REVIEW ARTICLE
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Pure neural leprosy or amyloid neuropathy? Systematic review and clinical case report

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SUMMARY

OBJECTIVE: To review the literature and to report a clinical case with initial suspicion of pure neural leprosy and final diagnosis of amyloid neuropathy.

METHODS: The study was conducted in two stages. In stage one, a systematic literature review was carried out, with searches performed in the PubMed, Medline, and Lilacs databases, as well as in the leprosy sectoral library of the Virtual Health Library, using the following descriptors: neuritic leprosy, pure neural leprosy, primary neural leprosy, pure neuritic leprosy, amyloid polyneuropathy, amyloid neuropathies, and amyloid polyneuropathy. The search was carried out on May 28, 2020. Clinical trials, cohort studies, cross-sectional studies, clinical cases, and case studies published in Portuguese, English or Spanish between 2010 and 2020 were included. Stage two reports a case with initial suspicion of pure neural leprosy. Laboratory tests, electroneuromyography, ultrasound, and biopsy of the sural nerve were requested.

RESULTS: Twenty-three scientific texts were included. No publications were found that contained both topics together. The challenging diagnosis of pure neural leprosy and the possibility of using auxiliary resources in diagnosis were the most emphasized themes in the studies. In the clinical case, the patient's electroneuromyography showed sensitive and motor polyneuropathy of the lower limbs, which was predominantly sensory and axonal, symmetrical, of moderate intensity, and the mixed type (axonal-demyelinating). Ultrasonography of the sural nerve revealed changes in the contour of the deep fibular nerves; biopsy of the sural nerve showed an accumulation of amorphous eosinophilic material in the nerve path, and Congo red stain showed apple-green birefringence of the deposit under polarized light. The final diagnosis was amyloid neuropathy.

CONCLUSIONS: The final clinical diagnosis was amyloid neuropathy. The diagnosis of pure neural leprosy in endemic areas in Brasil is still a challenge for the health system.

KEYWORDS: Leprosy. Mycobacterium leprae. Amyloidosis.

INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae*, an acid-resistant bacillus with an affinity for the cutaneous and peripheral nerves[1]. The high disabling potential of leprosy can result in social, economic, and psychological damage to patients, expanding the context of social vulnerability[2-4].

Brasil ranks first in prevalence rate and second in the absolute number of new leprosy cases[5]. In 2018 alone, there were 28,660 new cases of the disease (13.70 cases per 100,000 inhabitants). Of these patients, 8.5% already had grade 2 disability at the time of diagnosis (10.08 grade 2 patients per million inhabitants)[6]. It is noteworthy that the goal recommended by the World Health Organization[7] is less than one grade 2 cases per million inhabitants.

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A leprosy case is defined as the presence of at least one of the three following main manifestations:

1. lesions and/or areas of skin with changes in thermal and/or pain and/or tactile sensitivity;
2. peripheral nerve thickening, associated with sensory and/or motor and/or autonomic changes;
3. and presence of *M. leprae* bacilli, confirmed by intradermal smear microscopy or skin biopsy[1,8].

The absence of dermatological lesions does not exclude the diagnosis of leprosy[8]. In these cases, the disease may present only neural involvement, which is known as pure neural leprosy[1,9].

The diagnosis of pure neural leprosy is more complex, since it involves the exclusion of other clinical processes that also result in peripheral neural lesions, such as diabetes mellitus, hypothyroidism, collagenosis, vasculitis, syphilis, AIDS, and other less common diseases, such as amyloidosis[9-11]. The lack of precise diagnostic methods for this type of leprosy renders the diagnosis challenging[10].

Systemic amyloidoses constitute a large group of diseases, in which the main characteristic is the formation of amyloid protein deposits in the extracellular environment[12], causing dysfunction of several organs, such as the heart, kidney, liver, gastrointestinal tract, and nerves[10,12,13]. Systemic amyloidoses can be primary, secondary to inflammatory and autoimmune diseases, or hereditary; they are classified according to the deposited amyloid protein[14,15]. The most common type is primary amyloidosis, also known as immunoglobulin amyloid light chain (AL) amyloidosis, in which deposits occur[15]. Another common type is transthyretin (TTR)-related amyloidosis, which is the main cause of hereditary amyloidosis[15].

