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Clinical and morphological correlations in acute ischemic stroke

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Abstract

We studied the clinical and histopathological changes in twenty-seven cases of acute ischemic stroke, aged between 65 and 75 years. All deaths occurred within 30 days after stroke. The aim of our study was to establish the clinical and histological correlations in acute ischemic stroke to detect prognostic factors. Brain lesions after acute stroke were observed in all regions. Our study describes the heterogeneity of brain injury after acute ischemic stroke with the participation of all brain components and the chronology in which these lesions develop and evolve. By histological and immunohistochemical studies, we identified neuronal, glial and vascular damage. The neurons had undergone in the area of lesion a process of necrosis, ballooning or condensation process. In the ischemic penumbra, we observed the presence of red neurons. Vascular lesions were represented by the discontinuity of capillaries, always associated with a marked perivascular edema. The following clinical and morphological correlations were established: liquefactive necrosis, astrocyte gliosis, phagocytosis phenomena are the more intense the later the death of the patient; apoptosis phenomena are the more intense the faster the death of the patient; the entire cerebral microcirculation presented microscopic modifications following the ischemic strokes, regardless of the time since the lesion occurred and the histological examination was made; the major neurological complications of the ischemic stroke – the hemorrhagic transformation phenomena, cerebral edema, were microscopically objectified, regardless of the time since the lesion occurred and the histological examination was made.

Keywords: acute ischemic stroke, predictors, histopathology, correlations.

Introduction

The most recent definition considers a stroke as established if either clinical symptoms lasting more than 24 hours or symptoms resolve in this period, but imaging reveals an acute ischemic lesion and a clinical picture consistent with the ictus sets. Stroke is usually referred to as a condition caused by the occlusion or hemorrhage of blood vessels supplying the brain [1]. Worldwide cerebrovascular disease was the second leading cause of mortality [2], and also was the fifth leading cause of occupational impairment [3]. Worldwide, stroke kills every year five million individuals and causes severe disabilities in other five million people [4].

In USA, the incidence for stroke is more than 700 000 per year (500 000 – first-time stroke, 200 000 – recurrent episode), of which 20% of the patients will die within the first year after the onset of the stroke. This number is considered to rise up to one million per year by the year 2050 [5].

In Europe, the incidence of stroke varies from country to country, estimated at between 100 and 200 strokes per 100 000 persons annually, representing a huge economic burden. They found large differences in the incidence, prevalence and mortality between Eastern and Western Europe. This was attributed to differences in risk factors resulting in a more severe form of stroke in Eastern Europe [6].

Romania ranks sixth as a mortality rate almost double the European average. In 2004, there were 54 011 deaths with cerebrovascular disease (20.86% of all deaths).

During recent years, many studies have been conducted, in both humans and experimental animal models, in hope of finding and implementing new therapies with beneficial effects in stroke patients [7–10]. Ischemic stroke prognosis depends on the cerebral territory affected, cerebral infarct size, degree of pressure on the brain, the presence of associated diseases and patient age.

The aim of our study was to establish the clinical and histological correlations in acute ischemic stroke to detect prognostic factors.

Materials and Methods

Twenty-seven cases, aged between 65 and 75 years, clinically and imagistically diagnosed with acute ischemic stroke were selected from the archive of Pathology Department from the Clinical Hospital of Neuro-psychiatry Craiova, Romania, over a period of seven years (2005–2011). All patients underwent a CT scan.

According to the Committee of Ethics and informed consent, we collected biological material in the immediate vicinity of the ischemic stroke, from a more remote distance and the contralateral hemisphere.

Medical records were reviewed to retrieve information regarding signs and symptoms at admission, concomitant diseases, duration of survival from the date of admission until death and the complications. All deaths occurred within 30 days after stroke. Information obtained from the autopsy protocol included changes in small cerebral vessels, changes in brain parenchymal lesion and perilesional, the neural apoptosis, presence of local inflammatory process depending on the time from the stroke onset to death.

The histological specimens were collected during necropsy and were process by routine histopathological techniques (10% buffered neutral formalin fixation, paraffin embedding, 3–5 μm-thick section cutting), and stained with Hematoxylin–Eosin and Masson's trichrome.

Macrophages, astrocytes and apoptosis involved in cerebral infarction were studied by immunohisto-chemistry using "ABC"-peroxidase technique (with VECTASTAIN Elite ABC Kit, Vector Laboratories, PK-6200, Medikalkit, Craiova, Romania), and CD68 (Monoclonal Mouse Anti-Human, Clone: KP1, Dako, M0814 Medikalkit), GFAP (Polyclonal Rabbit Anti-Glial Fibrillary Acidic Protein, Dako, Z0334, Medikalkit), cleaved caspase-3 (Polyclonal Rabbit Anti-Activated caspase-3, Cell Signaling, Medicalkit), according to the manufacturer protocol (Table 1).

Table 1 – ***Description of antibodies utilized***

Antibody	Clonality	Dilution	Target	Dilution
CD68	IgG1K	KP 1	Macrophages, monocytes	1:100
GFAP	Polyclonal	–	Astrocytes	1:30000
Cleaved caspase-3	Polyclonal	–	Apoptotic cells	1:50

First, we investigated and characterized the clinical and morphological changes observed in the collected specimens, and second we grouped morphological changes in three chronological phases depending on the time from the stroke onset to death:

- phase of acute neuronal injury (death in the first three days after onset);
- phase of acute organization, according to the nature of the inflammatory infiltrate (death in four to seven days);
- phase of chronic organization, according to the nature of the inflammatory infiltrate (death after more than eight days).

