Review Article

An overview on Stroke Diagnosis & Management Approach

Saleh Saad T Alotaibi[1]*, Abdullah Khaled J Alzahrani[1], Lama Zaki Al Nasserullah[2], Bassam Al Abo Nasser[3], Nehal Mohammad Alhusayni[4], Leena Talal Alotaiby[5], Amjaad Mohammad Althagafi[5], Mariam Mohammed Alrawi[5], Futoon Saad Alobiri[5], Mishary Ali Shawani[6], Abdulaziz Alqarni[7]

[1] Faculty of Medicine, Taif University, Taif, KSA. [2] Department of Internal Medicine, Imam Abdulrahman Alfaisal Hospital, Riyadh, KSA.. [3] Faculty of Medicine, King Khalid University, Abha, KSA.[4] Faculty of Medicine, Alfarabi College of Medicine, Riyadh, KSA. [5] Faculty of Medicine, King Abdulaziz University, Jeddah, KSA. [6] Faculty of Medicine, Imam Muhammad Ibn Saud Islamic University, Riyadh, KSA.[7]Faculty of Medicine, Prince Sattam bin Abdulaziz University, Riyadh, KSA.

Abstract

Background: Stroke is a condition that is described as a clinical syndrome where a rapid focal or general neurological deficit appears as abnormal signs and symptoms and lasts for more than 24 hours. It can be classified as ischemic and hemorrhagic depending on the cause. It will lead to severe complications and may progress into coma and death. Overall, stroke is the third cause of mortality and, in some demographics, is considered the second most common cause of death. Diagnosing this disease is of vital importance because it will impact the start of the treatment and the overall outcome of the patients. Luckily, the treatment options have advanced in the last 20 years with multiple options depending on the clinical presentation. **Objectives:** We aimed to review the literature reviewing pathophysiology of acute ischemic stroke, risk factors, clinical features, evaluation, diagnosis, and management of this disease; with a focus on the medical approach. **Methodology:** PubMed database was used for articles selection, papers on were obtained and reviewed. **Conclusion:** Internal medicine clinicians must have a solid background clinically with a high clinical suspicion in order to identify stroke as soon as possible. This will impact the management approach and choices and prognosis of patients. Moreover, many treatment regimens and options have been heavily studied with new possible breakthroughs being under the scope in upcoming studies. These new modalities of management may offer a better future for patients, and help the clinicians in treating a major morbidity and mortality cause globally.

Keywords: Acute Ischemic Stroke, Presentation, Evaluation, Risk Factors, Diagnosis, Management.

Introduction

Stroke is a clinical syndrome that consists of the rapid development of the clinical signs of global or focal disruption of cerebral function that lasts more than 24 hours; and/or leads to death without any obvious cause other than a vascular-brain-origin [1-3]. Globally, it is the 2nd leading cause of death and the third in low-income countries [4]. Nevertheless, two-thirds of the deaths related to stroke happen in developing countries. Stroke can be subdivided into ischemic and hemorrhagic origins [5]. They share almost the same clinical presentation but differ significantly in management. Nevertheless, the relative prevalence of either of the two main types varies across countries. This disease causes a huge global burden on the economy and health care systems, with one-third of patients being dependent (partially or completely) on a caregiver. In the US, the incidence of acute ischemic stroke is approximately 800,000 patients per year. Moreover, researchers expect a rise in the number of cases in the next 10 years due to the increased life expectancy, with a higher rise expected in low-income countries to more than 100% [6, 7]. As a result, this disease causes a huge global burden on the economy and health care systems, with one-third of patients being dependent (partially or completely) on a caregiver [7]. Thus, management and treating such cases are of vital importance in the whole medical field, starting from the emergency department up till admission to the ward and long-term follow up. In this paper, we will review the proper literature discussing pathophysiology behind stroke with a focus on the ischemic type, risk factors, diagnosis, and management options for such cases.

Methodology

Address for correspondence: Saleh Saad T Alotaibi. Faculty of Medicine, Taif University, Taif, KSA.
Email: Saa.2017@hotmail.com

How to cite this article: Alotaibi, S. S. T, Alzahrani, A. K. J., Al Nasserullah, L.Z., Al Abo Nasser, B., Alhusayni, N. M., Alotaiby, L. T.. and *et al*. An overview on Stroke Diagnosis & Management Approach. Arch Pharma Pract 2020;11(4):60-5.

