2017 Yearbook of Neurorestoratology

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1 Introduction
The recognition of Neurorestoratology as a new clinical discipline depends a great deal on dissemination of its progress. For this reason, we published the first “Yearbook of Neurorestoratology” in 2016 [1]. Assembly of the 2017 “Yearbook of Neurorestoratology” is a work in progress, and is intended to collect and summarize: (1) new finding relating to disease pathogenesis or damage to the nervous system; (2) new neurorestorative mechanisms and theories; (3) new achievements in clinical neurorestorative therapy and therapeutic standards or guidelines. These yearbooks are intended to help readers conveniently follow the latest developments in Neurorestoratology.

2 New findings concerning disease pathogenesis or damage to the nervous system
Microglia is believed to play a key role in the

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pathogenesis of central nervous system diseases. Huang et al. found that lower expression of SPI1 (encoding PU.1) in microglial cells can reduce Alzheimer disease (AD) risk by regulating myeloid gene expression and phagocytic activity [2]. Microglia phenotypes were easily influenced by their environment, which might have a profound effect on the development of central nervous system neurodegenerative diseases [3]. Kaluski et al. reported that loss of SIRT6 lose or its downstream signaling leads to toxic tau stability and phosphorylation, which could result in AD and age-related neurodegeneration [4]. Lodato et al. found that the accumulation of somatic mutations with age might be important in human age-associated degeneration [5]. New explorative studies on AD pathogenesis were published in this year. For example, complement C3 or downstream complement activation fragments might play an important role in Aβ plaque pathology, glial responses to plaques, and neuronal cell dysfunction [6]. Sprecher et al. found that poor subjective sleep quality, together with sleep problems and daytime somnolence were associated with greater AD pathology in cognitively healthy adults at risk for AD [7].

3 New neurorestorative mechanisms and theories

Axonal degeneration is an early and prominent feature of many neurological disorders. Essuman et al. reported that the NADase activity of full-length sterile alpha and TIR motif-containing protein 1 was required in axons to promote axonal NAD+ depletion and axonal degeneration after injury. The authors suggest the SARM1 enzyme can be a novel therapeutic target for axonopathies [8]. Nicotinamide mononucleotide adenyltransferase-3, by decreasing calpastatin degradation, caspase-3 activity, and calpain-mediated cleavage, can reduce cerebral injury after neonatal hypoxia-ischemia [9]. Recombinant disintegrin and metalloprotease with thrombospondin type I motif, member 13 can markedly increase neovascularization and vascular repair in an animal stroke model [10]. Mechanisms of deep brain stimulation for Parkinson disease (PD) may enhance inhibitory synaptic plasticity, and frequency-dependent potentiation and depression [11]. Inflammatory stimulation could induce mesenchymal stromal cells (MSCs) to release extracellular vesicles with greater anti-inflammatory effects [12].

4 New results of clinical neurorestorative exploring therapy and clinical therapeutic standards or guidelines

4.1 Cell therapy

In addition to numerous basic research reports in this field, a number of exploratory clinical reports on cell therapy for nervous diseases or damage appeared in 2017. As some authors misused the identification standard of MSCs [13–15] in their papers, we correct those kinds of cells as MSCs. Vaquero et al. reported that injection of autologous adipose-derived stromal cells to the periurethral region was a safe and short-term effective treatment for stress urinary incontinence [16]. Numan et al. reported patients who received adipose-derived stromal cells showed significant improvement in their dysautonomia symptoms through the mechanism of modulating autoimmune components [17]. Vaquero reported that injection of MSCs in the syrinx of posttraumatic syringomyelia also was safe and associated with clinical and neuroimaging improvement [18]. Administration of repeated doses of MSCs by subarachnoid route was a well-tolerated procedure and able to achieve progressive and significant improvement in the quality of life of patients suffering incomplete spinal cord injury (SCI) [19]. Nguyen et al. reported that autologous bone marrow mononuclear cell transplantation is a safe and effective therapy for patients with cerebral palsy [20]. The report from Hess et al., may not be a good news for cell therapy; although administration of multipotent adult progenitor cells was safe and well-tolerated in patients with acute ischemic stroke, there was no significant improvement in neurological outcomes over a 90-day observation period [21]. We should note another 2-3 clinical trials for acute ischemic stroke within 18-36 h through intravenous infusion of MultiStem® and 90-day functional assessment in future [22]. Liu et al. reported that purified human fetal-derived retinal progenitor cells could improve visual acuity for patients with retinitis pigmentosa [23]; unfortunately, retinal pigment
epithelial cells differentiated from induced pluripotent stem cells did not show visual acuity improvement for a patient with neovascular age-related macular degeneration [24]. Thus, cell therapy to treat visual loss disorders still has a long way to go.

