AN OVERVIEW OF GENETIC FACTORS AFFECTING STROKE RECOVERY IN ELDERLY PEOPLE

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ABSTRACT

Stroke recovery outcomes vary widely among individuals, and emerging evidence suggests that genetic factors play a significant role in influencing rehabilitation success. This literature review explores key genetic variants associated with functional recovery, neuroplasticity, and drug response following stroke, with a particular focus on elderly populations.

Genes such as BDNF Val66Met, APOE ε4, CYP2C19, and PATJ have been linked to recovery outcomes by affecting processes like synaptic plasticity, inflammatory responses, and responsiveness to pharmacological treatments. Studies indicate that carriers of certain variants, including Val66Met and APOE ε4, may experience slower recovery trajectories and poorer long-term outcomes, highlighting the potential value of personalized rehabilitation strategies and genotype-guided therapies.

INTRODUCTION

Stroke can be considered a condition that affects the arteries within the brain and leads to it. It mainly occurs when one of the blood vessels in the brain gets blocked by a clot or ruptures, which results in the brain being unable to get oxygen and nutrients, causing the nearby brain cells to die. A stroke that occurs due to blockage of a blood vessel is known as an ischemic stroke, which is the most common type of stroke to occur. Another type of stroke is known as a hemorrhagic stroke, which occurs due to sudden bleeding within the brain. The leaked blood exerts pressure on the nearby brain cells, hence causing damage to them.

Stroke is one of the leading causes of disability and lower quality of life, especially for elderly patients, as they are more susceptible to a higher risk of mortality and poorer treatment outcomes. Approximately 75% of all strokes occur in persons older than 65 years. Age is considered one of the non-modifiable risk factors. It is also to be noted that the incidence of stroke disease increases with age, in both men and women, with around 50% of all strokes occurring in the age group 75+ year olds and 30% in the age group of 85+ year olds. One of the main effects after a stroke is impairment in cognitive function, as it affects around 1/3rd of stroke survivors. Alongside these effects, there are several more, such as infections, bladder and bowel dysfunctions, and reduced mobility. While several medical tools can predict the rehabilitation outcomes, such as FIM (Functional Independence Measure) and mRS (Modified Rankin Scale), and the Barthel Index (BI). Even though age has been thought of as a reliable predictor of functional outcomes in stroke patients in various studies, it is also important to consider the impact of genetics, as many drugs that are prescribed after an ischemic stroke seem to be lacking. Other clinical observations from diverse long-term outcomes in stroke patients also support the idea of genetic factors affecting recovery mechanisms, alongside other unknown factors. It is crucial to remember that stroke is a multifaceted condition, caused by interactions of various factors and not just one. Hence, it is quite difficult to narrow down which genes specifically affect the occurrence of strokes.

Strokes GWASs (Genome-Wide Association Study), consisting of polygenic scores and combining these scores from different ancestries for vascular risk factors, can help predict the risk of ischemic stroke in European, East Asian, and African populations. Although over 30 genetic risk loci have been linked to stroke susceptibility, only a few have been connected to stroke outcomes. This suggests that the genetic factors influencing recovery and prognosis may

differ from those affecting stroke risk, highlighting the need for further research on the genetics of stroke outcomes.

In this genetic context, pharmacogenomics has an impactful potential to assist in providing personalized treatment to elderly stroke patients based on their genetic profile, as genetic differences can affect drug efficiency and side effects, making such advances is going to be innovative. There is ongoing research to find the different variants of a gene that could affect the outcomes, as genetic research is quite holistic. This research paper aims to explore how the genetics of elderly patients affected by stroke can affect their recovery outcomes, such as drug treatment, rehabilitation, etc.

METHODOLOGY

When selecting the sources to write this literature review, I mainly selected research articles focused on stroke genetics and recovery. I utilised research articles from databases PubMed and the National Library of Medicine. I primarily used the keywords “Stroke recovery”, “Elderly people”, “genetic factors of stroke”, and “stroke rehabilitation”. These words enabled me to select sources relevant to my research question on genetic factors affecting stroke recovery. To ensure validity, I prioritized recent studies published and selected articles that directly examined the role of genetic variations, gene expression, or polymorphisms in stroke recovery outcomes. Even though my primary focus was on studies involving elderly patients, there was limited literature addressing elderly patients’ recovery about genetics. Therefore, I also included general population studies on stroke recovery as needed to provide a comprehensive background and understanding of the research topic. In total, I have reviewed 13 research articles and studies and

analyzed their participants, genetic factors studied, and usual functional recovery outcomes to identify common findings and research gaps.

