ANNOTATION

of the doctoral dissertation for the degree of Philosophy Doctor (PhD) on the specialty 6D110100 - "Medicine" **Aida Kondybaeva "Clinical and pathogenetic features of stroke in Kazakhstan"**

Relevance of the research topic.

Stroke is a serious and global public health problem of great social and economic importance, leading to premature mortality and disability in the world [World Health Organization. [World Health Statistics 2014. (2014). 180 p.; Global action plan for the prevention and control of no communicable diseases 2013-2020.P102].

Non-communicable diseases (Ncds) will account for about 75 per cent of mortality cases by 2030 [World Health Organization. World Health Statistics 2014. (2014). 180 p.]. The main guiding document for the practical implementation of policy decisions was the Global Plan of Action for the Prevention and Control of Non-Communicable Diseases 2013-2020, developed and adopted by the World Health Assembly «Global Plan of Action for the Prevention and Control of Non-Communicable Diseases 2013-2020», whose main aim is: to establish standardized national targets and indicators in accordance with internationally agreed monitoring mechanisms [World Health Organization. World Health Statistics 2014. (2014). 180 p.; Global action plan for the prevention and control of no communicable diseases 2013-2020. P 102].

According the Global Burden of Diseases (GBD) researches conducted in 188 countries around the world since 1990 to 2013, the overall mortality rate of people with stroke increased worldwide, in all age groups. Stroke has become the second leading cause of death worldwide. In 2013, almost 25.7 million people suffered a stroke, of which 71% of cases were ischemic stroke (IS) [Feigin V.L., Roth G.A., Naghavi M., Parmar P., Krishnamurthi R., Chugh S., Mensah G.A., Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Neurology. 2016;15:913–924.]. According to the same source, the mortality rate was about 6.5 million people, in more than 51% of cases, the cause of death was IS.

Disability due to stroke is ahead of all its other causes, so among patients after a stroke, more than half become disabled [Feigin V.L., Roth G.A., Naghavi M., Parmar P., Krishnamurthi R., Chugh S., Mensah G.A., Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Neurology. 2016;15:913–924.; GBD 2015 Neurological Disorders Collaborators Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 16, 877–897 (2017).].

In recent decades, in the developed countries of the world, the frequency of stroke has been decreasing, mainly due to control blood pressure efforts (BP) and quitting smoking [5]. However, according to many researchers, an ageing of the population, combined with a decrease in mortality, will lead to an increase in the prevalence of stroke by 3.4 million people in the period between 2012 and 2030 [Feigin V.L., Roth G.A., Naghavi M., Parmar P., Krishnamurthi R., Chugh S., Mensah G.A., Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet Neurology. 2016;15:913–924.; GBD 2015 Neurological Disorders Collaborators Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 16, 877–897 (2017).]..

Vascular diseases of the brain also cause enormous damage to the national economy. The estimated cost of diagnosing and treating stroke in the United States in 2010 was $ 73.7 billion, and in 2050 it will increase to $ 1.52 trillion [Ovbiagele B., Goldstein L.B., Higashida R.T., Howard V.J., Johnston S.C., Khavjou O.A., et al. Forecasting the future of stroke in the united states: A policy statement from the american heart association and american stroke association. Stroke; a journal of cerebral circulation. 2013;44:2361–2375.].

Stroke is also a leading reason of morbidity and mortality in our country, placing enormous difficulties and efforts on patients, health workers and society. According to the official statistics of the Ministry of Health of the Republic of Kazakhstan, more than 40 thousand cases of stroke are registered in our country every year, of which 5 thousand patients die on one of the first 7 days from the onset of a stroke and another 5 thousand within 30 days after being discharged [АкшулаковС.К., АдильбековЕ.Б., АхметжановаЗ.Б., МедухановаС.Г. Организация и состояние инсультной службы Республики Казахстан по итогам 2016 года //Нейрохирургия и неврология Казахстана – 2018 - №1 (50)].

Thus, the huge numbers of morbidity, leading to high mortality, disability, social consequences and significant material losses around the world and in our country, provide sufficient grounds for defining stroke as a medical and social problem of the state level.

Scientific research studies the role of numerous risk factors for stroke, including both non-modifiable, such as age, gender, race, and modifiable risk factors: arterial hypertension (AH), atrial fibrillation (AF), atherosclerosis, ischemic heart disease (IHD), chronic heart failure (CHF), diabetes mellitus (DM) and smoking, etc. [GBD 2015 Neurological Disorders Collaborators Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 16, 877–897 (2017); O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761–775].

