Original Paper

Metabolic Alterations in Acute Cerebral Ischemia

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ABSTRACT: Cerebral ischemia is a major health problem worldwide, that affects millions of people, leaving a major percentage of them with major disabilities, therefore becoming one of the most resource consuming pathology. Beside the blockage of blood supply of the brain that leads to loss of cellular function and neuronal necrosis, metabolic processes are modified in the whole body through mechanisms that are not fully explained yet. The results in the analysis of the 2 groups, one with 70 patients with stroke and another with 68 patients with no cerebral infarction, revealed that brain ischemia is more often found in patients with atrial fibrillation and higher blood pressure values. The metabolic changes, found in the stroke group, are represented by increased values of blood glucose, serum urea and lower levels of creatinine levels. Also, the value of leucocytes count and the erythrocyte sedimentation rate were shown to be increased in stroke patients, indicating that inflammation is highly present in cerebral infarction. In the regard of these findings, cerebral ischemia is associated with major systemic disruptions that could be significant pathogenic factors and also effects of the complex processes that take place in the affected brain region, but further investigation should be done in order to explain all the mechanisms involved and also the possible impact in prophylaxis and acute management of stroke.

KEYWORDS: Acute ischemic stroke, metabolic imbalance, cerebrovascular risk factors, neuroinflammation.

Introduction

Stroke is the main cause of long-term disability worldwide and, also, an important predisposing factor for dementia [1] so that cerebrovascular disease has become a major public health issue.

Cerebral ischemia, defined by a marked reduction of the blood supply in a brain region, is the main type of stroke, representing approximately 80% of cerebrovascular events.

It is the result of thromboembolic events caused by cardiac, arterial or hematological pathology, preventing brain tissue from getting oxygen and glucose in the region supplied by the affected vessel [2].

Ischemic strokes account for 66% to 91% of all strokes depending on the region of the globe affected.

The incidence and prevalence of stroke occupy the leading places in the global burden of neurological disorders, especially in middle and low-income countries [3].

Following data, provided by the American Heart Association, shows that, in 2017, 82.4 million people were diagnosed with ischemic stroke worldwide, with the highest prevalence in the states of Central and Eastern Europe as well as in East Asia.

Eastern European countries, as well as Romania, were in the first places also in terms of the mortality of these patients.

Globally, deaths due to this condition amounted to 2.7 million people in 2017 [4].

Regarding the cerebrovascular risk factors, it is known that the incidence of stroke increases with **age** and it doubles every decade after the age of 55.

There are also **genetic diseases** that include cerebral ischemia among their manifestations: autosomal dominant transmitted diseases (e.g. Ehler-Danlos type 4 disease, Marfan syndrome, conditions associated with alpha-actin mutations in the smooth muscle fiber), autosomal recessive transmitted diseases (sickle cell anemia), X linked (Fabry disease) [5].

Hypertension is considered the most important risk factor for cerebrovascular disease and is found in 54% to 64% of stroke patients [6].

At the same time, it is known that blood pressure values increase with age, the prevalence of hypertension being significantly higher in people over 65 years [7].

Current guidelines, both American (The American Guidelines for Management of Hypertension) and European (The European Guidelines for the Management of Arterial Hypertension), recommend reducing systolic blood pressure to less than 140mmHg, including the elderly, with a target of 130mmHg if tolerated [8].

Another important modifiable risk factor for cerebral ischemia is **atrial fibrillation.**

It is estimated that there are approximately 33 million people diagnosed with atrial fibrillation worldwide [4].

For these individuals, the risk of ischemic stroke can be quantified using the CHADS2 and CHA2DS2-VASc scales.

This risk varies between 1% and 20% annually.

In the United States, 10% to 12% of all cerebral ischemic events occur in patients with atrial fibrillation [9].

It has been observed that approximately 17% of patients diagnosed for the first time with an ischemic stroke have a second cerebral ischemic event within the next 5 years.

The American Heart Association has published that among patients aged 40 to 69 years, 13% of men and 22% of women will have a second stroke within 5 years of the first event.

For the people aged over 70 years, the incidence increases to 23% in men and 28% in women [10].

The most common risk factors associated with **recurrent ischemic stroke** are diabetes mellitus and atrial fibrillation, implying the need for antithrombotic or anticoagulant treatment in order to prevent cerebrovascular events.

