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Yusheng Li
The 1st Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China

Jianghong He
Tiantan Hospital, Capital Medical University, Beijing 100070, China

Bo Yang
The 1st Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China

Hui Zhang
Zhengzhou Central Hospital, Zhengzhou 450007, Henan, China

Zhonghua Yang
Tiantan Hospital, Capital Medical University, Beijing 100070, China

See next page for additional authors

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Authors

Yusheng Li, Jianghong He, Bo Yang, Hui Zhang, Zhonghua Yang, Jianhui Fu, Lian Huang, Hong Chen, Xiaofeng Yang, and Yijun Bao

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SPECIAL REPORTS

Guidelines of clinical diagnosis and neurorestorative treatment for chronic disorders of consciousness (2021 China version)

Yusheng Li[1](✉), Jianghong He[2], Bo Yang[1], Hui Zhang[3], Zhonghua Yang[2], Jianhui Fu[4], Lian Huang[5], Hong Chen[6], Xiaofeng Yang[7], Yijun Bao[8], On behalf of Chinese Association of Neurorestoratology (Preparatory) and China Committee of International Association of Neurorestoratology

[1] *The 1st Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China*
[2] *Tiantan Hospital, Capital Medical University, Beijing 100070, China*
[3] *Zhengzhou Central Hospital, Zhengzhou 450007, Henan, China*
[4] *Shanghai Huashan Hospital, Shanghai 200040, China*
[5] *The First Affiliated Hospital of Ji'nan University, Guangzhou 510630, Guangdong, China*
[6] *Tongji Hospital of Huazhong University of Science and Technology, Wuhan 430030, Hubei, China*
[7] *The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang, China*
[8] *The Fourth Hospital of China Medical University, Shenyang 110084, Liaoning, China*

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ABSTRACT

Chronic disorders of consciousness (DOC) include the vegetative state and the minimally consciousness state. The DOC diagnosis mainly relies on the evaluation of clinical behavioral scales, electrophysiological testing, and neuroimaging examinations. No specifically effective neurorestorative methods for chronic DOC currently exist. Any valuable exploration therapies of being able to repair functions and/or structures in the consciousness loop (e.g., drugs, hyperbaric medicines, noninvasive neurostimulation, sensory and environmental stimulation, invasive neuromodulation therapy, and cell transplantation) may become effective neurorestorative strategies for chronic DOC. In the viewpoint of Neurorestoratology, this guideline proposes the diagnostic and neurorestorative therapeutic suggestions and future exploration direction for this disease following the review of the existing treatment exploration achievements for chronic DOC.

1 Overview

An intact ascending reticular activation system–thalamus–cortex and cortex–cortex circuits are necessary for normal consciousness. Patients with a severe head injury and other critical neurological diseases can be rescued with the development of emergency and intensive care technology. However, coma becomes continuous or disorders of consciousness (DOC) become chronic because of the damaged structure and function of the consciousness circuit. Chronic DOC includes the vegetative state (VS) and the minimally consciousness state (MCS).

Corresponding author: YushengLi, E-mail: yushengli1970@163.com

In the USA, about 300,000 adults and 120,000 children have chronic DOC [1]. Although the accurate number of patients with chronic DOC in China is still unavailable, it is conservatively estimated to be about 100,000 new cases annually, which is a huge challenge for clinical medicine, especially for Neurorestoratology. The management of DOC needs to be solved, which is related to politics, economy, people's livelihood, and health in China. However, following the nonstandardized procedures, clinicians (even experienced clinicians) may cause about 40% of diagnosis errors [2]. Huge exploratory works have been done in neuroimaging, neuroelectrophysiology, and neurorestorative therapeutic technologies in recent years with increasing attention and cooperation for chronic DOC research by scientists and doctors in various fields. Consequently, great progress has been achieved in chronic DOC diagnosis, prediction, and treatment [2]. Those achievements and knowledge are scattered in the different disciplines in which the viewpoints for some of them are different. The Chinese Association of Neurorestoratology (Preparatory) and the Chinese Committee of the International Association of Neurorestoratology organized professional experts to draw up the recommendation guideline for the clinical diagnosis and neurorestorative treatment for chronic DOC based on these results. It aims to promote standardized diagnosis and gradual normalization of neurorestorative treatment for this disease. This guideline will be periodically updated with the exploration progress of neurorestorative treatment.