Particular attention should be paid to the progression of the clinical picture of the disease during the first days or weeks after IS, which can lead to an increase in mortality. Neurological complications, such as cerebral edema or hemorrhagic conversion, occur earlier than other complications and can influence results with potential serious short- and long-term consequences [O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761–775; Weimar C, Mieck T, Buchthal J et al. Neurologic worsening during the acute phase of ischemic stroke. Arch Neurol 2005;62:393–7.].

We hypothesize that different mechanisms may contribute to neurological deterioration in the acute early phase compared to the late phase of ischemic stroke.

Despite numerous stroke researches, the factors, which result the aggravation of clinical semiology in the acute period, leading to the progression, including fatality of patients, hospitalized with IS, are still insufficiently studied. Some of these complications can be prevented or, if this is not possible, early detection and appropriate treatment can be effective in reducing the negative effects on the severity of IS in order to ensure safe and effective treatment of patients with stroke.

The available researches to assess of the prognostic factors that lead to the progression of IS in the acute period were carried out abroad. There are no works in this aspect in our country. From the point of view of practical medicine, the great interest is to determine the prognostic value of a number of markers, IS in our conditions, because the current situation dictates the search for new strategic approaches to both treatment and prevention of early progression of neurological symptoms.

Researches of the pathogenesis of IS have shown that ischemic brain damage causes a chain of pathological processes, which include the development of glutamate excitotoxicity, oxidative stress, inflammation, apoptosis, disruption of intracellular ionic homeostasis or necrosis as a result of damage to the blood-brain barrier [Пирадов М.А., Максимова М.Ю., Танашян М.М. - М. : ГЭОТАР-Медиа, 2019. - 272 с. (Серия "Библиотека врача-специалиста") - ISBN 978-5-9704-4910-3].

The existing pharmacological elaboration of a potential treatment for stroke in clinical trials has failed. Intravenous injection of recombinant tissue plasminogen activator (rtPA) is the only FDA(USA)-approved treatment that restores blood flow and is usually given in the first hours of IS. However, rtPA has many significant limitations, one of which is the time factor. Some complications of this drug continue to be a subject of discussion. The difficulties associated with the use of rtPA include the risk of semeiotic intracerebral hemorrhage. Currently, only 2% to 5% of patients with IS receive rtPA treatment due to strict selection criteria [Kleindorfer D, Kissela B, Schneider A, Woo D, Khoury J, Miller R, Alwell K, Gebel J, Szaflarski J, Pancioli A, Jauch E, Moomaw C, Shukla R,

Broderick JP. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. Stroke. 2004;35:e27–29; Del Zoppo GJ, Saver JL, Jauch EC, Adams HP., Jr. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke. 2009;40(8):2945–2948].

To date, there are no approved treatments for many pathological processes that persist in the brain after the acute stage of stroke. Opinions differ among researchers regarding the degree of neuroprotection. In large-scale multicenter researches, a promising strategy for limiting the spread of infarcted tissue, aimed at protecting neurons from postischemic damage by pharmacological compounds, neuroprotective agents have demonstrated modest neuroprotective effects [Lo E.H, Dalkara T, Moskowitz M.A. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci. -2003.Vol.4.-P.399–415.; Moskowitz M.A., Lo E.H., Iadecola C. The science of stroke: mechanisms in search of treatments. Neuron. -2010.Vol.67.-P.181-198.; Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359:1317–1329.; Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after largevessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016; 387:1723–1731]. Numerous neuroprotective methods of treatment have been used and have shown great prospects in animal models. Unfortunately, almost all of them have failed to provide neuroprotection in human clinical trials.

Given the limited therapeutic window for thrombolysis and diagnosis of acute cerebrovascular disorder, the lack of effect of neuroprotective therapy in the acute period of IS, new therapeutic approaches are needed. More effective strategies of stroke prevention and treatment are required to stop and ultimately reverse the stroke pandemic, while universal access to organized stroke services should be a priority.

Modern innovative directions in the field of molecular researches have made it possible to identify quantitative changes in the expression level of microribonucleic acid (microRNA) encoding the synthesis of signal proteins.

The development and improvement of this area of molecular diagnostic methods has opened up new prospects for the rapid detection of miRNAs in clinical samples. New data have emerged about the various biological effects of miRNAs on components of the cardiovascular system. MicroRNAs are important regulators of gene expression and play a special role in the initiation and progression of a number of diseases, including CVD.