Peripheral neuropathy is a common complication of many systemic amyloidoses, affecting approximately 17% of the patients with primary amyloidosis[15]. In TTR-related hereditary amyloidosis, there is severe peripheral neuropathy, with significant sensory and motor impairment and bed restriction a few years after the onset of the disease[15].

Based on the above, this investigation aims to review the literature on pure neural leprosy, including the discussion of a clinical case with initial suspicion of pure neural leprosy and a final diagnosis of amyloid neuropathy.

METHODS

A systematic literature review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] focusing on pure neural leprosy. Searches were carried out in the PubMed, Medline, and Lilacs databases, as well as in the leprosy sectoral library of the Virtual Health Library (VHL), using the following search strategies, with the necessary adjustments for each database: strategy 1- only for pure neural leprosy: "neuritic leprosy" OR "pure neural leprosy" OR "primary neural leprosy" OR "pure neuritic leprosy"; strategy 2- amyloid neuropathy and pure neural leprosy: "neuritic leprosy" OR "pure neural leprosy" OR "primary neural leprosy" OR "pure neuritic leprosy" AND "amyloid polyneuropathy" OR "amyloid neuropathies" OR "amyloid polyneuropathy". The search was carried out on May 28, 2020.

Clinical trials, cohort studies, cross-sectional studies, clinical cases, and case studies published in Portuguese, English or Spanish between 2010 and 2020 were included. The ten-year period was defined due to the need of maintaining the topic up-to-date with the promulgation of Ordinance No. 3125/2010, which approves the Guidelines for Surveillance, Attention and Control of Leprosy[8]. The systematic review was performed according to the following algorithm (Figure 1):

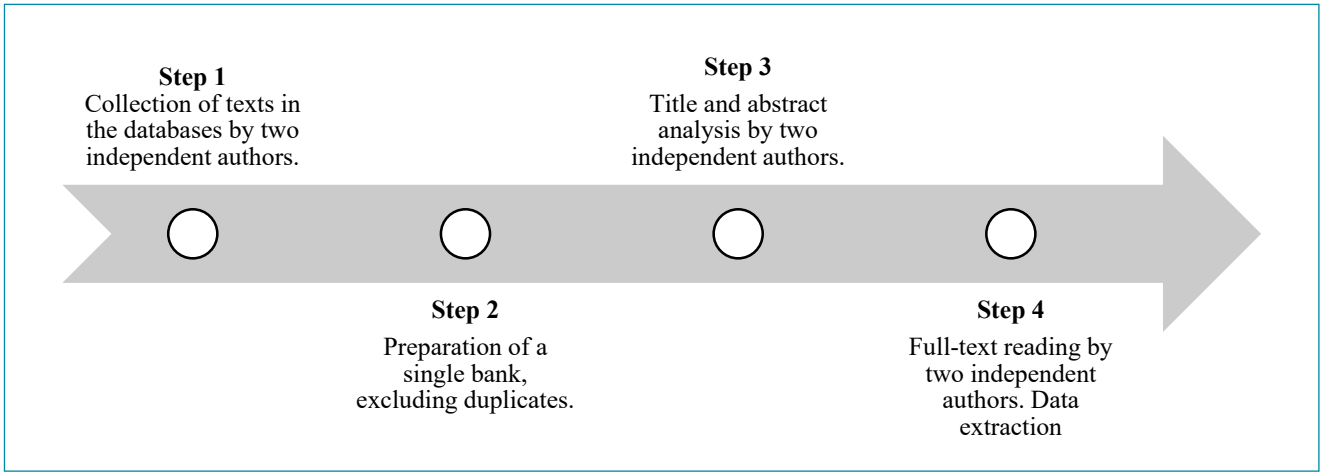

Figure 1. Stages of the systematic review. When discrepancies occurred, they were resolved based on the analysis of a third researcher.

Texts without full access to the content and those that, during full reading, did not comply with the inclusion criteria were excluded, as follows: duplicates (n=21), method not properly reported (n=24), lack of information about the diagnosis (n=16), literature review (n=8), and without full access (n=19). Divergences were analyzed and resolved by consensus.

