Research Progress of Mechanisms and Treatments for Neuropathic Pain

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***Abstract*—Neuropathological pain is a kind of clinical high-incidence disease that is difficult to cure. It not only affects the normal life of patients but also increases the incidence of anxiety and depression in patients. Neuropathic pain has many causes, ranging from physical and chemical injury to metabolic complex neuropathy. The common clinical manifestations include spontaneous pain, hyperalgesia, paresthesia, and so on. Current studies have shown that the pathogenesis of neuropathic pain is complex, including anatomical changes and functional impairment, often caused by a variety of mechanisms. These include peripheral sensitization, central sensitization, dysfunction of the descending inhibitory system, activation of glial cells in the spinal cord, and changes in ion channels. At present, the common treatment methods include drug therapy, neuromodulation, and minimally invasive treatment, but the efficacy of traditional treatment is not ideal. The emerging treatment methods include stem cell therapy and platelet-rich plasma, and the emergence of new treatment methods provides a new direction for the treatment of neuropathological pain. This article reviews the research progress of neuropathological pain, in order to provide a certain basis for the clinical treatment of neuropathological pain.**

***Keywords*—neuropathic pain, mechanism, pharmacotherapy, stem cell therapy, platelet-rich plasma therapy**

I. Introduction

Pain is an unpleasant feeling and emotional experience relating to actual or potential tissue damage [1]. Neuropathic pain is a type of pain caused by a lesion or disease of the somatosensory system [2]. The Data from European studies indicate that the prevalence of neuropathic pain in the general population is as high as 8.0% [3]. This long-term pain not only affects patients' ability to sleep, work, and live but also increases the incidence of emotional disorders such as depression and anxiety. The clinical manifestations of neuropathic pain are complex and diverse, with their own unique nature and characteristics. The course of neuropathic pain is very long, mostly exceeding 3 months. Usually, the site of neuropathic pain coincides with the area of its damage.

Neuropathic pain can happen for many reasons, ranging from physical and chemical damage to metabolic complex neuropathy [4]. The common causes include diabetes, shingles, trauma or postoperative nerve damage, spinal cord injury, stroke, multiple sclerosis, cancer, HIV infection, and lumbar or cervical radiculopathy. Diabetes is an endocrine disease caused by insufficient secretion or dysfunction of insulin. More than half of the estimated 460 million people with diabetes worldwide have neuropathy, and about one-third of them will also develop neuropathic pain [5]. Painful Diabetic Peripheral Neuropathy (PDPN) is one of the most common chronic complications of diabetes. PDPN presents with bilateral symmetrical distal limb pain, more in the lower extremities than in the upper extremities, worsening at night, early involvement of the distal feet, and progression to the lower legs and hands [6]. Postherpetic Neuralgia (PHN), which occurs after herpes zoster virus infection, is one of the main complications of herpes zoster [7]. This painful disease is one of the most intractable diseases in the medical world and is known as the "undead cancer". If not treated in a timely manner or improperly, the pain may persist for decades after the herpes disappears, and in some cases for decades.

II. Mechanisms

The mechanisms of neuropathic pain are complex, and the exact mechanism has not yet been discovered, which directly leads to difficulties in clinical treatment [8]. The mechanisms of neuropathic pain are reviewed as follows:

A. Peripheral Sensitization

Typical peripheral sensitization often occurs after inflammation or injury, including a decrease in the threshold of nociception and an increase in excitability in response to nociceptive stimuli [9]. External mechanical, thermal, and chemical stimuli are converted through ion channels into voltage changes in sensory neurons, allowing the body to respond to specific environmental stimuli. The reduced activation threshold of sensing channels induced by nerve injury, including changes in sodium, calcium, and potassium ion channels, is an important mechanism leading to peripheral sensitization [10]. The dorsal root ganglion expresses various ion channel proteins such as sodium and calcium. After neuronal damage, a series of functional and density changes occur in the voltage-dependent sodium and calcium ion channels on the cell membrane of dorsal ganglion neurons, resulting in a large number of

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abnormal action potentials in this area, which is one of the mechanisms leading to neuropathic pain [11].

