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The Mechanism and Treatment Strategy of Neurogenic Muscle Atrophy

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Abstract. After peripheral nerve injury (PNI), axial buds emerge from the proximal end of the injured area, providing nerve supply to the skin and muscles of the injured area. Lower nerve regeneration, however, may result from sluggish axonal renewal. As a result, it could take a while for the skin and muscles in the wounded area to regain innervation from the proximal nerves. PNI generally does not threaten the patient's life, but it may cause atrophy in muscles that have lost nerve control. Long term denervation can lead to corresponding skeletal muscle atrophy. Currently, many studies are gradually focusing on neurogenic muscle atrophy, but its mechanism of occurrence is still far from fully understood, and the treatment methods are also relatively limited. At present, surgical treatment and electrical stimulation therapy are mainly used in clinical practice to prevent and treat neurogenic muscle atrophy. In recent years, with the development of technologies such as cell biology, molecular biochemistry, immunohistochemistry, and electrophysiology, people have delved deeper into the mechanisms of neurogenic muscle atrophy, and the underlying mechanisms have been continuously understood and discovered. New treatment methods have also emerged.

Keywords: Neurogenic muscle atrophy; mechanism of of occurrence; treatment.

1. Introduction

Neurogenic atrophy (NA), also known as Parsonage Tourer syndrome, is a relatively rare neuromuscular disorder, manifested as rapid and programmatic loss of muscle size and performance due to denervation of skeletal muscles [1]. It mainly affects the brachial plexus nerves, with symptoms often manifested as pain and accompanying muscle weakness, which seriously affects the quality of life of patients, mainly caused by peripheral nerve damage. Peripheral nerve injury (PNI) is a common neurological disorder that can lead to motor and sensory impairments as well as neuropathic pain. Pathological changes not only occur at the site of direct injury, but also in the affected areas of the central nervous system. According to statistics, approximately one million people worldwide suffer from peripheral nerve injuries each year, with China having around 300000 to 500000 patients, accounting for 2.8% of the total number of trauma patients [2, 3]. Although PNI usually does not threaten the patient's life, it may cause atrophic changes in muscles that have lost nerve control. After peripheral nerve injury, the muscles it controls lose nerve nutrition and undergo atrophy and degeneration. With the prolongation of time and a series of pathological processes, neuromuscular fibrosis occurs and irreversible degeneration occurs, affecting the functional recovery after nerve repair [4]. Studies have shown that after nerve damage, the skeletal muscles it controls undergo atrophy within a few days. As the atrophy time prolongs, cell apoptosis gradually increases and the number of muscle cell nuclei gradually decreases, ultimately leading to permanent loss of skeletal muscle function [5].

The degree of muscle atrophy is usually closely related to the recovery of neurological function, so the treatment of neurogenic muscle atrophy is to some extent determined by PNI. Current treatment strategies for PNI include surgical treatment and non-surgical treatment. Surgical treatment mainly includes autologous transplantation and allogeneic transplantation and non-surgical treatments mainly include drug therapy, electrical stimulation (ES), stem cell therapy, physical therapy, acupuncture therapy, and so on.

There are often literature reports on the diagnosis and treatment of neurogenic muscle atrophy, but there is a lack of systematic review. Therefore, this article will comprehensively review relevant literature at home and abroad, and systematically summarize the latest progress in the mechanisms related to neurogenic muscle atrophy, in depth analysis of relevant treatment methods and their efficacy, in order to provide valuable references for the clinical treatment and practice of neurogenic muscle atrophy.

2. Manifestations and Mechanisms of Neurogenic Muscle Atrophy

Skeletal muscle atrophy can be detected by changes in muscle weight and muscle fiber size [6]. Diagnosis is mainly determined through clinical examination and nerve conduction studies (NCS), electromyography (EMG), and laboratory tests [7].

