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The 2021 yearbook of neurorestoratology

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Review

The 2021 yearbook of Neurorestoratology

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ABSTRACT

Breakthroughs with rapid changes are the themes of the development in Neurorestoratology this year. Given the very difficult circumstances of the persistent COVID-19 pandemic, most of the colleagues in Neurorestoratology have conducted meaningful research and obtained encouraging results, as described in the *2020 Yearbook of Neurorestoratology*. Neurorestorative progress during 2021 depicts recent findings on the pathogenesis of neurological diseases, neurorestorative mechanisms and clinical therapeutic achievements. The pathogenesis and risk factors of Alzheimer's disease were parts of the most prominent hot research topics. Yet, it remains controversial whether β-amyloid accumulation and tau protein deposition are the results of, or the reasons for the neurodegenerative processes. Neurogenesis is an important neurorestorative mechanism, however, it is questionable whether neural stem cells are present in the adult humans brain. Thus, neurogenesis may not derive from endogenous neural stem cells in the adult humans. Neurorestorative treatments were important areas of the 2021 research efforts and these therapies are improving the quality of life in patients with neurological diseases. There was major exploration of cell-based therapies for neurological disease and injury. However, unfortunately several multi-center, double-blind or observing-blind, placebo controlled, randomized clinical trials of mesenchymal stromal cells or products of mesenchymal stem cells failed to show positive results in ischemic stroke when employed in the sub-acute or recovery phases as there were no appreciable differences in the quality of life as compared with controls. Excitingly, increased numbers of clinical investigations of brain–computer interface (BCI) were reported that showed benefits for patients with neurological deficits. In pharmaceutical neurorestorative therapies, Aducanumab (Aduhelm) and Sodium Oligomannate are approved respectively by the United States Food and Drug Administration (USFDA) and the China National Medical Products Administration (NMPA) to treat patients with mild-to-moderate Alzheimer's disease. Although, the decisions to approve these drugs are highly contentious in the medical and scientific community because of the contradictory findings or other problems associated with the drug usage. We believe that repeating low-level evidence studies that showed negative results or scanty evidences in randomized control trials is of little significance. However, we strongly recommend conducting multi-center, double-blind, placebo controlled, randomized clinical trials for promising innovative therapeutic methods to facilitate their possible clinical translation.

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1. Introduction

Yearbooks of Neurorestoratology have become the most popular in the field of Neurorestoratology since they were compiled annually from 2016. Each year, major progresses in this discipline including pathogenesis of nervous system diseases, neurorestorative mechanisms, and clinically significant therapeutic achievements are introduced. Scientists, physicians, health care professionals and/or students greatly benefit from knowing major new progresses and developments in the field as described in these yearbooks.

In 2021, the COVID-19 worldwide pandemic persisted. Even during this dangerous situation, our global colleagues managed to conduct groundbreaking researches that are described in the 2021 yearbook.

2. New findings on disease pathogenesis or nervous system degeneration

It remains controversial whether the Aβ and tau protein deposition are the main reasons or the results of the Alzheimer's disease (AD) neurodegenerative processes. Ayalon et al. reported that Semorinemab reduced tau pathology in a transgenic mouse model as well as an increase in systemic tau concentrations in patients with AD.[1] Whether decrease in tau protein deposition improves or stabilizes the behavioral, cognitive and non-cognitive symptom in AD needs further investigations. In addition, there was increasing evidence that common infections persisting for the long term such as sepsis or pneumonia are associated with an increased risk of dementia.[2] Therefore AD pathogenesis may be in-part due to inflammatory reactions to chronic infections.

Sleep disturbances or impaired sleep may speed up β-amyloid accumulation and Aβ induced pathological progression.[3] Sleep may repair DNA damage possibly by reducing the accumulation of DNA double-strand breakages.[4]

3. New mechanisms for neurorestorative therapy

Neurogenesis is believed to be an important neurorestorative mechanism. Endogenous neurons derive from two neurogenesis sources. One is cell conversion from astrocytes or glia and the other is from the differentiation of neural stem cells (NSCs).