B. Central Sensitization

Central sensitization is one of the key mechanisms for the occurrence and maintenance of neuropathic pain, mainly involving the hyperexcitability of spinal dorsal horn neurons [12]. Normally, neurons in the dorsal root ganglion of the spinal cord receive peripheral input stimuli with insufficient intensity to induce action potentials that can be transmitted to higher brain regions [13]. In the presence of peripheral inflammation, continuous stimulation can lead to synaptic plasticity in the dorsal root ganglia of the spinal cord. This amplification of synaptic efficacy enables ordinary subthreshold stimuli to generate action potentials, which in turn transmit nociceptive signals to higher-level centers [14].

C. Astrocytes in Neuropathic Pain

Astrocytes can regulate neuropathic pain by releasing various neurotransmitters or pain transmitters [15]. When stimulated by external factors (nerve damage, viral infection, etc.) or secondary neuronal substances (nitric oxide, prostaglandins, etc.) that transmit pain, the expression of Glial Fibrillary Acidic Protein (GFAP) in astrocytes is elevated, which indicates the activation of astrocytes. Activated astrocytes can upregulate the expression of excitatory amino acids such as glutamate and aspartic acid receptors, and release a large amount of glutamate and aspartic acid. They can also promote the release of inflammatory factors such as Monocyte Chemotactic Protein 1 (MCP-1) and Interleukin-1 (IL-1) [16]. The released pro-inflammatory factors can participate in the regulation of excitatory amino acids or their receptors, thereby mediating the occurrence and development of neuropathic pain. Pro-inflammatory factors can also mediate synaptic signal transmission affect the potential duration of nerve fibers, and participate in the formation of central sensitization through the Mitogen-Activated Protein Kinase (MAPK) pathway [17].

D. Microglia in Neuropathic Pain

Microglia are widely distributed in the central nervous system. Bacterial infections, peripheral nerve trauma, cancer, spinal cord trauma, and other factors can activate microglia [18]. In addition to releasing TNF-α, IL-6 is involved in pathological pain, activated microglia can upregulate the expression of P2 receptors and p38 MAPK receptors [19].

III. Treatment of Neuropathic Pain

A. Pharmacotherapy

1) Antidepressant drugs

Their efficacy has been demonstrated in diabetic neuropathy and refractory postherpetic neuralgia. The mechanisms by which these drugs relieve pain include an increase in the content of the inhibitory amino acid GABA, an increase in central nervous reuptake inhibition of serotonin and norepinephrine, and an analgesic effect by reducing glutamate receptor activity [20]. However, long-term use can cause side effects such as central nervous system toxicity, anticholinergic adverse reactions, and cardiovascular system toxicity.

2) Anticonvulsant drugs

Commonly used anticonvulsants include calcium channel modifiers (gabapentin, pregabalin) and sodium channel blockers (carbamazepine and oxcarbazepine). Carbamazepine is widely used in the treatment of trigeminal neuralgia, glossopharyngeal neuralgia, and diabetes peripheral neuropathy [21]. Common adverse reactions include bone marrow suppression, liver and kidney dysfunction, and dizziness. The first two types of adverse reactions are common in patients who have been using carbamazepine extensively for a long time, while dizziness is more likely to occur in the early stages of using carbamazepine [22]. The following principles can be followed when using anticonvulsants in clinical practice: for dull pain, calcium channel blockers gabapentin, and pregabalin should be chosen. For acute pain, choosing the sodium channel blocker carbamazepine is more effective.

3) Opioid analgesics

Opioids play an important role in the treatment of neuropathic pain [23]. These drugs are thought to be used as second-line agents for neuropathic pain or in combination with first-line drugs to enhance the analgesic efficacy of first-line medications [24]. The opioids commonly used in China are morphine and oxycodone. It is recommended to use the sustained-release dosage form because it is slowly and evenly released in the body after taking it, which can avoid fluctuations in blood concentrations. Morphine is the gold standard drug for all types of pain relief [25]. It can significantly improve the quality of life of patients, and the adverse reactions are within the acceptable range.

4) Nonsteroidal Anti-inflammatory analgesics (NSAIDs)

This type of drug blocks the synthesis of prostaglandins by inhibiting cyclooxygenase and has strong anti-inflammatory and analgesic effects [26]. It is often used in clinical practice to relieve skeletal muscle and joint pain, as well as headache and menstrual pain. However, there is still much controversy about whether nonsteroidal drugs are effective in the long-term treatment of chronic pathological pain [27]. First, the long-term large-scale application of non-steroidal drugs is easy to produce adverse reactions in the digestive system. Second, there is no consensus on which types of neuropathic pain are suitable for the use of non-steroidal drugs.