Results

During the study period, twenty-seven cases of acute ischemic stroke, aged between 65 and 75 years were selected from the archive of Pathology Department from the Clinical Hospital of Neuropsychiatry, Craiova, Romania. There were more men than women (14 *vs.* 13, 51% *vs.* 49%) (Figure 1).

Of the 27 patients, 15 (56%) died in the first three days after the onset, four (15%) died in four to seven days, and eight (29%) died after more than eight days.

Baseline clinical characteristics

Hypertension was the most prevalent vascular risk factor (81%), followed by atrial fibrillation (53%), hypercholesterolemia (38%), coronary artery disease (34%), diabetes mellitus (30%), current cigarette smoking habit (28%), positive family history of cerebrovascular ischemic events (24%) (Table 2).

Table 2 – ***Risk factors***

Risk factor	No. of cases	%
Hypertension	22	81
Atrial fibrillation	14	53
Hypercholesterolemia	10	38
Coronary artery disease	9	34
Diabetes mellitus	8	30
Cigarette smoking habit	7	28
History of cerebrovascular ischemic events	6	24

Table 3 shows the baseline clinical characteristics of the 27 patients with acute ischemic stroke.

Table 3 – ***Clinical characteristics***

Characteristics	No. of cases	%
Motor deficits	22	81
Language and speech disorders	18	68
Impairment of perfusion in posterior territory	11	39
Sensory disabilities	10	37
Abnormal visual field	6	20
Altered level of consciousness on admission	5	17

Varied motor deficits (hemiparesis, hemiplegia, central facial paresis) were the most common neurological signs in the study group (81%). Motor disturbances were isolated or associated particularly with language and speech disorders. Central facial paresis was found in 4% of the cases studied, which is an interesting observation.

Language and speech disorders were after motor deficits the most common manifestations of ischemic stroke and have been found in 68% of the studied cases. Global or mixed aphasia was present in one third of the cases. Dysarthria was noted in 30% of studied patients.

Altered level of consciousness on admission (somnolence, confusion, coma) was reported at 17% of the patients in the study.

In the study group, neurological findings included not only motor, language and speech disorders or altered level of consciousness and sensory disabilities (37%), but also abnormal visual field (20%) or impairment of perfusion in posterior territory (vertigo, ataxia, paralysis of cranial nerves) (39%).

The most common complications in our study were the neurological complications (Table 3). Neurological complications, such as intracranial hypertension syndrome or hemorrhagic transformation occur earlier than do medical complications and can affect outcomes with potential serious short-term consequences.

Hemorrhagic transformation of acute ischemic stroke, in our study was high (16 cases, 58%). It was reported early (within 24 hours after stroke onset) or after several days of evolution. The analysis of the evolution of hemorrhagic transformation signaled the presence of several factors:

- stroke in the territory of the deep middle cerebral artery;
- high proportion of patients with diabetes, atrial fibrillation and hypertension with hemorrhagic transformation of acute ischemic stroke;

▪ positive correlation with advanced age and anti-coagulant treatment.

Intracranial hypertension syndrome, expression of cerebral edema and stroke, was objectified on CT on admission (within 24 hours) or during hospitalization in 11 patients (42%). It was present in extensive strokes (full middle cerebral artery territory or full internal carotid territory or cerebellar strokes) followed by cerebral edema with herniation, accompanied by secondary brain parenchyma and compression on the brainstem, thus resulting in death. Hypertension and hemorrhagic transformation (1/3 of the cases) contributes to the severity of prognosis. In the other 2/3 of the cases, intracranial hypertension syndrome occurred during hospitalization (2–5 days), marking the ischemic stroke severity.

The risk of neurological complications such as stroke extension and seizures appear to be elevated within the first three days of admission. Seizures are usually focal in nature, with or without secondary generalization. This is similar to earlier published data, which noted that neurological complications were more likely to occur in the first week [11].

Table 4 – ***Neurological complications***

Complications	No. of cases	%
Coma	21	76
Hemorrhagic transformation	16	58
Intracranial hypertension syndrome	11	42
Stroke extension	19	72
Seizures	6	22

Cardiovascular complications were frequent and serious (Table 5). Cardiac arrhythmias secondary to stroke are not unusual. Significant alterations in the ST segments and the "T" waves on the ECG may appear in the acute phase mimicking myocardial ischemia and cardiac enzymes may be elevated after acute stroke. Every stroke patient should have an initial ECG. If this is normal, usually no continuous ECG monitoring is required. However, patients with major stroke syndromes and some hemodynamic instability should be continuously monitored and be transmitted to a facility where monitoring can be continued.

Table 5 – ***Cardiovascular complications***

Complications	No. of cases	%
Angina attacks	12	43
Acute coronary syndrome	18	68
Paroxystic atrial fibrillation	9	32
Elevated blood pressure	6	22
Hypotension	4	14

Predictors of early mortality

Coma on admission was the main clinical predictor of early mortality. Relevant co-morbidities, like uncontrolled hypertension, atrial fibrillation, diabetes mellitus, acute coronary syndrome, were associated with early mortality.

Histological and immunohistochemical study of cerebral changes in the first three days of the onset of ischemia

Acute cerebral ischemia caused injury in all cellular components of the cerebral parenchyma (neurons, glial cells), as well as blood vessels. In the center of the ischemic outbreak, the great majority of neurons have suffered a process of liquefactive necrosis, with the disappearance of the neuronal body and also the extensions (Figure 2). Another part of the neurons, especially of larger neurons, suffered a process of swelling, or ballooning with an increase in size, vacuolization of neuroplasm, the disappearance of the core and nucleols, while other neurons appeared small, with irregular outline, neuroplasm and the core condensed. Both contraction and swelling or vacuolization of neurons betray the severe damage of cellular organelles and especially of the mitochondria that in the absence of oxygen are no longer able to provide energy for the neuronal metabolism. The process of liquefactive necrosis also affected glial cells, astrocytes, oligodendrocytes and microglial cells.