4.2 Neuromodulation and the brain-computer interface (BCI)
Neuromodulation and the BCI has become one of the most promising strategies in Neurorestoratology, which is moving from preclinical research to clinical practice [25]. Meng et al. (2016) reported that subjects were able to effectively control reaching the robotic arm by modulating their brain rhythms using non-invasive BCI [26]. Gao et al. reported that hybrid noninvasive EEG-EMG-BCI was robust and efficient for real-time multidimensional robotic arm control [27]. Nilakantan et al. reported that hippocampal posterior-medial network using network-targeted noninvasive brain stimulation could improve memory through enhanced reactivation of detailed visuospatial information at retrieval [28]. Migaudot et al. reported that training sessions with multidirectional gravity-assist improved locomotor performance tested without robotic assistance immediately after training, whereas walking the same distance on a treadmill did not ameliorate gait [29]. Some reports even showed that 5 days of repeated left prefrontal transcranial direct current stimulation [30] or repetitive transcranial magnetic stimulation [31] could improve recovery of consciousness in some chronic patients with disorders of consciousness such as minimally conscious state; however, the double-blind cross-over study showed that repeated transcranial direct current stimulation did not exert remarkable short-term clinical and EEG effects in patients with prolonged disorders of consciousness [32]. Spinal cord stimulation [33] or deep brain stimulation [34] could improve consciousness and motor function for vegetative state and minimally conscious state, but these results should be confirmed by a randomized, double-blind, sham-controlled study.

4.3 Neurorestorative surgery
Neurorestorative surgery may generally be divided into three categories: (i) neural reconstruction [35], such as bridging peripheral nerves between, above, and below the injury site, end-to-side facial-hyoglossal anastomosis [36]; (ii) neural decompression, such as cordotomy or myelotomy [25], and decompression for compression impairment of peripheral nerve fibers [37]; (iii) surgical revascularization [38]. Further evidence in support of functional recovery through neurorestorative surgery appeared this year [39, 40]. Nandra et al. reported that intercostal to phrenic nerve transfer could reduce or eliminate ventilator support for patients with C3 to C5 high spinal cord injury [41]. Finger flexion [42] or elbow extension [43] can be restored by nerve transfer or biceps-to-triceps transfers for patients with tetraplegia. Nerve transfer also could restore active picking-up function for patients with total brachial plexus avulsion injuries [44]. Zheng et al. in a single-center randomized controlled trial reported that transferring the C7 nerve from the nonparalyzed side to the paralyzed side of the arm could lead to greater improvement in function and reduction of spasticity for patients with chronic cerebral injury for more than 5 years [45].

4.4 Pharmacological neurorestorative therapy
There is some good news for pharmacological neurorestorative therapy in this year. Montalban et al. reported that Ocrelizumab was associated with lower rates of clinical and magnetic resonance imaging progression than placebo for patients with primary progressive multiple sclerosis [46]; and Hauser et al. reported that Ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a treatment of patients with relapsing-remitting multiple sclerosis [47]. Daclizumab beta is a humanized monoclonal antibody specific for the human interleukin-2 receptor alpha chain (CD25). Several clinical trials of Daclizumab beta for patients with relapsing-remitting multiple sclerosis showed improvement of physical and psychological functioning and general health status, disability, cognitive processing speed [48–51].

