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REVIEW ARTICLE

The 2020 Yearbook of Neurorestoratology

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ABSTRACT

COVID-19 has been an emerging and rapidly evolving risk to people of the world in 2020. Facing this dangerous situation, many colleagues in Neurorestoratology did their best to avoid infection if themselves and their patients, and continued their work in the research areas described in the *2020 Yearbook of Neurorestoratology*. Neurorestorative achievements and progress during 2020 includes recent findings on the pathogenesis of neurological diseases, neurorestorative mechanisms and clinical therapeutic achievements. Therapeutic progress during this year included advances in cell therapies, neurostimulation/neuromodulation, brain–computer interface (BCI), and pharmaceutical neurorestorative therapies, which improved neurological functions and quality of life for patients. Four clinical guidelines or standards of Neurorestoratology were published in 2020. Milestone examples include: 1) a multicenter randomized, double-blind, placebo-controlled study of olfactory ensheathing cell treatment of chronic stroke showed functional improvements; 2) patients after transhumeral amputation experienced increased sensory acuity and had improved effectiveness in work and other activities of daily life using a prosthesis; 3) a patient with amyotrophic lateral sclerosis used a steady-state visual evoked potential (SSVEP)-based BCI to achieve accurate and speedy computer input; 4) a patient with complete chronic spinal cord injury recovered both motor function and touch sensation with a BCI and restored ability to detect objects by touch and several sensorimotor functions. We hope these achievements motivate and encourage other scientists and physicians to increase neurorestorative research and its therapeutic applications.

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1 Introduction

We have serially compiled Yearbooks of Neurorestoratology since 2016. The aim of the Yearbook is to describe major progress and significant achievements in this field, with a focus on pathogenesis, neurorestorative mechanisms, and clinical therapies of neurological disease. The Yearbooks are intended to inform scientists, physicians and students the major progress in Neurorestoratology to attract interest in people to the field of Neurorestoratology.

In 2020, COVID-19, a worldwide pandemic, emerged, and induced rapidly evolving risks to people of the world. Facing this dangerous situation, colleagues in Neurorestoratology and its related disciplines continued their groundbreaking research in this field within the severe constraints of COVID-19. This 2020 Yearbook describes the global achievements and progress of Neurorestoratology for 2020.

2 New findings on disease pathogenesis or nervous system degeneration

Friker et al. [1] showed that exposure to apoptosis-associated speck-like protein containing a CARD (ASC)–β-amyloid (Aβ) composites amplified proinflammatory responses to cause pyroptotic cell death, release functional ASC, and induce a vicious cycle of feed forward reactions that contribute to pathogenesis of Alzheimer's disease (AD). Chun et al. [2] identified that excessive hydrogen peroxide (H_2O_2) secreted by from severe but not mildly reactive astrocytosis was a key determinant of neurodegeneration in AD. The above two studies imply that Aβ deposition is the result of the AD neurodegenerative process, but not its cause, and AD pathogenesis may in part be due to inflammatory reaction to harmful toxic substances.

Winer et al. [3] reported that impaired sleep may predict the speed with which Aβ is accumulating over time; even before cognitive symptoms of AD appear. Sleep disturbance may be an usful tool for forecasting β-amyloid accumulation and Aβ pathological progression.

3 New mechanisms for neurorestorative therapy

Depleting the RNA-binding protein polypyrimidine tract-binding protein 1 (PTB or PTBP1) could convert astrocytes to functional neurons, which innervate and repopulate endo-genous neural circuits. Astrocytes from different brain regions may differentiate to various neuronal subtypes. In a mouse model of Parkinson's disease (PD), Qian et al. [4] showed that dopamine (DA) neurons converted from midbrain astrocytes could provide nigral axons and reinnervate striatum, restoring dopamine levels and reducing motor deficits. Zhou et al. [5] reported that downregulating a single RNA-binding protein could convert Müller glia into retinal ganglion cells (RGCs), and alleviate symptoms associated with RGC loss. Furthermore, this approach also induced neurons with dopaminergic features in the striatum and alleviated motor defects in a PD mouse model. Giacomoni et al. [6] successfully converted human stem cell-derived glial progenitor cells (hGPCs) into functional neurons that made functional synaptic connections within a month. These converted cells had properties of GABAergic neurons, expressed subtype-specific interneuron markers (e.g., parvalbumin), and exhibited a complex neuronal morphology with extensive dendritic trees [6]. Finally, Nolbrant et al. [7] reported successful reprogramming of

human fetal and stem cell derived glial progenitor cells into dopaminergic neurons with dopaminergic phenotype.

