Medicine Insights

Review

Exploration of the Diagnosis and Treatment of Leprosy Reactional Neuritis Based on Acupuncture Theory

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Abstract: Leprosy reactional neuritis is one of the common complications of leprosy, and the main cause of permanent nerve damage and functional loss. The standard medical treatment is based mainly on glucocorticoids and immunomodulators, which typically are restricted by significant side effects, nonuniform efficacy and high rate of recurrence. Traditional Chinese medicine (TCM) considers that the essential pathogenesis of this disease has close relationship with the deficiency of healthy qi (zheng qi), invasion by wind-toxin and phlegm-stasis blockage meridians and that the treatment is based on supporting the healthy qi to eliminate the pathogens and unblocking meridians and collaterals. From the viewpoint of theory of acupuncture, the occurrence of this disease is primarily caused by the blockage of the qi and blood flow in meridians and the retention of pathogenic toxins. Acupuncture, by keeping the balance of yin-yang, dredging meridians, and reinforcing healthy qi to expelling pathogen, has the benefits of improving local microcirculation, regulating immune function, and attenuating neuroinflammatory response. Over the past few years, with the development of making combination of meridian syndrome differentiation and neuroanatomical localization for acupuncture intervention protocols, novelty appears in point selection and stimulation parameters, and combining therapies, such as electroacupuncture, warm needling, or acupoint injection to enhance the clinical efficacy, has emerged. In a word, the introduction of the theory of acupuncture into the diagnosis and treatment system for leprosy reactional neuritis can bring some new inspiration to overcome current bottlenecks in the diagnosis and treatment of leprosy reactional neuritis, and can open a new integrated traditional Chinese and Western medicine pathway of diagnosis and treatment for leprosy reactional neuritis. More mechanistic research, a more standardized clinical protocol and Multicenter Evidence-based validation should be focused in the future to provide a safe and effective integrated diagnosis and treatment strategy.

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1. Introduction

Leprosy reactional neuritis is one common complication of leprosy and one of the main causes of irreversible peripheral nerve damage. In spite of the great success of anti-leprosy therapy, clinical treatment for leprosy reactional neuritis still has prominent shortcomings including low curative effect, high recurrence rate and poor nerve repairing [1]. In the TCM, leprosy belongs to "lifeng"(lichitoxin wind, dafeng)(great wind), with its essence pathogenesis as the invasion of pathogenic toxin, meridian obstruction and disharmonization of qi and blood. As a traditional therapeutic mode, it is proved that acupuncture has unique advantages in the treatment of a variety of neuroinflammatory diseases, by the multi-effect mechanisms including regulation of neuro-endocrine-immune network, suppression of neuroinflammatory response, nerve repairing and so on,

a new perspective is offered by the acupuncture in the clinic treatment of leprosy reactional neuritis [2,3]. Based on the theory of the "prolonged pain entering the collaterals", acupuncture could realize the multi-target regulation of the neuropathic pain and chronic inflammatory conditions [4]. The recent research showed that the acupuncture may have the neuroprotection effects through regulation of the glial cell activation, the central sensitivity and microglia-mediated neuroinflammatory pathway [5,6]. This article aims to discuss the TCM pathogenesis, pathomechanism and new therapeutic protocols of leprosy reactional neuritis in a systematic way from the view of acupuncture theory, in order to offer an integrated diagnosis and treatment to clinic.

2. Background and Therapeutic Limitations of Leprosy Reactional Neuritis

Leprosy reactional neuritis is an acute host immune response driven inflammatory disorder in leprosy which affects mainly the peripheral nerves, causing nerve functional impairment irreversibly. It's central pathological mechanism is host immune response imbalance induced by released Mycobacterium leprae antigens, while in clinical practice it occurs more often in multibacillary (MB) leprosy patients. Type I leprosy reactions almost exclusively occur in tuberculoid or borderline tuberculoid leprosy and consist of erythema of skin lesion, neuralgia and gradually progressive sensorimotor degradation; whereas Type II (i.e., erythema nodosum leprosum, ENL) occur in lepromatous leprosy and are usually accompanied by cutaneous nodules, fever, arthralgia, iridocyclitis and multiple neuritis [7,8]. The pathological process comprises segmental demyelination, axonal degeneration and endoneurial edema compressing nerve fascicles, without timely treatment it can lead to permanent muscle atrophy, sensory loss and even disability of limbs (Table1) [9].

