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HEPATIC LIVER DISEASES – METHODS FOR DIAGNOSIS AND MEDICAL INFORMATICS FOR TREATMENT SUPPORT

Liver diseases and more specifically viral hepatitis are at the center of interest due to their global spreading, even in the most developed countries. The range of symptoms, the complications and the course of the disease have imposed the operation of liver centers at the outpatients' departments of hospitals, where the contribution of several specialized doctors the disease is diagnosed, prevented and treated. Many patients suffer from hepatitis without knowing it either because they manifest no symptoms or because the infection is not traced through the usual lab tests.

This paper focuses on studying and proving how the systematic reading of the main liver diseases and the methods through which the doctor makes the diagnosis can help the study and analysis of a series of steps that have to be followed in order to treat the disease. Then, the use of a modern information system using Medical Informatics technologies is proposed so as both the task of diagnosis and the efforts to treat and overcome the problems related to the liver disease to be supported.

1. INTRODUCTION

The term "hepatitis" is mainly attributed to hepatitis caused by viruses. Most common Viruses that can cause hepatitis are: hepatitis A, B, C, D, E.
Acute viral hepatitis lasts less than six months and ends either by complete cure of the liver lesion or rapid development of the acute lesion, in which case it is characterized as acute fulminant hepatitis.
In chronic hepatitis the inflammation and necrosis processes continue for at least six months. The causes of chronic hepatitis include: inflammation attributed to the virus B, B and D, C which is one of the most frequent causes, autoimmune hepatitis, drugs, cryptogenic hepatitis. Patients with chronic hepatitis have no symptoms at all, even though studies have shown that they report fatigue more frequently compared to the healthy population [7].

2. VIRAL HEPATITIS A

The clinical picture of hepatitis A is usually similar to other forms of hepatitis. Hepatitis A is the most benign disease and nearly always comes to full recovery within 2-4 weeks and confers permanent immunity, does not cause chronic liver damage and does not create chronic agents, even though a 15% of cases may be protracted with some relapse over a six to nine month period. The diagnosis of hepatitis A during the acute phase is made by detecting the anti-HAV/IgM antibody. After the remission of the acute disease, anti-HAV/IgG remains detectible indefinitely and the patients with serum anti-HAV are immune to re-infection [4].

3. VIRAL HEPATITIS B

The viral proteins, the so-called antigens, are used as markers for the detection of the infection and its progress. There are 4 main phases that constitute snap-shots of the disease with a duration that ranges from a few years to several decades:

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a) HbeAg-positive phase of proliferative phase or immunotolerance, b) phase of cleaning of HBeAg, c) HBeAg – negative inactive phase (integration phase or chronic inactive HBV carriers) and d) phase HBeAg negative chronic hepatitis B developed in approximately 25-35% of patients.
Acute infection remains asymptomatic in the majority of cases or is manifested as classic acute hepatitis. Both the chronic carriers of hepatitis B virus and patients with chronic hepatitis B do not present symptoms for decades until they have manifestations of advanced cirrhosis (jaundice, ascites, hepatic encephalopathy, esophageal varices).
People with HBsAg and normal transaminase need to check the transaminases and IgM anti-HBc levels every six months. Check for prompt diagnosis of hepatocellular carcinoma by checking every 3-4 months the α-fetoprotein and liver ultrasound is recommended for patients over 40 years old and those with clinical laboratory picture of cirrhosis. Patients with chronic infection and pathological levels of transaminases should undergo further control so as to explore whether the increase of transaminases is due to reactivation of HBV or other causes [6].

4. VIRAL HEPATITIS C

Chronic hepatitis C is a slowly developing disease that causes more serious liver damage than HBV. 70% of patients with hepatitis C develop cirrhosis, while 75% develop hepatocellular carcinoma within 15 years, without though this pathogenesis being fully understood.
Chronic hepatitis C in most cases follows a mild and long course. Sometimes it has its typical form (jaundice – discoloration of urine and stool–abdominal pain), but it usually goes unnoticed.
Viral testing for the diagnosis of the HCV infection are: serological tests that defines antibodies and tests based on molecular biology that reveal, quantify and characterize the genome of HCV.
One single negative test for the virus does not eliminate the presence of hepatitis C and needs retesting after a few months. The usual procedure is to check first for the existence of antibodies against the virus (anti-HCV) and then to see for HCV RNA in order to determine the existence of viraemia. Finally, the liver biopsy defines the prognosis [11].

