The 2019 yearbook of Neurorestoratology

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The 2019 yearbook of Neurorestoratology

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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.

Vaqueiro 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 treatments 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, through 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 \( \geq 50\% \) 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 macrophage 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 O3, 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.

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