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Charakterystyka zapaleń wątroby w przebiegu pierwotnych zakażeń herpeswirusowych (wirusem Epsteina-Barr oraz wirusem cytomegalii) u dzieci

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Streszczenie w języku angielskim

Characteristics of hepatitis in the course of primary herpesvirus infections (Epstein-Barr virus and Cytomegalovirus) in children

Introduction

Infectious mononucleosis (IM) is a common disease resulting from primary infection with the Epstein–Barr Virus (EBV, *Human Gamma-Herpesvirus 4* – HHV-4), which is a human-exclusive pathogen. Serological markers of past infection are found in more than 95% of adults worldwide, although the majority of individuals experience the infection asymptomatically. A clinical syndrome resembling IM may also be caused by cytomegalovirus (CMV), which likewise belongs to the *Herpesviridae* family. During primary EBV and/or CMV infection, hepatitis may develop (according to available data) in as many as 80–90% of adults with IM. The disease course is usually mild to moderate, although clinical and laboratory features of cholestasis as well as acalculous cholecystitis (AAC, *Acute Acalculous Cholecystitis*) have also been described. Literature data on hepatitis in children with primary EBV infection are limited compared with the adult population. The pathogenesis of hepatocellular injury in EBV and CMV infections remains incompletely understood. Neither of the viruses exhibits tropism for hepatocytes or biliary epithelium. The immune response triggered by the infection is presumed to play a key role in inducing inflammatory processes in the liver. In clinical practice, the treatment of IM is supportive. To date, the benefits of acyclovir therapy have not been confirmed, and the role of glucocorticoids remains limited to selected complications (e.g., airway obstruction).

The aims of the doctoral dissertation

The objectives of this dissertation were as follows:

1. To analyse the clinical course of hepatitis in children with primary EBV infection, taking into account laboratory assessment of liver function and abdominal ultrasonography (USG) (**Publication No. 1**).
2. To compare the course of hepatitis in children with primary EBV infection who were treated with glucocorticoids (administered for extrahepatic complications of IM) with patients not receiving glucocorticoids (**Publication No. 2**).

3. To compare the course of hepatitis in children with primary EBV infection and those with serologically confirmed EBV/CMV coinfection (**Publication No. 3**).

Material and Methods

The dissertation consists of a series of three full-text publications:

1. An observational study analysing the clinical course of hepatitis in children with primary EBV infection, with particular focus on temporal changes in liver aminotransferase activity, the incidence of cholestatic disease phenotype, and abnormalities identified on abdominal ultrasonography (**Publication No. 1**).
2. A case – control clinical study assessing the impact of steroid therapy**,** administered for the treatment of extrahepatic complications of IM**,** on the course of hepatitis in primary EBV infection **(Publication No. 2)**.
3. A case – control clinical study comparing the course of hepatitis in children with EBV monoinfection and children with serologically confirmed EBV/CMV coinfection (**Publication No. 3**).

Results

In **Publication No. 1**, the prevalence of liver and biliary tract–related symptoms in children with primary EBV infection was as follows: hepatomegaly – 80.72%, abdominal pain – 31.32%, nausea/vomiting – 27.11%, jaundice – 11.44%, pruritus – 11.44%, abdominal tenderness – 10.84%, dark urine – 4.82%, pale stools – 1.20%. Elevated ALT and AST levels were observed from the first to the third week of illness, with a tendency to normalise from the fourth week onward. ALT values exceeded five times the upper limit of normal (ULN) most frequently during the first week, in 44/95 patients (46.31%). AST exceeded five times ULN most often in the second week, occurring in 33/108 children (30.55%). ALT levels remained elevated for three weeks, whereas AST activity exhibited two peaks: in the first week (mean 186.34 ± 148.17 IU/L) and in the third week (mean 169.00 ± 140.98 IU/L). Gamma-glutamyltransferase (GGT) activity was elevated during the first three weeks, with the highest mean value in the second week (183.84 ± 97.48 IU/L). Elevated total bilirubin concentration was found in 60.53% of patients. Conjugated bilirubin exceeded 20% of total bilirubin in 18 children (47.37%), and in all cases this finding was associated with elevated GGT activity. In 18/166 (10.84%) patients, clinical and laboratory features of cholestasis were observed and 12 (66.66%) of them were older than 15 years. All children with cholestasis demonstrated ultrasound features of AAC.

