Ticks and Tick-borne Diseases 15 (2024) 102255

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Original article

Is there Lyme borreliosis in French Guiana? Descriptive study among patients referred for a suspected Lyme borreliosis in an Amazonian hospital between 2010 and 2022

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ARTICLE INFO

Keywords:
Lyme disease
Borreliosis
French Guiana
Amazonia
South America
Functional somatic disorders

ABSTRACT

Lyme borreliosis (LB) existence in South America is debated, especially in the Amazon region. The infection with Lyme borreliae has never been reported in French Guiana where *Borrelia burgdorferi* sensu lato is not found in ticks. We describe the final diagnosis and presumed place of acquisition in patients consulting for suspicion of LB.

We retrospectively collected data from all consecutive patients consulting for a suspicion of LB between 2010 and 2021 at Cayenne Hospital, French Guiana. Patients were classified by an adjudication committee as *confirmed* LB if they met the criteria of the French consensus, as *possible* LB if they had compatible symptoms and a good outcome after appropriate treatment, or excluded when a differential diagnosis was found. The place of acquisition was discussed in case of possible or confirmed case.

Twenty-six patients were included. Rheumatologic symptoms were the most reported (88 %) followed by neurological symptoms (61 %). Twenty-four (92 %) of these patients were born out of French Guiana. Diagnosis of LB was considered as confirmed in 2 patients (8 %), for whom the place of acquisition was likely mainland France, and as possible in 3 patients (11 %) with early localized LB presumably acquired in French Guiana. Functional somatic disorders were diagnosed in 13 (50 %) patients whereas 9 (35 %) were found with another disease.

This study did not confirm the acquisition of LB in French Guiana. However, three possible autochthonous cases encourage clinicians working in the Amazon area to stay aware of LB.

1. Introduction

Lyme disease, also known as Lyme borreliosis (LB), is an old-described zoonosis (Steere, 1977) caused by *Borrelia burgdorferi* sensu lato (Bbsl) complex and transmitted by ticks of the genus *Ixodes* (Figoni et al., 2019). Several studies have focused on the epidemiological distribution of LB or this vector but most of these data come from high-prevalence areas like the USA or Europe (Nagarajan et al., 2023). There are still gaps in tick-transmitted diseases in South America (Mantovani et al., 2007; Lopes et al., 2017).

French Guiana is a French overseas territory located on the north-eastern coast of South America and covered with an Amazonian rainforest over more than 95 % of its surface. Even if *Borrelia* species have already been found, notably in bird-associated ticks in French Guiana, its implication in possible human infection is unknown (Binetruy et al., 2020). No *Borrelia* sp. has been found in anthropophilic ticks in French Guiana (Duron, unpublished data), and no proven autochthonous case of LB has been described to date. Nevertheless, some patients regularly

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https://doi.org/10.1016/j.ttbdis.2023.102255
Received 9 May 2023; Received in revised form 25 August 2023; Accepted 1 September 2023
Available online 20 September 2023