PubMed database was used for articles selection, and the following keys used in the Mesh ((“Ischemic Stroke"[Mesh]) AND (“Diagnosis"[Mesh] OR "Management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics: ischemic stroke evaluation, management, and diagnosis. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

Ischemic stroke is one of the main causes of death; and thus, it has been noticed by physicians, and researchers in terms of understanding the pathophysiology, precise diagnosis, and appropriate management. Unfortunately, until the late 1990s, the general approach was to “wait and see” in most patients, which resulted in poor prognosis and increased the burden on both the community and health care system [8]. However, nowadays with the major advancements in the medical field, we have a better understanding of the processes behind the disease. Multiple medicines have been developed and proved effective. Nowadays, the overall prognosis and long-term outcome became better for such patients, rather than just waiting with no active intervention.

Pathophysiology

The main mechanism behind ischemic stroke is the reduction of blood flow delivered to the brain, which results in an insult to the tissue. Due to the complex brain circulation, ischemic strokes are usually focal. When the blood flow is obstructed, the central region suffers the most since it has almost no blood flow, and the area rapidly dies within minutes. While the surrounding tissue has its blood flow above the “death” threshold, it is still below functional levels and such zone is named “penumbra”. This area has a very limited period to be reperfused and cells usually die after a certain period of time. Thus, such a time window is the main focus of clinicians to try and restore the blood flow in order to save the penumbra from permanent death [9].

The concept behind cell death in the enteral area is that neurons continue to use adenosine triphosphate (ATP), the energy molecule, even though the cell cannot synthesize it due to cellular hypoxia. This results in the drop in the total ATP levels, an increase in the total adenosine diphosphate (ADP) levels, and the development of lactate acidosis due to the concomitant loss of ionic homeostasis. This, in turn, initiates the rapid and fatal ischemic cascade of multistep and multicellular series of downstream mechanisms. Another major event that affects neural tissue is the release of neurotransmitters and inhibition of their reuptake. Although there are multiple involved neurotransmitters the main one is glutamate, which is the key excitatory neurotransmitter. When it binds to ionotropic N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (iGluRs), it leads to a major influx of calcium. When cells are overloaded with calcium, it results in the activation of phospholipase lipases, nucleases, and proteases. These enzymes destroy the essential proteins and membranes within the cell. Glutamate also promotes high sodium and water influx, which results in cell swelling, edema, and thus shrinking of extracellular space [10].

The net result, from the aforementioned process, is an excessive mitochondrial oxygen radical production along with the other sources of free radicals, such as degradation of hypoxanthine and prostaglandin synthesis. Reactive oxygen species (ROS) will result in direct damage to cellular components; nucleic acid, carbohydrates, lipids, and proteins. Concurrently, cellular protection against ROS in the form of antioxidant enzymes –e.g. glutathione, catalase, and SOD- and scavenging mechanisms – e.g. α-tocopherol, and vitamin C- become unable to oppose ROS production [11]. Along with this process, other mechanisms responsible for neuronal death are activated. These include, but are not limited to: lipoxygenase cascade, poly ADP-ribose polymerase (PARP), mitochondrial transition pore formation, and amplified ionic imbalance, which happens due to the secondary recruitment of calcium-permeable transient receptor potential ion (TRPM) channels [12]. Moreover, in combination with ROS, reactive nitrogen species, which are prevalent in neurons, can modify the endogenous functions of proteins. Most of these function as neuroprotective proteins. As a result, these cascades will eventually lead to a complex mix of autophagy, apoptosis, and necrosis with ultimately neuronal death [13].

On the other hand, the white matter, which is primarily composed of axonal bundles sheathed with myelin –formed by oligodendrocytes-, is affected by other factors. One of the major factors is the difference in blood flow between the white and grey matter. It has significantly less blood supply with little collaterals when compared with the grey matter [14]. As a result, ischemia in this area is severe with rapid tissue edema and cellular swelling. Moreover, the process activates many proteases that weaken the myelin sheath and the structural integrity of axons. More importantly, it is essential for the white matter to be repaired and reconnected to other neuronal networks for recovery and restoration of function. This can be induced with different endogenous responses that fix the white matter damage [9].