The process of necrosis leads to the appearance of inflammatory infiltrate within the ischemic area, in which we noted the presence of granulocytes, lymphocytes and macrophages.

In the periphery of the outbreak, in the penumbra, we noticed the emergence of neurons defined as "red neurons" or "ischemic neurons", with acidophilic cytoplasm, which is an expression of changes of neuronal proteins and disintegration of the endoplasmic ribosome and endoplasmic Nissl's corpuscles, because of severe hypoxia (Figure 3).

Another change observed in patients taken into study with ischemic stroke was the hemorrhagic transformation, highlighted in the form of microscopic bleeding purpura elements (Figure 4). The occurrence of hemorrhagic infiltrates in the cerebral parenchyma may be due to necrosis of vascular endothelial cells and perivascular astrocytes, with the development of discontinuities of the blood-brain barrier and the penetration of blood vessels in the ischemic area by the anastomosing vessels.

In both ischemic and perilesional areas we noticed numerous inflammatory type cells, represented by lymphocytes, granulocytes and rare macrophages. The inflammatory infiltrate appeared well developed, which denotes that cerebral ischemia induced cellular necrosis led to the emergence of antigenic structures that drew leukocytes from blood vessels (Figures 5 and 6).

In the area of ischemic penumbra and away from the ischemic area, we frequently noted the presence of perivascular and perineuronal edema, because of the modified permeability of capillaries and disturbance of blood-brain barrier (Figure 7).

The immunohistochemical study of the monocyte–macrophage system cells that is the reaction of microglia and macrophages with blood origin allowed us to observe that the response of these cells was reduced in the first three days of the onset of cerebral ischemia, both in the focus of ischemic stroke and the rest of the cerebral parenchyma, including the area of ischemic penumbra.

Instead, specific astrocytes, as underlined by the immunohistochemical reaction to the monoclonal anti-GFAP antibody, have reacted quickly to cerebral ischemia, observing a reactive gliosis at three days after the ischemic attack. Astrocytes reaction was more

intense in the ischemic penumbra and around the blood vessels (Figures 8 and 9).

Regarding the process of neural apoptosis, we found that it was more intense in the cerebral cortex, perilesional, even in the first days from the onset of ischemia, many neurons presenting positive reaction to caspase-3 (Figure 10).

Histological and immunohistochemical study of brain changes from patients who died between four and seven days after the onset of ischemia

As expected, the cerebral parenchymal changes intensified with the passage of time from the onset of cerebral ischemia. The reduction of the neural population has been reported not only near the ischemic focus, but also at a distance, which denotes that an ischemic stroke has reach over the entire central nervous system and explains the major of neurological symptoms in these patients.

As seen in our images (Figure 11) it seems that the neurons of grey matter are more susceptible to ischemia and hypoxia, location where associative processes take place, which in good measure explains the psychic behavior of patients who have survived an ischemic attack.

Both in the focus of ischemic stroke and in the penumbra area we observed the presence of numerous large macrophages with eccentric core with homogenous cytoplasm, vacuole degeneration, which means that the process of phagocytosis of tissue remnants, at this time, is present and pretty intense (Figure 12).

In patients from this group, vascular changes were similar to those seen in the previous group. In addition, we noted in some areas the presence of hemorrhagic suffusions in the Virchow–Robin space because of damage to the walls of medium caliber vascular vessels with blood elements flooding the connective space around (Figure 13).

Immunohistochemical reaction to CD68 in patients of this group showed in the cerebral parenchyma of the focus an intensification of ischemic reaction to CD68, evidence of an increase in the number of microglial cells or macrophages derived from blood (Figure 14). Most often, the macrophage type cells occurred around blood vessels, which means that the vast majority of macrophages had blood origin and that, around blood vessels, because of the blood-brain barrier dysfunction, there are numerous antigenic structures that stimulate macrophages mobilization in this space.

Regarding the reaction of astrocytes in patients of this group, we noted an intensification of astrocyte reaction, especially at the periphery of the ischemic zone and around blood vessels. As seen on our images (Figure 15), the reactive gliosis is characterized by the multiplication of astrocytes, but also by increasing the sizes of both the cellular body and astrocytic extensions.

Neural apoptosis was not intensified with the passage of time. So, in patients who died after three days and after seven days from the onset of the stroke, the number of caspase-positive neurons appeared lower than in patients who died in the first three days, which makes us believe that most of the neurons in the area adjacent to the focus of the ischemic stroke die in the early days by necrosis and apoptosis. After this time point, the apoptotic process seems to be reduced.

Histological and immunohistochemical study of brain changes in patients who died after seven days after the onset of ischemia

As can be seen in our images (Figure 16), the cerebral parenchyma damage continued with the passage of time. Neural depletion, more or less intense, reached all the layers of the cortex, both perilesional and away from the focus of the ischemic stroke. The focus of ischemic stroke was occupied for the most part by macrophage-type cells (Figure 17), while in the area of ischemic penumbra we observed angiogenesis capillaries. Regarding the reaction of astrocytes, it was extremely intense in the area of ischemic penumbra and perivascular areas (Figure 18).

