INTERNATIONAL MULTIDISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
SJIF 2019: 5.222 2020: 5.552 2021: 5.637 2022:5.479 2023:6.563 2024: 7,805
eISSN :2394-6334 https://www.ijmrd.in/index.php/imjrd Volume 11, issue 05 (2024)

POST-STROKE COGNITIVE DISORDERS AND BIOMECHANICAL EFFECTS OF STROKE

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Abstract: Stroke is a leading cause of adult disability, affecting millions of people globally. The cognitive and motor impairments resulting from stroke diminish the quality of life and functional independence of those affected. There is an increased risk of a second stroke, as well as the development of secondary conditions with long-term social and economic implications. With the increasing number of stroke events, the shortage of medical professionals and the limited budgets of healthcare systems, these services struggle to provide the care needed to break the cycle of stroke.

Key words: Post-stroke, biomarker, neurological, rehabilitation.

Effective post-stroke care hinges on a holistic, integrated, and personalized approach, starting from improved diagnostics and treatment in clinical settings, to ongoing rehabilitation and community support[1]. To enhance stroke care pathways, efforts are underway to discover biomarkers that could provide valuable insights into the neurological, physiological, and biomechanical effects of stroke, as well as how patients respond to different interventions.In this review paper, we aim to summarize recent research on biomarker discovery, focusing on three main modalities: brain imaging, blood sampling, and gait assessments. We will look at both established and emerging biomarkers, discuss their potential usefulness and complementarity in the context of stroke care, and emphasize the importance of personalized interventions guided by biomarkers to enhance treatment and post-stroke recovery.[2]

Stroke is a complex neurological disorder, and its impact on patients varies depending on a variety of factors. These factors include the severity of the stroke, the area of the brain affected, the brain's ability to adapt (neuroplasticity), treatment options available, timely interventions such as physiotherapy and rehabilitation programs, community support from family and friends, comorbidities, as well as the patient's self-efficacy, motivation, and physical condition. Due to this complexity, it can be difficult to predict long-term outcomes for patients with stroke, and two patients with similarly severe strokes may experience different clinical and functional outcomes.[3]

Stroke biomarkers have already started revolutionizing stroke care from diagnosis to clinical outcome prediction and recovery monitoring. Notably, many of these biomarkers come from three modalities: brain imaging, analysis of blood samples and gait measurement. Brain imaging biomarkers are used for early diagnostics, confirming stroke and determining whether it is ischemic or hemorrhagic [4-9]. They are also useful for prognosis and studying neuroplasticity. Blood biomarkers, although not utilized for diagnostic purposes yet, can be useful for detection of comorbidities and evaluating the risk of post-stroke treatment complications and secondary conditions. Gait and mobility biomarkers, offering valuable information about patients' independence and quality of life, can be used for estimating fall risk, evaluating the effectiveness of rehabilitation programs and detecting undesired behaviors (e.g., prolonged sitting).

Here, we aim to provide a comprehensive, up-to-date review of post-stroke brain imaging (mainly focusing on magnetic resonance imaging), blood and gait biomarkers with an emphasis on their complementarity and potential integration for improving stroke care pathways. In this review, we focus on (i) ischemic stroke, (caused by restricted or blocked blood flow) which constitutes 70% of all stroke incidents, and (ii) post-stroke gait and balance disorders which affects almost 80% of patients. COVID-19 created significant hardships and challenges to clinics and patients in almost every aspect of stroke care from diagnosis to management, and long-term rehabilitation [7]. While there is evidence that COVID-19 might have increased the ischemic stroke risk by 3.6 times,the number of hospital admissions due to ischemic stroke decreased by 15% during the first 3 months of COVID-19. This is thought to be a result of the unwillingness of patients to go to a hospital due to the fear of contracting the virus. Due to extremely time-sensitive nature of ischemic strokes, the value of remote monitoring and telemedicine has become clear to medical professionals. Remote technologies utilizing accessible tools like smartphones can be helpful in monitoring recovery of the patients more effectively and avoiding complications by enabling expert medical attention to patients. Incorporating objective and quantitative biomarkers for remote monitoring systems will introduce immense medical information for medical professionals.

Biomarkers obtained from imaging, biochemical and biomechanical measurements combined with clinical assessments can allow for objective and reproducible evaluation and monitoring of the patient. Yet, there is still no established integrative approach to specific biomarkers that is commonly utilized in the clinics[9].