Last year, several reports showed that astrocytes or glia could be converted into neurons that have neuronal properties.[3] This year, the research by Tang et al. showed that NeuroD1-reprogrammed neurons could successfully develop and integrate into the visual cortical circuit that leads to vision recovery after ischemic injury.[5] Bruzelius et al. converted human adult skin fibroblasts into GABAergic neurons through direct reprogramming.[6] Maimon et al. reported that GFAP-expressing cells converted into new neurons and acquired mature neuronal character in a process mimicking normal neuronal maturation.[7] Liu et al. reported that Neurog2 could directly convert astrocytes into functional neurons in the midbrain and spinal cord.[8] However, using stringent lineage tracing in the mouse brain, Wang et al. found that the presumed astrocyte-converted neurons were actually endogenous neurons.[9] In another study, NG2+ glial cells (oligodendrocyte progenitor) with exhibiting high SOX2 expression were shown to produce new neurons and promote functional recovery after spinal cord injury (SCI).[10] Thus, the most important issue is to prove that those converted neurons if really possible are able to integrate into the existing neuronal circuit, and acquire functional properties specific in restoring the damaged functions.

In addition, through profiling single-nucleus transcriptomes or performing single-nuclei RNA sequencing did not define immature neurons existing in the adult human hippocampus.[11,12] This suggests that there are no neurons derive from endogenous NSCs in the adult humans. Until now, it is controversial whether NSCs are present in adult human brain. Even supposing that there are a few NSCs in adult human brain, they are still limited to proliferate and differentiate *in vivo*. Thus, there are not enough new endogenous neurons that are able to compensate for the lost neurons after brain injury or degeneration. Exogenous immature or mature neuronal transplantation may be the most important means of neuronal replacement for neurorestoration. Recently, olfactory neuron (ON) transplantation showed promising neurorestorative effects in patients with AD and vascular dementia (VD) in clinical pilot studies.[13,14] ONs are promising candidates for the neuronal replacement in neurotrauma and/or neurodegenerative diseases.

Hilton et al. found that critical components of the presynaptic active zone prevented axonal regeneration in the adult mice. Reducing neuronal excitability through down-regulating molecular constituents of the synapses could stimulate axonal regeneration after the adult spinal cord injury.[15] As distinct phases of synaptic plasticity play differential roles in memory consolidation; using optogenetics with long-term potentiation (LTP) within a defined temporal window may provide the precise localization, timing, and characteristic contributions to the neural plasticity events. This could also selectively eliminates LTP in the early phases of memory.[16] Álvarez et al. reported that bioactive scaffolds with enhanced supramolecular motion modulated the damaged neural tissues in a mouse model of severe SCI and promoted neurological recovery through mechanisms of vascular growth, axonal regeneration, myelination, survival of motor neurons, and reduced gliosis.[17]

4. Achievements and progress in clinical diagnosis and neurorestorative therapies

4.1. Cell therapy

This year, cell therapies remained one of the most prominent hot topics in Neurorestoratology. Kuang et al. reported transplanting olfactory ensheathing cells (OECs) into the spinal cord parenchyma adjacent to the injured site in 39 patients with chronic SCI. In this study, the majority of patients showed improvements of neurological functions and enhanced quality of life during a 7-year follow-up period.[18] Cheng et al. reported that 13 patients with chronic SCI received OEC transplantation in which 8 of 13 cases exhibited significant neurological improvements after a 10-year follow-up.[19] However, Zamani et al. reported that OEC and bone marrow mesenchymal stromal cells (MSC) co-transplantation through the lumbar puncture in 3 patients with chronic complete SCI did not improve in sensory scores in 2 of 3 patients and no motor improvements in all 3 participants.[20] This indicates that the lumbar puncture for OEC and bone marrow MSC therapy may not be the appropriate transplanting method. Oraee-Yazdani et al. reported that autologous MSC and Schwann cell transplantation through lumbar puncture in 11 patients with sub-acute complete SCI showed sensory and motor improvements in 8 of 11 patients.[21] Forty-one patients with SCI after repeated subarachnoid administrations of umbilical cord MSCs reported significant improvements in neurological function and enhancement of the quality of life.[22] Intrathecal transplantation of umbilical cord MSCs in 5 patients with chronic complete SCI induced sensory improvement in the segments adjacent to the injury site, but no motor improvement was seen.[23] Implanted scaffold with umbilical cord MSCs following scar resection exhibited some functional improvements in one third of the patients with acute complete SCI and nearly half of the patients with chronic complete SCI in 2 to 5 year follow-up period of observation.[24] However, the procedure of injured cord tissue