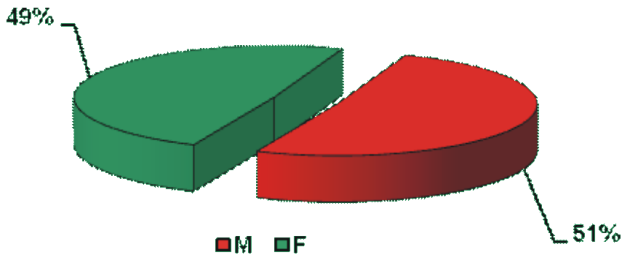

Figure 1 – ***Distribution by gender.***

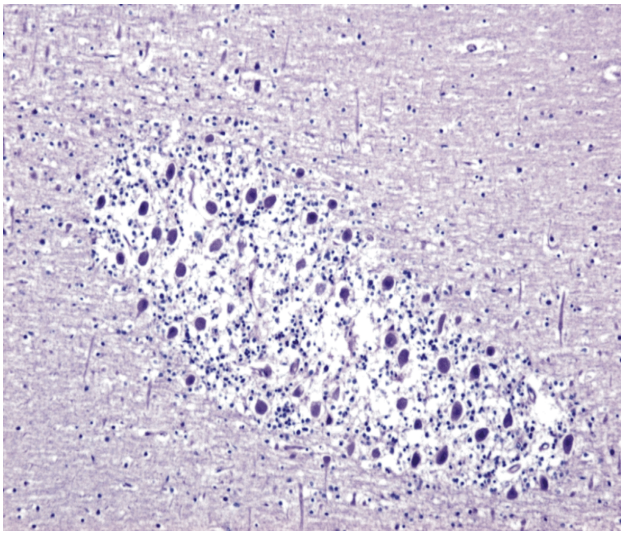

Figure 2 – ***Area of liquefactive necrosis in a patient deceased in three days after onset (Masson's trichrome stain, ×40).***

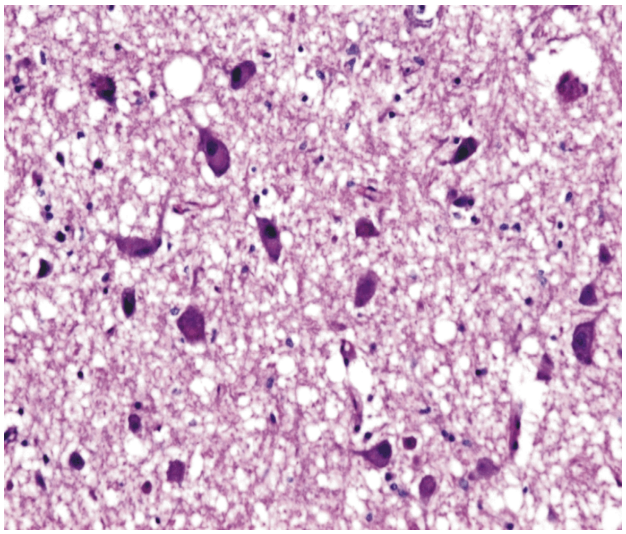

Figure 3 – ***Hypoxic neurons "red neurons" in the ischemic penumbra (HE stain, ×200).***

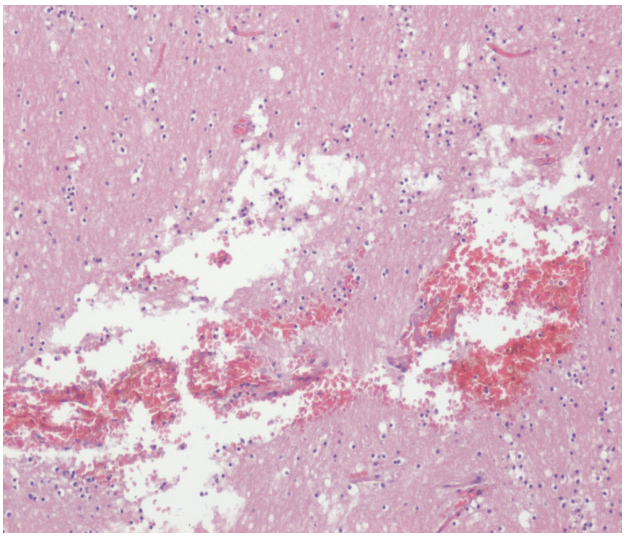

Figure 4 – ***Acute ischemic stroke with hemorrhagic transformation (HE stain, ×100).***

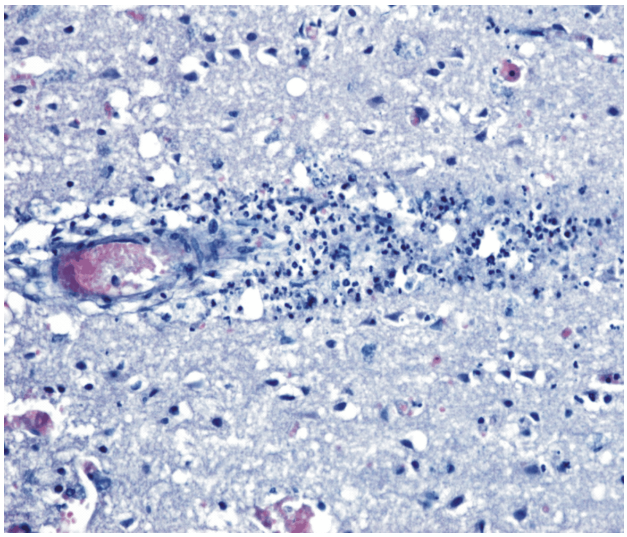

Figure 5 – ***Perivascular lymphocytic infiltrate (Masson's trichrome stain, ×200).***