During the second stage, a clinical case report was presented at the Dr. Altino Lemos Santiago Reference Center, in Juazeiro, Bahia, Brasil.

RESULTS

Systematic review

Initially, 479 scientific texts were identified. After the selection stage, 23 were included in the final qualitative analysis[11,17-38] (Figure 2). It should be noted that no text addressed both themes together. Case reports, with the largest number of publications (14 investigations), stood out[11,18,20,21,25-27,29-31,33,34,36,37].

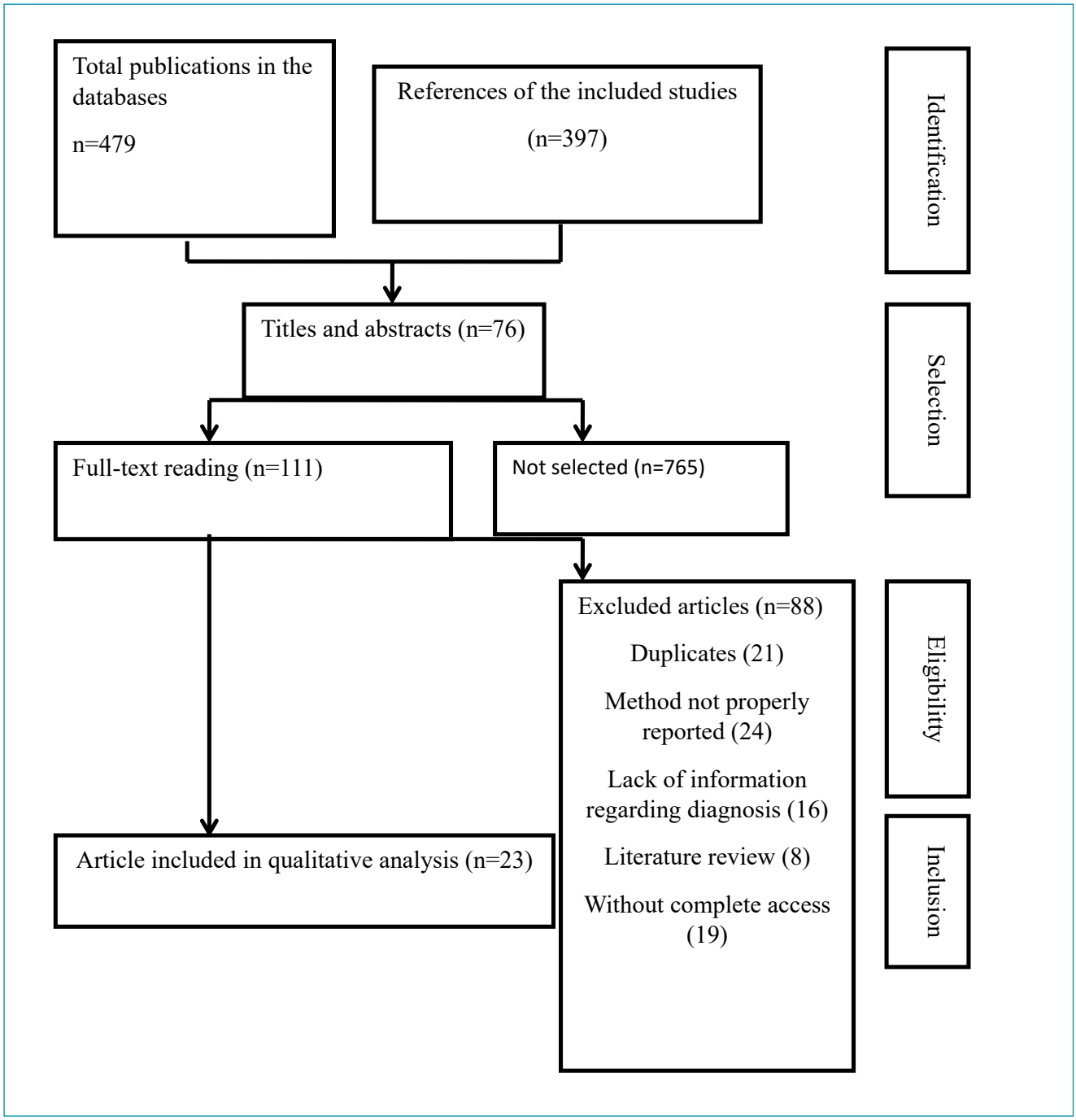

Figure 2. Flowchart for selection of studies included in the systematic review, 2020.