Table 1. - Types of Lepromatous Reactions and Clinical Manifestations

Leprosy reaction type	Common pattern of nerve involvement	Typical clinical manifestations	Bacterial index association
Type I reaction	Acute inflammation of single or multiple nerves	Tenderness of nerve trunk, worsening sensory impairment, decreased muscle strength	Predominantly low BI (<2)
Type II reaction (ENL)	Multiple symmetric neuritis	Fever, cutaneous nodules, neuralgia, malaise	High BI (≥2), significantly correlated
Pure neuritic leprosy reaction	Mononeuritis or multiple neuritis	Paresthesia, numbness, no skin lesions	BI usually negative

The clinical incidence of leprosy reactional neuritis is not so low. From 81 leprosy patients in Guizhou Province, a retrospective study indicated that 50.62% and 14.81% were Type II and I reactions, respectively; nerve damage was mostly bilateral and symmetric, the ulnar nerve being the most frequently affected one, and the degree of nerve damage was positively correlated with the bacterial index (BI)[8]. Patients with pure neuritic leprosy (PNL) do not present the typical skin lesions, but leprosy reaction as mononeuritis or multiple neuritis can still occur and are highly likely to be clinically misdiagnosed [10,11]. A few patients can still develop neuritis some time after completing multidrug therapy (MDT), indicating that the host still has immune dysregulation [12].

Glucocorticoids are the first-line agents in the treatment of leprosy reactional neuritis at present. Oral prednisone is frequently employed at a daily dose of 30–40 mg and tapered gradually in accordance to the extent of clinical remission, a course of weeks to months [7]. However, prolonged high-dose use can lead to a series of adverse reactions including osteoporosis, disorders of glucose metabolism, increased risk of infection and so on; some patients are not very sensitive to corticosteroid treatment and the nerve functional recovery is not satisfactory. Clinical case reports that some borderline lepromatous leprosy patients under high-dose corticosteroid pulse therapy in Type II

reactions nevertheless died of sudden coma and gastrointestinal bleeding [13]. Other findings showed that some paucibacillary leprosy patients may still suffer from delayed neuritis or even develop bullous pemphigoid after completion of standard MDT courses, which significantly increases the clinical management complexity [14].

Although the WHO-recommended MDT regimen has brought the overall leprosy transmission rate and new cases of leprosy down very substantially, its potential in preventing and controlling leprosy reactional neuritis appears to be extremely limited. Thalidomide is primarily reserved for Type II reactions; it has anti-inflammatory effects by inhibiting TNF-α release and works for controlling ENL symptoms [15], but its use in clinic is strictly limited due to its established teratogenicity and peripheral neurotoxicity. Anti-TNF-α monoclonal antibodies have demonstrated some usefulness in individual cases, but there is currently no high quality clinical evidence for their regular use [12]. The early diagnosis ability of the current diagnosis system for leprosy reactional neuritis is insufficient: in the non-endemic areas the disease is frequently misdiagnosed as cervical spondylosis or diabetic peripheral neuropathy, and diagnoses and treatment are therefore too late [16]. Therefore, the molecular markers detection should be integrated with the neuroelectrophysiological examination in clinical practice to bring an early warning system for early and accurate diagnosis of leprosy reactional neuritis [9,17].

3. TCM Perspectives on Leprosy Reactions

Classical TCM texts such as the Huangdi Neijing (Yellow Emperor's Inner Canon) and Zhubing Yuanhou Lun (Treatise on the Origins and Manifestations of Diseases) record diseases referred to as "lifeng", "dafeng", and "laibing" (scab disease), clinical manifestations of which-including cutaneous numbness, eyebrow loss, nerve thickening, and muscle atrophy-correspond closely to leprosy as the disease is understood in modern medicine. TCM theory strongly point out that "when healthy qi is preserved internally, pathogens cannot invade". Leprosy is considered to be caused by the integrated action of the internal pathogen and external pathogen factors in the TCM theory. The external cause is "liqi" (epidemic toxin) or "duwu" (toxic miasma), i.e., infectious pathogenic agents the activity of which often increases with abnormal changes in climatic factors; the internal cause is deficiency of healthy qi, core pathogenesis involving insecurity of the lung-defense, dysfunction of spleen transportation, and deficiency of liver and kidney, eventually leading to invasion of meridians, muscles and skin by pathogenic toxins. This holistic view agrees well with the modern medical view that "Mycobacterium leprae infection manifests along a clinical spectrum depending on host immune status".

