Chapter

# Introductory Chapter: Neurological Disorders - Therapy Approaches

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## 1. Introduction

Neurological disorders (ND) are diseases of the central or peripheral nervous system. In other words, they affect the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, vegetative nervous system, neuro-muscular junction, and muscles. These disorders include epilepsy, Alzheimer's disease and other dementias, cerebrovascular diseases including stroke, migraine and other headaches, multiple sclerosis, Parkinson's disease, nervous system infections, brain tumors, traumatic nervous system disorders such as head injuries, and neurological disorders related to malnutrition. The result of these imbalances is that human voluntary daily life movement is affected. In fact, the achievement of the human voluntary movement seemingly simple rather it is considerably complex. As it is a very complex mechanism which allows many nerve structures to make decisional and/or reflexional choices. Then this mechanism "defines" and "controls" the movement, through the nerve impulses intended for the musculoskeletal system. It is also known that ND are the main cause of disability and the second cause of death in the world [1–4]. Some approaches and relationships about the ND are presented **Figure 1**.

The etiology of ND is very varied due to complexity of nervous system. Among the causes of ND there are: lifestyle, infections, genetics, food and/or environmental influences. Genetic, epigenetic, and various external factors, such as physical trauma, infection, and different aspects of the environmental surroundings can be involved with the initiation and the progression of the ND. Hormonal, immune, and molecular/cellular pathways impact the clinical presentation of the ND involving various systems [5]. Moreover, gut dysbiosis (microbiota dysregulation) has been associated with some neurodegenerative diseases [6]. ND can negatively influence the bone physiology favoring decrease of the bone mineral density and bone mineral content, altered bone microarchitecture, and decrease bone strength, contributing to the development of osteopenia/osteoporosis and increased of risk of fracture [5].

The neurodegeneration is presented in several ND [6]. This condition occurs when the nervous system or neuron loses its structure, function, or both, leading to progressive degeneration or the death of neurons, and well-defined associations of tissue system, resulting in clinical manifestations. Studies have been reported that the neuroinflammation precede neurodegeneration in various ND [5]. In this context,

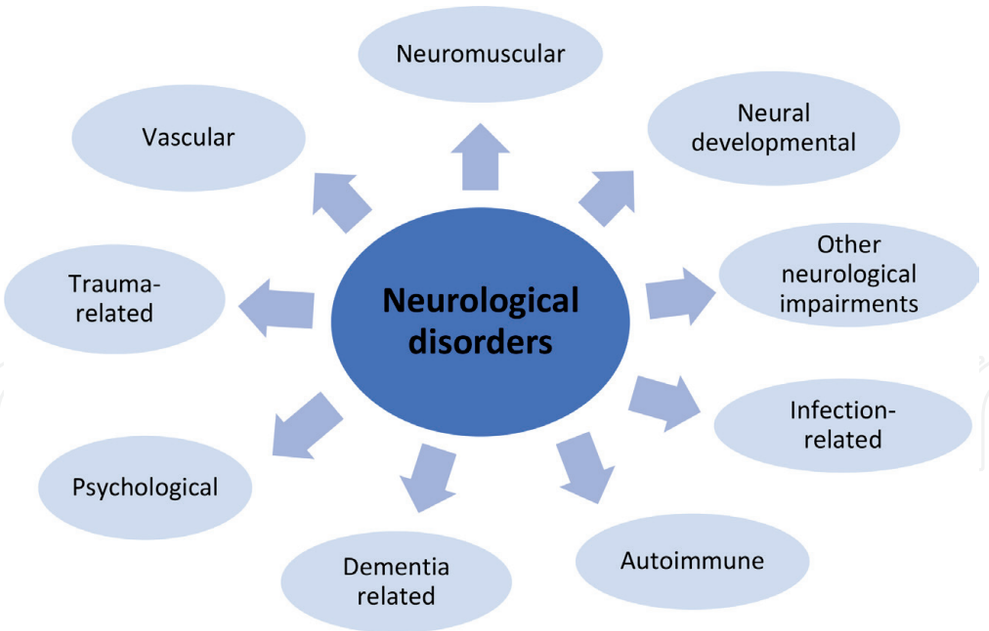


**Figure 1.**
*APPROACHES and relationships about the neurological disorders.*

appears that matrix metalloproteinases have a crucial role in the progression of ND related to neurodegeneration, although the etiology and potential causes remain widely indefinable [7].

