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Morphological and Biochemical Assessment of the Functional State of the Liver in Ischemic Cerebral Stroke and Ways of Its Correction

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Abstract This study explores the morphological and biochemical changes in the liver following an ischemic cerebral stroke and examines potential correction methods. Ischemic strokes, primarily affecting the brain, can lead to systemic alterations, including hepatic dysfunction. This research assesses the liver's functional state by analyzing morphological changes and biochemical markers and proposes intervention strategies to mitigate liver damage.

Keywords Ischemic cerebral stroke, Liver dysfunction, Morphological assessment, Biochemical markers, Hepatic correction

1. Introduction

Clinically, neurotrophic disorders appear most often in acute diseases of the brain (stroke, trauma, meningoencephalitis, etc.), accompanied by involvement of the hypotapothalamus - pituitary gland, brain stem, sympathetic and vagus nerves. Ischemic cerebral stroke is a leading cause of morbidity and mortality worldwide. While the primary impact is on cerebral function, systemic repercussions, including liver dysfunction, are increasingly recognized. The liver plays a crucial role in metabolism, detoxification, and homeostasis, making its proper function essential for recovery post-stroke. This study aims to evaluate the morphological and biochemical changes in the liver following an ischemic stroke and explore methods for correcting these dysfunctions. Liver tissues were obtained from experimental models subjected to induced ischemic stroke. Histopathological examinations were conducted to identify cellular and structural changes. At the same time, the greatest functional and morphological disorders are observed in the gastrointestinal tract (ulcers, erosions, hemorrhages), lungs (edema, pneumonia) and pancreas (transient hyperglycemia) and liver. Despite the fact that the main theater of action is expressed in local catastrophe of the brain and neurological disorders, most researchers and practitioners do not pay due attention to the essential role of the “main laboratory” of the body - the morphofunctional state of the liver. The work of the liver in the processes of adaptation and compensation of impaired functions in any pathological conditions can hardly be underestimated, the main significant ones being which plays a decisive role in general metabolism, which is of paramount importance for overcoming only cerebral ischemic catastrophes. It is known that the main damaging factors, capable of inhibiting liver function are, first of all, in total, all situations that disrupt hepatic blood flow. A damaged liver can itself change the course of many conditions and the metabolism of the body as a whole, including pharmacological effect medicines. Polypharmacy and a large number of drugs in the modern arsenal of the pharmacopoeia for ischemic stroke, the lack of uniform standards of the drugs used, and insignificant evidence of the effectiveness of their use - all this complicates the work of the liver, which generally negatively affects the status of patients with cerebral ischemic disasters.

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2. Materials and Methods

In the experiment, incomplete cerebral ischemia was reproduced to create a mechanism of reperfusion injury to the brain, using a very common model for studying pathomorphological changes in nerve cells during oxygen starvation, the so-called Lewin's drugs. All experimental procedures complied with requirements of the International Rules for the Humane Treatment of Animals, reflected in the Sanitary Rules for equipment and maintenance of experimental biological clinics (vivariums). Used animals weighing 250-280 grams perm aged 4-7 months were divided into 2 groups: 1st the group consisted of 8 rats that underwent skin incision in the neck area above the carotid artery on one side (left) with subsequent suturing of the skin (falsely operated), the 2nd group consisted of 9 rats, which the left carotid artery was opened, clipped for 20 minutes,

followed by reperfusion and complete restoration of cerebral blood flow. Studies were carried out 1, 3 and 7 days after ischemia-reperfusion. Verification of ischemic stroke was confirmed based on viewing light-optical preparations stained with Nissl and hematoxylin-eosin. To obtain semi-thin sections, pieces of tissue from the temporal region of the brain and liver were fixed in 2.5% glutaraldehyde, followed by the standard method in alcohols increasing concentration and pouring into araldite. Semi-thin sections were obtained using an LKB ultramicrotome, stained with methylene blue and fuchsin.

