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Viral Hepatitis A in 108 Adult Patients During an Eight-Year Observation at a Single Center in Poland

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Abstract

Background. Hepatitis A is related to significant morbidity and occasional mortality. Based on data from the Polish National Institute of Hygiene, from 2000 to 2013 a mean of 213 hepatitis A cases were reported yearly.

Objectives. The aim of the study was to assess selected data in adults hospitalized for symptomatic hepatitis A during an eight-year period in a single center in the Wielkopolska Region of Poland.

Material and Methods. All the hepatitis A patients hospitalized in the center from 2005 to 2013 were analyzed retrospectively. Data were extracted from the medical records of these individuals. The disease was confirmed by anti-HAV IgM testing.

Results. In total, 108 patients (71 men and 37 women), aged 18–65 years, were identified. All but 1 patient recovered (99.1%) and in 6 cases (5.6%) a relapse occurred. Risk factors for hepatitis A were identified in 56 patients (52%), with travel abroad being the most common one (32 patients); 19 cases were secondary and 5 patients were men who have sex with men. One hepatitis A outbreak was noted in the region during the study period. Acalculous cholecystitis was found in 33.3% of the patients who underwent abdominal ultrasound. This tended to be more common among older individuals (47.8% in patients over 40 vs. 22.6% in patients aged 18–40, $p = 0.0521$). Patients with this finding had significantly higher mean peak ALT in comparison to those with no gallbladder abnormalities.

Conclusions. Although hepatitis A in adults is typically a benign, self-limited disease, it can occasionally have a fatal course. In a significant proportion of patients with an evident risk factor for hepatitis A, the possibility of active prophylaxis was not used. Hepatitis A should be regarded as a sexually transmitted infection. Acalculous cholecystitis is a frequent finding among adults with symptomatic hepatitis A (*Adv Clin Exp Med* 2015, 24, 5, 829–836).

Key words: hepatitis A, HAV, acute hepatitis, acalculous cholecystitis.

Hepatitis A is a widespread acute infectious liver disease caused by the hepatitis A virus (HAV), a small (27 nm) non-enveloped icosahedral RNA virus belonging to the Picornaviridae family. Four distinct genotypes of HAV representing the same serotype have been identified. The prevalence of HAV infection is highest in countries with a hot or warm climate and poor sanitary and hygienic conditions. The virus spreads mainly by the fecal-oral route and is relatively resistant to environmental factors, detergents and low pH [1–3].

Hepatitis A is related to significant morbidity and occasional mortality. The incubation period of the disease lasts from 2 to 7 weeks, with a mean of 4 weeks. The clinical picture of HAV infection ranges from an asymptomatic course to (rarely) fulminant hepatitis. The typical symptomatic form of hepatitis A includes different combinations of symptoms belonging to 3 syndromes: flu-like, gastrointestinal and cholestatic. Sometimes the disease can also be complicated with extra-hepatic manifestations. Its silent forms are more common

in children, with the proportion of symptomatic illness increasing significantly in older age groups. The typical risk factors for contracting HAV in industrialized countries are international travel to endemic regions, close contact with a person who has hepatitis A, male homosexuality, consumption of contaminated food and injection-drug use.

Based on data from the Polish National Institute of Hygiene, from 42 to 738 cases of hepatitis A (mean: 213) were reported yearly in Poland from 2000 to 2013 (Fig. 1) [4].

The aim of this analysis was to assess selected demographic, epidemiological and clinical data, in addition to some laboratory parameters, in adult patients hospitalized for symptomatic hepatitis A during an 8-year period in the Department of Infectious Diseases at Jozef Strus Multidisciplinary Municipal Hospital (JSMMH) in Poznań, Wielkopolska (Greater Poland) Region in western Poland.

