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Research report

Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury

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HIGHLIGHTS

- Motor recovery after stroke is a multifactorial and dynamic process.
- Advanced age, African American race, and female gender are major socioeconomic factors affecting stroke recovery.
- Extent of initial injury after stroke is a major independent predictor of recovery.
- Neurorehabilitation strategies provide a unique opportunity for enhancing recovery.
- Genetic polymorphisms especially in BDNF may influence post-stroke recovery process.

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ABSTRACT

Neurological disorders are a major cause of chronic disability globally among which stroke is a leading cause of chronic disability. The advances in the medical management of stroke patients over the past decade have significantly reduced mortality, but at the same time increased numbers of disabled survivors. Unfortunately, this reduction in mortality was not paralleled by satisfactory therapeutics and rehabilitation strategies that can improve functional recovery of patients. Motor recovery after brain injury is a complex, dynamic, and multifactorial process in which an interplay among genetic, pathophysiologic, sociodemographic and therapeutic factors determines the overall recovery trajectory. Although stroke recovery is the most well-studied form of post-injury neuronal recovery, a thorough understanding of the pathophysiology and determinants affecting stroke recovery is still lacking. Understanding the different variables affecting brain recovery after stroke will not only provide an opportunity to develop therapeutic interventions but also allow for developing personalized platforms for patient stratification and prognosis. We aim to provide a narrative review of major determinants for post-stroke recovery and their implications in other forms of brain injury.

1. Introduction

Stroke has declined to the fifth most common cause of death in the United States after devoting extensive efforts for controlling stroke risk factors and optimizing acute care of stroke patients [1]. However, stroke remains a leading cause of disability among adults in the United States and globally [1–3]. Of the estimated 800,000 strokes that occur in the US per year, the majority of stroke survivors develop long-term functional deficits [1]. The NINDS sponsored r-tPA trials have reported that the percentage of patients that still had mild to moderate functional deficits (Modified Rankin Scale of 2–5) at 3 and 12 months after a stroke were 44% and 35%, respectively, despite the fact that they received r-tPA in the acute phase [4,5]. Although these functional deficits may include cognitive, speech, visual, sensory and motor deficits, the most commonly recognized deficit after stroke is motor impairment that have negative impact on subject's mobility and quality of life [5].

Functional deficits after stroke are also associated with huge financial burden on the patient, family, and society. It is estimated the average lifetime cost of caring for one stroke patient (across all stroke sub-types) was about $103,576 in 1990 which included the cost of acute care, long-term ambulatory care, and nursing home

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care [6]. The overall financial cost of post-stroke management of patients as well as the demand on rehabilitation therapy has also increased with the increase in numbers of stroke survivors reaching an annual total of $3.4 billion in the US [1].

Post-stroke motor recovery is a complex, dynamic, and multifactorial process in which an interplay among genetic, pathophysiologic, sociodemographic and therapeutic factors determines the overall recovery trajectory. Therefore, rehabilitation strategies that aim to improve post-stroke recovery outcomes require a thorough understanding of those major determinants. In this paper, we review the major factors influencing post-stroke motor recovery and its implication for neurotherapy after brain injury. We categorized those factors into three groups socio-demographic factors (age, gender, race, socio-economic status and others), clinical factors (the initial injury, co-morbidities, post-stroke depression and rehabilitation therapeutics), and genetic factors (Fig. 1).

2. Socio-demographic factors

2.1. Age

Older age is commonly identified as a significant prognostic factor for poorer outcome after ischemic and hemorrhagic stroke where nearly half of older stroke survivors experience mild-to-severe disability [7–11], However, the proposed prognostic value of age have been challenged by studies on long-term recovery [12,13]. Whereas age may be an independent predictor of early outcomes after stroke [14–16], the effect of age on long-term outcome measures is less pronounced and may have minimal clinical relevance after adjustment of other factors in regression analysis [12,17]. Therefore, the influence of age on post-stroke recovery should be distinguished from age-associated factors to assess for the independent prognostic value of age alone. Age-associated confounding factors including co-morbidities and social variables should be taken into consideration before interpretation.