resection was prohibited by International Association of Neurorestoratology (IANR) and Chinese Association of Neurorestoratology (CANR; Preparatory).[25,26] Autologous purified Schwann cell transplantation in 6 patients with subacute complete thoracic SCI did not show clinical improvements.[27] Although, thoracoabdominal motor connectivity was detected by longitudinal electrophysiological assessment in all the 6 patients during the late follow-up.[28] SCs were implanted in 8 patients with chronic SCI (4 complete and 4 incomplete), and one of them demonstrated partial motor and sensory function improvements.[29] It is widely expected that induced pluripotent stem cells (iPSCs) is able to restore patients' injured nerve. However currently there is only one clinical study protocol that focuses on safety of human iPSC-derived neural stem/progenitor cell for SCI cases.[30]

Ahn et al. showed that intravenously transplanted human umbilical cord-derived MSCs twice with an 8-d interval in an adult man who suffered an acute stroke with paralysis in the left upper and lower limbs returned to his previous occupation with no adverse reactions after 65 weeks of the treatment.[31] A patient with severe middle cerebral artery occlusion 14 days after stroke onset who received an intra-arterial infusion of autologous bone marrow MSCs combined with Cerebrolysin IV showed total motor functional recovery.[32] Another patient with acute ischemic stroke being administered intravenously umbilical cord blood (UCB) mononuclear cells (MNCs) showed significantly decreased in the National Institutes of Health Stroke Scale (NIHSS; from 9 to 1) and increase in Berg Balance Scale scores (from 0 to 48).[33] Three patients with chronic stroke were treated with stereotactic implantation of autologous adipose-derived stem cells and showed significant neurological improvement at 6 months follow-up.[34] Unfortunately, several double-blind or observing-blind, randomized controlled trials (RCTs) of intravenous MSCs did not show the positive results in ischemic stroke of sub-acute period or during the recovery phases[35–39] (Ref. 39 was missed in 2020 yearbook). There were no differences in outcome in evaluating the quality of life as compared to the controls in RCTs. In Law's study, 17 patients were recruited (9 in the treatment group and 8 in the control group). There were no between-group differences in median NIHSS score at 12 months, although there was improvement in absolute change in median infarct volume in the treatment group.[35] Chung's study was a RCT with blinded outcome evaluation, and 54 patients were recruited (39 in the MSC treatment group and 15 in the control group). There was no significant difference between the groups in the modified Rankin Scale (mRS) score at 3 months, although significant improvements in lower extremity motor function (lower limb of Fugl-Meyer assessment) were found in the MSC group compared to the control group.[36] Neuroimaging analysis in this study found that interhemispheric connectivity and ipsilesional connectivity significantly increased in the MSC group.[37] The post hoc analysis showed that younger patients and treatment initiated early after stroke onset may impact improvements in lower extremity motor function in this trial.[38] Jaillard's RCT study recruited 31 patients (16 in the treatment group and 15 in the control group). They did not observe treatment effects on the Barthel Index, NIHSS, and mRS scores, although significant improvements in motor-NIHSS, motor-Fugl-Meyer scores in treated group were observed.[39] To-date, there are no reports of remarkable improvements of quality of daily life activity in cell therapies except for OECs in multicenter, double-blind or observing blind RCTs for ischemic stroke cases. In addition, the safety of intravascular infusion MSCs from different sources should be considered.[40]

Kabataş et al. demonstrated that multiple triple-route (intrathecally, intravenously, and intramuscularly) Wharton's jelly-derived MSC administrations are safe and could improve the neurological functions in patients with hypoxic-ischemic encephalopathy.[41,42] Min et al. observed that concomitant administration of allogeneic umbilical cord blood (UCB) infusion and erythropoietin (EPO) exhibited therapeutic efficacy in children with cerebral palsy (CP)[43] (this work was missed in 2020 yearbook). Amanat et al. reported that the umbilical cord tissue-MSC transplantation is safe and improved the clinical and imaging outcomes.[44] Zhang et al. showed that the diffusion tensor imaging (DTI) tract-based quantitative susceptibility mapping demonstrated characteristic white matter changes associated with behavioral improvements in CP children who underwent cord blood cell therapy.[45]

