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Preliminary evaluation of a neurological clinical pathway for the early detection of leprosy in low-endemic settings: A single-center exploratory study

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The early diagnosis of leprosy remains challenging in low-endemic regions. However, the implementation of clinical pathways (CPs) to improve diagnostic accuracy and understand patterns of misdiagnosis and delayed diagnosis may help reduce disability burdens. We conducted neurologist training programs focused on leprosy-related disabilities in Beijing, China, and evaluated the effectiveness of an exploratory neurological CP. Diagnostic delays and misdiagnosis patterns were analyzed. Following CP implementation (2018–2023), the number of confirmed leprosy referrals from neurology departments increased to 13 cases (vs. 4 cases during 1990–2017). The cases included various subtypes (LL, BL, BB, BT, TT, PNL). The diagnostic intervals ranged from 1.5 months (PNL) to 25 years (LL from low-endemic regions). All confirmed cases required multidisciplinary consultations (neurology: 27 visits; dermatology: 6 visits). Common misdiagnoses included peripheral neuropathy (29 instances) and skin lesions (13 instances). The neurological CP implemented in this study has potential utility for early leprosy detection in low-endemic settings. However, the single-center design and small sample size necessitate multicenter validation. These findings underscore the need for integrated diagnostic approaches.

Keywords Leprosy, Neurological clinical pathway, Delayed diagnosis

Leprosy is a potentially disabling disease characterized by chronic dermatoneurological infection[1]. If mis- or not diagnosed, this condition can result in irreversible deformity and disability, with a visible disability rate of up to 30%[2]; deformities have also been associated with delayed diagnosis[3]. Early diagnosis of leprosy is particularly important for early treatment and infection control[4].

In settings with high leprosy endemicity, active case finding and household contact (HHC) screening strategies play important roles in detecting undiagnosed leprosy[5]. In most countries with high leprosy rates, the diagnosis of the disease is still mainly based on clinical observations, such as the appearance of hypopigmented or reddish lesions with hypoesthesia, the presence of acid-fast bacilli (AFB)-positive lymph node smears and compatible skin lesion histopathology[4].

The active case-finding strategy is not suitable in areas with low leprosy endemicity, and early diagnosis of leprosy cases, especially pure neuritic leprosy (PNL), is extremely challenging. A person with a suspicious pigmented skin lesion and/or peripheral nerve lesion will likely go through several steps before receiving a definitive diagnosis of leprosy, including self-detection; consultations with dermatology, neurology and/or other departments of general hospitals; evaluations by dermatologists, neurologists, and/or other medical workers; referral to leprosy prevention and control specialists for those with suspected leprosy; assessment by specialists; and AFB smear and histopathological examinations. Delayed diagnosis or misdiagnosis occurs frequently and may be due to the following: (1) leprosy, known as the great imitator, is difficult to diagnose, especially PNL; (2) communities lack leprosy knowledge; (3) medical staff in general hospitals receive insufficient leprosy training; (4) medical leprosy prevention and control staff in regions with low endemicity lack experience and theoretical and technical support due to the dramatic decrease in newly detected leprosy cases and narrowing of epidemic

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areas; and[5] skin lesions are widely recognized, while nerve lesions and other manifestations are less recognized. Therefore, urgent attention should be given to the early detection of cases before visible deformities develop[4].

Globally, the early diagnosis of leprosy cases is very important. On the basis of the current understanding of leprosy, we conducted this pilot study to explore the feasibility of a neurological clinical pathway (CP) as a potential tool to improve leprosy detection in low-endemic settings, where traditional active case-finding strategies are less effective.

Methods

Ethics statement

This single-center, clinical trial was conducted at Beijing Friendship Hospital, Capital Medical University, China. The study was approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University, Beijing, China. The study protocol was performed in accordance with the Declaration of Helsinki. Informed consent for participation in the study was obtained from all patients.

Study design

This single-center trial at Beijing Friendship Hospital compared the pre-CP (1990–2017) and post-CP (2018–2023) periods. The CP incorporated neurological screening tools and early diagnostic technologies.

Training program

Since 2008, the Beijing Tropical Medicine Research Institute has trained > 2000 healthcare professionals from 646 institutions through 16 course sessions.

Exploration and development of the neurological CP

We used the following roadmap to explore and optimize the neurological CP for the early diagnosis of leprosy patients (Supplementary Table S1). We established and performed serologic and molecular technology for leprosy patients[6–10]. We used clinical big data from the Leprosy Management Information System (LEPMIS) to reveal the endemic state, endemic regions, presenting symptoms, burdens and risk factors for disability in leprosy patients in Yunnan, China[11–15]. We elucidated neuromorphic features for clinically cured leprosy patients by ultrasound and neurological features for newly detected patients with leprosy by reviewing medical records[16,17]. We organized a multidisciplinary team (MDT) for consultation in regard to difficult leprosy cases. The studies' results were spread to medical workers as part of the neurological CP.