5) Local anesthetics

Local treatment has many advantages, such as less interaction with other drugs, minimal systemic side effects, and no need for titration of drug dosage. The 5% lidocaine patch is FDA-certified for the treatment of postherpetic neuralgia [28]. It is also effective for persistent and abnormal pain in patients with non-herpetic neuralgia.

B. Interventional Therapy

The purpose of interventional therapy is to reduce patient pain and restore function [29]. For neuropathic pain that cannot be controlled or has poor control effects with medication, and patients cannot tolerate the side effects of medication, timely intervention treatment should be considered [30]. There are many types of minimally invasive interventional therapies, which can be roughly divided into the following two categories [31]. The first category: minimally invasive treatment for the causes of neuropathic pain, including partial nerve block, release of nerve entrapment, radiofrequency thermocoagulation for trigeminal neuralgia, vertebroplasty, and minimally invasive intervention of intervertebral disc, and minimally invasive interventional treatment for partial treatment or reduction of tumor. The second category is the minimally invasive treatment for neuropathic pain symptoms, including partial nerve blocks, nerve damage, and nerve electrical stimulation.

1) Nerve block

Commonly used nerve block methods include nerve endings block, nerve trunk block, plexus block, ganglion block, sympathetic block, epidural block, subarachnoid block, etc. [32].

Nerve trunk block: One of the commonly used nerve block treatments in clinical practice, used for the treatment of trigeminal neuralgia, glossopharyngeal neuralgia, postherpetic pain, intercostal neuralgia, and nerve entrapment syndrome [33].

Plexus block: Plexus block includes brachial plexus, cervical plexus, celiac plexus block, etc., and can be used to treat stump pain, phantom limb pain, and abdominal cancer pain in the upper and lower limbs.

Sympathetic block: Sympathetic nerves are closely related to pain, and sympathetic pain can be relieved by sympathetic blockade. Thoracolumbar sympathetic block can be used to treat cancer pain, postherpetic neuralgia, phantom limb pain in the upper extremities, and diabetic neuropathic pain.

2) Nerve destruction

Nerve destruction refers to the use of surgical cutting or partial severance, injection of drugs, or physical methods to block the nerve conduction function of cranial nerves, spinal nerves, sympathetic nerves, and various ganglia [34]. Clinically used for neuropathic pain. Commonly used nerve damage in the treatment of neuropathic pain includes the following three types [35]: (1) peripheral nerve destruction, blocking the transmission of nociceptive stimuli to the center; (2) destruction of the spinal cord level, blocking the afferent pathway or upward transmission of nociceptive stimuli; (3) damage above the spinal cord. Such as intracranial destruction, blocking the transmission of nociceptive stimuli within the higher centers, or affecting the perception of painful stimuli.

Chemical nerve destruction: Chemical nerve destruction is the injection of nerve-destroying drugs near the nerve to degenerate the nerve tissue, thereby obtaining a long-lasting analgesic effect. It is currently commonly used in the treatment of cancer pain and some chronic intractable pain. Common nerve-destroying drugs include ethanol, phenol preparations, doxorubicin, glycerol, methylene blue, and mitomycin. Chemical nerve damage is injected with liquid drugs, the scope of the damage is not easy to control, it can affect the adjacent tissues of the target nerve, and the incidence of neuritis and hyperalgesia is high [36]. Therefore, with the development of neural radio frequency technology with more accurate positioning and easy control of damage range, the clinical application of chemical nerve damage has gradually decreased.

Radiofrequency therapy: Radiofrequency is a high-frequency alternating current that has a thermal effect on biological tissues but no electrolytic effect [37]. According to the way of RF current generation, RF can be divided into two types: continuous RF and pulsed RF. Continuous RF is generated by a continuous RF current with a high-temperature effect and precise control of temperature. If the temperature is high enough, the tissue can coagulate, lose biological activity, and achieve the effect of treatment, mostly used for the destruction of lesions, intervertebral disc ablation, and decompression. Pulsed RF is generated by intermittent RF current, which is emitted in the form of pulses, and the temperature generated is below 42 degrees Celsius, which has no destructive effect on the anatomy of nerve fibers and only inactivates pain conduction fibers. Radiofrequency therapy has the advantages of high safety, small trauma, accurate positioning, good efficacy, and few complications, and has been widely used in the treatment of neuropathic pain [38].