The studies emphasized the challenging diagnosis of pure neural leprosy[16,17,25,27,30] and the need for advances in the development of diagnostic methods[18,32], such as imaging tests (magnetic resonance imaging[27] and ultrasound[22,29,34]), cytology and histopathology[21,23,24,28,38], and serological and genomic tests[19,35]. Studies highlight the need of considering, for peripheral neuropathy, the differential diagnosis of pure neural leprosy in endemic areas[31,37]. Early diagnosis and timely treatment can reduce the occurrence of physical disabilities[11,26] (Table 1). The findings presented here will be further developed based on the clinical case described below.

CASE

A 65-year-old, brown, male patient, who worked as a construction worker and a former gold miner, born and currently living in Petrolina, Pernambuco, with suspected neural leprosy, was referred to a dermatologist by the neurologist for evaluation at the Hansen's Disease Reference Center in Juazeiro, Bahia. He came to the doctor's office complaining of pain, paresthesia, and decreased muscle strength in both hands and feet, which had started three years before. Complaints started in the lower limbs, progressing to the upper ones. He reported that he had already consulted with an orthopedist and a neurologist, and that he was treated with several medications, without improving his condition. He denied having diabetes mellitus, systemic arterial hypertension, and alcoholism, and reported having smoked in the past. He reported no family history of leprosy.

Physical examination showed a decrease in thermal and pain sensitivity in the upper and lower limbs, and a slight decrease in muscle strength in the right lower limb. The patient did not present dermatological lesions with altered sensitivity. Given that this is an endemic area for leprosy, the initial suspicion was pure neural leprosy, with a differential diagnosis of amyloidosis, owing to the pattern of progressive neural involvement. For diagnostic confirmation, the following complementary tests were requested:

1. Laboratory tests with normal values (blood count, platelets, alpha-fetoprotein, blood glucose, creatinine, PSA, TSH, T4, urea, alkaline phosphatase, GOT, and GPT were within the reference values. HBsAg was negative and Anti-HBs was positive, indicating cured or vaccinated hepatitis B; HIV 1 and 2 were negative, and vitamin B12 was high (2000 mcg).
2. Electroneuromyography: Sensitive and motor polyneuropathy in the lower limbs, which was of moderate intensity, mixed type (axonal-demyelinating), symmetrical, and predominantly sensitive and axonal.
3. Ultrasonography of the sural nerve: changes in the contour of the deep fibular nerves;
4. Biopsy of the sural nerve: accumulation of amorphous eosinophilic material in the nerve path. Congo red stain showed apple-green birefringence of the deposit under polarized light. Conclusion: amyloidosis (Figure 3).

It was not possible to define whether or not the amyloidosis was hereditary, because of the non-availability of genetic tests and the fact that no family member had been diagnosed with the disease. After diagnosis, the patient was referred for follow-up with a neurologist.

DISCUSSION

In the spectrum of clinical forms of leprosy, the pure neural form still represents a challenge for clinicians and dermatologists, especially in endemic areas for leprosy in Brasil[11,18,20,21]. Reviewing the literature on the diagnosis of pure neural leprosy is a sensitive topic in the Brazilian scientific community, mainly due to the magnitude of the endemic disease in the country. In this case, emphasis is on differential diagnosis with amyloid neuropathy.

In these cases, when the observed pattern is only of neural impairment, the physician must use other auxiliary resources that help to exclude other diseases that manifest with neuropathy and allow for confirmation of the diagnosis of neural leprosy[1,11,18,19]. Among the resources, electroneuromyography, ultrasonography[22,29,34], biopsies of peripheral nerves[21,24], and even magnetic resonance imaging of nerve trunks[27] stand out. Anti-PGL-1 (phenolic glycolipid antigen 1) serology and quantitative polymerase chain reaction can also be useful[1,10,19].

