



RESEARCH ARTICLE

Association of spirochetal infection with Morgellons disease

[version 1; referees: 2 approved]

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v1 First published: 28 Jan 2013, 2:25 (doi: [10.12688/f1000research.2-25.v1](https://doi.org/10.12688/f1000research.2-25.v1))
 Latest published: 28 Jan 2013, 2:25 (doi: [10.12688/f1000research.2-25.v1](https://doi.org/10.12688/f1000research.2-25.v1))

Abstract

Morgellons disease (MD) is an emerging multisystem illness characterized by skin lesions with unusual filaments embedded in or projecting from epithelial tissue. Filament formation results from abnormal keratin and collagen expression by epithelial-based keratinocytes and fibroblasts. Recent research comparing MD to bovine digital dermatitis, an animal infectious disease with similar skin features, provided clues that spirochetal infection could play an important role in the human disease as it does in the animal illness. Based on histological staining, immunofluorescent staining, electron microscopic imaging and polymerase chain reaction, we report the detection of *Borrelia* spirochetes in dermatological tissue of four randomly-selected MD patients. The association of MD with spirochetal infection provides evidence that this infection may be a significant factor in the illness and refutes claims that MD lesions are self-inflicted and that people suffering from this disorder are delusional. Molecular characterization of the *Borrelia* spirochetes found in MD patients is warranted.

Open Peer Review

Referee Status:

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How to cite this article: Middelveen MJ, Burugu D, Poruri A *et al.* **Association of spirochetal infection with Morgellons disease [version 1; referees: 2 approved]** *F1000Research* 2013, 2:25 (doi: [10.12688/f1000research.2-25.v1](https://doi.org/10.12688/f1000research.2-25.v1))

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Grant information: Partial funding for this study was provided by the Charles E. Holman Foundation, Austin, TX.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: RBS serves without compensation on the medical advisory panel for QMedRx Inc. He has no financial ties to the company. MJM serves without compensation on the scientific advisory panel of the Charles E. Holman Foundation. PJM and RBS serve without compensation on the medical advisory panel of the Charles E. Holman Foundation. DB, AP, JB, ES and DGK have no conflicts to declare.

First published: 28 Jan 2013, 2:25 (doi: [10.12688/f1000research.2-25.v1](https://doi.org/10.12688/f1000research.2-25.v1))

Introduction

Morgellons disease (MD) is an evolving skin disease associated with filaments found beneath unbroken skin or projecting from spontaneously-appearing, slowly-healing skin lesions¹. In addition to dermatopathy, patients may also exhibit debilitating musculoskeletal and neurological manifestations resembling the symptoms of Lyme disease^{1,2}. Similarities were found between MD and bovine digital dermatitis (BDD), a disease common in dairy herds and characterized by keratin filament formation in skin lesions that frequently occur above the hind feet of cows^{3,4}. Chronic BDD lesions demonstrate proliferation of long keratin filaments, and microscopic examination of histological sections from this tissue has revealed the presence of various *Treponema* spp. among enlarged keratinocytes throughout the stratum spinosum and dermal papillae⁵⁻⁹.

The etiology of BDD is considered to be multifactorial with involvement of spirochetes and other bacterial pathogens¹⁰⁻¹⁴. In the animal disease, repeated detection of spirochetes from lesions and sero-reactivity to *Borrelia burgdorferi* antigens provides evidence of spirochetal involvement¹⁰⁻¹⁴. Successful experimental infection with tissue homogenates and pure cultured treponemes has confirmed that spirochetes are primary etiologic agents^{15,16}.

Like BDD, MD filaments are produced by epithelial cells and stem from the stratum basale and from the root sheath of hair follicles, thus providing evidence that the filaments are cellular in origin^{3,4}. Furthermore, immunohistochemical and histological staining has demonstrated that these filaments have a collagen as well as a keratin component^{5,17}. Like cattle with BDD, patients with MD also produce antibodies reactive to *Borrelia burgdorferi* antigens¹⁸. Multisystemic symptoms resembling Lyme disease also imply a possible spirochetal etiology for MD^{1-3,18,19}. The frequent clinical diagnosis of Lyme disease and coinfecting tick-borne pathogens in MD patients suggests a multifactorial etiology and possible vectoring by ticks^{1-3,18,19}.

In light of the proven spirochetal association with BDD and the possible association with MD, we undertook a histological, electron microscopic and PCR study of MD dermatological tissue samples to investigate the presence of spirochetes in these samples. In addition, bacterial culture was conducted to investigate the possibility of viable spirochetes in MD tissue.

Materials and methods

Patient selection and dermatological samples

Representative non-biopsy dermatological specimens were collected from four randomly-selected patients who met the key clinical criterion for MD, namely that filaments visible with a hand-held microscope at 60X magnification must be present under unbroken skin or projecting from spontaneously appearing skin lesions. Patients 1 and 2 are Americans residing in Texas while patients 3 and 4 are Canadians residing in Alberta, Canada (Table 1). Written informed consent for submission of clinical samples and publication of clinical details and clinical images was obtained from each study subject. Patient anonymity and confidentiality were strictly maintained. The study was exempt from Institutional Review Board approval because all testing was performed as part of routine clinical care, and patient anonymity and confidentiality were strictly maintained.

The detailed histopathological findings in these patients were reported previously¹⁷. All patients were seroreactive to *Borrelia burgdorferi* antigens (strains B31 and 297, IGeneX Laboratory, Palo Alto, CA) and negative on rapid plasma reagin (RPR) testing (RPR Card Test Kit, BD Diagnostic Systems, Sparks, MD). Patient 1 was on doxycycline therapy for Lyme disease at the time of the study, while patient 2 had previously been treated with doxycycline for Lyme disease but had been off treatment for several years at the time of the study. Patients 3 and 4 were not on antibiotic therapy at the time of the study. None of the study patients had evidence of a delusional disorder, as determined by standard neuropsychiatric testing using the Rorschach, Minnesota Multiphasic Personality Inventory (MMPI), Millon Clinical Multiaxial Inventory (MCMI) and Wechsler Adult Intelligence Scale (WAIS) formats.

