

## A Cerebralstroke and the Problem of Inflammatory Complications

Murat Zhumabayev, Nurila Maltabarova and Alexey Kokoshko  
JSC “Astana Medical University”, Beybitshilik St. 49, 010000 Astana,  
A Republic of Kazakhstan

---

**Abstract:** A cerebral stroke in recent decades as a cause of death reaches the level like cardiovascular diseases. Against the backdrop of increasing the duration of life of modern society, this situation is becoming increasingly important. The reduction of length of life is a manifestation not only of cerebral stroke but also a great contribution to this process brings the development of inflammatory complications of stroke.

**Key words:** Cerebral stroke, systemic inflammation, complications, reduction, decades

---

### INTRODUCTION

The last few years the number of Cerebral Stroke (CS) progressively increases in all countries, in particular due to ischemic cerebrovascular disorder. The World's Health Organization (WHO) experts suppose a further increase in the number of Ischemic Stroke (IS) in the next few decades which is caused by the increasing number of elderly people and the prevalence of CS risk factors such as hypertension, obesity, diabetes, smoking, etc.. The problem of acute cerebral stroke is in the front burner also in the Republic of Kazakhstan (RK), where is the mortality rate is one of the highest in the world 239.9 per 100,000 deaths which is much more than, for example, in Japan, 75.8 and in the USA - 48.0 (Murray and Lopez, 1996). It is interesting that in developing countries two-thirds of deaths are caused by cerebral stroke. It was also found that for the first time in some countries it has exceeded the number of myocardial infarction. According to the results of major international studies (NICS, Syst-Eur, STONE), in the structure of cardiovascular disease cerebral strokes are dominated in frequency over myocardial infarctions by about 30% (Howard and Howard, 2002; Moiseev and Kobalava, 2002). As a result of increasing the duration of life, mortality due to stroke in 2020 will increase by almost half. However for study of a problem of cerebral stroke in comparison with studies of heart diseases or oncologic diseases, is expended much less financial a human resources.

The object of study: literary sources on the occurrence of cerebral stroke and the development of systemic inflammation in patients with this pathology.

### MATERIALS AND METHODS

Throughout last decade, major diseases which had carried away the most human lives become ischemic heart

disease, stroke, lower respiratory tract infections and chronic obstructive pulmonary disease (WHO, 2014b).

According to the WHO it should be noted that in comparison with the year 2000 the death rate from stroke increased in 2012 (Fig.1 and 2).

According to the global burden of disease study 2010 published in The Lancet in 2010 around the world the stroke occurred in 16.9 million people and almost 33 million people were living with the consequences of stroke. In 2010, on a global scale the number of stroke-related deaths totaled 5.9 million and for the whole year stroke caused nearly 102 million years of life lost due to disability and premature mortality. At the same time the dynamics of the number of strokes is expressed varies between countries and the largest increase over the past 20 years, recorded in low and middle-income countries (Feigin *et al.*, 2014).

Each year in all over the world recorded 6 million of cerebral strokes, of which for example, in Russia 450 thousand. At the same time in the Republic of Kazakhstan, for the year 2010 a cerebral stroke had >32 thousand people. In recent years a stroke is in 2-3 times higher than myocardial infarctions (Stepkina *et al.*, 2016).

WHO has published the data on which the incidence of stroke, also depends on national and racial characteristic (WHO, 2015). It is most commonly seen in Negroid, less - Mongoloid and even less from the Europeans. African Americans, Asians, Hispanic, white Americans - in that order reduced the risk of stroke in the United States. There was no found direct relationship between the professional activity and the probability of stroke. According to the WHO fact sheet 27-29% combined intellectual and physical work at the