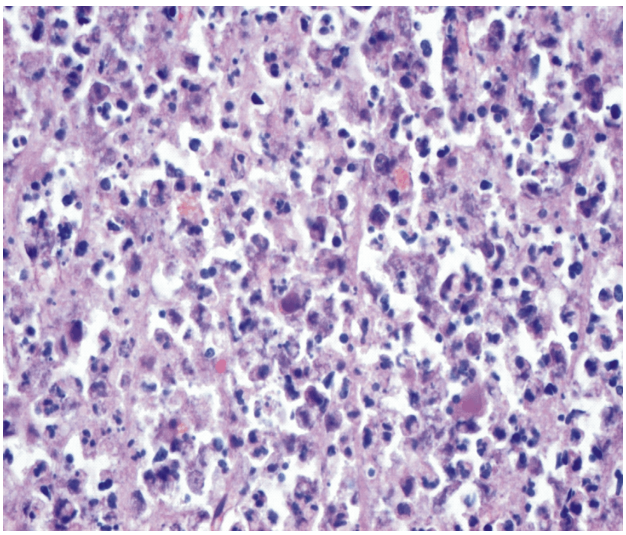

Figure 6 – ***Heavy granulocytic infiltrate in the ischemic penumbra (HE stain, ×200).***

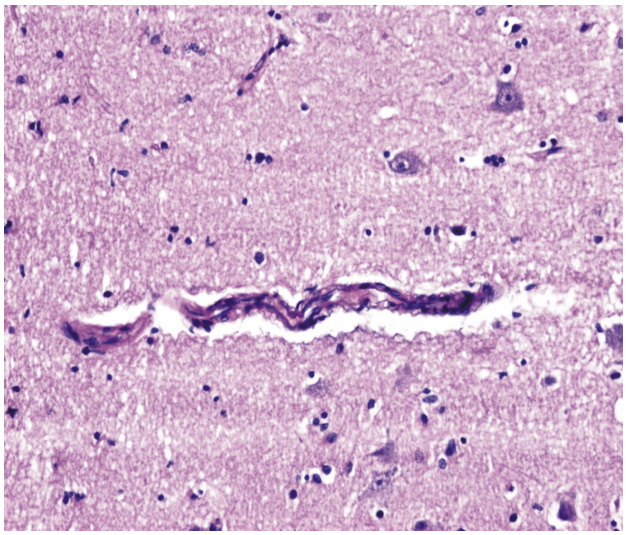

Figure 7 – ***Discontinuity of capillary associated with a marked perivascular edema (HE stain, ×200).***

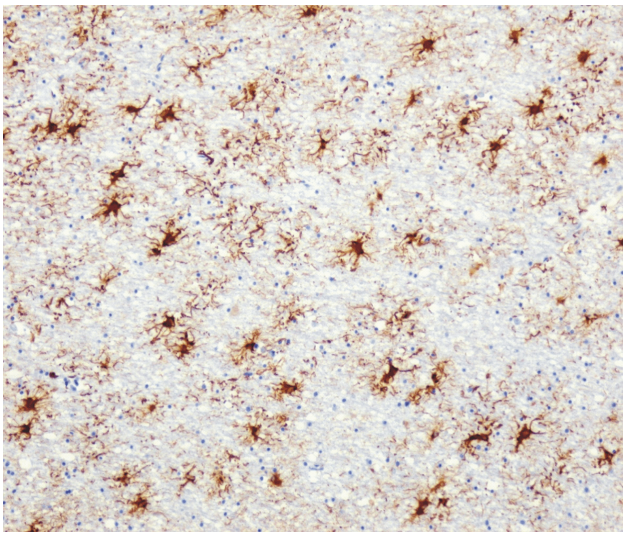

Figure 8 – ***Moderate gliosis in the ischemic penumbra at three days after onset (GFAP immunohistochemical stain, ×100).***

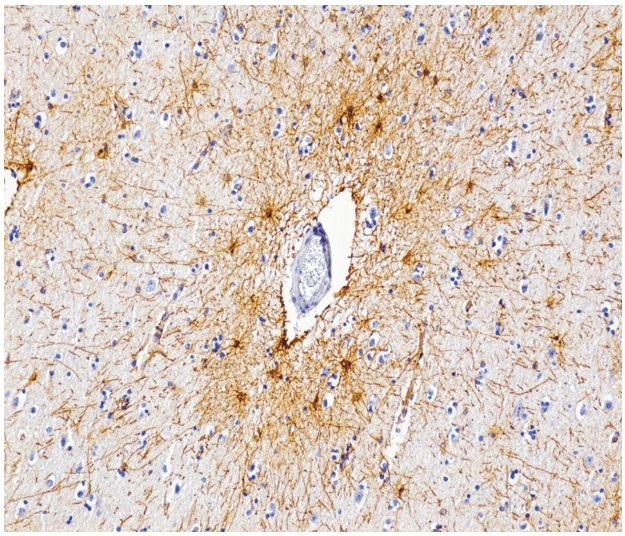

Figure 9 – ***Perivascular gliosis at three days after onset (GFAP immunohistochemical stain, ×100).***

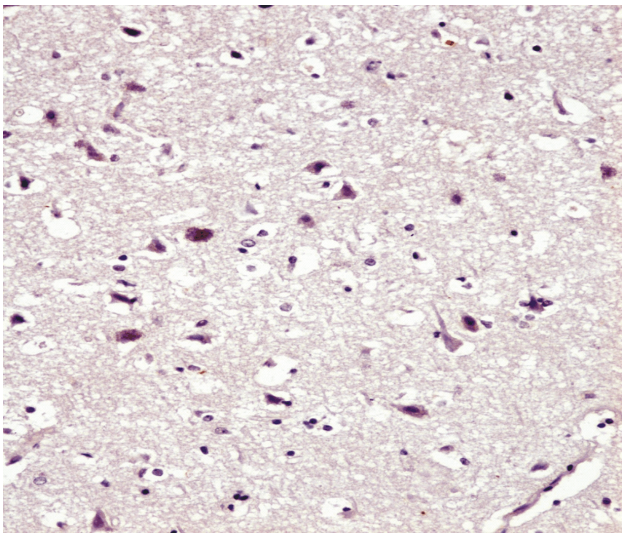

Figure 10 – ***Pyknotic neurons with irregular contour at three days after onset of ischemic stroke (Caspase-3 immunohistochemical stain, ×200).***