The late-stage BDD biopsies used for comparison were kindly provided by Dr. Dorte Döpfer, Faculty of Veterinary Medicine, University of Wisconsin, Madison, WI. Biopsies were taken as part of an intervention study conducted by the University of Wisconsin¹⁵. The diagnostic criterion for late-stage BDD was the presence of pronounced keratin projections from ulcerative lesions that were at least two centimeters in diameter and located above the heel bulb of the hind feet of cattle. Biopsy samples were stored and shipped in a fixative of 1.5% glutaraldehyde/1.0% formaldehyde in Sorensen's Buffer at pH 7.35 (Tousimis Research Corporation, Rockville, MD).

Table 1. Summary of Morgellons disease patient data.

Patient	Age/Sex	Residence	RPR	Lyme serology	Delusional illness	Antibiotic therapy	Coinfections
1	72F	San Antonio, TX, USA	Negative	Positive	None	Currently taking doxycycline	Babesiosis and Bartonellosis
2	49F	Hughes Springs, TX, USA	Negative	Positive	None	Previous doxycycline therapy	Ehrlichiosis
3	54F	Cardston, AB, Canada	Negative	Positive	None	None	Unknown
4	73F	Calgary, AB, Canada	Negative	Positive	None	None	Unknown

RPR, rapid plasma reagin test.

Duplicate samples were used for each of the light and electron microscopic studies described below.

Light microscopy

The gross morphology of dermatological specimens collected from Patients 1–4 was observed at 8X, 40X, and 100X magnification with illumination superior to the specimen, thus verifying the presence of filaments within and protruding from epithelial tissue. BDD biopsy material was examined at 8X to observe gross morphological characteristics.

Morgellons samples were formalin-fixed and embedded in paraffin, sectioned, and stained with Warthin-Starry and/or Dieterle silver nitrate-based staining for the light microscopic detection of spirochetes under oil immersion at 1000X magnification. Warthin-Starry staining and Dieterle staining were performed by Interscope Pathology Medical Group, Canoga Park, CA, and McClain Laboratories LLC, Smithtown, NY, respectively.

BDD biopsies were formalin-fixed and embedded in paraffin, sectioned, and stained for the detection of spirochetes by Warthin-Faulkner silver nitrate-based staining at Prairie Diagnostics, University of Saskatchewan, Saskatoon, Saskatchewan.

Formalin-fixed paraffin-embedded MD sections were processed for immunofluorescent anti-*Borrelia* staining and imaging as previously described²⁰ at the University of New Haven, West Haven, CT, by the following protocol: fixed specimens were pre-incubated with 10% normal goat serum (Thermo Fisher Scientific, Waltham, MA) in PBS containing 0.5% bovine serum albumin (BSA) (Sigma-Aldrich, St. Louis, MO) for 30 minutes to block non-specific binding of the secondary antibody. The slides were washed with PBS containing 0.5% BSA and then incubated for 1 hour with fluorescein isothiocyanate (FITC)-labelled *Borrelia*-specific polyclonal antibody (Thermo Fisher Scientific, #73005) at a 1:50 dilution in PBS containing 1% BSA pH 7.4. The slides were washed and then counterstained with 4', 6-diamidino-2-phenylindole (DAPI) for 10 minutes. In negative control samples, anti-specifically targeted antibody was replaced with normal rabbit IgG (Vector Laboratories, Burlingame, CA, #I-1000). Mounted slides were imaged using fluorescent microscopy.

Electron microscopy

Morgellons and BDD samples were fixed in buffered 2.5% glutaraldehyde. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were performed by the Electron Microscopy Facility, Department of Materials Science and Engineering, Clemson University, Anderson, SC, according to the protocols below:

SEM. Glutaraldehyde-fixed samples for SEM were washed in buffer and dehydrated in a graded series of ethanol concentrations. Samples were then immersed in hexamethyldisilazane (Electron Microscopy Sciences, Hatfield, PA) for 5–15 minutes and air dried at room temperature. Dried samples were mounted on A-1 mounts. Samples were not coated but placed into a Hitachi TM3000 microscope and imaged in the variable pressure mode.

TEM. Glutaraldehyde-fixed samples were washed in buffer, followed by dehydration in a graded series of ethanol concentrations. Samples were then immersed in a 50:50 mixture of LR White™ embedding resin and 100% ethanol for 30 minutes, followed by pure LR White™ resin until samples settled on the bottom of the vial. The resin-immersed samples were then placed into pure resin in beam capsules and put into a 60°C oven overnight for polymerization. Sections were cut on an Ultracut E microtome to produce sections 60–90 nm thick, placed onto copper grids and stained in uranyl acetate for 20 minutes. Images were taken on a Hitachi 7600 microscope.

PCR

Morgellons calluses from patients 1–4 were forwarded to Australian Biologics (Sydney, Australia) for *B. burgdorferi* detection by PCR using the Eco™ Real-Time PCR system with software version 3.0.16.0. DNA was extracted from the tissue samples using the QIAamp DNA Mini Kit (QIAGEN). The four samples were analyzed in duplicate with positive and negative controls using primers AB-B1 for the *Borrelia* 16S rRNA gene target, as previously described²¹. The thermal profile for all analyses involved incubation for 2 mins at 50°C, polymerase activation for 10 mins at 95°C then PCR cycling for 40 cycles of 10 secs at 95°C dropping to 60°C sustained for 45 secs.