Serapide et al. [8] reported that transplantation of tissues containing astrocytes into aged PD mice could restore the microenvironment via upregulation of astrocyte antioxidant self-defense and activate NF-E2-related factor 2 (Nrf2)/Wnt/β-catenin (WβC) signaling. This harnesses WβC signaling in the aged PD brain to restore neurogenesis, rejuvenate the micro-environment, and promote neurorescue and regeneration [9].

Chemokine receptor CCR5 is a negative modulator of learning and memory. Liraz-Zaltsman et al. [10] found that reducing CCR5 signaling also reduced lesion area in brain injured mice by protecting neurons. This may be a promising neurorestorative approach to improve functional recovery in stroke and traumatic brain injury (TBI).

Interferon-induced transmembrane protein 3 (IFITM3) was identified as a γ-secretase modulatory protein. Hur et al. [11] showed that inflammatory cytokines induces expression of IFITM3 in neurons and astrocytes in mouse brain injury models. IFITM3 binds and up-regulates γ-secretase activity, which increases the production of amyloid-β and risk of AD. Knockout of IFITM3 reduces γ-secretase activity and amyloid plaque formation in a transgenic mouse model of early amyloid deposition. This finding raises the question, whether silencing of IFITM3 reduces behavioral impairments or deficits in patients or animal models of AD.

Krukowski et al. [12] found that small-molecule integrated stress response inhibitor (ISRIB) reversed ISR activation in the brain by reducing activating transcription factor 4 (ATF4) and phosphorylated eukaryotic translation initiation factor eIF2. Through this mechanism, ISRIB treatment reverses spatial memory deficits and improves working memory in old mice [12]. Lu et al. [13] showed that genetic reprogramming of mouse retinal ganglionic cells may restore youthful epigenetic information in mouse RGCs and reverse vision loss in a mouse model of glaucoma and aged mice. If confirmed in clinical trial, this could be one of the most promising approaches to treat glaucoma.

Zhou et al. [14] found that Plexin-B2 is up-regulated in injury-activated microglia and macrophages (IAMs) after spinal cord injury (SCI), which engages axon guidance pathways by promoting microglia motility, steering IAMs away from colliding cells and facilitating matrix compaction. Human mesenchymal stromal cells derived adipose tissue exosomes promotes functional recovery through suppressing neuroinflammation, reducing neuronal apoptosis, and increasing neurogenesis in TBI rat model [15].

4 Achievements and progress in clinical diagnosis and neurorestorative therapies

4.1 Cell therapy

Cell transplantation continued to be a hot topic in Neurorestoratology in 2020. One multicenter, randomized, double-blind and placebo-controlled olfactory ensheathing cell (OEC) and Schwann cell (SC) therapy trial for patients with chronic ischemic stroke showed significant differences in functional recovery among the OEC treated, SC treated, and placebo groups [16]. This is the first positive result in multicenter, double-blind, randomized, and placebo-controlled cell therapy trial of stroke. A total of 30 patients were randomized into three groups: OECs, SCs, or medium (control) injected into olfactory sub-mucosa. Patients were assessed with the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index before and 1 month, 3

months, 6 months, and 1 year after treatment. The trial showed that OECs were safe and had improved quality of life.

Muir et al. [17] reported transplanted allogeneic human neural stem cell line CTX0E03 into brain of 23 patients with subacute chronic stroke, improving upper limb functions in 4 patients with residual upper limb movement, but not in those with absent upper limb movement at baseline [17].

Steinberg et al. [18, 19] showed neurological improvement after SB623 (modified bone marrow-derived mesenchymal stem cells) transplantation for chronic stroke in a phase 2a trial but the trial [20] did not demonstrate a statistically significant improvement compared to the sham (control) surgery group in a phase 2b study (involved 163 patients).

Schweitzer et al. [21] implanted dopaminergic progenitor cells, differentiated *in vitro* from autologous induced pluripotent stem cells (iPSCs), in a patient with idiopathic PD. The patient's progressive PD symptoms stabilized and improved at 18 to 24 months after implantation. Positron emission tomography with fluorine-18-L-dihydroxyphenylalanine showed graft survival.

