LIVER DAMAGE IN RHEUMATOID ARTHRITIS

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Drug-induced liver injury is an important problem not only within hepatology, but also for internal medicine in general [6;7]. Today, rheumatic diseases (RD) are considered in the scientific medical community as one of the most significant not only from medical, but also socio-economic positions. This is due, first of all, to their wide distribution and diversity. [1] . The essence of the pathological process in rheumatoid arthritis (RA) is generalized immunological inflammation, leading to the development of synovitis, as well as a wide range of extra-articular organ manifestations, of which the pathology of the gastrointestinal tract ranks first 11%, including hepatomegaly occurs in 19.5% [13]. The trend towards early disability and possibility of systemic manifestations with involvement in pathological process of internal organs dictate the need for timely diagnosis of complications and selection of adequate therapy. One of the vulnerable systems in patients with JRA is the hepatobiliary system. It is caused by autoimmune processes on the one hand, and the effects of drugs on the other [10].

Hepatotoxic reactions that occur during the use of basic therapy for RA depend on the duration of administration and dose of drugs [2]. The interpretation of changes in the functional capacity of the liver is also different . Most researchers, already at the early stage of RA, noted a violation of its detoxification , pigment, protein-forming and carbohydrate functions, others believed that the function of the organ suffers only with amyloid damage. Structural changes, on which the functioning of the liver directly depends, were described by domestic pathomorphologists as granular, fatty degeneration, deposition of amyloid masses, less commonly, ring cirrhosis and necrosis of hepatocytes. Currently, two types of functional and morphological changes in the liver in RA are generally recognized:

1. Deposition of amyloid masses along intralobular capillaries between stellate endothelial cells, in the reticular stroma of lobules, walls of vessels, ducts and interstitial tissue of portal tracts with hepatocyte atrophy.
2. Inflammatory and sclerotic changes in the portal tracts and stroma as a morphological expression of immune disorders. [13;14].

It is known that the likelihood of adverse reactions increases with an increase in the number of medications taken simultaneously. It has been established that if a patient takes six or more drugs at the same time, the likelihood of side effects is it reaches 80% [11;13]. Analysis of published information in regarding the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) for RA and gold standard treatment, methotrexate (MTX), indicates high probability of liver damage. Hepatotoxicity used in rheumatology drugs leads with slowing down the processes of

biotransformation of exo- and endobiotics , their accumulation in circulating blood and development of endogenous intoxication, aggravation of the pathological process and toxicity of the drugs used [10;12]. Methotrexate directly inhibits the activity of methylenetetrahydrofolate reductase, which leads to an increase in homocysteine levels, and V subsequent to increased fatty infiltration of hepatocytes, development of inflammation, activity of Ito cells and liver fibrosis [5;10]. Methotrexate can cause an increase in liver enzyme activity, the development of fibrosis and liver cirrhosis during long-term treatment [6;7;8]. However, data on frequency of development and severity of fibrosis and liver cirrhosis when using methotrexate in doses used for rheumatic diseases are controversial [10].

As a result of the progression of the pathological process in the liver develops successive stages of fibrosis, for the diagnosis of which in in recent years the safest and An informative non-invasive method is liver elastography [3;4;9;10;15]. In connection with As stated above, the problem of early diagnosis of liver damage, increasing the effectiveness of RA therapy while ensuring a minimum of side effects of drugs is extremely relevant, both with from a scientific point of view and practical medicine

Materials and methods. 78 patients with RA aged from 40 to 60 years were examined . Of these, 16 patients with oligo and 62 with polyarthritic variant of the disease. Of the 78 patients, 54 (69.2%) were women and 24 (30.8%) were men. The duration of the disease ranged from 1 year to 10 years. 59 patients showed clinical signs of liver damage (main group), and 28 patients with RA without liver damage formed the comparison group. Inclusion criteria were the absence of previous diseases of the hepatobiliary system, the absence of antibodies to hepatitis B, C, and D viruses, which were determined by the enzyme immunoassay. Ultrasound examination (US) of the hepatobiliary system and liver elastography were performed . Activity of the enzymes alanine aminotransferase (ALAT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP), total protein content, albumin, bilirubin with fractions, total cholesterol. In addition, the results of preparations from 30 studies of white outbred rats aged 18-24 months with simulated rheumatoid arthritis were studied. Histological sections from the liver were stained for general morphological study with hematoxylin and eosin, to identify collagen fibers, sections were stained using the van Gieson method, mucopolysaccharides were determined by the PAS reaction. Statistical processing of the obtained data was carried out on a personal computer using the Microsoft Office application package.