The magnitude of the PCR signal generated (ΔR) for each sample was interpreted as positive or negative compared to positive and negative controls.

Borrelia spp. culture

Borrelia culture was performed as described previously²². *B. burgdorferi* was cultured in Barbour–Stoner–Kelly H (BSK-H) complete medium, with 6% rabbit serum (Sigma Aldrich, #B8291) and the following antibiotics: phosphomycin (0.02 mg/l), rifampicin (0.05 mg/l), and amphotericin B (2.5 µg/l) (Sigma-Aldrich) and incubated at 32°C with 5% CO₂. Cultured spirochetes were observed by dark-field microscopy and/or heat-fixed and stained with crystal violet (Dalynn Biologicals, Calgary, AB) under oil immersion at 1000X. For the immunofluorescence studies, cultured spirochetes (1×10⁷ individual spirochete cells) were centrifuged at 8,000×g for 10 minutes at room temperature, washed once with PBS pH 7.4, and then centrifuged again at 8,000×g for 10 minutes at room temperature. The pellet was resuspended in 100 µl of PBS pH 7.4, and then spread on microscope slides (SuperFrost+, Thermo Fisher Scientific). Spirochetes were fixed by incubating the slides in cold acetone for 10 minutes at -20°C. Slides were then washed twice with PBS pH 7.4 at room temperature, and immunofluorescent staining with polyclonal anti-*Borrelia* antibodies was performed as described above.

Results

Gross microscopic observations

Calluses from the four MD patients demonstrated white, red and blue filaments, alone or in any color combination, each 10 to 40 µm in diameter, embedded in or projecting from epithelial tissue (Figure 1A). BDD biopsies demonstrated pronounced, unusual keratin filament production typical of late-stage proliferative infection (Figure 1B).

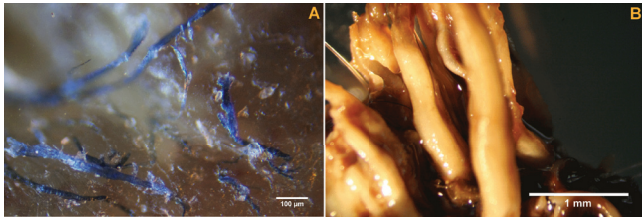


Figure 1. **A)** Morgellons disease filaments embedded in and projecting from epithelial tissue, 100X magnification. **B)** Proliferative bovine digital dermatitis (BDD) keratin filaments, 8x magnification.

A summary of the following histological, culture, electron microscopic and PCR results is shown in [Table 2](#).

Light microscopy

Silver nitrate-based staining. Staining of dermatological tissue from patients 1–4 revealed visible black-stained spirochetes among keratinocytes and inflammatory cells ([Figure 2A](#)). These spiral or curved structures ranged from 0.1 μm to 0.5 μm in diameter and up to 30 μm long, and they were present mostly in the interior areas of the sections and not along the peripheral edge.

Staining of BDD dermatological tissue revealed visible black-stained spirochetes among enlarged keratinocytes ([Figure 2B](#)). Spirochetes were approximately 0.1 μm to 0.2 μm in diameter and approximately 10 μm to 15 μm in length, and they varied in morphology from visibly spiral-shaped to straight or wavy in appearance.

Table 2. Summary of laboratory findings in Morgellons disease patients.

Patient	Silver nitrate staining	Culture	IFA staining	SEM/TEM	PCR
1	Spirochetes detected	Not performed	Positive, histological sections	Spirochetes observed, TEM	Weak positive
2	Spirochetes detected	Not performed	Positive, histological sections	Spirochetes observed, both SEM and TEM	Positive
3	Spirochetes detected	Positive, motile spirochetes detected, confirmed by IFA staining	Positive, both histological sections and cultured spirochetes	Not performed	Positive
4	Spirochetes detected	Positive, motile spirochetes detected	Positive, histological sections	Not performed	Negative

IFA, immunofluorescence assay; SEM, scanning electron microscopy; TEM, transmission electron microscopy; PCR, polymerase chain reaction.

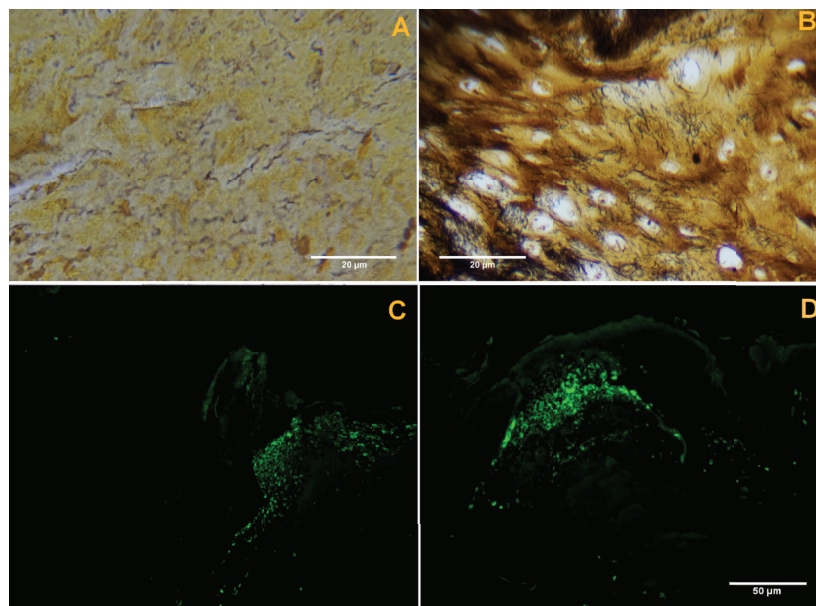


Figure 2. **A)** Black-stained spirochetes in representative tissue sample from patient 2. Dieterle stain, 1000X oil immersion. **B)** Black-stained spirochetes in bovine digital dermatitis (BDD) tissue sample, Warthin-Faulkner stain, 1000X oil immersion. **C)** Distinct patches of anti-*Borrelia* fluorescence in histological section of callus from patient 1, 400X magnification. **D)** Distinct patches of anti-*Borrelia* fluorescence in histological section of callus from patient 2, 400X magnification.