In this case, the initial suspicion was neural leprosy. However, after complementary tests, amyloid neuropathy was confirmed, and it was not possible to identify the etiology due to the absence of specific tests. In amyloid neuropathy, small sensory and autonomic fibers are initially involved. The initial symptoms are pain and paresthesia in the feet and thermal sensory loss, followed by loss of tactile sensitivity and distal hyporeflexia. About two years later, motor signs/symptoms begin[39].

Clinical manifestations of neuropathy are, in general, associated with AL amyloidosis, related to light chain immunoglobulin, which affects patients in the age group above 60 years, is predominant in males, and may be associated with multiple myeloma[15]. Among hereditary amyloidoses, the disease caused by mutations in the TTR gene stands out, and the Val30Met (p.Val50Met) variant is the most common in the world[15]. In hereditary TTR amyloidosis, clinical manifestations can

Table 1. Characterization of the studies included in the systematic review, 2020.

Author	Title	Design	Population	Results and Conclusions
a) Studies with large populations				
Kolleri et al.[17], 2019, India	A 10-year Retrospective Descriptive Study on Pure Neuritic Leprosy from a Tertiary Referral Centre.	Retrospective descriptive study	n=879	Delay in the diagnosis of pure neuritic leprosy due to the absence of dermatological lesions. Need for the training of health professionals for early detection of the disease.
Medeiros et al.[19], 2014, Brazil	An attempt to improve pure neural leprosy diagnosis using immunohistochemistry tests in peripheral nerve biopsy specimens.	Experimental study	n=28 Group cases (23) Control group (5)	The immunohistochemical technique suggests the presence of immunoreactivity to specific anti-LAM and anti-PGL-1 antibodies as an additional tool in the diagnosis of pure neural leprosy. Immunohistochemical techniques can contribute to the early diagnosis of the disease.
Bathala et al.[22], 2017, India	Extensive sonographic ulnar nerve enlargement above the medial epicondyle is a characteristic sign in Hansen's neuropathy.	Experimental study	n=48 Group cases (18) Control group (30)	Patients with ulnar neuropathy had a unique pattern of nerve enlargement on ultrasound examination. It starts at the ulnar sulcus and can increase up to four centimeters above the medial epicondyle.
Jaiswal et al.[23], 2018, India	Hansen's Neuritis Revisited – A Clinicopathological Study.	Retrospective study	n=81,013 (histopathological examination samples)	The common clinical presentation of Hansen's neuritis is mononeuritis multiplex. Neurological examination and nerve biopsy are recommended for diagnosis.
Antunes et al.[24], 2012, Brazil	Histopathological examination of nerve samples from pure neural leprosy patients: obtaining maximum information to improve diagnostic efficiency.	Experimental study	n=340 (144 with pure neuritic leprosy and 196 with non-leprosy peripheral neuropathies)	The study demonstrates the importance of performing nerve biopsy exams for the identification of leprosy neuropathy, with a predominance of non-inflammatory histopathological changes in pure neuritic leprosy samples.
Kulshreshtha et al.[28], 2018, India	Mandating nerve biopsy: A step towards personalizing therapy in pure neuritic leprosy.	Retrospective study	n=78	Predominance of the ulnar nerve. Only 16 of the 38 patients demonstrated bacilli in Wade-Fite staining.
Shukla et al.[32], 2020, India	Pathological, ultrasonographic, and electrophysiological characterization of clinically diagnosed cases of pure neuritic leprosy.	Observational study	n=100	Ultrasound, histological, and electrophysiological evaluation, taken together, constitute the best method for diagnosis of pure neural leprosy, showing greater accuracy and ability to exclude or confirm differential diagnoses.
De et al.[38], 2017, India	Use of Fine Needle Aspirate from Peripheral Nerves of Pure-neural Leprosy for Cytology and Polymerase Chain Reaction to Confirm the Diagnosis: A Follow-up Study of 4 Years.	Observational study	n=62	The use of fine-needle aspiration cytology in combination with Ziehl-Neelsen staining and PCR is a quick, simple and easy solution that can be used for the diagnosis of pure neural leprosy.

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Table 1. Continuation.