3) Electrical nerve stimulation

The methods of nerve stimulation used in clinical practice mainly include spinal cord electrical stimulation, peripheral nerve electrical stimulation, and transcutaneous electrical nerve stimulation [39].

Spinal cord electrical stimulation: Spinal cord electrical stimulation plays an important role in the treatment of neuropathic pain, and hundreds of thousands of patients worldwide have undergone the procedure since its clinical launch in 1967 [40]. Recently published studies have shown that spinal cord electrical stimulation mainly regulates pain perception in the peripheral and central sensory systems by the following mechanisms: (1) the release of analgesic neurotransmitters in the dorsal horn of the spinal cord to inhibit the upward transmission of pain sensation; (2) promotes descending inhibition by releasing norepinephrine, dopamine, and serotonin to act on their corresponding spinal cord receptors: (3) activates various brain regions related to pain perception and emotion [41]. The main complications of spinal cord stimulation are as follows: (1) Infection: It is the most common complication, with an incidence of less than 3%, often involving the implanted pulse generator and the wire connecting the electrode, and occasionally involving the epidural space. It can occur days to years after implantation and manifests as stubborn redness and tenderness of the skin on the surface of the implanted device. Treatment is with removal of the device and intravenous antibiotic therapy for more than 2 weeks; (2)

Secondary spinal cord compression injury: It is a fatal complication of spinal cord electrical stimulation, mainly nerve root or spinal cord injury during implantation, or secondary spinal cord compression injury formed by hematoma in the spinal canal; (3) Refractory cerebrospinal fluid leakage: can occur after percutaneous or surgical plate-type electrode implantation. Clinical manifestations include headache and accumulation of cerebrospinal fluid at the site of pulse generator implantation. Treatment is to use a ventral band with sufficient tension for 2 to 3 weeks to compress the path through which the pulse generator and the wire travel. For patients who do not respond to treatment, a small amount of autologous blood can be injected into the spinal canal epidural space to promote adhesion formation or surgical exploration and repair of leaks can be performed as soon as possible [42].

Peripheral nerve electrical stimulation: Peripheral nerve electrical stimulation is direct electrical stimulation of nerves outside the central axis to reduce pain in the distribution of targeted peripheral nerves [43]. This treatment has some efficacy in treating a variety of neuropathic, musculoskeletal, and visceral refractory pain. The mechanisms of peripheral nerve electrical stimulation in the treatment of neuropathic pain include inhibition of synaptic detachment, reduction of hyperexcitability of the dorsal root ganglia, reduction of neuralgia, improvement of neurological dysfunction, and acceleration of nerve regeneration. Peripheral nerve electrical stimulation has fewer adverse effects.

Transcutaneous electrical nerve stimulation: Transcutaneous electrical nerve stimulation has been used as a non-invasive treatment to treat various neuropathic pains [44]. The analgesic effect of transcutaneous electrical nerve stimulation is achieved by different neurobiological mechanisms affecting the peripheral and central nervous systems. Applying electrical impulses on the surface of the skin to activate nerve fibers, which in turn induces the release of different types of endogenous neurotransmitters and receptors in the peripheral and central nervous systems, as well as changes in electrical transmission and dilation of blood vessels, ultimately alleviating neuropathic pain [45].

IV. Treatment of Postherpetic Neuralgia

Postherpetic neuralgia is the most common type of neuropathic pain in clinical practice. It is defined as persistent pain in the innervation area for more than 3 months since initial infection with shingles virus, occasionally with autonomic and motor abnormalities [46]. Diseases such as malignant tumors, radiation therapy for tumors and chemotherapy, and diabetes mellitus are all risk factors for postherpetic neuralgia. According to epidemiological survey data, more than 24% of patients over 50 years old with herpes zoster virus infection are finally diagnosed with postherpetic neuralgia, which affects sleep and daily life, and is associated with anxiety and depression [47]. Therefore, treatment should start with early herpes virus infection and early intervention for people with high incidence. Prevention of postherpetic neuralgia, early use of antiviral drugs, antiepileptic drugs, Conservative treatment such as antidepressants and opioid analgesics, as well as transdermal patches of lidocaine, is essential; If pain relief is not satisfactory, intradural space injections with local anesthetics and corticosteroids may be considered. Compared with oral analgesics alone, the invasive neuraxial block has an adequate analgesic effect, significantly shortening the duration of pain and reducing the incidence of postherpetic neuralgia [48]. Treatment of postherpetic neuralgia that has been definitively diagnosed is tricky. In addition to antiepileptic drugs and strong opioid analgesics, interventional treatment options include continuous epidural analgesia, selective nerve root block, dorsal root ganglion pulsed radiofrequency, radiofrequency, and chemical destruction, intrathecal drug infusion system implantation, and spinal cord stimulation.

