ORIGINAL ARTICLE

HEPATITIS A. THE FEATURES OF DISEASE COURSE IN ADULTS

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ABSTRACT

The aim: To analyze the incidence of Hepatitis A in Ukraine and Poltava region and to study the clinical and epidemiological features of the course of Hepatitis A in adult patients.

Materials and methods: The course of HA in 96 hospitalized patients was analyzed. The diagnosis of HA was established on the basis of clinical and epidemiological data and confirmed by the results of laboratory studies (serological and molecular biological).

Results: In 2019, in the Poltava region, there was an increase in the incidence of Hepatitis A with a predominance among sick people of working age, among the urban population. This part of people aged from 60 to 75 years old constitutes 9.4%. This study showed that the waterway was the dominant way of HA transmission. The course of the disease in most hospitalized patients was typical and cyclic, with a predominance of a mixed variant of the pre-jaundice period and jaundice. One third of patients survey that they had fever, which persisted with jaundice.

Conclusions: The findings of this study indicates that the patients older than 40 years were more likely to have concomitant chronic pathology than younger patients, and Hepatitis A was more severe with the development of prolonged cholestasis, wave-like course and recurrence. In most patients under the age of 40, the course of Hepatitis A was mild, but splenomegaly and severe cytolytic syndrome were more common.

KEY WORDS: jaundice, hepatitis A, atypical course

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INTRODUCTION

Hepatitis A is recognized as being a widespread viral disease that occupies a leading position among acute infectious pathologies of the liver. According to the WHO (the acronym WHO stands for World Health Organization), about 1.4 million cases of hepatitis A (the acronym HA stands for hepatitis A) are registered annually in the world [1]. In Europe and the United States, the share of HA in the total incidence of viral hepatitis is from 10 to 30%, and in countries such as Asia, Africa, Latin America, endemic for this pathology is 70-80% [2, 3]. According to the WHO classification, Ukraine belongs to the regions with medium endemicity for HA, the criterion of which is IgG to HAV ≥50% in persons under 15 years old and <90% up to 10 years old [4]. However, the level of dissemination of this virus in Ukraine is uneven. In recent years, there has been a downward trend in the HA infections in Ukraine. Nevertheless, the epidemic situation in the country remains tense. Thus, in 2019 there was an increase in morbidity by 6.5 times (19.03 per 100 thousand population) in Poltava region. It raised significantly in comparison to 2018 (2.92 per 100 thousand population) and it has exceeded the national on average 4.2 times (4.56 per 100 thousand population).

One of the leading factors determining the incidence rate of of HA is considered to be the sanitary and communal improvement of territories, and the main route of transmission of this infection is the waterway. According to the WHO, the most risky factors for HA infection are contact with a patient, the presence of unsatisfactory social conditions and lack of cleaned drinking water consuming, travel to a highly endemic region without being vaccinated against HA, homosexuality, parenteral drug use [4].

With the start of a full-scale war in Ukraine, the risks of outbreaks of infectious diseases have greatly increased [5], especially with the fecal-oral transmission mechanism. The lack of access for the people in the occupied territories to clean water, basic hygiene and medical care, crowding of people, in particular in shelters and temporary refuges, violation of the conditions for the burial of the dead plays a significant role in this process [6, 7]. Stress and malnutrition also increase the susceptibility of the population to infections. According to the Center for Public Health, for 6 months of 2022, the incidence of acute intestinal infections increased by 41.6% (9052 cases against 6390 in 2021) compared to the same period in 2021. Thus, the incidence of rotavirus infec-

tion increased by 62.3% (3533 cases vs 2176 in 2021), shigellosis by 49.2% (97 cases vs 65 in 2021). Although the number of cases of hepatitis A in 6 months of 2022 is 2 times lower than in the same period of 2021 (103 vs. 222 in 2021) [8], the presence of risk factors due to military action on the territory of Ukraine increases the likelihood of an outbreak of this infection.