5. VIRAL HEPATITIS D

HDV uses the biological mechanism of hepatitis B virus to preserve its contagious ability. It proliferates inside the hepatic cells that are already contaminated with the hepatitis B virus and uses the exterior envelope of the virus B so as to exit the cell and contaminate others. HDV can contaminate a person simultaneously with HBV or infect a person that has already been contaminated by HBV. During the phase of acute HDV infection the anti-HDV of IgM class prevails and it could take 30-40 days before the onset of the symptoms, till the anti-HDV becomes detectible. In chronic HDV infection, there is high titre anti-HDV, anti-HDV/ IgM and IgG can co-exist. Symptoms are the same as for Hepatitis B [8].

6. VIRAL HEPATITIS E

The hepatitis E virus (HEV) has an incubation period following exposure to HEV ranges from 3 to 8 weeks. It is possible to detect IgM and IgG anti-HEV, but both reduce quickly after acute infection reaching low levels within 9 to 12 months. There is no serological routine examination for the infection by HEV [9].

7. AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic disease that is characterized by constant hepatocellular necrosis and inflammation, usually with fibrosis, which tends to develop to cirrhosis and hepatic failure. The progressive hepatic damage in patients with idiopathic/autoimmune hepatitis is an outcome of cellular immunity that turns against hepatic cells. The autoantibodies that have been described in such patients include antibodies against the core, the so-called anti-nuclear antibodies ANA, anti-smooth muscles antibodies ASMA, anti-LKM, antibodies against the “soluble hepatic antigen” as well as

antibodies against the special hepatic receptor of asialoglycoprotein or other proteins of the membrane of the liver cells [10].
The predominant abnormalities are elevated serum aminotransferase levels, which can mimic a severe acute hepatitis. Most patients have substantial increases in the serum gamma-globulin and immunoglobulin G levels. A disproportionately increased serum alkaline phosphatase level is an important clue to an alternative diagnosis [12].

8. ALCOHOLIC LIVER DISEASE

Histological damages of Alcoholic liver disease are divided into three types: the fatty liver or steatosis, the alcoholic hepatitis and fibrosis.
In the fatty liver is observed an asymptomatic or slightly painful hepatomegaly and a small rise of the transaminases or the γ-GT. The clinical picture can range from asymptomatic to severe fulminate hepatitis. It may appear as acute hepatocellular failure with ascites, encephalopathy and hemorrhage of the peptic system.
Severe alcoholic hepatitis can be suspected by the existence of coagulation disorders, anemia, and albumin concentration in the serum less than 2.5mg/dl, cholerythrin serum levels over 8mg/dl, renal failure and ascites [1].

9. NON ALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease is developed in individuals without an alcohol abuse history. Sugar diabetes type II, obesity, hyperlipidemia, abrupt weight loss and administration of certain drugs are conditions related to the nonalcoholic fatty liver disease.
The non-alcoholic fatty liver disease (NAFLD) includes two types: non-alcoholic hepatosteatosis (NASH) and non-alcoholic steatohepatitis (NAS).
Most patients with nonalcoholic fatty degeneration of the liver are asymptomatic or manifest atypical complaints such as loss of energy and a feeling of fullness at the right subchondral bone. The most frequent lab disorder is the rise of transaminases (2-3 times over the normal rates), with ALT topping AST, contrary to alcoholic liver disease. Alkaline phosphatase and γ-GT show mild rise, while bilirubin is rarely increased. Albumin and prothrombin time are normal, save for the cases when cirrhosis is developed. It is also mentioned that serum ferritin is risen in 50% of the cases [2].