Immunofluorescent anti-*Borrelia* staining. Immunofluorescent anti-*Borrelia* staining of fixed *Treponema denticola* spirochetes was performed as a negative control and immunofluorescence was not observed for these specimens (data not shown). Histological sections of dermatological material from patients 1–4 all demonstrated distinct patches of immunofluorescence at a magnification of 400X (Figures 2C and 2D). Patches of fluorescence appeared to occur most often in areas of sections corresponding to fibroblasts. Cultured spirochetes from patient 3 also demonstrated positive immunofluorescent staining with anti-*Borrelia* antibodies (see below and Figure 5C).

SEM and TEM

SEM revealed high-resolution surface imaging of a spirochete lying beneath a layer of dermatological tissue of a Morgellons calus and images consistent with morphological forms of *Borrelia* spp. (Figures 3A and 3B). TEM imaging of both Morgellons caluses and BDD biopsies revealed spirochetes in cross-section (Figures 3C and 3D).

PCR

Real-time PCR analysis was positive for Borrelial DNA in tissue samples from MD patients 1–3 and negative in the sample from Patient 4. Samples from Patients 2 and 3 were clear positives and the sample from Patient 1 was a weak positive. The PCR profiles are shown in Figure 4.

Borrelia spp. culture

Motile spirochetes ranging from approximately 0.1 μm to 0.5 μm in diameter and up to 30 μm long were visible in cultures inoculated with dermatological tissue from both patients 3 and 4 (Figures 5A and 5B). Cultured spirochetes from patient 3 were identified as *Borrelia* by immunofluorescent staining with FITC-labelled polyclonal antibodies at 1000X magnification (Figure 5C). The culture obtained from the inoculum from patient 4 was lost due to contamination and generic identification was not obtained.

Discussion

The presence of spirochetes in MD dermatological specimens demonstrates that Morgellons lesions are associated with spirochetal infection. Unlike *Treponema pallidum* spirochetes, which are seldom detected in secondary and tertiary syphilitic skin lesions^{23–25}, spirochetes were readily detectable in dermatological tissue from four MD patients using a combination of immunohistochemical, electron microscopic and PCR techniques. Motile spirochetes were also observed in cultures inoculated with MD dermatological tissue, thus indicating that our specimens contained viable organisms. These findings are similar to the observation of significant spirochetal loads in lesions of cattle with BDD, suggesting that spirochetes could be associated with unusual filament production in both bovines and humans. Although Ekbohm reported that syphilitic infection was associated with feelings of infestation²⁶, to our knowledge dermal fibers have not been reported in patients with syphilis.

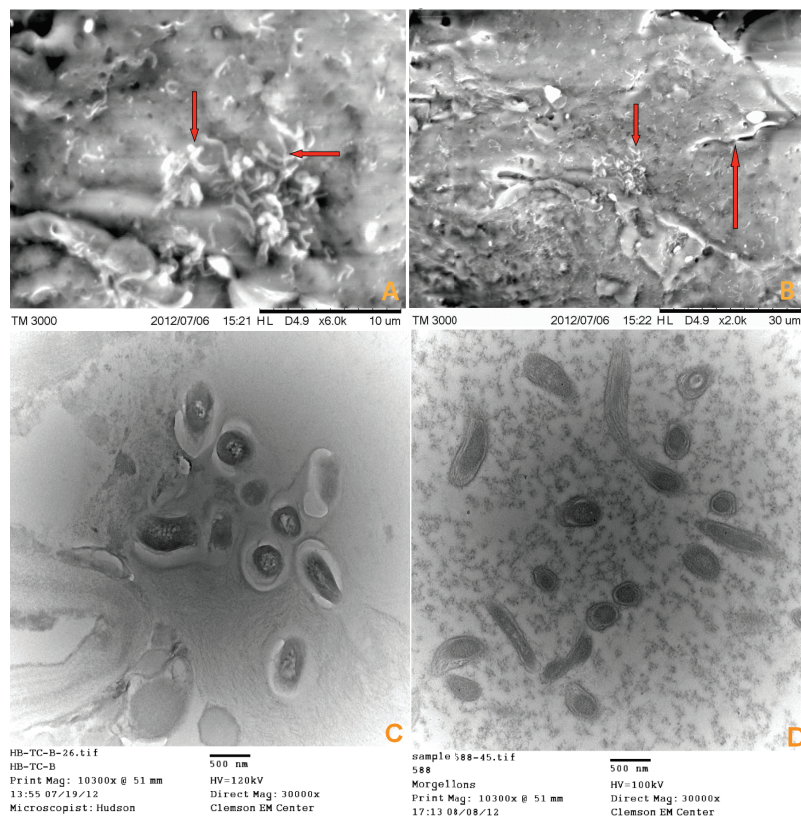


Figure 3. **A)** SEM from patient 2 tissue sample showing spirochete images that are consistent with morphological forms of *Borrelia* (arrows). **B)** SEM from patient 2 tissue sample showing single spirochete, upper middle right (long arrow) and morphological forms consistent with *Borrelia*, center (short arrow). **C)** TEM from patient 1 tissue sample showing sectioned spirochetes. **D)** TEM from BDD tissue sample showing sectioned spirochetes.