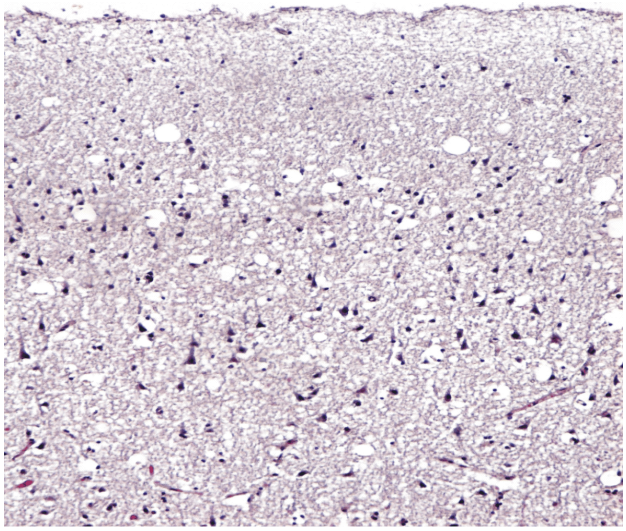

Figure 11 – ***Superior half of the cerebral cortex at seven days after stroke, with reduced neuronal population, especially in the external granular and molecular layer (Masson's trichrome stain, ×200).***

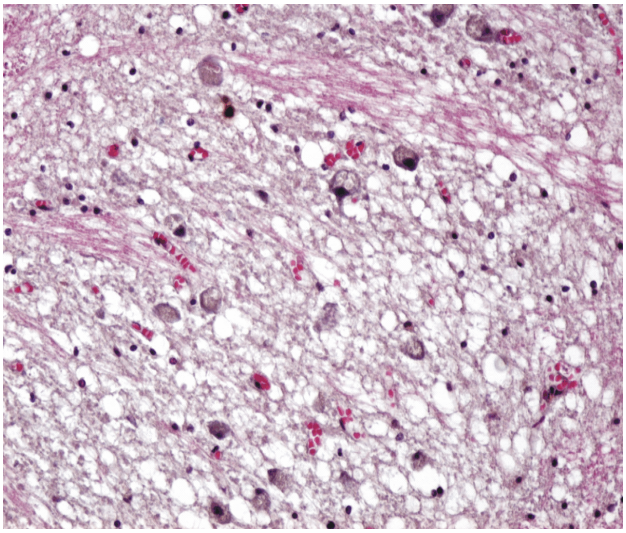

Figure 12 – ***Numerous macrophages in the ischemic penumbra at seven days after onset (HE stain, ×200).***

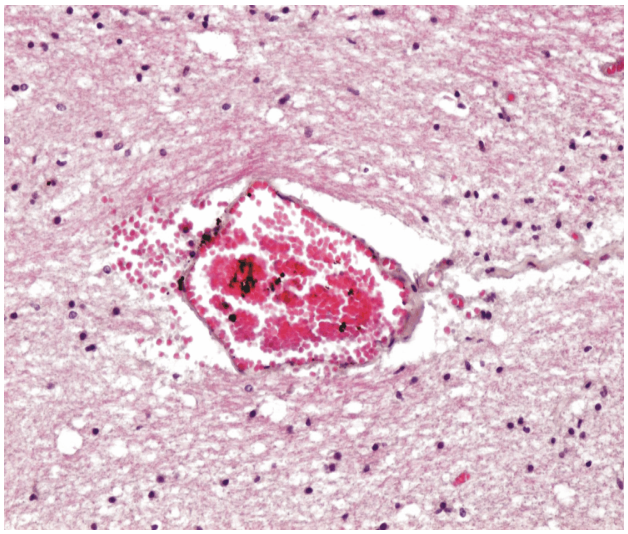

Figure 13 – ***Hemorrhagic suffusions in the Virchow–Robin space (HE stain, ×200).***

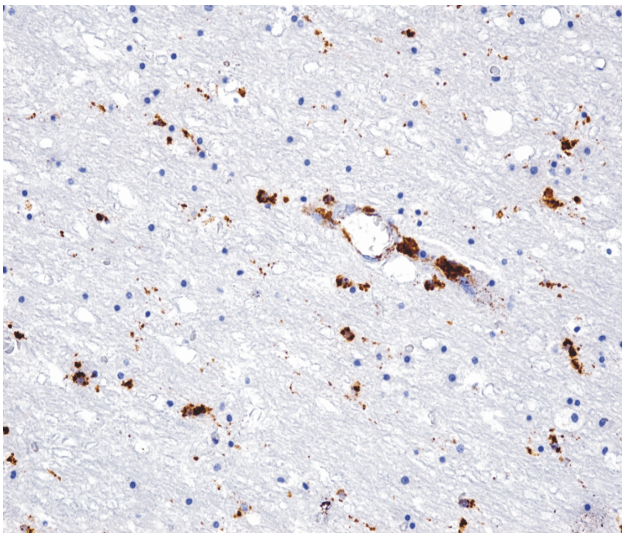

Figure 14 – ***Reaction of macrophage system cells in the ischemic penumbra at seven days after onset (CD68 immunohistochemical stain, ×200).***

