious itch–scratch cycle sustaining pruritic nodules, a known etiology for chronic pruritus on primary nondiseased or noninflamed skin.^{16,29,30}

Pruritus could occur as a consequence of an allergic, that is, delayed type hypersensitivity (DTH) reaction and would then begin soon after tickbites in sensitized patients, but this does not explain its cause in the examined population, because the histological picture was not suggestive of a DTH reaction, be it in addition to arthropod reaction or not. Besides, one of the authors (N.W.) – who was never previously exposed to these ticks – also experienced pruritus within hours after he was infested by several larval-ticks. A granulomatous foreign body reaction because of retained mouthparts of ticks could be excluded by virtue of our histological findings.

Rickettsial infestation

The study population showed a remarkably high prevalence of rickettsial seropositivity (79.2%), higher than in studies conducted in northern Colombian regions (25%–41%)^{11,31,32} (IFA cutoff 1/64, 1/128, respectively). However, in our setting no manifest disease was observed or had been reported before. The results may be biased by cross-reactivity among SFG-rickettsial species in IFA.³³

The PCR analysis of the tick samples did not detect rickettsiae. Within the tick samples, most ticks were larvae ($n = 100$). Although the density of rickettsia is usually not as high in mature ticks as it is in larval ticks,^{34–36} our results indicate that at the time of our sampling, larvae were not infected with rickettsiae. Nevertheless, several individuals in the population must have had contact to rickettsiae, and the high prevalence of ticks poses a high-risk potential for endemic rickettsioses.

Conclusion

Exposure to tickbites was remarkably high within the examined communities in southwest Colombia and caused highly symptomatic acute and chronic pruritus, which markedly impaired their quality of life. This is unusual for tick bites. The high prevalence of antibodies against SFG-rickettsiae, which was previously unknown, is an alert. This demands further investigation of the local tick population, its pathogens, and seroprevalences. It is crucial to improve public health measures to prevent tick bites and tick-borne diseases, such as the emergence of rickettsial diseases.

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