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The 2019 yearbook of Neurorestoratology

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REVIEW ARTICLE

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ABSTRACT

Time is infinite movement in constant motion. We are glad to see that Neurorestoratology, a new discipline, has grown into a rich field involving many global researchers in recent years. In this 2019 yearbook of Neurorestoratology, we introduce the most recent advances and achievements in this field, including findings on the pathogenesis of neurological diseases, neurorestorative mechanisms, and clinical therapeutic achievements globally. Many patients have benefited from treatments involving cell therapies, neurostimulation/neuromodulation, brain–computer interface, neurorestorative surgery or pharmacy, and many others. Clinical physicians can refer to this yearbook with the latest knowledge and apply it to clinical practice.

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1 Introduction

Despite recent developments in clinical, preventive, and rehabilitative medicine, when cures are unavailable it is necessary to restore damaged tissues and functions through what we call "restorative medicine" or "medical restoratology". Medical restoratology involves all organs and systems of the human body, particularly those of the central nervous system (i.e., the brain and spinal cord), which are most challenging to restore. Each year, to promote the development of neural repair, the yearbooks of Neurostoratology have been serially compiled since 2016. In this 2019 yearbook, we collect and introduce the global achievements of this field for the entire year. These include knowledge of the pathogenesis of neurological diseases, explorations of neurorestorative mechanisms, and clinical therapeutic exploration with current achievements and progress.

2 New findings on disease pathogenesis or nervous system degeneration

The pathogeneses and aging mechanisms of diseases are key to developing etiological treatments. Zada et al. [1] found that sleep could increase chromosome dynamics, which would lower the number of DNA double-strand breaks accumulated during wakefulness; hence less or poor sleep might favor the pathogenesis of several neurodegenerative diseases. Moreno-Jiménez et al. [2] reported that the number and maturation of immature neurons in dentate gyrus progressively declined in advanced Alzheimer's disease (AD), which was a potentially relevant pathogenesis underlying memory deficit. Higher numbers of neuroblasts, on the other hand, were associated with higher cognitive performance [3]. Mathys et al. [4] showed that perturbed myelination-related processes in multiple cell types played a key role in the pathogenesis of AD. Ising et al. [5] discovered that inflammatory activation of microglia and NLRP3 was the pathogenesis of tauopathies.

3 New mechanisms for neurorestorative therapy

This year, many studies have shown novel and interesting mechanisms for neural repair. A study by Dominy et al. [6] revealed that a new neurorestorative mechanism for AD could reduce the bacterial load of established *Porphyromonas gingivalis* brain infection (which is possibly one of the pathogeneses for AD), block Aβ1–42 production, reduce neuroinflammation, and rescue neurons in the hippocampus through gingipain inhibitors. Lourenco et al. [7] found that boosting brain levels of fibronectin type III domain-containing protein 5 (FNDC5)/irisin through regular exercise could improve synaptic plasticity and memory, which might be a potential neurorestorative mechanism for AD patients. Vrselja et al. [8] demonstrated a new neurorestorative mechanism to restore microcirculation in intact pig brains after a prolonged post-mortem interval with preservation of the cytoarchitecture, attenuation of cell death, restoration of vascular dilatory and glial inflammatory responses, spontaneous synaptic activity, and active cerebral metabolism in the absence of global electrocorticographic activity. Anumanchipalli et al. [9] designed a decoder synthesizing speech from cortical activity an innovative neurorestorative mechanism to restore spoken communication. Moda-Sava et al. [10] found that depression-related behavior with targeted, branch-specific elimination of postsynaptic dendritic spines on the prefrontal neurons could be restored by antidepressant-dose ketamine through selectively rescuing eliminated spines. Heckmann et al. [11] reported that LC3-associated endocytosis in microglia could protect from neurodegenerative pathologies resulting from

β-amyloid deposition (such as AD). Fultz et al. [12] discovered that the sleeping brain exhibited waves of cerebrospinal fluid (CSF) flow on a macroscopic scale and that these CSF dynamics were interlinked with neural and hemodynamic rhythms. They hypothesized that CSF clears metabolic waste products from the brain during slow waves, accompanied by neural activity and contributed to memory consolidation. A study by von Wild et al. [13] replicated central nervous system (CNS)-peripheral nervous system (PNS) graft-induced neuroregeneration of denervated skeletal muscle in spinal cord injury.