TCM considers the leprosy reactions as acute pathogenic processes of "latent toxin emerging outward" or "struggling between healthy qi and pathogens". Type I reaction can be demonstrated as "flaring of wind and fire" or "phlegm-stasis obstructing collaterals and transforming into heat", and manifests as erythematous skin lesions, severe neuralgia and functional loss of limbs progressively if not treated properly, it readily causes qi blood stagnation and meridian blockade, and leads to disability eventually. Type II reactions (ENL) are mostly of "accumulation of damp-toxin with disharmony of nutritive and defensive qi", and have subcutaneous nodule, high fever, arthralgia, iritis and multiple neuritis, the core pathogenesis is binding of damp-heat toxin with phlegm-stasis, disturbing nutritive and defensive qi circulation. Pure neuritic leprosy without the characteristic skin lesions can, following the TCM principle as "the presence of a single characteristic symptom is sufficient for diagnosis" and based on the manifestations as numbness of limbs, atrophy of muscles, deep hesitant pulse, etc, be differentiated as "bi syndrome" (impediment syndrome) or atrophy "wei syndrome" (atrophy syndrome), which embodies fully the "preventive treatment of disease" worth of clinic value in early prevention and treatment[Table2].

Table 2. TCM Diagnosis and Treatment of Leprosy Reactions

Reaction type	TCM syndrome pattern	Main symptoms	Treatment principle	Representative formula
Type I reaction	Wind-heat upward disturbance	Erythematous, hot, and painful skin lesions; tender nerve trunk resistant to pressure; dry mouth and throat; red tongue with yellow coating; wiry rapid pulse	Dispel wind and clear heat; invigorate blood and unblock collaterals	Modified Fangfeng Tongsheng San
Type I reaction	Phlegm-stasis obstructing collaterals	Dark red indurated lesions; numbness and stabbing pain in limbs; purple-dark tongue with ecchymoses; hesitant pulse	Resolve phlegm and remove stasis; unblock collaterals and stop pain	Zhimi Fuling Wan combined with Taohong Siwu Tang
Type II reaction	Damp-toxin accumulation	Red, swollen, ulcerated nodules; fever and chills; aching joints; poor appetite and loose stools; red tongue with yellow greasy coating; slippery rapid pulse	Clear heat and drain dampness; detoxify and reduce swelling	Bixie Shenshi Tang combined with Wuwei Xiaodu Yin
Type II reaction	Yin deficiency with fire effulgence	Dark-colored nodules; afternoon fever; night sweats and malar flush; red tongue with little coating; thin rapid pulse	Nourish yin and downfire; detoxify and harmonize nutritive qi	Modified Zhibai Dihuang Wan

TCM attends to regulating the disease holistically. In accordance to the clinical case reports, in case of a 51-year-old Male patient with tuberculoid leprosy and Type I reaction, on the basis of receiving MDT plus prednisona, the combined use of Chinese herbal formulas for benefiting qi, nourishing yin, activating blood and unblocking collaterals not only achieved inflammatory response control but alleviated corticosteroid adverse reactions greatly [15]. Another borderline tuberculoid leprosy with concomitant diabetes was TCM-diagnosed as "spleen deficiency with damp-exuberance and stasis-toxin internal obstruction"; treated with methods of strengthening the spleen, resolving damp, detoxifying, and unblocking collaterals significantly improved the neuropathy [18]. These clinical practices fully prove the TCM principal that "supporting healthy qi is itself eliminating pathogens": by regulating the function of organs and nourishing qi and blood, the disease-resistance ability of one's body can be greatly enhanced which is an effective interruption on the development of diseases.

Due to the development of modern detection technology, there is the possibility that the TCM syndrome differentiation introduces the objective measurement indicators, the molecular biology and immunology examination can be inducted to assist the disease diagnosis and accurate syndrome differentiation [17]. Clinical reports showed that for some borderline leprosy patients, the regimen of the medication can be adjusted according to the result of the susceptibility gene testing, which fully realizes the TCM diagnostic principle of "treating the patient according to individual characteristics [19]". In the future, more research can be done to study the correlation between the TCM syndromes and the biomarkers, and constructed the integrated diagnostic models of Chinese and Western medicine combined to reduce deformity and disability, and to improve the long-term prognoses of the patients.

4. Relationship between Acupuncture Theory and Leprosy Reactional Neuritis

4.1. Mechanisms of Action

Leprosy reactional neuritis is an acute neuroinflammatory complication during leprosy which may lead to nerve injury and functional loss. Glucocorticoid is widely used

for controlling the inflammatory responses in the modern medicine, but long time use will yield a great risk of side effects. Acupuncture can play its anti-inflammatory effects in the way of regulating the neuro-immune homeostasis and activating "neuro-endocrine-immune" network. Acupuncture can excite vagus nerve, activate cholingeric anti-inflammatory pathway, and inhibit the release of proinflammatory factors such as TNF-α and IL-1β, so that it can effectively reduce nerve edema [20,21]. In addition, acupuncture can also regulateHypothalamic-pituitary-adrenal (HPA) axis function, and promote endogenous glucocorticoid secretion to achieve the endogenous anti-inflammatory effect [22].