The literature summarizes the available data on the correlation of miRNA with both clinical and subclinical coronary artery disease, emphasizing the need to study miRNA as a potential diagnostic and prognostic biomarker for early detection of IHD in the adult population [Щеглова Н.Е. МикроРНК и полиморфизм генов их биогенеза в патогенезе атеросклероза: дис. ... канд. мед. наук: 14.03.03 / Щеглова Наталья Евгеньевна. - Казань, 2015.- 91 с.; Volvert M.L, Rogister F., Moonen G., MalgrangeB.,Nguyen L. MicroRNAs tune cerebral cortical neurogenesis. Cell Death Differentiation.- 2012.-Vol.19,N10.- P.1573–1581.].

In an experimental study, Gupta S.K. and co-author (2010) confirm that during ischemic stroke in rodents, miRNA regulation is interrupted. Further studies are required to better understand the role of miRNA in stroke, as well as the mechanisms of regulation of genes involved in cerebrovascular diseases [Gupta SK, Bang C, Thum T.Circulating microRNAs as biomarkers and potential paracrine mediators of cardiovascular disease. Circ Cardiovasc Genet. 2010;3:484–488].

Clinical researches have also demonstrated the role of circulating miRNAs as potential biomarkers that could facilitate the diagnosis of stroke [Cheng YD, Al-Khoury L, Zivin JA. Neuroprotection for ischemic stroke: two decades of success and failure. NeuroRx. 2004;1:36–45; Selvamani A, Sathyan P, Miranda RC, Sohrabji F. An antagomir to microRNA Let7f promotes neuroprotection in an ischemic stroke model. PLoS One. 2012;7:e32662].. The molecular mechanisms of brain damage in IS are not fully investigated.

In our country, studies in the field of the acute period of ischemic stroke are few, and the obtained data are often controversial. All of the above served as the basis for this clinical and molecular genetic research.

Purpose: to determine the regional clinical features and pathogenetic mechanisms of ischemic stroke progression in the most acute period, including the analysis of stroke genetic markers (miRNA).

Object and subject of the study: The method of continuous sampling was used to analyze all 979 patients admitted to the hospital with stroke in the acute period of the disease, for the period from May 31, 2017 to March 31, 2018. We carried out a detailed clinical, laboratory and instrumental examination according to the algorithm of actions at the level of the admission ward and diagnostic criteria, and the algorithm of actions at the level of the intensive care unit, the department of neuroresuscitation of patients with ischemic stroke. The examination and treatment was carried out in accordance with the approved clinical protocol of the Ministry of Health and Social Development of the Republic of Kazakhstan (December 27, 2014, Protocol No. 18), as well as standard for the organization of neurological care in the Republic of Kazakhstan (Order of the Ministry of Health and Social Development of the Republic of Kazakhstan No. 809 dated October 19, 2015). In order to obtain a more detailed clinical picture, a group of 663 patients with ischemic stroke was selected by the method of exclusion. The average age of the patients was 62.5 ± 5.6 years for men and 71.4 ± 5.1 for women. After the patient was admitted to the hospital strictly according to the clinical protocol in a short time (45 minutes), the diagnosis and differential diagnosis of ischemic stroke were carried out. The diagnostic process was organized as much as possible in the admission department and included the following elements: collection of complaints and anamnesis, general physical examination, neurological examination with auxiliary rating scales, emergency laboratory (clinical, biochemical analyzes, coagulogram) examinations, electrocardiogram (ECG) and X-ray examination chest, if necessary, expert advice. Mandatory urgent specific studies: CT or MRI, transcranial duplex Doppler study. According to the clinical protocol, during the first day of hospitalization, if necessary, in dynamics, mandatory scheduled examinations were carried out.

Objectives:

1. To study the prognostic factors (clinical, laboratory, functional outcome) determining the outcome in different pathogenetic subtypes of ischemic stroke, which can be used to optimize diagnosis and treatment in the acute period.

2. Calculate and compare the survival prognosis and mortality by various statistical methods of IBM SPSS Statistics 23.0 in patients after ischemic stroke, depending on the pathogenetic subtypes.

3. Create databases of candidate genes involved in the development of stroke and siRNA databases to determine the effect of miRNAs on the expression of candidate genes involved in the development of stroke.

4. To study the quantitative characteristics of the interaction of miRNA with mRNA of candidate genes involved in the development of stroke and to substantiate the pathophysiological significance of miRNA and candidate genes associations as biomarkers of ischemic stroke.