According to scientific studies, about 90% of cases of HA have a benign course and end in recovery. However, 10-20% of patients recorded an atypical course of the disease with recurrence, prolonged cholestasis, fulminant liver failure, and induction of latent autoimmune hepatitis with a corresponding clinical picture in about 3% of patients [9-11]. The mortality rate from HA among children and adults under the age of 50 ranges from 0.3 to 0.6%, while in adults ≥50 years old it reaches almost 5.4% [12].

Recent studies have shown that HA has ceased to be a childhood infection, as the largest number of cases is registered in the adult population, and the patient's age is the most important predictor of the severity of the disease [13-15]. Therefore, given the current relevance of HA in Ukraine and the world, changes in the epidemiology of the disease, namely the increase in the average age of patients and, accordingly, the risk factors for adverse disease (chronic liver disease, HIV, etc.), in this study we examined the features of the current course of HA in adults.

THE AIM

To analyze the incidence of HA in Ukraine and Poltava region and to study the clinical and epidemiological features of the course of HA in adult patients.

MATERIALS AND METHODS

We analyzed the case histories (form No. 003/o «Medical record of an inpatient») of 96 patients with HA who were treated in the departments of the municipal enterprise «Poltava Regional Clinical Infectious Diseases Hospital of Poltava Regional Council» during 2019 were analyzed, among them the women – 53 (55.2%), men – 43 (44.8%), the patients aged from 18 to 71 years old (average 39.9±1.5). The inclusion criteria for patients in the study were as follows: age over 18 years; presence of serum IgM to HAV, elevated alanine aminotransferase (ALT) activity. Patients younger than 18 years of age and those hospitalized with a diagnosis other than HAV were excluded.

The diagnosis of HA was established on the basis of clinical and epidemiological data and confirmed by the presence of IgM and IgG to HAV ("Vectogep"A-IgM, JSC «Vector Best», Russia) and the absence of markers of other viral hepatitis (anti-HBcor (total), HBsAg, anti-HCV (total), which was determined by the immune fermentative analysis and (HBV DNA, HCV RNA) in the polymerase chain reaction ("Amplisens", the reagent kit, Russia).

Clinical severity of HA was determined by peak laboratory values. Severe HA was defined as a five-fold increase compared with the upper limit of normal for a particular sex of ALT or aspartate aminotransferase (AST) and the presence of at least one of the following criteria: serum bilirubin level > 200 μmol/L, hepatic encephalopathy or coagulopathy (international normalized ratio > 1.5). All other patients were defined as having mild HA. According to studies, patients over 40 years of age have an increased risk of developing HA-associated complications and mortality, so we analyzed the course of the disease in this category of patients compared to those under 40 years of age. All patients underwent clinical, laboratory, and instrumental examinations upon hospitalization and in the course of their hospitalization.

Analysis of the incidence of HA was performed according to the statistical reports of the Ministry of Health of Ukraine «Report on certain infectious and parasitic diseases» (reporting form № 2) for 2010-2019. Statistical analysis of the data was carried out by using the computer program "SPSS Statistics 17.0".The normality of the data distribution was checked using the Kolmogorov-Smirnov test. The mean (M) and standard error of the mean (m) or median (Me) with upper and lower quartiles (Q1-Q3) were used to determine the central tendency. In the case of normal distribution, the probability of differences in quantitative results for different groups of patients was determined using the Student's t-test, in the case of a distribution that differed from normal - the Mann-Whitney U-test, qualitative results - by analysing the contingency tables using the Fisher's exact test and the $\chi 2$ criterion, depending on the prerequisites for the analysis.

RESULTS

It is established that during 2010-2018, an epidemic decline of HA with a morbidity rate 6.10 to 3.22 per 100 thousand population in 2010 and from 6.52 to 2.92 per 100 thousand population, respectively, in 2018 was reported as in Ukraine in general and in Poltava region in particular. In 2019, the incidence rates in the Poltava region and the city of Poltava exceeded the indicator for Ukraine (4.56 per 100 thousand population) by 6.5 and 11.2 times (19.03 and 51.19 per 100 thousand population, respectively) (Fig. 1).