Kobinia et al. reported that autologous bone marrow cell therapy resulted in sustained beneficial outcome in 4 patients with autism spectrum disorder (ASD).[46] Nguyen et al. found that autologous bone marrow mononuclear cell transplantation in combination with behavioral intervention is safe and well tolerated in children with ASD.[47] However, in a RCT study, Sharifzadeh et al. reported that intrathecal injection of autologous bone marrow MSCs only had limited clinical efficacy in patients with ASD.[48]

Petrou et al. showed that repeated intrathecal injections of autologous MSC were safe in patients with amyotrophic lateral sclerosis (ALS) and 13 out of 19 patients exhibited a >25% improvement in the slope of progression of ALS Functional Rating Scale Revised (ALSFRS-R) scores during the whole period.[49] Sharma et al. reported that bone marrow mononuclear cell (BMMNC) transplantation was safe and showed long term beneficial effect and increased survival in 150 patients with ALS in a controlled retrospective study.[50] The single-center, prospective, phase I, IIa open-label clinical trial in ALS designed by Nabavi et al. did not prove longer survival or improvement in 17 enrolled ALS patients after allogenic adipose-derived mesenchymal stromal cells injection.[51] Tavakol-Afshari et al. reported that a single-center, prospective, and open-label MSC study without a placebo control group in patients with ALS with combined administration intrathecal (IT) and intravenous (IV) resulted in delay of the disease progression during the first 3 months, but then the disease proceeded faster.[52]

Wang and Guo reported that ON transplantation sustainably improved the perturbed damaged neurological and psychological behavior in patients with vascular dementia and AD.[13,14] Kim et al. conducted a phase I clinical trial of umbilical cord blood-derived MSCs in nine patients with mild-to-moderate Alzheimer's disease via an Ommaya reservoir. The therapy was relatively safe and well-tolerated.[53] However, the effects of both ONs and MSCs in dementia should be confirmed by prospective, multi-center, double-blind or observing-blind, randomized controlled trials.

Nittala et al. found that no statistically significant difference in mean changes in total geographic atrophy (GA) area at month 12 after human central nervous system stem cell (HuCNS-SC) transplantation in eyes in 15 patients with non-neovascular age-related macular degeneration. However, HuCNS-SC transplantation seems to be associated with slower expansion of the GA lesion in the transplanted quadrant.[54] Kawabori used intracerebral stereotactic implantation of modified bone marrow-derived MSCs (SB623) for chronic traumatic brain injury (TBI). In this study, although the treated patients significantly exhibited reduction in motor impairment (FMMS) scale scores, the functional scale, Disability Rating Scale (DRS), Action Research Arm Test (ARAT), gait velocity (GV), NeuroQOL lower extremity function T scores and Global Rating of Perceived Change assessed by patient and clinician scores were not statistically significant from the control group.[55]

Petrou et al. found that repeated MSC injections in patients with progressive multiple sclerosis were safe at the short/intermediate term and induced clinical benefits (especially in patients treated with >2 injections) that lasted for up to 4 years.[56] Harris et al.

published 2-year follow-up protocol from treatment patients suffered multiple sclerosis with autologous mesenchymal stem cell-derived neural progenitors (MSC-NPs). The efficacy of repeated IT-MSC-NP treatment benefitted for 2 years but did not sustained thereafter.[57] Tuekprakhon et al. reported that intravitreal injection of BM-MSCs appeared safe and potentially effective (keeping stable) in patients with retinitis pigmentosa.[58]

Chung et al. reported that in intra-arterial administration of autologous Bone marrow-derived MSCs, the medium- and high-dose groups tended to show a slower increase in Unified MSA Rating Scale (UMSARS) scores than the low-dose group in patients with multiple system atrophy- (MSA-) cerebellar type (MSA-C) during the 3-month follow-up.[59]