V. Treatment of Trigeminal Neuralgia

Trigeminal neuralgia is a clinically common neuropathic pain with an incidence of about 20 per 100,000 in people over 60 years of age. Typical trigeminal neuralgia is described as fulminant severe pinprick-like, shock-like, or knife-like pain in one or two innervation areas of the facial trigeminal nerve that lasts from a few seconds to one minute and can be completely asymptomatic during remission, often triggered by unexpected small stimuli in daily life [49]. Most patients with trigeminal neuralgia can be satisfactorily relieved by B vitamin-trophic nerve and carbamazepine anti-epileptic treatment in the early stage of the disease. As the course of the disease prolongs, the efficacy of antiepileptic drugs gradually diminishes, and symptomatic relief needs to be achieved by increasing the dose. If the patient cannot tolerate carbamazepine or if the adverse reactions of carbamazepine are obvious or the analgesic effect is still unsatisfactory after increasing the dosage, they can consider switching to second-line antiepileptic drugs such as sodium valproate, gabapentin, or oxcarbazepine. The invasive treatment methods for trigeminal neuralgia include radiofrequency thermocoagulation or chemical drug damage, microvascular decompression, and balloon compression [50]. Currently, microvascular decompression surgery is more common. For those who experience recurrence or cannot tolerate surgery after microvascular decompression surgery, radiofrequency therapy can be considered. This surgical technique has low cost, a short course of treatment, and minimal trauma. The target of radiofrequency therapy for trigeminal neuralgia can be the semilunar ganglion, the maxillary nerve, and the mandibular nerve. Even the peripheral nerves such as the supraorbital nerve, the infraorbital nerve, or the chin nerve can be treated with thermal coagulation to alleviate pain symptoms.

VI. Treatment of Phantom Limb Pain

The proportion of amputees with phantom limb pain is as high as 50% to 80%. Phantom limb pain may be

related to the remodeling of the peripheral and central nervous systems. The mechanisms of its peripheral nervous system include coupling of the sympathetic and dorsal root ganglia and the formation of residual local neuromas [51]. The mechanism of the central nervous system includes over excitation of neurons after secondary nerve injury at the spinal cord level, as well as remodeling of the motor cortex and sensory cortex projection areas corresponding to the amputated limb. Conservative treatment includes antiepileptic drugs and weak opioid analgesics [52]. If conservative treatment is ineffective, surgical surgery may be considered. Generally speaking, if the limb MRI examination indicates the presence of a neuroma, exploration, and resection of the neuroma can be considered, but it is generally less commonly used. For patients with phantom limb pain, treatment at least needs to be performed at the spinal cord or cerebral cortex level to achieve therapeutic effects.

VII. The Treatment of Neuropathic Pain

At present, the treatment of neuropathic pain mainly includes two categories: drug treatment and non-drug treatment. However, they have limited relief from neuropathic pain and can bring certain side effects such as allergies, sedation, drug addiction, neurological irreversibility damage, etc. Therefore, it is important to seek safer and more effective treatment options.

A. Application of Stem Cell in Neuropathic Pain

Stem cells refer to cells with self-replication and multi-directional differentiation potential, which can differentiate into almost all cell types in the body under certain conditions, such as blood cells, liver cells, myocardial cells, and epithelial cells [53]. Stem cell transplantation has been widely studied in the treatment of various neurological diseases, such as stroke, Parkinson's disease, and Alzheimer's disease. In recent years, the use of stem cells to treat neuropathic pain has also received widespread attention from researchers [54]. Although stem cells have been shown to relieve neuropathic pain in a variety of animal models, their exact mechanism of action has not yet been fully elucidated. Existing studies believe that stem cells can ultimately alleviate neuropathic pain by migrating to damaged nerves and areas related to pain conduction, differentiating into neurons and glial cells, secreting neurotrophic factors, inhibiting glial cell activation, inhibiting inflammation, reducing oxidative stress in the body and improving microcirculation.