Scientific novelty:

1. For the first time, a prospective cohort study was conducted to study the early survival of patients with various pathogenetic subtypes of ischemic stroke in the most acute period depending on clinical and laboratory characteristics, stroke risk factors, functional outcome and comparison of results by gender, age indicators in Kazakhstan using the example of Almaty city.

2. The factors of progression of neurological symptoms leading to early mortality have been determined. The assessment of functional outcomes in the most acute period of ischemic stroke is given.

3. An assessment of the early survival rate (24-72 hours) of patients was carried out depending on clinical and laboratory characteristics, stroke risk factors, functional outcome and pathogenetic subtypes of ischemic stroke. To assess the prognostic factors of early outcomes of IS in the most acute period, statistical methods were used for the first time: in particular, the calculation of survival, the average lifetime in years of patients according to Kaplan-Meier, discriminant analysis, multiple Cox regression, the method of analysis of neural networks was carried out.

4. Associations of miRNA and target genes that can serve as markers for the diagnosis of ischemic stroke have been determined.

5. Identified miR-1181, miR-328-5p, and miR-7110-3p, which can influence the expression of candidate genes for stroke and the expression of alternative genes, which should be taken into account when developing biomarkers that appropriately reflect the interaction of miRNA with mRNA in ischemic stroke.

Provisions for Thesis Defence.
According to the results of the research, we found out (maybe have established) that:
1. Progression of neurological deficit in the most acute period of ischemic stroke is a poor prognostic factor. Patients with progressive course had lower GCS scores, high NIHSS and Rankin scores at admission. A progressive course in the most acute period (24-72 hours) was detected in 36.8% of patients, the clinical picture in 63.1% of patients remained more stable or regressive during the same hours. In the fatal group, early neurological deterioration was observed in 87.5% of patients, in the opposite group in 32.8% (p <0.001).
2. Aggravating risk factors for progression in the acute period are associated diseases: AH, AF, IHD, COPD, T2DM, CRD, as well as hyperglycemia, shortening of the activated partial thromboplastin time, the size of the heart attack focus more than 5 cm in diameter. Unfavorable outcome is associated with late delivery of patients to the hospital, statistically significant indicators were observed when patients were delivered more than 4 hours <0.001, and vice versa, favorable with early delivery up to 2 hours.
3. The increased risk coefficient of hospital mortality in the most acute period of ischemic stroke depends on: impaired swallowing function, respiration more than 28 per minute, disorders of consciousness according to GCS up to 4-9 points. The risk of death increases with scores 21-42 on the NIHSS scale for patients with atherothrombotic IS subtype (0.93) over the age of 65 years with low SBP, for patients with a cardioembolic subtype (0.90) over the age of 67 years, with high indicators of GARDEN. The mortality rate in the discriminant analysis is 6.7%. Discriminant analysis of the parameters of ischemic stroke in patients with different etiologies revealed the prevalence of mortality in patients with cardioembolic IS.
4. The best method of statistical calculation for predicting survival after ischemic stroke is the Kaplan-Meier method, which allows ranking patients according to the subtypes of IS, so the risk of death begins to increase after 40 years for atherothrombotic stroke, for cardioembolic after 56 years. The prediction method using computer intelligence "neural networks" in the training example showed 9.5% mortality from the total number of patients with ischemic stroke of various etiologies with a percentage of correct answers of 97.4%, and identifying the effect of cardiac components on patients' status after IS.

   The average survival time directly depends on the patient's status at admission; according to Wilcoxon, the significance of 0.531 for the NIHSS scale is 16-20 points.
5. Quantitative characteristics of the interaction between miRNAs and their target genes serve as the basis for the development of molecular laboratory methods for diagnosing stroke using the association of miRNAs and candidate genes: *CALM1, HTRA1, LDLR, MMP2, NOTCH3, SMARCA4, SORT1, ZDHHC22, ZFHX3.*

Practical importance:

1. A prospective cohort study made it possible to study the prognostic factors determining the outcome in different pathogenetic subtypes of ischemic stroke, which can be used to optimize diagnosis and treatment.
2. The most precise clinical and laboratory predictors, necessary for constructing models of prediction, have been determined.
3. The best method of statistical calculation for predicting the survival of Kaplan-Meier has been adapted, which made it possible to rank patients according to IS subtypes, as well as artificial neural networks of mathematical modeling.
4. The adapted algorithm: "Assessment of the swallowing function in patients in the acute period of stroke" (Implementation Act dated April 9, 2018) is available for use in practical healthcare, which allows timely diagnosis and determination of tactics of managing patients with impaired swallowing function in ischemic stroke.