4.2. Neurostimulation/neuromodulation and the brain–computer interface

Are people just machines? Some research highlights this year will support this type of thoughts. What is exciting is that the brain–computer interface (BCI) research advanced significantly in 2021. Willett et al. developed an intracortical BCI that decodes attempted handwriting movements from neural activity in the motor cortex and translates it to text in real time for people with paralysed hands after SCI.[60] Cajigas et al. reported that a fully implanted BCI can be safely used to reliably decode movement-intent from motor cortex, allowing for accurate volitional control of hand grasp.[61] Simeral et al. demonstrated the first human use of a wireless broadband intracortical BCI to control the standard commercial tablet computer to browse the web and used several mobile applications in an individual with tetraplegia.[62] Jovanovic et al. concluded that the new BCI-functional electrical stimulation therapy (FEST) intervention was safe, feasible, and promising for the rehabilitation of reaching and grasping after SCI, and the overall BCI sensitivities were observed between 74.46% and 79.08% for the sub-acute and chronic patients.[63–65] BCI-functional electrical stimulation (FES) has potential to be used as at home hand therapy by people with SCI or stroke.[66] Lopes-Dias et al. reported that it is possible to perform online asynchronous detection of error-related potentials in patients with SCI.[67] There were more BCI studies in patients with SCI for more accurately incorporate force control into real-time iBCI systems.[68,69]

Treatment by non-invasive electrical brain stimulation (repetitive transorbital alternating current stimulation (rtACS) and transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) demonstrated functional neurorestoration of dysfunction including visual and cognitive impairment in patients after stroke or COVID patients with emotional dysregulation and AD.[70–76] However, the effects of restoring cognitive impairment should be confirmed by prospective, multi-center, double-blind or observing-blind, randomized controlled trials.

Spinal cord epidural stimulation (scES) was shown to improve motor function in patients with severe SCI and increase their ability to stand.[77,78] Electroejacuation is a safe and reliable method for induction of ejaculation in men with SCI who failed in a trial of penile vibratory stimulation.[79]

4.3. Neurorestorative surgery

At present, for trauma or its sequelae, the reasonable choice of surgical intervention is very important for the prognosis of patients. An RCT showed that early surgical treatment produced regaining of similar motor ability 1 year after injury as compared to the delayed surgical treatment among patients with cervical incomplete SCI, and it showed accelerated recovery within the first 6 months.[80]

El-Gammal et al. confirmed the safety and effectiveness of phrenic nerve transfer for functional restoration of shoulder and elbow functions in brachial plexus avulsion injuries with long-term follow-up.[81] A retrospective cohort study demonstrated that double fascicular nerve transfer (Ulnar and Median nerve) for elbow flexion in upper brachial plexus injuries did not add clinically obvious morbidity to the patients but had definite benefits.[82] Fourteen children with traumatic and birth brachial plexus palsies received nerve transfers using the long thoracic nerve. The long term follow-up found that reinnervation of the obturator nerve in free functioning muscle transfers showed the best outcomes, as compared to the musculocutaneous and axillary nerves, in spite of poor innervation to the posterior interosseous fascicles of the radial nerve and the radial nerve branches to the triceps.[83]

4.4. Pharmaceutical neurorestorative therapy

Medication for nervous system diseases has always been a difficult task in research. The clinical exploration of new drug types gives patients more hope. Fortunately, some breakthroughs have been made. Risdiplam (Evrysdi) is an orally administered small molecule that modifies survival motor neuron-2 (SMN2) pre-messenger RNA splicing and increases levels of functional SMN protein and approved for use in children with SMA in the clinic. Baranello et al. reported that oral Risdiplam led to increased expression of functional SMN protein in the blood in infants with type 1 spinal muscular atrophy.[84] Darras et al. showed that Risdiplam resulted in higher percentage of improvements in motor function in infants with type 1 SMA than the percentage of improvements observed in historical cohorts.[85]

Mirea et al. found that that early treatment was more important than combined therapy of Nusinersen (Spinraza) and Onasemnogene Abeparvovec-xioi (Zolgensma) in Spinal Muscular Atrophy Type I.[86] Monotherapy and combined therapy had the same motor function trajectory.