4 Achievements and progress in clinical neurorestorative therapies

4.1 Cell therapy

Cell transplantation is a hot topic in neurorestoratology, highlighted by many new research findings this year. Levy et al. [14] reported that intravenous allogeneic mesenchymal stem cells [i.e., mesenchymal stromal cells (MSCs)] improved the neurological behaviors of patients with chronic stroke and substantial functional deficits. Zhang et al. [15] showed that the intracerebral injection of neural stem cells improved the neurological functions of patients with paralysis after an ischemic stroke. Guo et al. [16] reported that transplanting olfactory ensheathing cells in a patient with cerebral infarction sequela could improve his quality of life. Savitz et al. [17] conducted a randomized, sham-controlled, parallel-group, multicenter clinical trial for patients with subacute ischemic strokes by intra-arterially delivering autologous bone marrow-derived ALD-401; but reported no differences between cell therapy and the control. Brunet et al. [18] reported a patient who had received an intravenous infusion of bone marrow-derived allogeneic mesenchymal stem cells and had a better recovery than anticipated on day 3 post-bleed. Hammadi and Alhimyari [19] reported that autologous bone marrow-derived mononuclear cells through intra-arterial and intravenous injections resulted in improvements in the quality of life of patients with an ischemic stroke. Furthermore, Vahidy et al. [20] reported that the intravenous fusion of bone marrow mononuclear cells for acute ischemic stroke was a safe and feasible method, but there was no significant difference between the cell treatment and the control.

Vaquero et al. [21] found that intrathecal transplantation of autologous stromal cells increased cerebral glucose metabolism and improved previous symptoms in patients with Alzheimer's dementia.

Levi et al. [22] conducted a single-blind, randomized study of human neural stem cell transplantation in patients with chronic C5–C7 tetraplegia. However, their experiment did not reach the required clinical efficacy threshold and this study was terminated early. Bydon et al. [23] reported that intrathecal injections of adipose tissue-derived mesenchymal stem cells (actually MSCs) to a patient with incomplete spinal cord injury showed motor and sensory improvement. Phedy et al. [24] reported that transplanting bone marrow-derived mesenchymal stem cells in a chronic spinal cord injury (SCI) patient through direct parenchymal and intravenous injection improved his motor function.

Moore et al. [25] reported that transplanting autologous hematopoietic stem cells in patients with active relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis could achieve significant clinical improvement outcomes. Mariottini et al. [26] reported that autologous hematopoietic stem cell transplantation following natalizumab discontinuation in aggressive multiple sclerosis was safe and efficient.

Boruczkowski and Zdolińska-Malinowska [27] reported that transplanting allogeneic mesenchymal stem cells obtained from Wharton's jelly of umbilical cords to children with cerebral palsy improved their daily quality of life. They were also effective in patients with spina bifida: improving their motor functions, micturition/defecation control, cognitive functions, and quality of life [28].

Pan et al. [29] reported that intrathecal injections of allogeneic bone marrow-derived MSCs in neurological patients were safe, feasible, and showed promising results.

Goudie et al. [30] found that transplantation of hematopoietic stem cells did not prevent neurological deterioration in infants with Farber disease. However, Chen et al. [31] reported that allogeneic hematopoietic stem cell transplantation for X-linked adrenoleukodystrophy was safe, feasible and showed beneficial effects in preventing a worsening of the disease in some patients.

Riordan et al. [32] reported that the administration of mesenchymal stem cells derived from umbilical cord tissue was safe in children with autism spectrum disorders, with a few patients showing signals of efficacy.

4.2 Neurostimulation/neuromodulation and the brain–computer interface (BCI)

Neuromodulation is a promising field of medical engineering. Any new clinical application of the BCI will attract the attention of physicians related to neurorestoratology in the whole world. This is an important exploration for the treatment of human hopeless brain and spinal cord diseases and damage. Blok et al. [33] reported that clinical improvements could be achieved in patients with an overactive bladder, using the sacral neuromodulation system in a prospective, multicenter study. McCrery et al. [34] reported that sacral neuromodulation was a safe and effective approach to improve urinary urgency incontinence symptoms in a majority of patients with urinary dysfunction and fecal incontinence, when conservative treatlents failed. Yeh et al. [35] reported a linear correlation between the amplitude of dorsal genital nerve stimulation (GNS) ranging from 1 to 4 times the threshold and bladder capacity gain stimulation in acute SCI patients with neurogenic detrusor overactivity. Bourbeau et al. [36] also found that short term at home GNS could reduce urinary incontinence and help subjects to achieve adequate bladder control. Benabid et al. [37] reported that up to eight degrees of freedom of a four-limb neuroprosthetic exoskeleton could be simultaneously controlled by a complete brain–machine interface system using continuous, online epidural electrocorticographic signals to decode brain activity in a tetraplegic patient. Bockbrader et al. [38] reported that using an implanted BCI with forearm transcutaneous muscle stimulation allowed skillful grasp coordination of daily use in a tetraplegic individual .