5. The adapted algorithm: "Methods of secondary prevention of cardioembolic stroke in atrial fibrillation" (Implementation Act dated April 9, 2018) is rational for use in clinical practice and allows to improve secondary prevention and prognosis for cardioembolic stroke.
6. The "Cognitellect simulator" developed by us (Patent for industrial model No. 2692 dated September 18, 2017) is recommended for use in clinical practice. It improves motor and cognitive functions after suffering an ischemic stroke.
7. 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.

Personal contribution of the author of thesis.
The author of thesis was directly involved in the diagnosis and determination of tactics for the management and treatment of patients with stroke. Within the framework of the thesis work, all researches of the hospital stage with the interpretation of data and observation in dynamics were carried out directly with the participation of the author. In addition, the author assessed the neurological status using the appropriate scales. The author independently conducted a literary search on this issue, collecting a database with the creation of a hospital register, primary processing of the material, and interpretation of the obtained results.
 Candidate for the degree participated in molecular genetic research, statistical analysis. The thesis was written by the author independently, with the preparation of an algorithm for the diagnosis and management of patients with IS, and the formulation of conclusions and recommendations.

Work Testing
        The principal provisions of the thesis work were reported at a joint meeting of employees of the Department of Nervous Diseases of the NC JSC "KazNMU named after S.D. Asfendiyarov" and the Research Institute of Biology and Biotechnology KazNU named after Al-Farabi.

The principal provisions of the thesis work were reported and discussed at:
1. "The 2nd European Stroke Organization Conference 2016" (Barcelona, Spain, May 10-12, 2016)
2. "The 10th World Stroke Congress 2016" (Hyderabad, India, October 26-29, 2016)
3. International educational forum "Neurology Update in Kazakhstan 2017" (Almaty, Kazakhstan, March 28-30, 2017)
4. "Society of Vascular and Interventional Neurology 10th Annual Meeting" (Boston, USA, November 8-11, 2017)
5. Scientific-practical conference with international participation "Spring School of the Kazakhstan National Association of Neurologists "Neuroscience" (Almaty, Kazakhstan, April 27-28, 2018)

Published papers on the results of the thesis study:
3 articles – in the publication, indexed in the Scopus information database:
1. **A.M. Kondybaeva,** A.N. Akimniyazova, S.U. Kamenova, A.T. Ivashchenko. The characteristics of miRNA binding sites in mRNA of ZFHX3 gene and its orthologs. Babylonian Journal of Genetics and Breeding. 2018; 22(4). ISSN 2500-0462(Print). ISSN 2500-3259 (Online). Scopus CiteScore 2018 - 0,45. https://doi.org/10.18699/VJ18.380 c.438-444
2. **Aida Kondybaeva,** Aigul Akimniyazova, Saltanat Kamenova, Gulsum Duchshanova, Dana Aisina, Alla Goncharova, Anatoliy Ivashchenko. Prediction of miRNA interaction with mRNA of stroke candidate genes. Neurological Sciences. Springer International Publishing 2019; 41 ISSN 1590-1874 (Print). ISSN 1590-3478 (Online). Scopus CiteScore 2018 – 1,76 PMID: 31784845. IF – 2,484. https://doi.org/10.1007/s10072-019-04158-x
3. Abdoreza Ghoreishi, Shahram Arsang-Jang, Ziad Sabaa-Ayoun,‡,§ Nawaf Yassi, P.N. Sylaja, Yama Akbari, Afshin A. Divani, **Aida Kondybayeva** et all Stroke Care Trends During COVID-19 Pandemic in Zanjan Province, Iran. From the CASCADE Initiative: Statistical Analysis Plan and Preliminary Results. Journal of Stroke and Cerebrovascular Diseases Elsevier. Vol. 29, No. 12 (December), 2020. ISSN 105-321 (Print). ISSN 1532-8511 (Online). ScopusCiteScore 2019 – 2,9. IF – 1,787
     https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105321

5 articles – in the publications, recommended by Committee for Control in Education and Science of the Republic of Kazakhstan;