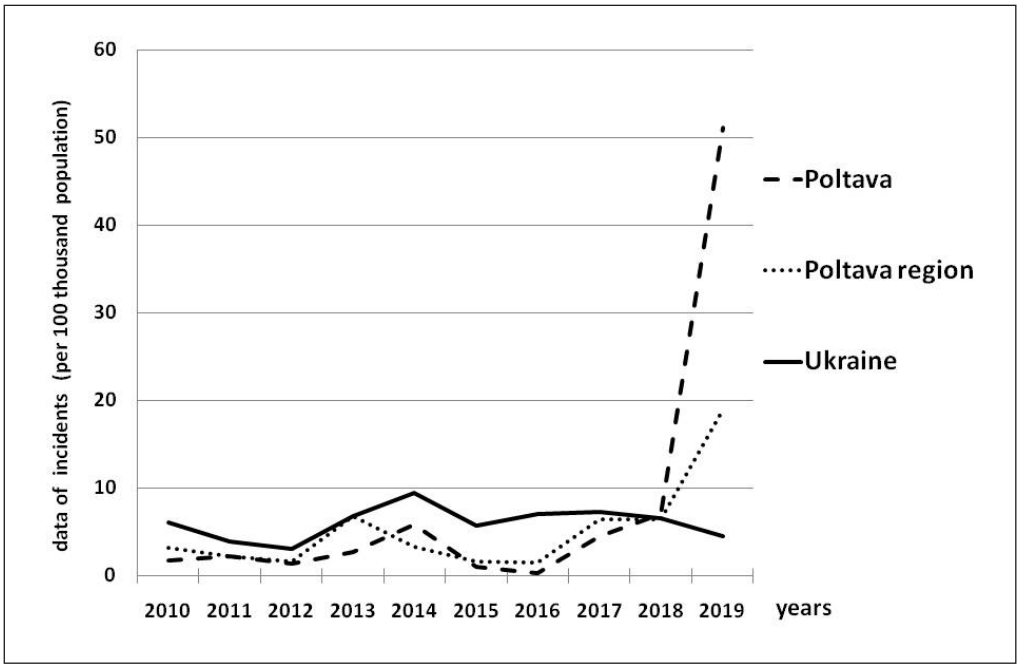

Fig. 1. Incidence of HA in Ukraine, Poltava region and Poltava (2010-2019)

Fig. 2. Epidemic situation on HA in Poltava in 2019

The majority of cases (144 out of 265) which were registered in Poltava region are cases which fall for Poltava city itself, where the incidence rate increased by 7.2 times (51.19 in 2019 in comparison with the data of 2018, 7.08 per 100 thousand population). A detailed analysis of cases in Poltava showed that most patients lived in the Podol and Levada neighborhoods of the city, where there are some natural water reservoirs and one water intake, and the rest of the patients-respondents in other areas either contacted with them or worked in these areas (Fig. 2).

In 2019, among the patients hospitalized with HA the young and middle-aged patients comprises the biggest part (75.0%, n=72). The share of elderly people (from 60 to 75 years old) was 9.4% (n=9). According to the epidemiological history, 28 (29.2%) responded persons indicated that they had contacted with a HA infected patient, 12 (12.5%) responded patients had a swim in the open water reservoirs in Poltava region, rest of them had contacts abroad – 5 (5.2%), and finally, the others consumed unboiled water – 61 (63.5%) patients. The

Table I. Clinical and laboratory characteristics of patients with HA (n=96)

Characteristics	mild HA (n=84)	severe HA (n=12)	P
Gender: men women	 36 (42.9%) 48 (57.1%)	 7 (58.3%) 5 (41.7%)	0.363
Average age, years (M±m)	38,9 ± 1,54	47,4 ± 4,9	0.042
Duration of the jaundice period, days Me (Q1-Q3)	13 (10-17)	21.5 (14.5-38.0)	0.002
Duration of hospitalization, days Me (Q1-Q3)	17 (14,25-21,0)	30,5 (26-36,25)	0.007
Maximum serum bilirubin, μmol/l Me (Q1-Q3)	96,65 (65,73- 123,7)	257,05 (209,17- 282,17)	<0.01
Maximum activity of ALT, IU/l Me (Q1-Q3)	1218,0 (628,0-2159,25)	1779,0 (730,0-2729,0)	0.461