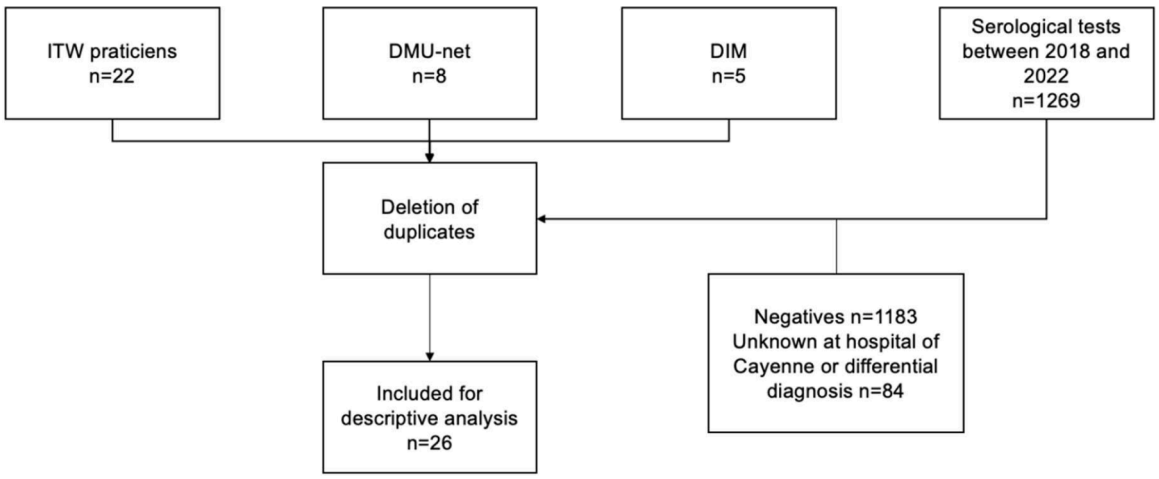

Fig. 1. Flow Chart, Selection of 26 patients who consulted at the Hospital of Cayenne with a suspicion of Lyme borreliosis between 2010 and 2021.
ITW: Interview; DMU-net: Dossier Médical des Urgences: Emergency Room Software, DIM: Département d'Information Médicale: Medical Information Department.

consult for suspicion of LB in the infectious diseases department of the general hospital at Cayenne.

We aim to describe the epidemiological, clinical, and biological characteristics of patients consulting for suspicion of LB in French Guiana to evaluate the final diagnosis and assess potential autochthonous cases of LB.

2. Materials and methods

We performed a single-center, descriptive, retrospective study. All consecutive patients who consulted at the Hospital of Cayenne, the main city of French Guiana, for suspicion of LB between January 1st, 2010 and December 31, 2021 were included. The inclusion criteria were those at least 15 years old (y.o.), consulting for suspected LB, who were symptomatic, and having at least one serological test for *B. burgdorferi*. The exclusion criteria included those younger than 15 y.o. or who refused to participate.

Patients were recruited using different strategies. First, hospitalized patients with a diagnosis code of "Lyme disease" in the International Classification of Diseases 10 (ICD10) were extracted from the databases of the hospital. Second, patients consulting for suspicion of LB were recruited by interviewing treating physicians. Third, serological tests performed between January 2018 and May 2022 (previous serological tests were not exploitable) in the French Guiana laboratories depending on Eurofins-Biomnis were screened (kit LIAISON® Borrelia IgG and IgM, DiaSorin, and kit RecomLine Borrelia IgG and IgM, Mikrogen Diagnostik).

The following variables were collected: age, gender, birthplace, date of arrival in French Guiana, profession category, medical history, activity at risk of tick bites, history of tick bites, history of symptoms, results of serological tests, results of radiology and other biological exams, and treatment with outcome. Continuous variables were given in the median and interquartile range (IQR), and categorical variables were given in percentage.

Disseminated LB was confirmed according to the French and European criteria (Figoni et al., 2019; Stanek et al., 2011) as follows: (1) compatible medical history (with exposure to ticks) (2) clinical signs of LB (3) positive serological tests or other recommended biological tests (ELISA were considered positive if IgG $\geq$ 14 mIU/mL and IgM $\geq$ 21 mIU/mL; immunoblots were considered positive if at least two bands were positive, or using PCR in synovial fluid in case of arthritis, or with intrathecal synthesis of *Borrelia* specific immunoglobulin in cerebral fluid) and (4) a good outcome after appropriate treatment. Localized LB was suspected when the patient described a typical erythema migrans-like lesion (circular expanding rash) with a good outcome after appropriate treatment.

All files were retrospectively reviewed by an adjudication committee of four infectious diseases (ID) specialists (TC, LE, EC, and CE) from four different ID departments in France to evaluate the diagnosis of LB (confirmed, possible, or excluded) and raise the most probable differential diagnosis when LB was excluded. Functional somatic disorders (FSDs) were defined as various medical conditions characterized by persistent and debilitating physical symptoms without any clinical, radiological, or biological evidence supporting the diagnosis of LB or any other disease (Burton et al., 2020). Appropriate treatment was defined as one of the antibiotic therapies recommended by French guidelines (amoxicillin, doxycycline, or ceftriaxone; Jaulhac et al., 2019).