The inflammatory response is another major event that is initiated primarily after the stroke. The main importance of it is that it modulates the immune system and may lead to a decrease in the overall size of the infarct. Examples of recruited inflammatory cells that play a major role are: microglia cells, macrophages/monocytes, neutrophils, and T-cells. However, this process might lead to negative changes as well. These include cerebral edema, neuronal cell death, and disturbances to the function of the blood-brain barrier. The main key in the inflammatory process appears to be the microglial cells. Their numbers are increased in the infarcted area after the stroke; However, it can act as a protective and/or destructive to the tissue. Their protective function is demonstrated by their ability to produce neurotrophic substances including Brain-derived Neurotrophic Factor (BDNF), insulin-like growth factor I (IGF-I), and other growth factors. On the other hand, by releasing several pro-

inflammatory cytokines, the microglial cells can be destructive to the nearby healthy tissue. These cytokines include interleukin-1β (IL-1β), TNF-α, and IL-6, along with Nitric Oxide (NO), ROS, and prostanoids. Besides, these cells can recruit other inflammatory cells to penumbras and possibly causing more harm. Thus, the new therapeutic approach has suggested a reduction in the overall inflammation in the infarcted area. Multiple mediators and cells have been proposed to assess the outcome of stroke and its severity. The main examples include IL-6 and Toll-like receptor 4 for the severity of stroke while other cells, such as regulatory T cells, have been shown to have a protective role during the stroke. Metalloproteinase, based on their anti-inflammatory properties, are suggested to help in the treatment of stroke [15].

Stroke can be subdivided into a large vessel, small vessel (Lacunar stroke), and cardioembolic stroke depending on the cause of blood flow disturbance. The large artery strokes are when major brain-supplying arteries are affected. These include the internal, middle, and anterior cerebral arteries, or the vertebrobasilar system. Lacunar strokes often involve the smaller or perforating blood vessels supplying the deeper structures of the brain. Cardioembolic variety usually has other diseases or risk factors associated with it, most notably atrial fibrillation [16].

Risk Factors

This condition has been heavily studied to determine the associated risk factors in order to lower the risk in special populations. Generally, these risk factors are divided into modifiable (which can be treated or changed) and nonmodifiable risk factors. The main nonmodifiable risk factors include a family history of transient ischemic attacks (TIAs) or stroke, fibromuscular dysplasia, history of migraine headaches, ethnicity, sex, race, and older age. Besides, modifiable risk factors are much more common and are of utmost importance to physicians since they can be approached and eliminated in most of the patients. The most important and prevalent modifiable risk factor is hypertension, which can be attributed to up to 50% of the total small vessel strokes. Compared to the general population, patients with resistant hypertension have a higher risk of developing stroke with up to 90% [17]. Other chronic diseases such as dyslipidemia, diabetes mellitus, carotid stenosis, hyperhomocysteinemia, and obesity all contribute to a higher risk for cerebrovascular attacks. Some lifestyle activities are proven to increase the risk as well. These include tobacco use, illicit drug use, excessive alcohol intake, and physical inactivity. Also, some drugs increase the risk with oral contraceptives and postmenopausal hormones as the main examples.

Since embolic events are one of the major causes of ischemic stroke, many cardiac diseases have been associated with and identified as risk factors, mostly due to dysfunctional heart valves. These include infective endocarditis, rheumatic mitral or aortic valve, the usage of bioprosthetic (or mechanical) heart valves, fibrous nonbacterial endocarditis (i.e., Libman-Sacks endocarditis), and antiphospholipid syndrome. Of particular notoriety, arrhythmias have been reported, in some studies, to accompany and possibly be the cause of strokes in up to 20% of cases. These arrhythmias are mostly atrial fibrillation and flutter. However, other arrhythmias could cause stroke, for example, paroxysmal atrial fibrillation and sick sinus syndrome. Existing structural heart abnormalities like dilated cardiomyopathy or any recent myocardial infarction, along with previous coronary artery bypass graft surgery are important points to be considered with any patient presenting with stroke [18, 19].