Material and Methods

This retrospective analysis summarizes the data of all patients discharged from the Department of Infectious Diseases at the JSMMH with a final diagnosis of hepatitis A during an 8-year period, from July 1, 2005, to December 30, 2013. These data were extracted from the medical records of these patients. The information that was retrieved included simple demographic factors (sex, age, place of residence) and epidemiological factors (month of hospitalization, travel abroad in the two months preceding the onset of hepatitis A, sexual contacts at risk or close contact with a person diagnosed with hepatitis A in the same time period). In addition to the descriptions of the clinical course of the disease, the peak values of certain biochemical parameters were analyzed as well. Abdominal ultrasound descriptions, if available, were also analyzed, particularly for characteristics of the gallbladder and spleen.

The diagnosis of hepatitis A was based on clinical grounds and confirmed with positive results of anti-HAV IgM antibody testing (AxSYM HAVAB-M 2.0 or ARCHITECT HAVAB-IgM). Screening tests for HBV (AxSYM HBsAg [V2] or ARCHITECT HBsAg Qualitative) and HCV (AxSYM HCV v. 3.0 or ARCHITECT Anti-HCV) infections were conducted on all the patients, and some of them were also tested for HIV infection (AxSYM HIV Ag/Ab Combo or ARCHITECT HIV Ag/Ab Combo). When necessary, additional testing for anti-HBc IgM (AxSYM Core-M or ARCHITECT Anti-HBc IgM) was also performed to exclude acute HBV infection. The manufacturer of all the tests for serological markers of hepatitis

viruses and HIV was Abbott Laboratories, Wiesbaden, Germany.

The statistical analysis was performed using STATISTICA 10 PL software (StatSoft, Inc.). Continuous variables were expressed as mean $\pm$ SD. Categorical variables were expressed as frequencies and percentages. The comparison between the analyzed groups was performed using Student's *t*-test in cases where the data followed normal distribution; normality was checked by the Shapiro-Wilk test. In other cases the Mann-Whitney test was used. Fractions were compared between the analyzed groups using the test of proportion. All tests results were considered significant at $p < 0.05$.

The study was approved by the Bioethics Committee of Poznań University of Medical Sciences, Poznań, Poland (resolution number of 819/13).

Results

During the eight-year period covered by this analysis, 108 patients diagnosed with hepatitis A were hospitalized in the Department of Infectious Diseases at the JSMMH; that number constitutes 7.7% of all registered cases of this disease in Poland in that period. In the study group there were 71 men (65.7%) and 37 women (34.3%), aged 18–65 years old (mean: 35.9 ± 11.3). Half of the patients were younger than 34.5 years (the median value). At some point before or during hospitalization, all the patients experienced some symptoms of a flu-like syndrome (low-grade fever, arthralgia, myalgia, headache) combined with different gastrointestinal complaints (loss of appetite, nausea, vomiting, abdominal pain or discomfort, diarrhea). All but 3 patients became icteric; nevertheless, in two of these non-icteric individuals some cholestatic symptoms (dark urine, pale stool) were present. The number of patients with hepatitis A in relation to different age brackets is shown in Table 1.

The patients were hospitalized at the JSMMH for 1–57 days (mean: 13.2 ± 7.6 days). All but 1 patient recovered (99.1%), although in 6 cases (5.6%) a relapse occurred. One patient died due to fulminant hepatitis. She was a 65-year old woman, who

Table 1. Age of patients with hepatitis A (n = 108)

Age range (years)	No. of patients	%
18–30	41	38.0
31–40	29	26.8
41–50	24	22.2
> 50	14	13.0

Table 2. Peak values of selected biochemical tests in patients with hepatitis A

Parameter	No. of patients	Mean $\pm$ SD (and range) of peak values	ULN*
ALT (IU/L)	108	2150.6 $\pm$ 1536.1 (30–9723)	40
AST (IU/L)	108	1231.1 $\pm$ 1200.6 (41–6647)	40
Total bilirubin (mg/dL)	108	7.9 $\pm$ 3.2 (0.6–16.4)	1.2
GGTP (IU/L)	105	255.7 $\pm$ 159.4 (17–917)	55
ALP (IU/L)	99	228.2 $\pm$ 143.7 (52–928)	123
INR	107	1.18 $\pm$ 0.48 (0.87–5.56)	1.3
Creatinine (mg/dL)	105	0.3–2.0 (0.8 $\pm$ 0.3)	1.4

*ULN – upper limit of reference range.