Assessment of the effectiveness of the neurological CP

The confirmed diagnoses of leprosy patients transferred from the neurology department were described in detail in a previous study[17]. The demographic and clinical data of neurological patients with leprosy were collected from medical records. The number of confirmed diagnoses, sex, endemic regions, detection modes, skin lesions, disability grades, diagnosis intervals, and classifications were collected.

Statistical analysis

GraphPad 10.3 statistical software (GraphPad Software, Boston, USA) was used to analyze the data. Count data, including the number of confirmed diagnoses, detection modes, skin lesions, disability grade, diagnosis interval, classification, endemic regions, and sex, before and after implementation of the neurological CP were analyzed via chi-square and Fisher's exact tests. $P < 0.05$ was considered to indicate statistical significance.

Results

Leprosy cases from the neurology department

The data of leprosy patients were retrieved from medical records and the LEPMIS. The preliminary data revealed that, before implementation of the neurological CP for the early diagnosis of leprosy cases, only 4 leprosy cases referred from neurology departments were confirmed over the course of 27 years (1990–2017). After implementation of the neurological CP, 13 leprosy cases were identified by a neurologist and transferred to the BTMRI over the course of 6 years (2018–2023) (Fig. 1).

All 17 cases were referred from neurology departments, and the confirmed diagnoses were as follows: 1 case of lepromatous leprosy (LL), 4 cases of borderline lepromatous leprosy (BL), 2 cases of mid-borderline leprosy (BB), 3 cases of borderline tuberculoid leprosy (BT), 3 cases of tuberculoid leprosy (TT), 2 cases of pure neuritic leprosy (PNL) (all newly detected), and 2 cases of relapsed leprosy. The clinical characteristics of the leprosy patients before and after implementation of the neurological CP are shown in Table 1.

Exploration and efficiency evaluation of the neurological CP

The neurological CP for leprosy is shown in Fig. 2.

Regarding the disease onset-to-diagnosis interval, before implementation of the neurological CP, the minimum interval was 1 year, and the maximum interval was 13 years. After implementation of the neurological CP, the minimum interval was reduced to 1.5 months, and the maximum interval was 25 years for one super early PNL patient and one leprosy patient, respectively, in a low endemic region of leprosy in China.

With respect to symptoms, before implementation of the neurological CP, 3/3 leprosy patients had associated skin lesions, and the symptoms and signs were relatively typical and easy to recognize. After implementation of the neurological CP, 84.61% (11/13) of the patients with newly detected leprosy had associated skin lesions, whereas 15.38% (2/13) did not.