Seier et al. [39] found that alternating stimulation patterns maintained better tremor control compared to constant stimulation in patients with tremors, throught the deep brain stimulation (DBS) of the ventral intermediate nucleus. Selfslagh et al. [40] reported that a surface functional electrical stimulation-generated step movement of the lower-limbs was triggered by cue-based decoding of cortical motor commands using a brain–machine interface, allowing patients with chronic paraplegia to walk safely and showing some partial neurological recovery. Fan et al. [41] reported that both the subthalamic nucleus and the globus pallidus internus had beneficial effects on reducing levodopa-induced dyskinesia; and globus pallidus internus–DBS provided greater anti-dyskinetic effects.

Krauth et al. [42] found that electroencephalographic (EEG)-electromyography (EMG) coherence could serve as a biomarker for motor

recovery and provide information about the cortical regions in patients with an ischemic stroke.

Yang et al. [43] reported that transcranial direct current stimulation for 14 consecutive days could significantly decrease seizure frequency in patients with refractory focal epilepsy. Elder et al. [44] showed that patients with treatment-resistant multifocal epilepsy had ≥ 50% reduction in debilitating seizures compared to the pretreatment baseline after they were implanted with a DBS system in the unilateral anterior nucleus of the thalamus.

4.3 Neurorestorative surgery

Several key articles on reparative surgeries have been published this year. Yu et al. [45] reported that contralateral hemi-5th-lumbar nerve transfer in two incomplete SCI patients with unilateral lower limb dysfunction was safe, and allowed patients to recover independent walking ability with crutches. van Zyl et al. [46] reported that nerve transfers could lead to significant functional improvement in patients with chronic cervical SCIs. Khalifeh et al. [47] found that transfers for the reinnervation of arm, hand, and finger extensors showed a more consistent and meaningful return in strength and function in patients with cervical SCI and tetraplegia. Even in late phase (> 4 years) high cervical SCI, patients still achieved beneficial outcomes from nerve transfers for motor and sensory restoration [48]. Ding et al. [49] reported that long-term follow-up studies of nerve segment insert grafting showed significant hand function recovery in quadriplegic patients with chronic incomplete lower cervical SCI.

Qiu et al. [50] reported that the contralateral lumbar to sacral nerve transfer in two stroke patients with hemiplegia resulted in significant improvements in ambulatory status. Guan et al. [51] reported that carrying out contralateral C7 nerve transfer via the posterior spinal route for hemiplegia improved shrug movement 1.5 months post-surgery.

Nerve transfers have been important optional therapeutic methods for peripheral injuries, such as cranial or brachial plexus nerve injuries. Wu et al. [52] reported that superficial radial nerve transfer to the dorsal cutaneous branch and the superficial branch of the ulnar nerve restored sensation in a patient with C7, C8, and T1 roots injury. Kannan et al. [53] reported that immediate repair showed no significantly different outcomes than late repair in extracranial branches of the facial nerve, however, their immediate repair showed the greatest likelihood of full recovery. Zang et al. [54] found that orthopedic operations combined with external fixators for deformities could help achieve complete correction of said deformity, the healing of ulcers, and in the restoration of functional activity in patients with spinal bifida sequelae.

4.4 Pharmaceutical neurorestorative therapy

Drug repair therapy is still a field being extensively explored by researchers. Historically, many drugs were known to be effective to facilitate nerve repair *in vitro* or in animal studies. However, the exploration of drug effectiveness in humans remains in its early stages. Excitingly, some neurorestorative drugs have been developed in the last year. Jost et al. [55], for example, found that injecting botulinum toxin to the right muscles could improve the symptoms and optimize treatment outcomes for different subtypes of cervical dystonia. Shieh et al. [56] reported that amifampridine phosphate showed significant benefits in quantitative myasthenia gravis score and subject global impression compared with placebo for patients with Lambert–Eaton myasthenic syndrome. Ma et al. [57] reported that using alteplase between 4.5 and 9 hours after a

stroke onset among patients with ischemic strokes and salvageable brain tissue resulted in a higher percentage of patients with no or minor neurologic deficits compared to placebo. However, a secondary ordinal analysis of the score distribution on the modified Rankin scale did not show a significant difference in functional improvement after 90 days between-groups. Howard et al. [58] reported that efgartigimod (IgG1 Fc-fragment, a natural ligand of the neonatal Fc receptor) was safe, well tolerated, and showed reduced levels of pathogenic IgG autoantibodies in patients with generalized myasthenia gravis. Shevela et al. [59] showed that the intranasal delivery of M2 macrophages soluble products was safe, and that it reduced neuropsychological deficits in patients with chronic cerebrovascular disease.