Day et al. reported that Onasemnogene abeparvovec showed statistical superior and clinically meaningful responses when compared to the observations from natural history cohort assessed by the Pediatric Neuromuscular Clinical Research for 22 patients with spinal muscular atrophy type 1 in phase III trial.[87] In another phase III trial, Onasemnogene Abeparvovec showed efficacy in 41 infants with symptomatic spinal muscular atrophy type 1.[88] With Onasemnogene Abeparvovec support, all 10 patients treated with the therapeutic dose maintained previously acquired motor milestones over 5 years follow up.[89]

Sovateltide (an endothelin-B receptor agonist) was safe and well-tolerated and resulted in improved neurological outcomes in patients with acute cerebral ischemic stroke 90 days post-treatment in a multicenter randomized controlled clinical trial.[90]

The advisory panel of United States Food and Drug Administration (USFDA) did not recommend approval of Aducanumab (Aduhelm). After the USFDA approved it for the clinical use as a new drug to treat AD, this drug's approval has been highly contentious in the medical and scientific community due to several contradictory findings.[91,92] Even more, the amyloid-related imaging abnormalities (ARIA) occurred in 362 of the 1029 patients (35.2%) in the 10-mg/kg group, and 94 patients (26.0%) experienced associated symptoms.[93] In 2021, Sodium Oligomannate received approval for mild-to-moderate AD by China National Medical Products Administration (NMPA). In a phase III clinical trial, the patients with mild-to-moderate Alzheimer's dementia showed cognition improvements.[94]

Secondary analysis of the randomized Systolic Blood Pressure Intervention Trial found that antihypertensive medications decrease rates of incident cognitive impairment, which may

prevent cognitive decline.[95] These results need to be confirmed in the randomized clinical trials.

Donanemab (an antibody that targets a modified form of deposited Aβ) treatment in patients with early AD showed a better composite score for cognition and for the ability to perform activities of daily living than placebo after 76 weeks.[96] Donanemab (LY3002813) dose-escalation study in AD showed that intravenous Donanemab 10 mg/kg can reduce amyloid deposits.[97] Single and multiple doses of Donanemab demonstrated a rapid, robust, and sustained reduction up to 72 weeks in brain amyloid plaques.[98]

4.5. Tissue engineering therapy

Gao et al. reported that patients in the experimental (nerve matrix membrane) and control (approved bovine tendon-derived type I collagen nerve wrapping) groups with excellent to good results were 98.00% and 94.44% in this prospective, randomized, single-blind, parallel-controlled multicenter clinical trial.[99]

4.6. Other relevant findings

In a multi-center, retrospective case-controlled study for patients with AD, 41 (39.42%) treated with Citicoline 1000 mg/day were given orally + Memantine + Rivastigmine (Cases) and 63 (60.58%) treated with Memantine + Rivastigmine (Controls). There was no statistically significant difference between Case and Control groups for the MMSE total scores, but there was a statistically significant increase of the MMSE total scores between the baseline and the end of the study in the case group.[100]

More evidences showed that hyperbaric oxygen therapy as a treatment intervention could significantly benefit patients with traumatic brain injuries, and elderly patients with significant memory loss or AD.[101,102]

4.7. Comprehensive therapy

New data demonstrated epidural electrical stimulation with specific training could benefit patients with SCI, and improve the quality of life such as bladder, bowel, and sexual functions.[103–107]

5. Summary

During the past year, the in-depth study of pathogenesis, and neurorestorative mechanism led to emergence of more effective treatments. This included the improvement of traditional surgical schemes, the development of new drugs, exploration of cell therapies and clinical RCTs of innovative therapies. In addition, new breakthrough of brain computer interface in human machine mode must be noted. Higher standards of evidence-based medicine identified some therapeutic techniques as effective for incurable or intractable neurological diseases, and also negated some of the once believed effective methods. Thus, it is unnecessary to repeat low-level evidence studies that had shown negative results in RCTs. Additional breakthrough therapies have been translated from preclinical to clinical practices and even become now the clinical treatment methods. These achievements and progresses have benefited patients with neurological diseases and improved their quality of life.

Conflict of interest

The authors report no conflict of interests in this work.

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