Table 3. Selected data in young adult patients (18–40 years) vs. older patients (> 40 years) with hepatitis A (n = 108)

Parameter	Young adult patients (n = 70)	Older patients (n = 38)	p
Men (no. of patients)	50 (71.4%)	21 (55.3%)	p = 0.0908
Duration of hospitalization (days)	12.9 $\pm$ 7.2 (range 1–57)	n = 37* 13.8 $\pm$ 8.3 (range 6–57)	p = 0.5092
Peak ALT (U/L)	1980.0 $\pm$ 1288.7 (range 30–7426)	2464.9 $\pm$ 1906.2 (range 162–9723)	p = 0.3694
Peak AST (IU/L)	1167.4 $\pm$ 1078.9 (range 41–6050)	1348.3 $\pm$ 1419.3 (range 79–6647)	p = 0.8118
Peak total bilirubin (mg/dL)	7.5 $\pm$ 2.9 (range 0.6–15.2)	8.7 $\pm$ 3.7 (range 0.8–16.4)	p = 0.0786
Peak GGTP (IU/L)	247.2 $\pm$ 155.6 (range 17–917)	n = 35 272.6 $\pm$ 169.9 (range 65–754)	p = 0.5294
Peak ALP (IU/L)	n = 64 213.7 $\pm$ 109.9 (range 52–614)	n = 35 254.7 $\pm$ 191.4 (range 86–928)	p = 0.6872
Peak INR	1.12 $\pm$ 0.21 (range 0.87–1.90)	n = 37 1.28 $\pm$ 0.76 (range 0.87–5.56)	p = 0.4489
Acalculous cholecystitis (no. of patients)	n = 31 7 (22.6%)	n = 23 11 (47.8%)	p = 0.0521
Death	0/70 (0%)	1/38 (2.6%)	p = 0.1728

*The patient who died was excluded from this analysis.

In instances where data were not available for all the patients, the sample size (n) is given for a particular comparison.

most probably acquired hepatitis A through close contact with her daughter, who had returned from a long stay in Africa (Mali) and had also been hospitalized at the JSMMH earlier, for the same reason.

The peak values of selected laboratory tests are shown in Table 2. A comparison of selected data in young adult patients (18–40 years) and in older patients (> 40 years) is presented in Table 3.

Among the patients studied, evident risk factors for hepatitis A were identified in 56 cases (52%). The most common risk factor was traveling abroad, reported by 32 patients. The countries visited by these patients are listed in Table 4. Five patients who visited the same region near Trento in northern Italy for ski holidays were victims of a local outbreak of hepatitis A. All these

Table 4. Travel destinations in patients with hepatitis A (n = 32)

Continent (no. of patients)	Country	No. of patients
Africa (n = 15; 46.9%)	Egypt	10
	Ghana	1
	Kenya	1
	Morocco	1
	Mali	1
	Sudan	1
Europe (n = 12; 37.5%)	Italy	5*
	Ukraine	3
	Belgium	1
	Czech Republic	1
	Denmark	1
	France	1
South America (n = 3; 9.4%)	Mexico	1
	Venezuela	1
	several countries (Brazil, Paraguay, Peru and Bolivia)	1
Asia (n = 2; 6.2%)	Turkey	1
	Turkey and Syria	1

*All these patients were victims of the same outbreak in 2013 (see Discussion).

individuals (4 men and 1 woman) were hospitalized in April and May 2013.

