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Review article

Malignant middle cerebral artery (MCA) infarction in people over 85 years old – Diagnosis, management and risk factors



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ABSTRACT

Introduction: Malignant ischemic stroke of the middle cerebral artery (MCA) territory causes neurological deterioration due to the effects of space occupying cerebral edema. The prognosis is poor, and death usually occurs as a result of brainstem compression. There is no information on ischemic stroke, especially the malignant ones, in patients over 85 years old.

Aim: The aim of this retrospective study was to evaluate the disease course, risk factors, survival rate and treatment of MCA malignant infarction in people over 85 years old.

Method: The medical history of 66 patients with malignant MCA stroke was analyzed. The frequency of the occurrence of the risk factors like hypertension, hyperlipidemia, atrial fibrillation, heart failure, diabetes was evaluated. Disability was measured with the use of the National Institutes of Health Stroke Scale (NIHSS). Safety and effectiveness of the anticoagulants used in the group of patients with atrial fibrillation were analyzed. Chi-squared test and Mann–Whitney U test were used for statistical analysis of data. We also described 85 year-old patient with malignant brain stroke who was treated neurosurgically with a positive effect.

Results: Atrial fibrillation was diagnosed in 65% of patients of the investigated group. There were no statistically significant changes in the survival rate between the group of patients treated with the use of mannitol and patients without this treatment.

Conclusion: The key risk factor in this group is the atrial fibrillation. The elderly patients require an intensive monitoring of the health condition by reference to brain stroke risk factors, especially atrial fibrillation.

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The malignant infarction can occur in case of the middle cerebral artery (MCA) stroke. It is a neurological deterioration caused by the severe cerebral edema. The malignant stroke manifests itself in hemiparesis, gaze deviation, headache, vomiting and disturbances of consciousness. That malignant edema usually develops one to several days after the stroke [1]. Treatment is often ineffective, the prognosis is still poor, the survival rate is low and among patients who survived there are many people with severe disabilities. There is a lack of publications related to the ischemic strokes – especially the malignant ones – in people over 85 years old. The incidence of the ischemic stroke increases with age. The risk of the brain stroke is twice higher in case of people over 80 years old than in case of people aged 60–79 [2]. Within the next 20 years, the incidence of stroke is expected to increase by about 100% [3,4]. The malignant edema develops in case of 10–15% of patients with MCA ischemic stroke. The mortality rate in this group is about 80% [1,5,6]. The prevalence of the malignant ischemic edema in the group of people over 85 years old is not accurately determined. Moreover, there is no information on the risk factors of ischemic stroke in people over 85 years old. The European population is getting older and this problem becomes more relevant [2,7,8]. Edema caused by the malignant infarction leads to intracranial pressure increase, reduction of the cerebro-spinal fluid circulation and blood flow in brain vessels, finally leading to compression of the brain stem and death [9]. If the normal cerebral blood flow is reduced and falls below a certain level, the reversible functional failure occurs leading to the morphological damage of neurons [10]. Appropriate treatment of the ischemic stroke, if applied fast, can give a chance to save a brain tissue called penumbra. Due to the lower blood flow, in this area of brain, the neurons' functions are disabled but the apoptosis does not occur [11,12]. The risk factors of the ischemic brain stroke in people over 85 years old remain elusive and they are even less known in case of malignant strokes.

The aim of this retrospective study was to evaluate the disease course, risk factors, survival rate and treatment of MCA malignant infarction in people over 85 years old. The presented study also concerned the case of 85 year-old patient with malignant ischemic stroke treated neurosurgically with a positive effect. Better knowledge of the malignant ischemic stroke in patients in this age group can contribute to the improvement of prophylaxis and treatment strategy.

1. Method

The medical history of 66 patients (M 13, W 53) with malignant MCA stroke (infarction of >50% MCA territory) was analyzed.

The patients were at the age from 85 to 102 years old (the average age: 89 years old, SD 4 years). The agreement of Bioethical Committee in Military Institute of Medicine was obtained for this study. Thrombolytic therapy, osmotic treatment or only anti-platelet agents were used in investigated group. One patient was treated neurosurgically. The frequency of risk factors like hypertension, hyperlipidemia, atrial fibrillation, heart failure, diabetes was evaluated in all patients. Severity of the disease and disability were measured with the use of The National Institutes of Health Stroke Scale (NIHSS). Computer tomography (CT) of brain, ultrasonography of carotid arteries and laboratory tests were also evaluated. Safety and effectiveness of anticoagulants used in the group of patients with atrial fibrillation were analyzed. The survival rate and the most frequent complications following hospitalization were evaluated. The neurological status measured with the use of NIHSS scale and survival rate were evaluated both in the group of people treated with mannitol and in the group of people without this treatment. Chi-quadrat and Mann-Whitney *U* tests were used to perform the statistical analysis of data.