2 Basic concepts

Consciousness is an individual's ability to perceive the surrounding environment and own state. Consciousness has been described as a combination of two components, i.e., arousal and awareness. Arousal refers to the degree of alertness or vigilance, whereas awareness refers to the capacity to interact with the environment or the self [3, 4].

Consciousness disorder is divided into decreased arousal and change of conscious content. Decreased arousal is characterized by lethargy, comatose, and coma. Change of the conscious content is characterized by confusion, delirium, and special disturbances of consciousness including decortical syndrome, decerebral rigidity, akinetic mutism, and VS [5].

VS characteristics. The patients' self- and environmental awareness disappear. In addition, no continuous, reproducible, purposeful, or autonomous behavioral responses to visual, auditory, tactile, or noxious stimuli were noted. The ability of language understanding or the expression disappears. A sleep–wake cycle and autonomic neurological function in the hypothalamus and brainstem exist. Furthermore, urination and defecation are incontinence, and the brain and spinal cord reflexes are retained in varying degrees. Its main clinical features are the loss of self-expression and communication ability. Moreover, patients with consciousness disturbance of ≥ 28 days can be identified as VS [6].

MCS characteristics. The patient is in an awakened state with fluctuating and repeatable conscious responses, i.e., having intermittent and repeatable simple cognitive functions [7]. The clinical manifestations are being able to respond to simple commands, being able to use gestures or words to answer yes or no, and speaking can be understood. Under special environmental stimuli, patients show up with temporary movement or emotional behaviors without a relationship to reflexive activities (e.g.,

patients may cry, smile, or laugh when emotional, non-neutral topics, or stimuli are expressed by verbal or visual form). Moreover, patients directly respond to the talking content of comments or questions, manifest as pronouncing or gesturing, or reaching out to fetch objects, wherein the position has a clear relationship with the direction of fetching. In addition, touching or holding the object enables the contact mode to identify which fits the size and shape of the object. Furthermore, patients manifest as eye-tracking movement or continuous gaze directly responding to a movement or prominent stimuli [6].

3 Diagnostic criteria

The diagnosis of chronic DOC relies on the evaluation of clinical manifestation, electrophysiological testing, and neuroimaging examination.

3.1 Clinical evaluation

Medical history has a clear cause of chronic consciousness disorder, excluding previous medications that affect consciousness. Moreover, records show the information of consciousness disorder state in the routine physical and neurological examinations. Furthermore, behavioral scales include Glasgow Coma Score, Coma Recovery Scale-revised (CRS-R; Table 1), Wessex Head Injury Scale, and Complete Unresponsiveness Scale, Sensory Morphology Assessment and Rehabilitation Skills Scale, Disorder of Consciousness Scale, and Nociceptive Coma Scale [5]. The CRS-R is the basic evaluation index for chronic consciousness disorder, which includes all MCS evaluation index scales [motor, visual, auditory, and/or cognitive impairment (e.g., language, memory, flexibility, and attention)] [2, 6–9].

3.2 Electrophysiological examination

Electroencephalogram. The electroencephalogram (EEG) of patients with chronic DOC showed θ wave (4–7.5 Hz) and/or δ wave (1–3.5 Hz) frequency, including focal or diffuse continuous

Table 1 Coma Recovery Scale-Revised.

Score	Test
Auditory function scale	
4	Consistent movement to command
3	Reproducible movement to command
2	Localization to sound
1	Auditory startle
0	None
Visual function scale	
5	Object recognition
4	Object localization: reaching
3	Visual pursuit
2	Fixation
1	Visual startle
0	None
Motor function scale	
6	Function object use
5	Automatic motor response
4	Object manipulation
3	Localization to noxious stimulation
2	Flexion withdrawal
1	Abnormal posturing
0	None/flaccid
Oral motor/verbal function scale	
3	Intelligible verbalization
2	Vocalization/oral movement
1	Oral reflexive movement
0	None
Communication scale	
2	Functional: accurate
1	Nonfunctional: intentional
0	None
Arousal scale	
3	Attention
2	Eye opening without stimulation
1	Eye opening with stimulation
0	Unarousable

slow waves, intermittent δ rhythm, weakened EEG signal, and equipotential in severe cases possibly appearing with γ wave, which is related to slow-phase eye movements [10].

