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Peripheral *BDNF* gene expression before and after rehabilitation in ischemic stroke: A preliminary study

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Abstract

Background: Ischemic stroke is a leading global cause of disability, accounting for approximately 87% of all stroke cases. Rehabilitation strategies that promote neuroplasticity show promise in improving recovery outcomes, with increased expression of the brain-derived neurotrophic factor (*BDNF*) gene playing a key role in neuronal survival and synaptic plasticity. However, the effects of rehabilitation therapy on *BDNF* gene expression in ischemic stroke patients are rarely reported. This study aims to compare *BDNF* gene expression levels in ischemic stroke patients before and after rehabilitation. *Methods:* In brief, total RNA was extracted from ischemic stroke patients before (n = 43) and after (n = 22) rehabilitation and converted into cDNA. Out of the 22 post-rehabilitation ischemic stroke patients, only 16 were paired. *BDNF* gene expression levels of pre- and post-rehabilitation were measured using a quantitative real-time polymerase chain reaction. A Mann-Whitney U test was applied to compare overall *BDNF* expression levels in ischemic stroke patients, while a Wilcoxon Signed-Rank test was used to assess changes in *BDNF* expression in the 16 paired ischemic stroke patients who completed the rehabilitation therapy. *Results:* The results revealed a significant 3.81-fold increase in overall *BDNF* gene expression in post-rehabilitation ischemic stroke patients (p-value = 0.048), as determined by the Mann-Whitney U test. Notably, the Wilcoxon Signed-Rank test showed a highly significant 7.78-fold increase in *BDNF* expression in the 16 paired patients post-rehabilitation compared to pre-rehabilitation (p-value = 0.004).
Conclusions: The results support the potential of *BDNF* gene as a molecular marker of rehabilitation-induced neuroplasticity. These findings warrant further validation in larger studies integrating both molecular and clinical outcome measures.

Keywords: Ischemic stroke, rehabilitation therapy, brain-derived neurotrophic factor, gene expression

INTRODUCTION

Strokes continue to pose a significant global health challenge. A recent study reported that the majority of stroke burdens are concentrated in low- and middle-income countries (LMICs).[1] These regions were responsible for 83.3% of new stroke cases, 76.7% of existing cases, 87.2% of stroke-related deaths, and 89.4% of disability-adjusted life years lost to stroke. Ischemic stroke represented the most significant proportion of incident strokes worldwide, at 65.3%, followed by hemorrhagic stroke at 34.6%, with the remainder primarily consisting of transient ischemic attacks.[1] Given that over half of stroke cases are attributed to ischemic stroke, these findings highlight the urgent need for targeted

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interventions for ischemic stroke in LMICs.

Patients who have experienced stroke exhibit a wide range of clinical outcomes, including impairments in motor control, cognitive function, speech, and sensory processing, resulting from damage to neuronal cells in the brain. Many stroke survivors continue to experience persistent motor impairments, which significantly affect their ability to perform daily activities. Increasing evidence has emphasized the potential of brain plasticity, neural regeneration, and targeted rehabilitation therapies in promoting recovery. As a result, rehabilitation therapy now prioritizes actively restoring function, particularly during the first three to six months after a stroke, when recovery is most rapid.[2] Central to this process is neuroplasticity, which refers to the brain's ability to adapt and reorganize by forming new neural connections in response to learning, experience, or injury.[3]

One gene crucial to neuroplasticity is brain-derived neurotrophic factor (*BDNF*). Located on chromosome 11p14.1, the *BDNF* gene encodes a protein essential for neuron survival and growth. Increased *BDNF* expression promotes both structural and functional adaptations, aiding recovery from impairments caused by stroke. Despite the critical role of B*DNF* in stroke recovery, existing studies have mainly focused on assessing *BDNF* gene levels in ischemic stroke-induced animal models.[4-6] However, clinical studies investigating *BDNF* gene expression in human ischemic stroke patients before and after rehabilitation therapy are limited and rarely reported. Therefore, this study aims to determine the levels of *BDNF* gene expression in post-rehabilitation ischemic stroke patients and compare them to pre-rehabilitation levels.

