Hematological Abnormalities in Patients With Acute Viral Hepatitis A and B

Akut Viral Hepatit A ve B Tanılı Hastalarda Hematolojik Anormallikler

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Summary

Aim: Acute viral hepatitis A (HA) and B (HB) are currently widespread health problems in developing countries, where poor hygienic conditions are prevalent. Extrahepatic abnormalities which involve many organs and systems can accompany these infections. Therefore we wanted to determine the rate of hematological complications in our cases diagnosed as HA and HB.

Material and Methods: Referral test results of a total of 322 cases hospitalized and monitored with diagnoses of HA (Group 1: 219 cases) and HB (Group 2: 103 cases) were analysed retrospectively. Diagnosis of HA was established by Anti-HAV IgM antibody positivity and diagnosis of HB by elevated liver function tests, HbsAg and HBeAg positivity.

Results: Mean leukocyte (8.405±2.682/mm^3), neutrophil (3.985±1.880/mm^3), hemoglobin levels (12.7±1.4 g/dl) and platelet counts (339.149± 123.578/mm^3) were determined. The total rate of hematologcal abnormalities was 59.32 % (HA 58 %, HB 61.6 %), while the rates of leukopenia (0.93 %), leukocytosis (20.81 %), neutropenia (6.21 %), anemia (15.52 %), thrombocytopenis (4.35 %) and thrombocytosis (11.49 %) were also assessed. No cases of pancytopenia was detected.

Conclusion: Hematological abnormalities were seen in nearly half of the cases with HA and HB, which constitute important public health problems in our country. The rates of hematological abnormalities were similar in HA and HB. *(J Pediatr Inf 2008; 3: 90-5)*

Key words: Acute hepatitis A, acute hepatitis B, extrahepatic abnormalities, anemia, thrombocytopenia, leukopenia, neutropenia

Özet

Amaç: Akut viral hepatit A (HA) ve B (HB) kötü hijyen koşullarının olduğu gelişmekte olan ülkelerde halen yaygın bir sağlık sorunudur. Çeşitli organ ve sistemleri tutan ekstrahepatik anormallikler de bu infeksiyona eşlik edebilir. İnfeksiyonun seyri sırasında kemik iliği hipoplazisi ve bazen de aplazi görülebilir. Bizde HA ve HB tanısı alan olgularda hematolojik anormalliklerin görülme oranlarını belirlemek istedik.

Materyal ve Yöntem: HA (Grup 1: 219 olgu) ve HB (Grup 2: 103 olgu) tanısı ile yatırılarak izlenen toplam 322 olgunun başvuru değerleri retrospektif olarak incelendi. HA tanısı anti-HAV IgM yanıtı pozitifliği ve HB tanısı ise artmış karaciğer fonksiyon testleri, HbsAg (+) ve HBeAg (+)'liği ile konuldu.

Bulgular: Ortalama lökosit sayısı (8.405±2.682/mm^3), nötrofil sayısı (3.985±1.880/mm^3), hemoglobin değeri (12.7±1.4g/dl) ve trombosit sayısı (339.149±123.578/mm^3) olarak saptandı. Toplam hematolojik anormalliklerin oranı %59.32 (HA %58, HB %61.6) iken lökopeni (%0.93), lökositoz (%20.81), nötropeni (%6.21), anemi (%15.52), trombositopeni (%4.35) ve trombositoz (%11.49) olarak saptandı. Pansitopeni gelişen olgu saptanmadı.