Results and its discussion. The studies showed that out of 78 patients, 41 (52.6%) showed signs of damage to the hepatobiliary system. In 15, reactive hepatitis was detected, in the remaining 26 patients there were signs of chronic hepatitis. According to ultrasound diagnostics, there was an increase in the size of the liver (+1cm - +3cm), a slight increase in the echogenicity of the liver parenchyma and an increase in the vascular pattern. In general, liver lesions on ultrasound were characterized by diffuse changes in the liver parenchyma, increased echogenicity, reactive hepatitis and

hepatomegaly. Drug-related liver damage usually manifests itself as an asymptomatic increase in liver enzymes, i.e. proceed subclinically, being a “biochemical finding” (anicteric variant of the course of acute drug-induced hepatitis). In patients with a disease duration of 1–3 years, functional disorders of the liver were observed, manifested in a violation of enzyme status. Of these, 58.1% of patients complained of nausea, vomiting, and unstable stools.

They did not exhibit classic clinical signs of hepatitis. An asymptomatic increase in the level of aminotransferases can be observed when using non-steroidal anti-inflammatory drugs, cytostatics, immunosuppressants, which are included in the standard of treatment when administered to patients with RA. With long-term use of such drugs, damage to the liver tissue of varying severity may develop. Based on this, it is necessary to pay attention to an isolated increase in aminotransferase activity, as it may indicate the development of drug-induced liver damage.

Detection of drug-induced hepatitis is a complex problem. Several criteria are proposed to clarify the diagnosis and confirm that the symptoms that arise are caused precisely by the medications: chronology of the occurrence of complications; reverse development of clinical symptoms after discontinuation of the drug; recurrence of complications after repeated administration of the drug; no other possible cause; results of laboratory and instrumental studies.

When diagnosing drug-induced hepatitis, it was based on chronological criteria, the absence of another possible etiology, and the results of laboratory and instrumental studies.

Reversal of clinical signs of complications after discontinuation of therapy is difficult to use, since long-term withdrawal of standard treatment will lead to exacerbation of the underlying disease (RA). In the studied patients, as the disease progressed and they continued to take drugs, often in increased doses, there were signs of hepatitis with all the characteristic clinical and laboratory manifestations and confirmed by ultrasound.

A study of the clinical manifestations of liver damage shows that complaints of pain in the right hypochondrium and abdomen were reported by less than half of patients with a disease duration of more than 5 years, decreased appetite was observed in more than 50% of patients, icterus of the skin was observed in 45% of patients, an increase in liver size was observed in almost all patients. Biochemical studies revealed an increase in the activity of aminotransferases in 9 (22%), GGT and alkaline phosphatase - in 13 (31.7%), hyperbilirubinemia - in 24 (58.5%) and direct bilirubin - in 4 (9.8%). In 27 (65.9%) patients, signs of protein metabolism disorders were revealed, manifested by hypoalbuminemia and in 7 (17.1%) - hypoproteinemia. The greatest changes were typical for patients using a complex of NSAIDs, prednisolone and methotrexate.

The data obtained coincide with the severity of clinical manifestations in patients with hepatitis. Persons in this group more often complained of headaches, malaise,

loss of appetite, asthenovegetative syndrome was more clearly manifested, etc. with a high frequency they were detected in persons receiving a combination of several drugs, especially in combination with methotrexate. According to liver elastography, out of 17 RA patients, 13 (76.4%) had no signs of fibrosis (F0). 2 (11.8%) patients were diagnosed with minimal fibrosis (F1) and 2 (11.8%) with moderate fibrosis (F2). Severe fibrosis and cirrhosis (F3, F4) were not detected. Fibrosis was assessed using the METAVIR scale. The average liver elasticity was 3.6 ± 0.5 kPa for F0, 5.8 ± 0.5 kPa for F1 and 6.4 ± 1.5 kPa for F2 stage of fibrosis, respectively. Indicators of fibrosis stage in the group of RA patients with liver damage were distributed in equal proportions between F0, F1, F2.