4.5 Bioengineering and tissue engineering therapy

Bioengineering and tissue engineering are at the frontier of neural repair. Christine et al. [60] reported that magnetic resonance imaging (MRI)-guided putaminal L-amino acid decarboxylase (AADC) gene therapy was well tolerated, increased enzyme expression and showed clinical improvements in patients with Parkinson's disease (PD). Heiss et al. [61] reported that MRI-guided putaminal gene therapy in patients with advanced PD was safe, well tolerated and increased the neurotrophic effect on dopaminergic neurons. Tabrizi et al. [62] observed that the intrathecal administration of an antisense oligonucleotide designed to inhibit HTT messenger RNA (HTTRx) in patients with early Huntington's disease was not accompanied by serious adverse events and showed dose-dependent reductions in concentrations of the mutant huntingtin protein. Kim et al. [63] reported that patient-customized oligonucleotide therapy (a splice-modulating antisense oligonucleotide drug tailored to specific patients) for a patient with rare genetic disease reduced his seizures without serious adverse events.

4.6 Other relevant findings

Behrman et al. [64] reported that activity-based therapies could significantly improve trunk and neuromuscular capacity in children with SCI. Xi et al. [65] also reported that respiratory muscle endurance training with normocapnic hyperpnoea could reduce the incidence of respiratory symptoms, improve pulmonary function and quality of life, and reduce depression in patients with chronic SCI. Even in healthy people, both unassisted and robot-assisted walking increased gait variability and somatosensory brain activity [66].

Wei et al. [67] found that acupuncture, combined with neuromuscular joint facilitation, could improve upper limb motor function, relieve pain, and increase joint mobility in patients with hemiplegic shoulder pain. Wang et al. [68] further reported that special acupuncture needling can effectively reduce post-stroke shoulder pain and significantly improve motor function of the upper limbs and shoulder-joint, as well as the quality of daily life of patients with shoulder pain after a stroke. Duan et al. [69] reported that internal heat-type acupuncture needle therapy showed therapeutic effects in relieving shoulder pain and improving upper limb motion function in post-stroke patients experiencing shoulder pain. When combined with the acupoint injection of O_3, this therapy has even more beneficial effects [70]. Pradines et al. [71] reported that guided self-rehabilitation, combined with conventional rehabilitation, increased muscle fascicle length, extensibility, and ambulation speed more than conventional rehabilitation alone in patients with chronic hemiparesis. Atan et al. [72] reported that body weight-supported treadmill training

improved walking distance and balance ability, relieved fatigue, and also reduced pain in patients with moderate to advanced PD. Edwards et al. [73] reported that intensive robot-assisted arm training could help in the clinical improvement of patients with chronic stroke.

Liao et al. [74] found that remote ischemic conditioning was effective and safe to improve cognitive function in patients with subcortical ischemic vascular dementia. Tang et al. [75] showed that computerized cognitive training significantly improved global cognitive function in patients with subcortical vascular cognitive impairment. Zhao et al. [76] reported that a combination of visual feedback balance training and conventional rehabilitation treatment could further improve gait stability in patients with cerebral small vessel disease. Najar et al. [77] also found that midlife cognitive and physical activities may play a role in preserving cognitive health at an old age or reduce the risk of dementia and dementia subtypes. Rabin et al. [78] found that engaging in physical activity and lowering vascular risk might also delay the progression of AD.

Marusiak et al. [79] reported that an eight-week moderate-intensity aerobic interval training program improved psychomotor behaviors, bimanual motor control, executive function, and neurological Parkinsonian symptoms in patients with PD. van der Kolk et al. [80] found that aerobic exercise at home for patients with mild PD severity could even attenuate off-state motor signs.

Gao et al. [81] reported that intensive moxibustion followed by acupuncture can further improve symptoms for patients with a frozen shoulder, compared to simply acupuncture. Syed and Kamal [82] found that video game-based therapy could increase self-motivated balance during functional tasks further than conventional therapies in patients with neurological deficits.

4.7 Guidelines

Puyade et al. [83] established guidelines that specified the eligibility criteria for transplantation of autologous hematopoietic stem cells in patients with chronic inflammatory demyelinating polyneuropathy, to describe the mobilization and the conditioning regimen for the autologous hematopoietic cell transplantation (AHCT) procedure and standardized clinical care follow-up.

5 Summary

Success is the accumulation of daily efforts. In 2019, physicians and scientists in neurorestoratology and its related disciplines have been exploring the pathogeneses, restorative mechanisms and evidence-based outcomes of medical practice using different restorative approaches, achieving promising results. Furthermore, these developed treatment have helped patients with neurological diseases by improving their quality of life.