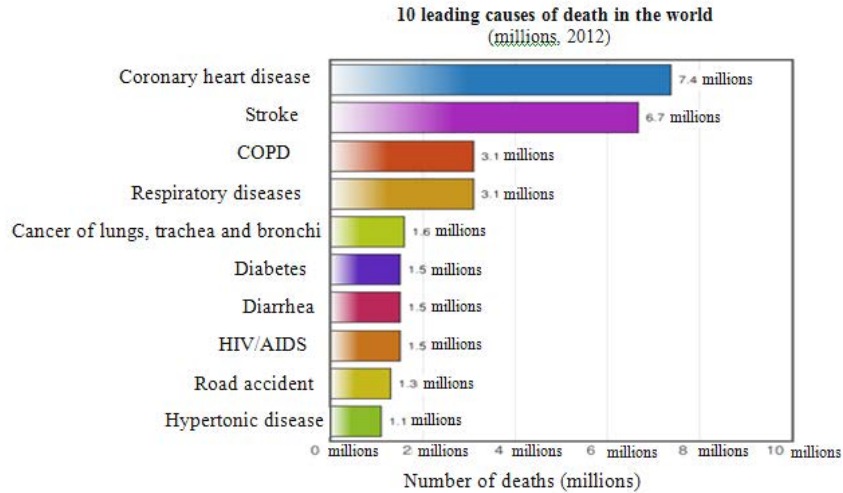


Fig. 1: 10 leading causes of death in the world (WHO, 2014b)

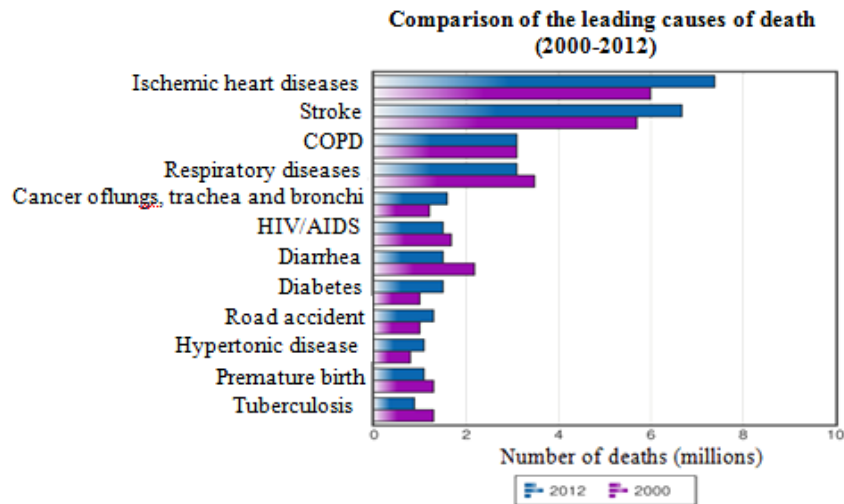


Fig. 2: Comparison of the leading causes of death over the years (WHO, 2014b)

time of occurrence of stroke; 31-33% was engaged in physical labor and 30% of mental activity (WHO, 2015).

There is a clear relationship between age and the incidence of stroke after 55 years, the risk of having a stroke sharply increases and doubled in the next ten years. Ischemic stroke is the most common type of stroke. It amounts 80% of all cerebral strokes, being the most common cause of disability. According to the WHO report of 2014 “World Health Statistics” is only 10-13% recovered completely after a stroke, while the rest either die or in one way or another become disabled. At the same time 31% of stroke survivors need help to care for themselves, while 20% are deprived of the ability to move independently (WHO, 2014a).

Most often from a stroke suffer people who already have atherosclerosis, hypertension or cerebral aneurysms. Embolization of cerebral vascular by a thrombus formed of atherosclerotic plaque in one of the arteries becomes the cause of ischemic stroke in 95% of cases. According to the anamnesis in 15% of patients stroke was preceded by a mini-stroke or transient ischemic attack. At the same time, these figures are clearly underestimated because most have had a mini-stroke do not attach importance to the existing symptoms and neglect medical care. This is due to the fact that over time, often in 24 hours the symptoms of a transient ischemic attack independently stopped (Moiseev and Kobalava, 2002).

According to the Statistical Abstract of the Republic of Kazakhstan for 2012 on death rate from cardiovascular diseases, we are in second place in the CIS after Moldova. In the Republic of Kazakhstan is about 2 million people suffering from cardiovascular diseases, it is approximately 12% of the working age population of the country. At the same time, Kazakh scientists contend that official data is statistically lower than the real picture. Following the statistics, we can trace the increase in the prevalence of cardiovascular disease in Kazakhstan: 2001-6755 100000 and in 2010-11304 per 100000 populations (Smailov, 2013).

In 2010, more than 32 thousand people in Kazakhstan suffered a stroke. More than 200 thousand people receive disability benefits, due to the prior stroke. 2.5 - 3.7 cases per 1,000 people - that the incidence of stroke in different regions of Kazakhstan, the mortality rate is from 1.0 to 1.8 cases per 1,000 per year. In comparison with the Russian Federation: 2.5-7.43 cases of stroke per 100 people per year (Smailov, 2011; FSSS, 2011).