2.2. Gender

Females appear less likely to achieve complete functional independence and/or are more likely to be disabled after stroke than male [18–20]. The underlying causes behind this gender difference are not fully understood, but women are more likely to suffer depressive symptoms [21] and fatigue [22] that can indirectly have negative impact on recovery. A gender-age interaction has been hinted as post-stroke outcomes are actually better in young females as compared to young males [14]. However, this has been challenged by studies reporting lower overall quality of life in female stroke survivors compared to males regardless of age [20,23].

2.3. Race

Compared to Whites, Blacks have significantly higher stroke incidence [24], less access to acute therapy [25], higher stroke mortality [26], greater initial stroke severity [27], and higher stroke recurrence [24]. Given the racial variation in co-morbidities, initial stroke severity and rehabilitation service utilization, it is logical to infer the presence of racial variation in post-stroke recovery outcomes. In general, Blacks, along with other minorities, have been shown to have poorer stroke outcomes when compared to Whites [28,29]. Nonetheless, racial disparities with regard to post-stroke recovery and rehabilitation remains poorly characterized [30,31]. It is still unclear whether Blacks and Whites follow different post-stroke recovery patterns regardless of associated socioeconomic racial disparities. Horner et al. has demonstrated a difference in the trajectory of functional recovery between Blacks and Whites stroke survivors even when there were no major disparities between the two groups in terms of access to or utilization of rehabilitation services [29]. Blacks tend to have greater functional impairment acutely and appear to improve slowly; however, within 3–6 months they reach the approximate activity of daily living (ADL) capacity of their Whites counterparts. Some studies have also reported racial variation in the detection of post stroke depression (PSD) showing that Whites are more likely to be diagnosed with PSD [32], even after controlling for socio-demographic and clinical characteristics. In addition, compared to Whites, Blacks are found to be less likely to accept or use antidepressants after stroke [33,34]. Collectively, these studies implicate racial disparities in altering post-stroke motor recovery especially when comparing Blacks and Whites; however, studies in this domain are still scarce, and there is a lack of focused and well-controlled studies comparing the effects of racial factors on stroke recovery.

2.4. Socioeconomic status (SES)

Several indicators are used as surrogate measures of SES (e.g., insurance status, education level, household income). SES is also tied with racial factor as Blacks, and other minority groups, have a relatively lower SES. Being uninsured or underinsured may delay or prevent the process of getting access to rehabilitation services and is likely to be associated with poorer recovery outcomes [35]. Higher educational level was significantly associated with a better motor and functional recovery during the inpatient rehabilitation period while income level was only associated with rehabilitation care after discharge from a rehabilitation facility [36]. From a global perspective, socioeconomically deprived individuals in low-, middle- and high-income countries are reported to have higher stroke incidence and poorer short and long-term outcomes after stroke [37]. The most likely underlying reasons for SES-based disparities is the lack of equal access to general healthcare as well as rehabilitation services. It is noteworthy that individuals of lower SES are also more likely to have co-morbidities and cerebrovascular risk factors [37].

2.5. Other factors

While other factors, such as, caregiver support, marital status, disease awareness, mistrust, healthcare system access have been suggested as potential determinants in stroke recovery, additional studies are required to investigate whether these socio-demographic factors independently or collectively contribute to the outcome of stroke survivors [9,30,38].

3. Clinical factors

3.1. Stroke subtype

The two major subtypes of stroke, hemorrhagic and ischemic stroke, result in different patterns of acute and chronic recovery. In general, hemorrhagic stroke patients tend to have greater functional impairment at presentation. However, patients with ICH tend to have a more pronounced and faster recovery than those with ischemic stroke of comparable severity [39–41].

3.2. The initial injury

Although several reparatory and regenerative processes occur following stroke, the extent of initial injury is a major determinant of chronic recovery as it defines the residual neuronal reservoir that is capable to engage in functional recovery. Therefore, a more severe acute motor impairment is a predictor of more severe chronic deficits, and at the same time, successful thrombolytic therapy may limit initial injury and result in less severe chronic deficits.

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