In 19 cases (17.6%), patients reported close contact with another person who had previously been diagnosed with the same disease. In 5 cases (4.6%), hepatitis A was diagnosed in men who had sex with men (MSM); 3 of them were infected with HIV when superinfection with HAV occurred, while the remaining two patients developed HIV infections within the next few years. One of these individuals was diagnosed with HIV infection during his hospitalization for hepatitis A; latent syphilis was also found in this man. All 5 MSM patients had had risky sexual contacts during the several weeks preceding their hospitalization.

From September 2009 to February 2010, a significant hepatitis A outbreak in Gostyń County (an area with about 76,000 residents in the southern part of the Wielkopolska Region) was registered. During this time period, the majority of cases from the outbreak were hospitalized at the JSMMH

(25 people – 15 men and 10 women – aged from 21 to 58; mean age 35.0 ± 11.0). In 8 patients (28.6%), the disease was secondary hepatitis A due to close contact with other infected individuals. The source of this outbreak was not identified. In 1 of the secondary cases hepatitis A was recognized in a pregnant woman (at 22 weeks of gestation), aged 24, who became ill after her father (living in the same household) was diagnosed with the disease. Hepatitis A had a mild clinical presentation in this case and the further course of the pregnancy was uncomplicated. The patient had a cesarean section after the completion of the 38th week of pregnancy because of ophthalmic indications (an important refractive disorder). Her daughter was born healthy and no hepatobiliary or developmental problems were observed.

In three out of 108 cases (2.8%), hepatitis A was observed in patients (two men, aged 25 and 56, and 1 woman, aged 56) with chronic hepatitis B (superinfection with HAV; HBsAg [i.e., hepatitis B surface antigen] positive, anti-HBc IgM negative). In both men, HBeAg and anti-HBe were also determined (the younger one was HBeAg positive and anti-HBe negative, while in the older man an HBeAg negative and anti-HBe positive status was found); this type of testing was not performed in the third patient. The only particularity noted in these patients was a prolonged cholestatic course of the disease in the youngest HBV-infected person, which resulted in a long hospitalization (57 days).

The sole patient who died was admitted to the hospital on the day of the onset of jaundice, with the following initial biochemistry: ALT: 4405 IU/L, AST: 2129 IU/L, GGTP: 65 IU/L, ALP: 166 IU/L, total bilirubin: 10.0 mg/dL, INR: 5.4, creatinine: 1.6 mg/dL. The next day, symptoms of encephalopathy (confusion, somnolence, asterixis) appeared and a liver transplantation center was contacted. Due to comorbidities in this 65-year old woman (symptomatic sinus bradycardia and atrial fibrillation after the implantation of a pacemaker, asthma, and significant obesity, with a BMI of 39.6 kg/m²) liver transplantation was not possible in this case. Unfortunately, the clinical status of the patient progressed to a hepatic coma and the patient died on the 4th day of hospitalization.

Abdominal ultrasound was performed in 54 patients (50%). In 18 out of these 54 cases (33.3%), acalculous cholecystitis, defined as the presence of gallbladder wall thickening (> 3.5 mm) and the absence of gallstones, was found. A comparison between patients with this finding and individuals with a normal gallbladder picture is presented in Table 5. There was no need for surgical intervention in the individuals with acalculous

Table 5. A comparison of hepatitis A patients with acalculous cholecystitis and patients without gallbladder abnormalities (n = 54)