2. Results

In the investigated group, 6% of patients after stroke were diagnosed with the spontaneous hemorrhagic transformation. In case of 7 patients, the thrombolytic treatment was applied. In case of 53% of patients, the malignant edema occurred on the first day of hospitalization. In case of 23 patients, the ultrasonography examination was performed. Clinically significant carotid artery stenosis was observed in case of one patient. In case of 60% of patients the mannitol was administered and 40% of patients did not obtain that treatment. NIHSS score on admission to the hospital, in the group of patients that survived 30 days, was 17.80 (SD 2.85) points and in the group of patients that died in the first month was 18.03 (SD 3.64) points. There was no statistical correlation between NIHSS on admission and survival rate (Table 1).

In the investigated group, 26% of patients had abnormal level of HDL, the same number of patients had abnormal level of total cholesterol and the LDL level of 18% of patients was too high. The abnormal level of triglyceride was observed in case of 8% of patients (Table 2).

The most frequent risk factor diagnosed before the occurrence of the brain stroke was the hypertension (present in case of 58% of patients). Heart failure was observed in case of 44% of patients and atrial fibrillation in case of 41% of patients. Diabetes was present in case of 24% of patients in the investigated group, while 14% of patients had suffered from

Table 1 – Correlation between NIHSS score on admission to the hospital and survival rate.

	Death in 30 days	N	M	SD	Min	Max
NIHSS on admission	No	30	17.80	2.85	8	24
	Yes	36	18.03	3.64	9	25
NIHSS on discharge	No	30	17.17	3.25	8	24
	Yes	36	18.97	3.42	10	25

where n denotes number of patients, data are shown as mean value (M) +/- SD.

Table 2 – Lipid profile abnormalities in patients with malignant ischemic stroke.

	Normal values		Abnormal values		No information	
	n	%	N	%	n	%
Total cholesterol (<200 mg/dl)	44	66.67	12	18.18	10	15.15
LDL cholesterol (<135 mg/dl)	41	62.12	12	18.18	13	19.70
HDL cholesterol (>35 mg/dl – M; >40 mg/dl – K)	36	54.55	17	25.76	13	19.70
Triglycerides (<150 mg/dl)	50	75.76	5	7.58	11	16.67

Where n denotes number of patients, data are shown as mean value (M) +/- SD.

Table 3 – Occurrence of atrial fibrillation in people over 85 years old with malignant ischemic stroke.

AF	Number of patients	Percentage
AF diagnosed before admission to hospital	27	40.91
AF diagnosed during hospitalization	16	24.24
Total	43	65.15

the ischemic stroke in the past. The ischemic heart disease was diagnosed in case of 9% of people. The transient ischemic attack was diagnosed in case of 8% of patients (in case of 80% it occurred in the last year). Only 6% of patients were treated due to hyperlipidemia. Three percent of patients underwent the ischemic heart attack, while 2% of people were diagnosed with the chronic renal failure.

The most frequent risk factor of the ischemic stroke diagnosed during hospitalization was AF which occurred in case of 24% of patients. The congestive heart failure was diagnosed in case of 14% of patients in the investigated group, while hyperlipidemia in case of 12% of patients. Hypertension was present in case of 3% of patients and diabetes in case of 2% of patients. Atrial fibrillation was diagnosed in case of 65% of patients in the investigated group. In case of 41% of patients, it was diagnosed before the stroke, while in case of 24% of patients it was diagnosed during hospitalization in the neurology department caused by the stroke (Table 3).

Among 41% of patients with atrial fibrillation diagnosed before their admission to the hospital only 5 people had taken anticoagulants (vitamin K antagonists) and one person had taken dabigatran. None of the patients in that group had therapeutic INR (between 2.0 and 3.0).

Moreover, there was no statistical correlation between NIHSS score on admission in the group of patients with AF and those without this disease (Table 4).

The Chi-quadrat test did not reveal any statistically significant differences between survival rate in the group of patients with atrial fibrillation and in patients without this disease ($p = 0.423$).