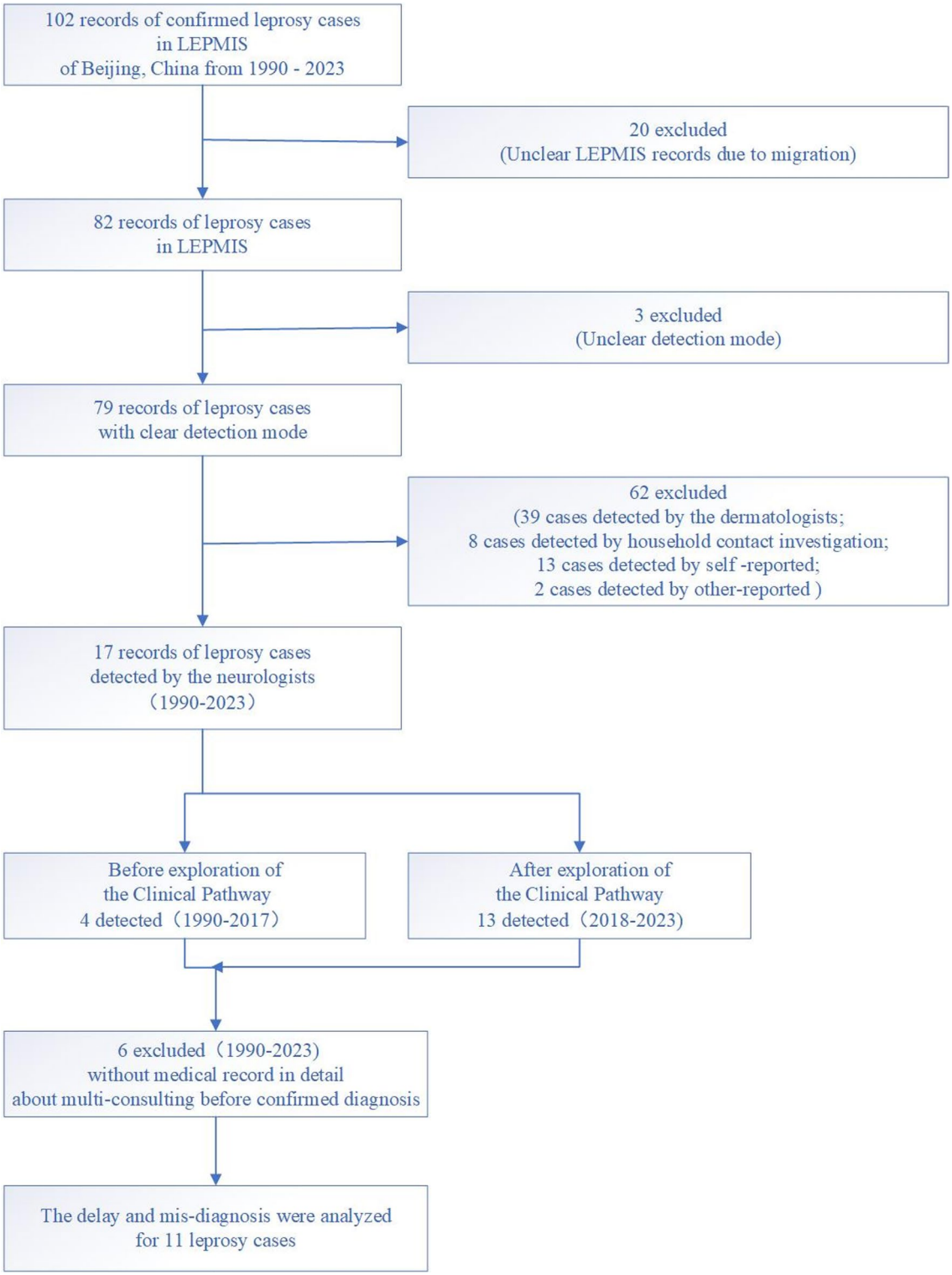

Fig. 1. Study cohort.

With respect to referral hospitals, before implementation of the neurological CP, all 4 leprosy cases were referred from the neurology department of Beijing Tiantan Hospital affiliated with Capital Medical University, which implied that the neurologist at the hospital had high leprosy awareness and a good ability to identify suspected leprosy cases. After implementation of the neurological CP, leprosy patients were referred from the neurology departments of Beijing Xuanwu Hospital affiliated with Capital Medical University (6 patients), Peking Union Medical College Hospital (PUMCH) (4 patients), Chinese People's Liberation Army General Hospital (1 patient), Beijing Tsinghua Changgung Hospital (1 patient), and Beijing Junyi Traditional Chinese

Clinical Pathway	Cases	Sex (M/F)	Diagnosis date (months, years)	Age at diagnosis (years)	Diagnostic intervals (months/years)	Diagnostic intervals (months)	Ethnic group	Birth-residence place (Province)	Endemic regions	Skin lesion (*n*)	Grade of Disability	Ridley-Jopling classification	Diagnosis	Therapy
Before	1	Male	May,2012	39	20 months	20	Han	Guizhou	High	(2–4)	G1D	BT	Newly detected	MDT
	2	Male	Aug, 2009	50	13 years	156	Han	Shaanxi	Middle	≥ 5	G2D	BL	Newly detected	MDT
	3	Male	Jan, 2016	21	1 year	12	N.D	Yunnan	High	(2–4)	G2D	TT	Newly detected	MDT
	4	Male	Jul, 2016	51	N.D	N.D	N.D	Yunnan	High	N.D	N.D	BL	Relapsed	MDT
After	1	Male	May, 2022	45	7 years	84	Han	Shaanxi	Middle	≥ 5	G2D	LL	Newly detected	MDT
	2	Male	Jul, 2021	29	10 years	120	Han	Anhui	Middle	≥ 5	G1D	BL	Newly detected	MDT
	3	Male	Jul, 2021	66	25 years	300	Han	Heilongjiang	Low	≥ 5	G2D	BL	Newly detected	MDT
	4	Female	Dec, 2019	56	7 years	84	Han	Hunan	High	≥ 5	G2D	BB	Newly detected	MDT
	5	Female	Api, 2022	47	2 years	24	Han	Sichuan	High	≥ 5	G2D	BB	Newly detected	MDT
	6	Male	Aug, 2022	46	18 years	216	Han	Hubei	Middle	≥ 5	G2D	BT	Newly detected	MDT
	7	Female	Dec, 2020	29	1 year	12	Han	Yunnan-Hebei	High-low	1	G2D	BT	Newly detected	MDT
	8	Male	May, 2021	28	11 years	132	Han	Hubei	Middle	(2–4)	G2D	TT	Newly detected	MDT
	9	Female	May, 2021	41	1 month	1.5	Han	Jilin	Low	0	G1D	PNL	Newly detected	MDT
	10	Female	Jun, 2021	27	6 months	6	Han	Shaanxi	Middle	0	G2D	PNL	Newly detected	MDT
	11	Male	Aug, 2023	54	6 years	72	Han	Sichuan-Xinjiang	High-low	≥ 5	G2D	N.D	Relapsed	MDT
	12	Male	May, 2019	32	9 years	108	Han	Jiangsu	Middle	≥ 5	G2D	BL	Newly detected	MDT
	13	Male	Jan, 2021	69	6 months	6	Han	Fujian	Middle	(2–4)	G1D	TT	Newly detected	MDT