According to the data provided by World Health Organization in 2020, stroke is ranked as the third leading cause of death worldwide, and the incidence and impact of cerebral ischemia are expected to increase considerably over the next 50 years in highly developed countries, as well as in developing countries.

This cerebrovascular event accounts for 7.8 million deaths annually in the whole world, and also for 13% of the total number of deaths across the globe [11].

Stroke represents a major medical emergency defined by the concept "time is brain".

Early recognition of the signs and symptoms of a stroke is particularly important in order to be able to act at the appropriate time, avoiding any kind of delay.

Although, a third of the patients who survive show an improvement in their general condition in the first week of evolution, about 40% show a slow evolution, with the appearance of permanent disabilities, and approximately 20% suffer an aggravation of the initial symptomatology in the first 7 days of evolution [12,13].

The major impact of ischemic stroke in terms of mortality and long-term disability could be in part explained by the significant changes induced in multiple organs and systems.

These alterations are supposed to be mediated by immune reactions and metabolic disruptions, but the physiopathology and significance of this process is not completely elucidated yet.

Inflammatory reaction occurs in multiple acute brain lesions, including ischemic stroke. This response is called **neuroinflammation** [14].

Brain damage following ischemic stroke results in necrosis and apoptosis, all these causes an inflammatory reaction controlled by discharge of reactive oxygen species, chemokines, and cytokines.

This process originates in the microcirculation and involves microglia and lymphocytes that cause neuronal death [15,16].

Cytokines are important mediators in the immune-inflammatory reaction induced by stroke, being involved in the progression of cerebral infarction and influencing its severity.

In association with the inflammatory process induced by cerebral infarction, significant **metabolic changes** are involved, not only as a consequence of the neuronal necrosis and apoptosis, but also in the pathogenesis of the ischemic stroke.

Diabetes favors the process of atherosclerosis, affecting also the cerebral vessels, thus favoring the occurrence of cerebral infarctions, especially the lacunar type of stroke [7].

In patients with known atherothrombosis, cerebral ischemia is closely related to **blood glucose values** above 5.5mmol/l.

Dyslipidemia represents a risk factor that can influence ischemic stroke in multiple ways.

Elevated values of **total cholesterol** increase the risk of cerebral ischemia, while elevated values of HDL (high-density lipoprotein cholesterol) represent a protective factor against atherosclerosis and ischemic stroke [17].

High serum cholesterol is also associated with a higher risk of ischemic stroke in the large cerebral arteries [18,23].

Materials and Methods

This is a cross-sectional study conducted at Neuropsychiatry Clinical Hospital, Craiova, in the period between the 1st January 2020 and 31st December 2021.

The study population consisted of two groups of patients admitted to Neurology Department of Neuropsychiatry Clinical Hospital, Craiova: Group 1 including 70 stroke patients with a confirmed CT scan and Group 2 including 68 non-stroke patients.

The diagnosis of acute ischemic stroke was established by neurology professionals, after the clinical assessment, based on the suspicion of a vascular syndrome then confirmed by brain imaging (CT scan), according to the international guideline's recommendations.

The research monitored the socio-demographic characteristics (age and sex), medical history data and a series of biological parameters for both groups, aiming to study the metabolic disturbances in acute ischemic stroke by analyzing differences between the two categories of patients.

The blood tests performed to determine the metabolic imbalance in stroke versus non-stroke patients were a complete blood count, metabolic panel (blood glucose, serum urea, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST)), cholesterol and erythrocyte sedimentation rate.

The data was collected from the hospital's official database and then analyzed using GraphPad 9.4.1 (GraphPad Software, San Diego, CA, USA).

Continuous variables were presented as mean±standard deviation, being compared using Mann-Whitney test in case of non-gaussian distribution.

Categorical variables were presented as number and percentages, being compared using chi-square test.

Violin plots were created to visually compare the laboratory data between the two groups.

Statistical significance was considered to be $p<0.05$.

The study was conducted respecting the ethical, deontological and legal norms and was approved by the Directing Committee of the Neuropsychiatry Clinical Hospital.

All the patients enrolled in the study were included only after signing the informed consent and their participation was absolutely voluntary.