In the Republic of Kazakhstan was developed and implemented a scientific and technical program. This program is dedicated to study problems in the field of cerebral circulation, namely, treatment and rehabilitation of patients undergoing hemorrhagic and ischemic strokes. This program, given the geographical and ethnic characteristics, enabled to investigate the epidemiology of stroke in different regions of Kazakhstan. According to WHO recommendations was chosen registry method which is the scientific basis for the organizing treatment and medico-social rehabilitation of patients with stroke and prevention of disease. According to the register of the incidence of stroke in the Republic of Kazakhstan are 2.5-3.7 cases per 1000 population per year, the death rate from 1 to 1.8 cases per thousand people per year. Depending on the age consistent with global trends, thus the average age of patients was 67 years. Among stroke 29% are in a working age (up to 60 years). Overall mortality in the acute phase of stroke was 35.2 % (60.1 % in women, in men -39.9%).

## RESULTS AND DISCUSSION

As a result of monitoring of cerebral strokes in Semey and Ust-Kamenogorsk, during the year were registered 280 cases per 100 000 men, 260 cases per 100,000 in women and 490 per 100 000 and 410 per 100 000 population, respectively. As a result of ischemic stroke in 10 years in Semey was observed increase in the number of acute cerebrovascular accident. In comparison to 2001 because of the increase in patients with ischemic stroke (2.2 times), the number after stroke in 2010 was increased

by 1.8 times. Most likely, this phenomenon is determined by improvement possibilities of therapeutic and diagnostic facilities, the transformation of primary care tactics, focused primarily on the hospital, not only the actual increase in the incidence. Increase in the number of hospitalized patients, to a certain extent can be explained by the increase in the resident population in the service area and the increase in life expectancy in the region (Khaibullin, 2007).

As a result of epidemiological study of cerebral stroke in 2008-2009 years Atyrau region in the Republic of Kazakhstan the incidence of stroke was 270 cases per 100 000 people, of which 173 100 000 were the incidence of the primary stroke. With that, the number of men of Kazakh nationality between the ages 40- 59 years was 143 per 100 000 population. The highest incidence of ischemic stroke is among the Kazakhs - 130 per 100 000 population ( $p > 0.005$ ). It should be noted that more than 50% of patients with ischemic stroke were in working age (Lee, 2009).

According to the monitoring study in year 2007 in the city Shymkent were revealed high rates of cerebral stroke - 291 per 100,000 people. As in the whole Republic, ischemic strokes prevailed over hemorrhagic, 74.9% versus 25.2%. During this observation period (2007), the death rate from cerebral stroke in Shymkent was 194 per 100 000 population. The average age of the men had a stroke - 57.4 years, women - 60.0 years. The same study showed that a greater number of cerebral stroke (Pazylybekov, 2007) have been reported among the Kazakhs.

As you can see from the above, a stroke is a terrible problem of the modern world which is clearly shown in the newsletter of the World Health Organization in May, 2014. From these data, the prevalence of cerebral stroke tends to repeated growth (WHO, 2015).

Johnston *et al.* (2009) performed a systematic review which analyzed the mortality due to stroke and the loss of DALY (disability -adjusted life years) associated with stroke in 192 countries around the world. This analysis traces a clear correlation between high medical and social burden and low well-being of the country which leads to widespread of cerebral strokes in this country. The difference between a developed and developing countries reached 10 times the amount. So in Eastern Europe, northern Asia and central Africa and in the southern region of Oceania, the highest mortality rates and the DALY are caused by stroke. Russia is on the first place in terms of mortality from stroke in the studied 192 countries (251 to 100 thousand. Population), followed by Kyrgyzstan (237-100 thousand of population), the Seychelles are located on the bottom line of this rating (24-100 thousand of population). Australia, USA, Canada,

Switzerland, occupy one of the last positions (184, 186, 189 and 191 th, respectively), because mortality from cerebral stroke in these countries was the lowest (33-100 kDa population in Australia, 32 - in the US, 27 - Canada, 26 Switzerland). The average mortality rate from strokes amounted to 111 100 thousand of population in the countries participated in the study. The DALY is demonstrated similar patterns. The mortality and DALY loss from stroke ( $p < 0.0001$ ) have revealed a clear link with low national income per capita which is unrelated by influences of other risks of cardio-vascular diseases. It should be noted that the relationship between mortality from strokes and middle level population's welfare was more pronounced than the effect of intra-known risk factors for these indicators (Johnston *et al.*, 2009).