In Publication No. 2, significant differences between groups included: the length of hospitalisation – was longer in glucocorticoid-treated patients: 5.0 ± 2.1 days vs. 4.3 ± 2.3 days, (p = 0.015); the prevalence of classic IM symptoms – occurred more common in glucocorticoid-treated patients: 84.61% vs. 61.29%, (p = 0.000); occurrence of fever – was more frequent in the glucocorticoid group: 90.38% vs. 79.03%, (p = 0.040); the duration of fever – was longer in steroid-treated children: 7.5 ± 4.7 days vs. 5.9 ± 4.8 days, (p = 0.049); hepatomegaly on physical examination was observed more frequently in the steroid-treated group: 85.58% vs. 72.58%, (p = 0.040); splenomegaly was also more frequent in children receiving glucocorticosteroids: 73.08% vs. 56.45%, (p = 0.027). Significant differences in laboratory findings included: mean ALT activity in the first week was significantly higher in children not receiving glucocorticosteroids: 288.82 ± 170.16 IU/L vs. 205.34 ± 115.40 IU/L, (p = 0.024); mean AST activity, which peaked in the first and third weeks in both groups, with statistically significant differences observed only in children not treated with glucocorticosteroids (p = 0.024). Between-group differences in AST activity were significant in the first week: 170.63 ± 159.47 IU/L (40,00 – 852,00) vs. 218.85 ± 128.22 IU/L (42,00 – 589,00), p = 0.009 and the third week: 151.09 ± 138.57 IU/L (31,00 – 578,00) vs. 235.50 ± 170.27 IU/L (67,00 – 617,00), p = 0.016.

In **Publication No. 3**, statistically significant differences in the course of hepatitis were demonstrated between children with serologically confirmed primary EBV infection (Group 1) and patients with serological evidence of primary EBV and CMV coinfection (Group 2). Regarding clinical manifestations: pharyngitis/tonsillitis was more frequent in Group 1: 148 (90.24%) vs. 65 (80.25%), p = 0.047; nausea/vomiting occurred more often in Group 2: 35 (43.21%) vs. 45 (27.44%), p = 0.010; OR = 2.01 [95% CI: 1.15–3.51]; abdominal pain was reported more frequently in Group 2: 37 (45.67%) vs. 52 (31.71%), p = 0.042; OR = 1.81 [95% CI: 1.05–3.13]; dark urine was observed more often in Group 2: 12 (14.81%) vs. 8 (4.88%), p = 0.006; OR = 3.39 [95% CI: 1.33–8.67]. Significant differences in laboratory and imaging findings included: higher CRP concentrations in Group 1: 21.93 ± 16.54 mg/dL vs. 15.15 ± 12.85 mg/dL, p = 0.001; a higher percentage of neutrophils in Group 1: 32.07 ± 13.25% vs. 25.33 ± 12.35%, p = 0.000; a higher frequency of abnormal abdominal ultrasound results in Group 2: 100% vs. 66.46%, p = 0.045. The criteria for a more severe course of disease (developed for this study) were met significantly more often by children in Group 2: 60 (74.07%) vs. 96 (58.54%), p = 0.018; OR = 2.02 [95% CI: 1.13–3.64].

Conclusions

1. In children with IM, laboratory assessment of ALT, AST, GGT activity and abdominal ultrasound play an important role in identifying patients with a more severe, cholestatic course of hepatitis or AAC. These patients require careful follow-up after the resolution of clinical symptoms (**Publication No. 1**).
2. Steroid therapy (most commonly used to treat airway obstruction in the course of IM) may alleviate the course of hepatitis during primary EBV infection in children, particularly in the first week of illness. However, it does not affect cholestasis parameters nor the frequency of abnormalities of the liver and biliary tract detected by ultrasound (i.e., it does not modify the risk of complications). Early reductions in ALT and AST activity in children treated with steroids may mask the true dynamics of the disease; therefore, post-treatment monitoring of these enzymes is essential (**Publication No. 2**).
3. In children with hepatitis resulting from the primary EBV infection, serologically confirmed CMV coinfection was associated with more pronounced cholestasis and more frequent liver and biliary tract abnormalities on ultrasound examination. These patients also demonstrated a more severe course of hepatitis (higher ALT and AST activity) in the early phase of the disease (**Publication No. 3**).