CHOLESTATIC SYNDROME IN VIRAL HEPATITIS A

Andrey I. Petrov, Nikolay T. Vatev¹, Maria V. Atanasova²
Department of Infectious Diseases, Parasitology and Tropical Medicine, ¹Department of Hygiene, Ecology and Epidemiology, ²Department of Microbiology and Immunology, St. George University Hospital, Medical University, Plovdiv, Bulgaria

ABSTRACT

Aim: To study the cholestatic forms of viral hepatitis A that are described as unusual and very rare, but that are of great significance because of their severe course and high morbidity rate.

Material and methods: We describe herein 17 cases of hepatitis A virus (HAV) infection with pronounced cholestasis treated in the Clinic of Infectious Diseases at St. George University Hospital between 2002 and 2006. They are taken from a contingent of 820 patients we studied in the course of the research: of these 400 were cases of sporadic disease and 420 patients were involved in an epidemic outbreak of the disease. All got this diagnosis based on an anti-HAV/IgM test. Eight parameters were analyzed: age, max TBil, max ALT, ALP, GGT, no urobilinogen in urine, ultrasound monitoring of hepatomegaly, and hospital stay.

Results: The 17 patients we discuss here are 2.07% of the total 820 patients with viral hepatitis A (VHA). In 14 the disease had a cholestatic component; 3 cases were a cholestatic form of the disease. The mean hospital stay was 49.1 ± 11.5 days, the longest - 75 days. The hyperbilirubinemia had high levels at the disease climax – the mean concentration was 356.6 μkmol/l, and remained greater than 150 μkmol/l for more than a month. In 10 patients (58.2%) transaminase activity was over 1400 U/l, (mean 2011 U/l).

Conclusion: Viral hepatitis A ran with cholestatic syndrome in 2.07%; 23.5% of these cases were classified as severe forms of the disease and 76.5% - as moderate. This is evinced by the enhanced transaminase activity, the elevated TBil, pronounced intoxication, the adynamia, vomiting, headache, the vertigo, all of these items in the objective severity score system we used.

Keywords: viral hepatitis A, cholestasis, epidemic, a score system

INTRODUCTION

After a certain period of stagnancy in the research of hepatitis A virus, probably because hepatitis B and C viruses and the chronic disease they cause had attracted the researchers’ interest more compellingly, there is a certain revival of the interest toward hepatitis A virus, its prevention and confinement and eventual eradication in the future.¹,² Viral hepatitis A keeps being a problem for Plovdiv region and Bulgaria: there is the high incidence it has reaching 426º/oooo during the 2006 outbreak of the disease, the distinctive clinical diversity in the disease progression not only impairing the health, the psycho-social balance and working ability of the individual, but also inflicting great economic losses by the loss of working hours, working ability and creativity of large groups of people.³,⁴

Cholestasis is defined as disturbance in the production and excretion of bile that leads to biochemical, physiological, morphological and clinical alterations.⁵ Cholestatic forms of VHA are rare and the correct definition is presence of cholestatic component in icteric cyclic form of the disease.⁶,⁷

Despite the pronounced pathomorphologic alterations, reliably showing intrahepatic cholestasis with limited necroses in the acinal region and periporal hepatitis with muff-like conflating necroses surrounding the inflamed portal ducts⁸, clinically manifested cholestasis in HVA is rare and present primarily in elderly patients.

The AIM of the study was to analyze the frequency and clinical course of these forms in modern viral hepatitis A.

MATERIAL AND METHODS

We present here seventeen patients with viral hepatitis A (VHA) with pronounced cholestasis treated in the Clinic of Infectious diseases at St. George
University Hospital; between 2002 and 2006. They are a subsample from 820 patients, of whom 400 are sporadic cases and 420 - cases of epidemiologic outbreak. The diagnosis in all was confirmed by anti-HAV IgM +. Eight parameters characterizing the cholestatic syndrome were analyzed: max TBil, max ALT, ALP, GGT, no urobilinogen in urine, ultrasound monitoring of hepatomegaly, hospital stay and age. Routine clinical and paraclinical methods were used. The diagnosis was verified by the presence of anti HAV IgM antibodies detected by ELISA with Dia-Sorin diagnostic kits in the Microbiology Department.

STATISTICS
Data were analysed using modern statistical software. The level of significance was accepted to be at p < 0.05. We used in the study ANOVA for quantitative parameters - Student-Newman-Keuls criterion and graphical analysis of statistical data and their relation have been used.

RESULTS
During the period of observation the disease was accompanied by significant cholestasis in 17 (2.07%) of 820 patients with VHA. Analysis shows that in 14 of them it is more correct to assume presence of cholestatic component – acute, cyclic icteric form, with markedly high aminotransferases and overlapping cholestatic signs. Cholestatic form of VHA was found in 3 patients – moderate cytolysis with prevailing cholestatic parameters. In the studied sample, one patient was 17 years old, eight were females and eight were males between 27 and 62, with mean hospital stay of 49.1 ± 11.5 days and longest hospital stay of 75 days for a 27-year-old man. No statistically significant difference between cholestatic sporadic cases – 9 (52.9%) and epidemiologic ones – 8 (47.1%) was found.