Brainstem auditory-evoked potential, visual evoked potential, auditory brainstem-evoked response, and somatosensory-evoked potential. The P100 in the evoked potential is a sensitive indicator that reflects the patient's alleviation from VS. Conversely, its absence indicates that the patient is in VS. The P300 in the event-related evoked potential can reflect the consciousness of patients with chronic DOC. Furthermore, N400 mainly reflects the process related to language processing, which has a certain value in judging whether the patient is out of MCS. The mismatch negative wave (MMN) means that patients recover from cognitive disabilities. Furthermore, > 1.5 μV is the reference value of MMN wave amplitude in the MCS [11].

3.3 Neuroimaging examination

Routine head computed tomography and magnetic resonance imaging (diffusion tensor imaging, perfusion-weighted imaging, and susceptibility-weighted imaging) examinations can provide information of the whole structures and damage degree to the patient's brain anatomy.

Resting-state fluorodeoxyglucose positron emission tomography and functional magnetic resonance imaging (fMRI) show the characteristics to define patients with VS and MCS [9], i.e., by comparing the response of the functional area with normal people to judge whether the patient has a consciousness activity.

Functional near-infrared spectrum technology can measure the changes in the concentration of oxygenated hemoglobin, deoxyhemoglobin, and total hemoglobin, which are related to the functional brain activity of the consciousness-related cortex (medial prefrontal cortex, dorsolateral prefrontal cortex, and so on), and indirectly evaluate the increase of cerebral cortex blood flow. Moreover, the increase of brain function metabolism indicates the recovery of the disease.

Combined multimodal evaluation can effectively evaluate the state of patients with impaired consciousness (VS and MCS), such as positron emission tomography, resting-state fMRI [9], functional magnetic resonance, or active paradigm and quantitative analysis of the high density of EEG [2]. In addition, transcranial magnetic stimulation combined with electroencephalogram (TMS–EEG) has higher sensitivity and specificity to differentiate VS.

The diagnosis of chronic DOC is mainly evaluated by a well-trained clinician concerning electrophysiological and neuroimaging examination information.

4 Clinical treatment

No specific neurorestorative therapeutic method for chronic DOC currently exists, and any restoring treatment for the consciousness loop may become an effective treatment method [12]. Each patient should obtain personalized comprehensive neurorestorative treatment according to their specific condition. The therapeutic principle is first to choose noninvasive intervention and then invasive intervention. The selection sequence for invasive procedures goes from low to high risks.

4.1 Basic clinical management and treatment [2, 12]

4.1.1 Nutrition management

Nutritional management involves giving reasonable and abundant enteral nutrition; maintaining the balance of hydroelectric physiology, protein, fat, fiber, and so on; and providing nutrition through nasogastric or

nasointestinal tube or percutaneous gastrostomy tube feeding for patients who cannot swallow.

4.1.2 Sphincter control

The sphincter is controlled by using a catheter, external bag, or absorbent pad to avoid complications of long-term indwelling catheterization; giving patients a balanced diet rich in dietary fiber; and using lubricants for assisting defecation to solve the problems of constipation and anal incontinence.

4.1.3 Infection prevention

Infections are prevented by maintaining good oral hygiene and preventing lung infections and reducing the frequency of using catheters to prevent urinary tract infections resulting in kidney or blood system infections [2].

4.1.4 Drug therapy monitoring

Drug therapy monitoring is used to monitor drugs that affect brain functions (e.g., epilepsy, muscle spasm, increased muscle tone, and abnormal bladder function). Spasticity is a frequency complication with DOC disorders, which may prevent the rehabilitation program. Several complications have also been associated with spasticity (e.g., muscle contracture, tendon retraction, and fixed equinovarus foo), which could further impede functional recovery, increase the cost of treatment, and negatively affect morbidity and mortality [2, 13].

4.1.5 Complication treatment

Treatment of complications aims to effectively stabilize or control complications (e.g., diabetes, heart, or lung diseases).

4.1.6 Prevention and treatment of primary complications for chronic DOC

Hydrocephalus, bedsores, osteoporosis, pulmonary embolism, and deep vein thrombosis in the lower limbs are aimed for the prevention and treatment of primary complications for chronic DOC. Thus, specialty physician coverage should be emphasized for the rapid management of those complications including daily physician rounds [1].

4.1.7 Maintaining sitting and standing positions

The best posture in sitting or standing is maintained.