Acupuncture can regulate the activity of spinal cord neurons and higher centers, inhibit central sensitization, and has a good analgesic effect on neuropathic pain [5,23]. Acupuncture can inhibit NLRP3flammasome activation, reduce high-mobility group box 1 (HMGB1) protein release, block the neuroinflammatory cascade, and therefore has a effect of neuroaxonal protection [24,25]. These mechanisms has been confirmed in animal models of spinal cord injury and vascular dementia which make up the important theoretical evidence for the intervention of leprosy neuritis by acupuncture[Table3].

Table 3. - Main Targets and Pathways of Acupuncture Intervention in Leprosy Reaction Neuritis

Level of action	Key mechanism	Related molecules/pathways	Clinical significance
Neuromodulation	Inhibit central sensitization; modulate pain transmission	Activation of right superior parietal lobule and postcentral gyrus; release of endorphins and 5-HT	Relieve neuralgia and paresthesia
Immunomodulation	Inhibit pro-inflammatory factor release; promote anti-inflammatory factors	Vagus nerve–cholinergic pathway; TNF-α ↓, IL-10 ↑	Reduce perineural inflammatory edema
Endocrine regulation	Activate HPA axis; endogenous anti-inflammatory effect	Increased cortisol and ACTH secretion	Replace or reduce exogenous steroid dosage
Cytoprotection	Inhibit NLRP3 inflammasome; reduce HMGB1 release	Decreased Caspase-1 activity; improved mitochondrial function	Prevent axonal degeneration and demyelination

Neuritis of leprosy commonly affects the superficial nerve trunks, e.g., ulnar nerve, common peroneal nerve and its clinical manifestations – numbness of limbs, stabbing pain, muscle atrophy, etc. conform well with the syndrome features of "bi syndrome"(impediment) and "wei syndrome"(atrophy) in TCM. Through the action of "dredging meridians and collaterals and harmonizing qi and blood", the acupuncture can improve the local microcirculation at the lesioned site, promote the expressions of neurotrophic factors (nerve growth factor[NGF] and brain-derived neurotrophic factor[BDNF]) and speed up the structural nerve repairing [26,27]. This "simultaneous treatment of root and manifestation" intervention strategy is not only able to control the acute inflammatory responses but also to expedite the nerve functional recovery, highly consistent with the clinical requirement for whole-course management of leprosy.

4.2. Innovations in Treatment Protocols

Traditional acupuncture treatment is gradually shifting to an individualized, precision-oriented protocol design. Clinical point selection schemes include meridian-based point selection and points of the neuro-innervation zones, for instance, if the ulnar nerve is affected, Shousanli (LI10), Quchi (LI11) and local Ashi points may be chosen. The setting of electroacupuncture stimulation is on the basis of the facts that low frequency (2HZ) electroacupuncture has analgesic effects, high frequency (100HZ) electroacupuncture has anti-inflamatory effects and the alternating dual-frequency stimulation can have analgesic and anti-inflamatory effects [28].

Combination therapy: Acupuncturist may combine therapy with the use of acupoint injection techniques. It is common to use vitamin B1 and B12 injections for acupoint injection, 0.5–1 ml per point, given every other day [29]. Chinese herbal formulas may be added to and adjusted according to acupuncture treatment for complex cases, such as modifications of Xijiao Dihuang Tang [14]. The early identification rate of leprosy reactional neuritis was raised up to 92% and new deformity and disability decreased by 40% by the management model of "combined acupuncture-medicine + informatized follow-up" adopted in Shandong Province [30].

In terms of technological innovation, the temperature change in the lesioned areas can now be estimated by infrared thermography, the accurate needling can be achieved under ultrasound guidance, and resting-state functional magnetic resonance imaging (fMRI) can be used to guide the targeted regulation of the brain areas [31,32]. Clinical case reports on the treatment of paucibacillary leprosy patients with electroacupuncture and vitamin B12 acupoint injection showed that pain score decreased from 7 to 2 points and that nerve conduction velocity improved by 15%[29,33].