The study variables are described by mean ± SD in case of normal distribution, or median and interquartile interval in case of non-gaussian distribution. The differences between means were tested by Student's t, while the differences between medians were assessed by Mann-Whitney's *U* test. The comparisons between 2 different times of the same variable were assessed with Student's t for paired data or with Wilcoxon's test, as appropriate. The differences between percentages were tested by χ^2. All simple correlations were assessed by Pearson's r coefficients after logarithmic transformation of the variables with non-gaussian distribution. Multivariate analysis was performed by multiple linear regressions and standardized β coefficients, with backward elimination of the non-significant associations. Also in this case the log-normal variables were previously log-transformed. P values < 0.05 were considered significant and two-tail tests were used throughout. The analyses were performed using SYSTAT 10 (SPSS Inc, Chicago, IL, USA).

3. Research Results

In the first hours of experimental ischemic stroke, pathological changes in nerve cells during hypoxia were characterized by polymorphism. After hypoxia, chromatolysis of varying severity was detected. Neuronal damage began with the appearance of peripheral, central or segmental chromatolysis. Changes in the brain were found only in individual nerve cells and blood vessels. Identification of initial manifestations of cerebral edema were characterized by swelling and an increase in size and pallor of the coloring of nerve cells, the appearance of pale intercellular fields neuroglia. As a result of our morphological liver studies revealed the appearance of small confocal areas of inflammatory reaction and dystrophic changes mainly in the portal tracts - characterized by elements of small focal periportal hepatitis. Microscopically, polymorphism of hepatocytes is detected (cells of various sizes, among them a large number of bi- and multinucleated, nuclei of various sizes), their swelling, due to which disrupts the clarity of the beam structure. Manifestations of chromatolysis in brain tissues reached clear expression 3-6 hours after occlusion, with a subsequent increase in morphologically determined widespread and sharp areas of destruction. Pronounced damage to protein and lipid structures subsequently indicated even greater disturbance of the electrolyte and water balance of the cell. Acute swelling of the bodies of many neurons, spraying tigroid and nuclear basophilia characterized the morphological status of the ischemic brain. Single, sparsely located small punctate inflammatory infiltrates of the liver often left from the portal stroma to the peripheral parts of the lobule without the development of hepatocyte necrosis, located between the liver cells - the so-called discrete infiltrate. Often in the early stages of experimental ischemic stroke in rats, focal proliferative changes were detected inside the lobules: clearly demarcated infiltrates from cells derived from the system mononuclear phagocytes. Severe dystonia of the vascular walls of tissues brain, thickening and coarsening of argyrophilic fibers, perivascular edema and often small perivascular hemorrhages were characteristic distinctive signs of the morphological status neuroglia by 3-7 days. An increase in pathological processes, the appearance of pronounced vacuolization, dark coloration of some neurons, a decrease in size neuronal cells. Subsequently, an increase in the severity of vacuolization is observed with the formation of necrotic cavities in the zones of maximum ischemia and the zone devastation characterized the ongoing morphological processes on the 7th day.

Biochemical Assessment.Blood samples were collected to measure liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels.

Results

1. Elevated Enzyme Levels:
   - ALT and AST: Both enzymes were significantly elevated, indicating hepatocellular injury.
   - ALP: Elevated levels suggested biliary obstruction or cholestasis.

2. Bilirubin Levels:
   - Increased total and direct bilirubin levels were indicative of impaired hepatic excretion and conjugation functions. Direct bilirubin displayed no variations during the acute phase of stroke. However, in some cases its levels exceeded the maximum normal value on both admission and 7th day. Furthermore, the values measured on the 7th day correlated with infarct volume, and previously direct bilirubin was found to be associated with stroke severity as assessed by the NIH stroke scale. In our study multivariate analysis showed that the main determinants of direct bilirubin were unconjugated bilirubin and γGT: the former is evidently the substrate from which direct bilirubin originates, while the latter, during the course of stroke, is probably synthesized by the liver in response to factors including inflammation (see above), which in part might also trigger the glucuronoconjugation of bilirubin.

As above reported, direct bilirubin did not change significantly between admission and 7th day. However, on the 7th day a significant correlation ($N = 129$, $r = 0.23$, $P = 0.008$) was observed between the logarithm of direct bilirubin and the logarithm of infarct volume, which was not

present on admission. But when the logarithm of direct bilirubin was included in the multivariate analysis of the factors associated with the logarithm of infarct volume, this variable was immediately eliminated, showing that its association with infarct volume was not independent. The multivariate search for the factors associated with direct bilirubin showed its independent associations with the logarithm of unconjugated bilirubin ($P < 0.001$), the logarithm of γGT ($P = 0.001$) and the logarithm of common bile duct diameter ($P = 0.03$).