METHODS

Subjects and ethics

Patients diagnosed with ischemic stroke between 2016 and 2017 at Queen Elizabeth Hospital, Kota Kinabalu, Sabah, were recruited for this study. This study involved 43 pre-rehabilitation ischemic stroke patients and 22 post-rehabilitation ischemic stroke patients. Out of the 22 post-rehabilitation ischemic stroke patients, only 16 of them were paired (the same patients who completed the rehabilitation therapy). The inclusion criteria were: patients recently (< 1 month) diagnosed with ischemic stroke, those who could provide written consent, those able to provide 3 mL of peripheral blood for laboratory analysis, and those willing to participate in a three-month standard rehabilitation therapy program at Universiti Malaysia Sabah (UMS) twice a week. Exclusion criteria included patients diagnosed with hemorrhagic stroke, patients in a coma, those with ischemic stroke for more than 1 month, those unable to provide written consent or a 3 mL blood sample, and those unwilling to participate in the rehabilitation therapy. The three-month rehabilitation program consisted of physical therapy and cognitive training. Participation in the program was entirely voluntary. Patients were permitted to withdraw at any time during the study (e.g., due to chronic health-related complications requiring hospitalization, lack of family support, etc.), in accordance with the approved ethical protocol. This study was approved by the Medical Research and Ethics Committee of the Ministry of Health Malaysia (reference no.: NMRR-16-38-28777 (IIR)) and UMS (reference no.: JKEtika 3/15 (11)).

Sample collection

A phlebotomist collected approximately 3 mL of fresh peripheral blood from each ischemic stroke patient, and transferred it into a Tempus Blood RNA Tube (Applied Biosystems, USA) before and after three months of rehabilitation therapy at UMS. The tube was shaken vigorously for 10 seconds to ensure thorough mixing of the blood with the stabilizing reagent, preventing RNA degradation and ensuring effective stabilization. The tube was then stored at 4°C until further analysis.

RNA extraction and cDNA synthesis

Total RNA was isolated from the collected blood samples using the Tempus™ Spin RNA Isolation Reagent Kit (Applied Biosystems, USA). The RNA purity and concentration were assessed using a nanophotometer (Implen, USA). Approximately 1 µg of RNA was reverse transcribed into cDNA using the High-Capacity RNA-to-cDNA Kit (Applied Biosystems, USA). Briefly, a master mix was prepared by combining 10 µL of 2X RT Buffer with 1 µL of 20X RT Enzyme Mix. To this mixture, 1 µg of RNA was added, and the volume was adjusted to 20 µL with sterile distilled water. The mixture was gently mixed and incubated in a thermal cycler at 37°C for 60 minutes for cDNA synthesis, followed by 95°C for 5 minutes to inactivate the

reverse transcriptase enzyme. The cDNA was stored at -20°C until further analysis.

Comparative gene expression analysis

TaqMan® assays targeting the *BDNF* gene (assay ID: Hs02718934_s1) and the reference gene, glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) (assay ID: Hs02786624_g1), were obtained from Applied Biosystems, USA. The real-time polymerase chain reaction (qPCR) mixture, with a total volume of 20 µL, included 4 µL of 5X HOT FIREPol® Probe Universal qPCR Mix (Solis BioDyne, Estonia), 1 µL of 20X TaqMan® gene expression assay, 2 µL of cDNA (10 ng), and 13 µL of nuclease-free water. Three technical replicates were performed for each sample to ensure reliability. The Azure Biosystems™ Cielo™ 3 Real-Time PCR System was programmed with the following cycling conditions: an initial activation step at 95°C for 10 minutes to activate the enzyme, followed by 40 amplification cycles. Each cycle consisted of a denaturation step at 95°C for 18 seconds and an annealing/extension step at 60°C for 60 seconds. After completing the run, the fold change in *BDNF* expression was calculated using the $2^{-\Delta\Delta Cq}$ method, with normalization to the *GAPDH* gene.

Statistical analyses

A Shapiro-Wilk test was conducted to assess the data from all samples, with the null hypothesis that the dataset follows a normal distribution. The Shapiro-Wilk test is used to evaluate data normality, determining whether the sample is normally distributed.[7] This step is essential for selecting appropriate measures of central tendency and determining suitable statistical methods for data analysis.[8]

Subsequently, a Mann-Whitney U test was performed to compare the overall mean quantitative cycle (Cq) values of 43 pre-rehabilitation ischemic stroke patients versus 22 post-rehabilitation ischemic stroke patients. As participation was voluntary, only 22 of 43 recruited ischemic stroke patients completed the three-month rehabilitation therapy program at UMS. The test assessed the statistical significance of differences in *BDNF* gene expression levels between the pre- and post-rehabilitation groups, with a significance threshold set at 0.05. The Mann-Whitney U test is a non-parametric statistical test used to compare differences between two independent groups. It assumes that the sample is randomly drawn from the population, the samples are independent, and the measurement scale is ordinal.[9]