In case of 55% of patients, death occurred during the first month of hospitalization. Among those patients the average survival time was from 2 to 30 days and the average life duration was 11 days (SD 9 days).

The most frequent complication of hospitalization was urinary tract infection occurring in case of 30% of patients. Pneumonia was less common – 23%; 14% of patients suffered from the acute respiratory insufficiency and 11% of patients were diagnosed with the chronic renal failure. Seizures were present in case of 11% of patients and deep vein thrombosis was diagnosed in case of 6% of patients in the investigated group.

Table 4 – Correlation between AF and NIHSS on admission to the hospital.

	FA	N	M	SD	P
NIHSS on admission	No	23	18.43	3.60	0.568
	Yes	43	17.65	3.11	

Where n denotes number of patients, data are shown as mean value (M) +/- SD.

Table 5 – Correlation between survival rate and treatment with the use of mannitol.

Death in 30 of hospitalization	Treatment				Total	
	With mannitol		Without mannitol		n	%
	N	%	n	%		
No	20	54.05	8	33.33	28	45.90
Yes	17	45.95	16	66.67	33	54.10
Total	37	100.00	24	100.00	61	100.00

Where n denotes number of patients, data are shown as mean value (M) +/- SD.

The correlation between administration of mannitol and survival rate was checked with the use of chi-quadrat test (Table 5). The statistical analysis revealed that there were no statistically significant changes in the survival rate between the group of people who were treated with mannitol and patients who did not obtain this kind of treatment ($p = 0.113$).

Statistical analysis performed with the use of Mann-Whitney U test did not reveal any correlation between the mannitol treatment and final NIHSS score (Table 6).

3. Discussion

The impact of factors such as male sex, cardiovascular disease, diabetes, hyperlipidemia on the risk of developing the ischemic brain stroke in people over 85 years old remains

Table 6 – Correlation between mannitol treatment and NIHSS in stroke survivors at the end of hospitalization.

	Treatment	N	M	SD	P
NIHSS on discharge	With mannitol	20	16.20	3.35	0.011
	Without mannitol	8	19.38	2.20	

Where n denotes number of patients, data are shown as mean value (M) +/- SD.

elusive [13]. Moreover, in case of the discussed population, the general health status was poor due to coexistence of dementia, lack of family and medical care. Multiple organ failure often leads to polypharmacy. Patients very often do not take medicines regularly, they have problems with daily activity and access to medical care [14]. One of the most important risk factors of the brain stroke, in addition to hypertension, is atrial fibrillation [15,16]. Given the asymptomatic and undiagnosed AF, the estimated occurrence of this disease in the general population is 1.5–2% but in case of people over 85 years old, it reaches 20% and it is more frequent in case of women [17,18]. Due to the increased occurrence of the atrial fibrillation in patients over 85 years old, it seems that this group could benefit most from the use of anticoagulants, however, the risk of hemorrhagic complications related to taking these medicines is higher compared to younger patients. In the presented study the most common risk factors of brain stroke in the investigated group were hypertension and atrial fibrillation. Atrial fibrillation was diagnosed in case of 65% of patients in the investigated group; in case of 41% of patients it was diagnosed before the occurrence of the stroke, while in case of 24% of patients it was diagnosed during hospitalization in the neurology department caused by stroke. Among 41% of patients with atrial fibrillation diagnosed before admission to the hospital, only 5 people had taken anticoagulants (vitamin K antagonists) and one person had taken dabigatran. None of the patients in that group had therapeutic INR (between 2.0 and 3.0). This proves that medical care in this group was poor and should be more intensive, especially in prophylaxis and diagnosis procedures. Furthermore, when anticoagulants are administered properly, medical care and monitoring of INR should be performed. It seems that this group of patients can benefit more from the above-mentioned treatment but, on the other hand, patients in this group are exposed to higher risk of hemorrhagic complications.

