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Review of clinical nerve repair strategies for neurorestoration of central nervous system tumor damage

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Review of clinical nerve repair strategies for neurorestoration of central nervous system tumor damage

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Review of clinical nerve repair strategies for neurorestoration of central nervous system tumor damage

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ABSTRACT

Central nervous system (CNS) tumors are common. In recent years, with the continuous development and popularization of neurosurgery and the advancement of diagnostic and therapeutic instruments, the diagnosis and treatment of diseases have made great progress, but the prognosis of patients depends on multiple clinical factors. In this study, we selected various literatures in the PubMed and Google Scholar search engines using the keywords “nerve repair strategies”, “central nervous system tumor” as well as searched scientifically reviewed historical perspectives and recent advancements and achievements in Neurorestoratology of the CNS. Therefore, this study focuses on the Neurorestoratology of the CNS and its prospects, aiming to provide scientific guidance for the clinical diagnosis and treatment of CNS tumors in the future, and improve the prognosis and quality of life of patients.

1 Introduction

For a long time, it has been believed that the hardware of the brain is indeed hard and that once an incident such as a central nervous system (CNS) tumor occurs, brain structure and function will be lost forever. CNS tumors are one of the most serious CNS injuries. Most patients with CNS tumors are unable to live independently or take care of themselves, which imposes a huge burden on their families and the society. In 2016, a total of 329,673 new cancers occurred globally, with an age-adjusted incidence of 4.63 per 100,000 person-years, a

significant increase of 17.3% between 1990 and 2016. In 2016, there were 227,039 deaths from CNS cancer worldwide, with an age-standardized mortality rate of 3.24 per 100,000 person-years, and there was no significant change in mortality from 1990 to 2016 [1], which was higher in males than that in females, and was mostly thorax or cervix related [2–6]. In recent years, with the establishment and popularization of the science of Neurorestoratology, which is a branch of neuroscience that studies nerve regeneration, repair or replacement of nerve structure, nerve remodeling, and nerve regulation, aiming to promote the reconstruction

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and recovery of nerve function in various neurodegenerative diseases and damages. The traditional viewpoint, which is still popular in the medical community, is that there is currently no effective treatment to completely, or even partially restore neurological functions lost due to intractable CNS damage or disease. Thus, current nerve repair strategies (NRS) only achieve limited partial or moderate recovery. However, these achievements are more than enough to answer the question of whether patients with intractable CNS damage or disease could benefit from various clinical NRS such as cell therapy, neurostimulation or neuromodulation, neuroprosthesis, or related advanced assistive devices, nerve bridging, neurorehabilitation, drug or growth factors, and other novel treatment procedures [7–10]. In this review, we discuss the treatment of tumor-induced injury of the CNS, including commonly used nursing and drugs. We also discuss some novel approaches such as cell therapy and neuroprotectants, and discuss the limitations of current therapies and the future direction of treatment.

2 Methods

We performed a search of the PubMed and Google Scholar databases since 1995 for peer-reviewed papers published in the English language using the keywords “nerve repair strategies”, “central nervous system tumor”, cell therapy, and neural prostheses, all of which display the historical events and recent main advancements and achievements. Also, meeting abstracts, case reports, and editorials were excluded from our review. The authors reviewed all the titles and abstracts independently, and screened them according to the inclusion criteria. All the references of included literature were also screened systematically. Original papers reporting a definitive intervention in a stated number of patients were included in the analysis. In the case of two or three publications emanating from one study, the version with the longest follow-up period and most complete reporting was included. All the included studies had been approved by local institutional review boards. The flow chart is shown in Fig. 1.