Note: p - level of significance obtained using Fisher's exact test, Student's and Mann-Whitney's tests, depending on the prerequisites of the analysis and the type of data

Table II. Clinical and laboratory characteristics of patients with HA younger and older than 40 years

Characteristics	Patients <40 years old (n=49)	Patients >40 years old (n=47)	P
Gender: men women	 22 (44.9%) 27 (55.1%)	 21 (44.7%) 26 (55.3%)	0.983
Course of HA: mild severe	 45 (91,8%) 4 (8,2%)	 39 (83,0%) 8 (17,0%)	0.228
Duration of the jaundice period, days Me (Q1-Q3)	13 (10-17)	14 (12-25)	0.049
Maximum serum bilirubin, μmol/l Me (Q1-Q3)	93.3 (59.3-137.25)	111.6 (88.8-177.8)	0.047
Maximum activity of ALT, IU/l Me (Q1-Q3)	1655 (751-2507.5)	946 (475-1779)	0.015
ESR increase, mm/h Me (Q1-Q3)	14 (28.6%)	23 (48.9%)	0.040

Note: p - level of significance obtained using Fisher's exact test, χ2 and Mann-Whitney tests, depending on the prerequisites of the analysis and the type of data

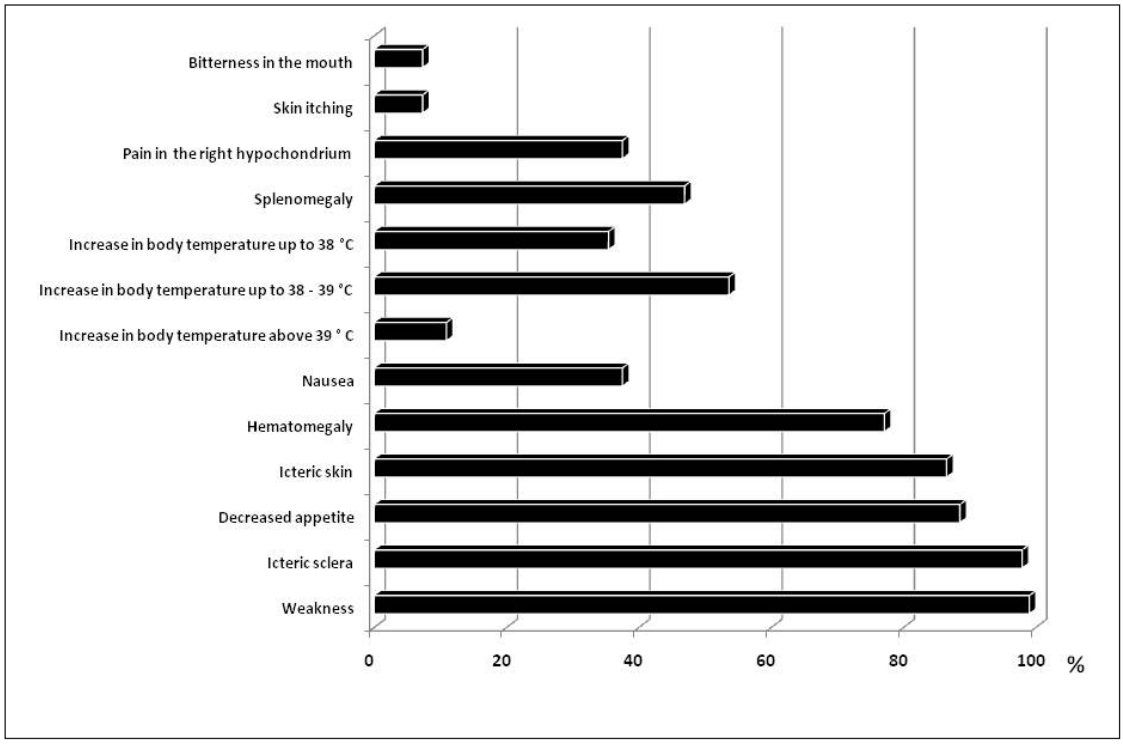

Fig. 3. Frequency of the main clinical manifestations in patients with HA

general clinical examination revealed that 83 (86.5%) patients had chronic concomitant pathology, with a predominance of 74 (77.1%) diseases of the gastrointestinal tract (GI tract), which were more often represented by cholecystitis – in 34 (45.9%), gastroduodenitis – in 23 (31.1%), non-alcoholic steatohepatitis – in 11 (14.8%).