Clinical Features

Depending on the area affected, the clinical presentation of stroke varies greatly. American heart association and American stroke association (AHA/ASA) presented an algorithm “FAST” in order to ease the recognition of stroke signs among the public in a pre-hospital setting and improve the outcome of patients [11]. This acronym includes the rapid onset of facial droop, arm weakness (but can include leg, face, or all), slurred or not clear speech, and time of onset with all these signs alerting heading to the emergency department immediately. Vertigo (lightheadedness or spinning feeling), severe headache, and disturbance of balance are other signs that should alert the public to the possibility of stroke. Other acronyms are in use, which include the 6S and the BEFAST that all can indicate the possibility of stroke when criteria are met. The 6S stands for sudden onset of symptoms, side weakening, slurred speech, spinning, and severe headache. The BEFAST stands for balance loss, eyes (disturbance of vision), face drop, arm weakness, speech slur, and time to call an ambulance.

Diagnosis

Time from the onset is the most important factor in stroke diagnosis and management. The sooner the stroke is recognized and its type is identified, the sooner therapy can be initiated and the better the overall prognosis. Diagnosing stroke is one of the most fundamental skills any physician should have. Lately, the NIH stroke scale has taken a great role in the clinical assessment of stroke probability in patients, especially since it assesses the patient’s multiple clinical points. This scale addresses the patient’s level of consciousness, vision of the patient (demonstrated by horizontal eye movements and visual field), facial palsy, motor function extremities, ataxia, sensations, speech dysarthria, or aphasia, and attention to multiple types of stimuli. The scoring goes from 0 (which indicates a normal function) up to 3 or 4 (no or absent function) constituting of a total of 42 points. Moreover, the score is based on ranges going from 0 (no stroke symptoms), 1-4 (minor stroke probability), 5-15 (moderate stroke probability), 15-20 (moderate to severe stroke probability), and 21-42 (severe stroke probability) [20]. However, every clinician must have the differential diagnoses of stroke in the back of his/her mind in order not to miss any other possible causes. The most common differential diagnoses are TIA, cerebral venous

thrombosis, meningitis, subarachnoid hemorrhage, seizure, systemic infection, brain tumors, and toxic-metabolic disorders (e.g. hyponatremia and hypoglycemia) [21].

Imaging studies are the next step in the diagnosis; it must be as urgent as possible. Recently, a non-contrast CT scan has become the mainstay in stroke suspected patients as it immediately differentiates between hemorrhagic and ischemic strokes. Moreover, Multimodal CT imaging, with CT angiography and perfusion, has proven essential as it can identify possible large vessel occlusions and, most importantly, the areas of salvageable tissue that can be targeted and followed up. Imaging should be done within a 20-minute period after the arrival of the patient to the emergency department in at least half the patients. Another important imaging modality is MRI with angiography (MRA), which can provide much more structural details, detect acute intracranial hemorrhage, and detect early cerebral edema. However, MRA is used less due to a multitude of reasons, mainly since it is not always available in emergency departments. Also, MRI is increasingly becoming not feasible in most old patients due to pacemakers and implants in patients. Moreover, MRA is much more difficult to interpret compared with CT [22].

Carotid duplex is becoming used more recently and much earlier in the management process in order to define the cause behind the stroke. If severe carotid stenosis was diagnosed early, it can guide clinicians in choosing the medical or the surgical pathway. However, digital subtraction angiography remains a definitive method for recognizing different vascular lesions including stenosis, dissections, and aneurysms. Moreover, transcranial Doppler ultrasonography is used to evaluate proximal vascular anatomy, for instance, middle cerebral artery (MCA), intracranial carotid artery, and vertebrobasilar artery [23, 24]. Other radiographic modalities can be utilized to determine the cause of the stroke provided it does not delay the treatment. These include echocardiography, which is done when cardiogenic embolism is suspected, and chest radiography. Single-photon emission CT (SPECT) scanning in stroke patients is indicated to further define areas of altered regional blood flow. However, it is used exclusively in selected institutions [25, 26].

