ROLE OF ECHOGRAPHY AND COMPUTED TOMOGRAPHY IN DIAGNOSIS OF CHRONIC DIFFUSE LIVER DISEASES

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ABSTRACT

In three-stage prospective cohort controlled research of 2876 persons with chronic diffuse liver diseases (2076 cases of fatty liver disease, 509 cases of chronic hepatitis, 139 cases of liver cirrhosis) and 152 healthy controls the clinical significance of radiation methods of investigation in quantitative evaluation of liver morphofunctional state in patients with chronic diffuse liver diseases was estimated. Diagnosis-prognostic algorithm for patients with this pathology was developed, validated and recommended for practical application. Further perspectives are related to detailed chronic diffuse liver diseases stratification by intensity of steatosis (in fatty liver disease), activity (in chronic hepatitis) and fibrosis (in chronic hepatitis and liver cirrhosis).

KEYWORDS

Fatty Liver Disease, Chronic Hepatitis, Liver Cirrhosis, Ultrasound Diagnosis, Computed Tomography

1. INTRODUCTION

Chronic diffuse liver diseases cause not only significant medical problem, promoting portal hypertension, hepatocellular failure, oncological diseases etc. [1], but also social and economical, associated with loss of ability to work in active population; particularly, mortality due to liver cirrhosis in European countries vary from 100 to 400 per 1 million of male population and from 40 to 150 per 1 million among females [2, 3, 4, 5].

In last decade is an impetuous development of chronic diffuse liver disease takes place. Technical progress, improvement of hardware and software have made it possible to significantly go forward in understanding of etiology and pathogenesis of hepatobiliary pathology, noticeably improve treatment results. In many respects these changes became possible only due to introduction and development of new highly-technological methods of radiation (visual) diagnosis in general and ultrasonography – as well [6, 7].

Results of radiological diagnostic methods are widely used in order to build prognostic models and calculate a prognosis in each certain clinical case about functional compensation of liver, presence of indications for radical intervention etc. [8]. Both mathematical [9, 10, 11, 12] and virtual [13], dimensional models based on morphological investigation of liver come in handy and give an opportunity to more exactly and objectively evaluate changes which develop in vivo, formulate an individual prognosis for a patient.

Despite the availability of wide spectrum of other modern non-invasive and low-invasive radiation methods of diagnosis for chronic diffuse liver diseases, ultrasonography does not lose its topicality and is the leader of practical application in public health service. Undoubted perspective is characteristic for methods which base not only on immediate primary results of investigation, but on results of their further objectivization using mathematical modeling and building of prognostic model of the pathological process. Reasonability of ultrasonography application for diagnosis of chronic diffuse liver diseases is related to its following characteristics: non-invasive [14], safe [15], easily done [16], relatively cheap and capable to simultaneous evaluation of comorbid pathology [17], also in dynamics, reproductible and precise, standardized [18], easily combined with other methods [19, 20], capable for further improvement and including contrast-enhance.

While, some limitation of ultrasonography in diagnosis of chronic diffuse liver diseases takes place in medical practice [21, 22]. This problem may be solved by improvement of ultrasonography diagnosis approach with automation of image analysis [23], introduction of index parameters etc.

Thus, despite general success of ultrasonography in diagnosis of chronic diffuse liver diseases, till nowadays improving of this approach remains vital.

2. MATERIAL AND METHODS

Aim of research – optimization of diagnosis of chronic diffuse liver disease by development of diagnosis-prognostic algorithm using USI and CT parameters.

On first phase an estimation of diagnostic capabilities (values) of ultrasonography in chronic diffuse liver diseases was performed. It included investigation of 103 cases of chronic diffuse liver disease: fatty liver disease (n=63), chronic hepatitis (n=12), liver cirrhosis (n=28), cases with intact liver (control group, n=2). This phase was conducted on the base of Kharkiv Regional Clinical Hospital – Center of Emergency Medical Care and Disaster Medicine in 2012–2013 with the aim of evaluation of accordance of ultrasonographic data with results of liver autopsy (both n=105).

Second phase was aimed on development of a diagnosis-prognostic algorithm of ultrasonography application and profound instrumental-laboratory tests (apart of ultrasound – anamnestic and physical data collection, complete blood count and biochemical blood tests) were performed. Two hundred fifty three persons, including patients with fatty liver disease (n=142), chronic hepatitis (n=43), liver cirrhosis (n=27), and 50 healthy people shared this phase of the research. It has been conducted in clinical hospital of Grigoriev Institute of Medical Radiology of National Academy of Medical Science of Ukraine in 2013–2014. All participants underwent detailed repetitious instrumental and laboratory investigations. In this cohort male and female age medians did not significantly differ.

Third phase was most large in the research as aimed on evaluation of ultrasonography capabilities in prospective evaluation of chronic diffuse liver disease course by validization of developed diagnosis-prognostic algorithm for pathologic process severity evaluation and course prediction, and also building a mathematic model of pathologic process. In order to reach the goal, 2206 persons were examined, including patients with fatty liver disease (n=1660), chronic hepatitis (n=416), liver cirrhosis (n=45), control healthy individuals (n=85). This phase of the research was performed on the base of LTD Medical Diagnostic Center «Expert-Kharkov» in 2013–2014. Age median was 56.1 (47.1; 64.1) years, 55.0 (44.3; 64.2) years in men, 56.4 (47.7; 64.1) years in women (difference is reliable by p=0,053).