Conflict of interests

The authors declare that they have no competing interests.

References

[1] Zada D, Bronshtein I, Lerer-Goldshtein T, et al. Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. *Nat Commun*. 2019, **10**(1): 895.

[2] Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat Med*. 2019, **25**(4): 554–560.

[3] Tobin MK, Musaraca K, Disouky A, et al. Human hippocampal neurogenesis persists in aged adults and Alzheimer's disease patients. *Cell Stem Cell*. 2019, **24**(6): 974–982.e3.

[4] Mathys H, Davila-Velderrain J, Peng ZY, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*. 2019, **570**(7761): 332–337.

[5] Ising C, Venegas C, Zhang SS, et al. NLRP3 inflammasome activation drives tau pathology. *Nature*. 2019, **575**(7784): 669–673.

[6] Dominy SS, Lynch C, Ermini F, et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv*. 2019, **5**(1):eaau3333.

[7] Lourenco MV, Frozza RL, de Freitas GB, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med*. 2019, **25**(1): 165–175.

[8] Vrselja Z, Daniele SG, Silbereis J, et al. Restoration of brain circulation and cellular functions hours post-mortem. *Nature*. 2019, **568**(7752): 336–343.

[9] Anumanchipalli GK, Chartier J, Chang EF. Speech synthesis from neural decoding of spoken sentences. *Nature*. 2019, **568**(7753): 493–498.

[10] Moda-Sava RN, Murdock MH, Parekh PK, et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*. 2019, **364**(6436): eaat8078.

[11] Heckmann BL, Teubner BJW, Tummers B, et al. LC3-associated endocytosis facilitates β-amyloid clearance and mitigates neurodegeneration in murine Alzheimer's disease. *Cell*. 2019, **178**(3): 536–551.e14.

[12] Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science*. 2019, **366**(6465): 628–631.

[13] von Wild T, Brunelli GA, von Wild KRH, et al. Regeneration of denervated skeletal muscles – brunelli's CNS-PNS paradigm. *J Med Life*. 2019, **12**(4): 342–353.

[14] Levy ML, Crawford JR, Dib N, et al. Phase I/II study of safety and preliminary efficacy of intravenous allogeneic mesenchymal stem cells in chronic stroke. *Stroke*. 2019, **50**(10): 2835–2841.

[15] Zhang GZ, Li Y, Reuss JL, et al. Stable intracerebral transplantation of neural stem cells for the treatment of paralysis due to ischemic stroke. *Stem Cells Transl Med*. 2019, **8**(10): 999–1007.

[16] Guo XL, Wang X, Li Y, et al. Olfactory ensheathing cell transplantation improving cerebral infarction sequela: a case report and literature review. *J Neurorestoratology*. 2019, **7**(2): 82–88.

[17] Savitz SI, Yavagal D, Rappard G, et al. A phase 2 randomized, sham-controlled trial of internal carotid artery infusion of autologous bone marrow-derived ALD-401 cells in patients with recent stable ischemic stroke (RECOVER-stroke). *Circulation*. 2019, **139**(2): 192–205.

[18] Brunet MC, Chen SH, Khandelwal P, et al. Intravenous stem cell therapy for high-grade aneurysmal subarachnoid hemorrhage: case report and literature review. *World Neurosurg*. 2019, **128**: 573–575.

[19] Hammadi AMA, Alhimyari F. Intra-arterial injection of autologous bone marrow-derived mononuclear cells in ischemic stroke patients. *Exp Clin Transplant*. 2019, **17**(Suppl 1): 239–241.

[20] Vahidy FS, Haque ME, Rahbar MH, et al. Intravenous bone marrow mononuclear cells for acute ischemic stroke: safety, feasibility, and effect size from a phase I clinical trial. *Stem Cells*. 2019, **37**(11): 1481–1491.

[21] Vaquero J, Zurita M, Mucientes J, et al. Intrathecal cell therapy with autologous stromal cells increases cerebral glucose metabolism and can offer a new approach to the treatment of Alzheimer's type dementia. *Cytotherapy*. 2019, **21**(4): 428–432.

[22] Levi AD, Anderson KD, Okonkwo DO, et al. Clinical outcomes from a multi-center study of human neural stem cell transplantation in chronic cervical spinal cord injury. *J Neurotrauma*. 2019, **36**(6): 891–902.

[23] Bydon M, Dietz AB, Goncalves S, et al. CELLTOP clinical trial: first report from a phase 1 trial of autologous adipose tissue-derived mesenchymal stem cells in the treatment of paralysis due to traumatic spinal cord injury. *Mayo Clin Proc*. 2020, **95**(2): 406–414.