Blood biomarkers can be used for a variety of applications following stroke, including diagnosis and identification of stroke subtypes, predicting clinical outcomes, selecting personalized treatments for patients, and monitoring recovery. However, as the search for finding a specific blood biomarker continues, it is becoming clearer that a single marker will probably not be adequate in capturing the heterogeneity of stroke and its systemic effects. Hence, integrating various techniques and approaches will be necessary to define a comprehensive and global biomarker system for stroke.[9] Some of the promising cutting-edge blood biomarker candidates for predicting clinical outcomes post-ischemic stroke. Post-stroke epilepsy is seen in 2–20% of patients with stroke. Following an ischemic stroke, hypoxia, hypoperfusion, glutamate excitotoxicity and BBB disruption may lead to seizures, with cortical lesions carrying a higher risk. Most common post-stroke epilepsy predictors are related to ischemic lesion size and location. In more recent studies, researchers are trying to pinpoint some blood biomarkers to better understand and diagnose post-stroke seizures and epilepsy. In a study including 14 blood biomarkers and 895 acute stroke patients, decreased S100B and heat shock 70 kDa protein-8 (Hsc70) and increased endostatin levels were found to be associated with increased risk of developing post-stroke epilepsy[10]. Hsc70 is involved in the synthesis of proteins important in BBB structure and functioning, whereas endostatin acts as an angiogenesis inhibitor that may damage cellular repair at higher levels. Neuropeptide Y is an important antiepileptic factor that is being researched as a therapeutic agent for epilepsy. Decreased neuropeptide Y levels were also predictive of post-stroke epilepsy in 164 patients with acute ischemic stroke whereas there was no correlation between hemorrhagic transformation and the levels of neuropeptide [11].

Post-stroke cognitive impairment is another complication that can be experienced following stroke. 64% of people post-stroke suffer from some type of cognitive impairment including dementia, depression, and memory impairment. CRP was found to be an important predictor of long-term cognitive decline in a study of 5257 subjects. Additionally, higher levels of CRP were associated with an increased risk of post-stroke depression. In a smaller study, lower serum BDNF levels, and higher serum amyloid-beta levels were indicative of increased cognitive impairment risk post-stroke. Increasing levels of plasma trimethylamine-N-oxide were also found to be correlated with the risk of cognitive impairment. Increased plasma endostatin levels and serum uric acid levels are also able to suggest an increased cognitive impairment.[12]

Various clinical instrumented assessment and rehabilitation techniques have been used in post-stroke patients. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that can be used in post-stroke rehabilitation as part of recovery focused on re-learning lost skills and regaining independence as much as possible. When this technique is applied superficially to the primary motor cortex, it stimulates the corticospinal pathway, generates a motor-evoked potential (MEP) at the contralateral limb, and elicits an MEP in muscles of the contralateral limb.The presence or absence of MEPs provides information about the functional integrity of the corticospinal tract. The amplitude and latency of the MEPs are considered as measures of the corticomotor system excitability[13].

In recent years, the use of TMS in stroke research has increased dramatically to treat motor function, depression, and aphasia in post-stroke patients. While single pulse TMS can predict the post-stroke recovery of motor function, repetitive TMS (rTMS) can be used to modify the excitability of the motor cortex to complement standard rehabilitation techniques. Motor training, together with rTMS, optimizes plastic changes in the brain and strengthens the benefits of physical exercise. Following stroke, the high incidence of depression is known. Patients may benefit from rTMS because this procedure significantly improves the mood and depression symptoms[14]. Functional electrical stimulation (FES) is a non-invasive technique which is used to stimulate muscles during rehabilitation. The FES was shown to improve gait function when implemented along with a gait training protocol The FES can be combined with electromyography (EMG) to evaluate improvements in muscle activation and provide real time feedback to patients and clinicians. It has been previously shown that the EMG based acoustic feedback can aid in increasing peak ankle power, gait velocity and stride length in chronic stroke. A vibrotactile biofeedback system consisting of an insole, a plantar force acquisition unit, and a vibration feedback unit was also helpful in reducing the foot inversion on the affected side and knee flexion and hip abduction on the unaffected side [15]. (EEG) is used in clinics to record brain activity during various conditions, including epileptic seizures, but it has not yet been widely utilized for gait rehabilitation or clinical assessments following stroke[14]. Few research studies show that gait kinematics and intent can be decoded from EEG signals, informing robot-assisted gait training[12] Extracorporeal shock wave therapy (ESWT) uses a probe to deliver high-energy shock waves to the selected tissue. A study investigating the effects of ESWT found that lower limb spasticity in subacute stroke patients was improved after ESWT, but the improvement was not long-lasting and diminished after four weeks [13], virtual reality can provide a safe, controlled and fun environment for rehabilitation. Home-based individual post-stroke rehabilitation techniques with portative devices gain popularity due to their low cost and ease of accessibility. These devices rely on novel balance and motion-sensing technologies and wearable devices developed utilizing either inertial measurement units such as accelerometers, force sensors, goniometers, inclinometers, gyro sensors, strain gauges or plantar pressure sensors.

Such devices can be worn over or attached to the various parts of the patient's body, like pressure sensors located inside footwear or body-weight accelerometers installed

Stroke can be experienced as ischemia and haemorrhage, and the effect of stroke depends largely on the duration of abnormal blood flow, and the location of the stroke in the brain. The structure of the lesion, levels of blood biomarkers, gait impairments, and psychological and social well-being of the patient before and after stroke, all have implications for the clinical outcome of the patients. When the heterogeneity of strokes in terms of symptoms and severity is considered, the necessity to implement an interdisciplinary approach to investigate the disease becomes clearer. In the future, developing smart systems supported with artificial intelligence enhanced by inputs from various modalities to assist medical professionals is promising for better patient care, and will be very valuable in clinical settings. Here, we attempted to offer a general overview of the functions of various modalities for stroke diagnosis, treatment, and management. We wish to highlight the integrative perspectives for the amelioration of the diagnosis and prognosis of patients with stroke.

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