Results

During the two years period, a total of 70 stroke patients and 67 non-stroke patients admitted to Neurology Department of the Neuropsychiatry Clinical Hospital, Craiova were included in the study.

The demographic distribution of age and gender for the two groups in the study is shown in Table 1.

The male to female ratio was 4:3 for stroke patients.

Table 1. Demographic distribution of the study population.

	Stroke group (N=70)	Control group (N=67)	*p*-value
Age	71.76±10.11	56.04±16.59	<0.0001
Gender, male	40 (57.1%)	25 (37.3%)	0.026

Studying the co-morbidities, 53 (75.7%) stroke patients had hypertension, with significant difference compared to non-stroke patients, from which only 35 (52.2%) had hypertension (*p*-value=0.016).

No differences were found between the two groups for diabetes mellitus: 10 (14.3%) stroke patients had diabetes mellitus vs. 11 (16.4%) non-stroke patients had diabetes mellitus (*p*-value=0.814).

A significant higher percentage of stroke patients had atrial fibrillation: 18 (25.7%) stroke patients vs. 3 (4.5%) non-stroke patients (*p*-value=0.001), as in Table 2.

Hypertension and atrial fibrillation are significant risk factors for the incidence of stroke, but not the diabetes mellitus.

Table 2. Co-morbidities of the study population.

	Stroke group (N=70)	Control group (N=67)	*p*-value
Hypertension			
No	17 (24.3%)	32 (47.8%)	
Grade 1	4 (5.7%)	5 (7.5%)	0.016
Grade 2	46 (65.7%)	26 (38.8%)	
Grade 3	3 (4.3%)	4 (6%)	
Diabetes mellitus, yes	10 (14.3%)	11 (16.4%)	0.814
Atrial fibrillation, yes	18 (25.7%)	3 (4.5%)	0.001

Regarding the hyperglycemia, even if no differences exist between the two groups, the level of glucose was significantly higher in stroke group compared to non-stroke patients: 121.8±24.87 vs. 114.73±32.86 (*p*-value=0.004) and we can confirm with Figure 8.

The mean of cholesterol was approximately equal to 200mg/ml for both groups of patients, no differences were found between them (*p*-value=0.545).

The results can be observed in the Figure 5.

Regarding the lipid profile, it was found that 34 (48.57%) stroke patients had cholesterol equal or greater than 200mg/dl, which was almost the same percentage as the non-stroke patients: 33 (49.25%).

No differences were found between the two groups of patients for hemoglobin and platelet count, as in Table 3 and Figure 1.

A much higher number of leukocytes were found in stroke patients' group, $9.51*10^9$/L (±3.82) compared to $7.65*10^9$/L (±2.24), *p*-value=0.002.

The differentiation between the two groups is related in Figure 2.

Regarding the erythrocyte sedimentation rate, it was found that stroke patients had significantly higher levels compared to non-stroke patients (*p*-value<0.0001) as in Figure 7.

The level of creatinine was significantly lower in stroke patients than in non-stroke patients (*p*-value<0.0001), as is shown in Figure 6.

Regarding the urea level, it was found that stroke patients had significantly more urea concentrations than non-stroke patients (*p*-value <0.0001), as in Figure 10.

All the information provided by Table 3 is visually present as violin plots in the figures included below.

Table 3. Laboratory data of the study population.