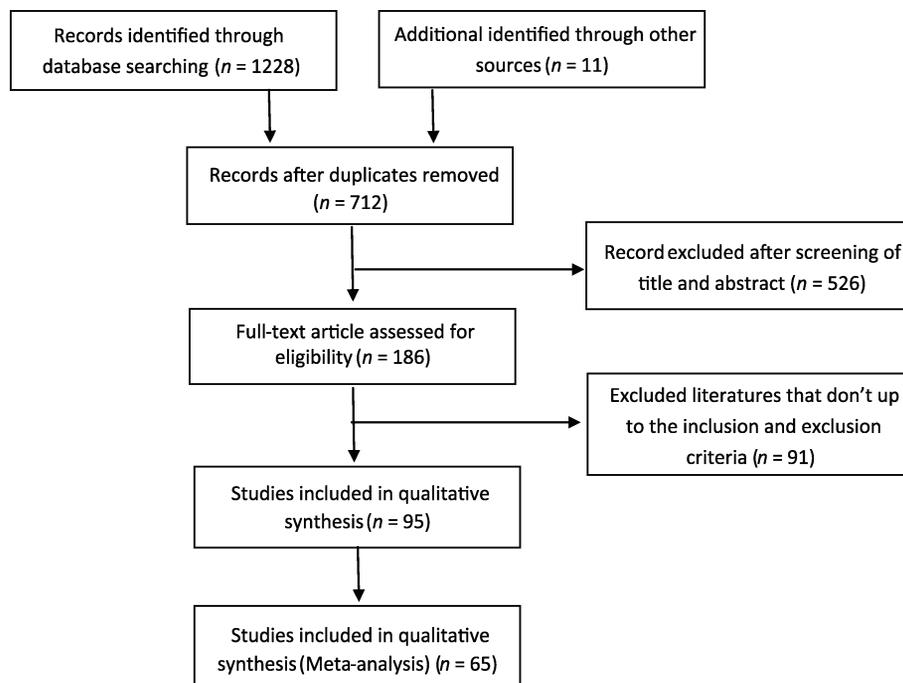


Fig. 1 Flow diagram of literature and screen strategy.

3 Results and discussion

There are two main types of CNS damage: primary injury, including neural cell damage and vascular destruction; and secondary injury, including inflammation, excitotoxicity, edema, ischemia, chronic demyelination, and the formation of glial scars, etc., which causes apoptosis and aggravates damage [11, 12]. CNS damage or disease could be treated by various clinical NRS, such as cell therapy, neurostimulation or neuro modulation, neuroprosthesis or related advanced assistive devices, bioengineering or tissue engineering, neurotization or nerve bridging, neurorehabilitation, drug or growth factors, and other novel therapeutic procedures.

3.1 Pharmacotherapy

3.1.1 Melatonin

Reiter et al. [13] reported that melatonin's actions in organisms are more widespread than originally envisaged, which has been linked to circadian rhythms, immune function, sleep, retinal physiology, and endocrine function in general. In *in vivo* trials, the pharmacological dose of melatonin has been found to be effective in reducing the macromolecular damage that is the consequence of free radical generation induced by a variety of toxic agents, exogenous organisms and experimental paradigms. The lack of toxicity of melatonin and the ease of crossing morphophysiological barriers and entering subcellular compartments are essential features of neurorestoration. In a recent study, all the results suggested that melatonin could reduce nerve cell death and cerebral damage, and the effect of a caudal vein injection was better than that of an intraperitoneal injection. This may be associated with the drug levels of the areas with brain injury [14].

3.1.2 Mecobalamin

Matsushita et al. [15] reported that mecobalamin,

a coenzyme of vitamin B12, promotes the metabolism of nucleic acids, proteins, and lipids via a methyl conversion reaction. Mecobalamin readily enters nerve tissues and promotes the restoration of injured nervous tissue. Mecobalamin significantly upregulates growth associated protein 433 mRNA levels in nervous tissue after sciatic nerve injury. Mecobalamin promotes functional and morphological recovery after nerve injury. The molecular mechanism underlying the restorative effects of mecobalamin on injured nerves may involve upregulation of the genes for multiple neurotrophic factors [16].