[24] Phedy P, Djaja YP, Gatam L, et al. Motoric recovery after transplantation of bone marrow derived mesenchymal stem cells in chronic spinal cord injury: a case report. *Am J Case Rep*. 2019, **20**: 1299–1304.

[25] Moore JJ, Massey JC, Ford CD, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2019, **90**(5): 514–521.

[26] Mariottini A, Innocenti C, Forci B, et al. Safety and efficacy of autologous hematopoietic stem-cell transplantation following natalizumab discontinuation

in aggressive multiple sclerosis. *Eur J Neurol*. 2019, **26**(4): 624–630.

[27] Boruczkowski D, Zdolińska-Malinowska I. Wharton's jelly mesenchymal stem cell administration improves quality of life and self-sufficiency in children with cerebral palsy: results from a retrospective study. *Stem Cells Int*. 2019, **2019**: 1–13.

[28] Boruczkowski D, Zdolińska-Malinowska I. A retrospective analysis of safety and efficacy of Wharton's jelly stem cell administration in children with spina bifida. *Stem Cell Rev And Rep*. 2019, **15**(5): 717–729.

[29] Pan K, Deng LN, Chen PY, et al. Safety and feasibility of repeated intrathecal allogeneic bone marrow-derived mesenchymal stromal cells in patients with neurological diseases. *Stem Cells Int*. 2019, **2019**: 8421281.

[30] Goudie C, Alayoubi AM, Tibout P, et al. Hematopoietic stem cell transplant does not prevent neurological deterioration in infants with Farber disease: Case report and literature review. *JIMD Rep*. 2019, **46**(1): 46–51.

[31] Chen Y, Zhang XH, Xu LP, et al. Haploidentical allogenetic hematopoietic stem cell transplantation for X-linked adrenoleukodystrophy (in Chinese). *Beijing Da Xue Xue Bao Yi Xue Ban*. 2019, **51**(3):409–413.

[32] Riordan NH, Hincapié ML, Morales I, et al. Allogeneic human umbilical cord mesenchymal stem cells for the treatment of autism spectrum disorder in children: safety profile and effect on cytokine levels. *Stem Cells Transl Med*. 2019, **8**(10): 1008–1016.

[33] Blok B, van Kerrebroeck P, de Wachter S, et al. A prospective, multicenter study of a novel, miniaturized rechargeable sacral neuromodulation system: 12-month results from the RELAX-OAB study. *Neurourol Urodyn*. 2019, **38**(2): 689–695.

[34] McCrery R, Lane F, Benson K, et al. Treatment of urinary urgency incontinence using a rechargeable SNM system: 6-month results of the ARTISAN-SNM study. *J Urol*. 2020, **203**(1): 185–192.

[35] Yeh SD, Lin BS, Chen SC, et al. Effects of genital nerve stimulation amplitude on bladder capacity in spinal cord injured subjects. *Evid Based Complement Alternat Med*. 2019, **2019**: 1248342.

[36] Bourbeau DJ, Gustafson KJ, Brose SW. At-home genital nerve stimulation for individuals with SCI and neurogenic detrusor overactivity: a pilot feasibility study. *J Spinal Cord Med*. 2019, **42**(3): 360–370.

[37] Benabid AL, Costecalde T, Eliseyev A, et al. An exoskeleton controlled by an epidural wireless brain-machine interface in a tetraplegic patient: a proof-of-concept demonstration. *Lancet Neurol*. 2019, **18**(12): 1112–1122.

[38] Bockbrader M, Annetta N, Friedenberg D, et al. Clinically significant gains in skillful grasp coordination by an individual with tetraplegia using an implanted brain-computer interface with forearm transcutaneous muscle stimulation. *Arch Phys Med Rehabil*. 2019, **100**(7): 1201–1217.

[39] Seier M, Hiller A, Quinn J, et al. Alternating thalamic deep brain stimulation for essential tremor: a trial to reduce habituation. *Mov Disord Clin Pract*. 2018, **5**(6): 620–626.

[40] Selfslagh A, Shokur S, Campos DSF, et al. Non-invasive, brain-controlled functional electrical stimulation for locomotion rehabilitation in individuals with paraplegia. *Sci Rep*. 2019, **9**(1): 6782.

[41] Fan SY, Wang KL, Hu W, et al. Pallidal versus subthalamic nucleus deep brain stimulation for levodopa-induced dyskinesia. *Ann Clin Transl Neurol*. 2020, **7**(1): 59–68.

[42] Krauth R, Schwertner J, Vogt S, et al. Cortico-muscular coherence is reduced acutely post-stroke and increases bilaterally during motor recovery: a pilot study. *Front Neurol*. 2019, **10**: 126.