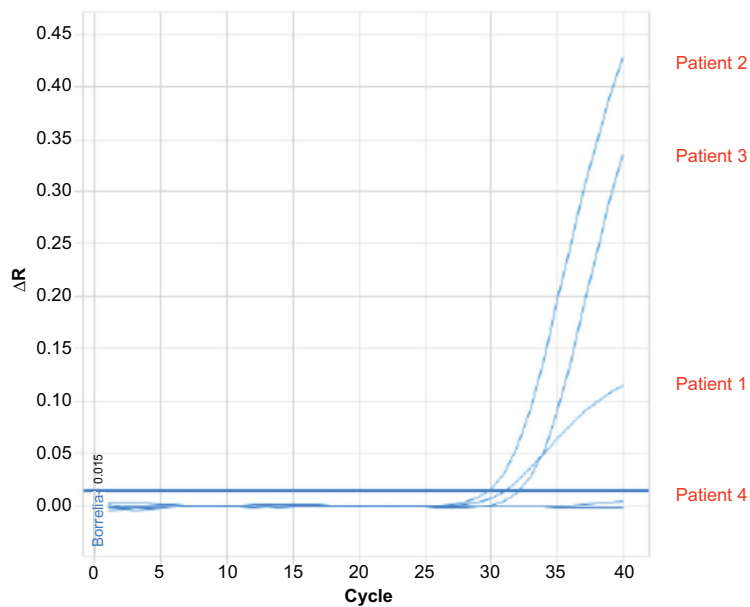


Figure 4. Results of polymerase chain reaction (PCR) amplification in tissue samples from patients 1–4. See text for PCR protocol. Samples from patients 2 and 3 were strongly positive, while the sample from patient 1 was weakly positive. The sample from patient 4 was negative.

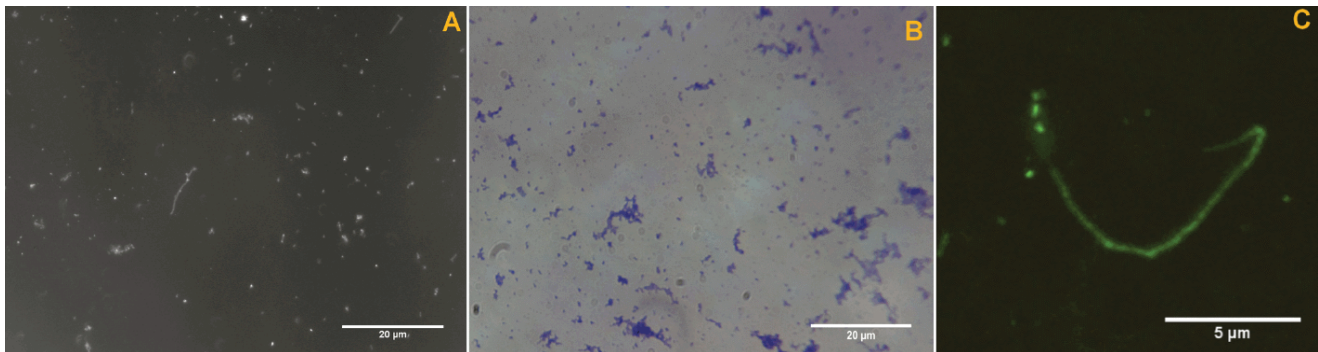


Figure 5. A) Cultured spirochetes from patient 3 tissue samples, 1000X darkfield microscopy, oil immersion. **B)** Cultured spirochetes in clumps from patient 4 tissue sample, heat fixed and stained with crystal violet, 1000X oil immersion. **C)** Borrelial spirochetes demonstrating fluorescence from tissue culture of patient 3, 1000X oil immersion, enlarged and cropped.

Unlike BDD, which is associated with a variety of treponemal spirochetes^{15,16}, the MD dermatological tissue in this study contained spirochetes that were identified as *Borrelia* by immunofluorescent staining with anti-*Borrelia* antibodies. Furthermore the MD spirochetes were specifically classified by targeted PCR as *Borrelia burgdorferi*. Given the fact that all four MD patients in this study were seroreactive to *Borrelia burgdorferi* antigens, some of which are thought to be species-specific, and were RPR negative, we speculate that the Morgellons phenomenon observed in our group of study patients is a manifestation of Lyme disease. At present it is not understood if MD filaments are associated exclusively with *Borrelia burgdorferi sensu stricto*, perhaps a particular genotype, or with a *Borrelia* species more appropriately placed in the *Borrelia burgdorferi sensu lato* complex. As our study sample was small, we cannot ascertain at this stage whether Morgellons

filaments are associated with spirochetes belonging to other genera as well as *Borrelia*.

The etiology of MD appears to be multifactorial, and at this stage secondary etiologic factors are not well understood. MD is most often reported in middle-aged Caucasian females. It is a disease reported mostly in the Northern Hemisphere, and it is often associated with known tick exposure, a Lyme disease diagnosis, and serological evidence of coinfecting tick-borne agents^{1,2,18,19}. Two of our study patients had laboratory-confirmed tick-borne coinfections (see Table 1), and these coinfections may contribute to the pathology of this disease.

The filaments seen in MD are composed of keratin and collagen derived from keratinocytes and fibroblasts, respectively^{4,17}. We

hypothesize that spirochetes associated with MD trigger the production of unusual collagen and keratin filaments. In our study, spirochetes were detected in Morgellons dermatological tissue from both Patient 1, who was currently taking antibiotics, and from Patient 2, who had been on antibiotic therapy in the past but was not on treatment at the time that samples were obtained. *B. burgdorferi* has been reported to invade human fibroblasts, and viable *B. burgdorferi* spirochetes have been isolated from lysates of fibroblast monolayers, even after antibiotic therapy²⁷. Our findings suggest that *Borrelia* spirochetes may be capable of sequestering within keratinocytes and fibroblasts, causing both persistent infection that is refractory to antibiotic therapy and aberrant fiber production by these infected cells in MD patients.