Malignant middle cerebral artery (MCA) infarctions still constitute one of the most life-threatening and destructive forms of ischemic stroke. Computer tomography (CT) and magnetic resonance imaging (MRI) can help reach an early diagnosis as well as predict a malignant course of the disease [19]. In addition, CT is crucial for the exclusion of other causes of the deterioration of neurological status. The first symptom of ischemic stroke that can be observed in CT is inability to differentiate the gray-white matter at the cortex level. If these changes cover over 50% of the MCA territory, it is possible to predict the malignant infarction with a specificity of 94% [1,20,21]. Furthermore, an extent of infarction can be used to predict the malignant course of disease. The infarction volume of >220 ml observed in CT and of >145 ml observed in MRI (DWI sequence) indicates a severe brain edema and herniation [1,22,23]. Development of CT perfusion, PET, SPECT can

contribute to the establishment of earlier diagnosis of malignant edema, however, the qualification of patients for surgery is performed according to classic CT and MRI. Hemispherectomy, hypothermia and pharmacological therapy are used in malignant ischemic stroke treatment [1]. In case of 53% of patients covered by the presented study, the malignant edema was observed in CT images performed on admission to the hospital, on the first day of disease. In other cases the neurological status deteriorated in the first few days of disease and for this reason control CT was performed revealing the occurrence of malignant edema. The important question is therefore whether the earlier image diagnostics performed before deterioration of the neurological status and before development of the malignant edema would improve the treatment outcomes in this group.

Pharmacological treatment is related to the osmotic therapy with the use of mannitol, glycerol, hypertonic saline solutions. In spite of the fact that they reduce existing edema and minimize tissue shifts, they do not significantly improve the outcome [24,25]. In addition, the steroids also proved to be ineffective [25]. The osmotic therapy causes many side effects in people over 85 years old, such as acute renal failure, intensification of heart failure, pulmonary edema, hypotony, and this kind of therapy is still controversial [26]. In case of our study, the osmotic therapy with the use of mannitol did not improve the survival rate. Both in the group treated and untreated with this medicine, the mortality was high (about 50%). On the other hand, in the group of people treated with mannitol, who survived first 30 days of the disease, the final NIHSS score was a little bit lower than in the untreated group.

In case of patients treated pharmacologically, the mortality rate is high and amounts to about 80% [27]. In our study, almost half of patients died during the first month of hospitalization, despite the pharmacological treatment. Moreover, there was no correlation between the survival rate and the occurrence of atrial fibrillation or lipid profile. There was no correlation between disease severity measured with NIHSS score and mean time of survival.

Due to the fact that the pharmacological treatment is usually ineffective, neurosurgical treatment was introduced about 30 years ago [28,29]. The European Stroke Organization developed the guidelines for hemispherectomy to perform operations on people aged 18–60 suffering from MCA occlusion ischemic stroke with malignant edema and severe neurological status deterioration (NIHSS higher than 15 points), disturbances of consciousness, ischemic stroke (covering over 50% of MCA territory). It is very important to perform the surgery during the first 48 h after the occurrence of stroke [29]. In spite of the fact that people who qualified for the surgical treatment were between 18 and 60 years old, 85 year-old woman in the investigated group was operated on with the satisfactory effect. The family of this patient found her unconscious lying on the bedroom floor. She was treated due to hypertension. Before stroke patient was independent. The disturbances of consciousness, global aphasia and right limbs paresis were observed on admission to the hospital. CT scan revealed large ischemic loci with secondary hemorrhage in the left MCA territory. On the fifth day of hospitalization, the CT scan was repeated due to neurological status deterioration and increasing consciousness deterioration, and revealed