RESULTS

Before moving on to discussing the results of various studies focusing on genetics and stroke recovery, it is important to note that a majority of vital improvements happen during the first 30 days, according to Duncan et al. 2000. In this study, it was reported that full recovery was visible in 25% to 50 % of the patients. However, despite these statistics, recovery is usually incomplete, and the recovery process is majorly different from patient to patient. It is necessary to consider the fact that there are a very limited number of studies on stroke recovery and genetics, let alone the effect of these very factors on elderly patients specifically. The findings in a lot of these genetic studies are mixed and hence difficult to conclude.

→ Stroke patients' degree of recovery

An analysis done found that only 65% of stroke patients with motor dysfunctions show some degree of recovery, and less than 15% of patients with paralysis issues after stroke experienced full recovery, according to Hendricks et al. 2002. It was also found in several studies that nearly a quarter of stroke survivors displayed no significant improvement.

→ Role of BDNF

Among various studies on genetics and stroke, the most well-studied gene is the BDNF val66met polymorphism. BDNF (brain–derived neurotrophic factor) is an important neurotrophin that is present in the CNS and plays a crucial role in neuronal growth, memory, and synaptic plasticity (important for learning and recovery, especially in motor deficits)

In several studies, BDNF was observed to have many positive effects on stroke recovery by assisting the brain during the recovery process. For instance, BDNF was found to lead to better

functional recovery after stroke (Chen et al., 2000; Muller et al., 2008), as well as improving motor function, specifically in the stroke-damaged regions of the brain, according to Clarkson et al. (2011).

→ BDNF val66met variant

This particular variant of BDNF, discovered recently, is found in at least 40-50% of Asians and 25-32% of Caucasian populations. There are several studies suggesting that carriers of this variant of the gene show much poorer outcomes, particularly in memory and memory performance, as it is also shown to decrease the hippocampal volume. But evidence of this particular variant was not found in older adults, even though it has a significant impact on the function of BDNF and neuroplasticity.

Another important finding for elderly stroke recovery reported by Sohrabji and Lewis (2006) is that the beneficial effects of BDNF on learning, memory, and neuroplasticity and protection decline, which makes the recovery process for these people much slower. Since there is enough evidence suggesting that the val66met can impact cortical plasticity, we could imply that elderly people with val66met would have a poorer recovery compared to non-carriers.

STRONG Study Investigators, & Shah, S. C. (2024) investigating stroke rehabilitation outcomes over 12 months, found that with 763 participants with a mean *age of 63+* found that the Val66Met variant was significantly associated with poorer cognition score when assessed by the Montreal Cognitive Assessment. This variant was also found to decrease BDNF release, preventing essential recovery. The same study tested and replicated the effects of the **rs1842681** variant, and this variant showed better functional outcomes and better mRS.

→ Impact of the APOE ε4 gene

In another study, functional outcomes were compared among APOE ε4 and non-carriers; after a 3-month follow-up period, it was found that approximately 43% of the APOE ε4 carriers showed comparatively worse functional outcomes with an average mRS score of greater than 2, which demonstrates poor recovery when compared to only 15.6% of non-carriers having a mRS score greater than 2.

Another finding relevant to the NLR (Neutrophil to lymphocyte ratio), which is used to show that there is inflammation in the body. Among APOE ε4 carriers, it was noted that high NLR patients have an increased risk of unfavorable stroke outcomes, and an association was observed between high NLR and poor functional outcomes in APOE ε4 carriers.

→ Effect of genes on drug treatment of strokes

Zhang et al.(2023) produced a study investigating the effect of personalized platelet therapy on outcomes post stroke, and the study used 650 patients with an average age of 68; it is also to be noted that around 73% of the participants were male.

Participants classified as carrying a certain variant of the CYP2C19 gene were given aspirin and an alternative drug based on their genotype and clinical profile. It was found that the group that was given treatment after analysis of their genotypes had fewer recurrent strokes and reduced disability compared to the control which only received general stroke medication. This suggests that a more personalized approach towards treatment could benefit stroke patients. The same technique could be applied to other forms of stroke treatment, such as blood pressure medications.

In the same study, gene variants of COX-1 and COX-2 were tested against aspirin, too; however, the findings were not significant and consistent enough to be considered. Variants of enzymes used to activate clopidogrel were also examined, and it was found that the CYP2C19 gene's 2

and 3 alleles were less effective in converting clopidogrel. This means that were would be a higher risk of strokes recurring, and the drug provided to patients should be modified or an alternative one overall to reduce risk.