Sonuç: Ülkemizde halen önemli bir halk sağlığı sorunu olan HA ve HB olgularının yaklaşık yarısında hematolojik komplikasyon görülmektedir. HA ve HB'de görülen hematolojik anormallik oranları benzerdir. *(Çocuk Enf Derg 2008; 3: 90-5)*

Anahtar kelimeler: Akut hepatit A, ekstrahepatik anormallikler, anemi, trombositopeni, lökopeni, nötropeni

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Introduction

Acute viral hepatitis A (HA) and B (HB) are currently widespread health problems in developing countries where poor hygienic conditions are prevalent. (1, 2) In childhood, acute viral hepatitis caused by hepatitis A virus is a self-limiting benign disease. (3) Since viral hepatitis is transmitted enterically, it is more prevalent in populations having lower socioeconomical levels, where hygienic and sanitary conditions are worse. In Turkish children the seroprevalence of hepatitis A was detected to range between 44. 4-71.3 %. (2) Anti-HBs and HbsAg positivities in Turkish children were ascertained to be 13.3-17 and 3.2-5.4 % respectively. The rate of seropositivity of all HA and HB is increasing up to 30 years of age. (4-6)

In children, HA generally has a mild or asymptomatic course. Jaundice is only seen in 5 % of children younger than 3 years. Extrahepatic abnormalities involving various organs and systems thought to be of immunological origin can accompany HA infections. (5-8) Miscellaneous extrahepatic manifestations (glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, thrombocytopenia, agranulositosis, aplastic anemia, pancreatitis) are seen in 6.4 % of cases with viral hepatitis. These manifestations disappear completely with the recovery of viral hepatitis. (8) In HAV infection, extrahepatic immunologic signs are rarely encountered. (9)

It was shown that, in cases with viral hepatititis, bone marrow hypoplasia and pancytopenia (0.1-0.2 %) had developed. (10) Therefore we wanted to determine the rates of hematological abnormalities (leukopenia, leukocytosis, neutropenia, anemia, thrombocytopenia, pancytopenia) in cases diagnosed as HA and HB.

Material and Method

Referral test results of the total of 322 cases with diagnoses of HA (Group 1: 219 cases) and HB (Group 2: 103 cases) hospitalized and monitored on June in 2005 in Firat University were analysed retrospectively. Diagnosis of HA was estabilished by Anti-HAV IgM antibody positivity (11) and diagnosis of HB by elevated liver function tests, HbsAg and HBeAg positivity. (4) Cases with hepatitis B positivity (>6 months) were excluded from the study. HBsAg and antibodies to HBsAg (anti-HBs) were examined using enzyme-linked immunosorbent assay methods in 322 patients. None of the children had received hepatitis A and B vaccine.

In cases with HA or HB, leukocyte (WBC), neutrophil (ANC), hemoglobin (Hb) and platelet counts were evaluated. The rates of leukopenia, leukocytosis, neutropenia, anemia, thrombocytopenia and thrombocytosis were determined. Established criterias for leukopenia (WBC <4.000 /mm^3), leukocytosis (WBC >10.000/mm^3), neutropenia (ANC <1.500/mm^3), anemia (Hb <2SD of age-adjusted normal values), thrombocytopenia and thrombocytosis (platelet counts <150.000/mm^3 and >500.000/mm^3) were accepted. (11-14)

Statistical differences between mean values of HA and HB groups were investigated. Independent t test and chi- square test were used for statistical analyses.

Results

Our patient population consisted of 151 girls (46 %) and 171 boys (54 %). Mean age of our patients was 94.1±39.7 months (24-192 months). Mean ages for HA and HB patients were 95.1±38.9 months (24-180 months) and 91.9±41.4 months (24-192 months) respectively (Table 1).

At the time of referral, mean WBC counts were 8.405±2.682/mm^3 (3.200-18.400/mm^3), ANC were 3.985±1.880/mm^3 (1.280-14.364/mm^3), Hb values were 12.7±1.4 g/dl (5.7-16 g/dl) and platelet counts were 339.149±123.578/mm^3 (49.000-845.000/mm^3).