The peripheral nervous system maintains the function of skeletal muscles through two mechanisms: one is neurotrophic factor control, which maintains the normal morphology and structure of muscle cells by utilizing soluble factors released by motor neuron nerve endings at the neuromuscular junction, another is neuromuscular activity control, which triggers depolarization of the muscle membrane and electromyographic coupling through the transmission of nerve impulses to maintain normal muscle contraction [8].After PNI, muscle fiber blood supply disorders and insufficient muscle nutrition factors can lead to malnutrition atrophy of skeletal muscles. In addition, the transmission of nerve impulses can only be achieved through the motor endplate to deliver the neurotransmitter acetylcholine (ACh) to skeletal muscles, causing contraction. The acetylcholine receptor (AChR), as the main component of the motor endplate, plays an important role in the transmission and conversion of nerve impulses, so the loss of function of the motor endplate and abnormal quantity and distribution of AChR can lead to disuse atrophy of skeletal muscle contraction disorders [5].Chronic long-term loss of nerve innervation in skeletal muscles can have permanent adverse effects, and even with nerve regeneration, the resulting skeletal muscle function cannot be fully restored.

3. Treatment Strategies for Neurogenic Muscle Atrophy

3.1. Surgical Treatment

3.1.1. Autologous transplantation.

The most common treatment for bridging large nerve gas (>3 centimeters), critical nerve injuries, and more proximal injuries is autologous transplantation, it includes the use of autografts extracted from another nerve in the patient's body, which means using functional but less critical nerves from various possible locations, such as lateral, superficial epidermal nerves, or lateral femoral cutaneous nerves, as donor sites [9-11].Liron S. Duraku et al. pointed out that multiple neural branches have better effects, although Chen et al. chose to use plantar muscle branches as donor nerves because the diameter and total number of motor nerve fibers matched the number of axons in DPN, using multiple branches seemed to bring more favorable results [12, 13].

The incidence rate of the donor site, the requirement for future surgical procedures, the loss of donor site function, the potential for scarring, the discomfort of a neuroma, and the limited durability of the graft are some of the disadvantages of this treatment, though [9]. If there is a limited supply, a second incision is needed to harvest the transplanted tissue and bundle mismatch [10].

3.1.2. Allogeneic transplantation.

Other sources must be taken into consideration when the length of the graft surpasses the accessible nerve autograft and the nerve gap is more than the crucial size, which is approximately 3 centimeters in people. The use of cadavers or donor nerves for allogeneic transplantation can serve as an alternative clinical option. Neural allogeneic transplantation can help guide and facilitate feasible SC, promote axonal connections, and facilitate target tissue reinnervation [11,14].Kelly C.S. Roballo et al. pointed out that if live peripheral nerve allografts are not immunogenic, there are several methods

that may be more effective than sensory autografts [15].First, peripheral nerve allografts recovered and stored from donor cadavers do not cause incidence rate to the host. Secondly, peripheral nerve allografts can match sensory movement with the defect site, resulting in better axonal regeneration than using only sensory grafts.

Nevertheless, there are certain disadvantages to this method, including the need for immunosuppressive medication to be administered for roughly 18 to 24 months following implantation in order to prevent transplant rejection and to allow host axons and stem cells to rebuild along the allosteric scaffold [10,14]. Patients are more vulnerable to other issues including opportunistic infections or other systemic consequences as a result of the long-term immune suppression. Consequently, this strategy is only taken into account in the direst situations of damage [9].

3.2. Non-surgical Treatment

3.2.1. Drug therapy.

In order to prevent scar formation between surrounding tissues and injured nerves through surgery, and to supplement with pharmacological agents such as steroids [16].They can promote myelination and have neuroprotective properties [2].Mainly including corticosteroids, erythropoietin, 4-aminopyridine and other drugs [9].Medicine therapy still has certain negative effects, though, and further study is required to guarantee both a safer use of the medicine and a greater usage of it as an adjuvant therapy.

3.2.2. Acupuncture treatment.

Acupuncture promotes the expression of nerve growth related factors, inhibits glial cell activation, reduces the release of inflammatory factors and pain mediators, thereby improving the microenvironment of peripheral nerve repair and regeneration, promoting blood supply reconstruction of peripheral nerve tissue, reducing oxidative stress damage to peripheral nerves, delaying apoptosis of peripheral nerve cells, regulating neural plasticity of the brain, regulating axonal reflexes, and playing a role in pain relief, anti-inflammatory, anxiety regulation, and delaying neurogenic muscle atrophy [17].Jianqi Yu et al. found that EA stimulation of ST36 and GB30 can alleviate muscle atrophy, upregulate agrin and AChR - ε expression, and downregulate AChR - γ expression [6].Other studies have shown that the mechanism by which acupuncture improves neurogenic muscle atrophy is closely related to the increase in sodium potassium ATPase and acetylcholinesterase activity.