malignant edema. On the fifth day of hospitalization, the patient was operated on and the hemicraniectomy was performed. During the next few days the neurological status improved, the patient started to say a few words and was able to perform commands. In the neurology department, the patient was diagnosed with *Clostridium difficile* gastrointestinal infectious but after treatment with vancomycin the patient recovered. The ultrasonography examination of carotid arteries did not show any abnormalities. After two weeks in the hospital, the patient was discharged and admitted to rehabilitation department. The patient was operated on the fifth day of hospitalization, which was also quite unusual and after the surgery, the neurological status of patient improved. In case of patients under 60 years old, currently, the hemicraniectomy constitutes a routine treatment for the clinical management of malignant MCA infarction but the presented study confirms that the indications for decompressive surgery need to be individually investigated. However, there are still some important questions concerning the individual indications for decompressive surgery that need to be resolved. The ideal timing for hemicraniectomy, a potential cut-off age for the procedure constitute the most important questions [19]. Two European randomized, multicenter, controlled trials were performed to investigate the effectiveness and safety of hemicraniectomy in malignant ischemic infarct [6,11]. In the first trial made in France, called DECIMAL, the number of patients with moderate disability increased by more than half due to early decompressive craniectomy which also significantly reduced the mortality in the group of 38 investigated patients [30]. Next study called DESTINY made in Germany covered 32 patients and showed that early hemicraniectomy was effective and patients had better functional outcome as well as survival rate [6]. In DECIMAL study the number of deaths was about 50% lower in the group of people treated with hemicraniectomy when compared to control group which did not obtain this treatment. Moreover, the number of patients with delicate and moderate disability was about 50% lower than in control group [6]. In HAMLET study, the number of patients who died as a result of malignant stroke was about 38% lower when compared to healthy controls [31]. Both trails covered patients under 60 years old. However, as regards the older patients, the results cannot be generalized and there are no sufficient information about the benefits of the procedure in the elderly population. The final results of the DESTINY II study confirm that decompressive hemicraniectomy contributes to the increase of the survival rate without the occurrence of severe disability in patients aged 61 or older who suffered from brain swelling after a malignant middle cerebral artery stroke. In this study 112 patients aged on average 70 years old took part in that study [11,32]. Unfortunately, there are no studies evaluating hemicraniectomy effectiveness and safety in case of people over 85 years old with malignant ischemic infarction. On the other hand, another study revealed that the age exceeding 50 years and the male gender were associated with a high death risk in case of patients with malignant ischemic stroke [33]. Similar results were presented in another study in which patients over 60 years old were operated for malignant MCA infarction [34]. Mortality rate in case of patients with malignant ischemic stroke was different depending on the

time which has elapsed since the operation and after 3 months it was 8% and after year 44%. The risk is higher in case of older patients and when other ischemic loci in brain are present [27]. Hemicraniectomy in malignant brain stroke infarction is a procedure accepted by Polish Neurological Company as well as European Stroke Organization and American Brain Stroke Company [1,35]. Due to the fact that a great amount of patients with the large ischemic stroke is older than 60 years and the benefits from the surgery in this group remain unclear, further scientific investigations are extremely necessary to determine the real value of the surgical procedure in elderly people [11]. In case of patient covered by the presented study, hemicraniectomy was performed successfully despite the fact that it was carried out on the fifth day after the occurrence of stroke. It means that the indications for this procedure should be considered individually and that even patients over 85 years old can benefit from hemicraniectomy.

Another important issue concerning treatment of people with the brain stroke belonging to the above-mentioned age group, is the effectiveness and safety of thrombolysis. In one of the studies, 6 patients with ischemic brain stroke aged over 80 years old received thrombolysis. In this group, no significant long-term impact on the mortality was reported. Nevertheless, the number of patients was very small and studies performed in larger group need to be evaluated. In case of thrombolysis, the age should not be the decisive factor for disqualification of patients from such treatment but there is still lack of information about this treatment in case of very old people [10]. The impact on survival rate and neurological status in patients with malignant infarct also remains elusive. Among seven patients treated with thrombolysis under the presented study, 4 people died within first 30 days after the stroke. Among people who survived, only in case of one person a little improvement of neurological status (of 1 point in NIHSS score) was observed but this patient was still severely disabled.

Another option for treatment in patients with malignant ischemic stroke is hypothermia. Hypothermia reduces post-ischemic hyperperfusion, blood-brain barrier disruption and brain edema in animal models and therefore the neurons apoptosis is minimized in the area of penumbra [36]. In addition, it can reduce mortality caused by malignant infarction to 44% but it is still less effective than decompressive hemicraniectomy [37]. On the other hand another study revealed that hypothermia can reduce effectiveness of thrombolytic treatment [38,39]. According to this data, hypothermia can be useful when it accompanies pharmacological and neurosurgical treatment but further studies evaluating its effectiveness and safety need to be performed. Especially, safety and effectiveness of hypothermia in the above-mentioned age group should be verified as there are no studies evaluating this problem.

Malignant middle cerebral artery infarction is a life threatening event characterized by high mortality. Older people are in the group of high risk of ischemic stroke, including the malignant ones. Many problems related to risk factors profile, proper therapy, indications to neurosurgical treatment, safety and effectiveness of hypothermia in this age group need to be resolved. Moreover, obtaining more information on the malignant ischemic stroke in people over 85 years old is necessary to develop better prophylaxis and treatment

strategy. In the presented work we also describe a case of 85 year-old patients who successfully underwent the surgery due to malignant brain edema. This case shows that the indications to hemicraniectomy in case of very old patients need to be analyzed individually because even very old people can benefit from this procedure.

Conflict of interest

None declared.

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