[43] Yang DJ, Wang Q, Xu CP, et al. Transcranial direct current stimulation reduces seizure frequency in patients with refractory focal epilepsy: a randomized, double-blind, sham-controlled, and three-arm parallel multicenter study. *Brain Stimul*. 2020, **13**(1): 109–116.

[44] Elder C, Friedman D, Devinsky O, et al. Responsive neurostimulation targeting the anterior nucleus of the thalamus in 3 patients with treatment-resistant multifocal epilepsy. *Epilepsia Open*. 2019, **4**(1): 187–192.

[45] Yu BF, Qiu YQ, Du MX, et al. Contralateral hemi-fifth-lumbar nerve transfer for unilateral lower limb dysfunction due to incomplete traumatic spinal cord injury: a report of two cases. *Microsurgery*. 2020, **40**(2): 234–240.

[46] van Zyl N, Hill B, Cooper C, et al. Expanding traditional tendon-based techniques with nerve transfers for the restoration of upper limb function in tetraplegia: a prospective case series. *Lancet*. 2019, **394**(10198): 565–575.

[47] Khalifeh JM, Dibble CF, van Voorhis A, et al. Nerve transfers in the upper extremity following cervical spinal cord injury. Part 2: Preliminary results of a prospective clinical trial. *J Neurosurg Spine*. 2019: 1–13.

[48] Dibble CF, Khalifeh JM, VanVoorhis A, et al. Novel nerve transfers for motor and sensory restoration in high cervical spinal cord injury. *World Neurosurg*. 2019, **128**: 611–615.e1.

[49] Ding WB, Zhang S, Wu D, et al. Hand function recovery using nerve segment insert grafting in patients with chronic incomplete lower cervical spinal cord injury: a preliminary clinical report. *J Neurorestoratology*. 2019, **7**(3): 129–135.

[50] Qiu YQ, Du MX, Yu BF, et al. Contralateral lumbar to sacral nerve rerouting for hemiplegic patients after stroke: a clinical pilot study. *World Neurosurg*. 2019, **121**: 12–18.

[51] Guan JY, Lin J, Guan XQ, et al. Treatment of central paralysis of upper extremity using contralateral C7 nerve transfer via posterior spinal route. *World Neurosurg*. 2019, **125**: 228–233.

[52] Wu FR, Ng CY. Sensory nerve transfer for lower roots brachial plexus injury: superficial radial nerve to the dorsal cutaneous branch and the superficial branch of the ulnar nerve. *J Hand Microsurg*. 2019, **11**(3): 178–180.

[53] Kannan RY, Hills A, Shelley MJ, et al. Immediate compared with late repair of extracranial branches of the facial nerve: a comparative study. *Br J Oral Maxillofac Surg*. 2020, **58**(2): 163–169.

[54] Zang JC, Qin SH, Vigneshwaran P, et al. The treatment of neurotrophic foot and ankle deformity of spinal bifida: 248 cases in single center. *J Neurorestoratology*. 2019, **7**(3): 153–160.

[55] Jost WH, Tatu L, Pandey S, et al. Frequency of different subtypes of cervical dystonia: a prospective multicenter study according to Col-Cap concept. *J Neural Transm*. 2020, **127**(1): 45–50.

[56] Shieh P, Sharma K, Kohrman B, et al. Amifampridine phosphate (Firdapse) is effective in a confirmatory phase 3 clinical trial in LEMS. *J Clin Neuromuscul Dis*. 2019, **20**(3): 111–119.

[57] Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019, **380**(19): 1795–1803.

[58] Howard JF Jr, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology*. 2019, **92**(23): e2661–e2673.

[59] Shevela E, Davydova M, Starostina N, et al. Intranasal delivery of M2 macrophage-derived soluble products reduces neuropsychological deficit in patients with cerebrovascular disease: A pilot study. *J Neurorestoratology*. 2019, **7**(2): 89–100.

[60] Christine CW, Bankiewicz KS, van Laar AD, et al. Magnetic resonance imaging-guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease. *Ann Neurol*. 2019, **85**(5): 704–714.

[61] Heiss JD, Lungu C, Hammoud DA, et al. Trial of magnetic resonance-guided putaminal gene therapy for advanced Parkinson's disease. *Mov Disord*. 2019, **34**(7): 1073–1078.

[62] Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting huntingtin expression in patients with Huntington's disease. *N Engl J Med*. 2019, **380**(24): 2307–2316.

[63] Kim J, Hu CG, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N Engl J Med*. 2019, **381**(17): 1644–1652.