4.1.8 Muscle tension control and deformity prevention

This aims to reduce muscle tension and avoid limb deformities or contractures. Muscle tension control and deformity prevention are done by preventing harmful irritation, maintaining a well-supported position, taking oral antispasmodic drugs (e.g., baclofen), injecting botulinum toxin into muscles, infusing baclofen through intrathecal way, or transecting the spinal motor nerve root [13–15].

4.2 Neurorestorative treatment

4.2.1 Drug therapy

Dopaminergic-like drugs (e.g., amantadine, bromocriptine, and dopaserizide), glutamatergic-like drugs (e.g., zolpidem tartrate and baclofen), cholinergic-like drugs (e.g., citicoline), and Chinese medicine (e.g., Angong Niuhuang Wan and Xingnaojing) are used for treatment. Moreover, neurotrophic and vasodilator drugs (e.g., neurotrophic factor, naloxone, niacin, and ganglioside) are also used [16, 17].

Large studies have shown the positive behavioral effects of amantadine in patients with prolonged disorders of consciousness. Amantadine has cerebral neurogenic anti-inflammatory and anti-excitotoxic effects and upregulates selective neurologic dopaminergic pathway [18], which is recommended as a conventional treatment drug (200 mg twice a day) [2].

The intake of 10 mg of zolpidem shows

behavioral improvement and transient functional recovery. In addition, some researchers have found that receiving 20 or 30 mg of zolpidem may induce stronger effects in patients with disorders of consciousness [19]. Studies with EEG, fMRI, and PET have shown an increased brain cortex activity and suggest that the mechanisms of zolpidem's response may be by modulating the thalamic–cortical network [20].

4.2.2 Hyperbaric oxygen (HBO_2) therapy

One treatment course recommends 30 times. Some studies provide strong proof for treating severe brain injury with HBO_2 therapy, which could improve physiologic function without fewer side-effects [21]. The neuroprotective effect of HBO_2 therapy includes reduced lesion size, brain water content, and apoptosis through an anti-inflammatory mechanism [22].

4.2.3 Neurostimulation therapy

Right median nerve electrical stimulation. The electrode is placed at the median nerve point of patients, which is 2 cm above the ventral carpal stria. The right nerve for electrical stimulation with direct current stimulation, current intensity (10–20 mA), frequency (40–70 Hz), 1 time/day (30 min/time to 8 h/time for 7–30 days), is generally chosen [23].

Repetitive transcranial magnetic stimulation. The stimulation intensity, total number of stimulations, and treatment course are 90–100% MT, 300–1,500 pulses, and 1–20 days, respectively, to use 5–20 Hz TMS to stimulate the dorsolateral prefrontal cortex (DLPFC) or M1 area in the dorsolateral prefrontal lobe [6, 24–27]. However, TMS therapy is not recommended for patients with a history of epilepsy or metal implants in their bodies.

Transcranial direct current stimulation [28–36]. DLPFC or posterior parietal cortex at 10–20 min/time (1–2 mA for 10–20 days) was chosen. The treatment precautions are similar to rTMS.

Transcutaneous electrical stimulation to the ear branch of the vagus nerve. This procedure stimulates the autonomic nerve of the ear to regulate the function of the vagus nerve, which is based on superficial branches of this nerve and the acupuncture principle of traditional Chinese medicine (20 min/time, 1 mA, and 4–8 weeks) [37–40].

The mesocircuit frontoparietal model for mechanisms underlying the effects of interventions in severe brain injuries may explain the potential mechanisms of various therapeutic interventions and the neural mechanisms of impaired consciousness [41].

4.2.4 Sensory and environmental stimulation therapy

The sensory and environmental stimulation therapy is according to the patients' habits, hobbies, and working conditions to design and give patients' favorable or unfavorable sounds, colors, smells, touch, taste, and other auditory, visual, tactile, olfactory, taste and oral, and more sensory stimulations [42–44].

4.2.5 Neurorehabilitation

Verticalization is beneficial to patients in DOC in early rehabilitation. Interventions involved ten 1-h sessions of this specific treatment over 3 weeks [45].

4.2.6 Acupuncture combined with Chinese herbal medicine

Xing Nao Kai Qiao acupuncture combined with Angong Niuhuang and Xingnaojing significantly improved consciousness for a patient with VS after a 50-day treatment [46].