10.CIRRHOSIS

The diagnosis of cirrhosis includes the clinical, laboratory, imaging and histological examination. The clinical characteristics of cirrhosis concern all organic systems. Anemia is present in blood, hypersplenism and disorders of the haemostatic mechanism. From an endocrinology standpoint, we see disorder of the glucose metabolism. Pulmonary hypertension is observed in the respiratory system, which is related to portal hypertension. This disorder is rare, but has unfavorable prognosis. Moreover, it is observed hepatopulmonary syndrome (increased alveolar-arterial oxygen difference and intrapulmonary vascular dilatation). The cardiovascular system presents tachycardia, low arterial pressure and a wide range of pulses.
The most important biochemical disorders are those indicating derogation of the liver's synthetic capability and the extension of the prothrombin time, the reduction of the albumin and hyperbilirubinemia.
Imaging results indicating cirrhosis are the existence of a hump on the dorsal side of the liver, the high inequality of the liver parenchyma with marking of reproductive nodules, the dilatation of the portal vein, the existence of splenomegaly and ascetic collection. The Doppler examination offer additional diagnostic elements to assess the flow towards the portal vein – slow or backflow – and the presence of collateral flow. Liver biopsy can always confirm diagnosis of cirrhosis [3].

11.HEPATOCELLULAR CANCER (HCC)

HCC is the most important primary neoplasia of the liver. Risk factors for the development of HCC are the infection by the Hepatitis B and C viruses, liver cirrhosis, the metabolic diseases of the liver, alcohol, alfatoxins, chemical factors etc.

Suspicions for HCC rise for patients with liver cirrhosis when they present pain at the right hypochondrium, tangible mass or when they do not present any improvement of ascites, hepatic encephalopathy or hemorrhage on the grounds of esophageal varices that are sufficiently treated. Also, there should be suspicion for HCC development in patients with hemochromatosis or chronic hepatitis B or C that manifest sudden or causeless deterioration of their clinical picture.

During the physical examination it is possible to auscultate a friction sound or murmur at the right hypochondrium due to increased vascular blood flow. The patient can also be admitted with the dramatic image of haemoperitoneum.

The most important of the blood tests is the determination of A-Fetoprotein (AFP) that is rather increased at 50-70% of the cases of primary liver cancer.

Liver ultrasound is an image test that plays the most prominent role in the diagnosis of HCC, yet its sensitivity is relatively small, especially in small sized nodules. The best diagnostic methods are spiral CT and MRI with contrast media, whose accuracy exceeds 80%. Cancer can only be confirmed by liver biopsy [5].

12.THE PRESENT HOSPITAL CONDITIONS

The Gastroenterology – hepatology specialist at the Liver Center that the patient visits shall at first fill in a complete history about the patient. This background information shall include demographic details, the clinical picture and the findings arising from the physical examination, any hereditary or other preexisting diseases as well as any test results that patient may have produced with him/her. These details are entered in the patient's record, which from now on will accompany the patient and will be updated with new data at every visit he makes to the Liver Center. At every visit, the doctor assesses the patient's clinical picture and after taking into account all clinical findings (table 1) fills in a brief history and gives instructions for further tests. Such tests firstly aim to identify the disease and then the patient is followed-up to see the course – progress of the disease. In performing this task, s/he uses mainly the lab tests (table 3) and or imaging tests and biopsy (table 2), as required. The patient's medical record may become quite big, include dispersed information and the doctor shall have to go through numerous test results, instructions and background information, something that is not always feasible in the framework of his work in a hospital.

Table 1. Clinical Findings.

clinical findings	Acute Viral Hepatitis						Chronic Hepatitis							HCC
	HAV	HBV	HCV	HDV	HBV/HDV	HEV	HBV	HCV	HDV SUPER	Alcoholic	NAFLD	Autoimmune	Cirrhosis	
Jaundice	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Nausea and vomiting	x	x	x	x	x	x	x	x	x	x	x	x	x	
Diarrhea	x	x		x										
Fatigue or weakness	x	x	x	x	x	x	x	x	x	x	x		x	x
Fever	x	x	x	x	x	x		x	x	x				x
Anorexia	x	x	x	x	x	x	x	x		x	x	x	x	
Weight loss	x						x				x		x	x
Indigestion	x													
Itching	x										x	x	x	
Asymptomatic disease	x	x	x				x	x		x	x			
Muscles and joint pain	x	x	x	x	x	x	x	x		x		x		
Confusion and difficulty to concentrate			x						x	x				