| Parameters	Stroke group (N=70)	Control group (N=67)	*p*-value
Hemoglobin (g/dl)	13.88±1.61	13.5±1.61	0.220
Leukocyte (10^9/L)	9.51±3.82	7.65±2.24	0.002
Platelet count (10^9/L)	255.44±80.85	249.03±66.2	0.716
Erythrocyte sedimentation rate (mm/h)	39.73±32.04	16.25±19.01	<0.0001
Alanine aminotransferase (U/L)	35.45±25.06	28.79±35.82	0.001
Aspartate aminotransferase (U/L)	37.26±34.98	37.52±60.27	0.471
Creatinine (mg/dl)	1.25±0.45	2.26±10.51	<0.0001
Glucose (mg/dl)	121.8±24.87	114.73±32.86	0.004
Urea (mg/dl)	56.95±51.93	37.05±35.03	<0.0001
Cholesterol (mg/dl) ≥200mg/dl	197.59±57.98 34 (48.57%)	200.95±55.27 33 (49.25%)	0.545
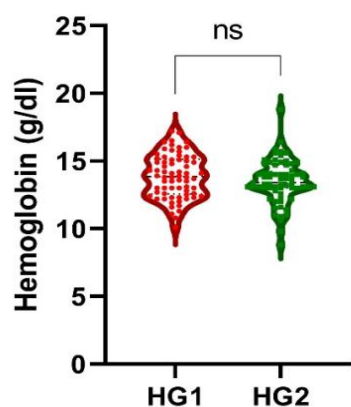
Figure 1. Violin plot showing the distribution of hemoglobin values (g/dl) in stroke group (HG1-in red) and non-stroke group (HG2-in green). The results are insignificant between the two groups (ns).
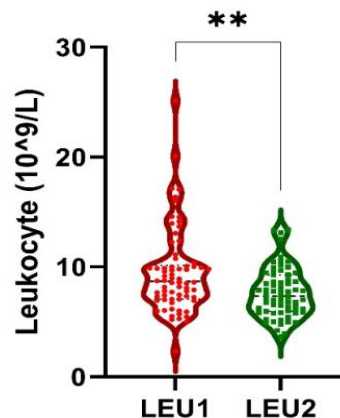

Figure2. Violin plot showing the distribution of leukocyte count values (10^9/L) in stroke group (LEU1-in red) and non-stroke group (LEU 2-in green).
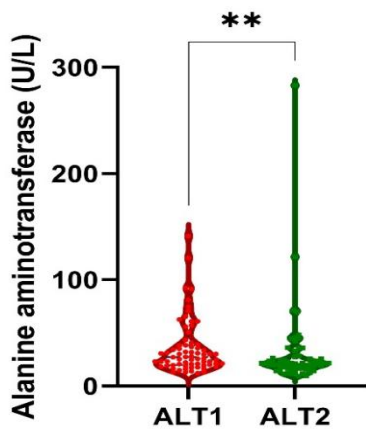
Figure 3. Violin plot showing the distribution of Alanine aminotransferase (U/L) in stroke group (ALT1-in red) and non-stroke group (ALT2-in green).
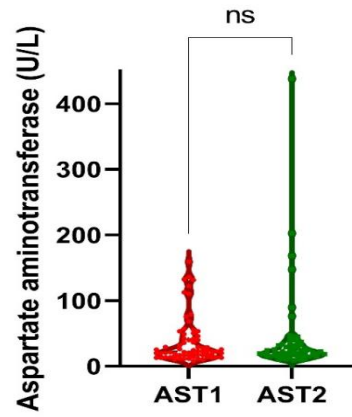

Figure 4. Violin plot showing the distribution of Aspartate aminotransferase (U/L) in stroke group (AST1-in red) and non-stroke group (AST 2-in green). The results are insignificant between the two groups (ns).
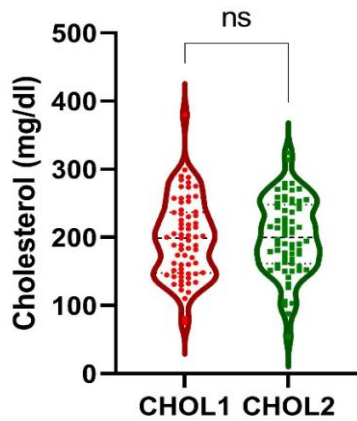

Figure 5. Violin plot showing the distribution of the cholesterol values (mg/dl) in stroke group (CHOL1-in red) and non-stroke group CHOL2) in green). The results are insignificant between the two groups (NS).
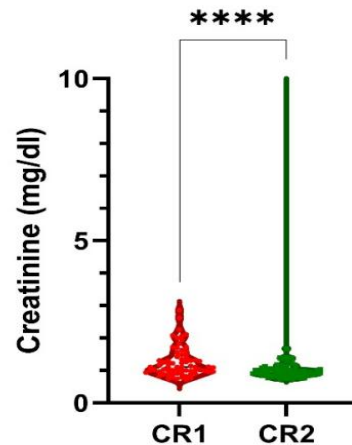