However, there is still a lack of research on the specific mechanism of how acupuncture alleviates nerve damage, which is closed-loop and interconnected. There is relatively little research on the animal model of "disease syndrome combination", dose effect relationship studies, and imaging data analysis methods to support the mechanism of acupuncture treatment for peripheral nerve injury.

3.2.3. Electrical stimulation (ES) therapy.

The great majority of patients can benefit from ES, which is a safe and efficient therapy choice when compared to other approaches [18]. It can stop the loss of muscular mass. Further restoration can be achieved by combining exercise, seizure characteristics, fatigue index, and mechanical sensitivity. In the meantime, in human neural progenitor cells (hNPC), ES can enhance the expression of neurotrophic factors (BDNF, NTF-3) and neurotrophic factor receptor (Trk). Consequently, it can speed peripheral nerve regeneration and functional recovery while promoting angiogenesis, axonal development, and myelin sheath thickening [6]. Additionally, Xiao Lei Chu et al. noted that ES can lessen the neuropathic discomfort associated with PNI and hasten its functional recovery. For one hour, ES can speed up axon regeneration, and for one hour, 20 Hz stimulation can temporarily compress and alternate regeneration. Furthermore, the reference reinnervation of muscle nerves can be considerably accelerated by constant 20Hz ES of axons close to the healing site [19].

At the electrode insertion site, however, there is a chance of consequences including infection and wire movement, as well as the necessity for surgery. Animal trials have been the basis for most ES therapies for PNI damage sites to date. However, the length and breadth of human and animal nerves differ significantly [19].

3.2.4. Stem cell therapy.

Stem cell therapy can differentiate into mature cells under appropriate conditions and specific signals, repair tissue damage, and improve its function [16]. At present, the stem cells used in treatment mainly include embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, muscle stem cells, etc. Kimura et al. implanted neural crest cells derived from human iPSCs with low affinity for nerve growth factor receptor positive and thymocyte differentiation antigen-1 positive into a 6mm defect in the sciatic nerve of mice, promoted axonal growth, myelination, and angiogenesis, and restored motor function, achieving a similar effect as autologous transplantation [20]. The transplanted cells were able to survive for 12 weeks and migrate uniformly throughout the entire neural conduit.

However, up to now, the repair mechanism of PNI by stem cell transplantation is still not fully understood, and the treatment of peripheral nerve and muscle injuries with stem cell transplantation is mostly in the preclinical stage [5]. At the same time, it is also necessary to continue to pay attention to and evaluate the safety and effectiveness of stem cell therapy to ensure that it can bring real help and improvement to patients.

4. Conclusion

The neural system innervates human movement-controlling skeletal muscles. Muscle contractions are the basis for all voluntary activities performed in daily life. Impaired motor and sensory function is a common result of PNI. Researchers have focused more on neurogenic muscle atrophy than skeletal muscle atrophy because of its intricate process. Exploring the mechanism of muscle atrophy under PNI and finding effective methods for treating neurogenic muscle atrophy are important issues that urgently need to be addressed in clinical medicine, rehabilitation medicine, and other fields. After PNI, nerves can regenerate to a certain extent, but the regeneration rate of axons is relatively slow, usually 1mm per day, atrophic changes occur before muscles regain nerve innervation, and the degree of muscle atrophy is usually closely related to the recovery of nerve function. If muscle atrophy is caused by long-term damage, it will seriously affect the quality of life of patients, so early and timely treatment is particularly crucial.

With the continuous deepening of research on the mechanism of neurogenic muscle atrophy and the development of clinical medicine and rehabilitation medicine except the traditional therapies such as surgery and medication, many new therapies for treating neurogenic muscle atrophy have been proposed one after another. While currently, stem cell therapy is mostly in the preclinical stage, and clinical research also has limitations such as small sample sizes. Therefore, it is necessary to actively carry out more clinical research on neurogenic muscle atrophy, further understand the mechanism of neurogenic muscle atrophy, and determine the safety and effectiveness of stem cell clinical therapy and other treatment methods.

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