

REVIEW

for thesis work by Dr. Aida Kondybayeva "Clinical and pathogenetical features of stroke in Kazakhstan", presented for the degree of PhD in the specialty 6D 110 100 - "Medicine"

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1. Relevance of the research topic

The thesis work's relevance is unquestionable, because of extremely high frequency and prevalence of stroke around the world, including Kazakhstan, and also due to this disease there is a significant level of disability. Despite the modern achievements and huge efforts of the world community aimed at fighting against stroke and its consequences, a number of issues still remain controversial and unclear and require further research. The success of measures to improve the system of medical care for patients with ischemic stroke largely depends not only on its diagnosis, but also on the verification of factors that determine the outcome of cerebral stroke and its prognosis. Special attention should be paid to the progression of the clinical situation during the first ours, when various mechanisms can influence neurological deterioration.

In the thesis work of Dr. Aida Kondybayeva from the position of an integrated approach, including the analysis of clinical and laboratory characteristics, neuroimaging research methods, various pathogenetic subtypes, the patterns of progression of ischemic stroke were studied. Taking into account the aim and the importance of scientific and practical tasks solved in the thesis, this scientific research is relevant.

2. The most substantive results obtained personally by the author and their novelty.

The analysis carried out during the research made it possible to determine the clinical features and pathogenetic mechanisms of the progression of ischemic stroke in the most acute period. A progressive course in the most acute period (24-72 hours) was detected in 36.8% of patients, the clinical situation in 63.1% of patients remained more stable or regressive during the same hours. In the fatal group, earlier neurological deterioration was in 87.5% of patients, in the opposite group in 32.8%. The main factors influencing the progression of neurological status in different pathogenetic subtypes of IS in the most acute period were identified.

High mortality rates in the acute period of ischemic stroke are associated with late delivery of patients to the hospital and with concomitant disorders: atrial fibrillation, IHD, COPD, T2D, CKD hyperglycemia, shortening of APTT, and the local area of the heart attack has size more than 5 cm in diameter.

For the first time in Kazakhstan, a neural network model was used for mathematical calculation and prediction survival rate in the first 24-72 hours after the beginning of IS disease. By the method of "neural networks" the prognostic value was determined, which was 9.5% of mortality from the total number of patients with ischemic stroke of various etiology. Using the Kaplan-Meier method the survival threshold was identified: for atherothrombotic stroke - 65 years, for cardioembolic stroke - 69 years, and also their correlation with factors aggravating the process of IS progression was researched. Thus, the risk of death increases with scores of 21-42 on the NIHSS scale for patients with atherothrombotic IS subtype (0.93) with low SBP, but for patients with cardioembolic subtype (0.90), a correlation with high SBP was found.

The use of a set of methods of mathematical modeling is the most adequate for solving the problem of predicting early outcomes for various subtypes of ischemic stroke in the most acute period (24-72 hours), which make it possible to detect a reliable relationship with various factors and highlight the most unfavorable ones regarding to prognostic. Multiple regression analyses of Cox, Kaplan-Meier, analyses of neural networks make it possible to obtain results that allow to comprehensively consider the issues of predicting the lifetime, survival rate and mortality of patients after ischemic stroke with an information capacity of more than 97.4%.

Databases of possible genes of candidates influencing the process of state progression in IS were calculated and created. Using quantitative characteristics of interactions between miRNA and their target genes as biomarkers of stroke diagnostics using the association of miRNA and candidate genes: *CALMI*, *HTRA1*, *LDLR*, *MMP2*, *NOTCH3*, *SMARCA4*, *SORT1*, *ZDHHC22*, *ZFH3*. These results can become the basis for the development of further molecular laboratory researches of the associations of microRNA and genes of stroke candidates.

The thesis work was written by the author independently, the results and conclusions were obtained using modern methods of statistical processing.