→ Influence of PATJ gene

Mola-Caminal, M., et al. (2019) conducted a 2-phase meta-analysis of GWAS to analyse ischemic stroke cases and their functional outcomes measured by the mRS. The G allele in the PATJ gene was associated with a poorer functional outcome. This finding was consistent across 11 of 12 cohorts, hence increasing reliability. The reason this is so important is that the variants in PATJ may affect neurovascular repair, as this gene is mainly responsible for the encoding of a protein that forms tight connections between cells. Hence, genetic therapy can be used to alter the activity of the G-allele variant of the PATJ gene, which could speed the recovery process and make it more efficient.

For all the above genes identified, the implementation of genetic screening when prescribing medications or treatments can avoid worsening of stroke-induced disabilities in already old and weak patients. Tailored rehabilitation and treatments will make the recovery process for elders easier and much more effective, as time is not wasted by receiving medications that will not work with certain gene variants.

DISCUSSION

It is important to understand that studying genetic influences on stroke recovery is a challenging task because the impact of genetics is multifaceted, and it is not easy to pinpoint which genes are affecting a particular case unless a lot of extensive research has been done, that are expensive and perfectly designed to assess such factors. The main findings in this study were on BDNF

val66met variant, APOE ε4, CYP2C19 and PATJ. Most of the studies focused on BDNF's potential to enhance the recovery process in stroke patients because its release is associated with neuroplasticity and memory. Injection of BDNF's other harmless variants could improve stroke recovery outcomes in patients. Alongside that, genetic engineering or therapy could be done to reverse the effects of the val66met variant in the gene's carriers. Genetic screening should be used to evaluate stroke patients to reveal the presence of genes such as APOE ε4, which is usually associated with neuroinflammation. Doctors could then prescribe drugs that reduce the inflammatory effect of this gene, such as DMARDS. Stronger rehabilitation efforts can also be employed for these gene carriers so that their recovery is complete. Unfortunately, research regarding target drugs for these genes is quite sparse and has not yet been implemented. Even though some of the genetic consequences are known, healthcare professionals can only prescribe general drugs due to the unavailability of such medications.

These studies' data can be used to develop potential therapies related to stroke recovery for the elderly, as many of these studies consist of participants aged 60+. This aligns with the paper's research topic of focusing on stroke recovery outcomes for elderly people. Furthermore, many of these studies used statistical analysis to evaluate their patient data. For instance, Rong, X., *et al.* (2023) research regarding the APOE e4 gene consists of such statistical tests as T-tests that make the data more reliable and valid.

→ Limitations

A number of these studies were used to study the genetic influences of strokes do not make clear the gender used or use a majority of one particular gender in their sample population. The problem that arises with this limitation is generalisability. For example, Zhang et al.(2023) used

around 73% male participants, which means the female population's findings are less reliable due to a smaller sample size. It is also difficult to conclude about female stroke patients.

Another limitation to keep in mind is that these studies have not been designed to track long-term changes in participants. For example, STRONG Study Investigators, & Shah, S. C. (2024) observed the stroke patients for only 1 year. We also have to bear in mind that outcomes can change over longer periods of time. This may lead to a random error that could change the findings of the study. Moreover, the sample sizes of these studies are not enough to generalise the findings. This is because with a 700-800 population, and genetic variation in each individual can make it difficult to apply findings to every elderly stroke patient.

However, while STRONG Study Investigators, & Shah, S. C. (2024) did repeat to examine certain variants of a gene associated with stroke outcomes to increase reliability, other studies used in the review did not include any details of repetition of their studies, which decreases the reliability of their findings.

Another limitation to keep in mind is the sample sizes used to examine genetics in the study. These studies have sample sizes of 700-800 participants, which may seem large enough; however, these might not be generalizable. This is mainly because genes are different in each participant, and genetic variation in each participant may make it difficult to come to a rigid conclusion regarding genetic influences.

CONCLUSION

In conclusion, this literature review mainly focuses on the vital role that genetics plays in shaping recovery for the elderly stroke-affected patients. Some of the main genetic influences discussed were the BDNF val66met variant, APOE e4, CYP2C19, and PATJ variants. These

have been shown to affect cognitive and motor functional outcomes alongside neuroplasticity and damage recovery. Even though research in this area is very limited, findings suggest that targeted genetic therapy and the use of pharmacogenetic treatments may help enhance the recovery process for patients. While some findings seem relevant, it is also important to note that there is not much replication and in-depth study, along with follow up hence making it difficult to come to definite conclusions. To summarize, gene therapy holds great potential in the stroke recovery process for patients; however, more research is required on how to initiate such therapy and more in-depth research on the selective genes affecting recovery.

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