WBC counts were detected to be <4.000/mm^3 in 0.93 % (n: 3), 4.000-10.000/mm^3 in 78.26 % (n: 252) and >10.000/mm^3 in 20.81 % (n: 67) of the cases. None of the patients demonstrated ANC values less than 500/mm^3 and 500-1.000/mm^3, while ANC values were 1.000-1.500/mm^3 in 6.21 % (n: 20) and more than 1.500/mm^3 in 93.79 % (n: 302) of the patients. Platelet counts were found to be less than 150.000/mm^3 in 4.35% (n: 14) and more than 500.000/mm^3 in 11.49% (n: 37) of the cases. Total rate of hematological abnormalities (59.32 %), and incidences of leukopenia (0.93 %), leukocytosis (20.81 %), neutropenia (6.21 %), anemia (15.52 %), thrombocytopenia (4.35 %) and thrombocytosis (11.49 %) were also assessed. None of the cases developed pancytopenia (Table 2, Figure 1).

Tablo 1. Demographic characteristics of cases and liver function tests

	Acute Hepatitis A mean±SD	Acute Hepatitis B mean±SD	Total mean±SD	p<0.05
Number of patients n (%)	219 (68.01)	103 (31.99)	322 (100)	
Sex (Male (%)/female (%))	114 (52)/105 (48)	37 (36)/66 (64)	151 (46)/171 (54)	
Age (mean, months) (min-max)	95.1±38.9 (24-180)	91.9±41.4 (24-192)	94.1±39.7 (24-192)	p<0.05

Tablo 2. Hematological parameters of the cases

	Group 1 Acute Hepatitis A Mean±SD n: 219	Group 2 Acute Hepatitis B Mean±SD n: 103	Total Mean±SD n: 322	p
WBC (/mm^3, n [%])	8.434±2.671	8.337±2.717	8.405±2.682	p>0.05*
<4.000	2 (0.91)	1 (0.97)	3 (0.93)	p>0.05**
4.000-10.000	171 (78.08)	81 (78.64)	252 (78.26)	p>0.05**
>10.000	46 (21)	21 (20.39)	67 (20.81)	p>0.05**
Leukopenia n (%)	2 (0.91)	1 (0.97)	3 (0.93)	p>0.05**
Leukocytosis n (%)	46 (21)	21 (20.39)	67 (20.81)	p>0.05**
Neutrophils (/mm^3, n (%))	3.946±1.825	4.068±1.998	3.985±1.880	p>0.05*
<500	-	-	-	
500-1.000	-	-	-	
1.000-1.500	11 (5.02)	9 (8.74)	20 (6.21)	p>0.05**
>1.500	208 (94.97)	94 (91.26)	302 (93.79)	p>0.05**
Neutropenia n (%)	11 (5.02)	9 (8.74)	20 (6.21)	p>0.05**
Hemoglobin level (g/dl, n (%))	12.7±1.4	12.7±1.3	12.7±1.4	p>0.05*
<7	1 (0.46)	-	1 (0.31)	p>0.05**
7-10	8 (3.65)	2 (1.94)	10 (3.10)	p>0.05**
>10	210 (95.9)	101 (98.06)	311 (96.58)	p>0.05**
Anemia n (%)	34 (15.52)	16 (15.53)	50 (15.52)	p>0.05**
Platelets (/mm^3, n (%))	349.191±125.762	317.796±116.537	339.149±123.578	p<0.05*
<150.000	9 (4.10)	5 (4.85)	14 (4.35)	p>0.05**
150.000-500.000	184 (84.01)	87 (84.47)	271 (84.16)	p>0.05**
>500.000	26 (11.87)	11 (10.68)	37 (11.49)	p>0.05**
Thrombocytopenia n (%)	9 (4.10)	5 (4.85)	14 (4.35)	p>0.05**
Thrombocytosis n (%)	26 (11.87)	11 (10.68)	37 (11.49)	p>0.05**
Pancytopenia n (%)	-	-	-	
Total rate of hematological complications n (%)	128 (58.44)	63 (61.16)	191 (59.32)	p>0.05**

p: Group 1-Group 2, *: İndependent t- test, **: Chi-square test *** WBC, White blood cell