Conventional angiography remains the gold standard investigation in evaluating cerebrovascular disease, and also diseases involving the great vessels and aortic arch in the neck. It can be done to confirm and treat disease or to clarify equivocal findings observed on ultrasonography, transcranial Doppler, CTA, or MRA of the neck [27]. On another note, blood tests are crucial in these patients in order to stabilize them and even diagnose the possible pathologies behind the stroke. A complete blood count (CBC) should be ordered immediately in order to establish a baseline study. Furthermore, its result can be of great help in exposing the cause of the stroke in cases where thrombocytosis, thrombocytopenia, polycythemia, and leukemia are the culprit. Moreover, CBC can identify possible concurrent illnesses that may affect the reperfusion approach in cases of thrombocytopenia. Electrolyte are of utmost importance since it can detect stroke-like conditions such as hypoglycemia and hyponatremia. Also, it is useful to establish a baseline and detect concurrent diseases. Coagulation studies are crucial in these patients especially when fibrinolytics or anticoagulants are intended to be used. Cardiac biomarkers can be ordered when suspecting the origin of the stroke to be due to myocardial infarction. Additionally, the elevation of these markers has been associated with poorer prognosis in many studies [28]. If fibrinolytic therapy is considered, arterial blood gas studies are contraindicated since arterial punctures should be avoided when using fibrinolytic agents unless it absolutely necessary and under supreme care. Lumbar puncture can be done to rule out other differential diagnoses, for instance meningitis or subarachnoid hemorrhage if CT negative for stroke. Urine pregnancy test must be ordered to all women of child bearing age. This is due to the questionable safety of fibrinolytic agent recombinant tissue-type plasminogen activator (rt-PA) as it is classified as a class C drug in pregnancy. Other tests like toxicology screening, antinuclear antibody (ANA), rheumatoid factor, homocysteine levels can be taken if the clinician has a high suspicion for a cause of the stroke or to rule out differential diagnosis that may be identified via such tests.[29]

Management

The main concept in the management of stroke is to be as fast as possible since time is the most crucial factor. Stroke patients lose up to 1.9 million brain cells per minute and 14 billion synapses in the setting of ischemic stroke. Always remember that time = brain tissue [30].

Management of ischemic stroke used to be a “wait and see” but it has changed drastically over recent years. It has been modified and updated into a more active approach thanks to medical advancements. New modalities of treatments have been implemented due to these breakthroughs. In addition, intravenous thrombolysis, endovascular therapy (EVT), and mechanical thrombectomy had shown very efficient results in treating patients. Nevertheless, the principal aims in treatment revolve around reducing mortality and improving quality of life after survival, which are dependent on good and early management. Moreover, the hospital stay is influenced by the onset-to-arrival time. The earlier the patient arrives at the hospital, the shorter the stay for patients in the hospital [29].

In the emergency setting, clinicians should always focus on the ABC approach to achieve hemodynamic stability of the patients. The patient’s airway, breathing, and circulation must be assessed and managed accordingly in order to advance in the management of these cases. Some large strokes, and/or posterior circulation strokes, may present with bulbar dysfunction, loss of consciousness, and respiratory distress. Physicians must never let these patients desat and intubation should be thought of immediately if the airway was not protected or a ventilator support need is arising. As per protocols, before initiating thrombolytic treatment, a finger stick glucose test must be done and a non-contrast CT scan to determine whether the stroke is hemorrhagic or not.

However, if the patient has any history of a bleeding disorder, using anticoagulants, and/or history of thrombocytopenia extra tests might be indicated including electrocardiogram, CBC, Troponin, PT, INR, aPTT, ecarin clotting time, thrombin time, and direct factor Xa activity assay if the patient started taking oral anticoagulants recently [29].

The general management approach afterward depends on the time of onset of symptoms, which is why it is critical to present as soon as possible in order to take advantage of this "golden" window. CT is indicated immediately once the patient is stable. However, it depends on the patient's time of presentation. If the patient presents within first 6 h of symptoms onset, a CT scan should be combined with the CT angiogram of the brain and neck to rule out large vessel occlusion. Moreover, MRI or MR angiogram or MR perfusion is not indicated within the first 6 hours of symptom onset. CT angiogram should not be delayed to wait for serum creatinine and whenever possible the angiogram should be completed with the CT scan to save time for possible mechanical intervention [31].

Treatment Modalities

The main modalities available form of treatment are intravenous thrombolysis and mechanical thrombectomy. Choosing a treatment depends on the patient's condition [30].

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) remains the cornerstone to improve patient outcomes in acute ischemic stroke. Thrombolytic agents act by aiding in clot dissolution and timely restoration of the blood flow to the ischemic brain tissue. Thus, preventing the death of neurons and lead to clinical improvement [32]. Thrombectomy was introduced after thrombolytics in the treatment regimen. It is used as an adjunctive tool in the treatment of cerebral aneurysms with detachable stents. However, its usage as endovascular thrombectomy was halted lately due to recent publications. Those papers have shown that endovascular treatment showed no significant improvement compared with intravenous treatment alone. However, after 2015, numerous RCTs obviously confirmed the benefits of using endovascular thrombectomy on the clinical outcomes of patients with stroke, in comparison to the patients who received standard medical care only [28].

