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About Viral Hepatitis*

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Several viral infections, like infectious mononucleosis, cytomegalovirus, herpes, rubella, rubeola, chicken pox, mumps and coxsackie, are well known hepatitis agents. But the most common agents are hepatitis A (MS_1) and hepatitis B (MS_2) viruses. The differentiation of the last two types of hepatitis has been done according to the criteria below (Table I). In the last decade, hepatitis B antigen, HBc Ag and Dayne particles in blood and in tissues have been used more specifically to show the presence of hepatitis B viruses.[1] Recently an agent related to hepatitis B antigen has been serially transmitted in rhesus monkeys.[2] The agent has also been propagated in chimpanzees and hepatitis A is inoculated to marmoset monkeys.[3] More recently HA Ag particles are detected in the stool by immuno electronmicroscopy in the incubation period of hepatitis A virus infection.[4] In spite of these developments, reproducible methods, for isolation and cultivation of hepatitis virus A and B in tissue culture, have not yet been developed.

Although the placental passage of several viral infections like cytomegalovirus, rubella, herpes are well established, it is still doubtful in cases of HBs Ag. In general, it is accepted that the virus particle is not inherited transplacentally;[5, 6] however, there are few reports that HBs Ag was shown in cord blood.[7, 8] For the clarification of this issue we looked for HBs Ag and anti HBs in 1002 pairs of mothers and their full term babies, cord blood, by using counter immuno-electrophoresis. None of these mothers had had a history of jaundice in their lives. HBs Ag was shown in 37 of the mothers' blood specimens (3.69 %) and only once in the mother and her baby's cord blood (2.7 % of the mothers who were carriers of HBs Ag (Table II). Unfortunately the placenta of that one case was not available and therefore no possible cause that might be related to it could be sought. During the 4 months of the follow-up period, none

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TABLE I

CHARACTERISTICS OF TYPES A AND B HEPATITIS

Features	Type A	Type B
Incubation Period	15 to 40 Days	50 to 180 Days
Type of Onset	Usually Acute	Usually Insidious
Fever	Common	Less Common
Age Group Affected	Usually Children and Young Adults	All Age Group
Jaundice	Rare in Children More Common in Adults	Same
Abnormal SGOT	Transient - I to 3 weeks	More Prolonged - I to 8 (+) months
Thymol Turbidity	Usually Increased	Usually Normal
IgM levels	Usually Increased	Usually Normal
Virus in Feces	Present During Late Incubation Period and Early Acute Phase	Probably Present Early Acute Phase
Virus in Blood	as above	Present During Late Incubation Period Acute Phase; Occasionally persists for months and years
HBs Ag in Blood	Not Present	As Above
Immunity		
Homologous	Present	Present
Heterologous	None	None

From "Krugman and Ward"

TABLE II

HBs Ag AND ANTI HBs IN MATERNAL AND CORD BLOOD

	Mother	Cord Blood
HBs Ag	37 (3.69 %)	1 (0.1 %)
Anti HBs	2 (0.2 %)	2 (0.2 %)

of the babies had either hepatosplenomegaly or jaundice, with the exception of physiologic icterus of the newborn. Anti HBs was shown in only two pairs of cord and maternal blood. This finding is easily explained in that anti HBs being in IgG fraction of the mother, passes through the placenta. HBs Ag positivity in the mothers (3.69 %) is fairly compatible with the general Turkish population of HBs Ag positivity which is

3.2 %. These findings should be interpreted as follows: HBs Ag does not pass through the placenta, and in exceptional cases, causes should be looked for.

A case will shortly be presented as more evidence for this conclusion. A two day old premature baby was transferred to Hacettepe Children's Hospital because her mother had hepatitis with jaundice for the last two weeks. HBs Ag was found in the mother but not in cord blood or in the baby, when he was one week of age. The mother's SGOT (280 U) and SGPT (225 U) were found elevated. Although the baby's SGOT was slightly elevated (245 U), her SGPT was normal (30 U) at birth. The baby's bilirubin elevated up to 18 mg/dl (only 0.8 mg/dl was conjugated) in the second day of life, but SGOT (60 U) and SGPT (18 U) stayed the same and bilirubin level became normal at 10 days (Figure 1). Liver biopsy of the baby did not disclose any evidence of hepatitis. Two cases with similar histories have also been reported previously.[9, 10]