In future, the application value of acupuncture in the clinical treatment of leprosy neuritis will be further enlarged. By integrating the neuroelectrophysiological, immunomic, and imaging data, the construction of the integrated "syndrome – disease – target" diagnosis and treatment model could not only help to optimize the current acupuncture protocol, but also provide alternative treatments to patients with glucocorticoid dependence or contraindications to corticosteroid use, to achieve the final goals of less deformity and disability and better quality of life of the patients.

5. New Therapeutic Strategies and Future Directions

Leprosy reactional neuritis has become leading disability cause in leprosy patients and its clinical management goes from single anti-inflammatory paradigm towards multi-target integrated intervention. Though traditional glucocorticoid and thalidomide regimen are able to make the inflammatory response under control very quickly, they are typically confined considerable side effects and high recurrence rate. In the recent years, new therapeutic approaches based on the neuro-immune regulation are blooming. Acupuncture can activate vagus nerve – cholinergic anti-inflammatory pathway, suppress NLRP3 inflmasome, and regulate HPA axis function, which can be proved to have direct neuro-protect effect both on animal experiments and clinical trials [2,24]. Previous study in spinal cord injury model and stroke model showed the acupuncture can upregulate the BDNF and NGF expression, axonal regeneration, microcirculation, and etc, and given a new direction for the research of nerve repairing for leprosy neuritis[34,35,Table4].

Table 4. - Treatment of Leprosy Reaction Neuritis

Therapeutic strategy	Core mechanism	Advantages	Limitations	Clinical evidence
Conventional corticosteroids/thalidomide	Systemic immunosuppression	Rapid onset; controls acute reactions	Significant side effects; strong dependence; high relapse upon discontinuation	[39]
Acupuncture neuromodulation	Activates cholinergic anti-inflammatory pathway; inhibits NLRP3; promotes nerve regeneration	High safety; combines analgesic and reparative effects	Longer treatment course; requires individualized operation	[2,34,24]

Immunomodulators (e.g., cyclosporine A)	Inhibits T-cell activation; modulates neuroimmune microenvironment	Strong targeting; may reduce corticosteroid dosage	High cost; long-term safety to be verified	[40]
Multidisciplinary integrated management	Early screening + medication + rehabilitation + psychological support	Whole-course management; reduces deformity and disability rate	Dependent on medical resources and coordination capacity	[30]

Advances in precision diagnosis technology strongly support the early intervention in the leprosy reactional neuritis. Neuritis in pure leprosy(PNL) can be noninvasively detected by high-resolution ultrasound, magnetic resonance imaging(MRI) and multiplex PCR(M-PCR), to avoid the delay of clinical diagnosis and treatment [36,37]. The "informatized management + early screening" mode of Shandong Province improved the leprosy identification rate by >90%, and reduced the rate of new deformity and disability, fully demonstrated the importance of establishing leprosy prevention and control system [30]. Besides, clinical prediction rules (with key indicators including pain characteristics and nerve tenderness) can assist primary care physicians to identify neuritis in an early stage (diagnostic sensitivity: 35%; specificity: 94%), and greatly improve the efficiency of primary care [38].

Future research directions are in the direction of precision, integration and translational application. On one hand, fMRI, neuroelectrophysiology and immunomic technologies can be used to explain the regulation mechanism of acupuncture on brain functional regions (such as insula, superior parietal lobule) and peripheral neural networks, so as to facilitate the clinical application of precision acupuncture approaches [41,42]; in the meantime, the synergistic action of acupuncture with novel immunomodulators (e.g., anti-TNF-α biologics and JAK inhibitors) can be researched on, benefiting from the experience of targeted treatment in autoimmune diseases [43,44,45]. Furthermore, based on the primary mechanisms of nerve injury (neurotrophic factor imbalance, Remak bundle degeneration, etc) [46]., typical Chinese herbal formulae for regeneration of nerves could be constructed.

6. Conclusion

Although the leprosy belongs to the neglected tropical disease, its neuroimmune pathological mechanism has high similarity with many chronic Inflammatory neurodiseases (such as rheumatic arthritic, Multiple neuritis and so on). Therefore, therapeutic innovation of leprosy neuritis can benefit the leprosy patient directly, and provide a paradigm reference for other neuroimmune diseases in neuroimmune disease diagnosis and treatment. In the future, multicenter and large-sample randomized controlled trials should be further conducted to clarify the applied limits of integrated therapies including acupuncture in different kinds of leprosy, and unified efficacy evaluation standards should be constructed to accelerate the transformation of clinic practice from empirical medicine to evidence-based medicine as earlier as possible.

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