1. **Kondybaeva A.M.,** Sharaphanova A.M., Ospanbekova D.M., Kamenova S.U., Abdikadirova J.B., Kharchenko V.V. Cerebrovascular accident due to thrombosis of the transverse sinus. Medicine (Almaty). 2016; 11(173). c.50-54 ISSN 1728-452X(Print). ISSN2518-1009(Online).
http://www.medzdrav.kz/images/magazine/medecine/2016/2016-11/M_11-16_050-054.pdf
2. **A.M. Kondybaeva,** G.A. Dushanova, K.K. Kuzhibaeva, Zh.B. Dyusembaeva, G.A. Umutbaeva. Features of ischemic stroke in different age groups of hospital patients. KazNMU Bulletin 2018; 2. c.110-112 ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). RSCI Citation Index 2018г. – 403
3. **A.M. Kondybaeva,** G.A. Dushanova, K.K. Kuzhibaeva, Zh.B. Dyusembaeva, G.A. Umutbaeva. The role of transient ischemic attack in the development of ischemic stroke. KazNMU Bulletin 2018; 2. c.113-115 ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). RSCI Citation Index 2018г. – 403
4. **A.M. Kondybaeva,** S.U. Kamenov, K.K. Kuzhibaeva, Zh.Kh. Zheldybaeva, Zh.B. Dyusembaeva, G.A. Umutbaeva. Assessment of swallowing function in patients in the acute period of stroke. KazNMU Bulletin 2018; 3. c.85-87 ISSN 2524-0684 (Print). ISSN 2524-0692 (Online). RSCI Citation Index 2018г. - 403
5. T. Ivashchenko, R. Ye. Niyazova, Sh. A. Atambayeva, A. Yu. Pyrkova, D. E. Aisina, O. Yu. Yurikova, **A. Kondybayeva,** A. Akimniyazova, D. Bayzhigitova, A. A. Bolshoy. miRNA: achievements, misconceptions, perspectives. News of the NAS RK. Institute of Biology and Biotechnology. Biological and Medical Series. 2018; 4(328). c.36-46 ISSN 2224-5308 (Print). ISSN 2518-1629 (Online)

5 abstracts - in collections of foreign international conferences (including foreign - 5 and indexed in the Scopus database - 3).

1. **Kondybayeva,** S. Kamenova, K. Kuzhibaeva, M. Zhanuzakov, A. Sharaphanova. Stroke in Kazakhstan. European Stroke Journal, 2016, Vol.1(1). The 2-nd European Stroke Organisation Conference. c.59-60. ISSN: 2396-9873 (Print). ISSN: 23969881 (Online)
2. **Kondybayeva,** S. Kamenova, M. Zhanuzakov. Dementia in patients with Ischemic stroke in Almaty. International Journal of Stroke 2016, Vol. 11(3S) Abstracts for the 10th World Stroke Congress, 2016. c.162. ISSN: 17474930 (Print). ISSN: 17474949 (Online). DOI: 10.1177/1747493016670567
3. **Kondybayeva,** S. Kamenova, K. Kuzhibaeva, M. Zhanuzakov. Ischemic stroke in patients with overweight, obesity and comorbid disorders. International Journal of Stroke 2016, Vol. 11(3S) Abstracts for the 10th World Stroke Congress, 2016. c.251. ISSN: 17474930 (Print). ISSN: 17474949 (Online). DOI: 10.1177/1747493016670567
4. **Kondybayeva A.M.,** A.Akimniyazova, G.Duchshanova, S. Kamenova, A.Ivashchenko. The characteristics of miRNA interaction mRNA of ZFHX3 gene and orthologs. Abstracts Collection of the International Conference «Clinical Proteomics. Postgenome Medicine». Between October 30 and November 1, 2017 Moscow, Russia. c.121-122. ISBN: 978-5-89152-024-0
5. **Aida Kondybayeva,** Saltanat Kamenova, Murat Zhanuzakov. Cerebral infarction due to thrombosis transverse sinus. Interventional Neurology 2017, Vol.6, suppl.1. Society of Vascular and Interventional Neurology. 10th Annual Meeting and 5th Annual Stroke Center Workshop, Boston, MA, November 2017: Abstracts. c.9. ISSN: 1664-9737 (Print). ISSN: 1664-5545 (Online). DOI: 10.1159/issn.1664-5545

The volume and thesis structure of the thesis work for the degree of Doctor of Philosophy (PhD).

The thesis work is covered in 147 typewritten pages.

The structural elements of the thesis work consist of: introduction, main part (literature review, materials and methods, research results, discussion), conclusions, practical recommendations and applications.

Scientific work is illustrated with 25 figures, 31 tables, 3 appendices. Information about the literature used in writing the thesis contains 312 sources, in Russian and English.