Table 1. Leprosy cases from the neurology department were diagnosed by the BTMRI before and after implementation of the CP (1990–2017 vs. 2018–2023). ND: not described. MDT: multidrug therapy.

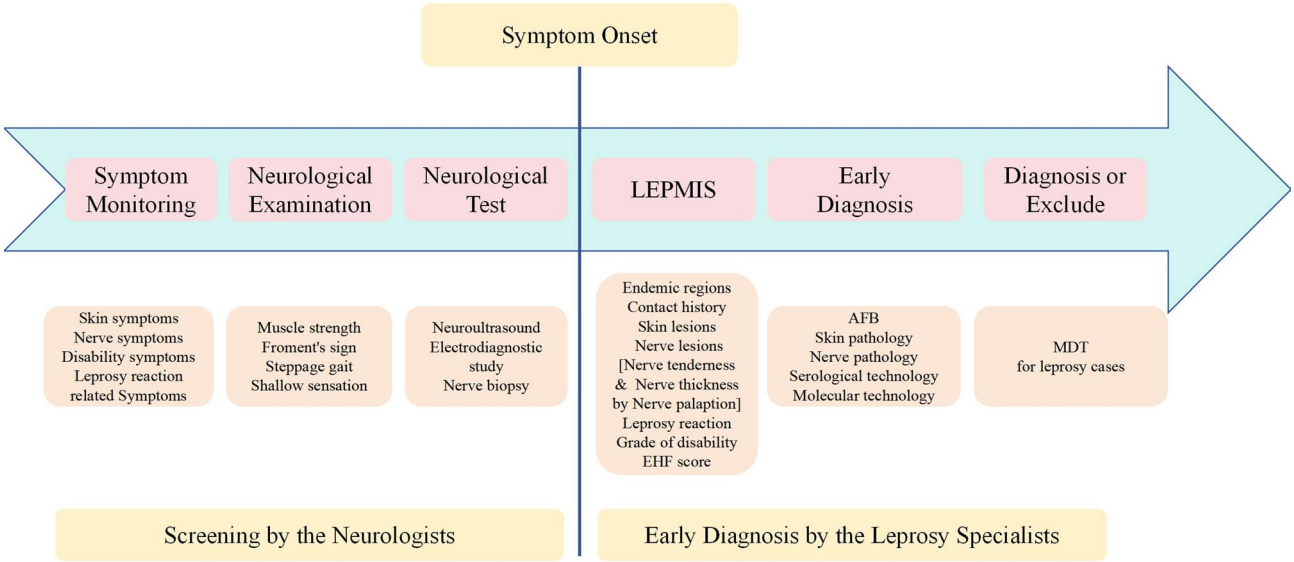

Fig. 2. The proposed neurological screening algorithm for suspected leprosy cases (requires validation).

Medicine Hospital (1 patient). The number of referral hospitals increased from 1 to 5 ($p = 0.0008$), and there was a 225% increase in referrals post-CP (13 vs. 4).

With respect to the Ridley–Jopling classification, before implementation of the neurological CP, 2 cases were classified as BL, 1 case was classified as BT, 1 case was classified as TT, and no cases were classified as PNL. After implementation of the neurological CP, 2 cases of PNL were found, which implied that the ability to identify suspected leprosy and awareness of the need for referral by neurologists had obviously improved.

With respect to disability and the diagnostic interval, 25.00% (4/16) of patients with leprosy disease had G1D, 75.00% (12/16) had G2D, 87.50% (14/16) of patients had delayed diagnosis, and only 25.00% (2/16) had early diagnosis (Table 2).