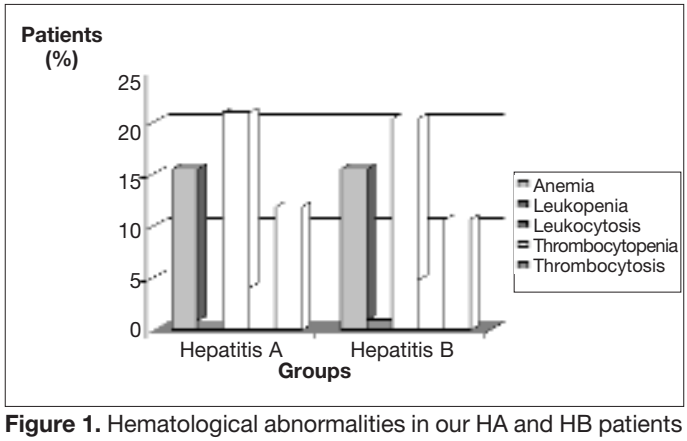

Figure 1. Hematological abnormalities in our HA and HB patients

Discussion

The seroprevalence of HAV increases with age. The rate of seroprevalence ascertained for different age groups have been determined in Adana (n: 711) (2) as follows: 2-6 years: 28.8 %; 6.1-12 years: 49.8 % and 12.1-16.5 years: 68 %; in Kahramanmaras (n: 1142) (15) as follows: 6-23 months: 35.5 %, 2-5 years: 19.2 %, 6-10 years: 74.3 %, 11-14 years: 83.0 %, 15-18 years: 92.8 %, all patients 57.2 %; and in Istanbul (n: 909, 6 month-15 years) (16) as follows 29 %. Total seropositivity was found to be 44.6 % while age related values in Manisa (n: 1395, 6 months-17 years) (17) was as fol-

lows: 6-23 months: 47.8 %, 2-6 years: 23.7 %, 7-10 years: 43.4 %, 11-14 years: 52.4 % and 15-17 years: 76.6 %. Its seroprevalence demonstrated increases from 42.7 % to 91.1 % between 25 and 29 years of age. Hepatitis A seropositivity was detected in 50 % of 16 year-old Turkish adolescents (4,800 subjects under the age of 30 and each from five large provinces [Istanbul, Ankara, Izmir, Adana, Diyarbakır, Samsun, Erzurum, Trabzon, Edirne]). (11) The seroprevalence of HBV was determined as 15.9 % (n: 909, 6 month-15 years, Istanbul). (16) The overall seropositivities for HBsAg, anti-HBs and anti-HBc have been found to be 5.4 %, 17 % and 15.1 %, respectively in Ankara. (18)

Although HA infection generally has a mild course, in rare cases, development of extrahepatic abnormalities are determined. (19) The most frequently encountered extrahepatic signs are observed in hematological and renal systems. (5) In our country, extrahepatic abnormalities rate was detected to be 34.5 %. Hematological abnormalities including leukopenia (9.5 %), anemia (9.5 %) and thrombocytopenia (11.3 %) constituted 30.3 % of the total rate (Table 3). (11)

In a group consisting of adult acute HA, acute HB and acute non-A non-B hepatitis patients, thrombocytopenia (<120.000/mm^3; %19.3), anemia (boys Hb <12 g/dl; girls Hb <10 g/dl, 12.6 %), leukocytosis (WBC>10.000/mm^3; 10.8 %) and leukopenia (WBC <4.000/mm^3; %7.4) were detected. Aplastic anemia (0.9 %) was also seen. (12) During the course of HA, hypoplasia and agranulocytosis in granulocyte parent cells can be observed. (20) Virus-associated hemophagocytic syndrome (VAHS) is a rare abnormality. (21) We did not encounter this diagnosis in our cases. A case where pure red cell aplasia developed has been reported (Table 3). (22)

In our cases with HA, prominently lower (4.10 %) rates of thrombocytopenia was detected, while anemia (15.52 %) and leukocytosis (21 %) was markedly higher. Anemia detected in cases with HA or HB may be hypochromic microcytic, normochromic, normocytic or immune hemolytic anemia. (23-25) The causes of anemia in our cases is not only HA or HB, but may also be nutritional or infectious. In order to determine the causes of anemia, detailed laboratory investigation was needed. In cases with HB, similar values were obtained. The incidences of hematological complications were also comparable. Absence of any case of pancytopenia supports the lower rates of 0.1-0.2 %. No severe neutropenia was determined in our cases. Patients diagnosed as HA and HB should be monitored closely as for secondary infections.