Several investigators transplanted autologous bone-marrow derived mononuclear cells (BMMNC). Liem et al. [22] infused autologous BMMNC intrathecally into five children who had drowned and were in persistent vegetative states. Children had improved motor function and cognition as well as reduced muscle spasticity 6 months after treatment. Autologous BMMNC intrathecal transplantation also improved motor function and reduced muscle spasticity in 4 children who had intracranial hemorrhage during the neonatal period [23]. Yang et al. [24] repeatedly injected human umbilical cord mesenchymal stromal cells into the subarachnoid space for chronic SCI once a month for 4 months. Follow-up results showed that the treatment was safe and effective, and led to significant reductions in neurological dysfunction and improved quality of life.

A randomized, double-blind, placebo-controlled trial (involved 48 patients) of mesenchymal stem cell (MSC)-neurotrophic factor cells showed that the rate of disease progression, which is demonstrated by Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) slope change, in the overall study population was similar in treated and placebo participants, and even a higher proportion of treated participants was significant in rapid progressions at 4 and 12 weeks [25]. (This paper was published in the end of December 2019, and was missed in the 2019 Yearbook of Neurorestoratology)

4.2 Neurostimulation/neuromodulation and the brain–computer interface

Brain–computer interface (BCI) research advanced significantly in 2020. Beauchamp et al. [25] showed that stimulating electrodes can traces shapes on the visual cortex surfaces in both sighted and blind participants to allow accurate recognition of western letter and Chinese characters. This means that a brain prosthetic can produce coherent perceptions of visual forms [26].

Shi et al. [27] applied steady-state visual evoked potential (SSVEP) based BCI for a patient with amyotrophic lateral sclerosis (ALS). They developed a personalized BCI design for this patient to achieve computer input with high accuracy and reasonable speed, which was practical and efficient enough to provide a means to communicate for patients with ALS [27].

Ortiz-Catalan et al. [28] reported the use of a bone-anchored, self-contained robotic arm with both sensory and motor components over 3 to 7 years in 4 patients after transhumeral

amputation. Daily use of this prosthesis resulted in increasing sensory acuity and effectiveness in work and other activities of daily life. No serious adverse events, infections, bleeding, or discontinuation of use of the prosthesis due to adverse events occurred as a result of the implants [28]. This neuromusculoskeletal prosthesis allowed extraction of control signals from electrodes implanted on viable muscle tissue and stimulation of severed afferent nerve fibers to provide somatosensory feedback [29]. Patients using the prostheses adapted and integrated the technology into functional and social arenas of daily living, with positive psychosocial effects on self-esteem, self-image, and social relations [30]. The relationship between users and sensate neural–machine interface prostheses is dynamic and changes with long-term use. The presence of touch sensation had a near-immediate impact on how the users operated their prostheses. Participants more appropriately integrated their prostheses into their body images after the take-home period [31].

Ganzer et al. [32] reported that a patient with a clinically complete SCI used a BCI to control motor function and to sense touch. Using the closed-loop demultiplexing BCI, he regained ability to detect touch and significantly improved several sensorimotor functions [32]. A patient with SCI at-level pain was treated by peripheral subcutaneous field stimulation (PSFS) during 5-year follow-up, which may be the longest published follow-up of PSFS therapy [33]. In a patient with severe refractory neuropathic pain and sensory impairment, high-frequency spinal cord stimulation (SCS), considerably reduced his pain [34].

In two participants with chronic complete loss of motor and sensory functions below thoracic-level SCI, epidural spinal electrical stimulation enhanced seated reaching-performance [35]. Peña Pino et al. [35] reported that sustained spontaneous volitional movement without active stimulation even in participants with chronic and complete SCI after long-term epidural SCS [36]. This means "complete" SCI is not as commonly believed and that preserved pathways may contribute to epidural SCS or other neurorestorative therapies mediated recovery in clinically motor-complete SCI.

Several studies indicate that transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that can be used effectively to treat neurological or neuropsychiatric disorders, including poststroke aphasia [37–40], primary progressive aphasia [41], postanoxic leukoencephalopathy [42], disorders of consciousness [43, 44], high autistic traits [45], schizo-obsessive disorder [46], risk-taking behavior [47], prosocial decision making [48], and chronic ankle instability [49].