A number between 1 and 26 was attributed to each patient, alphabetically by the source of inclusion, and patients are denoted by Pt followed by this number below. The place of acquisition of LB was considered French Guiana if the patients did not travel outside the country during the month preceding the onset of EM and during the six months preceding the onset of signs of early disseminated LB.

The study was consistent with the French MR004 reference methodology and was performed under the control of the local department of clinical research (CIC Inserm 1424). All data were collected in an anonymized database. Each patient was contacted by telephone to obtain a nonobjection to the study. In case of no response, a letter was sent to evaluate their outcomes. The study summary was published on the health data hub register under French legislation.

3. Results

During the study period, 26 patients were included (Fig. 1). The characteristics of the patients are reported in Table 1. About half were male, and the median age at first consultation was 42.5 y.o. [IQR 33–51]. Most (73 %) displayed at-risk behavior, and 58 % had a tick bite history. Two patients were born in French Guiana and had never traveled abroad. Four were born abroad (Brazil, Peru, Senegal, and Reunion Island). The remaining 20 were born in mainland France. The median living time in French Guiana was 20 years [7–29] for those born elsewhere.

Patients reported mostly rheumatological symptoms, such as myalgia or arthralgia (88 %), followed by neurological symptoms (61 %). Asthenia was less described (46 %). Two of the 11 patients in whom the serological tests included an immunoblot were confirmed positive (18 %). Fifteen patients had two or more serological tests. Seven patients had serological tests performed that were not certified for humans in France, including one in a veterinary laboratory. The results of the first

Table 1
Epidemiological, clinical characteristics, biological and complementary exams, rate of final LB and differential diagnosis, and treatment of 26 patients with suspicion of Lyme borreliosis assessed at Hospital of Cayenne between 2010 and 2021.

Variable	Number of patients (n = 26)
Gender	
Male n (%)	14 (54)
Age at first consultation (years), median [IQ1-IQ3]	42.5 [33–51]
Place of birth	
Mainland France n (%)	20 (77)
French Guiana n (%)	2 (8)
Abroad including Reunion Island n (%)	4 (15)
Scholar level n (%)	
Middle school	3 (11)
High school graduate	1 (4)
Professional diploma	7 (27)
University graduate	14 (54)
Unknown	1 (4)
History of tick bite n (%)	15 (58)
Reported history of EM n (%)	7 (27)
Neurological signs n (%)	16 (61)
Headache, dizziness, concentration n (%)	15 (58)
Paresthesia or paresis n (%)	6 (23)
Diplopia or facial paralysis n (%)	3 (11)
Rheumatic signs n (%)	23 (88)
Myalgia n (%)	5 (19)
Arthritis, joints pain n (%)	19 (73)
Cardiac signs n (%)	3 (11)
Asthenia n (%)	12 (46)
Duration between first sign and first consultation, months (median, [IQR 1–3])	5.5 [2–44]
Serological test n (%)**	26 (100)
Negative n (%)	12 (46)
IgG+ IgM - n (%)	9 (35)
IgG - IgM + n (%)	5 (19)
IB + n (%)	2 (8)
IB+ on 11 IB practiced n (%)	2 (18)
At least one MRI or CT-scan n (%)	16 (62)
Electromyography n (%)	6 (23)
Lumbar puncture n (%)	4 (15)
LB diagnosis n (%)	
Possible localized stage LB	3 (11)
Confirmed disseminated LB	2 (8)
Differential diagnosis n (%)	22 (85)
Functional Somatic Disorder, n (%)	13 (50)
Neurological disorders	4 (16)
Infectious disorders	2 (8)
Rheumatologic disorders	2 (8)
Systemic diseases	1 (4)
Treatment n (%)	
Targeted antibiotic regiment	19 (71)
2 or more lines of treatment	11 (42)

IQ1–3: interquartile 1–3; EM: Erythema migrans; MRI: Magnetic Resonance Imagery; CT-Scan: Computed Tomography Scanner; IB: Immunoblot Blot; LB: Lyme borreliosis.
History of EM was defined by a reported EM by the patient, whatever it was objectivized by a physician or not.
Neurological signs were defined as headaches, dizziness, trouble of concentration, paresthesia, paresis, paralysis, or diplopia.
Rheumatic signs were defined as joint pains, bone pains, arthritis, or myalgia.
Cardiac signs were defined as chest pain, chest oppression, palpitation, abnormalities on electrocardiogram.
** Results of first serological test, in an certified laboratory.