Additionally, a Wilcoxon Signed-Rank test was employed to compare the mean Cq values of the 16 paired patients (only 16 out of 22 post-rehabilitation ischemic stroke patients were the same patients who completed the three-month rehabilitation therapy program at UMS) before and after rehabilitation, to determine the significant differences in *BDNF* gene expression levels, with a significance threshold of 0.05. The Wilcoxon Signed-Rank test is another non-parametric statistical test used to compare two related samples or paired observations. It assumes independence within pairs and that the data are not normally distributed.[10]

RESULTS

The overall Cq values for the *BDNF* gene before (n = 43) and after (n = 22) therapy were 32.51 and 32.27, respectively (Table 1). The overall Cq values for the *GAPDH* gene pre-rehabilitation (n = 43) and post-rehabilitation (n = 22) were 23.62 and 25.31, respectively. After normalization to *GAPDH*, the overall *BDNF* expression increased 3.81-fold following rehabilitation therapy (Figure 1). A Mann-Whitney U test was conducted to compare the *BDNF* expression levels across these ischemic stroke patients, revealing a statistically significant association (p-value = 0.048).

Additionally, the Cq values for the *BDNF* gene among 16 paired patients pre- and post-rehabilitation therapy were 32.73 and 32.33, respectively (Table 2), while the Cq values for the *GAPDH* gene were 22.43 and 24.99, respectively. Interestingly, after normalization to *GAPDH*, the *BDNF* gene in the 16 paired post-rehabilitation therapy ischemic stroke patients showed a 7.78-fold increase compared to pre-rehabilitation therapy (Figure 2), with a highly significant relationship (p-value = 0.004) as determined by the Wilcoxon Signed-Rank test.

DISCUSSION

This study demonstrated a significant increase in peripheral blood *BDNF* expression following a three-month standard rehabilitation therapy program in patients with ischemic stroke. This finding aligns with a recent meta-analysis by Li *et al.*, which examined 15 independent studies and reported that moderate to high-intensity aerobic exercises during rehabilitation enhanced *BDNF* concentrations in stroke patients.[11] Similarly, another meta-analysis involving 2,567

Table 1: The overall mean Cq values of ischemic stroke patients, both pre-rehabilitation (n = 43) and post-rehabilitation (n = 22), and the gene expression fold change

Sample	*BDNF* (Mean Cq)	*GAPDH* (Mean Cq)	ΔCq	ΔΔCq	$2^{-\Delta\Delta Cq}$
Pre-rehabilitation (n = 43)	32.51	23.62	8.89	0	1
Post-rehabilitation (n = 22)	32.27	25.31	6.96	-1.93	3.81

BDNF: brain-derived neurotrophic factor; *GAPDH:* glyceraldehyde-3-phosphate dehydrogenase; Cq: quantification cycle; Δ: delta; $2^{-\Delta\Delta Cq}$: fold change

stroke patients suggested that rehabilitation led to a significant increase in serum BDNF levels, with these changes associated with functional improvement.[12] Additionally, comparable effects have been observed in preclinical studies using animal models. Ribeiro *et al.* reported a significant improvement in BDNF protein levels in post-stroke rehabilitated rats, particularly with mild exercise.[13] Although peripheral blood is a practical and non-invasive source for assessing *BDNF* gene expression, it is important to note that peripheral *BDNF* expression may not directly reflect brain BDNF protein activity. However, a previous study reported that peripheral BDNF levels correlate with learning-related brain activity in healthy humans.[14] Further research is needed to investigate the correlation between peripheral BDNF levels and BDNF protein levels in the brain, especially in the context of stroke recovery. Nonetheless, the results of this study highlight the importance of exercise in rehabilitation therapy and support the potential of the *BDNF* gene as a promising biomarker for monitoring recovery progress and evaluating intervention efficacy.

Exercise positively influences brain health and cognitive function, mediated through several molecular pathways. One key mediator is irisin, a hormone cleaved from the membrane protein type III domain-containing 5 (FNDC5) and released by skeletal muscles during physical activity. Irisin production increases with exercise and has been shown to stimulate the expression of *BDNF* in the hippocampus, a brain region essential for memory and learning. This effect occurs via the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/FNDC5 signaling pathway, where PGC-1α is upregulated during exercise, enhancing FNDC5 expression and irisin release, as shown in animal studies.[15] Once in the brain, irisin promotes hippocampal BDNF production and initiates a