[64] Behrman AL, Argetsinger LC, Roberts MT, et al. Activity-based therapy targeting neuromuscular capacity after pediatric-onset spinal cord injury. *Top Spinal Cord Inj Rehabil*. 2019, **25**(2): 132–149.

[66] Xi JN, Jiang HY, Zhang N, et al. Respiratory muscle endurance training with normocapnic hyperpnoea for patients with chronic spinal cord injury: a pilot short-term randomized controlled trial. *J Rehabil Med*. 2019, **51**(8): 616–620.

[66] Berger A, Horst F, Steinberg F, et al. Increased gait variability during robot-assisted walking is accompanied by increased sensorimotor brain activity in healthy people. *J Neuroeng Rehabil*. 2019, **16**(1): 161.

[67] Wei YH, Du DC, Jiang K. Therapeutic efficacy of acupuncture combined with neuromuscular joint facilitation in treatment of hemiplegic shoulder pain. *World J Clin Cases*. 2019, **7**(23): 3964–3970.

[68] Wang M, Zhang ZL, Wang X, et al. Clinical trials of acupuncture treatment of post-stroke shoulder pain (in Chinese). *Zhen Ci Yan Jiu*. 2019, **44**(8): 605–609.

[69] Duan YX, Zhang ZQ, Luo XJ, et al. Randomized controlled trial of internal heat-type acupuncture needle therapy in the treatment of post-stroke shoulder pain (in Chinese). *Zhen Ci Yan Jiu*. 2019, **44**(3): 205–210.

[70] Duan YX, Zhang ZQ, Luo XJ, et al. Short-term and long-term therapeutic effects of internal heat-type acupuncture needle therapy combined with acupoint injection of O_3 for post-stroke shoulder pain (in Chinese). *Zhen Ci Yan Jiu*. 2019, **44**(1): 51–56.

[71] Pradines M, Ghedira M, Portero R, et al. Ultrasound structural changes in triceps surae after a 1-year daily self-stretch program: a prospective randomized controlled trial in chronic hemiparesis. *Neurorehabil Neural Repair*. 2019, **33**(4): 245–259.

[72] Atan tuğba, Özyemİşcİ Taşkiran Ö, Bora Tokçaer A, et al. Effects of different percentages of body weight-supported treadmill training in Parkinson's disease: a double-blind randomized controlled trial. *Turk J Med Sci*. 2019, **49**(4): 999–1007.

[73] Edwards DJ, Cortes M, Rykman-Peltz A, et al. Clinical improvement with intensive robot-assisted arm training in chronic stroke is unchanged by supplementary tDCS. *Restor Neurol Neurosci*. 2019, **37**(2): 167–180.

[74] Liao ZY, Bu YL, Li MJ, et al. Remote ischemic conditioning improves cognition in patients with subcortical ischemic vascular dementia. *BMC Neurol*. 2019, **19**(1): 206.

[75] Tang Y, Xing Y, Zhu ZD, et al. The effects of 7-week cognitive training in patients with vascular cognitive impairment, no dementia (the Cog-VACCINE study): a randomized controlled trial. *Alzheimers Dement*. 2019, **15**(5): 605–614.

[76] Zhao WJ, You H, Jiang SR, et al. Effect of Pro-kin visual feedback balance training system on gait stability in patients with cerebral small vessel disease. *Medicine (Baltimore)*. 2019, **98**(7): e14503.

[77] Najar J, Östling S, Gudmundsson P, et al. Cognitive and physical activity and dementia: a 44-year longitudinal population study of women. *Neurology*. 2019, **92**(12): e1322–e1330.

[78] Rabin JS, Klein H, Kirn DR, et al. Associations of physical activity and β-amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. *JAMA Neurol*. 2019, in press, DOI10.1001/jamaneurol.2019.1879.

[79] Marusiak J, Fisher BE, Jaskólska A, et al. Eight weeks of aerobic interval training improves psychomotor function in patients with Parkinson's disease-randomized controlled trial. *Int J Environ Res Public Health*. 2019, **16**(5): E880.

[80] van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol*. 2019, **18**(11): 998–1008.

[81] Gao L, Li X, Wang DB, et al. Clinical trial of treatment of frozen shoulder by intensive moxibustion plus acupuncture (in Chinese). *Zhen Ci Yan Jiu*. 2019, **44**(4): 297–301.

[82] Syed UE, Kamal A. Video game-based and conventional therapies in patients of neurological deficits: an experimental study. *Disabil Rehabil Assist Technol*. 2019: 1–8.

[83] Puyade M, Labeyrie C, Badoglio M, et al. Indication of autologous stem cell transplantation in chronic inflammatory demyelinating polyneuropathy: Guidelines from the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) (in French). *Bull Cancer*. 2020, **107**(1S): S104–S113.