ELISA serological tests are presented in Table 1. The median time from the first symptoms to the first consultation was 5.5 months [2–44].

Sixteen (62 %) patients had at least one MRI or CT scan. These exams contributed to a differential diagnosis in five cases. One helped diagnose myocarditis (Pt 22), whereas all others were within normal ranges. Six (23 %) patients had an electromyography, contributing to another diagnosis in three patients. Four (15 %) patients had a lumbar puncture, which was normal in three cases, whereas one had meningitis (Pt 25) (Table 1).

After the adjudication committee, two patients (Pts 11 and 22) were diagnosed with a confirmed disseminated LB (knee arthritis and myocarditis), three patients (Pts 3, 5, and 16) had possible localized LB, and 22 patients had an alternative diagnosis (including Pt 16 who also had a localized LB diagnosis).

Patient 11 was a 34 y.o. male suffering from left knee arthritis for more than three years. The patient reported lots of tick bites without skin reaction. The ultrasound found synovitis. The puncture of the synovial fluid found inflammatory liquid with 2880 leukocytes/mm^3 of which 84 % of polynuclear neutrophils. Moreover, the ANA, rheumatoid factor, HLA B27, and serology test for *Chlamydia trachomatis* were negative. The PCR test for *Borrelia* in synovial fluid was negative. The serology test for LB was positive with positive IgG (240 mIU/L), negative IgM, and a positive confirmation test by WB (four bands). We confirmed Lyme borreliosis-related knee arthritis. The patient was treated with doxycycline for three months with a good outcome.

Patient 22 was a 43 y.o. male who consulted at the emergency department for chest pain. The EKG was without abnormalities. Troponins were elevated, and the cardiac MRI concluded myocarditis. The investigations were negative for angiotensin-converting enzymes, ANCA and ANA. Serology tests for brucellosis, Q fever, and toxoplasmosis were negative. A biopsy of the salivary glands was conducted and was normal. The serology test for borreliosis was positive, with the IgG titer at 81 mIU/L, negative IgM, and a positive confirmation test by WB (two bands). We confirmed Lyme borreliosis-related myocarditis. The patient was discharged from the hospital after two weeks of treatment using ceftriaxone with a good outcome. He was then lost to follow-up.

Table 2 presents the details of the five patients with confirmed or possible LB.

Thirteen patients (50 %) were diagnosed with FSD. This diagnosis was associated with a vitamin C deficiency in one case (Pt 8) and with possible localized LB in another (Pt 16; Table 1). Nineteen patients (73 %) received appropriate treatment for LB, two (8 %) for a confirmed disseminated LB (Pts 11 and 22), and three (11 %) for a possible localized LB (Pts 3, 5, and 16). Others received treatment without a LB diagnosis. Eleven patients (42 %) received at least two treatments (Table 1).

Concerning the acquisition of LB in French Guiana, three patients (Pts 3, 5, and 16) with possible localized LB reported exposure in French Guiana. Four patients (Pts 1, 2, 10, and 20) experienced localized erythema after a tick bite in French Guiana but did not meet the diagnosis criteria for confirmed or possible localized or disseminated LB. The place of acquisition was likely in mainland France for the two patients with confirmed disseminated LB (Pts 11 and 22).

Appendix A details the results of the first serological test, the final retained diagnosis, and the treatment received for each patient.

4. Discussion

We showed that only 19 % of the patients had a possible or confirmed LB, whereas 50 % had FSDs. The two patients with confirmed LB probably acquired the disease in mainland France, whereas local acquisition may have occurred in three patients with possible localized LB. The precise place of infection was difficult to determine because of the retrospective approach. Indeed, all five patients were native to mainland France where many regions are endemic for Bbsl. Moreover, symptoms may appear months after exposure in cases of disseminated LB. Regarding the anamnesis of these patients, the two confirmed cases with LB were likely acquired in mainland France.