According to the type of ND and the specific affected area, the symptoms are presented. The symptoms can be: i) complete or partial paralysis, ii) muscle weakness, iii) partial or complete loss of sensitivity, iv) convulsions, v) headache, vi) pain without apparent causes, vii) poor coordination and viii) reduced state of consciousness [8]. They can be individually observed or together. As the nervous system is strongly related of the behavior, some neurological diseases also manifest themselves with emotional or behavioral changes. In this context, the symptoms can be sudden changes in mood, or sudden outbursts of anger, depression, altered memory, hallucinations, sleep disorders, mental confusion, among others [9].

The evaluation in ND can identify signs that suggest alteration of the nervous system and can indicate the most appropriate complementary examinations to stablish an accurate diagnosis. Among the complementary exams there are: i) imaging studies [10–13] (such as Magnetic Resonance Imaging, Computed Tomography, positron emission tomography, Ultrasonography and Doppler); ii) physiological studies (such as neurophysiological examinations [14]: electroencephalogram, electroneuromyography, evoked potentials); iii) neuropsychological tests (tests that involve interviews, questionnaire applications and specific tests, with the aim of testing areas such as attention, memory, language, reasoning, and learning); iv) analysis of cerebrospinal fluid; v) blood tests (including genetic tests, research of therapeutic levels of drugs in the body, tests for specific antibodies, and general tests for numerous other diseases that can cause neurological symptoms); and vi) biopsies (of nervous tissue, skin, or muscles). The rapid and accurate diagnosis of ND allows for early treatment, improving the quality of life and the prognosis of the disease, often being the difference between life and death [15].

ND are multifactorial and can affect several areas of functionality and if left untreated, they can result in serious consequences. The evolution and the results are depending on the severity of the disease, the type of the disease, the time between onset of symptoms and treatment, among other factors. Thus, the treatment of ND can involve medication, surgeries, multidisciplinary interventions, and other types

| Neurological disorder | Definition/Etiology/Prevalence | Signals and symptoms |
|---|---|---|
| Multiple sclerosis [17–19] | It is considered as the most prevalent chronic inflammatory disease of the central nervous system associated with inflammatory demyelination and astroglial activation, where the neuronal and axonal injury as the leading factors of disability. Young individuals (20 to 40 years old), generally, are more affected, and late-onset multiple sclerosis characterized when symptoms initiating after 50 years. About 2,500,000 individuals have multiple sclerosis in worldwide. | The symptoms are different for each person, depending on location of neural injury in the body. The most common are fatigue, vision problems, failure to control the bladder and loss of balance. The demyelinating lesions in the brain and spinal cord contributions to progressive disability, impacting negatively on the daily physical and social activities, and cognition. |
| Alzheimer disease [20–22] | It is the most cause of dementia (60–80% of dementia cases), with clinical presentation of progressive anterograde episodic memory impairment, affecting memory, thinking and behavior. Generally, most people with Alzheimer's are 65 and older. The early-onset Alzheimer's occur when affect individuals under the 65 years. It is the sixth leading cause of death in the United States and its worldwide prevalence is estimated in 24 million. | The early symptom is related the difficulty remembering newly learned information. The symptoms can grow severe and interfere with daily tasks, including disorientation, mood and behavior changes, confusion about events, time and place, unfounded suspicions about family, friends and professional caregivers, and difficulty speaking, swallowing, and walking. |
| Parkinson disease [23, 24] | It is a neurodegenerative disorder that affects dopamine-producing neurons in the substantia nigra. It is the second most common neurodegenerative disease worldwide, leading to significant physical, mental, social, and financial burden on patients and caregivers. According to the increase in age, the incidence of it increases too, however, four percent of people are diagnosed before age 50. It is estimated that more than 10 million people worldwide are living with Parkinson Disease. | The cardinal features are resting tremor, cogwheel rigidity, bradykinesia, and postural instability, often preceded by prodromal symptoms such as autonomic dysfunction appearing 5 to 20 years earlier. Generally, the symptoms develop slowly over years, differing from one person to another due to the diversity of the disease. |
| Cerebral palsy [25, 26] | It is a complex motor disorder at the level of the central nervous system caused by irreversible brain lesions that occur before, during or shortly after birth. It is the most common physical disability in childhood. It affects people in different ways that can compromise body movement, muscle control, muscle coordination, muscle tone, reflex, posture, and balance. Cerebral palsy is a permanent life-long, but some of these signs can improve or worsen over time.<br>Cerebral palsy has a prevalence of 1 in 700 live births, affecting about 18 million people worldwide. | It is common the presence of reduction in the motor repertoire of gestures and a loss in the quality of movement with reduction of normal motor patterns. The postures which the child adopt and maintain, as well as their stability, is altered: the child has difficulty in both moving and staying still. The more alterations are, the more severe is the final paralysis and consequently the greater the disability. |

