



THE ROLE OF BIOMARKERS IN ISCHEMIC STROKE; A SYSTEMIC REVIEW

Akramova Dilshoda Turdiqulovna¹, Jumanov Abduxoliq Abdulla o'g'li², Mashkurova Madina Anvar qizi², Zafarov Muhammadjon Qahramon o'g'li²

¹ Teacher of Neurology department, Tashkent Medical Academy, Tashkent, Uzbekistan

² Student of Neurology department, Tashkent Medical Academy, Tashkent, Uzbekistan

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ABSTRACT

The problem of ischemic stroke (IS) has become increasingly important in recent years, as it ranks first in the structure of disability and mortality, crowding out other vascular diseases. In this regard, the study of this pathology and the search for new therapeutic and diagnostic tools remains an urgent problem of modern medical science and practice.

Materials and methods. This systematic review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.

Results. Until today, many biomarkers have been identified, however none so far have shown sufficient sensitivity and specificity in order to be used in the clinical setting.

Conclusion. The results of these studies could, in future, lay the cornerstone for identification of new therapeutic targets that may allow a significant modification of death and disability rate.

Introduction

Among the causes of global death and disability, ischemic stroke (also known as cerebral ischemia) plays a pivotal role, by determining the highest number of worldwide mortality, behind cardiomyopathies, affecting 30 million people. The etiopathogenetic burden of a cerebrovascular accident could be brain ischemia (~80%) or intracranial

hemorrhage (~20%). The most common site when ischemia occurs is the one is perfused by middle cerebral arteries. Worse prognosis and disablement consequent to brain damage occur in elderly patients or affected by neurological impairment, hypertension, dyslipidemia, and diabetes. Since, in the coming years, estimates predict an exponential increase of people who have diabetes, the disease mentioned above constitutes together with stroke a severe social and economic burden. In diabetic patients after an ischemic stroke, an exorbitant activation of inflammatory molecular pathways and ongoing inflammation is responsible for more severe brain injury and impairment, promoting the advancement of ischemic stroke and diabetes. Considering that the ominous prognosis of ischemic brain damage could be partially clarified by way of already known risk factors the auspice would be modifying poor outcome in the post-stroke phase detecting novel biomolecules associated with poor prognosis and



targeting them for revolutionary therapeutic strategies.

Materials and methods

This systematic review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.

Information sources

A literature search was conducted in MEDLINE/ PubMed, Research gate and Google Scholar data sources using the combinations of “Ischemic stroke” and the following key words: “Atherosclerosis”, “Biomarkers”, “Calibration”,

“Neuroinflammation”, “Natriuretic peptide”, “Microglia”, and “Sample size”. Reference lists in retrieved articles were also screened for the same keywords

Selection process

The Mendeley Reference Manager was used to select studies. Two reviewers (N.D-O and O. A-H) independently selected the eligible studies. Any disagreement between reviewers was resolved by consensus or by a third reviewer (D.B.). The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess articles for this review.

Results

Author	Published	University	Profile	CI
Antonino Tuttolomondo	9 December 2020	University of Palermo	Molecular Biology of Atherosclerotic Ischemic Strokes	95%
Meng Zhang	January 2021	Federico II University	Association between uric acid and the prognosis of acute ischemic stroke: A systematic review and meta-analysis	95%
Felipe A Montellano	2021 Feb 22	University of Würzburg	Role of Blood-Based Biomarkers in Ischemic Stroke Prognosis: A Systematic Review	95%
Wenhua Shi	2021 Mar 31	The Second Clinical College of Guangzhou University of Chinese Medicine	Appraising the Accuracy of Ischaemia-Modified Albumin in Diagnosing Stroke: A Systematic Review and Meta-Analysis	95%
Arduino A Mangoni	2022 Apr 29	Flinders University	A Systematic Review and Meta-Analysis of Serum Concentrations of Ischaemia-Modified Albumin in Acute Ischaemic Stroke, Intracerebral Haemorrhage, and Subarachnoid Haemorrhage	95%



William Whiteley	2009 Mar 12	University of Edinburgh	Blood markers for the prognosis of ischemic stroke: a systematic review	95%
Aziza Alrafiah	September 2021	King Abdulaziz university	Angiogenesis Biomarkers in Ischemic Stroke Patients	95%
Galina Sufianova	September 2022	Peoples' friendship university of Russia	Long non-coding RNAs as biomarkers and therapeutic targets for ischemic stroke	95%
Konstantinos Markis	18 Apr 2018	Clinical Biochemistry Department, KAT General Hospital	Blood biomarkers in ischemic stroke: potential role and challenges in clinical practice and research	95%