Vagus nerve stimulation (VNS) remarkably restored mental development and cardiac autonomic function in two pre-school children with refractory epilepsy. Another two patients with intractable pediatric epilepsy due to different gene mutations showed promising effects on controlling refractory epilepsy through VNS. Patients with a minimally conscious state also showed effects on recovering consciousness and visual perception after 6-month VNS stimulation [34]. Lu et al. [50] reported the clinical application of deep brain stimulation in patients with primary PD. Patients with PD could gain clinical efficiency with optimizing stimulation parameters.

4.3 Neurorestorative surgery

Badhiwala et al. [51] published a pooled analysis of individual patient data derived from 4 independent, prospective, multicenter data sources showed that surgical decompression within 24 hours of acute SCI was associated

with improved sensorimotor recovery. Yamawaki et al. [52] showed that elbow flexion reconstruction using concomitant nerve transfer from the median and ulnar nerves did not improve the touch sensory deficit in fingers.

A retrospective study including 325 patients with adult traumatic brachial plexus injury found that nerve injury with vascular injury leads to worse functional outcomes after reconstructive surgery than without vascular injury [53]. Pages et al. [54] showed that brachial plexus injury could be functionally or structurally restored by nerve reconstruction, with early nerve surgery yielding satisfactory functional outcomes. Patients younger than 30 years old and those operated upon earlier than 6 months from the accident having better functional recovery [55] through intercostal nerve transfers [56]. Generally, patients with distal nerve transfers had faster motor recovery and better elbow flexion power than patients with intercostal nerve transfers. However, there were no significant differences in motor outcomes between two nerve transfer methods for patients with upper-type brachial plexus injuries [57].

4.4 Pharmaceutical neurorestorative therapy

Hajjar et al. [58] studied neurocognitive effects of candesartan versus lisinopril in older adults with mild cognitive impairment (MCI) in randomized clinical trial and found that 1-year treatment of older adults with candesartan resulted superior neurocognitive outcomes compared with lisinopril. Two aducanumab phase III clinical trials of AD were stopped prematurely by Biogen, but *post hoc* analyses led the sponsor to assert the trial provided a sufficient efficacy signal to justify a new drug application as a treatment for AD. Biogen plans to conduct another phase III trial with high-dose aducanumab for AD [59].

Nerinetide is a neuroprotectant that improve recovery in preclinical stroke models of ischemia-reperfusion, but it did not increase the proportion of patients achieving good clinical outcomes after endovascular thrombectomy compared with patients receiving placebo in a multicenter, double-blind, randomized controlled trial (RCT) [60]. Oral fluoxetine 20 mg daily for 6 months after acute stroke did not improve recovery of neurological function or functional outcome in randomized, double-blind, placebo-controlled trials [61–63]. Mullard [64] reported that three anti-tau antibodies (semorinemab, gosuranemab, and ABBV-BE 12) in AD failed to show positive results. These results are consistent with data suggesting that tau protein is the result of AD neurodegenerative process, but not its cause.

Honjo et al. [65] retrospectively analyzed the scores of pharmacological and nonpharmacological treatments of AD after 12 months. They found that mild or moderate AD progressed more rapidly than moderate-to-severe AD treated with medical interventions that suppressed the progression of advanced AD more than mild AD. Ton et al. [66] reported that continuous dietary supplementation with milk fermented with kefir grains could improve cognitive function in the patients with AD. These mechanisms of this treatment may be reduction of systemic inflammation, oxidative stress, and blood cell damage [66]. But RCTs are necessary to confirm these findings. Eptinezumab has demonstrated efficacy, tolerability, and safety in patients with episodic and chronic migraine and received approval by the US Food and Drug Administration (FDA) as a medicine for migraine prevention [67]. Ocrelizumab is a monoclonal antibody and is effective in treating both relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS). Based on these results, ocrelizumab was the first

drug to be approved for PPMS and RMS by US FDA [68].

4.5 Bioengineering and tissue engineering therapy

Bioengineering and tissue engineering are at the frontier of neurorestoration. Nutt et al. [69] reported that aromatic L-amino acid decarboxylase gene therapy enhanced levodopa response in PD, which improved motor responses to intravenous levodopa. Postmortem studies on two patients with advanced PD 8 and 10 years after adeno-associated virus serotype 2 (AAV2)-neurturin gene therapy found no difference Lewy pathology in treated and untreated control patients with PD, possibly due to the limited neurturin expression [70]. Analyzed postmortem, Castle et al. [71] found AAV2-nerve growth factor did not directly engage the target cholinergic neurons. Thus, it remains uncertain whether growth factor gene therapy was ineffective for AD.