| Neurological disorder | Definition/Etiology/Prevalence | Signals and symptoms |
|---|---|---|
| Autism spectrum disorder [27, 28] | It is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. This neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain. It is estimated about 1.68% of United States children aged 8 years (or 1 in 59 children) are diagnosed with ASD and this estimate can be extrapolated to the worldwide. | Considering behavior, these individuals can present aggression, self-mutilation, crying, lack of eye contact, shouting, hyperactivity, involuntary imitation of someone else's movements, impulsivity, inappropriate social interaction, irritability, repetitive movements, repetition of meaningless words, meaningless repetition of the words themselves or persistent repetition of words or actions; related to the development, they can present speech delay in a child or learning disability; about cognition, can be presented lack of attention or intense interest in a limited number of things; considering psychological symptoms, they can present depression or ignores the emotions of others; in speech, they can present speech disorder or loss of speech. These individuals can also present tiptoeing, anxiety, lack of empathy, sensitivity to sound or tic. |
| Amyotrofic lateral sclerosis [29, 30] | It is characterized as a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord, affecting controlling voluntary muscle movement compromising movements like chewing, walking, and talking. As this disease is progressive, the symptoms get worse over time. The prevalence is estimated in 5 per 100,000 in the United States; being about 30,000 individuals present this condition. | The common symptoms are fasciculations (muscle twitches) in the arm, leg, shoulder, or tongue, muscle cramps, tight and stiff muscles (spasticity), muscle weakness affecting an arm, a leg, neck, or diaphragm, slurred and nasal speech, difficulty chewing or swallowing. |
| Myastenia graves [31–34] | It is an autoimmune disorder of neuromuscular transmission, characterized as an error in the transmission of nerve impulses to muscles, that promote fluctuating weakness and disabling fatigability. The prevalence is estimated in approximately 20 cases per 100,000 population, affecting twice as many women as men, however, considering older individuals, men appear are affected more often. | The mainly symptom is muscle weakness that worsens after periods of activity and improves after periods of rest. Muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are compromised, generally, but not always. The symptoms that ca be presented are ocular myasthenia, ptosis, diplopia, dysarthria, weakness in the arms, hands, fingers, legs, and neck. The severe weakness of myasthenia gravis may cause respiratory failure. |
| Spinal cord injury [35, 36] | It is often the result of an unpredictable accident or violent event. This condition is frequently associated with severe clinical-neurological deficits leading to persisting physical and psychological sequela. It can be caused by: a violent attack (as a stabbing or a gunshot), diving into water that's too, shallow and hitting the bottom trauma during a car accident (as a trauma to the face, head, and neck region, back, or chest area), falling from a significant height, head, or spinal injuries (as during sporting events), and electrical accidents.<br>It is estimated that 327 million people are affected with this condition annually | The symptoms can be related to difficulty in walking, loss of control of the bladder or bowels, inability to move the arms or legs, feelings of spreading numbness or tingling in the extremities, headache, pain, pressure, and stiffness in the back or neck area, signs of shock, unnatural positioning of the head. |