The results of a pathomorphological study showed that in the liver of white outbred rats with simulated rheumatoid arthritis, the development of disorganization, dystrophic and immunopathological processes was noted. Initially, disorganized changes in the vascular wall and interstitium of the liver develop, which are manifested by swelling of the intercellular substance, loosening of fibrous structures, and collapse of the cellular elements of the connective tissue. These changes were more pronounced in the wall of the central vein and the space of Disse. Disorganization of the wall of the central vein and sinusoids was accompanied by the development of liver dyscirculation in the form of diapedetic hemorrhage. Venous discirculation led to the development of dystrophic changes in the liver parenchyma and they manifested themselves in the form of hyaline-droplet and vacuolar degeneration of hepatocytes.

During a histochemical study to identify mucopolysaccharides in the composition of stroma-vascular components and glycogen in the cytoplasm of hepatocytes using the PAS reaction, it was noted that the content of mucopolysaccharides in the stroma increases in the form of more intense staining of the intercellular substance in a pink-red color, which indicates the accumulation of glycosaminoglycans, characteristic of disorganization processes connective tissue.

On the part of the liver parenchyma, a decrease in the PAS of the positive substance in the cytoplasm of hepatocytes was noted, which proves the increased breakdown of glycogen and the predominance of protein and vacuolar degeneration of hepatocytes. In the liver of people who had suffered from RA for a long time, the development of deeper disorganization processes was noted in the form of mucoid, fibrinoid swelling and myxamatosis of the connective tissue of the liver vessel wall. It was noted that the wall of the central vein of the liver is thickened due to fibroelastosis and myxamatosis of fibrous structures, which continue towards the wall of the sinusoids. These changes resulted in paralytic dilatations of the sinusoids, perivascular hemorrhages, and pigmentation. The beam arrangement of hepatocytes is destroyed in the form of the formation of both randomly located and hepatocytes subjected to cytolysis and apoptosis.

The nuclei of the latter are in a state of karyolysis, karyopyknosis. Moreover, cholestasis manifests itself in the form of accumulation in the inner side of the cytoplasm of hepatocytes in the form of multiple small brown pigment inclusions. The main pathomorphological changes of the immunopathological nature of RA were identified around the vessels of the liver triads, which were manifested by the appearance of a pronounced cellular infiltrate of lymphoid and histiocytic cells with an admixture of eosinophils.

The cellular infiltrate mainly surrounds the arterial vessels of the triads and extends towards the liver parenchyma along the sinusoids. In this case, the walls of the vessels are in a state of mucoid and fibrinoid swelling. In the liver parenchyma, especially in the space of Disse, activated lymphoid cells appear, which tightly adhere to the liver cells. Hepatocytes located around the triads are subject to dystrophic changes and cholestasis.

A histochemical study showed a significant decrease in the PAS positive substance in the cytoplasm of hepatocytes in all functional areas of the liver. The results of a morphological study showed that in the liver of white outbred rats with simulated rheumatoid arthritis that did not receive methotrexate, the development of both general morphological changes in the form of disorganization and dystrophy of the connective tissue of the vascular wall, and immunopathological processes in the form of periportal lymphohistiocytic infiltrate with an admixture of eosinophils and mucoid , fibrinoid swelling of the walls of blood vessels and connective tissue of the interstitium of the liver.

The results of a morphological study of the liver of white outbred rats with simulated rheumatoid arthritis, which received NSAIDs (meloxicam) 1 mg/kg, methotrexate at a dose of 0.5 mg/kg showed that, in contrast to animals that did not receive methotrexate, there was a development of more pronounced disorganization, dystrophic and immunopathological processes with transition for sclerotic and fibromatous changes. With an increase in the dose of methotrexate, proliferative activity of histiocytic cells was noted with the accumulation of fibrillar substance in the wall of the sinusoids and the central vein with the development of fibrous connective tissue, more pronounced in the wall of the central vein.