Parameter	Acalculous cholecystitis group (n = 18)	Normal gallbladder group (n = 36)	p
Age [years]	41.2 ± 11.1 (range 18–58)	35.8 ± 10.9 (range 21–54)	p = 0.0983
Men [no. of patients]	14 (77.8%)	25 (69.4%)	p = 0.5160
Duration of hospitalization [days]	15.3 ± 11.3 (range 5–57)	14.5 ± 8.8 (range 4–57)	p = 0.8758
Peak ALT [IU/L]	3058.7 ± 1998.5 (range 799–9723)	2042.1 ± 1168.2 (range 572–5013)	p = 0.0223
Peak AST [IU/L]	1942.4 ± 1656.7 (range 136–6647)	1132.7 ± 848.9 (range 79–3097)	p = 0.0517
Peak total bilirubin [mg/dL]	9.4 ± 3.1 (range 5.2–16.4)	8.1 ± 3.2 (range 2.2–14.9)	p = 0.1494
Peak GGTP [IU/L]	286.8 ± 143.5 (range 76–501)	n = 33 280.9 ± 192.5 (range 42–917)	p = 0.4479
Peak ALP [IU/L]	246.7 ± 143.6 (range 86–658.5)	n = 34 221.3 ± 144.4 (range 52–816)	p = 0.4473
Peak INR	1.20 ± 0.24 (range 0.93–1.71)	1.09 ± 0.17 (range 0.87–1.64)	p = 0.0984

In instances where data were not available for all the patients, the sample size (n) is given for a particular comparison.

cholecystitis; only a few of them received antibiotic treatment (third-generation cephalosporin with or without metronidazole). No complications were observed.

An enlarged spleen was visualized in 16 out of 54 patients (29.6%).

Discussion

The present study of hepatitis A patients who were hospitalized in a single center between 2005 and 2013 provides additional data on epidemiology issues related to this disease in the Wielkopolska Region by complementing the authors' previous HAV seroprevalence analysis among inhabitants of the same territory [5]. The two reports clearly demonstrate that the Wielkopolska Region can

currently be described as an area of very low endemicity for HAV infection. A low level of anti-HAV IgG positivity among young individuals, low hepatitis A incidence and a mean age of > 20 years among people with hepatitis A are typical characteristics of such a profile of endemicity [6]. In this situation the constant risk of an outbreak exists – an assertion supported by the two peaks of hepatitis A cases in Poland visualized in Fig. 1 – and during this study period one such outbreak was noted in Gostyń County from September 2009 to February 2010 [7, 8]. During this outbreak, a total of 33 symptomatic HAV infection cases were registered (28 in 2009 and 5 in 2010), and more than 90% of them occurred in adults aged 30–39. The source of this outbreak was not identified.

Another important feature of low-endemicity areas for hepatitis A is the presence of recent travel

Fig. 1. Registered cases of hepatitis A in Poland, 2000–2013 [4]

history as a major risk factor for contracting the disease by non-immune inhabitants of these areas [6]. In fact, travel abroad (mainly, but not exclusively, to developing countries – see Table 4) was the most commonly identified risk factor for hepatitis A in the present analysis.

A few susceptible inhabitants of Wielkopolska Region were infected with HAV during trips to Italy. Since January 1, 2013, 10 other laboratory-confirmed cases of hepatitis A have been identified in Germany and the Netherlands in travelers to the same destination. Preliminary investigations, based on strong evidence, have suggested that the most likely vehicle of HAV infection for these travelers were mixed frozen berries (red currants, blackberries, raspberries and blueberries). Interestingly, during the same time period, Italy experienced an unusual increase in hepatitis A cases registered at both the local level (in the vicinities of Trento, Bolzano and five other areas of northern Italy) and the national level [9].

It should be stressed that all the cases in this study related to travel abroad could have been easily prevented with pre-exposure vaccination prophylaxis (at least 1 dose of vaccine administered two to 4 weeks or more before travelling to an endemic region; the vaccination is completed when the second dose is given, preferably 6 to 12 months later) [10].

The sporadic presence of a risk factor previously undervalued in Poland – sexual contact between males – is worth noting in the patients in the present study. Its increasing importance was signaled for the first time in connection with an increase of hepatitis A cases in men having sex with men (MSM) in 2008 and 2009 in Warsaw [11]. The authors of that report observed 50 cases of symptomatic HAV infection among patients who had not travelled to hepatitis A-endemic countries in the time period corresponding to the incubation of the disease. Out of 40 of those men tested for HIV, 6 (15%) were positive. These data suggest that hepatitis A should be also regarded as a sexually transmitted infection (STI); patients should be routinely interviewed for risky sexual practices and, if appropriate, they should be tested for other STIs, including HIV, syphilis and HBV infection. In the present authors' opinion, these observations add to the great value of active pre-exposure hepatitis A vaccination prophylaxis in this population.