The basic hepatic functional parameters, including cholestatic enzymes are shown in Table 1.

Pronounced manifestations of cholestasis are present in all patients: itching with skin scratches – in 13 patients; hypocholic and acholic faeces for 7 to 21 days (13.3 ± 4.3) – in 17 patients; no urine urobilinogen for a long period – in 14 patients; mild verdin hue of jaundice was present in patients with hyperbilirubinemia for more than

<table>
<thead>
<tr>
<th>Initials /age years</th>
<th>Max. TBil μmol/l</th>
<th>Max. ALT U/l</th>
<th>ALP U/l</th>
<th>GGT U/l</th>
<th>Hepatomegaly mm</th>
<th>no urobilinogen days</th>
<th>Hospital stay days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. R.A.C. - 27</td>
<td>420</td>
<td>1071</td>
<td>522</td>
<td>231</td>
<td>175</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>2. G.I.H. - 29</td>
<td>410</td>
<td>2010</td>
<td>558</td>
<td>275</td>
<td>164</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>3. L.S.S. - 28</td>
<td>325</td>
<td>1248</td>
<td>435</td>
<td>241</td>
<td>146</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>4. L.G.D. - 31</td>
<td>464</td>
<td>2710</td>
<td>342</td>
<td>98</td>
<td>158</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>5. S.Z.S. - 38</td>
<td>222</td>
<td>2223</td>
<td>256</td>
<td>106</td>
<td>142</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>7. F.N.T. - 62</td>
<td>618</td>
<td>373</td>
<td>1533</td>
<td>396</td>
<td>145</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>8. G.S.P. - 50</td>
<td>300</td>
<td>1463</td>
<td>653</td>
<td>264</td>
<td>148</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>9. Z.A.P. - 33</td>
<td>362</td>
<td>19241</td>
<td>543</td>
<td>213</td>
<td>150</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td>10. S.A.B. - 38</td>
<td>260</td>
<td>3680</td>
<td>311</td>
<td>246</td>
<td>152</td>
<td>7</td>
<td>38</td>
</tr>
<tr>
<td>11. A.D.P. - 47</td>
<td>312</td>
<td>2020</td>
<td>345</td>
<td>264</td>
<td>146</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>15. V.K.I. - 46</td>
<td>140</td>
<td>1027</td>
<td>406</td>
<td>212</td>
<td>147</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>17. N.T.N. - 38</td>
<td>232</td>
<td>1778</td>
<td>677</td>
<td>744</td>
<td>165</td>
<td>-</td>
<td>38</td>
</tr>
</tbody>
</table>
40 days - №№ 1, 2, 3, 5, 6, 7, 8, 9,13, 14, 15 and 16.

The ultrasound control of liver size shows moderate hepatomegaly (140-155 mm) in 10 patients, and pronounced hepatomegaly (over 155 mm) - in 7 patients.

In 10 patients transaminase activity is more than 1400 U/l at the peak of the disease – mean 2011 U/l, with highest value in a single patient - 4923 U/l. ALT decrease during the first decade compared to the levels at the time of hospital admission is statistically significant (p < 0.001). They approximate the reference values at hospital release after hospital stay of 51 days (Fig. 1).

According to our data, in 14 patients the acute jaundice form of VHA presented with pronounced cytolytic syndrome – e.g. hepatocellular type of injury (ALT/ALP ratio >5) overlapped with cholestatic symptoms – itching with scratching, acholic faeces, lack of urine urobilinogen, increase in serum alkaline phosphatase - ALP and γ-GT, especially prominent during the disease climax.

Hyperbilirubinemia over 200 μmol/l was present in almost all patients with cholestatic component (Fig. 2).

Bilirubin levels are high during the disease climax – mean value 356.6 μkmol/l, and remain over 150 μkmol/l for more than a month. Bilirubin levels at hospital release are 2.5 times above the upper limit of the normal.

In three cases we were able to assume the cholestatic form of VHA (№№ 1, 7 ,14 in Table 1). They are presented separately in terms of ALT and membrane-bound enzymes (ALP and γ-GT) dynamics (Table 2).

Transaminase activity is moderately increased – between 373 and 1071 U/l, ALP is significantly increased, reaching 1533 IU/l in one patient, and γ-GT is 5-8 times more elevated in 2 and almost normal in 1 of the patients. The hospital stay is over 2 months with more than 20 days of lack of urobilinogen in urine in those 3 patients. An interesting fact is that two of the patients are 27 and 35 years old, and the third is 62 years old.