Author	Title	Design	Population	Results and Conclusions
Rodriguez et al.[35], 2013, Colombia	Pure neuritic leprosy in patients from a high endemic region of Colombia.	Descriptive observational study	n=36	21 of the 36 individuals initially suspected of pure neural leprosy were confirmed, based mainly on epidemiological and clinical findings, and on changes in amplitude and nerve conduction on electroneuromyography. Five of them had positive PCR for *M. leprae* DNA on nerve biopsy.
b) Case report studies				
Freitas et al.[11], 2019, Brazil	Primary Neural Leprosy mimicking rheumatological disorders	Case report	n=1	Clinicians who are alert and trained to recognize this clinical form of leprosy are necessary. Correct referral to reference centers accelerates the investigation, contributing towards early diagnosis, correct classification, and treatment, preventing irreversible sequelae with severe functional disability.
Serrano-Coll et al.[18], 2018, Colombia	A case series of pure neural leprosy in patients diagnosed in a specialized center for the control of Hansen's disease in Colombia.	Case report	n=4	There is a need for advancement of the development of a diagnostic method, using serological and genomic mechanisms. Health professionals should mandatorily include peripheral neuropathy as a differential diagnosis of leprosy disease.
Santos et al.[20], 2019, Brazil	Anterior tarsal tunnel syndrome: an atypical involvement in primary neural leprosy.	Case report	n=1	The anterior tarsal syndrome can be a finding of primary neural leprosy, even if it is atypical. It is necessary to include leprosy as one of the differential diagnoses of anterior tarsus syndrome.
Omar & Hussein[21], 2012, Egypt	Clinically unsuspected neuritic leprosy with caseation necrosis.	Case report	n=1	Caseation necrosis (abscess) can be a clinical finding, although atypical and rare, of neuritic leprosy. Mass lesions with necrosis, when found in biopsy samples, must be taken into account for discussing a possible case of leprosy.
Jaramillo et al., 2016[25] Colombia	Lepra neural pura de 18 años de evolución.	Case report	n=1	Pure neural leprosy remains a challenge for healthcare professionals.
Pardal-Fernández et al.[26], 2016, Spain	Lepra neural pura. Aspectos diagnosticos en un caso clinico	Case report	n=1	Early diagnosis and treatment of the disease allowed for better patient recovery.

Continue...

Table 1. Continuation.

Author	Title	Design	Population	Results and Conclusions
Beltrame et al.[27], 2017, Italy	Magnetic resonance imaging in pure neural leprosy	Case report	n=1	Health professionals have few techniques to analyze the signs of leprosy. Magnetic resonance imaging can be an auxiliary tool in diagnosis.
Rai et al.[29], 2013, India	Nerve abscess in primary neuritic leprosy.	Case report	n=1	Caseous necrosis of nerve injuries occasionally coalesces to form a nervous abscess. Data suggest that abscess is more common in borderline tuberculoid leprosy. Ultrasound seems to be the best diagnostic technique.
Gupta et al.[30], 2017, India	Nerve abscess in pure neural leprosy mistaken for peripheral nerve sheath tumor with disastrous consequence: what can we learn?	Case report	n=1	Diagnosing pure neural leprosy is a challenge for doctors. Presence of nerve abscess without thickening of peripheral nerves. Among the non-invasive methods, ultrasound seems to be the best method for diagnosis.
Shrestha et al.[31], 2019, Nepal	Neuritic Leprosy; An Intriguing Re-visit to a Forbidden Ailment.	Case report	n=1	Pure neuritic leprosy, although rare, should be considered as a differential diagnosis in cases where there is a presentation of peripheral neuropathy in endemic areas of leprosy. Prompt diagnosis and treatment are imperative to avoid permanent neurological damage.
Pradhan et al.[33], 2016, India	Polyneuritic variant of pure neuritic leprosy with extensive involvement of peripheral nerves and sparing of the polio-affected limb: a rare case report.	Case report	n=1	The association of poliomyelitis and leprosy in the same patient showed that a "protection" of the nerves affected by poliomyelitis, which were not affected by leprosy may be possible.
Karjigi et al.[34], 2015, India	Primary Neuritic Hansen's Disease presenting as Ulnar Nerve Abscess in a Human Immunodeficiency Virus Positive Patient.	Case report	n=1	Coinfection between HIV and leprosy can result in atypical manifestations. The patient also had a silent ulnar nerve abscess, diagnosed by ultrasound.
Payne et al.[36], 2015, United States of America	Pure neuritic leprosy presenting as ulnar nerve neuropathy: a case report of electrodiagnostic, radiographic, and histopathological findings.	Case report	n=1	Pure neural leprosy is a challenging diagnosis. Delayed diagnosis can lead to permanent neural damage.
Almeida Neto et al.[37], 2019, Brazil	The first report of pure neuritic leprosy with involvement of the anterior femoral cutaneous nerve.	Case report	n=1	This is the first case report involving the superficial femoral cutaneous nerve as a manifestation of leprosy. Pure neural leprosy is a diagnostic challenge. In endemic countries, any clinical manifestation involving the peripheral nervous system should be considered as a possible case of leprosy.