Mis- and delayed diagnosis

The mis- and delayed diagnoses are described in Table 3.

Before confirmed diagnosis, all neurological patients with leprosy (11/11, 100.00%) underwent multiple consultations. The consulting hospitals were located in Beijing (26), Guangdong (9), Hubei (6), Sichuan (4), Hebei (4), Hunan (2), Shaanxi (1), Jilin (1), and Shanghai (1).

For all of the confirmed neurological patients with leprosy (11/11, 100.00%), healthcare-seeking behavior ranged from local hospitals to regional medical centers and national medical centers. The consulting departments involved neurology (27 times), dermatology (6 times), hand microsurgery (5 times), Chinese medicine (3 times), and orthopedics (2 times).

Mis- and delayed diagnoses included the following: (1) nerve-related (33 times): peripheral neuropathy (23 times), multiple peripheral neuropathy (4 times), right cubital tunnel syndrome (3 times), mixed peripheral neuritis (1 time), chronic inflammatory demyelinating polyneuropathy (CIDP) (1 time), and spinal cord lesions (1 time); (2) skin-related (13 times): skin lesion (5 times), facial infiltration (3 times), mycosis fungoides (1 time), generalized eczema (1 time), annular granuloma of the skin (1 time), erythema (1 time), and pale erythema (1 time); and (3) disability-related: right foot ulcer (2 times) and (4) rheumatoid (1 time).

Discussion

As a proof-of-concept study, our findings should be interpreted with caution. The observed increase in case referrals may reflect improved clinician awareness rather than pathway efficacy per se, given the lack of control groups.

CPs have the potential to improve patient outcomes and reduce health care costs[18]; therefore, we developed a neurological CP for leprosy for use in areas with low leprosy endemicity in China, assessed the effectiveness of the neurological CP and provided evidence that CP implementation coincided with increased case detection, but its impact on long-term outcomes and cost-effectiveness requires further evaluation.

Since implementation of the optimized neurological CP for the diagnosis of suspected leprosy in patients whose main complaints are neurological symptoms, the number of leprosy cases referred from neurology departments has increased significantly. Although the diagnostic intervals increased slightly after implementation of the neurological CP, the minimum diagnostic interval was reduced to as short as 1.5 months for PNL patients. Moreover, patients who had leprosy for as long as 25 years were also detected. Suspected leprosy patients with skin lesions (Ridley-Jopling classification) and without skin lesions (PNL) from high, middle, and low endemic regions of leprosy in China were successfully screened, referred, and diagnosed. In addition, 2 patients experienced early diagnosis after implementation of the neurological CP and received early therapy from

Total (*n*)		Before the CP* (*n*,%)		After the CP (*n*,%)		*P* value
Diagnosis (n)	Confirmed leprosy	4	23.53%	13	76.47%	0.0702
Detection modes (n)	Referral hospitals	1	16.67%	5	83%	0.3156
	Beijing Tiantan Hospital	4	100.00%	0	0.00%	0.0008*
	Beijing Xuanwu Hospital	0	0.00%	6	46.16%	
	Peking Union Medical College Hospital (PUMCH)	0	0.00%	4	30.77%	
	Chinese People's Liberation Army General Hospital	0	0.00%	1	7.69%	
	Beijing Tsinghua Changgung Hospital	0	0.00%	1	7.69%	
	Beijing Junyi Traditional Chinese Medicine Hospital	0	0.00%	1	7.69%	
Skin lesions	With skin lesions	4	100.00%	11	84.62%	> 0.9999
	Without skin lesions	0	0.00%	2	15.38%	
Disability grade	G0D	0	0.00%	0	0.00%	> 0.9999
	G1D	1	33.34%	3	23.08%	
	G2D	2	66.67%	10	76.92%	
Diagnostic interval	Median (Min–Max)	20 (12–156)		84 (1.5–300)		0.8214
	Mean ± SD (95% CI)	62.67 ± 80.93 (−138.40-263.70)		89.65 ± 89.32 (35.68–143.60)		
Classification	LL	0	0.00%	1	9.09%	> 0.9999
	BL	2	50.00%	3	18.18%	
	BB	0	0.00%	2	18.18%	
	BT	1	25.00%	1	9.09%	
	TT	1	25.00%	2	18.18%	
	PNL	0	0.00%	2	18.18%	
	Relapsed	0	0.00%	2	9.09%	
Endemic region	High	3	75.00%	4	30.78%	0.2824
	Middle	1	25.00%	7	53.84%	
	Low	0	0.00%	2	15.38%	
Sex	Male	4	100.00%	8	61.54%	0.2605
	Female	0	0.00%	5	38.46%	

Table 2. Clinical characteristics of leprosy patients before and after implementation of the CP. *CP: implementation of the neurological clinical pathway for leprosy. LL lepromatous leprosy, BL borderline lepromatous, BB mid-borderline leprosy, BT borderline tuberculoid leprosy, TT tuberculoid leprosy, PNL pure neuritic leprosy

the MDT to avoid permanent disability. The preliminary data revealed an increase in case referrals after CP implementation (13 vs. 4), although diagnostic intervals remained highly variable (1.5 months to 25 years).