Conclusion

1. In 52.6% of patients with RA, liver damage was detected, manifested in all cases by signs of mesenchymal inflammation, 65.9% - hypoalbuminemia, 58.5% - hyperbilirubinemia, 31.7% - cholestasis and 22% - hyperenzymemia up to 2 norms.

2. Ultrasound elastography makes it possible to identify fibrosis phenomena and monitor MTX toxicity of the liver in patients with RA at the early stages. The advantages of liver elastography are ease of performance, non-invasiveness, speed in obtaining results, and the possibility of repeated studies.

3. The depth and severity of pathomorphological disorders depends on the dose and duration of standard therapy drugs taken and is characterized by: disorganization

and dystrophy of connective tissue, lymphohistiocytic infiltrate of the vascular wall and connective tissue of the interstitium of the liver, up to fatty degeneration of hepatocytes, pronounced proliferative activity of both histiocytic and lymphoid cells with the formation of foci of granulomatous inflammation and pronounced fibromatosis in the wall of the central vein.

REFERENCES:

1. Бобокуловна, Д. М. ., & Мухидиновна, С. М. . (2023). Гастропатическая Комарбидность У Больных Ревматоидным Артритом. Amaliy va tibbiyot fanlari ilmiy jurnali, 2(1), 1–6. Retrieved from https://sciencebox.uz/index.php/amaltibbiyot/article/view/5297

2. Геппе Н. А., Подчерняева Н. С., Лыскина Г. А. Руководство по детской ревматологии. — М.: ГЭОТАР Медиа, 2011. — С. 162–325.

3. Горячева Л. Г., Котев М. Я., Ефремова Н. А. Эластография печени в детской практике // Журнал инфектология. — 2009. — № 2/3. — Том 1. — С. 64–68.

4. Жолобова Е. С., Конопелько О. Ю., Гешева З. В. Гепатотоксичность нестероидных противовоспалительных препаратов, применяемых в детской ревматологии // Педиатрия. — 2009. — № 5. — С. 154–160.

5. Игнатева Т. М. Лекарственное поражение печени // Гепатологический форум. — 2008. — № 2. — С. 2–8.

6. Мельдеханов Т. Т. и др. Токсические лекарственные поражения печени //Вестник Казахского Национального медицинского университета. – 2019. – №. 1. – С. 63-66.

7. Мухин Н. А., Моисеев С. В. Лекарственная гепатотоксичность // Клин. гепатология. Москва, 2010. — № 6. — С. 3–7.

8. Полунина Т. Е. Лекарственные поражения печени // Лечащий врач. Москва, 2005. — С. 8–13.

9. Пирогова И. Ю., Пышкин С. А. Диагностические возможности методов неинвазивной оценки фиброза при диффузных заболеваниях печени // РЖГГ-2009. — № 4. — С. 48–53.

10. Шомурадова Ш. Ш., Алимов А. В. Лекарственное поражение печени при ювенильном ревматоидном артрите //Экспериментальная и клиническая гастроэнтерология. – 2016. – №. 7 (131). – С. 38-42.

11. Aithal G. Hepatotoxicity related to ant rheumatic drugs // Net. Rev. Rheumatol., 2011. — № 7 (3). — С. 139–150.

12. Analli M., Scioscia C., Grattagliano I., Lapadula G. Old and new antirheumatic drugs and the risk of hepatotoxicity // Th er. Drug Monit., 2012. — № 34 (6). С. 622–628.

13. Kholmurodovich, U. F. (2022). Liver Pathology In Rheumatoid Arthritis. Central Asian Journal of Medical and Natural Science, 3(1), 11-15. https://doi.org/10.47494/cajmns.v2i7.543

14. Kocharla L., Taylor J., Weiler T. Monitoring methotrexate toxicity in juvenile idiopathic arthritis // J Rheumatol., 2010. — № 36 (12). — C. 2813–8.

15. Laharie D., Seneschal J. Assessment of liver fi brosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: A case-control stady // Jounal of Hepatology. — 2010. — vol. 53. — P. 1035–1040.