These results resonate with data of Feigin *et al.* (2009). The researchers analyzed the materials of 56 population-based studies from 1970 to the present day. Hoping to find out the dynamics of the incidence of cerebral strokes, they found that the incidence of stroke is increasing much more intense in the "poor" countries (compared with economic development). 42% - this is the increased incidence of stroke in the past 40 years in countries with high income per capita, while in countries with low and middle-income countries increased incidence of stroke amounted to >100%. From 2000-2008, the difference between the incidences of stroke was more than 20% in the "rich" and "poor" countries.

It should be noted that not only the stroke lead to death and neurological deficits but also a significant stake in these processes brings the development of inflammatory complications. Conducted by Westendorp *et al.* (2011) meta-analysis showed that in the acute phase of stroke it develop in every third patient. Course and prognosis of stroke have a clear link with the development in the patient infectious and inflammatory complications that have a pronounced negative effect on the outcome of the disease (Kumar *et al.*, 2010). The successful patient recovery after a stroke is needed prevention, diagnosis and timely treatment of complications (Kutlubaev, 2014).

Inflammation is a nonspecific protective response of the body to tissue injury and the basis for most of the pathological processes. Cytokines are a group of modulators of inflammation and immune response (Vilenskii, 2003). The high rate of respiration (Oxygen consumption) in the body and the greatest consumption of glucose provide the intensity of energy metabolism in the brain. Cortex occupies the first place on these indicators. The vulnerability of neurons in the cerebral cortex by a violation of local hemodynamic function are caused by small reserves of carbohydrates and a limited

ability to use other substrates oxidation. Changes in the area of ischemia are not homogeneous. The central part of it meanly dead cells on which are adjacent "deafened" functionally depressed viable cells. During hemodynamic crisis microglia and astrocytes are activated and proliferate and starts a cascade of hemodynamic, metabolic and ionic changes.

Focus point of dead cells provokes an inflammatory reaction which is accompanied by a massive release and the formation of pro-inflammatory cytokines not only by brain cells, but also by infiltrated and accumulated in the ischemic hearth polymorphonuclear leukocytes, monocytes macrophages. The penetration of the formed elements is caused by damage the Blood Brain Barrier (BBB), due to ischemia (Sharkey *et al.*, 1997).

It should be noted that, it is dangerous not only macrofocal brain damage but also micro ischemic foci entail the permanent maintenance of the inflammatory process. Caused at the first moment by inflammation "mediator storm" in view of the uncontrolled in its development, can ruin not only "deafened" cells but also healthy, not involved in the process, brain cells that generates a new wave of release of pro-inflammatory cytokines and the fixation of pathological range: death cells-inflammatory response (Barone and Feurstein, 1999).

In old age for the immune system is peculiar to be pre-inflammatory and pre-autoimmune, what condone self-propagation of such pathological range. In this regard the appearance of early disorders of higher mental activity and other cognitive functions which are caused by cerebral ischemia and followed by a "bouquet" of hypertension, atherosclerosis or diabetes, are often not identified with modern diagnostic equipment (Koistinaho and Koistinaho, 2005).

In recent years are marked by the publication great number of works that explain the pathogenesis of immune-inflammatory processes of ischemic stroke. "Mediator storm" is accompanied by a lack of protective anti-inflammatory interleukins and nutrition due to formation of infarct changes in the brain tissue. There are several different mechanisms that lead to inflammation (e.g., an increased concentration of the anion peroxide oxidation of phospholipids, chemotactic cytokines, cell adhesion of leukocytes and m. P.) and a variety of genes which is expressed in the various cell types, involved both the inflammatory processes and in processes of the immune response to inflammation. Polymorphisms of several of these genes have been associated with cardiovascular diseases (Gromova and Torshin, 2008). Activated by ischemia microglia and astrocytes produce a number of pro-inflammatory cytokines such as Tumor