| Neurological disorder | Definition/Etiology/Prevalence | Signals and symptoms |
|---|---|---|
| Traumatic Brain Injury [37, 38] | It is characterized as a damage in the brain by an external mechanical force, leading to temporary/permanent secondary injuries. This alteration can promote impairment of cognitive, physical, and psycho-social functions with altered consciousness. The mainly mechanism responsible for neuronal damage in this condition is an increase in oxidative reactions initiated by free radicals generated by the injury. It is considered as a leading cause of mortality, morbidity, and disability worldwide, and it is estimated that 5.3 million of individuals in United States (2 percent of the population) present a disability as a result of a traumatic brain injury. | The signs and symptoms related to mild traumatic brain injuries are: physical symptoms (headache, nausea or vomiting, fatigue or drowsiness, problems with speech, dizziness or loss of balance, sensory symptoms, sensory problems - such as blurred vision, ringing in the ears, a bad taste in the mouth or changes in the ability to smell<br>Sensitivity to light or sound; cognitive, behavioral, or mental symptoms; loss of consciousness for a few seconds to a few minutes; without loss of consciousness, but a state of being dazed, confused or disoriented; memory or concentration problems; mood changes or mood swings; feeling depressed or anxious; difficulty sleeping; sleeping more than usual. Considering moderate to severe traumatic brain injuries can be present: physical symptoms; loss of consciousness from several minutes to hours; persistent headache or headache that worsens; repeated vomiting or nausea; convulsions or seizures; dilation of one or both pupils of the eyes; clear fluids draining from the nose or ears; inability to awaken from sleep; weakness or numbness in fingers and toes; loss of coordination; cognitive or mental symptoms; profound confusion; agitation; slurred speech; coma and other disorders of consciousness. |
| Stroke [39, 40] | There are 3 types of strokes: ischemic stroke (when blood flow through the artery to the brain becomes blocked, such as blood clots); hemorrhagic stroke (when an artery in the brain breaks and puts too much pressure on brain cells damaging them, that can be intracerebral hemorrhage or subarachnoid hemorrhage); and transient ischemic attack (when blood flow to the brain is blocked for only a short time—usually no more than 5 minutes). The ischemic stroke corresponds to 87% of strokes. More than 795,000 individuals in the United States have a stroke, annually. | The symptoms related to this condition can be sudden numbness or weakness in the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking, or difficulty understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance, or lack of coordination, and sudden severe headache with no known cause. |

**Table 1.**
*Considerations about determined neurological disorders.*

of available treatments to help the improvement of these patients. Among the physical therapies and other treatments, there are: i) movement, exercise, and physical activity therapies to improve the individual's motor capacity; ii) speech therapy, which improves the functioning of swallowing and a language; iii) occupational/cognitive therapies to stimulate functionality, working on the affected cognitive areas, such as memory, verbal and written communication, language, etc.; iv) psychotherapy for the treatment of the emotional components of the disease. Drug treatments for many ND, such as selective serotonin reuptake inhibitors, antipsychotics, anti-epilepsy drugs have independent and overlapping roles in mediating bone loss [5, 16].

In this introductory chapter, some considerations about determined ND will be presented and discussed, as indicated in **Table 1**.

## 2. General approaches in ND

The functional capacity and quality of life of individuals with ND can be affected in different ways according to the injured area, the extension of the injury, the time of the injury and the age of the patient. The symptoms associated differing to each ND and can be related to impairments in movements, cognition, behavior, balance, tonus, bone and spasticity among others [41, 42].

The therapeutical approaches are stablished according to the type of ND and evolution of them. These approaches can involve pharmacological and non-pharmacological interventions, neurological physical therapy, biological and molecular approaches, among other that aim to management of the ND, improving functionality, daily activities, and quality of life of these individuals [43, 44].

## 3. Conclusion

It is known that Neurological disorders include all diseases and dysfunctions of the central or peripheral nervous system under the same name. It is known that Hundreds of millions of people worldwide suffer from neurological disorders. It is also known that neurological conditions pose an economic burden to society. The purpose of this chapter is to summarize the impact of neurological disorders on patients' quality of life and to acknowledge their importance. This chapter will provide a better understanding of neurological disorders, assessments, prevention decisions, medical consultation, and treatments. In our present chapter, it is concluded that ND can impact the life of the individual in all aspects and the lesions are related to the area, injury, time, and age of them. The therapeutical approaches are selected according to type and evolution of ND and involves multidisciplinary treatments. These approaches seek to promote a cure or the autonomy of individual for a long time as possible with quality of life.

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## References

[1] Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Neurology. 2017;16(11):877-897.

[2] Collaborators GUND. Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study. JAMA Neurology. 2021;78(2):165-176.