Headache	x	x	x	x	x	x								
Malaise	x	x	x	x	x	x								
Photophobia	x	x	x	x	x	x								
Cough	x	x	x	x	x	x								
Hepatomegaly					x	x	x	x		x		x		
Splenomegaly	x	x	x	x	x	x		x					x	
Cervical adenopathy	x	x	x	x	x	x								
Vacular spider					x	x	x	x		x	x	x	x	
Pharyngitis	x	x	x	x	x	x								
Depression							x							
Irritability							x							
Abdominal and ankle swelling							x			x	x			x
Palm erythema								x						
Ascites								x			x		x	x
bruises									x					
bleeding		x							x		x		x	
encephalopathy									x				x	
skin eruption												x		
Gynecomastia							x	x		x			x	x
Libido decrease											x		x	
Abdominal pain and sensitivity to the upper right quadrant of the abdomen	x	x	x	x	x	x	x	x	x	x		x	x	x

Table 2. Imaging Tests.

Imaging tests	Acute Hepatitis						Chronic Hepatitis							HCC
	HAV	HBV	HCV	HDV	HBV/HDV	HEV	HBV	HCV	HDV SUPER	NAFLD	Alcoholic	Autoimmune	Cirrhosis	
Abdominal ultrasound (us)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Computed Tomography (CT)													x	x
Magnetic Resonance Imaging (MRI)													x	x
Spiral CT - liver & spleen														x
Liver biopsy							x	x	x	x	x	x	x	x
Gastroscopy														x
Colonoscopy														x

Table 3a. Lab Tests.

	Lab tests	Acute Hepatitis						Chronic Hepatitis							HCC
		HAV	HBV	HCV	HDV	HBV/HDV	HEV	HBV	HCV	HDV SUPER	Alcoholic	NAFLD	Autoimmune	Cirrhosis	
Viral	anti-HAV IgG (Immunoglobulin G)	x													
	anti-HAV IgM (Immunoglobulin M)	x													
	HBsAg		x					x							
	HBeAg							x							
	anti-HBc							x							
	anti-HBc IgG							x		x					
	anti-HBc IgM		x			x									
	anti-HBs		x												
	anti-Hbe							x							
	HBV-DNA							x							
	anti-HCV			x					x						
	HCV-RNA			x					x						
	anti-HDV					x				x					

	anti-HDV IgG				x										
	anti-HDV IgM				x										
	anti-HEV IgG						x								
	anti-HEV IgM						x								
Serological	anti-SLA (anti-soluble liver antigen)												x		
	anti-ANA (antinuclear antibodies)												x		
	anti-AMA (anti-mitochondrial antibodies)												x		
	anti-ASMA (anti-smooth muscle antibody)												x		
	anti-LKM1 (anti-liver kidney microsome 1)												x		
Coagulation	PT (prothrombin time)	x	x	x	x	x	x	x	x	x	x	x	x	x	
	PTT (partial thromboplastin time)										x				
	INR (international normalized ratio)										x			x	
	fibrinogen													x	x
	Erythrocyte Sedimentation Rate (ESR)	x	x	x	x	x	x								

Table 3b. Lab Tests.

Lab tests		Acute Hepatitis						Chronic Hepatitis							HCC
		HAV	HBV	HCV	HDV	HBV/HDV	HEV	HBV	HCV	HDV SUPER	Alcoholic	NAFLD	Autoimmune	Cirrhosis	
Biochemical	Alanine transaminase ALT	x	x	x	x	x	x	x	x	x	x	x	x	x	
	Aspartate transaminase AST	x	x	x	x	x	x	x	x	x	x	x	x	x	
	gamma-glutamyl transferase GGT										x	x		x	
	Alkaline phosphatase ALP	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	total bilirubin TBIL	x	x	x	x	x	x	x	x	x	x	x	x	x	
	direct bilirubin	x	x	x	x	x	x	x	x	x	x	x	x	x	
	indirect bilirubin	x	x	x	x	x	x	x	x	x	x	x	x	x	
	Serum glucose GLU	x	x	x	x	x	x				x	x		x	x
	Urea													x	
	Creatinine													x	
	Cholesterol											x			x
	Triglycerides											x			x
	Lactate dehydrogenase LDH													x	
	Leukoma							x	x	x	x		x	x	
	Albumin	x	x	x	x	x	x	x	x	x	x	x	x	x	
	gamma-globulin	x	x	x	x	x	x	x	x	x	x		x	x	
	alpha-fetoprotein (AFP)							x							x
	Potassium K										x			x	
	Sodium Na										x			x	
	Calcium Ca														x
	Urine test														
	Ferum Fe											x		x	
	Ferritin											x		x	
CBC	White blood cells (WBC)	x	x	x	x	x	x				x			x	
	Polymorphonuclear neutrophils														
	Lymphocytes	x	x	x	x	x	x								
	Large mononuclear cells														
	Eosinophil cells														
	Platelets PLT										x			x	
	Hemoglobin Hb														
	Hematocrit Ht										x			x	