However, some challenges still exist. After implementation of the neurological CP, among patients with newly diagnosed leprosy, the rates of G2D and delayed diagnosis were extremely high. This may be due to the following. In borderline leprosy patients, especially those with PNL, neurological symptoms and signs are the first or only symptoms and are characterized by insidious onset and a slow course of illness; thus, diagnosis is difficult. The inherent and notable link between peripheral nervous system symptoms and signs and leprosy has not attracted widespread attention in communities, general hospitals or professional leprosy control and prevention institutions. Clinical dermatological findings in outpatients have received much attention, whereas neurological manifestations associated with leprosy have received little attention.

Considering the results of our previous study, we propose that neurological symptoms may be the primary symptoms of leprosy, that patients with peripheral nerve damage are potential candidates for leprosy screening, that neurology clinics can potentially aid in the identification of suspected leprosy cases, and that neurologists should be the target population for training in leprosy prevention and control. Learning more about neurological features combined with early diagnosis technology and strengthening the training of neurologists will be helpful in identifying leprosy patients early, reducing the risks of disability and deformity, and mitigating the harm caused by leprosy[6–17].

After the neurological CP was implemented, the benefits were confirmed. Notably, before a confirmed diagnosis of leprosy in Beijing, the capital of China, neurological patients with leprosy often seek healthcare in local hospitals, which are often regional medical centers located in large cities. Expanding the scope of application for this neurological CP is expected in the future.

Leprosy is an infectious neglected tropical disease that can cause irreversible disability if not diagnosed in time. The high rates of leprosy-related disability are mainly due to a delay in diagnosis. The determinants of

Patients' Number	Disease onset to diagnosis	Province/	Hospital	Department	Main diagnosis	Secondary diagnosis	Treatment
Case 1	10 years ago (2012y)	Beijing	First-class	Chinese Medicine	Rheumatoid	N.D	Symptomatic treatment
	0 years ago (2022y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Skin lesion	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2022y)	Beijing	*BTMRI	Leprosy Department	Leprosy (LL)	**G2D	***MDT
Case 2	10 years ago (2012y)	Hebei	Second-class	Chinese Medicine	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2021y)	Beijing	First-class	Neurology	Peripheral neuropathy	Skin lesion	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2021y)	Beijing	*BTMRI	Leprosy Department	Leprosy (BL)	**G2D	***MDT
Case 3	10 years ago(2011y)	Shanghai	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2021y)	Beijing	Second-class	Dermatology	Mycosis fungoides generalized eczema	N.D	Symptomatic treatment
	0 years ago(2021y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Skin lesion	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2021y)	Beijing	*BTMRI	Leprosy Department	Leprosy (BL)	**G2D	***MDT
Case 4	7 years ago(2013y)	Beijing	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	1 year ago(2019.08)	Beijing	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	1 year ago(2019.12.06)	Hunan	First-class	Dermatology	Leprosy	N.D	BI: positive
	1 year ago(2019.12.09)	Hunan	Third-class	Dermatology	Leprosy	N.D	Skin pathology confirmed as Leprosy
	Confirmed Diagnosis	Beijing	*BTMRI	Leprosy Department	Leprosy (BB)	**G2D	**MDT
Case 5	10 years ago(2011y)	Sichuan	Second-class	Dermatology	Skin lesion	N.D	Symptomatic treatment
	1 years ago(2021y)	Sichuan	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2022y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Erythema	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2022y)	Beijing	*BTMRI	Leprosy Department	Leprosy (BB)	**G2D	***MDT
Case 6	16 years ago (2006y)	Guangdong	Second-class	Chinese Medicine	Peripheral neuropathy	N.D	Symptomatic treatment
	16 years ago (2006y)	Guangdong	Third-class	Neurology	Multiple peripheral neuropathy	N.D	Symptomatic treatment
	10 years ago (2012y)	Hubei	Third-class	Neurology	Multiple peripheral neuropathy	Right foot ulcer	Symptomatic treatment
	10 years ago (2012y)	Hubei	Third-class	Neurology	Suspected as leprosy	N.D	Cerebrospinal fluid for acid-fast bacilli: Negative
	10 years ago (2012y)	Hubei	First-class	Dermatology	Suspected as leprosy	N.D	Skin Slit Smear: BI: negative
	10 years ago (2012y)	Hubei	Third-class	Orthopedics	Right foot ulcer	Multiple peripheral neuropathy	Debridement and suture of right heel ulcer
	8 years ago (2014y)	Guangdong	Third-class	Hand microsurgery	Right cubital tunnel syndrome	N.D	Right elbow tube incision for decompression
					Peripheral neuropathy	N.D	Anterior transposition of ulnar nerve
					Right foot ulcer	N.D	Excision of ulcer of right foot with random skin flap plasty
	8 years ago (2014y)	Guangdong	Third-class	Neurology	Peripheral neuropathy	Right hand Scalded	Symptomatic treatment
	5 years ago (2017y)	Guangdong	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 year ago (2022y)	Guangdong	Third-class	Neurology	Mixed peripheral neuritis	N.D	Symptomatic treatment
	0 year ago (2022y)	Hubei	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 year ago (2022y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Skin lesion	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2022y)	Beijing	*BTMRI	Leprosy Department	Leprosy(BT)	**G2D	***MDT
Case 7	2 years ago(2019y)	Hubei	Third-class	Hand microsurgery	Multiple peripheral neuropathy	N.D	Neurolysis
	0 year ago (2021y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Pale erythema	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2021y)	Beijing	*BTMRI	Leprosy Department	Leprosy(TT)	**G2D	***MDT
Case 8	3 years ago(2017y)	Hebei	Second-class	Orthopedics	Right cubital tunnel syndrome	N.D	Anterior transposition of right ulnar nerve
	0 years ago(2020y)	Hebei	Second-class	Hand microsurgery	Right cubital tunnel syndrome	N.D	Transfer to Neurology
	0 years ago(2020y)	Hebei	Second-class	Neurology	Multiple peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2020y)	Beijing	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2020y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Facial infiltration	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2020y)	Beijing	*BTMRI	Leprosy Department	Leprosy(TT)	**G2D	***MDT