3.1.3 Ganglioside

Geisler et al. [17] reported that ganglioside did not demonstrate any significant differences between the treatment group and the control group in a multicenter randomized, double-blind, and placebo-control clinical trial; as such, ganglioside is not recommended as a routine therapy in CNS damage. However, according to Gusheng Wu [18], who reported that ganglioside is widely used in the nervous system and plays an important role in the recovery of nervous system function. Therefore, whether or not ganglioside plays a role in the recovery of nervous system injury needs further exploration.

3.1.4 Metformin

Insulin resistance influences ATP production emission in neurons and astrocytes, as well as mixed-glial cultures [19]. The effect of metformin on cognition is clinically controversial, and observational studies have shown no clear effect [20]; however, it is likely to be associated with high metformin-induced vitamin B12 deficiency [21], and causes cognitive deficiency [22]. Although it has been found in recent research developments that metformin reverses brain mitochondrial function, they showed that insulin resistance caused significant impairment

of brain mitochondrial function, which is mitigated by metformin, thereby restoring neurological function [23].

3.2 Nerve repair surgery

3.2.1 Nerve transplantation

Vascular bundle implantation can rapidly reconstruct the blood supply of the nerve segment compressed by the tumor of the nervous system, which can significantly promote nerve regeneration and functional recovery [24]. The authors' threshold for adequate nerve health is at least 75% preservation of fascicular architecture [25, 26]. The two weeks following nerve injury is the best time for nerve repair [27]. The vascular bundle is extracted by the chemical method to cell allogeneic nerve preservation of the basement membrane tube, which has an instructive effect to promote the regeneration of nerve fibers [28]. More experts started to perform similar surgical procedures and showed partial neurological functional improvements [29–32].

3.2.2 Nerve decompression

Nerve decompression involves the removal of tumors and the muscles that compress the nerve. For example, in patients with acoustic neuroma or trigeminal neuralgia, the nerves are compressed, and it is necessary to remove the compression surgically [33]. An acoustic neuroma results from an overproduction of Schwann cells (myelin sheath-producing cells) on the vestibulocochlear nerve [34, 35]. As the tumor grows, it compresses nearby nerves, such as the cochlear or vestibular nerve, against the bony auditory canal. This compression leads to hearing loss and balance issues. If tumor growth extends outside the auditory canal, additional cranial nerves would be at risk for compression, including the trigeminal nerve and the facial nerve [36]. As a tumor enlarges, it displaces

surrounding brain structures. Other CNS tube tumors and acoustic neuromas are the same. After surgical treatment, the symptoms of compression are alleviated, and most of the nerve function can be restored [37–39].

3.2.3 Other

The patient can choose stereotactic radiosurgery, but it does not work fast enough. Decisions about treatment are based on patient factors, such as physical condition, willingness to receive treatment, curability of the lesion with radiation, and so on [40].

3.3 Nursing intervention

3.3.1 Nursing

Nursing is divided into perioperative nursing and postoperative nursing. As surgical removal is the best treatment option, the patient needs a perioperative continuum of care, but postoperative care is more important for the recovery of neurological function. Effective nursing intervention measures can promote recovery of the neurological function of patients, improve their cognitive function, improve postoperative quality of life, and prolong their survival time [41].

3.3.2 Physical activity

Physical activity is effective as a rehabilitation tool for recovery and promoting neurological functional [42, 43]. Indeed, it was found that physical training not only promoted cerebral angiogenesis, vasomotor reactivity, and neurotrophic factor release; but also reduced apoptosis and excitotoxicity, and could improve the regulation of motor unit activation [44–47].