A randomized, double-blind, placebo-controlled trial of the anti-oxidant Edaravone for amyotrophic lateral sclerosis (ALS) showed a significantly smaller decline of ALSFRS-R score compared with placebo [52]; the U.S. Food and Drug Administration subsequently approved this agent for ALS. This result is a major
success for pharmacological neurorestorative therapy in ALS [53]. Early administration of anticonvulsants for SCI could significantly improve motor recovery. This beneficial effect remained significant for one month [54]. A randomized, placebo-controlled, double-blind phase 2 trial of natalizumab, an antibody against the leukocyte adhesion molecule α4 integrin, administered up to 9 h after stroke onset did not reduce infarct size [55]. A randomized, controlled clinical study of hydrogen gas inhalation treatment showed effective neuroprotection in patients with acute cerebral infarction [56].

Ultra-micronized palmitoylethanolamide as add-on therapy slowed disease progression and disability in advanced PD patients [57]. Levodopa/carbidopa intestinal gel, in a multicenter, open-label study in advanced PD improved daily living experiences, including motor and non-motor functions [58]. Granulocyte colony-stimulating factor was shown to alleviate disease deterioration in early-stage PD patients, possibly due to its ameliorating progressive dopaminergic neuron degeneration [59].

4.5 Bioengineering and tissue engineering therapy

Spinal muscular atrophy took great strides in 2017 with the report that a single intravenous infusion in patients with adeno-associated viral vector containing DNA coding for survival motor neuron lengthened their survival and improved motor function compared to historical cohorts [60]. Another good news is for patients with retinitis pigmentosa, Dias et al. reported that Luxturna, a phase 3 clinical trial showed significant efficacy for RPE65-mediated inherited retinal dystrophy and was approved by FDA as the first ocular gene therapy biologic product [61].

Zhao et al. reported that combined application of NeuroRegen scaffold and human umbilical cord blood-mesenchymal stem cells (should be named as mesenchymal stromal cells [13–15] according to authors’ description) was effective in improving neurological functions for patients with chronic SCI. The authors described that they totally resected all injured spinal cord or “scar” after two months of SCI [62]. This procedure should be viewed with caution, as: (1) patients still have the chance to recover some functions spontaneously or by neurorestorative therapies which include cell therapy, neuromodulation, neurotization or nerve bridging, neurorehabilitation, etc. two months or even several years after SCI [63]; (2) potential harms for patients may outweigh the benefits.

4.6 Other therapies

Innes et al. reported that meditation or listening to music significantly enhanced both subjective memory function and objective cognitive performance in adults with subjective cognitive decline [64]. Song et al. reported that Xingnao Kaiqiao acupuncture, oral Angong Niuhuang Wan, and Xingnaojing intravenous drip applied for three months to an unconscious child resulted in the subject’s awakening with near full recovery of health [65].

4.7 Guidelines

Aghayan et al. reported a draft of Iranian national guidelines for cell therapy manufacturing, which covered all aspects, including ethical issues, manufacturing processes, quality control, transportation, harvesting, storage, and release of cell-based products [66]. Huang et al. issued clinical cell therapy guidelines for neurorestoration (China version 2016) by the Chinese Association of Neurorestoratology, which standardized clinical procedures of cell therapy [67]. Feng et al. published clinical therapeutic guidelines for neurorestoration in SCI (Chinese version 2016) by the Chinese Association of Neurorestoratology, covering clinical neurorestorative therapeutic guidelines for SCI [68]. Xiao et al. reported on neurorestorative clinical application standards for the culture and quality control of olfactory ensheathing cells [69], which included standardized training and management procedures for laboratory operators; standardized use and management of materials and equipment; standardized collection, culture, and proliferation of olfactory ensheathing cells obtained from fetal olfactory bulbs; standardized management for cell preservation, transportation, and related safeguard measures; and the standardization of a clean environment, routine maintenance, and related tests and examinations. This is first single cell culture standard issued by a professional society anywhere in the world.

5 Summary

In 2017, there were more studies to understand disease
neurorestoratology, and seek better therapeutic strategies in the field of neurorestoratology, which are introduced in this yearbook. We are pleased to see a growth in the number of reports covering evidence-based neurorestorative therapeutic strategies. These new developments will undoubtedly help patients receive greater benefits from advancements in neurorestoratology.

Disclosure

The authors declare that they have no competing interests.

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