4.2.7 Invasive neuromodulation therapy

Spinal cord stimulation. This is done by placing stimulating electrodes on the epidural on the dorsal cervical sites 2–4 with voltage (2–5 V),

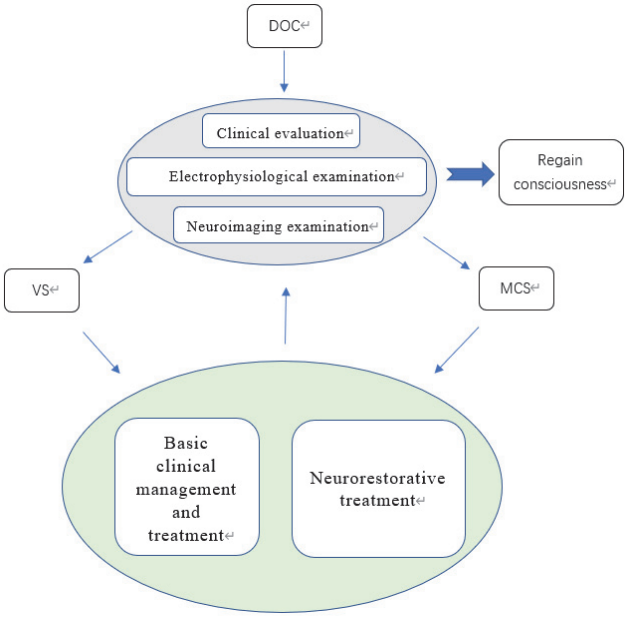

Fig. 1 Consciousness disorder treatment process.

stimulation frequency (5 or 70 Hz), and working time (12 h in one day). Moreover, 70 Hz and 100–240 μs are recommended as the priority stimulation frequency and the pulse width, respectively [47–49].

Deep-brain stimulation (*DBS*). The unipolar stimulation is the main DBS function to place the stimulating electrode on the central nucleus with a stimulation frequency (25–100 Hz), wave width (100–240 μs), and voltage (1–4.0 V). The accuracy of DBS implantation cannot be guaranteed when the thalamus in one side is severely damaged or the third ventricle and thalamus are significantly displaced owing to obvious brain atrophy. Thus, DBS surgery should be carefully selected [5, 50–55].

Vagus nerve stimulation. This is done by placing the electrode on the vagus nerve trunk in the neck to increase to the maximum intensity (1.0–1.5 mA) [56], pulse width (500 μv), frequency (25–30 Hz), stimulation time (30 s), interval (5 min), and conduct the regulation according to the response.

Extradural cortical stimulation. This is done by placing the electrodes on the epidural site, which corresponds to the frontal cortex, stimulation voltage (3.5–7.0 V), pulse width (210–300 μs), frequency (30–50 Hz), stimulation time (30 min), and interval (30 min) [57].

Baclofen pump implantation (*intrathecal baclofen*). The low blood–brain barrier permeability of baclofen, which is pumped into the intrathecal site of the lumbar spine, can significantly increase drug concentration in the central nervous system and improve the therapeutic effect in both consciousness and spasticity. The maximum daily dose is 1,000 μg. Moreover, it can be adjusted from 2 to 3 μg/h according to the clinical manifestation of the patient [58].

4.2.8 Cell therapy

Cell therapy is promising for neurological diseases including DOC [59]. However, many questions need to be answered for clinical application (e.g., cell type, cell dosage, transplanted route, and therapeutic time window). Moreover, olfactory ensheathing cells were implanted into the key points of the neural network repair on both sides. Cell dosage is 1 million per side [60]. Furthermore, autologous bone marrow mesenchymal stromal cells (5×10^6) were injected through the intrathecal way by lumbar puncture [61].

Both of these two kinds of cells showed some help in recovering consciousness. These two kinds of cell preparation currently follow the standardization of cell culture [62, 63].

5 Limitation and prospective direction

Neurorestorative treatments for chronic DOC are still currently in the stage of clinical exploration. The majority is not conventional or routine therapeutic strategies. Although some treatments have been shown helpful in recovering consciousness, strong support from higher-level evidence-based medicine of clinical trials is not obtained. Exploring key effective factors for each patient and giving personalized

precision therapy is necessary for clinical practice. Cell therapy, neurostimulation/neuromodulation, and so on, which have shown some effects in clinical practice, should be explored with higher-level evidence-based medical clinical trials in the future to prove their neurorestorative effects for chronic DOC.

Conflict of interests

The authors declare that they have no competing interests.

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