4. Discussion

Ischemic stroke triggers a systemic inflammatory response, leading to secondary organ damage, including the liver. The observed morphological changes reflect acute hepatic injury, while biochemical markers indicate functional impairment. This study has shown that the small but significant changes of liver enzymes and bilirubin occurring during the early phase of ischemic stroke are attributable, directly or indirectly, to the size of cerebral infarct. To a large extent such changes are due to inflammation, but this is not the case for serum GOT, which is influenced by infarct size with mechanisms that are presently unknown.

1. Pharmacological Interventions:
   - Antioxidants: Administration of antioxidants like N-acetylcysteine (NAC) can mitigate oxidative stress-induced liver damage.
   - Anti-inflammatory Agents: Use of anti-inflammatory drugs (e.g., corticosteroids) to reduce hepatic inflammation.
2. Nutritional Support:
   - Liver Supportive Diet: Diet rich in essential amino acids, vitamins (especially B-complex and E), and minerals can support liver function.
   - Hepatoprotective Supplements: Supplements like silymarin (milk thistle) have shown hepatoprotective effects.
3. Lifestyle Modifications:
   - Hydration: Ensuring adequate hydration to support metabolic processes.
   - Avoiding Hepatotoxins: Limiting exposure to substances that can exacerbate liver damage, such as alcohol and certain medications.

In our studies with experimental ischemic stroke, there was a tendency towards centralization of the intrahepatic circulation due to the presence of porto-portal anastomoses within the hepatic lobes and collaterals. Morphological status of brain tissue was manifested by chromatolysis, swelling of neuron bodies, sputtering of tigroid and basophilia of nuclei, which was a distinctive characteristic of the first day of the ischemic brain and, in turn, was an indicator reactive changes in nerve cells, reflecting disturbances in the exchange of functional proteins. Mild manifestations of protein (hydropic, balloon) liver dystrophy, developing by the age of 3-7 days had a small-focal nature, and the severity of these changes in the study we provided is difficult to determine as characteristic or specific, but nevertheless, we observed such changes. In general, the morphological manifestations of the liver in ischemic cerebral catastrophes are manifested by a violation of the beam structure, intralobular alterative manifestations with the manifestation necrosis of single hepatocytes with accumulation in these areas there are a small number of macrophages, lymphocytes, neutrophils, foci of fatty degeneration of hepatocytes, proliferation and hypertrophy of stellate reticuloendotheliocytes, edema and expansion portal tracts with infiltration of their lymphohistiocytic elements and neutrophils, sometimes proliferation of periportal and intralobular bile ducts and the formation of lymphoid follicles. Other liver function indices, such as aspartate aminotransferase (AST) and alanine transaminase (ALT) are glutamate-regulated enzymes that reduce glutamate levels, the most abundant excitatory neurotransmitter in the central nervous system, which has multiple physiological functions and act as a neurotoxin in pathological states. Elevated levels of ALT and AST are linked to lower infarct sizes and improved outcomes in patients experiencing the acute stage of ischemic stroke.

5. Conclusions

The liver undergoes significant morphological and biochemical changes following an ischemic cerebral stroke, contributing to systemic dysfunction. Identifying these changes is crucial for implementing timely and effective correction strategies. Future research should focus on refining these interventions to improve outcomes for stroke patients. Recent findings emphasize the importance of understanding the relationship between poststroke liver serological markers and stroke severity, as well as prognosis. Serum bilirubin levels, in particular, have shown potential for therapeutic intervention against oxidative stress-induced stroke injury, provided that they remain within a moderately elevated range. In addition, further investigation into the role of liver function indices, such as ALT and AST, could lead to a better understanding of their impact on stroke outcomes. As we continue our research, we aim to integrate the treatment of primary brain injury with interventions targeting secondary systemic complications. By tailoring our approach to individual patient characteristics, we hope to optimize stroke outcomes and advance the field of stroke treatment. Ultimately, a comprehensive understanding of the brain–liver interaction could open new avenues for stroke management and improve patient care, potentially reducing the global burden of ischemic stroke.

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