Figure 6. Violin plot showing the distribution of creatinine (mg/dl) in stroke group (CR1-in red and non-stroke group (CR 2-in green).
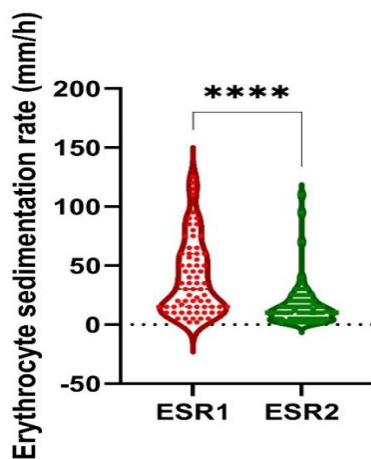

Figure 7. Violin plot showing the distribution of erythrocyte sedimentation rate (mm/h) in stroke group (ESR1-in red) and non-stroke group (ESR2-in green).
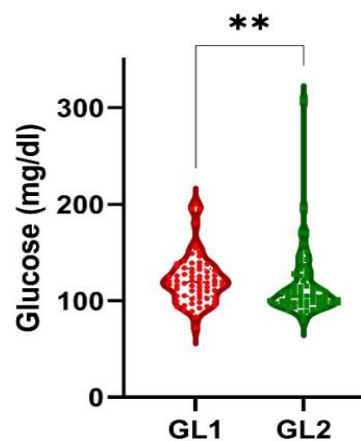

Figure 8. Violin plot showing the distribution of glucose (mg/dl) in stroke group (GL1-in red) and non-stroke group (GL 2-in green).
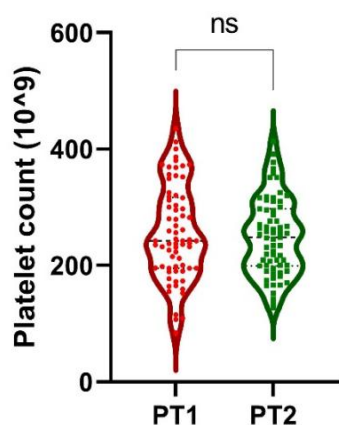
Figure 9. Violin plot showing the distribution of platelet count (10^9l) in stroke group (PT1-in red) and non-stroke group (PT 2-in green). The results are insignificant between the two groups (NS).
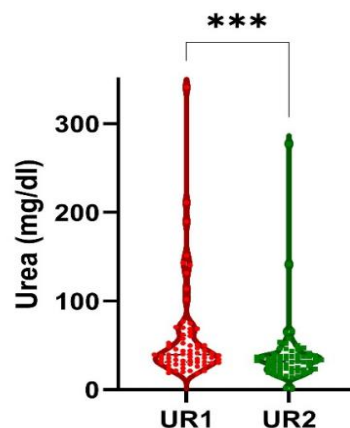

Figure 10. Violin plot showing the distribution of urea (mg/dl) in stroke group (UR1-in red) and non-stroke group (UR 2-in green).

Discussion

Despite the scientific progress recently made in the medical field, the association between ischemic stroke in the acute phase and the complex of metabolic systems is not completely understood yet.

On one hand, regarding the demographic characteristics of the patients, the study shows that in the stroke group, men are more affected than women, so the male gender is a non-modifiable risk factor for ischemic stroke.

On the other hand, it also has been observed that modifiable risk factors, as hypertension and atrial fibrillation, are more common in the stroke group.

These observations are consistent with data provided by studies conducted on larger cohorts, which also suggest that the risk of ischemic stroke in people with atrial fibrillation varies not only by race, but also by geographic area [19].

These observations support the international guidelines treatment recommendations, given the fact that oral anticoagulation reduced the risk of cerebral ischemia compared with the use of antithrombotic medication [20].

Hypertension is found in over a half of stroke patients [6].

Despite all the well-known effects of high blood pressure values in the case of hemorrhagic stroke, the hypertension is also an important risk factor for the occurrence of cerebral ischemia, especially over 65 years old [7].

Discussing the main objectives of this research, a significant difference has been observed regarding the metabolic panel between the two groups.

Thus, the stroke patients had higher levels of serum glucose, urea, erythrocytes sedimentation rate and higher numbers of leucocytes.