Despite contrary evidence, some medical professionals have attributed MD to delusions of parasitosis or delusional infestation. MD is thought to result from psychiatric illness and is diagnosed on the basis of patient belief in infestation by parasites, or the presence of inanimate objects such as fibers that are thought to be deliberately self-implanted^{28–32}. As stated above, spirochetal infection associated with itching and crawling sensations and feelings of infestation dates as far back as 1945 in Ekbohm's original description of delusions of parasitosis²⁶, and many of the patients in that study were diagnosed with syphilis. This clinical observation provides valuable insight into MD.

The insistence that MD is delusional has prevented the establishment of universally accepted, objective diagnostic criteria for this disease. Consequently, some studies have included diverse groups of research subjects, including patients who may not actually have had MD^{30–32}. In the present study, the key diagnostic criterion is that filaments visible with a hand-held microscope at 60X magnification must be present under unbroken skin or projecting from spontaneously-appearing skin lesions^{1,2}. This important clinical feature forms the basis for an accurate MD diagnosis.

Although a study from the Centers for Disease Control and Prevention (CDC) found no evidence that pathogens play a role in MD, the search for spirochetal pathogens in that study was confined to Warthin-Starry staining on limited tissue samples and commercial serological testing for *Borrelia burgdorferi*³¹. Tissue staining in that study was performed on samples from patients who reportedly did not have confirmed clinical evidence of MD³², and serological testing was interpreted in accordance with Lyme surveillance criteria that are inappropriate for clinical diagnosis³³. Thus the findings in the CDC study were influenced by failure to examine the appropriate group of patients and by the clinical insensitivity of surveillance testing for tickborne disease^{32,33}. These limitations leave open the possibility that a spirochetal association with MD could have been missed in the CDC study.

Controversy surrounding MD has been detrimental to those afflicted with this illness. It has stifled scientific research and has prevented appropriate treatment and control strategies from being investigated and implemented. In some cases it has resulted in treatment with ineffective and potentially harmful antipsychotic drugs^{28–32}. Some patients have been stigmatized by a diagnosis of mental illness that

resulted in social isolation, loss of employment, loss of custody of children, and a high rate of suicide (Casey C. 2012. Personal communication. <http://www.thecehf.org/>). Further MD research is urgently needed to delineate the possible infectious etiology of the disease and to assure that patients can be appropriately diagnosed and treated in the future.

Conclusions

This report demonstrates the presence of *Borrelia* spirochetes in dermatological samples collected from four MD patients who were seroreactive to *Borrelia burgdorferi* antigens. The findings suggest that MD has a spirochetal etiology and raises the possibility that this emerging dermatopathy may be a manifestation of Lyme disease in a subgroup of tickborne disease patients. The demonstration of an infectious agent associated with MD contradicts the belief that patients with this disease suffer from a factitious or delusional illness. Although our sample size was small, our study indicates that, at least in some patients, MD appears to be an important emerging infectious disease. Further research is needed to assure the correct diagnosis and define the optimal treatment for this spirochetal infection so that MD patients are not stigmatized with a diagnosis of mental illness.

Author contributions

MJM performed the light microscopic studies and spirochete cultures, coordinated the electron microscopic studies and wrote the original manuscript. DB, AP and ES performed the IFA studies. JB and PJM performed the PCR studies. DGK performed the immunohistochemical studies. RBS coordinated all studies, rewrote the manuscript and edited it for publication. All authors approved the manuscript for publication.

Competing interests

RBS serves without compensation on the medical advisory panel for QMedRx Inc. He has no financial ties to the company. MJM serves without compensation on the scientific advisory panel of the Charles E. Holman Foundation. PJM and RBS serve without compensation on the medical advisory panel of the Charles E. Holman Foundation. DB, AP, JB, ES and DGK have no conflicts to declare.

Grant information

Partial funding for this study was provided by the Charles E. Holman Foundation.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors thank Drs. Stewart Adams, Gordon Atkins, Robert Bransfield, Douglas Demetrick, Dorte Dopfer, JoAnn Hudson, Alan MacDonald, Elizabeth Rasmussen, Virginia Savely, Matthew Shawkey, Jyotsna Shah, Leo Shea, Janet Sperling, and Michael Sweeney for helpful discussion. We thank Dr. Robert B. Allan for technical support and Lorraine Johnson for manuscript review, and we are grateful to Harriet Bishop and Cindy Casey for providing first-hand information about Morgellons disease.

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Open Peer Review

Current Referee Status:



Version 1

Referee Report 03 April 2013

doi:10.5256/f1000research.304.r760



John English

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It would be nice to know if treating the *Borrelia* helped the Morgellons disease?

Publisher's note added on 19 Apr 2013: Since the publication of this referee report, a potential conflict of interest has come to light. It appears that just prior to John English completing his report, he and Peter Mayne had been collaborating on another manuscript. Following the publication of the article by *Middelveen et al.* in *F1000Research*, Peter Mayne asked Raphael Stricker to become an additional author on this subsequent manuscript, which has since been submitted to *F1000Research* with Stricker, Mayne and English among the authors. Given this potential conflict of interest, the original referee status has been greyed out on this report but the comments of the reviewer on the article are still accessible.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 03 April 2013

doi:10.5256/f1000research.304.r876



Bernhard Zelger

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 03 April 2013

doi:10.5256/f1000research.304.r867

**Judith Miklossy**

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Pathological characteristics of skin lesions in bovine digital dermatitis and Morgellons disease (MD) show strong similarities. As the role of spirochetal infection in bovine digital dermatitis is established in a comparative analysis, the authors examined the presence of spirochetes in Morgellons disease. They detected *Borrelia* spirochetes in skin lesions in four randomly selected Morgellons patients who were seroreactive to *Borrelia burgdorferi*. For the detection of spirochetes various techniques were used, including histochemistry, immunohistochemistry, electron microscopy and polymerase chain reaction. They conclude that spirochetal infection may be a significant factor in the illness and refute claims that the symptoms of patients are delusional and that Morgellons skin lesions are self-inflicted.