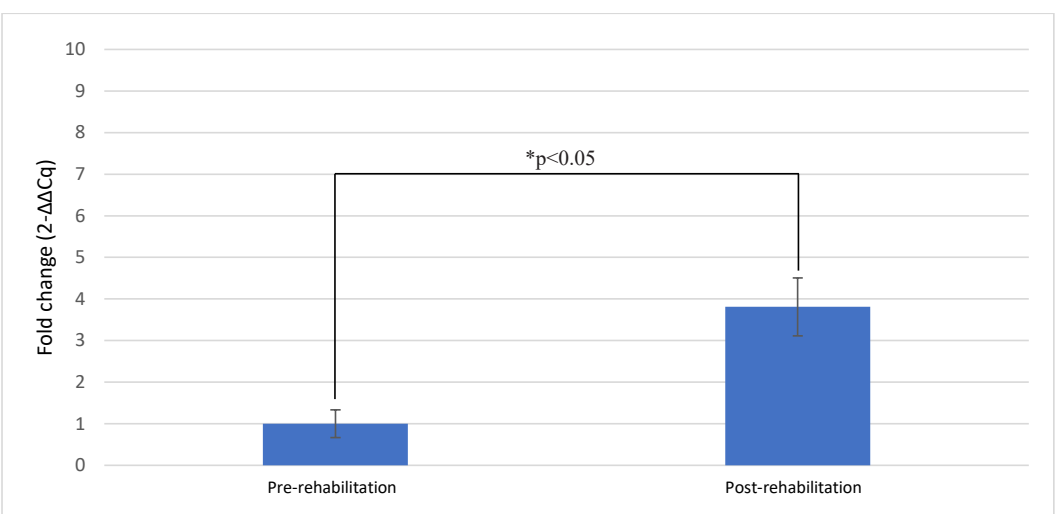

Figure 1. The overall fold change of *BDNF* gene expression in post-rehabilitation ischemic stroke patients. *Statistically significant.

Table 2: The mean Cq values of 16 paired ischemic stroke patients, both pre-rehabilitation and post-rehabilitation, and the gene expression fold change

Sample	*BDNF* (Mean Cq)	*GAPDH* (Mean Cq)	ΔCq	ΔΔCq	$2^{-\Delta\Delta Cq}$
Pre-rehabilitation (n = 16)	32.73	22.43	10.3	0	1
Post-rehabilitation (n = 16)	32.33	24.99	7.34	-2.96	7.78

BDNF: brain-derived neurotrophic factor; *GAPDH:* glyceraldehyde-3-phosphate dehydrogenase; Cq: quantification cycle; Δ: delta; $2^{-\Delta\Delta Cq}$: fold change

cascade of molecular events that benefit neuronal health.[16] This supports the increase of *BDNF* gene expression in post-rehabilitation ischemic stroke patients in this study. BDNF plays a central role in exercise-induced brain adaptations by binding to its high-affinity tropomyosin receptor kinase B (TrkB).[17] This interaction activates the BDNF/TrkB signaling cascade, triggering several downstream pathways.[13] These include the PI3K/AKT pathway, which enhances neuronal survival by inhibiting programmed cell death; the Ras/MAPK/ERK pathway, which regulates gene expression to support synaptic plasticity and neuronal differentiation; and the phospholipase C-y/diacylglycerol/inositol 1,4,5 triphosphate (PLCy/DAG/IP3) pathway, which regulates calcium signaling critical for synaptic function. Collectively, these pathways support neuronal survival, synaptic plasticity, and neurogenesis. Genetic variations in the *BDNF* gene can influence its expression by altering regulatory regions, potentially impairing transcription factor binding and reducing BDNF production. Szarowicz *et al*. reported that a common single-nucleotide polymorphism (SNP), the valine-to-methionine substitution at codon 66 (Val66Met), disrupts the interaction between the BDNF pro-peptide of proBDNF and sortilin.[18] Sortilin, a type 1 transmembrane protein, plays a key role in the intracellular trafficking, processing, and secretion of BDNF, particularly its precursor form, proBDNF.[19] It works with the neurotrophin receptor $p75^{NTR}$ to ensure proper conversion of proBDNF into mature BDNF (mBDNF), which is crucial for activating TrkB receptors involved in neuronal survival and memory formation.[19] Given these effects, future studies should investigate the role of *BDNF* SNPs in stroke recovery and their potential implications for targeted therapies.