1) Bone marrow mesenchymal stem cell

Bone marrow mesenchymal stem cells can be isolated from hematopoietic cells and differentiate into osteoblasts, chondrocytes, adipocytes, muscle cells, and astrocytes. In animal experiments on neuropathic pain, bone marrow mesenchymal stem cells can alleviate the sciatica caused by mechanical injury and neuropathic pain caused by diabetes peripheral neuropathy. Research has shown that bone marrow mesenchymal stem cells can not only alleviate the symptoms of neuropathic pain to a certain extent, but also regulate inflammatory reactions related to nerve injury, activate the expression of anti-inflammatory factors, and alleviate the progression of neuropathic pain. Another advantage of bone marrow mesenchymal stem cells in the treatment of neuropathic pain is the flexibility of the transplant method. Commonly used transplantation methods include lateral ventricle infusion, intrathecal infusion, tail vein injection, orthotopic transplantation, etc. Regardless of the method of transplantation, human bone marrow mesenchymal stem cells can reduce inflammatory factor levels in the circulatory system in animal models of neuropathic pain and enrich around the damaged spinal cord or peripheral nerves, relieving mechanical and thermal pain sensitivity symptoms. More notably, studies have shown that the therapeutic effect of bone marrow mesenchymal stem cells can last up to three months after transplantation. The researchers also screened the subtypes of bone marrow stromal stem cells before transplantation to improve the degree of inhibition of inflammatory factors by transplanted stem cells and relieve pain levels more effectively. At the same time, the relatively single-cell subtype ensures the safety of stem cell transplantation.

2) Adipose tissue-derived stem cells

Adipose tissue-derived stem cells are located in subcutaneous adipose tissue. The advantage is that the acquisition of these cells is less traumatic, and it is easier to perform autologous transplantation without the need for an exogenous donor, which minimizes the incompatibility of the graft with the host's tissue. In addition to the advantages of low immunogenicity, adipose tissue-derived stem cells also have the characteristics of high immunomodulation. Many studies have pointed out that adipose tissue-derived stem cells show effective anti-inflammatory effects in the treatment of neuropathic pain, and neuroinflammatory response plays a crucial role in the occurrence and development of neuropathic pain. These properties make adipose tissue-derived stem cells have great potential in the treatment of neuropathic pain.

3) Umbilical cord-derived mesenchymal stem cells

Umbilical cord mesenchymal stem cells are another easily accessible type of stem cell, and umbilical cord mesenchymal stem cells have a similar gene expression lineage to embryonic stem cells. Umbilical cord mesenchymal stem cells not only have a faster self-renewal rate than bone marrow mesenchymal stem cells, but also have many other attractive advantages, including (1) the non-invasive nature of the collection process; (2) low immunogenicity; (3) good immunosuppressive effect; (4) umbilical cord mesenchymal stem cells can not only be used for allogeneic transplantation, but also can be stored for long-term autologous transplantation; (5) compared with other sources of mesenchymal stem cells, the infection rate of umbilical cord mesenchymal stem cell transplantation was low; (6) the risk of malignant transformation of umbilical cord mesenchymal stem cells in the host is relatively low; (7) finally, and most attractively, umbilical cord mesenchymal stem cells are pluripotent.

4) Problems and prospects of stem cell therapy

In recent years, stem cell transplantation has attracted a lot of attention as a new treatment for neuropathic pain. A growing number of animal tests have demonstrated the positive role of stem cells in relieving neuropathic pain. Compared with the current clinical treatment methods, the advantages of stem cell therapy are (1) a short treatment period; (2) rapid onset of action and long-lasting efficacy; and (3) it can alleviate inflammation and improve motor function to a certain extent. Despite the positive results and advantages described above, there are still many issues to consider if you want to implement a successful clinical stem cell transplant. These questions include the type and source of transplanted cells, the method and route of transplantation, the dose and concentration of transplantation, the survival of transplanted stem cells, the efficiency of transplantation, the migration of transplanted cells in the host, and the criteria for ultimately judging the effect of transplantation. Taking transplantation methods as an example, transplanting stem cells into damaged tissue is the most direct method, but there is a potential risk of bleeding and secondary injury. Although the method of blood transfusion is simple and easy, the transplantation efficiency is low, and the host immune system may produce an anti-graft response, or the transplanted cells do not migrate to the damaged tissue that needs to be treated, but arrive with the blood circulation and stay in other tissues, resulting in transplant failure and even adverse reactions and serious complications. In addition, although the transplanted stem cells themselves are unlikely to become malignant, transplanted stem cells can significantly suppress the host's own immune response, which may lead to an increased risk of the host developing tumors. Although there are still many questions to be studied in the treatment of neuropathic pain by stem cell transplantation, there is hope that it will become a new method of safe and efficient treatment of neuropathic pain.