This is an important work showing invasion of skin lesions by spirochetes in four Morgellons patients with positive *Borrelia* serology. The manuscript is well written, and importantly, the authors used various techniques for the detection of spirochetes, which is crucial for such a study. Their results are convincing and only a few and minor comments or changes are suggested, and some propositions for future research. I share the opinion of the authors that these skin lesions are not self-inflicted and they do not correspond to delusional parasitosis. Infection is a significant factor in their pathogenesis.

1. "Representative non-biopsy dermatological specimens" or "representative tissue sample" might be better defined: In the Material and Methods it might be useful for those who would like to perform similar studies to indicate the site of tissue samples, their size and also how they were taken and how they were stored until the analysis.
2. With respect to the detailed histopathological findings of these patients, the authors refer to their previous report (Middelveen *et al.*, 2013) but an inflammatory component of skin lesions cannot be found, probably as skin biopsy was not performed. In future studies, the presence of an inflammatory reaction might be important to analyze as it will support an infectious origin of skin lesions.

3. Figures and figure legends

Figure 1: B) With respect to the keratin filaments of bovine digital dermatitis (BDD), it would be useful to insert the method used or refer to a previous publication.

Figure 2: Representative tissue sample – should be more precise. It is not clear whether panel A is a histological section or not? Paraffin or frozen section from skin lesions?

Figure 3: Panels A and B were both taken from the same region of a sample from patient 2. The presence of spirochetes is convincing, however the large "spirochete" in panel B is not comparable to the group of spirochetes seen in the center. I would suggest removing panel B.

Figure 5 : Panel B: Heat shock instantly induces atypical and agglutinated forms of spirochetes, therefore, this panel is not representative to show cultured spirochetes. I would recommend removing this panel. The authors have enough other convincing results. It is not necessary for the study.

C: Probably the spirochete was visualized by immunofluorescence using *Borrelia*-specific antibody. This should be mentioned.

4. "Although a study from the Centers for Disease Control and Prevention (CDC) found no evidence that pathogens play a role in MD, the search for spirochetal pathogens in that study was confined to

*Warthin-Starry staining on limited tissue samples and commercial serological testing for Borrelia burgdorferi*³¹. Tissue staining in that study was performed on samples from patients who reportedly did not have confirmed clinical evidence of MD³², and serological testing was interpreted in accordance with Lyme surveillance criteria that are inappropriate for clinical diagnosis³³. Thus the findings in the CDC study were influenced by failure to examine the appropriate group of patients and by the clinical insensitivity of surveillance testing for tickborne disease^{32,33}. These limitations leave open the possibility that a spirochetal association with MD could have been missed in the CDC study."

The work done by the "Unexplained Dermopathy Study Team" was an important initiative and a well organized and executed work (Pearson *et al.*, 2012), however the population examined in the study was indeed not homogeneous enough, which can make the interpretation of the results difficult. In case definition, to consider the presence of the unusual blue, red or white filaments and if possible, the same stage of skin lesion, would be important. That the authors of this paper examined four Morgellons patients with a positive serology for *Borrelia burgdorferi* and the case definition of CDC study did not include positive serology for this spirochete may also explain why they did not find *Borrelia* in their cases. The discrepancy of the results may also be explained if, following the example of bovine digital dermatitis (Döpfer *et al.*, 2012) we anticipate that various types of *Treponema* species might also be involved in MD. Perhaps the authors may wish to mention that further studies in this direction would be useful. Indeed spirochetes are present not only in ticks but in various other ectoparasites as well. Morphologically diverse populations of spirochetes are abundant and consistently present in termite hindguts (Paster *et al.*, 1996; Ohkuma *et al.*, 1999; Breznak, 2002). *Borrelia burgdorferi sensu lato* was also detected in mites (Netusil *et al.*, 2005). Spirochetes were detected in lice and also in snails around lakes and fresh waters (Sitnikova *et al.*, 2012). Both humans and cattle are at risk for infection.

5. "Filament formation results from abnormal keratin and collagen expression by epithelial-based keratinocytes and fibroblasts"; "Like BDD, MD filaments are produced by epithelial cells and stem from the stratum basale and from the root sheath of hair follicles, thus providing evidence that the filaments are cellular in origin. Furthermore, immunohistochemical and histological staining has demonstrated that these filaments have a collagen as well as a keratin component^{5,17}."

I would suggest to stay open with respect to the origin of dark and white filaments and just refer to the literature "it was suggested" or "reported" (References) as we have not enough data for a definite conclusion. Helminths show similar properties to those of Morgellons filaments. They show morphological similarities, they are birefringent, they show autofluorescence, and contain keratin- (Shibui *et al.*, 2001; Shinn *et al.*, 1995; Cottee *et al.*, 2006) and collagen-like proteins (e.g. Johnston, 1994; Yang *et al.*, 2012; Kingston and Pettitt, 1990). In schistosomiasis the coexistence of blue and white adult worms is well known. Particularly, the adult female is frequently described as a dark or dark-blue elongated filament (Figure 1 in Kolárová *et al.*, 2010), and cercarial forms (Figure 3 in Savely *et al.*, 2006), might also occur in Morgellons disease. The skin manifestations of cercarial dermatitis or swimmer's itch caused by bird schistosomes are also similar. Compare the skin manifestations in a Morgellons patient with a patient having cercarial dermatitis or swimmer's itch. I would encourage research in this direction. Recent findings show that the parasite may migrate throughout the viscera and the nervous system of mammals, suggesting that the pathogenicity of *Trichobilharzia* may have been underestimated in the past (Horak *et al.*, 2002). Schistosomiasis is one of the most prevalent parasitic infections worldwide. One should also consider that several helminths can infect together.