During stroke recovery, several genes are upregulated to promote neuroprotection,

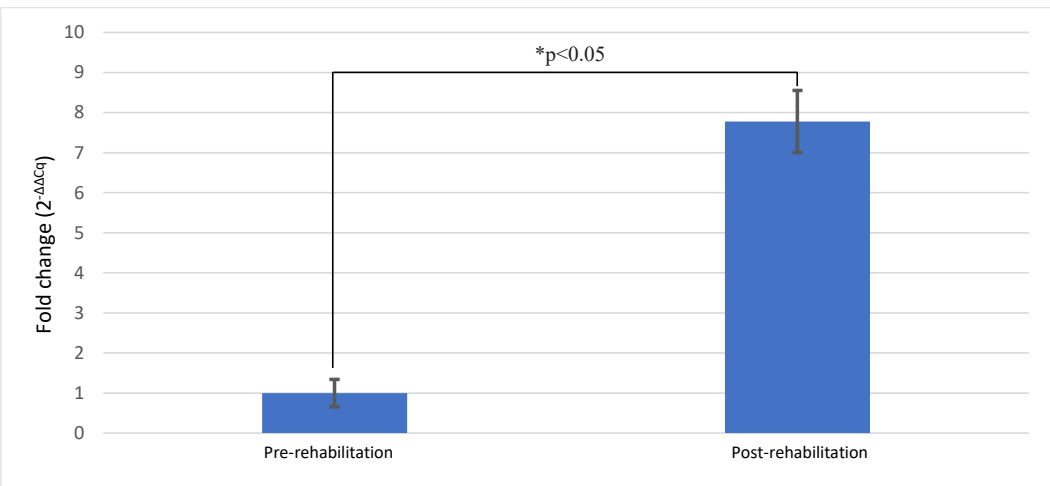

Figure 2. The fold change of *BDNF* gene expression for 16 paired post-rehabilitation ischemic stroke patients
*Statistically significant.

neuron growth, and functional improvement. Many of these genes are closely linked to BDNF through shared signaling pathways or functional interactions. Understanding these connections provides insight into the molecular mechanisms that support stroke recovery. One such gene is *VGF*, a nerve growth factor-inducible protein. Gillis *et al*. first identified *VGF* as rapidly upregulated in PC-12 cells after stimulation by nerve growth factors.[20] Further studies revealed that *VGF* mRNA increases in cortical and hippocampal neurons in response to neurotrophic factors such as BDNF and neurotrophin-3, emphasizing its role in neuronal repair and functional recovery after brain injury.[21] Exercise has also been shown to elevate *VGF* expression, likely contributing to post-stroke recovery via BDNF-dependent mechanisms[22], as demonstrated in mouse models by Choi *et al*.[23] and Beckmann *et al*.[24] Another relevant gene is growth-associated protein 43 (*GAP43*), which is involved in neural regeneration. It plays a key role in axonal growth and synaptic remodeling by regulating F-actin dynamics.[25] *GAP43* is also upregulated in response to neurotrophic factors like VGF and BDNF, as noted by Chung *et al.*[26] This upregulation highlights its regenerative function and reinforces its role as a critical mediator of BDNF-driven neuroprotection, further supporting its importance in post-stroke neuronal repair mechanisms.

Another important gene in stroke recovery is insulin-like growth factor-1 (*IGF-1*), which supports brain repair by crossing the blood-brain barrier and acting through autocrine, paracrine, and endocrine mechanisms. *IGF-1* also stimulates *BDNF* expression, contributing to brain development and recovery.[27] Physical exercise promotes *IGF-1* release from muscle and liver into the bloodstream, potentially increasing its uptake in the brain, though reported effects on circulating IGF-1 levels vary.[28] Therefore, the upregulation of *IGF-1* and related genes is closely linked to BDNF signaling. This highlights the importance of physical rehabilitation in improving post-stroke recovery by activating these essential molecular mechanisms, offering potential therapeutic targets after stroke.

This study has several notable limitations. The relatively small sample size, with only 22 participants and 16 paired samples, limits subgroup analyses such as examining the influence of medications, comorbidities, or stroke types on *BDNF* expression levels. Additionally, functional outcome measures such as the NIHSS, mRS, or Barthel Index were not collected, restricting the ability to correlate changes in *BDNF* gene expression with clinical recovery.

In conclusion, this study demonstrates that a three-month standard rehabilitation therapy program provided by UMS significantly increases *BDNF* expression in ischemic stroke patients. While the functional implications of this molecular change remain unclear due to the absence of clinical outcome measures, the findings support the role of *BDNF* as a potential marker of rehabilitation-induced neuroplasticity and recovery. Larger studies integrating molecular and clinical outcome data are needed to determine whether *BDNF* can be used to inform or personalize stroke rehabilitation strategies.

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DISCLOSURE

Data availability: Raw data are available upon request.

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Conflict of interest: None.

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