[3] Chin JH, Vora N. The global burden of neurologic diseases. Neurology. 2014;83(4):349.

[4] Erkkinen MG, Kim MO, Geschwind MD. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. *Cold Spring Harb Perspect Biol.* 2018;10(4).

[5] Kelly RR, Sidles SJ, LaRue AC. Effects of Neurological Disorders on Bone Health. *Frontiers in Psychology.* 2020;11(3399).

[6] Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases. Neurobiology of Disease. 2020;134:104621.

[7] Behl T, Kaur G, Sehgal A, et al. Multifaceted Role of Matrix Metalloproteinases in Neurodegenerative Diseases: Pathophysiological and Therapeutic Perspectives. *International Journal of Molecular Sciences.* 2021;22(3).

[8] Borsook D. Neurological diseases and pain. Brain. 2012;135(2):320-344.

[9] Butler C, Zeman AZJ. Neurological syndromes which can be mistaken for psychiatric conditions. *Journal of Neurology, Neurosurgery & Psychiatry.* 2005;76(suppl 1):i31.

[10] Delin S, Bošnjak Nađ K, Martinec S, Čokolić Petrović D, Šimic Klarić A, Mejaški Bošnjak V. Prognostic value of cranial ultrasonography in comparison with magnetic resonance imaging in children with cerebral palsy: a population-based study. Acta Clin Croat. 2020;59(2):260-269.

[11] Lim M, Jassar H, Kim DJ, Nascimento TD, DaSilva AF. Differential alteration of fMRI signal variability in the ascending trigeminal somatosensory and pain modulatory pathways in migraine. The Journal of Headache and Pain. 2021;22(1):4.

[12] Michler E, Kaiser D, Eleftheriadou K, Falkenburger B, Kotzerke J, Hoberück S. Comparison of 6-[18F]FDOPA PET with Nigrosome 1 detection in patients with parkinsonism. EJNMMI Research. 2021;11(1):16.

[13] Palermo F, Pieroni N, Maugeri L, et al. X-ray Phase Contrast Tomography Serves Preclinical Investigation of Neurodegenerative Diseases. *Frontiers in Neuroscience.* 2020;14(1137).

[14] Guérit JM, Amantini A, Amodio P, et al. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): Electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). Neurophysiologie Clinique/Clinical Neurophysiology. 2009;39(2):71-83.

[15] Boersma I, Miyasaki J, Kutner J, Kluger B. Palliative care and neurology: time for a paradigm shift. Neurology. 2014;83(6):561-567.

[16] Ortuño MJ, Robinson ST, Subramanyam P, et al. Serotonin-reuptake inhibitors act centrally to cause bone loss in mice by counteracting a local anti-resorptive effect. Nature medicine. 2016;22(10):1170-1179.

[17] Momtazmanesh S, Shobeiri P, Saghazadeh A, et al. Neuronal and glial CSF biomarkers in multiple sclerosis: a systematic review and meta-analysis. Reviews in the Neurosciences. 2021.

[18] Naseri A, Nasiri E, Sahraian MA, Daneshvar S, Talebi M. Clinical Features of Late-Onset Multiple Sclerosis: a Systematic Review and Meta-analysis. Multiple Sclerosis and Related Disorders. 2021;50:102816.

[19] Marin CE, Kfouri PP, Callegaro D, et al. Patients and neurologists have different perceptions of multiple sclerosis symptoms, care and challenges. Multiple Sclerosis and Related Disorders. 2021;50:102806.

[20] Shea Y-F, Pan Y, Mak HK-F, et al. A systematic review of atypical Alzheimer's disease including behavioural and psychological symptoms. *Psychogeriatrics.* 2021;n/a(n/a).

[21] Fowler NR, Judge KS, Lucas K, et al. Feasibility and acceptability of an acceptance and commitment therapy intervention for caregivers of adults with Alzheimer's disease and related dementias. BMC Geriatrics. 2021;21(1):127.

[22] Mayeux R, Stern Y. Epidemiology of Alzheimer disease. *Cold Spring Harb Perspect Med.* 2012;2(8).

[23] Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. Nature Reviews Neurology. 2016;12(11):622-634.

