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EDITORIAL

Role of biomarkers in stroke neurorehabilitation – an important tool to help predict recovery

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Stroke is a leading cause of disability, especially in the Indian subcontinent. While rehabilitation promotes recovery through neuroplasticity and motor learning, individual factors like biomarkers are gaining attention for their predictive value. Genetic markers such as **Brain Derived Neurotrophic Factor (BDNF)**, **Catechol-o-Methyltransferase (COMT)**, and **Apolipoprotein E (APOE)** influence recovery, with **BDNF Val66Met** linked mainly to poorer upper limb motor outcomes. Neurophysiological and imaging biomarkers, including **motor evoked potentials** and **diffusion-weighted magnetic resonance imaging (MRI)**, help predict motor recovery and inform tools like the **predict recovery potential 2 (PREP2)** algorithm. Blood-based biomarkers, particularly those in the **kynurenine pathway**, are associated with cognition and post-stroke depression, offering potential treatment insights through repetitive transcranial magnetic stimulation (rTMS). Overall, biomarkers may enable more personalized rehabilitation, but larger, context-specific studies are needed to confirm their role across motor, language, and cognitive recovery.

Keywords: stroke recovery, neurorehabilitation, biomarkers, prognostic indicators, functional outcomes

Stroke continues to be a leading cause of morbidity worldwide and especially in the Indian subcontinent (1). Along with medical management, the provision of rehabilitation services helps enhance recovery after stroke. In addition to mechanisms of spontaneous recovery, improvements seen after stroke can be attributed to adaptive neuroplasticity and motor learning (2). Traditionally, research has focused on factors related to the type, dose, and fidelity of the intervention provided. Recently, there has been a renewed focus on the role of individual-related factors, including the role of biomarkers (3). Stroke-related biomarkers are defined as "*indicators of disease state that can be used clinically as a measure reflecting underlying molecular and cellular processes that may be difficult to measure directly in humans and could be used to predict recovery or treatment response* (4)." Biomarkers addressed in the field of stroke recovery and rehabilitation includes those based on biology (e.g., genetics and blood-based levels), structural and/or functional imaging, and neurophysiological markers of central nervous system excitability and electrical activity (3).

The role of genetics-based biomarkers in predicting post-stroke recovery varies depending upon the area of rehabilitation addressed. Genes most commonly studied in the field of stroke rehabilitation include Brain Derived Neurotrophic Factor (BDNF), Catechol-o-Methyltransferase (COMT), and Apolipoprotein E (APOE). A common polymorphism consists of one or both valines replaced with methionine in BDNF (val^{66}met, met^{66}met) and COMT (val^{158}met, met^{158}met). A polymorphism in APOE involves replacement of cystine by arginine (APOEε4). Individuals with a polymorphism in BDNF have lower levels of general stroke recovery, measured using the National Institutes of Health (NIH) Stroke Scale or Modified Rankin Scale. Individuals post-stroke with polymorphisms in BDNF and COMT have lower levels of upper limb (UL) motor

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improvement compared to those without the polymorphism. The presence of APOEε4 polymorphism does not influence UL motor improvement levels (3). In the same vein, polymorphisms in BDNF do not negatively influence recovery of naming in post-stroke aphasia (5) or walking ability after stroke (6). Additionally, the replacement of valine with methionine does not negatively influence improvements in cognition, expression, and comprehension after stroke (7). Thus, the effects of genetically based polymorphisms seem to be related most strongly to UL motor improvement. Given the preponderance of BDNF polymorphisms in the Southeast Asian population, the role of ethnicity should be additionally considered (3).

Both neurophysiological and imaging-based biomarkers are individually useful in predicting improvements in gait and UL motor impairment and activity levels (6). Similarly, imaging-based biomarkers are useful in predicting recovery in cognition and aphasia (8). A combination of neurophysiological and imaging-based biomarkers has been found to be useful for predicting improvements in UL activity levels (6). A clinical prediction algorithm, predict recovery potential 2 (PREP2), has been developed combining neurophysiological and imaging-based biomarkers (6). The strength of shoulder abductors and wrist extensor muscles is the first step to help predict excellent or good improvement in UL functional capacity (combined muscle strength ≥5/10).

In case the muscle strength is <5/10, the presence of motor evoked potential (obtained by use of transcranial magnetic stimulation) in the wrist extensors suggests good recovery potential. In the absence of a motor evoked potential, diffusion-weighted magnetic resonance imagings (MRIs) are used, and fractional anisotropy values are calculated. Fractional anisotropy values <0.15 indicate the potential for at least limited recovery. If values are ≥0.15, then recovery is poor. Similar results have been found while combining motor evoked potentials (MEPs) and anatomical connectivity measures for predicting recovery from aphasia (9). However, it has not yet been proven to be effective for lower limb recovery after stroke. A previous approach for prediction of independent walking after stroke revealed that use of clinical measures alone was useful to predict recovery of walking, with no additional benefits of using imaging outcomes or measures of corticospinal integrity.

In terms of blood-based biomarkers, there is an increasing focus on the role of the kynurenine pathway, which plays a role in tryptophan metabolism. The kynurenine pathway is initiated by the breakdown of tryptophan into kynurenine by indoleamine 2,3-dioxygenase 1 (IDO). In healthy individuals, kynurenine is further degraded into greater amounts of kynurenic acid (KNA), which is neuroprotective, via kynurenine aminotransferase (KAT) activity and lesser amounts of other neurotoxic metabolites, including 3-hydroxy kynurenine and quinolinic acid (QA). After a stroke, there is an increased breakdown of kynurenine into the neurotoxic components, with lower levels of neuroprotective KNA and KAT (10). Lower levels of global stroke recovery assessed using the NIH Stroke Scale and global cognition assessed using the Mini Mental Scale Examination are also associated with greater IDO activity (10).

Previous studies have shown that individuals with post-stroke depression have higher levels of 3-hydroxy kynurenine. One of the non-pharmacological evidence-based treatments for post-stroke depression involves the use of repetitive transcranial magnetic stimulation (rTMS). One previous study (11) has shown that provision of rTMS to the non-lesioned hemisphere (i.e., inhibitory rTMS) influences the kynurenine tryptophan ratio. This has potential implications for treatment as well, as a potential marker for recovery or to better understand reasons behind a lack of improvement seen.

While some studies have been performed using different types of biomarkers, there is still a long way to go. It is an interesting field that has implications for helping personalize rehabilitation delivery. Planning of appropriate types of interventions based upon biomarker profiles can be seen as one way forward. However, these studies need to be replicated, especially in different contexts. Given that factors including sex, ethnicity, extent, and severity of initial insult, as well as other known and unknown confounding factors, the role of these factors will also need to be studied. There is a remarkably interesting list of questions that still need to be answered. Answers to these questions will help us better understand the utility of biomarkers to help better predict stroke recovery levels, especially in areas like walking recovery, aphasia, and cognition.

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Conflict of interest

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