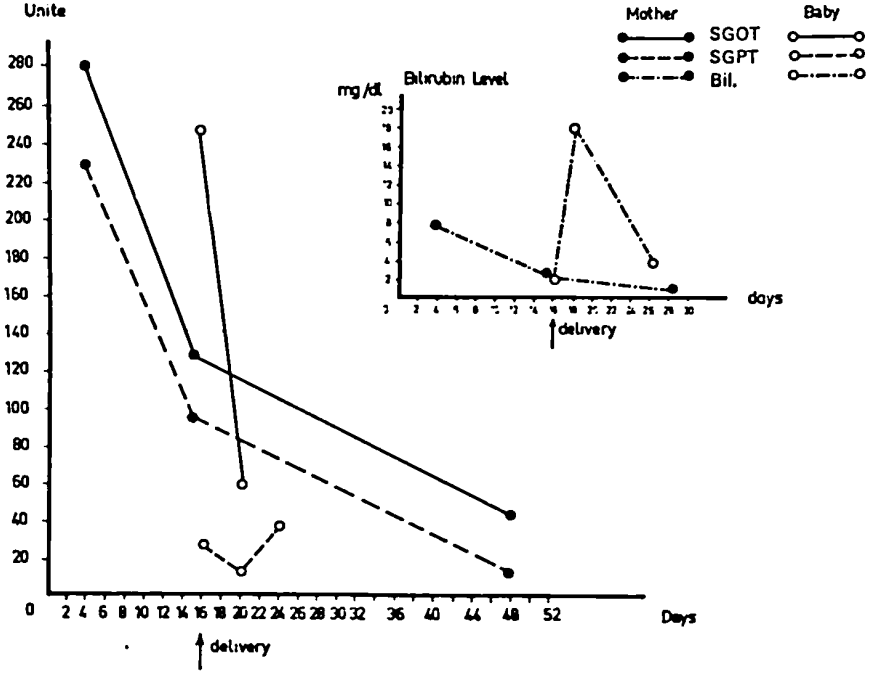

Figure 1

This antigen was also looked for in 39 cases of neonatal hepatitis with the mean age of 80 days (ranged 14 days to 8 months), and was found in 12.82 % of the babies and 22 % of their mothers (Table III).

TABLE III

HBs Ag in PATIENTS WITH NEONATAL AND ACUTE HEPATITIS

In Babies with Neonatal Hepatitis	5/39 (12.82 %)
In the Mothers	2/ 9 (22 %)
In Patients with Acute Hepatitis	16/83 (19. 3 %)

None of these babies had had exchange transfusions and only 14 of 39 were girls. HBs Ag was found more often in girls (21.4 %) compared to boys (8 %). The diagnosis of neonatal hepatitis was verified by histologic examination in 24 of them. The babies of two HBs Ag positive mothers also had the antigen in their circulation. It was not shown in three mothers in spite of the fact that their babies had it. It has to be emphasized that this antigen was found more frequently in the mothers, whose babies had neonatal hepatitis, than in the general population.

HBs Ag was looked for the blood of 83 patients, 25 girls and 58 boys, with acute hepatitis with jaundice, in whom other rare causes of acute hepatitis were ruled out as much as possible. The antigen was shown in 16 (19.3 %) of the cases (Table III), but no history of injection was obtained in 56.3 % of those 16 patients. Fourty-one of the patients were seen in the relatively late period of the disease. HBs Ag was shown less frequently in those 41 i.e. only in 6 (14.7 %), compared to the other 42 cases in whom HBs Ag could be shown in 10 (23.8 %) in the early icteric period. But no difference was found between boys and girls. Our findings were compatible with the knowledge that HBs Ag is more frequently shown in the late incubation and early period of jaundice than in the late period.[11, 12]

In one study from our laboratory, it has been shown that lymphocytes of half of the children who had acute hepatitis a year ago, show blastic transformation with HBs Ag. All the above findings are indications that type B hepatitis is also a fairly frequent cause of acute hepatitis in Turkey and the absence of a history of injection does not rule out the possibility of serum hepatitis.

Coagulation studies have rarely been reported in children with acute hepatitis. For that reason coagulation studies of 18 patients with acute hepatitis were carried out in our laboratory and some kind of acquired abnormality was shown in almost one third of them. (Table IV). Most of these abnormalities are related to vitamin K dependent factors but vitamin K administration alone did not help in correction of these defects. Fibrinogen was also found decreased (less than 150 mg/dl) in 2 of 17 cases (11.8 %). Since the above factors are synthesized in the

TABLE IV

THE ABNORMALITIES OF COAGULATION STUDIES IN PATIENTS WITH ACUTE HEPATITIS

Tests	Number of Patients	Percent of Abnormality
Prothrombin Time (PT)	18	22.2 % (in 4 Patients)
Partial Thromboplastin Time (PTT)	18	11.1 % (in 2 Patients)
Thromboplastin Generation Time (With N. P. Pat's Serum)*	18	11.1 % (in 2 Patients)
Factor II	18	11.1 % (in 2 Patients)
Factor VII	3	33.3 % (in 1 Patient)
Factor VII-X	7	28.5 % (in 2 Patients)
Fibrinogen	17	11.8 % (in 2 Patients)
AHG (Factor VIII)	7	Elevated 71 % (in 5 Patients)

*= N. P. Normal Plasma Pat's Serum= Patient's Serum

liver, a decrease in these factors in liver disease is easily explained. Factor V activity was found normal but antihemophilic globulin procoagulant activity was found elevated in all patients; mean activity of factor VIII was 198 % with the range of 121 to 263 %. F-VIII activity of 71 % of the patients was more than 200 %. Elevated AHG activity in patients with hepatitis was also reported previously.[13, 14] No evidence of disseminated intravascular coagulaton or fibrinolysis[15] was shown in any of the cases.