Endovascular recanalization treatment is the major therapy of acute ischemic stroke because of large vessel occlusion. Neuroimaging is mandatory for an appropriate selection of patients for endovascular therapy (EVT). The use of advanced neuroimaging techniques in the form of DWI MRI, MRI perfusion, and CT, leads to the selection of wake-up stroke with large vessel occlusion for EVT or patients with late-presenting (>6h), or. However, its indications for the management of acute stroke are not fixed and are subject to change especially with the development of new and current recanalization techniques and devices [33]. In recent years, various recommendations have been issued for EVT with continuing revisions. European Stroke Organization (ESO)-Karolinska Stroke Update statements are regularly published and updated in collaboration with the European Society of Neuroradiology (ESNR) and the European Society for Minimally Invasive Neurological Therapy (ESMINT) [33]. It covered the treatment of acute stroke in patients with more than 85 years of age, EVT effect in patients with relatively unfavorable risk factors evidenced by the modified Rankin Scale (mRS) being more than 2, patients presenting beyond the golden period, and patients with unknown time of onset [33].

In-hospital mortality in patients suffering from ischemic stroke remains high. Patients tend to seek medical attention later than advised; This could contribute to poor prognosis. Increased creatinine in the serum was highly related to poorer prognosis in terms of in-hospital mortality. Several factors were identified to be related to in-hospital mortality upon bivariate analysis. However, serum creatinine and BUN were the only factors that predicted in-hospital mortality independently, with serum creatinine being associated with more than an eightfold increase in in-hospital mortality [28].

Some specific types of ischemic stroke are associated with poorer outcomes compared with other types. Acute ischemic stroke in the posterior circulation is associated with poor prognosis with the latest standard medical therapy. Basilar artery occlusion (BAO), a form of posterior circulation stroke, results in higher rates of in-hospital mortality and poor recovery of normal functions if not recanalized. A systematic analysis of BAO patients treated with the latest standard medical therapy found that, without recanalization, only 2% of patients were likely to have a good outcome [34].

In practice, most hospitals are influenced by pragmatic factors that may affect the implementation of the latest stroke treatment guidelines. These factors include the local stroke treatment expertise, the availability of stroke specialists, and the local healthcare infrastructure and organization [33].

Conclusion

Stroke is one of the most fatal and common diseases that is faced almost daily. Our understanding of its pathology pathophysiology does not only directly impact patients' life but also their environment exemplified by their families and close ones and our society as a whole. Therefore, lowering the overall mortality and morbidity is critical in these cases. It can be simply by the early detection of stroke signs and symptoms and immediately requesting medical help. This is especially true since many options of treatment significantly improve outcome when early given. On another note, many new options are being heavily studied and may, in the near future, prove to be the most needed breakthroughs in dealing with one of the greatest causes of mortality and morbidity around the world.