Secondary cases of hepatitis A were common in the current study cohort (17.6%). Among the 2009–2010 Gostyń County outbreak patients hospitalized at the JSMMH Department of Infectious Diseases, this proportion was even higher. It is worth noting that an important percentage of secondary cases can be effectively prevented

with post-exposure hepatitis A vaccine prophylaxis [12]. Unfortunately, despite information about this possibility having been provided to some patients, none of them chose to have the vaccine. Considering Poland's potential for hepatitis A outbreaks, knowledge of active post-exposure prophylaxis (PEP) in cases of possible secondary HAV infection and its good efficacy should be propagated among health-care personnel. Although the efficacy of vaccine-based hepatitis A PEP has been proved only for adults under the age of 40–50 years [12, 13], in the current authors' opinion, active PEP would also be a reasonable choice for older people in contact with acute HAV infection, considering the unavailability of hepatitis A immunoglobulin in Poland [14].

In this study, acalculous cholecystitis was noted in one third of the individuals in whom abdominal ultrasound was performed. A similar observation was reported by the authors of a clinical report on hepatitis A in adults from Mexico, who observed acalculous cholecystitis in 10 out of 41 patients (24.4%) [15]. A description of one clinical case and an analysis of the literature conducted by authors from Turkey suggest that, to date, this complication of hepatitis A has rarely been described, and among 16 cases cited in that publication only one third concerned adults (including one case of a person older than 40 years) [16]. The current study found that acalculous cholecystitis was observed among almost half of the patients aged over 40 years, which tended to be more common than in younger individuals. The true prevalence of this finding remains to be determined. The current authors propose that hepatitis A testing should be considered in patients with acalculous cholecystitis of undefined etiology.

The present study provides also some casuistic information. Hepatitis A diagnosed in a pregnant woman in the second trimester of her pregnancy had no adverse influence on the fetus. This is in accordance with past observations showing that the clinical course of hepatitis A does not differ in pregnancy [17, 18]. Nevertheless, it is worth mentioning that cases of intrauterine HAV transmission with meconium peritonitis as a consequence in an early stage of pregnancy have also been described [19, 20].

A detailed analysis of the only fatal case observed during the period covered by this study is consistent with known factors related to the risk of a fulminant course of liver disease and death in hepatitis A patients. Older age, encephalopathy and coagulopathy are all well identified poor prognosis parameters in this a clinical context [21]. The fatal case in the current study had all these variables.

In the study cohort there were 3 cases of hepatitis A occurring in HBV-infected individuals, but a severe clinical course of liver disease not observed in any of them. The possibility of a severe clinical course has, however, been suggested by some reports from Asia. For example, in a study from Thailand, 29% of patients with HAV superinfection died, and all of them were older than 50 (2 of the 3 superinfected patients in the present study were in this age group) [22, 23]. Authors from South Korea found a 22-fold increase in the risk of fulminant hepatitis in hepatitis A superimposed on HBsAg carriage; in their analysis, this clinical scenario was observed in 12% of the cases [24]. It is

possible that race has some influence on the clinical consequences of HAV superinfection in HBsAg carriers, because a large study from Italy does not mention any deaths in such a context [25].

The authors concluded that although hepatitis A in adults is most commonly a benign and self-limited disease, it can occasionally result in fatal course. In a significant proportion of patients with an evident risk factor for hepatitis A, active pre- or post-exposure prophylaxis was not used. An effort must be made to change this situation. Hepatitis A should be regarded as a sexually transmitted infection. Acalculous cholecystitis is a frequent finding among adults with symptomatic hepatitis A.

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