Hyperglycemia aggravates the consequences of stroke through increased reperfusion injury by increasing oxidative stress, stimulating systemic inflammation, and increasing blood brain barrier permeability.

Acute ischemic stroke patients with hyperglycemia have also increased platelet aggregation and adhesion to the endothelium.

A study conducted in Glasgow showed that higher blood glucose predicted a worse prognosis even after it was adjusted for age, stroke severity and stroke subtype [21].

Renal function is also affected in the complex systemic changes during acute phase of a ischemic stroke.

So, the level of creatinine was lower in the stroke group, but the urea level was significantly higher in stroke patients, suggesting that renal dysfunction is associated with the cerebrovascular disease.

This data suggests that patients with cerebral ischemia are affected by major metabolic disturbances, involving multiple organs and systems, as the glomerular filtration or the glucose metabolism.

Regarding the neuroinflammation, the higher leucocytes blood count suggests that the known local inflammatory process in the ischemic brain tissue is accompanied by a significant systemic inflammatory reaction in the acute ischemic stroke.

Although, the mechanism of this effect is not completely understood, it is known that first inflammatory neutrophils generate chemokines in the acute phase which will attract others

neutrophils in ischemic tissues, through a graded concentration [22].

Neutrophils contribute to the production of secondary tissue damage by releasing pro-inflammatory cytokines and other cytotoxic products [23,24].

Another biomarker, considered nowadays a not so specific parameter, the erythrocytes sedimentation rate, has proved to be significantly increased, in the blood samples of the stroke patients, supporting the theory of an intense inflammatory process induced by brain ischemia.

The study has not found a statistic significant difference between the stroke and non-stroke group regarding the rest of biological parameters, despite the fact that some of them were mainly recognized as contributive factors to the global cerebrovascular risk.

Such parameters are the serum cholesterol and the platelet count, variables that had similar values in the both groups.

On the one hand, the broad spectrum of metabolic disturbances, identified in the stroke group, is suggestive for the major role of the metabolic imbalance in cerebral infarction pathogenesis, a part of it being already discussed in the medical literature, but not completely explained yet.

On the other hand, a part of this imbalance is also a consequence of the brain ischemia, such as the neuroinflammatory process or hyperglycemia known to be associated with acute stroke, but not completely explained at the moment, despite the major research efforts done in the scientific and medical fields.

Conclusions

This study provides valuable data regarding the brain ischemia associated metabolic disturbances and the impact of the major cerebrovascular risk factors by analyzing the differences between two groups of patients, with, and without stroke.

Across the cerebrovascular risk factors, hypertension and atrial fibrillation had significantly higher prevalence in the stroke group than in the non-stroke one.

Although, there was no difference in the prevalence of diabetes mellitus in the studied groups, the analyzed data shows significant higher levels of blood glucose in the stroke group.

The mean cholesterol level was not different in the studied groups from a statistically point of view.

It has been shown that renal function is also impaired in cerebral ischemia, as it follows: the serum creatinine level was lower, but higher serum levels of urea were found in stroke patients.

A much higher number of leukocytes and also a higher erythrocyte sedimentation rate were found in stroke patients, supporting the existence of an important inflammatory reaction in cerebral infarction pathogenesis.

Conflict of interests

None to declare.

References

1. Mas JL, Leys D. Troubles cognitifs et depressifs. In: Accidents vasculaires cérébraux: thérapeutique (13th ed), Doin, 2018, France, 597-609.
2. Das R, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, Kase CS, Benjamin EJ, Polak JF, O'Donnell CJ, Yoshita M, D'Agostino RB, De Carli C, Wolf PA. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. Stroke, 2008, 39(11):2929-2935.
3. O'Donnell MJ, Xavier D, Liu L, Zhang Hchin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, MCQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Yusoft K, Dans AL, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wan X, Yusuf S. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet, 2010, 376(9735):112-113.
4. Salim S, Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CC, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, KwanTW, Lackland DL, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, Van Wagner LB, Tsao CW. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation, 2020, 141(9):139-596.
5. [Matarin M, Brown WM, Singleton A, Hardy JA, Meschia JF. Whole genome analyses suggest ischemic stroke and heart disease share an association with polymorphisms on chromosome. Stroke, 2008, 39(5):1586-1589.