References

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976;54(5):541-53.
2. Ahmed HG, Alquwaiay FK, AlDhamadi HF, Alquwaiay DA, Alshammari A, Alsunitan HH. Stroke-associated comorbidities in Saudi Arabia. Int. J. Pharm. Res. Allied Sci. 2020;9(2):91-8.
3. Hosseinzadeh SA, Mazhari S, Najafi K, Ahmadi M, Aghaei I, Niazi M, Shabani M. Impact of Anodic Transcranial Direct Current Stimulation (TCDS) on Changes in Movement and Life–Related Functions in Patients with Chronic Ischemic Stroke: A Clinical Trial. Entomol. Appl. Sci. Lett. 2018;5(3):13-20.
4. Ahmed GM, Fahmy EM, Elkholy SH, Semary M, Mohammed AA, Badawy WM. Cortical activation after constraint induced movement therapy in stroke patients: A randomized controlled trial. J. Adv. Pharm. Educ. Res. 2018;8(3):24-9.
5. Areshidze DA, Mischenko DV, Makartseva LA, Kucher SA, Kozlova MA, Timchenko LD, Rzhepakovsky IV, Nagdalian AA, Pushkin SV. Some Functional Measures of the Organism of Rats at Modeling of Ischemic Heart Disease in Two Different Ways. Entomol. Appl. Sci. Lett. 2018;5(4):19-29.
6. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67-e492.
7. Malhotra K, Gornbein J, Saver JL. Ischemic Strokes Due to Large-Vessel Occlusions Contribute Disproportionately to Stroke-Related Dependence and Death: A Review. Front Neurol. 2017;8:651.
8. The top 10 causes of death. Fact sheets [Internet]. 2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
9. Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. Int J Stroke. 2012;7(5):378-85.
10. Lipton P. Ischemic cell death in brain neurons. Physiol Rev. 1999;79(4):1431-568.
11. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci. 2003;4(5):399-415.
12. Aarts M, Iihara K, Wei WL, Xiong ZG, Arundine M, Cerwinski W, MacDonald JF, Tymianski M. A key role for TRPM7 channels in anoxic neuronal death. Cell. 2003;115(7):863-77.
13. Sen N, Hara MR, Ahmad AS, Cascio MB, Kamiya A, Ehmsen JT, Aggrawal N, Hester L, Doré S, Snyder SH, Sawa A. GOSPEL: a neuroprotective protein that binds to GAPDH upon S-nitrosylation. Neuron. 2009;63(1):81-91.
14. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. Stroke. 2009;40(3 Suppl):S40-4.
15. Famitafreshi H, Karimian M. Overview of the Recent Advances in Pathophysiology and Treatment for Autism. CNS Neurol Disord Drug Targets. 2018;17(8):590-4.
16. Chugh C. Acute Ischemic Stroke: Management Approach. Indian J Crit Care Med. 2019;23(Suppl 2):S140-s6.
17. Maïer B, Kubis N. Hypertension and Its Impact on Stroke Recovery: From a Vascular to a Parenchymal Overview. Neural Plasticity. 2019;2019:6843895.
18. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):15-39.
19. Lasek-Bal A, Kopyta I, Warsz-Wianecka A, Puz P, Łabuz-Roszak B, Zaręba K. Risk factor profile in patients with stroke at a young age. Neurol Res. 2018;40(7):593-9.
20. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke. 1994;25(11):2220-6.
21. Runchey S, McGee S. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. Jama. 2010;303(22):2280-6.
22. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46-e110.
23. Camerlingo M, Casto L, Censori B, Ferraro B, Gazzaniga GC, Mamoli A. Transcranial Doppler in acute ischemic stroke of the middle cerebral artery territories. Acta Neurol Scand. 1993;88(2):108-11.
24. Sorensen AG, Copen WA, Østergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology. 1999;210(2):519-27.
25. Sagar G, Riley P, Vohrah A. Is admission chest radiography of any clinical value in acute stroke patients? Clin Radiol. 1996;51(7):499-502.
26. Meerwaldt R, Slart RHJA, van Dam GM, Luijckx G-J, Tio RA, Zeebregts CJ. PET/SPECT imaging: From carotid vulnerability to brain viability. European Journal of Radiology. 2010;74(1):104-9.
27. Vilela P, Rowley HA. Brain ischemia: CT and MRI techniques in acute ischemic stroke. Eur J Radiol. 2017;96:162-72.
28. Gebreyohannes EA, Bhagavathula AS, Abebe TB, Seid MA, Haile KT. In-Hospital Mortality among Ischemic Stroke Patients in Gondar University Hospital: A Retrospective Cohort Study. Stroke Research and Treatment. 2019;2019:7275063.
29. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, de Leeuw FE. Epidemiology, aetiology, and management of ischaemic stroke in young adults. Lancet Neurol. 2018;17(9):790-801.
30. Saver JL. Time is brain--quantified. Stroke. 2006;37(1):263-6.
31. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology. 1999;210(1):155-62.
32. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine. 1995 Dec 14;333(24):1581-8.
33. Van der Zijden T, Mondelaers A, Yperzeele L, Voormolen M, Parizel P. Current concepts in imaging and endovascular treatment of acute ischemic stroke: implications for the clinician. Insights into Imaging. 2019;10(1):64.
34. Sun X, Tong X, Gao F, Lao H, Miao Z. Endovascular treatment for acute basilar artery occlusion: a single center retrospective observational study. BMC Neurology. 2019;19(1):315.