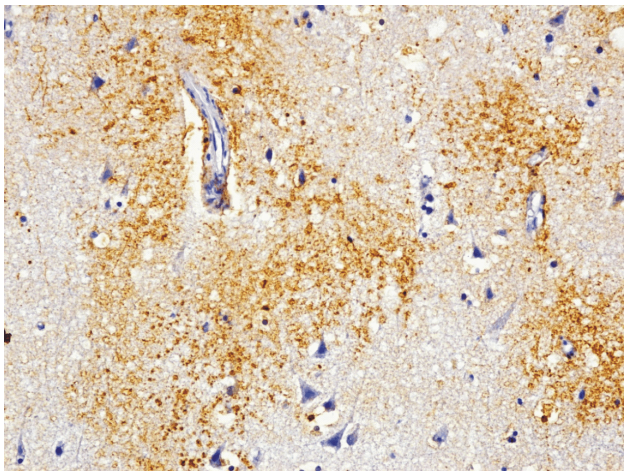

Figure 15 – ***Perivascular gliosis at five days after onset (GFAP immunohistochemical stain, ×100).***

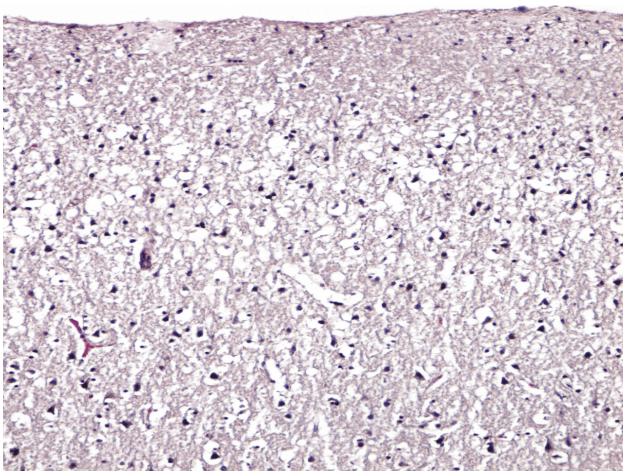

Figure 16 – ***Microscopic image from the contralateral hemisphere, unaffected by the ischemic stroke, with the same massive destruction of neurons and neuropil, induced by the mass effect (HE stain, ×100).***

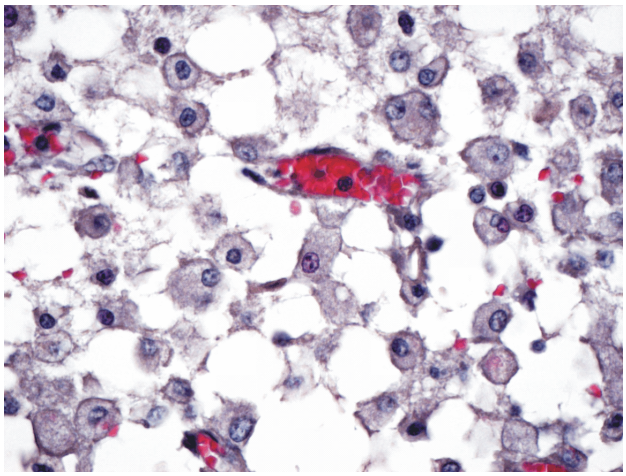

Figure 17 – ***Area of liquefactive necrosis invaded by macrophages (HE stain, ×400).***

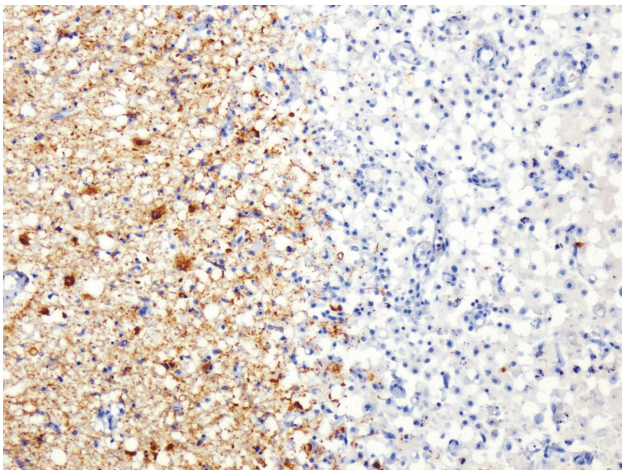

Figure 18 – ***Area of transition from absent glial reaction to the ischemic penumbra with intense glial reaction, eight days after stroke (GFAP immunohistochemical stain, ×100).***

Discussion

The aim of our study was to establish the clinical and histological correlations in acute ischemic stroke.

In the present study, we did not observe gender differences in early mortality after ischemic stroke (51% in men and 49% in women). A recent study assessed the 30-day mortality in Switzerland. In this sample of 467 patients, 13% died within 30 days of their first-ever stroke, and there were more men than women (63% *vs.* 37%) [12].

Several factors are known to influence early mortality. Stroke severity on admission is a well-established predictor of mortality. Several clinical variables that reflect the severity of the neurologic lesion have been analyzed to predict the clinical outcome, such as motor deficits, level of consciousness. In our study coma on admission was the main clinical predictor of early mortality. In many previous studies, the level of consciousness was the main early cause of mortality after acute ischemic stroke [12–14]. Dysphagia and hypertermia have also been reported to predict 30-day mortality after stroke [15–18].

An uncontrolled hypertension was associated with a 30-day mortality in our study. Previous studies have shown considerable variations of blood pressure in the acute phase of ischemic stroke [18]. Variables describing the course of blood pressure over the first three days have a marked and dependent relationship with the outcome at 30 days [20]. Patients with the highest and lowest levels of blood pressure in the first 24 hours after stroke were more likely to develop early neurological deterioration and a worse prognosis [23]. A blood pressure within the normal or low normal values at the onset of stroke is unusual [21].