3. The degree of validity of scientific provisions, conclusions, recommendations formulated in the thesis.

It should be noted the correct methodological approach, in which a detailed study of the features of the clinical manifestations of the most acute period of ischemic stroke using rating scales in relation to laboratory characteristics, risk factors of stroke, comparing the time of delivery of patients to the hospital, gender, age indicators, and also assessing the degree of influence of the size of local area in the compared groups, allowed the author to develop the concept of early survival with different subtypes of IS.

Clinical, neuroimaging, laboratory, molecular genetic studies were carried out with the personal participation of the applicant and interpreted correctly by her.

4. Assessment of novelty and reliability.

The author carried out a prospective research to study the early survival of patients with various pathogenetic subtypes of ischemic stroke in the most acute period, the dependence of the progressive course on clinical and laboratory characteristics and risk factors of stroke was studied. The factors of progression of neurological symptoms leading to early mortality were determined. The assessment of functional outcomes in the most acute period of ischemic stroke was given. The novelty of the research is represented by the mathematical model of predictive factors of early outcomes of IS in the most acute period developed by the author.

For the first time in Kazakhstan, the calculation of lifetime after the transferred IS was carried out by Dr. Aida Kondybayeva, the average survival time in years of patients according to Kaplan-Meier was determined, a discriminant analysis was conducted using the method of analysis of neural networks.

An important aspect of the work is the determination of the association of miRNA and target genes that can serve as markers for the diagnosis of ischemic stroke. Using high computer technologies, miR-1181, miR-328-5p, and miR-7110-3p have been identified, which can affect the expression of candidate stroke genes and the expression of alternative genes, which can be used in the development of biomarkers that adequately reflect the interaction of miRNA with mRNA during ischemic stroke.

The volume of the research and its design are quite appropriate and sufficient for the stated purpose of the work. A detailed examination of 663 patients, including 48 with fatal outcomes in the most acute period of ischemic stroke, followed by the use of modern methods of science research and the results obtained by the author, confirmed by acts of implementation and patents and other official documents, confirms the practical value of the dissertation.

The use of modern methods of statistical processing of research results should be recognized as sufficient and reliable to substantiate the scientific provisions, conclusions and recommendations formulated in the thesis work.

5. Assessment of the internal unity of the obtained results.

The research results obtained by the author have internal unity, all sections and provisions of the thesis are logically interconnected. Scientific provisions, results and recommendations are consistent with the set goals and objectives. The new solutions proposed by the author are fully reasoned.

6. The focus of the obtained results on the solution of the related urgent problem, theoretical or applied problem.

The practical value of the thesis research is undoubted and is aimed at solving an important applied problem of studying the clinical features and pathogenetic mechanisms of ischemic stroke progression in the most acute period, including the analysis of genetic markers of stroke (miRNA). Databases of candidate genes involved in the development of stroke and miRNA databases have been created to determine the effect of miRNAs on the expression of candidate genes involved in the development of stroke, which in the future can be used to develop molecular laboratory methods for the diagnosis and treatment of IS.

7. Confirmation of sufficient completeness of publications of the main provisions, results, findings and conclusions of the thesis work

The main conclusions and provisions of the dissertation work were reported and discussed at international conferences (USA, Spain, India, Kazakhstan). Based on the results of the dissertation research, 2 articles were published - in a publication indexed in the Scopus information base.

There are 5 abstracts in the foreign international conferences (including those indexed in the Scopus-3 database).

The defender of thesis upholds the principle of academic honesty. The author respects the rights and legitimate interests of other authors by using links to the author and the source of borrowing.

8. Conclusion on the possibility of awarding the degree of Doctor of Philosophy (PhD) in the relevant specialty

Dr. Aida Kondybayeva's thesis work on the topic: "Clinical and pathogenetical features of stroke in Kazakhstan", presented for the degree of Doctor of Philosophy (PhD) in the specialty 6D 110 100 - "Medicine" is a complete independent project, which contains a solution to a problem that is essential for management of patients with various pathogenetic subtypes of ischemic stroke in the most acute period. The obtained results are of theoretical and practical importance. The thesis work meets the requirements for dissertations for the degree of Doctor of Philosophy (PhD) and can be recommended for defense.

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