Li et al. [72] showed that nerve repair membrane derived from xenogeneic decellularized nerves retained the main extracellular matrix components had good biocompatibility, and repaired transected sciatic nerve in preclinical studies. A clinical trial using this membrane is underway, test its effect on peripheral nerve disruption and nerve compression syndromes [72].

4.6 Other relevant findings

The purpose of day services (DS) is to help elderly individuals maintain mental and physical functions, and a study found that DS use after 6 months significantly improved the cognitive function of patients with AD [73]. Andreassen et al. [74] reported beneficial effects of an interactive digital calendar with mobile phone reminders (RemindMe) to support everyday life for patients with acquired brain injury. The results showed that using reminders in activities in everyday life could support their autonomy [74].

Hachmo et al. [75] tested the effect of hyperbaric oxygen therapy (HBOT) exposures on telomere length (TL), senescent cell concentrations in 35 healthy independently living adults, aged 64 and older. They found that 60 daily HBOT induced significant senolytic effects, including significantly increasing TL and clearance of senescent cells in the aging populations.

4.7 Comprehensive therapy

A randomized clinical trial of sequential psychological and medication therapies for insomnia disorder showed that behavioral therapy and zolpidem medication produced an equivalent response and remission rates. Adding a second treatment may help those whose insomnia failed to remit with initial therapies [76].

Activity-based recovery training in combination with epidural stimulation of the spinal cord (scES) for 85 individuals with bladder control dysfunction after SCI resulted in improvements in overall bladder storage parameters compared to a control cohort. Because the functional relationship between urinary bladder distention and blood pressure regulation was disrupted, both bladder and cardiovascular function by intersystem stimulation and integrating scES may further improve bladder storage [77].

Krucoff et al. [78] reported an individual with chronic complete L1 paraplegia due to conus medullaris injury preceded with SCS implantation and rehabilitation. His motor zones of partial preservation went down from L1 to L5 on the left and from L1 to L3 on the right 18 months after implantation; his lower extremity exhibited qualitative increases in electromyography amplitudes, and his three validated

functional and quality of life surveys substantially improved.

4.8 Guidelines

Standards and guidelines are important instructive documents for the clinical practice of neurorestoratology. The Chinese Association of Neurorestoratology (Preparatory) and the China Committee of International Association of Neurorestoratology made or revised, and approved 4 sets of guidelines or standards. Of them, *Clinical diagnostic and therapeutic guidelines of stroke neurorestoration (2020 China version)* [79] provides therapeutic recommendations for neurorestoration during different stroke stages. These recommendations will hopefully improve survival and quality of life for stroke patients. *Clinical neurorestorative therapeutic guideline for brainstem hemorrhage (2020 China version)* [80] provides standardization of diagnosis and neurorestorative treatments for brain stem hemorrhage. *Standards of clinical-grade olfactory ensheathing cell culture and quality control (2020 China version)* [81] and *Standards of clinical-grade mesenchymal stromal cell preparation and quality control (2020 China version)* [82] make all standardized procedures, including donor evaluation, sample collection, cell culture, cell testing, packaging marks, storage, transportation, and quality control, and also training and management procedures of laboratory operators, use and management of materials and equipment, and etc. for OECs and mesenchymal stromal cells. These standards and guidelines are instructive documents of clinical practice for Chinese physicians, and are valuable references for global clinicians in Neurorestoratology and its related disciplines. Undoubtedly, these standards/guidelines will promote further the development of Neurorestoratology.

5 Summary

The unforgettable year 2020 has passed, and we experienced a challenging time due to COVID-19. However, clinicians and scientists working in Neurorestoratology worldwide and its related disciplines still achieved many exciting results from basic, preclinical, clinical research, and enhanced scientific support for evidence-based medicine. Those developing strategies have been used to improve the quality of life for patients with neurological diseases. Hopefully, the epidemic will be under control during this New Year, and our discipline will achieve even greater results.

Conflict of interests

The authors report no conflict of interests in this work.

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