[24] Muangpaisan W, Mathews A, Hori H, Seidel D. A systematic review of the worldwide prevalence and incidence of Parkinson's disease. J Med Assoc Thai. 2011;94(6):749-755.

[25] McNamara L, Scott KM, Boyd RN, Novak I. Consensus of physician behaviours to target for early diagnosis of cerebral palsy: A Delphi study. *Journal of Paediatrics and Child Health*. 2021;n/a(n/a).

[26] McMorris CA, Lake J, Dobranowski K, et al. Psychiatric disorders in adults with cerebral palsy. Research in Developmental Disabilities. 2021;111:103859.

[27] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* American Psychiatric Publishing; 2013.

[28] Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 2020;9(Suppl 1):S55-S65.

[29] Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. Curr Opin Neurol. 2019;32(5):771-776.

[30] Yang T, Hou Y, Li C, et al. Risk factors for cognitive impairment in amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry.* 2021:jnnp-2020-325701.

[31] Nalbantoglu M, Akalin MA, Gunduz A, Kiziltan M. Electro-physiological investigation for autonomic dysfunction in patients with myasthenia gravis: A prospective study. Ideggyogy Sz. 2021;74(1-2): 33-40.

[32] Hou J, Cao J, Tan P, Yu Y. Pneumocystis jiroveci pneumonia, Nocardia brasiliensis, and *Mycobacterium tuberculosis* co-infection in a myasthenia gravis patient: A case report. *Medicine.* 2021;100(1).

[33] Spillane J, Higham E, Kullmann DM. Myasthenia gravis. BMJ: British Medical Journal. 2012;345:e8497.

[34] Li Y, Arora Y, Levin K. Myasthenia gravis: newer therapies offer sustained improvement. Cleve Clin J Med. 2013;80(11):711-721.

[35] Sohn S, Kim J, Chung CK, Lee NR, Sohn MJ, Kim SH. A Nation-Wide Epidemiological Study of Newly Diagnosed Primary Spine Tumor in the Adult Korean Population, 2009-2011. J Korean Neurosurg Soc. 2017;60(2):195-204.

[36] Lo J, Chan L, Flynn S. A Systematic Review of the Incidence, Prevalence, Costs, and Activity and Work Limitations of Amputation, Osteoarthritis, Rheumatoid Arthritis, Back Pain, Multiple Sclerosis, Spinal Cord Injury, Stroke, and Traumatic Brain Injury in the United States: A 2019 Update. Archives of Physical Medicine and Rehabilitation. 2021;102(1):115-131.

[37] Kaur A, Jaiswal G, Brar J, Kumar P. Neuroprotective effect of nerolidol in traumatic brain injury associated behavioural comorbidities in rats. Toxicology Research. 2021;10(1):40-50.

[38] D. M. Sosin JESDJT. Incidence of mild and moderate brain injury in the United States, 1991. Brain Injury. 1996;10(1):47-54.

[39] Mozaffarian D, Benjamin Emelia J, Go Alan S, et al. Heart Disease and Stroke Statistics—2016 Update. Circulation. 2016;133(4):e38-e360.

[40] Esmael A, Elsherief M, Eltoukhy K. Predictive Value of the Alberta Stroke Program Early CT Score (ASPECTS) in the Outcome of the Acute Ischemic Stroke and Its Correlation with Stroke Subtypes, NIHSS, and Cognitive Impairment. Stroke Research and Treatment. 2021;2021:5935170.

[41] Nonnekes J, Goselink RJ, Růžička E, Fasano A, Nutt JG, Bloem BR. Neurological disorders of gait, balance and posture: a sign-based approach. Nature Reviews Neurology. 2018;14(3):183.

[42] Duclos H, Desgranges B, Eustache F, Laisney M. Impairment of social cognition in neurological diseases. Revue neurologique. 2018;174(4):190-198.

[43] Tamburin S, Lacerenza MR, Castelnuovo G, et al. Pharmacological and non-pharmacological strategies in the integrated treatment of pain in neurorehabilitation. Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. European journal of physical and rehabilitation medicine. 2016;52(5):741-752.

[44] Pieramico V, Esposito R, Cesinaro S, Frazzini V, Sensi SL. Effects of non-pharmacological or pharmacological interventions on cognition and brain plasticity of aging individuals. Frontiers in systems neuroscience. 2014;8:153.