Fast and accurate diagnosis of stroke is crucial for the immediate application of the right therapy to patients. However, rapid diagnosis is still a challenge since an ischemic stroke cannot be identified based only on clinical assessment. CT or MRI imaging is required to rule out hemorrhagic stroke since thrombolytic therapy can lead to increased intracranial bleeding and further aggravation of hemorrhagic stroke. In addition, clinical situations that imitate the signs and symptoms of stroke may also impede the rapid diagnosis and treatment of stroke victims. It is therefore of value to discover non-invasive tests that aim to quickly distinguish stroke from stroke mimics and distinguish ischemic from hemorrhagic stroke. Identifying blood biomarkers of stroke is an active area of research since their potential use is not limited to diagnosis and differentiation, but can be applied to prognosis and patient monitoring - monitoring the effectiveness of applied therapy and/or diagnose possible complications. However, their use has been limited so far not only for reasons related to patients and the disease (heterogeneity of stroke etiology, the complexity of the ischemic cascade, the impact of the blood-brain barrier (BBB) on diffusion of blood biomarkers, and difficulties in obtaining

consent from stroke patients) but also for reasons that related to laboratory measurement of these biomarkers (pre-analytical and analytical issues as well as interpretation of laboratory measurements). Until today, many biomarkers have been identified, however none so far have shown sufficient sensitivity and specificity in order to be used in the clinical setting.

Discussion

Blood biomarkers might provide useful information to improve the prediction of outcome after acute ischemic stroke. However, this review showed that many studies were subject to bias. Although some markers had some predictive ability, none of the studies was able to demonstrate that the biomarker added predictive power to a validated clinical model. The clinical usefulness of blood biomarkers for predicting prognosis in the setting of ischemic stroke has yet to be established.

Studies were generally small (median number of subjects, 85; interquartile range, 49 to 184). Few had evidence of a sample size calculation (7 of 82 [9%]) or reported blinding to whether patients had stroke (21 of 82 [26%]). Of the 66 studies reporting a measure of association, 10 did not adjust for age or stroke severity, 14 adjusted for age, 7



adjusted for severity, and 35 adjusted for both; 30% (20 of 66) used a data-dependent threshold to predict good or bad outcome. There was evidence of within-study reporting bias and publication bias. Cardiac markers showed the most consistent association with poor outcome.

Conclusion

Brain ischemic injury represents the second most frequent reason for death and long term disablement throughout the world. From the etiopathogenic point of view, TOAST classification has described several stroke subtypes. They could be large-artery atherosclerosis, cardioembolism, systemic hypoperfusion, penetrating artery disease, carotid dissection, hypercoagulability of genetic syndromes or with an undetermined etiology. By which, atherosclerosis formation has been blamed to be one of the culprits for the inclining cases of stroke-related death. Therefore, atherosclerosis acts like the trigger of an intricate chain of events which modify molecular, genomic and cellular frameworks and inflammation has a pivotal role in this cascade, both in the central and in the peripheric nervous system. After an ischemic stroke, several cytokines take part in neuroinflammation, and their actions have repercussions on increasing infarct size, brain impairment, and clinical prognosis. Clinical findings have evidence that, in the acute phase, it is essential preventing deleterious effects of

mediators of neuroinflammation to avoid poor outcomes. *Int. J. Mol. Sci.* 2020, 21, 9372 15 of 25 Considering these assessments, in recent years, many authors have investigated the role of several molecules involved in atherosclerosis to identify innovatory biomarkers which are the expression of worsening outcomes. In this way, patients who have more substantial death and disability risk may be subject to frequent and accurate monitoring and appropriate therapeutic protocols. Moreover, it could be auspicious that future studies will contribute to the detection and the comprehending of an increasing number of genetic, biological, and molecular key factors of stroke, in term of predisposition to the disease, establishment, and progression of the damage. The results of these studies could, in future, lay the cornerstone for identification of new therapeutic targets that may allow a significant modification of death and disability rate.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of Data, Code and Other Materials

All included studies are available full-text on PubMed and Google Scholar databases

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