3.4 Hyperbaric oxygen therapy

Although surgical resection of tumors can improve the clinical symptoms and relieve the pain of patients, the incidence of postoperative cerebral edema is extremely high. Edema and

compression can easily cause visual and neurological damage, which would seriously affect the outcome of surgery and prognosis of patients [39]. Its occurrence is mainly due to the preoperative compression of the tumor tissue of the nervous system, resulting in hypoxia and edema of the tissue surrounding the brain tumor, and the brain edema still exists after the resection of the tumor [48]. Hyperbaric oxygen will promote the survival of surrounding tissues, reduce edema, improve microcirculation, break the edema-hypoxia-edema vicious cycle, promote healing, promote the up-regulation of growth factors, and improve neovascularization. Timing is also important. The treatment time for acute nerve injury is approximately 6 hours. If hyperbaric oxygen therapy begins after this time window, it may also have a negative effect on the tissues. It was found that hyperbaric oxygen, if administered early, promotes nerve repair, regeneration, and functional recovery as early as 10 days after injury. The effect persisted after 14 weeks, suggesting that it was not a short-term effect. Also, studies have shown that hyperbaric oxygen can enhance the vitality of Schwann cells while improving microcirculation, and Schwann cells play an important role in nerve tissue regeneration [49–52].

3.5 Other methods

3.5.1 Music treatment

During the past years, subjective experiences of the emotional and cognitive impact of music have received increasing experimental and scientific support that music evokes strong emotions [53], influencing our autonomic nervous and neuroendocrine systems [54], enhances cognitive functioning [55], and activates the brain extensively, engaging multiple temporal, frontal, parietal, cerebellar, and limbic regions [56]. Similarly, in response to the growing prevalence of many aging-related

severe neurological conditions, many music-based rehabilitation methods have been developed to enhance recovery or sustain functioning in the cognitive, motor, language, emotional, or social domain [57].

3.5.2 Rehabilitation treatment

Shi et al. [58] reported that rehabilitation training can individually and synergistically improve the recovery of neurological function and motor function after cerebral ischemic injury. Therefore, rehabilitation requires comprehensive treatment, and parents and rehabilitation workers are still looking forward to finding more treatments [59].

3.5.3 Acupuncture

Acupuncture is a form of alternative medicine that has been commonly used to relieve symptoms in the Chinese medical system for more than 2000 years [60]. Yu et al. [61] reported that acupuncture was helpful in the neurorestoration of CNS tumor damage. Many rehabilitation hospitals offer acupuncture in China.

3.5.4 Neuroprotectants

In the past 50 years, more than 1,000 drugs have been expected to improve neuropathy after acute ischemic stroke (AIS), but none of them has been recognized by the academic community. Na-1 is the first drug demonstrated to have a neuroprotective effect after AIS. It maintains neural activity by blocking the production of nitric oxide (NO) by cells in an anoxic environment. Researchers did not rush to the clinic with such a positive result, but there is no doubt that the first positive result for a drug in nearly 50 years must have surprised the medical world [62].

3.6 Novel treatment

Novel treatment methods are mainly embodied

in cell therapy. Cell therapy is well known as the most promising treatment in regenerative medicine. Embryonic stem cells, induced pluripotent stem cells, neural stem cells, and other functional cells such as Schwann cells have demonstrated their effectiveness in treating certain diseases. However, these cell groups face barriers in cell source, ethics, tumorigenicity, or limited functional recovery [63–65].

4 Summary

Nerve repair has been a problem in the medical profession, although there is a lot of ongoing research now, and many meaningful results have been achieved, there still exist many problems to be solved, such as many drugs on nerve regeneration and repair, yet the specific mechanism remains unclear and requires further research. Most of the relevant experiments are conducted on animals. Although these drugs or surgeries are effective on animals, they may not be effective on humans; as such, clinical verification is still lacking. Many treatments can improve the function of injured nerves to different degrees, but none of them achieves the goal of complete cure. Therefore, it is necessary to prove effective and optimal combinations of nerve repair methods, actively explore new methods, and constantly improve the effective degree of nerve function repair.

Conflict of interests

The authors declare no conflict of interests for this work.

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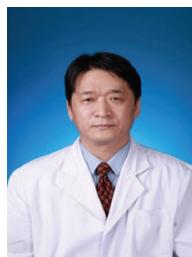
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