Ultrasound investigation was performed with Xario SSA 660A system (Toshiba Medical Systems, Japan). Pathomorphological investigation has been conducted according to standard protocols with evaluation, where applicable, of liver steatosis [24] and liver fibrosis intensity degree [25], level of activity (Knodell R. G., 1981). Nonparametric methods of statistical analysis were applied [26]. Median (Me) and interquartile interval with representing lower, 25 %, quartile (LQ) and upper, 75 % quartile (UQ) were calculated, result was expressed by Me (LQ; UQ) way for shortness. Kruskal-Wallis ANOVA & median test method, Mann-Whitney U-criterion, Wilcoxon method, correlation by Spearman, Fisher angular transformation were used where applicable. Comparative analysis in groups of separate diagnostic criteria distribution using ANOVA and Wald sequential analysis (Wald A., 1947) in its interpretation for medical diagnosis (Genkin A. A., 1962; Gubler E. V., 1978) by ranging of parameters by their differential-diagnostic information capacity allowed to define diagnostic value, prognostic significance and influence power of factors on parameters divergence in clinical groups and prognostic coefficients. Only independent prognostic parameters were included in the algorithm. In cases when correlation strengths between factors were more than |0,70|, one of factors was excluded from list of parapeters. Ranking of parameters by influence strengths, evaluation of prognostic and information capacity of parameters allowed choosing the most reliable parameters. At the last phase, mathematic modeling using discriminant analysis and building of artificial virtual neural networks with their further training was performed.

The research has been conducted according to requirements of European Convention (Strasburg, 1986), ICH GCP (2008), GLP (2002) principles, local Ukrainian legislation.

3. RESULTS AND DISCUSSION

In 1st phase the age median was 62 (46; 71) years without significant gender differences, while gender comparisons in different nosologic groups showed the age difference ($p=0.0001$) – the oldest in fatty liver disease group, 64.0 (60.0; 73.0) years; youngest in chronic hepatitis group, 41.6 (31.0; 52.5) years; intermediate in liver cirrhosis group, 52.0 (41.5; 65.5) years. Age comparison in different nosologic groups in further phases showed above mentioned (in 1st phase) differences in general and among women (both $p<0.001$).

Pathomorphological verification of ultrasonography results in evaluation of disease character in patients with chronic diffuse liver diseases revealed 1.9 % probability of false-positive ultrasound diagnosis of this pathology, diagnostic capacity of 14–97 % (with central value of 56 %).

Using results of profound clinical, instrumental and laboratory investigation including frequency of separate ultrasonography parameters and prognostic value of each of criterion the screening algorithm was elaborated in order to predicting of complication risk. It has table form, which includes demographic-antropometric (age, gender, body mass index), sonographic (liver size, characteristics of capsule, parenchyma, ascites, hepatic vein circulation, caudal to right lobe transverse size, degree of steatosis, congestion index, modified hepatic index, hepatic vascular index, index of arterial perfusion, portolienal venous index, pulsatory index of spleen artery, platelets to spleen diameter ratio, right lobe width to albumins ratio) parameters, appropriate prognostic coefficients and prognostic result evaluation scale. By each parameter its presence or absence has to be evaluated, corresponding prognostic coefficients are to be summarized. By achievement of threshold sum of coefficients a risk group was stated by using the scale: if equal or less than -19.8, risk is minimal; if more than -19,8 and less than 19.8, risk is uncertain; if equal or more than 19.8, risk is high.

For each of three diseases canonic discriminant functions were built. Predicted appliance to groups of low, uncertain, high progression risk in fatty liver disease was 78.9 %, 69.3 %, 99.7 % accordingly; in chronic hepatitis – 63.7 %, 61.1 %, 93.2 % accordingly; in liver cirrhosis – 93.1 %, 64.8 %, 99.7 %.

Neural networks (three-level perceptron with descending number of nodes) were built, trained and sensitivity, specificity evaluated. After training the square below ROC-curve to each of risk groups became increased > 80 %.

4. CONCLUSIONS

1. Prospective randomized three-phase populational (on 3rd phase) research has proved the clinical significance of ultrasonography in evaluation of morphofunctional state of liver and portohepatolienal bloodstream in chronic diffuse liver diseases (fatty liver, chronic hepatitis, liver cirrhosis).

2. Diagnosis-prognostic algorithm which includes anthropodemographic, clinical and ultrasonographic parameters has been elaborated, intending on forecast of risk of unfavourable course of chronic diffuse liver diseases.

3. Predicting value of ultrasonography has been boosted by discriminant mathematic model development, artificial virtual neural networks application.

4. Longitude multicenter study of proposed approach in diagnosis of chronic diffuse liver disease using non-invasive ultrasonography and evaluation of treatment efficacy might be further perspectives of the research.

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