In cases with HB miscellaneous studies reported diverse hematological complications separately. (26) In our cases diagnosed as HB total rate of hematological complications was 61.16 %, while the frequency of leukopenia (0.97 %), neutropenia (8.74 %), anemia (15.53 %), thrombocytopenia (4.85 %) and thrombocytosis (10.68 %) were comparable to those found in HA.

In HA, thrombocytopenia and autoimmune anemia in addition to aplastic anemia have also been reported. (27-30) Development of severe aplastic anemia, and thrombocytemia have been reported in 3 children with HA. (31) In our cases with HA, thrombocytopenia was seen at a rate of 4.10 %, however no evidence of autoimmune hemolytic anemia was encountered.

Acute and chronic hepatitis are characterized with marked infiltration of lymphocytes into the liver. (32) Infiltration of leukocytes into the liver results in the development of liver injury in hepatitis. The reactive oxygen radicals, complement components, proteases, cytokines (TNF-alfa, IL-I beta, IL-12) and chemokines can be enumerated. (33, 34) The acute-phase response is a well-recognised reaction chronic disease. Elevated cytokine levels from such a response have been shown to increase the liver production of the hormone Hepcidin. Hepcidin up-regulation has a negative impact on the iron transport and absorption channels within the body, and may explain a potential new mechanism causing iron deficiency in inflammation. (23) IL-6-mediated bone marrow suppression is the main mechanism for development of anemia of chronic disease. (24) Aplastic anaemia following hepatitis may develop in patients with non-A, non-B and non-C hepatitis. Several causative factors have been discussed, such as viral infections and autoimmunity. (25)

Tablo 3. Hematological abnormalities of our cases with HA and HB compared with literature findings

Hematolocigal complications	Our patients	References (10)	References (11)	References (13)
Leukopenia (%)	0.93	-	9.5	7.4
Leukocytosis (%)	20.81	-	-	10.8
Neutropenia (%)	6.21	-	-	-
Anemia (%)	15.52	-	9.5	12.6
Thrombocytopenia (%)	4.35	-	11.3	19.3
Thrombocytosis (%)	11.49	-	-	-
Pancytopenia (%)	-	0.1-0.2	-	0.9
Total (%)	59.32	-	30.3	-

In our cases VAHS and pure erythrocytic anemia were not observed. In HA hematological manifestations can be severe, which do not parallel with the severity of the liver disease.

IL-11 is a pleiotropic cytokine with biological activities on many different cell types. rhIL-11 has shown effects on multiple hematopoietic cell types. Its predominant in vivo hematopoietic activity is the stimulation of peripheral platelet counts in both normal and myelosuppressed animals. This activity is mediated through effects on both early and late progenitor cells to stimulate megakaryocyte differentiation and maturation. The hematopoietic effects of rhIL-11 are most likely direct effects on progenitor cells and megakaryocytes in combination with other cytokines or growth factors. (35) A shortening of platelet life span apparently contributes moderately to the platelet deficit as well. (36)

The decrease in bone marrow production of neutrophils leads to neutropenia. (37)

Hematological abnormalities in all cases diagnosed as HA improved spontaneously without requiring treatment. Normalization of all hematological values took 6 days. The patients should be monitored closely for secondary infections especially, because of leukopenia and neutropenia seen at a rate of 0.93 and 6.21 % respectively.

Currently in our country, HA and HB continue to be important public health problems. In both HA and HB groups, hematological abnormalities are anticipated in approximately 60% of the cases. Despite the rarity of these signs, we support systemical hematological evaluation. HA and HB are an important health problem in our region, and all children should be given Hepatitis B vaccine. The results suggest that the seropositivity increases significantly among children of school age and also increases parallel to age. It should be supportive of the routine hepatitis A vaccination of young children.

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