However, we considered three possible localized LB cases acquired in French Guiana, and four patients described skin lesions several years before consulting for a presumed chronic LB. Without a clinical picture and using a retrospective approach, it was not possible to confirm the EM diagnosis because various other kinds of skin reactions can occur after a tick bite or arthropod exposure (Haddad et al., 2018). Skin

Table 2
Epidemiological characteristics, clinical characteristics and results of complementary exams leading, and treatment received by two patients with a confirmed Lyme borreliosis and three patients with a possible Erythema migrans.

Pt	Age	Sex	Place of birth	Time between first sign and first consultation for Lyme disease	Symptoms	Result of serological test	Other complementary exams	Retained diagnosis	Treatment
3	70	F	Mainland France	12	EM ; Knee pain	IgG + (42mIU/L) IgM – WB -	0	Possible EM in FG	Doxycycline 100 mg td 14 days
5	72	M	Mainland France	1	EM	IgG (19 mIU/L) IgM -	0	Possible EM in FG	Doxycycline 100 mg td 10 days
11	34	M	Mainland France	47	Arthralgia, left knee arthritis	IgG + (240 mIU/L) IgM – WB + (anti-p100: 5,4, anti VlsE: 8, anti p41: 7,8, anti OspC: 7,4)	Ultrasound: knee synovitis. Synovial puncture: 2880 leukocytes per mm3, 84 % of polynuclear neutrophiles, negative direct examination, negative PCR for LB in synovial fluid, negative ANF, negative rheumatoid factor and HLAB27, negative serology test for *Chlamydiae*	LB related knee arthritis	Doxycycline 100 mg td 90 days
16	61	F	Mainland France	1	EM ; Arthralgia, cervical pains, headaches	Negative	Normal CT-Scan. Normal lumbar puncture with negative intrathecale synthesis of Borrelia antibodies. Negative serological test for HTLV, Q fever, HCV, HIV, EBV, CMV.	Localizated stade LB - FSD	Doxycycline 100 mg td 10 days - Intravenous ceftriaxone od 21 days
22	43	M	Mainland France	1	Chest pain	IgG + (81 mIU/L) IgM – WB + (VlsE: 68, anti-membrane lipids 44)	MRI : myocarditis. Negative ACE, ANCA, ANF. Negative serological test for brucellosis, toxoplasmosis, Q fever. Normal salivary glands biopsy	LB related myocarditis	Intravenous ceftriaxone 2 g od 14 days

Pt: patient; EM: Erythema migrans; M: male; F: female; LB: Lyme borreliosis; WB: Western Blot; MRI: magnetic resonance imaging; ACE:Angiotensin converting enzyme; ANCA: anti nuclear cytoplasmic antibody; ANF: antinuclear factors; td: twice daily; od: once daily; HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; HTLV: Human T lymphotropic Virus; EBV: Epstein Barr Virus; CMV: cytomegalovirus; FSD: Functional Somatic Disorder.
Bands of WB are expressed in intensity which is proportional to the rate of antibodies.

biopsies were not available to confirm or exclude the EM diagnosis. *Borrelia* was already found in the skin biopsies of EM of 22 patients in Amazonian Brazil, with a direct microscopic exam confirmed by PCR (Talhari et al., 2010). These possible cases of LB contracted in French Guiana encourage clinicians to be cautious about LB even in this territory.

Nonetheless, some literature supports the presence of LB in South America. The first case of probable LB contracted in South America was described more than 30 years ago (Yoshinari et al., 1989). Ticks from the genus *Ixodes ricinus* and *I. pararicinus* are described in Amazonian South America and could be a vector of LD (Robles et al., 2018). There is molecular evidence for the presence of Bbsl in *Ixodes* ticks in Uruguay, and transmission to humans is possible (Barbieri et al. (2013). Detection of the flgE gene by PCR in blood samples of three and four patients demonstrated molecular evidence of human infection by Bbsl in South America (Mantovani et al., 2012; Lopes et al., 2017). There is also serological evidence of Bb in Bolivia, Peru, and Columbia (Robles et al., 2018).