Serum electrophoresis results of 76 patients with acute hepatitis indicated hypoalbuminemia (less than 40 %) and hyperglobulinemia (more than 24 %). in 51 % and 44.7 % of the cases respectively. The range of these determinations were between 22.5 and 60 % for albumin, 6 and 47.8 % for globulin. However, the mean percentage of both albumin and globulin, being 40 % and 24 %, were not different than our normals. Moderate hypogammaglobulinemia (less than 500 mg/dl), detected by serum electrophoresis, was found in two cases. Immunoelectrophoresis studies of six patients without HBs Ag, did not indicate any specific changes. But it has been reported that IgM is increased in patients with hepatitis A, but not with hepatitis B.[16, 17]

Alpha-fetoprotein is a normal plasma protein fraction in human fetuses older than six weeks, which reaches maximal concentration between 12 and 16 week of fetal life. A few weeks after birth it disappears from the circulation. It was looked for in 33 patients with acute viral hepatitis by using double diffusion agar technique using the anti alpha

fetoprotein serum of Behring-Werke and was shown in only one case (3 %). This protein was found in 32.5 % of patients with acute hepatitis by Buffe and Rimbaut[18] using the same method, and we don't have any explanation for this discrepancy.

Alpha-l-antitrypsin is an enzyme in the circulation; when its deficiency occurs, periodic acid Schiff-positive material in hepatocytes can be demonstrated. The findings suggest that alpha-l-antitrypsin deficiency is linked to the neonatal cholestasis[19] and some kind of childhood cirrhosis[20] and emphysema in adults.[21] This enzyme activity was determined in 8 patients with acute hepatitis and was found normal in all.

Chest X-rays of 59 patients with acute hepatitis were studied since high frequency of pleural effusion has been reported,[22] but it was present in the right hemithorax of only one case (1.7 %).

The outlook for complete recovery is very good in childhood acute hepatitis. However, fulminating cases are not very rare; 39 such cases with hepatic encephalopathy have been treated in Hacettepe Children's Hospital.[38] 14 of them had exchange transfusions (100 cc/kg) and 12 were given corticosteroid (solu-cortef 2 mg/kg I.V.). All the patients were given our supportive treatment equally which consist of elimination of precipitation factors, control of gastro-intestinal (G.I) bleeding, decreasing (G.I.) bacteria by neomycin, treatment of infections, correction of hyponatremia and hypokalemia, I.V. glucose, plasma and/or albumin administration, according to the patient's needs. Only 3 out of 14 patients (21.5 %) who had 1 to 3 exchanges survived, but none in the steroid treated group (Table V).

TABLE V

CORTICOSTEROID, EXCHANGE TRANSFUSION, AND LEVODOPA IN THE TREATMENT OF FULMINATING HEPATITIS

Treatment	Number of Cases	Survived
With Corticosteroid	12	0
With Exchange Transfusion	14	3 (21.5 %)
With L-Dopa Combined with the Above	25	9 (36 %)
L-Dopa Only	14	7 (50 %)

Levodopa has been recently used orally for the treatment of patients with acute hepatic failure and so far 33 cases have been reported,[23, 32] only two in the pediatric age group.[24, 29] It was given by nasogastric tube (100 mg/kg) in the treatment of 25 children with fulminating he-

patitis, in addition to the supportive management. In 14, it was used without corticosteroid or exchange transfusions. Eight out of 14 of these patients improved and seven of them (50 %) survived. Liver function tests of L-dopa responsive and unresponsive patients were compared and were not found significantly different; with the exception of total bilirubin values.

The collected data from literature on the effect of exchange transfusion[33] and corticosteroid are equivocal; and we can not advocate them. But it seems that L-dopa helps the patients in hepatic encephalopathy due to fulminating hepatitis.

L-dopa is a precursor of dopamine which is mainly confined in the C.N.S. to the substantia nigra, striatum and caudata nucleus.[34] When L-dopa is given in hepatic coma, it enters easily into tissues and increases the dopamine concentration.[23, 28] Certain neurological manifestations occasionally seen in chronic hepatic encephalopathy, namely rigidity, tremor and akinesia, are common in Parkinson's disease, in which dopamine depletion of the substantia nigra and striatum has been proved.[34, 35] It has also been shown that L-dopa considerably decreases the S-adenosyl methionine concentration which is elevated during liver failure[36] in the brain by combining with it.[37] Thus levodopa by decreasing the S-adenosyl methionine level may depress the production of some false neurochemical transmitters such as phenylethanolamine, and by increasing the dopamine level in the substantia nigra, striatum and especially in reticularis would be effective on the deranged brain functions in hepatic coma.

Very recently levodopa has been used intravenously without any reportable complication. By this route we are hopeful of obtaining better results since it is not possible to administer levodopa orally in some patients, due to vomiting or gastro-intestinal disturbances.

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