start early, at the age of 33, or they may have late onset, after the age of 50[15]. It is necessary to highlight that, in this case, it was not possible to confirm the patient's type of amyloidosis.

The most important differential diagnosis for amyloid neuropathy includes diabetic neuropathy, toxic neuropathies, Charcot-Marie-Tooth disease, chronic inflammatory demyelinating polyradiculoneuropathy, leprosy, and others[39]. It should be noted that, in the case of neural leprosy, mononeuropathy is observed to be multiple and asymmetric, unlike the pattern observed in amyloid neuropathy (symmetrical and ascending sensory-motor polyneuropathy)[10]. This involvement pattern and the absence of a family history of leprosy were important for the suspicion of amyloid neuropathy.

In addition to this difference in the neural involvement pattern, the histopathological profile contributes to the elucidation of the diagnosis. In amyloid neuropathy, peripheral nerves will exhibit important deposition of amyloid substance and a globular or diffuse pattern in the epineural and endoneurial tissue and around the blood vessel walls[39]. Congo red stain shows apple-green birefringence of the deposit under polarized light. Additionally, active axonal degeneration and severe loss of small myelinated and unmyelinated fibers are important histological features[40]. In leprosy, the nerves may show thickening, fragmentation by the inflammatory process, and the presence of a caseous center[21,23]. Lamination of the perineurium with the formation of an "onion bulb" is a common finding in leprosy[24].

In Brasil, the disease-modifying treatments recommended by the clinical protocol and therapeutic guidelines of the Ministry of Health for TTR-related hereditary amyloidosis are tafamidis meglumine and liver transplantation, both of which are indicated only for the initial stage of the disease, that is, when the patient can walk without support[41]. The treatment of AL amyloidosis consists of chemotherapy and autologous bone marrow transplantation, with an average survival of 42 months[41]. The treatment of pure neural leprosy is much simpler, and it depends on the operational classification. In the case of a single affected nerve, the disease will be classified as paucibacillary (PB), and polychemotherapy treatment lasts for six months,