A LB-like syndrome known as Baggio–Yoshinari syndrome (BYS) in South America has similar symptoms but a higher rate of relapse episodes. The BYS is caused by other *Borrelia* and is transmitted by other ticks, such as *Amblyomma* or *Rhipicephalus* (Mantovani et al., 2007; Yoshinari et al., 2022). Serological tests adapted to LB seem to be less sensitive to detecting BYS, which could explain why de Oliveira et al. (2018) recently reported that only 0.2 % of the considered positive LB serological tests in South America were negative regarding CDC criteria and why patients with compatible symptoms could have a negative serological test even in the case of a real LD-like syndrome (Miziara et al., 2018).

In French Guiana (Binetruy et al., 2019), the presence of *Ixodes luciae* was recently found, parenting the *Ixodes* genus but was not anthropophilic, contrary to *I. ricinus, I. scapularis, I. pacificus,* or *I. persulcatus*, known vectors of LB. Transmission of *Borrelia* or other pathogens by *I. luciae* to humans is poorly studied but improbable. Another study found molecular evidence of *Borrelia* in neotropical passerine-associated ticks in French Guiana but not parenting the Bbsl group (Binetruy et al., 2020). Thus, no *Borrelia* sp. has been found in anthropophilic ticks in French Guiana (Duron, unpublished data).

The number of patients misdiagnosed because they are certain they are suffering from LB, reinforced by “Lyme Doctor” and patients associations, is to be questioned. We retained a high diagnosis rate (50 %) of FSD, a real recognized group of diseases (Roenneberg et al., 2019), with precise criteria, which is neither only a somatic disorder nor only a psychiatric disorder but also the result of the partially known interactions between these two parts (Burton et al., 2020). The rate of retained FSD was surprisingly higher in the studied population than in previous studies and could reflect the higher medical wandering in French Guiana than in mainland France. Surprisingly, this diagnosis was advocated in only one case (Pt 16), and the clinicians’ awareness of this disease should be questioned. The high rate of differential diagnosis of patients consulting for suspected LB shows the need for a rigorous approach to manage patients with nonspecific symptoms who are certain they have LB. The dedication to treat an inexistent LB is accompanied by adverse effects, leading to ignore a differential diagnosis with a potentially unfavorable evolution (Marques, 2008). Our role as a practitioner is to promptly find the correct differential diagnosis using a rigorous approach.

Appendix B compares the data to previous studies on this subject in mainland France.

Strengths and limitations

This retrospective study has an inherent bias in this method. The absence of proof of autochthonous cases could be explained by a lack of available data. Another limitation is the small sample size of patients consulting for suspected LB in this territory where LB is not described to date. This population did not represent the French Guiana population, where only 10 % came from mainland France. This study is monocentric,

but the hospital of Cayenne is the reference hospital for the territory, with about 800 beds and 42,000 hospital stays per year. Most patients with suspicion of LB in French Guiana would consult at this hospital. Finally, no data on the performance of validated serological tests are available in mainland France to diagnose LB in French Guiana if LB exists there.

5. Conclusion

This is the first study focusing on patients investigated for suspicion of LB in French Guiana. We retrospectively determined three possible localized LB acquired in French Guiana, but with no certainty, and two confirmed disseminated LB probably acquired in mainland France. Thus, we did not manage to prove the acquisition of LB in French Guiana, but physicians must be aware of the possible existence of this disease, although the bacterium has not been found in anthropophilic ticks in French Guiana, and no vector ticks of LB have been identified to date.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Tom Cartau: Conceptualization, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Carole Eldin:** Writing – review & editing. **Paul Le Turnier:** Writing – review & editing. **Anaïs Eskenazi:** Resources. **Gaëlle Walter:** Resources. **Catherine Coignard:** Resources. **Ward Schrooten:** Resources, Writing – review & editing. **Eric Caumes:** Writing – review & editing. **Félix Djossou:** Resources. **Loïc Epelboin:** Conceptualization, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Paul Le Turnier is currently benefiting from a grant from the Agence Nationale de Recherche sur le SIDA, les Hépatites et Maladies Infectieuses Emergentes (ANRS-MIE).

Data availability

Data will be made available on request.

Acknowledgments

We would like to thank all the clinicians and biologists of the Hospital of Cayenne, who helped us with pleasure and quickness to obtain the study data and cared for the included patients. We are thankful for the patients in this study who accepted inclusion despite the difficult journey.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ttbdis.2023.102255.

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