Jaundiced form of the disease was registered in 95 (99.0%), non- jaundice disease was registered in only 1 (1.0%) patient. According to the severity of HA, the subjects were distributed as follows: mild occurrence in 84 (87.5%), severe – in 12 (12.5%) patients. Patients were hospitalized from the 2nd to the 17th day from the onset of the disease, on average on the 7th day (interval 5-10), almost all were hospitalized after the onset of jaundice. The pre-jaundice period lasted from 1 to 15 days, the median for severe HA was 6.5 (5-9.75 days), and for mild HA - 5 (4-8) days. The mixed variant of the pre-jaundice period with signs of dyspeptic (91.7%), flu-like (77.1%) and astheno-vegetative (92.7%) syndromes prevailed over the others (95.8%, n=92). The first manifestations of the disease were the followings: general weakness (100.0%), loss of appetite (88.5%), pain in the right hypochondrium and nausea (37.5%). The patients 82 (85.4%) in the pre-jaundice period had a fever, which in a third (32.3%, n=31) of them persisted with the appearance of jaundice.

The frequency of the main clinical manifestations in the examined patients is presented in Fig. 3.

Comparison of clinical and laboratory characteristics in patients with mild and severe HA is presented in Table I. The mean age was higher in the group of patients with severe HA compared with mild HA (47.4 vs. 38.9 years, p=0.042). Patients with severe HA had a longer duration of the jaundice period and hospitalization, a higher median maximum bilirubin level as compared to patients with mild disease.

Since age over 40 years is a predictor of the severity of HA and worsens the prognosis, we analyzed the course of the disease in this category of patients (Table II). It was found that in patients over 40 years old, more often (87.2%, n=41), compared with younger ones (67.3%, n=33; p=0.022), chronic diseases of the gastrointestinal tract were recorded, which were represented by pancreatitis – 59.6%, cholecystitis (34.0 %) and non-alcoholic steatohepatitis – (34.0%) (in patients under 40 years old – 24.5% (p<0.01), 14.3% (p=0.038) and 10.2% (p<0.001) respectively). Severe HA was registered in patients older than 40 years 2 times more often, but without a significant difference when compared between groups (p=0.228). In patients older than 40 years, the duration of the icteric period was longer, the median maximum level of bilirubin was higher, and an increased erythrocyte sedimentation rate (ESR) was recorded more often. In contrast, in patients under 40 years of age, cytolysis rates were higher, in particular, the maximum of ALT activity was 1655 (751-2507.5 IU/l), in patients over 40 years of age – 946 (475-779) IU/l, p=0.015). According to the results of ultrasound examination of the abdominal organs in patients younger than 40 years, splenomegaly was detected more often – 57.1% (in patients older than 40 years – 36.2%, p=0.042).

The course of HA was typical and cyclic for 90 (93.7%) patients. A typical course of HA was registered in general – in 6 (6.3%) patients, only in persons older than 40 years (12.8%, n=47). It was represented by the development of long-term cholestasis – in 3.1%, wavy course – in 1.0% and relapses – 2.1% of patients.

DISCUSSION

HA is a cyclical disease characterized by epidemic outbreaks at certain intervals, which leads to a decrease in their clinicians' vigilance about this infection during periods of relative well-being. Our study shows that the relative epidemiological well-being of HA is imaginary, and is determined by large cycles disease characteristics as well as by a number of social factors. Therefore, the epidemic potential of HA with the evident threat of epidemic outbreaks today remains extremely significant. The increase in fatalities as a result of stratification of HA on other diseases affecting the liver and the possible development of autoimmune hepatitis after HA seem likely to prove that the problem of this infection is quite urgent for clinical investigations [14, 16].