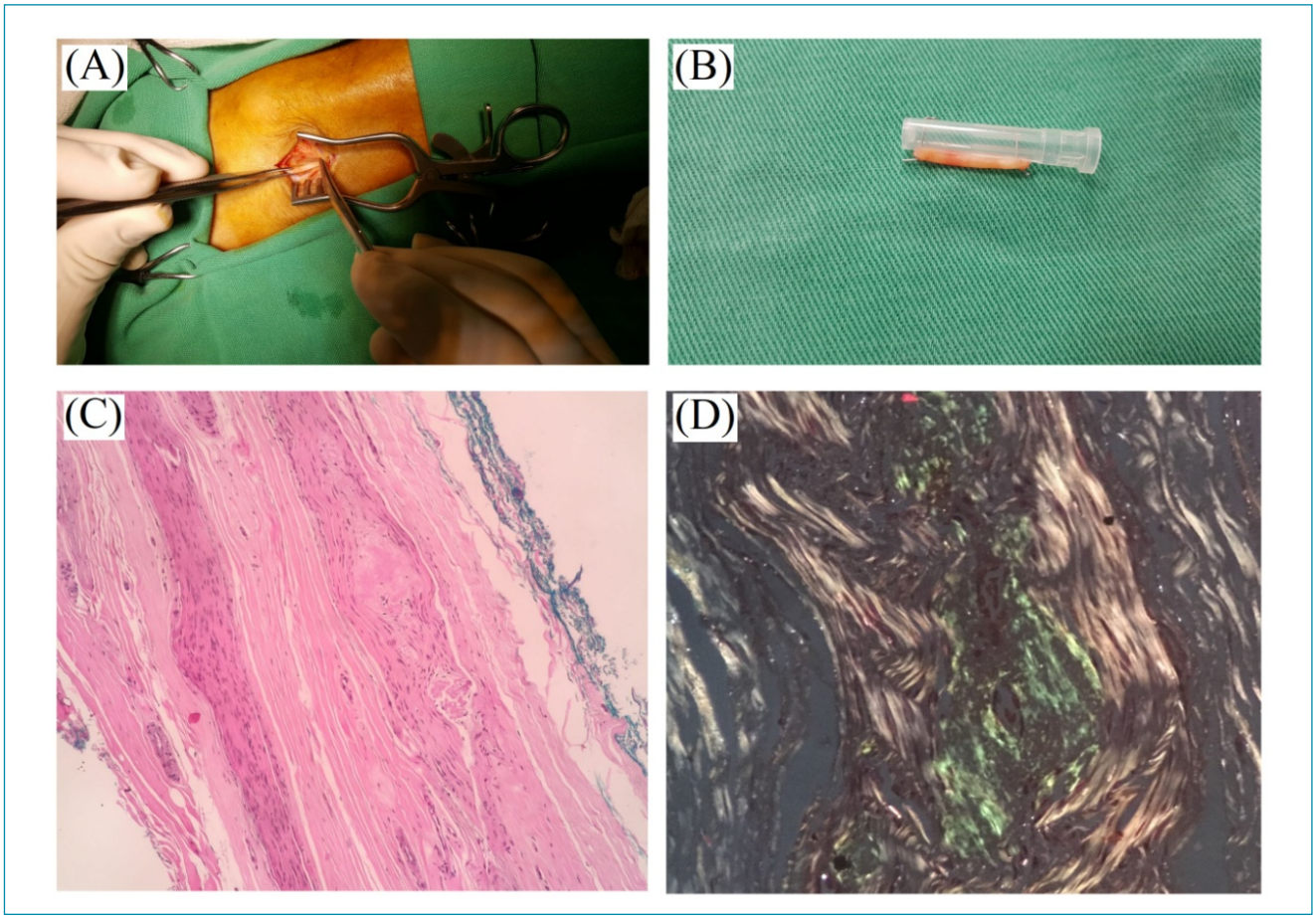

Figure 3. Biopsy of the sural nerve diagnosed with amyloidosis, 2019. (A) and (B) Collection of biopsy material; (C) Accumulation of amorphous eosinophilic material in the nerve pathways; (D) Congo red stain showing apple-green birefringence of the deposit under polarized light.

with the use of rifampicin and dapsone; patients with two or more affected nerves are classified as multibacillary (MB), and polychemotherapy treatment lasts for 12 months, with the use of rifampicin, clofazimine and dapsone[1,8].

It is important for clinicians and dermatologists who work in areas that are endemic for leprosy to know the main differential diagnoses of leprosy and to properly manage the complementary exams to provide early diagnosis and correct and timely treatment of patients. At the same time, the public health system, in order to guarantee integrated care for patients, must provide all of the necessary diagnostic and therapeutic resources.

This study has limitations, including the absence of analyses that discuss amyloid neuropathy as a differential diagnosis of pure neural leprosy and the small number of studies with larger populations. On the other hand, as it discusses a little explored theme, namely, the clinical and pathological differences between pure neural leprosy and amyloid neuropathy, this study is highly relevant for health professionals in endemic areas.

CONCLUSIONS

In the presented case report, the clinical history, the neural involvement pattern, the neurological clinical exam, and the complementary exams contributed towards the adequate diagnosis of the patient's neuropathy of amyloid etiology. The systematic review showed the importance of considering differential diagnoses of leprosy, especially in endemic areas.

AUTHORS' CONTRIBUTION

LOS: Conceptualization, Data Curation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. **TRMOF:** Conceptualization, Data Curation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. **JASB:** Writing – Original Draft, Writing – Review & Editing. **TRSB:** Writing – Original Draft, Writing – Review & Editing. **CDFS:** Conceptualization, Data Curation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing.

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