6. Feigin VL, Krishnamurthi R, Bhattacharjee R, Parmar P, Theadom A, Hussein T, Purohit M, Hume P, Abbott M, Rush E, Kasabov N, Crezee I, Frielick S, Barker-Collo SP, Barber A, Arroll B, Poulton R, Ratnasabathy Y, Tobias M, Cabral N, Martins SCO, Furtado LETA, Lindsay P, Saposnik G, Giroud M, Béjot Y, Hacke W, Mehndiratta MM, Pandian JD, Gupta S, Padma V, Mandal DK, Kokubo Y, Ibrahim NM, Sahathevan R, Fu H, Wang W, Liu L, Hou ZG, Goncalves AF, Correia M, Varakin Y, Kravchenko M, Piradov M, Saadah M, Thrift AG, Cadilhac D, Davis S, Donnan G, Lopez AD, Hankey GJ, Maujean A, Kendall E, Brainin M, Abd-Allah F, Bornstein NM, Caso V, Juan Marquez-Romero JM, Akinyemi RO, Bin Dhim NF, Norrving BO, Sindi S, Kivipelto M, Mendis S, Ikram MA, Hofman A, Mirza SS, Rothwell PM, Sandercock P, Shakir R, Sacco RL, Culebras A, Roth G A, Moradi-Lakeh M, Murray C, Narayan KMV, Mensah GA, Wiebers D, Moran A E. New strategy to reduce the global burden of stroke. Stroke, 2015, 46(6):1740-1747.

7. Vasan S, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study," JAMA, 2002, 287(8):1003-1010.

8. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, Hel J. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis," JAMA Cardiol, 2017, 2(7):775-781.

9. Flint AC, Banki NM, Ren X, Rao VA, Go, "Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: The Stroke and Monitoring for PAF in Real Time (SMART) Registry. Stroke, 2012, 43(10):2788-2790.

10. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA, "Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke, 2003, 34(6):1457-1463.

11. Ropper AH, Samuels MA, Klein J, Prasad S. Aproach to the patient with neurologic disease. Adams and Victor's principles of neurology (11th ed) McGraw-Hill Education, 2019, New York, 778-885.

12. Băjenaru O. Ghid de management al accidentului vascular cerebral ischemic si atacului ischemic tranzitor. In: Bajenaru O (Ed): Ghiduri de diagnostic şi tratament în neurologie (2th ed), Almatea, 2005, Bucuresti,10-79.

13. Hankey GJ, Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovasc. Dis. Basel Switz, 2003, 16 (1):14-19.

14. Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory Mechanisms in Ischemic Stroke: Focus on Cardioembolic Stroke, Background and Therapeutic Approaches. Int. J. Mol. Sci, 2020, 21(18):6454.

15. Ip CW, Kroner A, Groh J, Huber M, Klein D, Spahn I, Diem R, Williams SK, Nave KA, Edgar JM, Martini R. Neuroinflammation by cytotoxic T-lymphocytes impairs retrograde axonal transport in an oligodendrocyte mutant mouse. PloS One, 2012, 7(8):e42554.

16. Na KS, Jung HY, Yong-Ku Kim YK. Kim. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2014, 48:277-286.

17. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH. Folsom. Risk factors for ischemic stroke subtypes: The Atherosclerosis Risk in Communities study. Stroke, 2006, 37(10):2493-2498.

18. Tirschwell L, Smith NL, Heckbert SR, Lemaitre RN, WT Longstreth WT, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology, 2004, 63(10):1868-1875.

19. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, NAlmahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet Lond. Engl, 2016, 388 (10050): 1161-1169.

20. Azoulay L, Dell'Aniello S, Simon TA, Renoux C, Suissa S. Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes. Eur. Heart J,2014, 35(28): 1881-1887

21. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. BMJ, 1997, 314 (7090):1303-1306.

22. Barone FC, Feuerstein GZ. Inflammatory mediators and stroke: new opportunities for novel therapeutics. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab,1999, 19 (8):819-834.

23. Kriz J. Inflammation in ischemic brain injury: timing is important. Crit. Rev. Neurobiol, 2006, 18(1-2):145-157.

24. Yilmaz G, D Neil Granger DN. Cell adhesion molecules and ischemic stroke. Neurol. Res., 2008, 30 (8):783-793.

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