Continued

Patients' Number	Disease onset to diagnosis	Province/	Hospital	Department	Main diagnosis	Secondary diagnosis	Treatment
Case 9	6 month ago(2021y)	Shaanxi	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2021y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Facial infiltration	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2021y)	Beijing	*BTMRI	Leprosy Department	Leprosy(PNL)	G2D	***MDT
Case 10	1.5 month ago(2021y)	Jilin	Third-class	Neurology	Peripheral neuropathy	N.D	Symptomatic treatment
	0 years ago(2021y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Facial infiltration	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2021y)	Beijing	*BTMRI	Leprosy Department	Leprosy(PNL)	**G2D	***MDT
Case 11	5 years ago(2018y)	Sichuan	Third-class	Neurology	Spinal cord lesions	Leprosy	Symptomatic treatment, dermatology consultation
	5 years ago(2018y)	Sichuan	Third-class	Dermatology	Annular granuloma of skin	N.D	Halometasone
	4 years ago(2019y)	Guangdong	Third-class	Neurology	Chronic inflammatory demyelinating polyneuropathy(CIDP)	N.D	Symptomatic treatment
	0 years ago(2023y)	Beijing	Third-class	Neurology	Peripheral neuropathy	Skin lesion	Suspected leprosy, transfer to BTMRI
	Confirmed diagnosis (2023y)	Beijing	*BTMRI	Leprosy Department	Leprosy(Relapsed)	**G2D	***MDT

Table 3. Missed- and delayed diagnosis of leprosy patients. *BTMRI: Beijing Tropical Medicine Research Institute, Beijing Friendship Hospital, Capital Medical University. **G2D: grade 2 disability. ***Multi Drug Treatment (MDT).

diagnostic delays in leprosy patients, a cross-national analysis of contributing factors and intervention strategies, is shown in Supplementary Table S2.