Necrosis Factor (TNF), Interleukin-1a (IL-1a), Interleukin 6 (IL-6) and chemokines and also other potentially toxic molecules including Nitric Oxide (NO), prostanoids (Adams *et al.*, 1993; Alberts, 2004; Flomann *et al.*, 2004). Increased production of pro-inflammatory cytokines, particularly IL-1 and IL-6, lead to the activation of the synthesis by the liver cells a proteins in acute phase (C-reactive protein, fibrinogen, ferritin) which along with other cellular (leukocyte count, neutrophil count) and a molecular (proinflammatory cytokines, chemokines, metalloproteinases) factors which act as markers of systemic inflammatory response (Poiseev, 1999; Alberts, 1991; Markus *et al.*, 1995; Hou *et al.*, 2001). Unfortunately, it is hidden from the understanding the clinical value of indicators of systemic inflammation in cerebral ischemia. The main anti-inflammatory cytokines of interleukins family - IL-1, IL-6, TNF - are synthesized and activated in an hour after the ischemic stroke (Barone and Feuerstein, 1999). Provoking the development of the inflammatory response and as a kind of "labels" for leukocytes, these mediators contribute to their passage through the blood-brain barrier, at the same time causing the activation of adhesion molecules (of ICAM) and tissue metalloproteinases (Lo *et al.*, 2003; Maier *et al.*, 2006). Thus, the study of genes which control the activity of cytokines that are the mediators of inflammation can be one of the way to the study mechanisms and course of cerebral ischemia and detecting predisposition.

### CONCLUSION

Despite the large number of studies, this subject remains poorly understood and requires further analysis and study. In our opinion, the problem of cerebral stroke is not only in cause of its appearance, but also in its further flow, the development of inflammatory complications. And as a result, deterioration of neurological outcome and quality of life of patients after occurred vascular accident.

What are the ways to solve this problem? As mentioned above, probably the easiest way will be to prevent and/or decrease the severity of inflammation in the acute phase of cerebral stroke. The solution of this problem is evidenced by numerous inflammatory diagnostic methods. However, these methods of identification an inflammation and degree of severity are expensive tools and are applicable only in the major scientific and clinical centers. Their use in routine practice of conventional hospitals is enough difficult and "unprofitable".

In our research, we aim to provide a tool which allows without considerable financial costs and "exclusive"

laboratory studies to assess inflammatory changes on the basis of clinical and routine laboratory tests to help the physician, regardless of hospital status, to identify early signs of inflammation and apply appropriate methods of correction system inflammation. The use of early diagnosis of inflammation will allow to prevent inflammatory complications in patients with stroke.

### REFERENCES

- Adams, H.P., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon and E. Marsh, 1993. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 24: 35-41.
- Alberts, M.J., 1991. Genetic aspects of cerebrovascular disease. *Stroke*, 22: 276-280.
- Alberts, M.J., 2004. Genetics of cerebrovascular disease. *Stroke*, 35: 342-344.
- Barone, F.C. and G.Z. Feuerstein, 1999. Inflammatory mediators and stroke: New opportunities for novel therapeutics. *J. Cereb. Blood Flow Metab.*, 19: 819-834.
- FSSS., 2011. Statistical yearbook of the Russian Federation 2010. Federal State Statistics Service, Moscow, Russia.
- Feigin, V.L., C.M. Lawes, D.A. Bennett, S.L. Barker-Collo and V. Parag, 2009. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol.*, 8: 355-369.
- Feigin, V.L., M.H. Forouzanfar, R. Krishnamurthi, G.A. Mensah and M. Connor *et al.*, 2014. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *Lancet*, 383: 245-255.
- Floâmann, E., U.G. Schulz and P.M. Rothwell, 2004. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. *Stroke*, 35: 212-227.
- Gromova, O.A. and I.Y. Torshin, 2008. Vascular diseases of the heart, brain and molecular genes. Part 1: Associative research and the pathophysiology of cardiovascular disease. *J. Difficult Patient*, 4: 5-7.
- Hou, L., D. Osei-Hyiaman, H. Yu, Z. Ren, Z. Zhang, B. Wang and S. Harada, 2001. Association of a 27-bp repeat polymorphism in eNOS gene with ischemic stroke in Chinese patients. *Neurology*, 56: 490-496.
- Howard, G. and V.J. Howard, 2002. Stroke Incidence, Mortality and Prevalence. In: *The Prevention of Stroke*, Gorelick, P.B. and M. Alter (Eds.). The Parthenon Publishing Group, London, UK., pp: 1-10.