6. Melanin pigments are produced by a broad variety of microorganisms, including bacteria, fungi, and helminths (Taborda *et al.*, 2008, Esposito *et al.*, 2012) and a high amount of melanin accumulates in the host around invading worms and cercaria (Babu and Hall, 1974), In this view the Fontana-Masson-stained

section from patient 3 from a previous work of the authors (see Figure 3 in Middelveen *et al.*, 2013) demonstrating positive melanin staining “of blue filament sections (arrow)” might be compatible with helminthiasis.

7. Epidermal parasitic skin diseases occur worldwide and a wide range of parasitic infections can involve the skin and subcutaneous tissues, including protozoa, trematodes, cestodes, nematodes and arthropods (Goldsmid and Melrose, 2005). Despite the considerable burden caused by them, they have been widely neglected by the scientific community and health-care providers (Feldmeier & Heukelbach, 2009). The WHO has included them in a program to remediate this situation. Following the various findings available with respect to 'Morgellons disease' it seems that various parasites should be considered and investigated in each case. Efficient treatments would be available. In order to contribute to this goal and to avoid controversies, open discussions will be necessary. Further research is essential.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Discuss this Article

Version 1

Author Response 11 Mar 2014

Raphael Stricker, USMA, USA

Reply from Raphael B. Stricker, MD, and Marianne J. Middelveen, Mdes:

We would like to address the "Objection" to our study of Morgellons disease that was posted by Steven Salzberg on the *F1000Research* website. Salzberg has a PhD in computer science and appointments in genetic medicine, biostatistics and computer science at Johns Hopkins University. Based on his

comments he appears to have limited knowledge of the recent medical literature about Morgellons disease and limited understanding of the sophisticated scientific methods used in our study to demonstrate the presence of the Lyme disease spirochete, *Borrelia burgdorferi*, in patients with Morgellons disease.

Salzberg starts by praising the deeply flawed CDC and Mayo Clinic Morgellons studies, which were extensively criticized in the Discussion section of our article and elsewhere¹. For example, the retrospective CDC study by Pearson et al. failed to identify patients with dermopathy, used insensitive serological testing and limited tissue staining in an attempt to detect spirochetal infection, and failed to include specific culture or PCR testing for *B. burgdorferi* in any of their patients^{1,2}. The retrospective Mayo Clinic studies by Hylwa *et al.* noted that patients with “delusional” dermopathy had a high rate of psychiatric symptoms and no evidence of “infestation”. However comparable rates of psychiatric symptoms occur in patients with other chronic non-delusional medical conditions, suggesting that the symptoms are the result rather than the cause of the condition, and specific testing for spirochetal infection was not performed^{1,3}. Thus these flawed studies failed to look for the right infection in the right patients using the right techniques.

Salzberg goes on to say that our article is “little more than 4 PCR results”, ignoring the detailed culture, immunohistochemical and electron microscopical evidence presented in this study and in our previous investigations of Morgellons disease^{4,5}. He then misinterprets the PCR data, somehow confusing it with the study of Australian Morgellons patients who had spirochetes in their lesions that were shown to be *Borrelia garinii* by PCR in one case⁶. In fact, the Australian study confirms that *B. burgdorferi* strains are associated with Morgellons disease⁶. In the Discussion section of our article we made it clear that we had not subtyped the *B. burgdorferi* PCR sequences because we were only using PCR to confirm the extensive and convincing scientific findings in the rest of the study that point to *B. burgdorferi* involvement in Morgellons disease. Thus the weight of scientific evidence confirms an association between *B. burgdorferi* and Morgellons disease.

We think that it is irresponsible and antiscientific for Salzberg to characterize our careful, detailed, multifaceted and peer-reviewed article as “pseudoscience”, and his “Objection” has no merit. In contrast, the link between Morgellons disease and *B. burgdorferi* infection merits further scientific investigation.

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Competing Interests: None

Objection

Reader Comment (*Member of the F1000 Faculty*) 13 Oct 2013

Steven Salzberg, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, USA

This article contains very serious scientific flaws and should never have been published. The disorder called 'Morgellons Disease' (MD) was only recently described based on patients' own self-diagnoses, and it has been examined extensively and found to have no physical basis. The CDC reported (<http://www.cdc.gov/unexplaineddermopathy/>) that the fibers on the skin of patients were clothing fibers.

They also found that "Upon thorough analysis, most sores appeared to result from chronic scratching and picking, without an underlying cause". The CDC and a recent review from the Mayo Clinic (<http://www.ncbi.nlm.nih.gov/pubmed/22264448>) concluded that MD is a form of delusional parasitosis, and that patients complaining of Morgellons likely need psychiatric treatment.

The authors of this study deny the published evidence, and instead are trying to claim that MD is caused by a form of chronic Lyme disease. Chronic infection with *B. burgdorferi*, like MD, has been shown in multiple studies to have no scientific basis.

The evidence presented in this article is little more than 4 PCR results, of which one showed no evidence of *B. burgdorferi*, one was weakly positive, and two were positive. The sequences amplified, which are shown in the Opinion article (<http://f1000research.com/articles/2-118/v1>) but not here, supposedly have BLAST alignments to another *Borrelia* species, *B. garinii*, but the alignments are so weak that they could easily represent other common skin bacteria. The authors also fail to explain why the sequences don't match *B. burgdorferi*, the primary Lyme disease spirochete. Thus even their positive samples don't match the right species.

The claims and assertions made in this article are not only flawed, but they represent dangerous pseudoscience. Patients could easily be misled into taking long-term antibiotics for a condition that instead requires psychiatric care or other treatment.

Competing Interests: None