In our study, diabetes mellitus and the presence of atrial fibrillation were associated with the 30-day mortality. It may be that blood glucose levels and atrial fibrillation are related to age and/or stroke severity, thus, the effects they exert on mortality are not independent. Previous studies revealed that low or high admission blood pressure, elevated pulse pressure, elevated serum glucose levels in patients with diabetes, hyperglycemia in non-diabetic patients, and the presence of atrial fibrillation have been associated with poor clinical

outcome and increased mortality three months after stroke onset [19, 22–25].

Hemorrhagic transformation of acute ischemic stroke, in our study was high (16 cases, 58%), consistent with studies in the literature.

Data from the study confirm the traditional data, according to which the extended mass effect is the expression of a severe risk of hemorrhagic transformation and death. Cerebral edema is the leading cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening cerebral edema usually develops between the second and fifth day after installation of stroke, but up to one third of patients may have neurological damage in the first 24 hours after the onset of symptoms [26, 27].

In this sample, cardiac complications (acute coronary syndrome and paroxystic atrial fibrillation) were associated with early mortality. Cardiac arrhythmias, particularly atrial fibrillation, are common after stroke and heart failure, myocardial infarction and sudden death are also recognized complications [28, 29].

As we have seen, most authors consider that the most sensitive cells of the brain in ischemia are neurons, followed, in that order, by oligodendrocytes, astrocytes and vascular cells. We consider that neurons are the most vulnerable to ischemia because their metabolism relies mostly on two elements: oxygen and glucose. The death of neurons through ischemia is a well-defined process. Thus, in the centre of the territory with arrested blood flow, the first signs of cellular injury are neuronal ballooning or contraction of the neuronal body, cytoplasm with microvacuoles, which ultrastructurally, have been associated with mitochondrial bloating [30].

The hemorrhagic transformation of ischemic stroke, in our study, was pretty commonly viewed. This layout indicates severe injury of microscopic blood-brain barrier. According to some authors [31], hemorrhagic transformation occurs frequently in the second and third phase of evolution of stroke, when macrophages and new blood vessels are formed. From the macroscopic point of view, red stroke contains multifocal bleedings, which are more or less confluent and prevails in the cerebral cortex and the basal ganglia, which are richer in capillaries than white substance [32].

Brain-blood barrier changes occur relatively rapidly in acute ischemic stroke. For all the patients studied we found the presence of extravasates and especially perivascular edema. With the evolution of tissue necrosis and the degradation of the basal membrane, blood-brain barrier breaks down [33] and after 4–6 hours, serum proteins begin to pass from blood vessels into the brain. This disturbance initiates a type of vasogenic edema that increases the water content of the tissue. Vasogenic edema reaches its peak at 1–2 days after the onset of ischemia and causes an increase in tissue water by more than 100%.

Regarding the inflammatory reaction, it seems to play a very important role in the pathogenesis of ischemic stroke and other forms of ischemic cerebral injuries. In our study, we noticed a variety of immune cells that were present in the stroke area as well as in the penumbra or at a distance from the ischemic injury. According to some authors, the post-injury inflammatory reaction of the brain is characterized by a rapid activation of resident cells (mainly microglial cells), followed by infiltration with circulating inflammatory cells, including granulocytes (neutrophils), T-cells, monocytes/macrophages and other cells in the region of cerebral ischemia, as was demonstrated on animal models [34, 35] and in patients with stroke [36–38].

In addition to the process of necrosis, well highlighted using the classic histopathology techniques, neuronal death also occurs through apoptosis, a process that, as we have shown, was increased in cerebral ischemia. For marking neuronal apoptosis, we used the anti-caspase-3 antibody. Other authors have also noticed that in cerebral ischemia, caspase-3, caspase-2 and caspase-9 play an important role in post-injury neuronal death [39, 40].

The role of caspase-3 was largely supported by animal studies. Administration of caspase inhibitors reduced infarct size, while the excess of caspase-3 has increased the volume of the lesion in the moments following cerebral ischemia [41].

In the central nervous system, microglial cells are blood monocyte-derived cells. They have the same properties as macrophages. Microglial cells are the primary effector immune cells present in the brain, often referred to as brain macrophages. In the normal brain microglia appear morphologically as cells with branched extensions and represent about 5–20% of the total glial population. It was observed that the cellular processes and the protuberances of microglial cells interact dynamically with the neighboring neurons, astrocytes and blood vessels [42].

In response to various types of brain damage, microglia become reactive and suffers morphological and functional transformations [43]. More specifically, the cellular body increases, with thickened and lowered processes, releases the pro-inflammatory proteins and cells become proliferative, migratory and acquire the phagocytic properties. Although the role of microglial cell/macrophages after stroke is to remove the remnants of the nervous tissue, reactive microglial cells/macrophages express and release a variety of potentially toxic factors such as cytokines, chemokines, proteases, cyclooxygenase-2, ROS, prostaglandins and HO-1, and their metabolites [44].

After an acute stroke, astrocytes in the brain become activated and strengthen the production of glial fibrillary acid proteins (GFAP), forming the so-called "reactive gliosis". In recent studies a strong activation of the astrocytes in the perilesional region was observed, which was higher in the regions closest to the lesion and gradually decreased with the increasing distance from the lesion [45, 46], results similar to those observed by us.

Conclusions

By corroborating the results, the following clinical and morphological correlations were established: liquefactive necrosis, astrocytic gliosis, and phagocytosis phenomena are the more intense the later the death of the

patient; apoptosis phenomena are the more intense the faster the death of the patient; the entire cerebral microcirculation presented microscopic changes following the ischemic stroke, regardless of the time passed since the lesion occurred and the histological examination was performed; the major neurological complications of the ischemic stroke – the hemorrhagic transformation phenomena, cerebral edema (histologically observed as perivascular and perineuronal edema) – were microscopically objectified, regardless of the time since the lesion occurred and the histological examination was performed.

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