In Brazil, the main reasons for the delayed diagnosis of leprosy involved participants who suspected that they had leprosy but feared community isolation, who thought that their symptoms were not serious, and who initially received a diagnosis other than leprosy. Educating patients regarding leprosy symptoms, reducing stigma to encourage patients to seek treatment, and increasing clinician suspicion of leprosy are the main strategies to prevent delayed diagnosis[19]. In India, the major contributors to the delayed diagnosis of leprosy are patient-related factors. Patient delay is a crucial factor responsible for disability among new leprosy patients, which reflects that the community is not aware of the signs and symptoms of leprosy. Reducing patient delay is very important for reducing disabilities in newly diagnosed patients[20]. In Colombia, the main reasons for the delayed diagnosis of leprosy at the health system level include accessibility issues, such as a lack of expertise by health staff, and barriers related to the organization of the care pathway. Individual- and community-level factors included a lack of leprosy awareness among the general population and leprosy-related stigma. Structural changes within the health system, such as organizing integral leprosy care centers and highlighting leprosy in the medical curriculum, as well as awareness-related interventions among the general population, might help reduce diagnostic delays[21]. In Shaanxi Province, China, newly detected leprosy patients have a long time to diagnosis and a high rate of deformity[22]. In Wuhan, Hubei Province, China, the top 5 misdiagnosed cases were rash (23/71, 32.39%), rheumatism (10/71, 14.08%), skin ulceration (9/71, 12.68%), dermatitis (9/71, 12.68%), and neuritis (9/71, 12.68%)[23]. In this study, the neurological patients with leprosy were subjected to multiple consultations in different departments of different hospitals, and misdiagnosis and delayed diagnosis occurred before confirmed diagnosis. These findings are consistent with those of previous studies. It is highly important to gain professional knowledge about leprosy, establish and perform MDT consultation, and make timely referrals.

Leprosy classically presents with cutaneous and neural involvement. In addition to being detected by a dermatologist, leprosy can be detected by a neurologist[24–28] or a rheumatologist[29].

Kar et al.[30] noted that leprosy involves peripheral nerves sooner or later in the course of the disease, leading to gross deformities and disabilities. Sadly, by the time it becomes clinically apparent, nerve damage is already quite advanced. However, if preclinical damage is detected early during disease, it can be prevented to a large extent[30]. Learning more about neurological manifestations can decrease the degree of disability and deformity associated with leprosy.

In addition to neurological manifestations, rheumatological manifestations are also common in leprosy patients but are often underrecognized[31]. A study involving North Indian leprosy patients reported that musculoskeletal manifestations included arthritis (22/44, 50.00%), swollen hands and feet syndrome (SHFS) (11/44, 25.00%), tenosynovitis (9/44, 20.45%), painful swollen feet (9/44, 20.45%), arthralgias (7/44, 15.90%) and vasculitis (1/44, 2.27%). The distribution of joints mimicked rheumatoid arthritis (14/44, 31.81%) and spondyloarthropathy (7/44, 15.90%)[32]. A study involving Brazilian leprosy patients also revealed that leprosy involves the musculoskeletal system and that systemic manifestations with nonspecific symptoms such as fever, fatigue and myalgia occur. Therefore, leprosy can often mimic autoimmune diseases such as arthritis, vasculitis, or collagenosis and can be misdiagnosed[33]. Autoantibodies such as rheumatoid factor and anticardiolipin are markers of rheumatic autoimmune diseases but are also present in leprosy patients[34].

Despite having a low prevalence, rare diseases affect more than 300 million people worldwide. Almost half of these diseases are neurological. Research progress is gaining momentum; for example, the integration of

whole-genome sequencing into routine clinical practice could substantially increase the number of diagnoses of rare diseases. Collaboration is essential to avoid geographic or disease-based silos[35]. In China, the overall low prevalence and highly imbalanced endemic status of leprosy (endemic region in the southwest) make it a rare disease, especially in eastern developed cities. The following strategies would be helpful for the early diagnosis of leprosy: making more efforts for basic scientific research; further developing early diagnostic technology; establishing collaborative relationships in high-, medium-, and low-prevalence regions; and applying a multidisciplinary consultation model for leprosy disease.

Limitations

This study has three principal limitations. First, its single-center design and small sample size limit its generalizability. Second, the absence of randomization prevents causal inferences about the neurological CP's efficacy. Third, the lack of cost–benefit analysis precludes health economic assessments. Future studies should prioritize prospective, cluster-randomized designs across endemic gradients.

Conclusion

This pilot study provides preliminary evidence that a neurological CP may enhance leprosy detection in low-endemic settings, particularly for PNL patients. However, the high rates of delayed diagnosis and disability underscore the need for (1) multidisciplinary collaboration, (2) enhanced neurologist training, and (3) integrated dermatological-neurological screening protocols. This exploratory study provides preliminary evidence supporting neurological CPs for leprosy detection in low-endemic regions. Future research should prioritize multicenter validation and economic evaluations.

Data availability

All the data generated or analyzed during this study are included in this published article.

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Declarations

Competing interests
The authors declare no competing interests.

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