13.SUPPORTING DIAGNOSIS AND TREATMENT WITH THE USE OF MEDICAL INFORMATICS – FUTURE PERSPECTIVES

The condition in the Greek hospitals seems to have not changed a lot over the previous decades. Despite the extensive use of all types of informatics, there is still tons of medical related paperwork. Even an attempt to find, sort or use significant data that will help the doctors provide the diagnosis, treatment and support of the patient is a complex task.

Certainly, the long-waited introduction of the EHR [Electronic Health Record] in the hospitals and its adoption by the personnel are expected to solve part of the problem and mainly those related to the reception, admission and treatment of the patient. Keeping EHR in clinics is a difficult task whose success is determined by several parameters, such as: user-friendly applications, lack of immediate access at all times, difficulties in the upgrade of the application and collaboration with others, the accurate and time-consuming training of the users, problems related to assuming responsibilities and observation of the procedures by the employees working at so many different posts.

We propose a New After-EHR System that will collect information from the patient's Health Record and will sort, select and prioritize the information based on the clinic, the user, the specialty, the position and the grade.

The main features of the New After-EHR system will be:

- Accessibility. The internet technologies will be highly used so that the user has access to the system at all times, via several different electronic devices and from different locations, even via his/her mobile phone. So, a special edition of the system will have fewer requirements and will be appropriate for use through smart mobile device (smartphones, tablets etc),
- The doctor's task will be assisted both by quick finding and presenting only the useful information existing in the classic EHR and by using artificial Neural Networks,
- The presentation of the record will be different for each department-clinic of the Hospital, taking into account the special needs of each department, while special emphasis will be placed on the multimedia dimension of the record, so that it can integrate imaging tests, charts, photos and even sound messages,
- Distant learning – "Help". The user, via easy-to-use wizards that will be regularly updated, will be able to see all features of the software and the edition he uses, while individualized help will be also provided through forums and/or search in several medical databases on the web.

The use of the after-EHR will yield a series of advantages regarding the traditional EHR, such as:

Greater help for the doctor in sorting information and in creating a plan for the diagnosis, treatment and healthcare of the patient.

Easier access to numerous medical tests using the multimedia features and automatic elimination of the traditional method of transferring on paper.

Easier follow-up of the patient by distance, since the use of the network and through websites that will allow a more efficient monitoring of the patient's course from anywhere on the network that has access to the network.

Greater flexibility of organization and presentation of the information by department and specialty, by choosing the form of the record depending on the user.

Ability to better assess the diagnostic tests and the outcome of the treatment, by using comparative data and presenting the results in a chart's form.

User-friendly. The use of the Internet, where the work environment is familiar and easy for the majority of the users, in combination with the provision of distant accessories, such as step-by-step papers' guides and webinars and/or the operation of a forum and a library of users' questions will allow the more efficient and cost-effective support of the user.

Finally the upgrade – extension of the system will be easy and cheap since it will be based on the programming of the websites and will easily integrate new technologies without requiring a huge investment on infrastructure, as is the case of the HER.

14.CONCLUSION

Hepatological center is a very demanding department with many patients that usually are visiting the center with an appointment at scheduled hours. The daily routine for the doctors is to take the medical record and have a look at the information that includes in just a few minutes before they examine and give instructions to the patient. The time is valuable and the papers they need to check before they take a decision are always a lot. Under these conditions there is a great possibility to make a mistake, to miss or confuse some critical information.

The proposed Medical Record system is a new presentation that allows the doctor to have a quick look at those data that s/he needs, by following the progress-course of the patient and by identifying at first glance those data that would help in the diagnosis, follow-up, treatment and cure. So, there is significant saving in time, cost and resources that are a crucial issue in the field of Healthcare nowadays.

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