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ORIGINAL ARTICLE

The effects of obstructive jaundice on the brain: An experimental study

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Summary *Background/Objective:* The study aims to evaluate the alterations in the brain due to oxidative stress and lipid peroxidation resulting from obstructive jaundice.
Methods: Forty-one Wistar albino rats were used in this study. Simple laparotomy was performed in the sham group ($n = 5$). In the remaining 36 rats, the common bile duct (CBD) was found and ligated. They were divided into six groups. Group I, Group II, and Group III were sacrificed at the 3rd, 7th, and 14th day of ligation, respectively. In Group Id, Group IId, and Group IIId ligated bile ducts were decompressed at the 3rd, 7th, and 14th day, respectively. One week after decompression these rats were also sacrificed and samples were taken.
Results: After the CBD ligation, serum levels of bilirubin and malondialdehyde were found to be increased progressively in parallel to the ligation time of the CBD. After decompression these values decreased. In electron microscopy evaluation, the damage was found to be irreversible depending on the length of the obstruction period. In Group II, the damage was mostly reversible after the internal drainage period of 7 days. However in Group III, the tissue damage was found to be irreversible despite the decreased values of oxidative stress and bilirubin.
Conclusion: Ultrastructural changes in brain tissue including damage in the glial cells and neurons, were found to be irreversible if the CBD ligation period was >7 days and did not

Conflicts of interest: All contributing authors declare no conflicts of interest.

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regress even after decompression. It is unreliable to trace these changes using blood levels of bilirubin and free radicals. Therefore, timing is extremely critical for medical therapies and drainage.

1. Introduction

Obstructive jaundice (OJ) is the partial or total blockage of the extra- or intrahepatic biliary ducts that leads to a corruption of the normal biliary passage to the intestines. OJ may lead to high morbidity and mortality. In OJ, bile acids cause injury via free radicals and create oxidative stress in extrahepatic tissues.

Previous studies have suggested that altered gut barrier functions on the grounds of OJ, resulted in the migration of bacteria and endotoxins to the different organ systems.[1] In animal models, by the means of oxidative stress, these toxins and molecules increase lipid peroxidation products. This affects extrahepatic tissues such as the kidneys, the lungs, and the brain. One of the well-known products is malondialdehyde (MDA), and is used as a marker of lipid peroxidation.[2]

In the brain, this oxidative stress may lead to neuropsychiatric abnormalities known as "hepatic encephalopathy" (HE) which at the end leads to symptoms varying from tremor and behavioral changes, to ataxia and coma which are eminently mortal.[3]

In 1991, Lockwood et al[4] provided the first direct evidence in patients with ammonia and HE pathogenesis using positron emission tomography, which showed an increase in the cerebral metabolic rate of ammonia, and they suggested that ammonia was the main neurotoxin in the pathogenesis of HE. Astrocytes are responsible for the detoxification of ammonia during the conversion of glutamate to glutamine in the brain. Astrocytes regulate the extracellular matrix and influence neuronal excitability and neurotransmission.[3]

In clinical daily experience, if OJ patients are not operated on early and biliary drainage is not provided soon, the morbidity and mortality of the patients increase. These injuries in the end-organs are not reversible if the obstruction period gets longer. However, electron microscopic findings on functional changes regarding obstructive injury, pathophysiology of the reversibility, and the healing process are not fully understood. The unsolved dilemma is whether there is a period of reversibility, and what are the ultrastructural changes that lead to cell death.

The aim of the present study was to evaluate the alterations in the brain tissue resulting from OJ. After the release of the obstruction in different time periods, the hypothesis of whether the ultrastructural injury is reversible is also evaluated together with the correlations between OJ, oxidative stress, and injury.

2. Methods

2.1. Ethical approval

The study was approved, and the animals were treated according to the institutional guidelines of the Ethical Committee of Animal Research, Ankara University, Ankara, Turkey (protocol no: 37194).

2.2. Study design

Forty-one female Wistar albino rats, weighing 237 g (228–246 g) were used. Animals were housed in standard cages under appropriately dominated temperature and humidity conditions. They were fed with the standard rat diet (chow) and tap water. The night before the surgery feeding was stopped for preoperative fasting.

Rats were randomized into seven groups at the beginning of the study and kept in separate cages. Rats in the sham group ($n = 5$) underwent simple midline laparotomy. In the remaining 36 rats, which were randomized into three groups of 12 animals, after midline laparotomy, the common bile duct (CBD) was found and ligated. Half of the rats ($n = 18$, six from each group) in Group I, Group II, and Group III were sacrificed at the 3rd, 7th, and 14th day of the ligation, respectively, and samples were taken. In the remaining eighteen animals, ligated bile ducts were decompressed under anesthesia at Day 3, Day 7, and Day 14, respectively (groups designated as Group Id, Group IId, and Group IIId). One week after decompression, all these rats were sacrificed and samples were collected (Figure 1).

2.3. Surgical procedures

After topical povidone-iodine antisepsis, the animals were anesthetized with ketamine hydrochloride (50 mg/kg intraperitoneal) and xylazine hydrochloric acid (2 mg/kg intraperitoneal). All procedures were performed approximately at the same time of the day, between 11:30 AM and 01:30 PM, at the animal research laboratory of Ankara University Medical School. After sterile conditions were maintained, laparotomy was performed with a midline incision. In the sham operated group, after laparotomy was performed, the operation was terminated without manipulating the CBD ($n = 5$). In the remaining 36 rats, the CBD was isolated and ligated at the middle third by 5-0 polypropylene. Ligation was performed by placing a half