**DISCUSSION**

Our observations are consistent with the opinion of majority of authors that despite the pathomorphologic alterations, showing intrahepatic cholestasis in VHA, clinically manifested cases are rare and are found primarily in the elderly.9-12 A similar point of view is shared by WHO experts, who consider that cholestatic VHA with high bilirubin levels for months, is very rarely seen (WHO/CDS/CSR/EDC/2000). A plausible explanation of that fact is the suggestion of Eisenburg J that the lack of a chronic process and the temporary increase of bile capillaries permeability influence reversibly the osmotic gradient and the activity of Na+, K+, ATP-transport, and the disturbed production, secretion and drainage

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**Figure 1.** Changes in the transaminase activity in the course of cholestatic forms of VHA.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT hospitalization</td>
<td>2011.4</td>
<td>1207</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ALT 2 decade</td>
<td>958.1</td>
<td>512</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ALT 3-4 decades</td>
<td>254.5</td>
<td>118</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>ALT discharge</td>
<td>1210</td>
<td>58</td>
<td></td>
</tr>
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</table>
bile is partial.\textsuperscript{13,14} Our data support A. Bluger that cholestatic form of VHA is rare and presence of cholestatic component in cyclic form of VHA is a more correct definition.\textsuperscript{9,15,16} We do not share his opinion that these forms are moderate or mild. In the 17 patients we followed (2.07\% of 820 patients between 27 and 62 years old) we have not found mild hepatitis A. In 4 (23.5\%) patients VHA was severe, and in 13 (76.5\%) – moderate. A proof for that is high transaminase activity – mean ALT 2011.4 U/l, very high bilirubin at the peak of the disease - TBil 356.6 \(\mu\)mol/l, as well as pronounced adynamia, intoxication, vomiting, headache and vertigo, etc., objectively assessed by a point-system, created by us.\textsuperscript{17} The most significant increase is in ALP and GGT: 403.3 U/l and 215.5 U/l, respectively. The findings of other clinicians are similar.\textsuperscript{18-20} Corpechot C, Cadranel JF report 9 cases of pronounced cholestasis in VHA between 1988 and 1992. Eight of them are in patients over 45 years old with an accompanying disease in 3 cases – chronic colitis, epilepsy and bronchial asthma, probably reinforcing the cholestasis.\textsuperscript{21}

The cases with pronounced cholestatic form of viral hepatitis A are defined as protracted, but with good prognosis (no chronication) by Ferreira and Koff RS.\textsuperscript{19,22} Turkish authors describe a case of cholestatic hepatitis A in 14 year-old boy. Recovery is favourable 4 months after symptoms onset.\textsuperscript{23}

**CONCLUSIONS**

Viral hepatitis A may present with cholestatic syndrome in 2.07\% of the cases, 23.5\% of them classified as severe forms of disease, and 76.5\% - as moderate. Hospital stay is long, but with no evidence for chronication.
REFERENCES


Cholestatic Syndrome in Viral Hepatitis A

А. Петров, Н. Ватев, М. Атанасова

РЕЗЮМЕ

Цель: Анализировать холестазные формы при вирусном гепатите А, описанные как необычайные, казуистически редкие, но и очень значимые из-за тяжелого течения и продолжительного morbidитета.

Материал и методы: Рассматриваются 17 случаев вирусного гепатита А с выраженным холестазом. Пациенты лечены в Клинике инфекционных болезней, УМБАЛ “Св. Георгия” за период 2002 – 2006 г. Эти 17 случаев являются частью обследованных 820 больных. В 400 случаях речь идет о спорадическом заболевании, а в 420 случаях являются частью эпидемического взрыва. Во всех случаях диагноз подтвержден anti HAV IgM+. Анализировано 8 параметров: возраст, max T BIL, max ALT, ALP, GGT, отсутствие уробилиногена в моче, сонографический контроль за гепатомегалией и продолжительность пребывания в больнице.

Результаты и обсуждение: Обследованные 17 больных представляют 2.07% среди всех 820 пациентов с вирусным гепатитом А. У 14 больных заболевание протекло с холестазным компонентом, а у 3 больных налицо оказалась холестазная форма заболевания. Средняя продолжительность больничного простоя 49.1 ± 11.5 дн., при чем самый продолжительный простоя – 75 дней. Гипербилирубинемия высока в разгаре болезни – средняя стоимость 356.6 μkmol/l и удерживается свыше 150 μkmol/l больше месяца. У 10 больных (58.2%) трансаминазная активность свыше 1400 U/l – средняя стоимость - 2011U/l.

Заключение: Современный вирусный гепатит A протекает с холестазным синдромом в 2.07% случаев, при чем 23.5% - это случаи с тяжелой формой заболевания, а 76.5% - со среднетяжелой. Подтверждением вышеизказанного является подчеркнуто повышенная трансаминазная активность, высокий T BIL, выраженная интоксикация, адинамия, рвота, головная боль, головокружение, объективизированные согласно созданной авторами score system относительно тяжести заболевания.