- Johnston, S.C., S. Mendis and C.D. Mathers, 2009. Global variation in stroke burden and mortality: Estimates from monitoring, surveillance and modelling. *Lancet Neurol.*, 8: 345-354.
- Khaibullin, T.N., 2007. Clinical and epidemiological and ethnic features of the main risk factors and somatic pathology in stroke in the population of East Kazakhstan synopsis. Dok. Honey Science, Almaty, Kazakhstan.
- Koistinaho, M. and J. Koistinaho, 2005. Interactions between Alzheimer's disease and cerebral ischemia-focus on inflammation. *Brain Res. Rev.*, 48: 240-250.
- Kumar, S., M.H. Selim and L.R. Caplan, 2010. Medical complications after stroke. *Lancet Neurol.*, 9: 105-118.
- Kutlubaev, M.A., 2014. [Infectious-inflammatory complications of cerebral insulitis]. *Klin. Med.*, 92: 66-72, (In Russian).
- Lee, E.Y., 2009. Epidemiology of stroke in Atyrau. Medical Genetic Prediction Abstract, Kand. Honey Science, Almaty, Kazakhstan.
- Lo, E.H., T. Dalkara and M.A. Moskowitz, 2003. Mechanisms, challenges and opportunities in stroke. *Nat. Rev. Neurosci.*, 4: 399-414.
- Maier, C.M., L. Hsieh, T. Crandall, P. Narasimhan and P.H. Chan, 2006. Evaluating therapeutic targets for reperfusion-related brain hemorrhage. *Ann. Neurol.*, 59: 929-938.
- Markus, H.S., J. Barley, R. Lunt, J.M. Bland, S. Jeffery, N.D. Carter and M.M. Brown, 1995. Angiotensin-converting enzyme gene deletion polymorphism a new risk factor for lacunar stroke but not carotid atheroma. *Stroke*, 26: 1329-1333.
- Moiseev, V. and J. Kobalava, 2002. Arterial hypertension in older age groups. Monograph, Medical News Agency, Moscow, Russia, pp: 1-448.
- Murray, C.J.L. and A.D. Lopez, 1996. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. 1st Edn., Harvard School of Public Health, Cambridge, ISBN-13: 978-0674354487, Pages: 1022.
- Pazyzbekov, T.T., 2007. Clinical and epidemiological features of stroke in the urban population (for example, in Shymkent) synopsis. Kand. Honey Science, Almaty, Kazakhstan.
- Poiseev, I.I., 1999. Sustainable Development of the North: The Environmental and Economic Aspects. Nauka, Novosibirsk, Russia, Pages: 139.
- Sharkey, J., J.S. Kelly and S.P. Butcher, 1997. Inflammatory Responses to Cerebral Ischemia. In: *Clinical Pharmacology of Cerebral Ischemia*, Ter Horst, G.J. and J. Korf (Eds.). Humana Press, Totowa, NJ., USA., ISBN: 978-1-4757-4783-6, pp: 235-263.
- Smailov, A.À., 2011. Statistical yearbook of the Republic of Kazakhstan 2010. Agency on Statistics of the Republic of Kazakhstan, Astana, pp: 1-213.
- Smailov, A.À., 2013. Statistical yearbook of the Republic of Kazakhstan 2012. Agency on Statistics of the Republic of Kazakhstan, Astana, pp: 1-206.
- Stepkina, E.L., A.B. Utegenova and Y.A. Tairov, 2016. The organization of care for patients with acute stroke in the prehospital phase in Talgar district of Almaty region. *Vestnik KazNMU No. 1*, Moscow, Russia.
- Vilenskii, B.S., 2003. Somatic complications of stroke. *Nevrologicheskii Zhurnal*, 3: 4-10.
- WHO., 2014a. World health statistics 2014. World Health Organization, Geneva, Switzerland, pp: 1-177. [http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf).
- WHO., 2014b. The top 10 causes of death. Newsletter of the World Health Organization No. 310, May 2014. <http://www.who.int/mediacentre/factsheets/fs310/en/>.
- WHO., 2015. Cardiovascular Diseases (CVDs). Newsletter World Health Organization No. 317, January 2015. <http://www.who.int/mediacentre/factsheets/fs317/en/>.
- Westendorp, W.F., P.J. Nederkoorn, J.D. Vermeij, M.G. Dijkgraaf and D. van de Beek, 2011. Post-stroke infection: A systematic review and meta-analysis. *BMC Neurol.*, Vol. 11. 10.1186/1471-2377-11-11.