B. Application of Platelet-Rich Plasma in Neuropathic Pain

Platelet-rich plasma is derived from autologous whole blood and refers to plasma concentrates rich in platelets, fibrin, bioactive proteins, and different concentrations of white blood cells obtained by concentrated centrifugation [55]. Studies have shown that platelet-rich plasma can promote microcirculation reconstruction, inhibit local inflammatory response, and slow down apoptosis [56]. Moreover, due to its simple and convenient production method, which does not cause immune rejection in the body, it has been widely used in multiple fields. Related experiments have shown that platelet-rich plasma can also be used to treat neuropathic pain, but its mechanism for treating neuropathic pain still needs further research [57]. Therefore, this section discusses its therapeutic mechanisms.

Peripheral sensitization plays an important role in neuropathic pain caused by peripheral nerve injury. There are a variety of inflammatory cell infiltrates at the site of nerve injury, such as neutrophils, macrophages, and mast cells. Excessive accumulation of inflammatory cells forms the basis for overexcitation and continuous firing of nerve fibers. Injured tissue releases a large number of chemical mediators, such as cytokines and chemokines. This makes the nociceptor sensitive and excited and causes changes in the local chemical environment. Platelets have strong immunosuppressive and anti-inflammatory effects. By regulating and secreting various immune regulatory factors, angiogenic factors, and nutritional factors, platelet-rich plasma can reduce harmful immune responses and inflammation, and repair tissue damage. Platelet-rich plasma can block the release of pro-inflammatory cytokines from Schwann cells, macrophages, neutrophils, and mast cells, and inhibit the gene expression of pro-inflammatory factor receptors.

C. Acupuncture Therapy

As a part of traditional medicine, acupuncture has a history of more than 3000 years. According to the theory of meridians in traditional Chinese medicine, meridians are the channels that circulate blood and communicate viscera, body surface, and various parts of the body. Acupuncture points on the upper surface of meridians are also called acupoints. These points in the body can balance and store flowing vital energy. According to traditional Chinese medicine, blood movement disorders caused by various reasons, such as stagnation of blood circulation, or abnormal rise and fall of vital energy, eventually lead to pain symptoms. Through the stimulation of acupoints, acupuncture can play the role of dredging meridians, promoting vital energy and blood circulation, thus improving the qi and blood running state in the diseased area and relieving neuropathic pain [58].

D. Individualized Psychotherapy

Patients with neuropathic pain, especially postherpetic neuralgia and trigeminal neuralgia, often experience moderate to severe pain. These patients often suffer from varying degrees of depression, anxiety, fear, and even suicidal tendencies, which seriously affect their quality of life. Therefore, the treatment mode of neuropathic pain should not only pursue individualization and the combination of multiple treatment methods but also pay attention to the psychological treatment of patients according to the situation [59].

VIII. Conclusion

Neuropathological pain is considered to be a disease that disturbs patients for a long time. It not only affects the normal life of patients but also increases the incidence of anxiety and depression. At present, the efficacy of traditional treatment is not very satisfactory. Emerging treatment methods including stem cell therapy and platelet-rich plasma therapy provide a new direction for the treatment of neuropathic pain. In order to better prevent and treat this disease, the government and relevant departments should greatly carry out disease education and how to prevent it, and popularize it to the public on a large scale, such as communities, schools, factories, and large-scale enterprises. So as to enhance the

awareness of prevention of the masses. At the same time, help and care were given to patients, and psychological counseling was given in time to protect patients from depression and anxiety. It is important to increase the prevalence of this disease, and we should enhance the awareness of prevention among the general public.

CONFLICT OF INTEREST

The author has claimed that no conflict of interest exists.

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