At the present stage, HA has been acquiring new features different from the classical disease picture, which sometimes complicates the timely recognition of the disease. According to the scientific literature, this trend is especially observed in adult patients, who currently predominate among patients, and associate it with a premorbid background, which determines the severity of the disease [14, 15]. This is consistent with the results of our study, where 41 (87.2%) of 47 patients over 40 years of age were diagnosed with chronic comorbidities, most often gastrointestinal. In this age group of patients, HA was characterized by a more severe course with higher bilirubin levels, longer duration of the jaundice period and the development of atypical manifestations in 12.8% of hospitalized.

According to wide-ranging examination of the scientific literature, it is known that the frequency of atypical HA is from 1 to 20% (average about 7%) and its manifestations may be the development of relapses, prolonged cholestasis, acute liver failure and autoimmune hepatitis [16]. Much work on the issue mentioned above has been carried out, however there are still some data on the atypical course of HA which are need to be investigated. An increasing number of studies have found that the incidence of prolonged cholestasis in HA is less than 5%, and among the reasons for its development are coinfection with chronic hepatitis B, old age and high bilirubin [17]. The fulminant course of HA

with the development of acute liver failure in the developing countries is registered in 3.1-26% of patients over 50 years old. It is suggested that in addition to age, the causes for adverse disease may be provoked by genetic factors and excessive immune response involving CD8 lymphocytes and natural killer cells [18]. In 3% of patients, the HA virus induces latent autoimmune hepatitis I for 5 months after HAV infection [19, 20]. It was found that after infection in these patients there was a specific activation of CD4 T lymphocytes, as well as increased titers of antibodies specific to the asialoglycoprotein receptor of hepatocytes, which is considered to be the main target antigen in autoimmune hepatitis I. Relapses of HA, according to various studies, occur in 1.5-20% of patients and are defined as recurrent episodes of HA after an asymptomatic period of 4 to 10 weeks, with clinical and biochemical manifestations and the presence of HAV replication in the blood or stool by PCR. [21]. Scientific publications cite immune disorders as relapses, such as decreased ability to produce adequate levels of specific antibodies required for virus elimination, as demonstrated in studies in HIV-infected patients with HA [22].

Thus, the analysis of literature sources and our research results show that HA does not lose its relevance and topicality. Today there is a change in the epidemiology of HA with a predominance among sick adults with background somatic pathology, which can change and determine the course of the disease and complicate its diagnosis. Therefore, at the present stage, clinical variants, outcomes and long-term consequences of HA are of interest, and the most promising task is effective prevention of HA based on vaccination and its inclusion in the National Calendar of preventive vaccinations in Ukraine [23].

CONCLUSIONS

During 2010-2018, both in Ukraine and in Poltava region, HA was characterized by an epidemic decline, with incidence rates of 6.10 and 3.22 per 100 thousand people, respectively, in 2010 and 6.52 and 2.92 per 100 thousand people, respectively, in 2018.

In 2019, in Poltava region and Poltava city, there was a 6.5 and 11.2-fold increase in the incidence of HA (19.03 and 51.19 per 100 thousand people, respectively) with a predominance (75.0%, n=72) of people of working age and an increase in the proportion (53.4%, n=144) of the urban population.

According to the epidemiologic anamnesis, 76.0% (n=73) of hospitalized patients were diagnosed with waterborne transmission of HA.

The course of the disease in 90 (93.7%) of the examined patients was typical and cyclical with a predominance (95.8%, n=92) of a mixed variant of the prejaundice period and jaundice form (99.0%, n=95) of HA.

The majority (85.4%, n=82) of patients had fever in the prejaundice period, which in 32.3% (n=31) persisted with the onset of jaundice.

Patients over 40 years of age were more likely (87.2%, n=41) to have concomitant chronic gastrointestinal pathology compared to younger patients (67.3%, n=33; p=0.022). HA in this age group was characterized by a longer duration of the jaundice period (p=0.049), higher bilirubin levels (p=0.047) and, accordingly, a more severe course with the development of prolonged cholestasis in 3.1%, a wave-like course in 1.0% and relapses in 2.1% of patients.

Splenomegaly was more frequently detected in patients under 40 years of age (57.1%, 36.2% in patients over 40 years of age, p=0.042) and higher cytolysis rates were recorded (p=0.015).

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